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会议发言

mitochondrial tRNAThr mutation promotes Leber's hereditary optic neuropathy by repressing PINK1/Parkin-dependent mitophagy and activating intrinsic apoptosis

Juanjuan Zhang
Wenzhou Medical University

Leber's Hereditary Optic Neuropathy (LHON) is a rare, maternally inherited eye disease caused by mutation in multiple genes encoded by mitochondrial DNA (mtDNA). We previously discovered that m.15927G>A mutation resulted in mitochondrial dysfunction. However, whether the abnormity caused by the $tRNA^{Thr}$ mutation affected autophagy and apoptosis were unknown. In this study, we showed that the cybrids bearing the m.15927G>A mutation exhibited the increased levels of autophagy protein LC3, decrease of autophagic substrate P62, autophagy activation by ATGs pathway and impaired PINK1/Parkin-dependent mitophagy. The m.15927G>A mutation mediated apoptosis, evidenced by elevating release of cytochrome c into cytosol and increasing levels in apoptotic-associated proteins BAK, BAX, cleaved PARP, as well as cleaved caspases 3 and 9 in the mutant cybrids. These suggested that the m.15927G>A mutation resulted in LHON by aggravating autophagy, impaired mitophagy and abnormal apoptosis.

基于量子化学技术的一种基因治疗新策略的探索

薛晋杰
山西省儿童医院（山西省妇幼保健院）

目的 筛选出可诱发鸟嘌呤(G)发生质子转移且结构稳定的胞嘧啶类似物(Ca)分子模型，以探索一种通过改变鸟嘌呤配对性质而实现基因治疗的新策略。
材料与方法 构建经典胞嘧啶分子模型 Ca_0,并通过原子替换形成 17 个 Ca_n 分子模型作为研究对象，采用密度泛函理论和 M06-2X/def2svp 方法，对 Ca_0～Ca_{17} 以及其与 G 形成的 18 个复合物进行结构优化、分子内质子转移后与转移前能量差(△E)、质子转移过渡态能垒($\triangle G^{\ddagger}$)和反应平衡常数(Keq)等评价分子稳定性和诱发质子转移能力的参数进行计算。
结果 经典 CG 碱基对模型的解离能、分子间质子转移模式、过渡态能垒和反应平衡常数等计算值，均与以往研究相一致，提示本研究所建分子模型和计算方法是合理的。17 个 Ca 模型△E 值在-22.51～4.25kcal/mol 之间，该值越高提示分子越稳定；17 个 Ca_nG 复合物中，有 15 个呈双质子转移模式，2 个呈单质子转移模式；$\triangle G^{\ddagger}$值在-2.02～8.72 kcal/mol 之间, 该值越低越有利于质子转移；Keq 值在 4.75×10^{-6} ～1.28×10^{7} 之间，该值越高越有利于质子转移。
结论 在 17 个设计的胞嘧啶类似物中有 2 个分子（Ca_3 和 Ca_4）稳定性较好（△E>0）且具有诱发鸟嘌呤质子转移（Keq>1）的可能性。这两个胞嘧啶类似物有望作为候选分子进行化学合成，通过实验验证其诱发鸟嘌呤质子转移的性能，以改变鸟嘌呤配对性质实现点突变基因治疗的作用。

MYCT1 经 NAT10 调控 FASN 影响肝脏脂质代谢

王悦 丁冬雪 孙媛媛 丁锶钰 常林 克丽颜 吴岳霖 富伟能
中国医科大学

目的 探讨 MYCT1 通过 NAT10/FASN 对肝脏脂质代谢的影响。
方法 应用 HE 染色检测小鼠肝脏组织形态结构；应用油红 O 染色检测小鼠肝脏组织及 HepG2 细胞脂滴含量；应用试剂盒检测小鼠肝脏组织及 HepG2 细胞甘油三酯、胆固醇含量；应用实时荧光定量 PCR 和 Western Blot 检测小鼠肝脏组织及 HepG2 细胞中 MYCT1、NAT10、FASN 的表达水平。

结果 与野生型小鼠相比，Myct1 基因敲除小鼠肝脏脂质代谢失调；Myct1 基因敲除小鼠肝脏组织中 NAT10 及 FASN 的表达水平显著高于野生型小鼠（P<0.05），且 NAT10 与 FASN mRNA 水平呈正相关（P<0.05）；在 HepG2 细胞中，MYCT1 显著下调 NAT10 及 FASN 的表达水平，NAT10 显著上调 FASN 的表达水平（P<0.05）；过表达或敲减 MYCT1 分别显著抑制和促进 HepG2 细胞的脂滴含量，同时过表达或敲减 NAT10 可恢复 MYCT1 对细胞脂滴含量的影响（P<0.05）。
结论 MYCT1 经 NAT10 抑制 FASN 的表达进而影响肝脏脂质代谢。

个体 MHC 单倍体从头组装新方法及其在基因表达调控研究中的应用

刘赟
复旦大学上海医学院

人类主要组织相容性复合体（MHC）位于 6p21.3，包含 200 多个基因，其在免疫应答、应答调控及免疫监视中起到核心作用，迄今已被发现与超过 200 种疾病的发生密切相关。然而，该区域具有的高度多态性及强连锁不平衡等复杂特征，为对其进行疾病关联等位基因的精确定位及致病机制的解析带来了极大挑战。在不依赖参考基因组的基础上，构建个体特异的高分辨 MHC 区单体型是解决上述挑战的基础和关键。但是，现有 MHC 区单体型构建策略仍存在依赖已有参考序列、家系样本，无法实现个体单体型的高分辨率完整组装等局限性。针对目前 MHC 区研究面临的挑战，我们最新的工作使用 CRISPR 切割富集及长片段测序技术，探索并完善一种全新的不依赖参考序列的个体 MHC 区单体型组装技术；在从头组装获得的单体型基础上，我们建立高准确性的 MHC 区等位基因表观遗传调控及基因表达的分析方法。我们最新的工作将为在不同疾病类型中进行 MHC 区风险等位基因的精确定位及致病机制解析提供一个崭新的研究策略。

Asrgl1 基因缺失导致小鼠光感受器受损

周玉 田万里 刘文静 朱献军
四川省人民医院

目的 天冬酰胺酶和异天冬氨酰肽酶 1 (Asrgl1) 同时具有 L-天冬酰胺酶和 β-天冬氨酰肽酶活性。尽管已经在视网膜色素变性 (RP) 患者中报道了 ASRGL1 的变异，但由于缺乏合适的疾病模型，ASRGL 在 RP 中的体内功能和机制仍然未知，因此，本研究目的在于探索 ASRGL 在 RP 中的体内功能。
方法 使用 CRISPR/Cas9 技术构建 Asrgl1 基因敲除小鼠模型 Asrgl1 KO。用视网膜电图 (ERG)检测小鼠视网膜功能。免疫组化染色检测 Asrgl1 KO 小鼠视网膜内核层（INL），外核层 (ONL)，内节 (IS) ，外节 (OS)，视杆细胞和视锥细胞的改变。RNA-seq 和数据分析检测 Asrgl1 KO 小鼠视网膜转录组的改变。
结果 Asrgl1 敲除小鼠大约 8 个月大时 ERG 反应减弱，ONL 的厚度在 9 个月左右时开始减少，并在 12 和 15 个月时急剧减少。Asrgl1 KO 小鼠的 IS 和 OS 比正常小鼠更薄，视杆细胞和视锥细胞表现出进行性退化现象。Asrgl1 KO 视网膜中发现了 149 个转录差异表达基因 (DEG)。分析发现了与这些 DEG 相关的几个生物过程，包括胃肠道疾病、机体损伤和异常。糖皮质激素受体信号是 Asrgl1 KO 视网膜中改变最重要的经典信号通路途径。包括 NFE2L2、IL-4、Foxp3 和 Fos 在内的几种分子位于 Asrgl1 KO 视网膜相互作用网络的中心节点中。
结论 我们的研究为 ASRGL1 相关 RP 提供了急需的敲除模型，研究了 RP 相关表型，并阐明了 Asrgl1 敲除后小鼠光感受器发病机制中的转录调控变化。

利用单细胞核转录组和空间转录组研究人类肥厚型心肌病细胞类型特异性的转录调控改变

刘宣雨
中国医学科学院阜外医院

目的 肥厚型心肌病（Hypertrophy cardiomyopathy，HCM）是最常见的心脏遗传性疾病，其病理上表现为心肌细胞肥大，不规则排列和心脏纤维化。HCM 患者的心脏会逐渐发生病理性重塑，在无治疗干预的情况下有可能最终进展为心衰。近年来针对 HCM 治疗药物的研发成为全球医药研究领域的热点之一。对 HCM 在病理性心脏重塑中心肌组织的转录调控改变，尤其是对细胞类型特异性改变的深入认识是药物研发的重要基础，有助于发现新的治疗靶点。
方法 我们利用最前沿的大规模单细胞核转录组测序对来自 10 个 HMC 患者和 2 个健康捐献者的心脏室间隔组织进行了包括差异基因表达、细胞亚群组成改变、差异调控网络分析、细胞间信号交流改变在内的系统比较分析。同时，我们对 4 张来自 HCM 患者的冰冻组织切片进行了空间转录组测序，对关键候选靶点基因、通路和细胞亚群的空间表达模式进行了分析和验证。
结果 对 HCM 和健康状态下的共 55122 个细胞核进行无偏聚类，发现了 9 种心脏细胞类型和 29 个细胞亚群。血管相关的细胞类型在相对比例上发生了显著增加，而心肌细胞和成纤维细胞发生了显著减少。同时在各个细胞类型中我们发现了在细胞相对比例上发生了明显改变的细胞亚群，例如高表达 NPPB 的心肌细胞亚群和高表达 NRXN3 的成纤维细胞亚群在 HCM 中比例显著增加。我们重建了心肌细胞从肥厚到心衰状态转变过程中的轨迹，结合拟时间排序、差异表达分析和差异调控网络分析筛选到了可以阻止 HCM 向心衰进展的潜在治疗靶点基因，例如 FGF12，IL31RA，BDNF，S100A1，CRYAB 和 PROS1。同样地，我们揭示了 HCM 中成纤维细胞活化过程中的转录动态，并筛选到了可以缓解 HCM 中心脏纤维化的潜在治疗靶点基因，例如 RUNX1，MEOX1，AEBP1，LEF1 和 NRXN3。通过整合空间转录组数据，这些关键候选靶点基因、通路和细胞亚群的空间表达模式得到了验证。
结论 本研究首次提供了人类 HCM 心脏组织中细胞类型特异性的转录调控改变，并发现了一系列有望预防或延缓 HCM 进展的药物治疗靶点基因、通路和细胞亚群。同时，作为一套非常有价值的资源，我们的数据集为将来在单细胞和空间精度上进一步研究 HCM 发病的细胞分子机制奠定了基础。为方便利用，我们开发了可交互式的数据库网站 http://snsthcm.fwgenetics.org。

致病基因解读相关数据库及工具

李津臣[1,2] 夏昆[1] 孙中生[3]
1.中南大学医学遗传学研究中心
2.中南大学湘雅医院
3.中科院北京生命科学研究院

目的 如何通过系列生物信息分析从疾病患者的测序数据及临床数据中准确有效地鉴定疾病相关致病变异与候选基因是医学遗传学领域关键的科学问题。
方法 本团队围绕变异检测、致病性预测、候选基因鉴定、基因型-表型关联分析、疾病数据库等方面开发了系列具有自主只是产权的数据库及分析工具。
结果 我们开发了一系列整合临床资料、遗传信息、表达数据及调控网络，精准鉴定致病变异及候选基因的生物信息学分析方法及数据库：（1）在系统比较 23 款软件不同使用情境下的优缺点以后，通过整合多款软件的优势与特点开发了高准确率的错义变异致病性预测工具 ReVe；（2）整合了编码区域超过 1.1 个基因变异及其详细注释信息的基因变异解读和候选基因鉴定的数据库 VarCards (http://varcards.biols.ac.cn/)；（3）整合了 28 种疾病表型共 58,011 例样本的 670,082 个新发变异数据及注释信息的数据库及分析平台 Gene4Denovo (http://genemed.tech/gene4denovo/); (4) 整合个体基因变异信息及临床表型新的基因型-表型数据库 GPCards (http://genemed.tech/gpcards/)，为自闭症等复杂遗传疾病的病因学研究及遗传咨询提供了工具支撑与数据保障。

结论 上述工具为鉴定复杂遗传疾病的致病突变和候选基因提供了独立自主的信息资源和方法支撑，对建立具有自主知识产权、国际领先的遗传数据解读体系具有重要意义。

Identification of de novo mutations in the Chinese ASD cohort via whole-exome sequencing unveils brain regions implicated in autism

Zilong Qiu[1,2]
1.Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China
2.Institute of Neuroscience, State Key Laboratory of Neuroscience, CAS Center for Excellence in Brain Science and Intelligence Technology, Shanghai Center for Brain Science and Brain-Inspired Intelligence Technology, Chinese Academy of Sciences

Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental disorder characterized by deficits in social interactions and repetitive behaviors. Although hundreds of ASD risk genes, implicated in synaptic formation and transcriptional regulation, have been identified through human genetic studies, the East Asian ASD cohorts is still under-represented in the genome-wide genetic studies. Here we performed whole-exome sequencing on 369 ASD trios including probands and unaffected parents of Chinese origin. Using a joint-calling analytical pipeline based on GATK toolkits, we identified numerous de novo mutations including 55 high-impact variants and 165 moderate-impact variants, as well as de novo copy number variations containing known ASD-related genes. Importantly, combining with single-cell sequencing data from the developing human brain, we found that expression of genes with de novo mutations were specifically enriched in pre-, post-central gyrus (PRC, PC) and banks of superior temporal (BST) regions in the human brain. By further analyzing the brain imaging data with ASD and health controls, we found that the gray volume of the right BST in ASD patients significantly decreased comparing to health controls, suggesting the potential structural deficits associated with ASD. Finally, we found that there was decrease in the seed-based functional connectivity (FC) between BST/PC/PRC and sensory areas, insula, as well as frontal lobes in ASD patients. This work indicated that the combinatorial analysis with genome-wide screening, single-cell sequencing and brain imaging data would reveal brain regions contributing to etiology of ASD.

Comprehensive analysis of spectral distribution of a large cohort of Chinese patients with non-syndromic oculocutaneous albinism facilitates genetic diagnosis

Jianjun Chen Zilin Zhong
Department of Medical Genetics, Tongji University School of Medicine, Shanghai, China

Non-syndromic oculocutaneous albinism (nsOCA) is a group of genetically heterogeneous autosomal recessive disorders with complete lack or decrease pigmentation in skin, hair, and eyes. TYR, OCA2, TYRP1, SLC45A2, SLC24A5, and LRMDA were reported to cause OCA1-4 and OCA6-7, respectively. By sequencing all the known nsOCA genes in 114 unrelated Chinese nsOCA patients combined with In silico analyses, splicing assay, and classification of variants according to the standards and guidelines of American College of Medical Genetics and Genomics, we detected seventy-one different OCA-causing variants separately in TYR, OCA2, SLC45A2, and SLC24A5, including thirty-one novel variants (13 in TYR, 11 in OCA2, and 7 in SLC45A2). This study shows that OCA1 is the most common (75/114) and OCA2 ranks the second most common (16/114) in Chinese. 99 patients of our cohort were caused by variants of all the known nsOCA genes. Cutaneous phenotypes of OCA1, OCA2, and OCA4 patients were shown in this study. The second OCA6 case in China was identified here. We also identified a novel homozygous variant (NM_201280.3: c.181delC, p.Val61*) in BLOC1S5 in the patient who presents OCA and mild bleeding diathesis, and his healthy parents are heterozygous carriers.In this study, we also

explored bloc1s5 in zebrafish. bloc1s5 mRNA can be detected during early development of zebrafish. bloc1s5 knockdown zebrafish present with retinal hypopigmentation, thrombocytes loss and pericardial edema, and dll4/notch1 signaling and vascular integrity signaling are down-regulated at mRNA level in bloc1s5 morphants. The data from the first HPS-11 patient in Chinese population expand phenotypic and genotypic spectrum of HPS-11. Disruption of bloc1s5 in zebrafish recapitulates HPS-11-like phenotypes, and the potential signaling pathways associated with bloc1s5 are proposed.These data expand the spectrum of OCA variants as well phenotype and facilitate clinical implement of Chinese OCA patients.

基于外显子组测序在中国西部汉族人群中筛查非综合征型腭裂新易感基因及功能分析

贾仲林
四川大学

目的 腭裂（cleft palate，CP）是最常见的口面裂先天畸形之一，发生率为 1.3-25.3/10,000 活产儿，在不同种族和人群中存在显著差异，在我国约为 2.57/10,000 活产儿。腭裂的危害广泛，几乎波及口腔颌面部除视力以外包括口腔咀嚼、吞咽、发音、中耳听力等功能，且会抑制颌骨的正常发育而导致畸形容貌。其治疗需要外科、语音、正畸等多专业专家团队的序列治疗，治疗周期长，总体花费大，严重降低患者生存质量和国民素质，对家庭和社会都带来严重负担。明确腭裂发病机制，从源头上降低其发生率，对于我国这样的人口大国意义非凡，也是世界各国一直在努力的方向。本研究在前期唇腭裂候选基因、全基因组关联分析及目标区域测序研究的基础上，利用外显子组测序技术在中国西部汉族人群非综合征型腭裂（Non-syndromic cleft palate only, NSCPO）中筛查新易感基因，并通过功能分析阐明其作用机制。
材料与方法 采用 Illumina 公司的 HiSeq X Ten 测序平台对 184 例 NSCPO 患者进行全外显子组测序，Sanger 测序技术验证候选变异位点。借助华大基因内部数据库的 710 个正常对照测序数据，利用 R 软件包进行基因负荷分析，PLINK 等软件进行全外显子组关联分析。利用 1199 个 NSCPO 患者和 5068 个正常对照进行验证分析。最后选择具有较强遗传效应的易感位点/基因，利用人腭部间充质细胞（HEPM）初步探讨新易感基因的作用机制。
结果 通过针对罕见变异位点（次等位基因频率<1%）负荷分析、常见变异位点（次等位基因频率≥1%）关联分析和大样本人群队列验证，发现有 7 个新位点/基因与 NSCPO 的发生显著相关。生物信息学分析结果显示其中 1 个易感变异位点位于增强子区域，双荧光素酶报告实验结果进一步证实了该位点不同等位基因能显著影响增强子活性；通过对携带者及父母进行 sanger 测序验证，发现了 3 个新发有害变异位点 NM_001166160.1:c.328G>T (PPP1R9A), NM_002903.2:c.169T>C (RCVRN) and NM_018346.1:c.601C>T (RSAD1)。
结论 综上所述，我们发现了 NSCPO 新易感位点/基因和新发有害变异位点，为今后的唇腭裂的遗传和致病机制研究提供了新的线索。

正辛酸激活神经元父源性 Ube3a 表达改善 Angelman 综合征行为学异常

王艳艳 瞿宋 官兴颖 陈雪丹 张茂 李红艳 王郡旖
陆军军医大学

目的 印记基因 UBE3A 在神经元中只由母源等位基因表达，其母源性表达缺失引起的 Angelman 综合征(AS)是罕见性神经遗传病，尚无有效干预措施。本研究探索有效的早期干预措施，通过激活父源 UBE3A 表达，消除 UBE3A 父系印记，补偿母源的基因功能缺失。
方法 采用 Ube3a-YFP 融合报告基因小鼠，筛选人体母乳中对神经发育有益的营养素，通过检测 $Ube3a^{m+/pYFP}$ 神经元内 YFP 的荧光表达，免疫荧光和免疫印迹法体内外观察神经元内父源 Ube3a

激活水平；在 Ube3a$^{m-/p+}$的缺失型 AS 小鼠模型中，通过转棒、旷场、筑巢、Morris 水迷宫、埋珠、三箱社交系列行为学测试评估营养素干预前后的运动、认知和社交功能。定量 PCR 检测处理前后神经元内 Ube3a 及其反义长链非编码 RNA Ube3a-ATS 在 mRNA 水平的表达改变。重亚硫酸盐测序法分析神经元父源和母源染色体上的 DNA 甲基化水平。

结果 筛选发现营养素中链脂肪酸正辛酸可以激活体外培养和在体神经元内父源性 Ube3a 表达，出生后给小鼠喂饲含有三辛酸甘油酯的饲料（胃肠内代谢后产生正辛酸）能够改善 AS 小鼠运动、认知和社交行为。正辛酸处理神经元后抑制 Ube3a-ATS 的表达，增加 Ube3a 在 mRNA 和蛋白水平的表达，但父源和母源 Ube3a-ATS 启动子区和上游印记中心的 DNA 甲基化水平并未发生明显改变。

结论 中链脂肪酸正辛酸能够激活神经元中父源 Ube3a 的 mRNA 和蛋白表达，抑制其反义 RNA 的表达，改善 AS 小鼠行为学障碍，与目前已知的影响 Ube3a 印记基因表达的调控元件的 DNA 甲基化无关。

ORMDL3 通过限制神经酰胺的生成促进白色脂肪细胞褐变

宋煜 龚瑶琴
山东大学

目的 全基因组关联研究(GWAS)鉴定 ORMDL3 为肥胖相关基因，其表达与体重指数呈负相关。然而，ORMDL3 在肥胖和脂质代谢中的确切生物学作用尚不明确。因此，我们研究了 ORMDL3 在白色脂肪组织褐变和高脂饮食诱导的胰岛素抵抗中的作用。

方法 利用 Ormdl3 缺失(Ormdl3$^{-/-}$)小鼠研究 Ormdl3 在白色脂肪褐变中的作用。在高脂饮食下评估 Ormdl3$^{-/-}$小鼠的糖和脂稳态。用质谱法鉴定白色脂肪组织(WAT)的脂质组成。分离并培养原代脂肪细胞，分析 ORMDL3 调控白色脂肪褐变的机制。

结果 在冷暴露或给予 b3 肾上腺素能激动剂后，Ormdl3$^{-/-}$小鼠白色脂肪组织中脂肪细胞褐变明显受损。此外，与野生型小鼠相比，Ormdl3$^{-/-}$小鼠在高脂饮食中表现出体重增加和胰岛素抵抗的增加。Ormdl3$^{-/-}$小鼠的原代脂肪细胞中产热标志物解偶联蛋白 1 (UCP1)减少。Ormdl3$^{-/-}$小鼠脂肪组织神经酰胺水平升高。此外，通过抑制神经酰胺的产生，可以拯救由于 Ormdl3 缺乏而导致的脂肪细胞褐变的减少。

结论 我们的研究结果表明，ORMDL3 参与了脂肪细胞褐变的调控，其可能是改善全身代谢的潜在靶点。

miR-4431 targets TRIP10/PRKD1 and impairs glucose metabolism

Chongge Pan Jun Zhang Cuizhe Wang
Medical College of Shihezi University

Aims Obesity is considered as an important risk factor for many metabolic disorders, especially type 2 diabetes mellitus (T2DM). microRNAs play a vital role in the development of T2DM. In this study, we investigated the role of miR-4431 in the obesity-associated pathobiology of T2DM.

Materials and methods Subjects were divided into normal control (n=36), obesity (n=36) and T2DM (n=12) groups and the level of miR-4431 in serum were tested. Adenovirus-mediated miR-4431 mimic or sponge was intraperitoneally injected into ND and HFD mice to detect the glucose tolerance, insulin sensitivity, and lipid levels. The downstream target genes of miR-4431 were predicted by bioinformatics technology and verified in vitro.

Results Serum miR-4431 was significantly overexpressed in obesity and T2DM individuals, and was significantly positively correlated with BMI and FPG. In HFD mice, the level of miR-4431 in serum, WAT, and liver were dramatically overexpressed. Moreover, miR-4431 impaired glucose tolerance, insulin sensitivity, and lipid metabolism in mice. Bioinformatics prediction suggested that TRIP10 and PRKD1 could be the downstream target genes of miR-4431. Then, HFD mice

presented a remarkable reduction in the mRNA expression levels of TRIP10 and PRKD1 in liver, which were overturned by blocking miR-4431. In HepG2 and L02 cells, we also discovered that miR-4431 could downregulate TRIP10 and PRKD1, meanwhile block the glucose uptake. Luciferase reporter assay showed that miR-4431 could target to bind TRIP10 and PRKD1 3'UTR. **Conclusion** miR-4431 targets TRIP10/PRKD1 and impairs glucose metabolism.

CUL4B 通过 miR-32-5p/ER-α36 轴调控乳腺癌他莫昔芬耐药

王宇星[1] 潘晓华[2] 李彦军[1] 王茹[1] 杨园园[1] 蒋百春[1] 孙龚萍[1] 邵常顺[3] 王墨林[1] 龚瑶琴[1]
1.山东大学齐鲁医学院
2.山东第一医科大学附属山东省立医院
3.苏州大学转化医学研究所

目的 研究 CUL4B 在乳腺癌他莫昔芬（TAM）耐药中的作用并探明其相关机制。
方法 采用 MTT 方法检测 CUL4B 高表达或敲低后乳腺癌细胞对 TAM 的敏感性变化；采用 qRT-PCR 和 Western blot 方法检测 CUL4B、ER-α36 等相关分子的 RNA 和蛋白表达情况；RNA-seq 结合 TargetScan、miRBD 等软件分析确定参与 CUL4B 对 ER-α36 调控的候选 miRNA；利用 ChIP 和 qChIP 分析 CUL4B 复合物在 miR-32-5p 启动子区域结合情况；采集乳腺癌临床样本分析 CUL4B 和 ER-α36、miR-32-5p 表达水平并分析其内在联系；小鼠荷瘤实验对细胞实验结果及分子机制进行进一步验证。
结果 CUL4B 的上调可显著降低乳腺癌细胞对 TAM 的敏感性，而敲低 CUL4B 或稳定表达具有显性负效应的 CUL4B 突变体则可以恢复细胞对 TAM 的敏感性。机制研究表明 CUL4B 可通过抑制 miR-32-5p，进而上调 ER-α36 表达促进乳腺癌细胞对 TAM 耐药；CUL4B 复合物（CRL4B）通过催化 miR-32-5p 启动子区域 H2AK119 单泛素化并协同 PRC2 和 HDAC 复合物促进 H3K27 的三甲基化，进而抑制 miR-32-5p 转录。
结论 CUL4B 通过调控 miR-32-5p-ER-α36 轴调控乳腺癌 TAM 耐药；为乳腺癌的内分泌治疗用药及辅助用药的研制提供了可能的新靶点。

体外激活 PTEN-PI3K 信号通路对高龄卵巢卵泡发育影响的研究

吴帮勇 马燕琳
海南医学院第一附属医院

目的 通过体外激活高龄卵巢组织中始基卵泡的 PTEN-PI3K 信号通路，探讨 PTEN-PI3K 信号通路对高龄卵巢卵泡发育的影响。
方法 获取新鲜高龄 ICR 小鼠（40 周）卵巢组织，解冻高龄女性（40 岁~49 岁）卵巢组织，分别设置对照组和激活组进行体外培养。激活组在卵巢组织培养液中添加 PI3K 激活剂 740Y-P 和 PTEN 抑制剂 bpV (HOpic)进行激活。分别于实验第 0、2、6 天收取卵巢组织行包埋、切片或提取组织总蛋白。做 HE，观察始基卵泡、初级卵泡和次级卵泡形态，对各阶段卵泡进行计数，并统计分析占比情况。做 IHC，观察 PTEN-PI3K 下游卵泡休眠因子 FOXO3a 蛋白移出卵母细胞核情况，统计分析对照组和激活组移出卵母细胞核的卵泡占比。进行 WB，分析 PTEN-PI3K 信号通路中 p-PTEN/PTEN 蛋白和 p-Akt/Akt 蛋白表达变化情况。将高龄女性卵巢组织异体移植至 Balb/c-nu 品系的裸鼠背阔肌中，观察激活后的高龄女性卵巢组织生长状况和卵泡发育情况。
结果
高龄小鼠卵巢组织 IVA：1. 激活后第 2 天，激活组中始基卵泡占比比对照组低（P＜0.001）；激活组中初级卵泡占比比对照组高（P＜0.01）。激活后第 6 天，激活组中始基卵泡占比也比对照组低（P＜0.01）；激活组中初级卵泡占比也比对照组高（P＜0.05）。对于次级卵泡，第 2 天和第 6 天两组之间的占比都没有显著性差异（P＞0.05，P＞0.05），但激活组的占比都有比对照组高的趋势。2. 激活组卵泡休眠因子 FOXO3a 蛋白移出卵母细胞核卵泡数的占比比对照组多（P＜0.05）。

3. 激活组第 2 天和第 6 天的 p-Akt 蛋白表达水平都比对照组高（P＜0.05，P＜0.05）；激活组第 2 天和第 6 天的 p-PTEN 蛋白表达水平也都比对照组高（P＜0.05，P＜0.01）。
高龄女性卵巢组织 IVA：1. 激活后第 2 天，激活组中始基卵泡占比比对照组低（P＜0.001）；激活组中初级卵泡占比也比对照组高（P＜0.001）。激活后第 6 天，激活组中始基卵泡占比也比对照组低（P＜0.01）；激活组中初级卵泡占比也比对照组高（P＜0.05）。对于次级卵泡，第 2 天和第 6 天两组之间的占比也都没有显著性差异（P＞0.05，P＞0.05），但激活组的占比都有比对照组高的趋势，尤其是第 6 天升高的趋势更为明显。2. 激活组第 2 天和第 6 天的 p-Akt 蛋白表达升高水平和对照组比较都没有显著性差异（P＞0.05，P＞0.05），但激活组 p-Akt 蛋白的表达水平有升高趋势；激活组第 2 天和第 6 天的 p-PTEN 蛋白表达升高水平和对照组比较同样都没有显著性差异（P＞0.05，P＞0.05），激活组 p-PTEN 蛋白的表达水平也有升高趋势。没有显著性差异的原因可能是由于高龄女性卵巢储备减少，导致组织总蛋白中卵泡蛋白的表达量减少，所以引起激活组中 p-Akt 和 p-PTEN 蛋白表达水平升高的趋势不明显。3. 异体移植两周后，在对照组和激活组卵巢组织中均能观察到新血管的形成和形态完整的卵泡。两个月后，对照组卵巢组织出现明显萎缩，激活组卵巢组织重量明显大于对照组（P＜0.01），并且在激活组的卵巢组织中观察到窦卵泡的生长。
结论 1. 新鲜高龄小鼠卵巢组织和解冻高龄女性卵巢组织均可通过体外添加 PI3K 激活剂 740Y-P 和 PTEN 抑制剂 bpV (HOpic)激活始基卵泡。2. 高龄卵巢始基卵泡 IVA 可能是通过 PTEN-PI3K 信号通路实现的。

mircoRNA-222 影响法洛四联症发生发展的机制研究

李超 王红艳
复旦大学附属妇产科医院

目的 miRNA 的剂量效应可以影响胚层分化和胚胎期心脏发育，但是对于 miRNA 的剂量效应如何影响先天性心脏病的发生发展任然知之甚少。本研究旨在探究 mircoRNA-222 在一种最常见的复杂性先天性心脏病（法洛氏四联症，TOF）发生发展中的作用。
方法 通过数据筛选和实时荧光定量的方法确定了 miR-222 在 TOF 流产胎儿右心室中的高表达。构建了 b-MHC 驱动的胚胎心脏特异性表达 miR-222 的 KI 小鼠的体内模型和人胚胎干细胞稳定过表达 miR-222 并诱导分化成心肌细胞的体外模型。分别使用生物信息学、钙成像、组织学、分子和细胞学方法对我们体内和体外模型进行下游机制分析。
结果 我们发现 miR-222 在 TOF 胎儿的右心室中高表达。类似于人类 TOF 的表型在具有纯合 miR-222-KI 的胎鼠中重现。机制上，miR-222 同时靶向负调控 DICER1 和 AGO2，强烈抑制心脏关键 miRNA 的成熟，减少这些 miRNA 的剂量，并在体外和体内模型促进心肌细胞铁死亡。通过补充 DICER1 或 AGO2，可以逆转 miR-222 高表达诱导的心肌细胞肥大和铁死亡。值得注意的是，miR-222-KI 小鼠中 TOF 的发生率可通过依诺沙星或 ferrostatin-1 的治疗显着降低。
结论 我们的结果将 miR-222 确立为能够强烈抑制心脏 miRNA 成熟的关键控制因子并在我们成功构建的 TOF 小鼠模型中进一步证明了 miR-222 调节的 miRNA 剂量的重要性。

Zebrafish double knockout mutant line doc2am/mdoc2bm/m mutants show ASD-like behaviors

Yali Chi[1] Tao Feng[1] Xinping Yang[1,2,3]
1.Center for Genetics and developmental Systems Biology, Department of Obstetrics and Gynecology, Nanfang Hospital, Southern Medical University
2.Key Laboratory of Mental Health of the Ministry of Education, Southern Medical University
3.Department of Bioinformatics, School of Basic Medical Sciences, Southern Medical University

Copy number variation (CNV) at 16p11.2 results in multiple neurodevelopmental disorders including autism spectrum disorder (ASD), schizophrenia and epilepsy. The gene DOC2A is located in 16p11.2. It has an ortholog DOC2B. Using CRISPR-Cas9, we generated a frameshift

mutation in doc2a and a frameshift mutation in doc2b in zebrafish, respectively, and obtained double mutant by cross the single mutant. The double mutant doc2a^{m}/^{m}doc2b^{m}/^{m} exhibited dysfunction in the nervous system including deformity and mortality, attenuated locomotion activity, reduced susceptibility to pentylenetetrazol-induced seizure and impaired social interaction. We carried out brain transcriptome sequencing and found that the differentially expressed genes were enriched with ASD candidate genes and ASD-related signaling pathways such as synaptic signaling pathways. The differentially expressed transcription factors, npas4a and npas4b, are involved in multiple synaptic-signaling pathways. We are carrying out functional experiments to demonstrate the key role of these two transcription factors in this ASD model.

C1orf194 deficiency leads to incomplete early embryonic lethality and dominant intermediate Charcot-Marie-Tooth disease in a knockout mouse model

Fu Xiong[1] Cheng Huang[1] Zongrui Shen[1] Jin Huang[1] Shunchang Sun[2] Di Ma[1] Meiyi Li[1] Xiangmin Xu[1]
1.Southern Medical University
2.Shanghai Jiao Tong University School of Medicine

Objective and methods Charcot-Marie-Tooth (CMT) disease is the most common inherited peripheral neuropathy, and shows clinical and genetic heterogeneity. Mutations in C1orf194 encoding a Ca^{2+} regulator in neurons and Schwann cells have been reported previously by us to cause CMT disease. In here, we further investigated the function and pathogenic mechanism of C1or194 by generating C1orf194 knockout (KO) mice.
Results Homozygous mutants of C1orf194 mice exhibited incomplete embryonic lethality, characterized by differentiation abnormalities and stillbirth on embryonic days 7.5 to 15.5. Heterozygous and surviving homozygous C1orf194 KO mice developed motor and sensory defects at the age of 4 months. Electrophysiologic recordings showed decreased compound muscle action potential and motor nerve conduction velocity in the sciatic nerve of C1orf194-deficient mice as a pathologic feature of dominant intermediate-type CMT. Transmission electron microscopy analysis revealed demyelination and axonal atrophy in the sciatic nerve as well as swelling and loss of mitochondrial matrix and other abnormalities in axons and Schwann cells. A histopathologic examination showed a loss of motor neurons in the anterior horn of the spinal cord and muscle atrophy. Shorter internodal length between nodes of Ranvier and Schmidt-Lanterman incisures (SLIs) were detected in the sciatic nerve of affected animals.
Conclusions These results indicate that C1orf194 KO mice can serve as an animal model of CMT with a severe dominant intermediate CMT phenotype that can be used investigate the molecular mechanisms of the disease and evaluate the efficacy of therapeutic strategies.

PRRT2 and MAPK3 were key genes of 16p11.2 microdeletion in children with neurodevelopmental disorders

Fang Liu[1,2] Liang Chen[1,2] Li Zhengchang[1] Shangguan Shaofang[1] Zou Liping[4] Wen Suiwen[5] Yuan Haiming[6,7] Liu Yan[8] Shen Yiping[9,10,11] Chen Xiaoli[1,2,3]
1.Department of Medical Genetics, Capital Institute of Pediatrics
2.Graduate School of Peking Union Medical College
3.Beijing Municipal Key Laboratory of Child Development and Nutriomics, Capital Institute of Pediatrics
4.Department of Pediatrics, Chinese PLA General Hospital
5.Department of Obstetrics, Qingyuan People's Hospital (6th Hospital, Guangzhou Medical University)
6.Dongguan Maternal and Child Health Care Hospital
7.Dongguan Institute of Reproductive and Genetic Research
8.Department of Obstetrics, Beijing Obstetrics and Gynecology Hospital, Capital Medical University
9.Department of Medical Genetics, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine
10.Division of Genetics and Genomics, Boston Children's Hospital
11.Department of Neurology, Harvard Medical School

Background As a recurrent CNV, 16p11.2 microdeletion is recognized as important pathogenic risk for children's neurodevelopmental disorders. Meanwhile, the neurodevelopmental phenotypes of 16p11.2 microdeletion carriers are highly heterogeneous, and the pathogenesis of the 16p11.2 microdeletion is not yet clear. Using peripheral blood obtained from 16p11.2 microdeletion carriers of two pedigrees and controls, we generated induced pluripotent stem cells (iPSCs) and differentiated them into neurons to identify causal cellular mechanisms underlying neurobiological phenotypes and find the key genes of 16p11.2 microdeletion. At last, deep sequencing of 16p11.2 region was performed of four 16p11.2 microdeletion carriers to explore the remaining haplotypes regulating the expression of the key genes.
Methods 1.The peripheral blood obtained from 16p11.2 microdeletion carriers of two pedigrees and controls were reprogrammed using Sendai virus to generate induced pluripotent stem cells (iPSCs) and differentiated them into neurons by transduction Neurogenin 2 (NGN2) factors. The pluripotency of iPSCs was identified using AP staining, immunofluorescent staining, STR site analysis, karyotype analysis, Array CGH assay and teratoma formation. And the neurons were identified by immunofluorescent staining and recording the electrophysiological activity with microelectrode array system (MEA).
2.The transcriptome of neural precursor cells and neuron cells were detected by RNAseq. The cell body sizes were measured by living cell staining and immunofluorescence staining, and the electrophysiological activity was recorded by microelectrode array system (MEA).
3.We investigated the expression of multiple proteins using western blotting and increased the expression of PRRT2 and MAPK3 by lentiviral infection. After lentiviral infection, the expression of multiple proteins and the electrophysiological activity were detected again.
4.Deep sequencing of 16p11.2 region was performed of four 16p11.2 microdeletion carriers to explore the remaining haplotype regulating the expression of MAPK3.
Results 1.We have successfully established twenty induced pluripotent stem cells (iPSCs) of 16p11.2 microdeletion carriers and normal controls and differentiated them into neurons.
2.The biophysical basis of 16p11.2 microdeletion contributing to neurodevelopmental disorders was clarified. Transcriptome level data suggested that 16p11.2 microdeletion may affect the development of neurons and synaptic function. Functional experiments confirmed the 16p11.2 microdeletion could enhance the electrophysiological activity but did not affect the size of cell body.
3.PRRT2 and MAPK3 were key genes of 16p11.2 microdeletion. The transcriptome data showed that most (95.4%) of the genes in the 16p11.2 region were reduced in the carriers compared with the normal controls. In NPC, PRRT2 was the most decreased gene in the 16p11.2 region. Meanwhile, MAPK3 was involved in pathway enriched by differentially expressed genes. Further, the expression of PRRT2 and its related proteins in 16p11.2 microdeletion carriers was decreased, and the activity of ERK signaling pathway was enhanced. Overexpression of PRRT2 and MAPK3 could reverse the expression of the above proteins and the electrophysiological activity of 16p11.2 microdeletion carriers.

4.The residual haplotypes of 16p11.2 microdeletion carriers affected the expression of MAPK3 gene at transcriptome and protein level. At the same time, it affected the rescue effect of electrophysiological activity in 16p11.2 microdeletion carriers when overexpression of MAPK3 gene.
Conclusions
16p11.2 microdeletion affected the transcription of genes associated with neurodevelopmental and enhanced the electrophysiological activity of neurons. PRRT2 and MAPK3 were key genes of 16p11.2 microdeletion and the remaining haplotypes that might regulate the expression of MAPK3, which will promote the study of the potential mechanism of phenotypic heterogeneity of 16p11.2 microdeletion.

通过纠正 mRNA 异常剪接缺陷治疗 β 地贫

鲁丹[1,2] 龚秀丽[1,2] 方彧聃[1] 郭歆冰[1] 陈雁雯[1] 杨帆[1,2] 赵贵军[1,2] 马晴雯[1,2] 曾溢滔[1,2] 曾凡一[1,2,3]
1.上海交通大学附属儿童医院，上海医学遗传研究所
2.上海市胚胎与生殖工程重点实验室，国家卫健委医学胚胎分子生物学重点实验室
3.上海交通大学基础医学院组织胚胎学与遗传发育学系

目的 β 地中海贫血（地贫）是一种遗传性溶血性血红蛋白病，至今尚无有效的根治方法。β^{654} 地贫是中国人特有和常见的 β 地贫，其致病分子机制是 β 珠蛋白基因第二内含子第 654 位核苷酸的突变，导致 mRNA 剪切异常，β 珠蛋白合成减少。本研究旨在探索通过 CRISPR/Cas9 基因编辑方法纠正 β 珠蛋白 mRNA 异常剪切的可行性，为 β^{654} 地贫的基因治疗提供新的策略。
方法 将 sgRNA 和 Cas9 mRNA 显微注射到 β^{654} 小鼠受精卵中制备原代基因编辑的 β^{654} 地贫小鼠（简称编辑小鼠）。分析编辑小鼠中 β 珠蛋白 mRNA 异常剪切的纠正情况和 β 珠蛋白的表达情况，阐明编辑小鼠遗传学、血液学、病理学和表型的变化，并分析编辑小鼠后代治疗效果的遗传稳定性。
结果 原代 β^{654} 小鼠中，83.3%的 β^{654} 小鼠被成功基因编辑，其中 70%的编辑小鼠能够产生正确剪接的 mRNA，并恢复了 β 珠蛋白的表达。与 β^{654} 地贫小鼠相比，编辑小鼠的血液学参数得到显著改善，红细胞形态恢复正常，脾脏体积和重量明显减少，肝脏和脾脏髓外造血情况得到显著改善。同时编辑小鼠能够将基因编辑的治疗效果稳定遗传给后代，杂合子和纯合子 β^{654} 地贫小鼠的存活率显著提高。
结论 通过本研究的 CRISPR/Cas9 基因编辑方法有效纠正了 β^{654} 地贫小鼠模型中 β 珠蛋白 mRNA 的剪切异常，在个体水平上验证了基因编辑策略的有效性，为该策略在 β^{654} 地贫基因治疗的临床应用奠定良好的实验基础。

cerkl 突变引起斑马鱼视网膜变性及其机制研究

刘木根 吕月霞 刘希良 李井振 李培 刘飞 于珊珊 唐朝晖 刘木根
华中科技大学

目的 视网膜色素变性（Retinitis pigmentosa）是一类重要的遗传性眼科疾病，其致病基因众多且发病原因复杂，迄今临床上尚没有有效的治疗手段，阐明不同 RP 基因功能，是实行视网膜变性精准预防和治疗的关键。CERKL 是一个重要的 RP 致病基因，其突变引起常染色体隐性遗传的视网膜色素变性。CERKL 在视网膜中的功能尚不清楚，其突变引起视网膜感光细胞死亡的机制尚有待探索。本文的研究目的是率先建立 CERKL 突变引起 RP 的动物模型，通过动物模型研究该基因在视网膜中的生理功能，阐明其突变引起 RP 的病理机制，并在此基础上发现该基因突变引起视网膜病变的预防和治疗方法。
方法 应用基因编辑手段构建 cerkl 敲除的斑马鱼模型，HE 染色观察早中晚各期视网膜组织切片，免疫荧光分析视网膜视杆和视锥细胞外节的病变情况和发病的病理特征，应用电镜观察分析外节的结构和脂类堆积情况，应用 RNA-seq 分析其导致病变的相关信号通路，应用代谢组学分析 cerkl 突变引起视网膜代谢产物的改变，探讨该基因突变引起 RP 的代谢途径。

结果 应用基因编辑技术成功获得了 cerkl 敲除的斑马鱼模型，发现突变斑马鱼视杆细胞较视锥细胞首先受累。和野生型斑马鱼相比，突变体视网膜存在大量的外节片段堆积，提示 cerkl 突变破坏了视网膜色素上皮细胞的吞噬能力。发现 cerkl 突变体视网膜内呈现大量的脂滴积累，表明该基因在脂代谢过程中可能发挥重要的生理功能。RNA-seq 和代谢组学分析以及进一步的细胞学研究，发现突变体视网膜组织代谢相关信号通路发生异常。

结论 建立了世界上第一个 cerkl 突变的视网膜色素变性的动物模型。发现 cerkl 敲除导致斑马鱼呈现类似人类的视杆视锥萎缩的表型，可用于进一步的机制分析和药物筛选研究。发现 cerkl 在 RPE 自噬和吞噬过程中发挥重要生理功能，发现该基因在视网膜中参与脂类代谢，其突变导致斑马鱼视网膜中脂质累积。该研究发现 cerkl 新的生理功能和视网膜色素变性发病新的调控机制，并为该基因突变引起的视网膜色素变性的预防和治疗指明了方向。

Population-based Carrier Screening and Prenatal Diagnosis of Fragile X Syndrome in East Asian Populations

Qiwei Guo[1] Yih-Yuan Chang[2] Chien-Hao Huang[2] Yu-Shan Hsiao[2] Yu-Chiao Hsiao[3] I-Fan Chiu[3] Yulin Zhou[1] Haixia Zhang[1] Tsang-Ming Ko[2]

1.Women and Children' s Hospital, School of Medicine, Xiamen University, Xiamen, Fujian.
2.Ko' s Obstetrics and Gynecology, Taipei, Taiwan.
3.Biofast Biotechnology Co., Ltd., Xiamen, Fujian.

Fragile X syndrome (FXS) is the leading monogenic cause of autism and autism spectrum disorders and the second most common cause of inherited intellectual disability. The genetic basis of FXS is the translational silencing of FMR1, an X-linked dominant gene. A segment of CGG trinucleotide repeat is located in the untranslated region of the first exon of FMR1 and the number of CGG repeats is polymorphic. FMR1 is categorized into four allelic forms based on the number of CGG repeats: normal alleles have a range of ~5 to ~44 repeats and are meiotic or mitotic stable; intermediate alleles range from ~45 to ~54 repeats and their repeat number can slightly increase or decrease in intergenerational transmission; premutation (PM) alleles range from ~55 to ~200 repeats and can expand to full mutation (FM) during maternal transmission; FM alleles have more than 200 repeats and account for most cases of FXS. Therefore, asymptomatic women with PM or FM alleles are considered to be FXS carriers since their children are at risk of FXS. Identification of FXS carriers with the subsequent prenatal diagnosis, and knowledge of FXS-associated genetic profiles are essential for FXS intervention in specific populations.

Here, we report the results of carrier screening of 39,458 East Asian adult women and prenatal diagnosis from 87 FXS carriers. The prevalence of FXS carriers and FM fetuses was estimated to be 1/581 and 1/3124 in East Asian populations, respectively. We confirmed the validity of the current threshold of CGG repeats for FMR1 categorization; the integral risks of FM expansion were approximately 6.0%, 43.8%, and 100% for PM alleles with 55-74, 75-89, and ≥90 CGG repeats, respectively. The protective effect of AGG interruption in East Asian populations was validated, which is important in protecting PM alleles with 75-89 CGG repeats from FM expansion.

Moreover, we performed a decision-analytic model to evaluate the cost-effectiveness of two carriers screening strategies. According to this model, population-based screening and family history-based screening strategies to identify a FM fetus would cost approximately 305,707.69 USD and 6125 USD respectively. However, the family history-based screening strategy would miss approximately 69.2% (9/13) of FM fetuses, suggesting that 1.25 equivalent FXS patients would be born for every FM fetus identified. Therefore, a potential cost of 625,000 USD would be required due to the life-cycle burden of FXS patients. In this context, population-based screening would be more cost-saving than family history-based screening for preventing the birth of FXS patients. In view of the 100% effectiveness and advanced cost-effectiveness, population-based screening represented a dominant strategy compared to family history-based screening.

In conclusion, our study provides an insight into the largest carrier screening and prenatal diagnosis for FXS in East Asian populations to date. The FXS-associated genetic profiles of East Asian populations are delineated and population-based carrier screening is shown to be promising for FXS intervention.

Functional analysis of a novel single-base deletion RUNX2 mutation in patient with cleidocranial dysplasia and clinical orthodontic treatment

Yuhua Pan[1,2] Xiong Fu[1] Buling Wu[2]
1.Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University
2.Department of Stomatology, Southern Medical University,

Objectives Cleidocranial dysplasia (CCD) is a rare autosomal dominant hereditary disorder characterized by skeletal malformations and dental abnormalities. This disease is mainly caused by heterozygous mutations in runt-related transcription factor 2 (RUNX2), which is essential for osteoblast differentiation and skeletal development. The purpose of this study was to explore the functional role of the novel mutation in CCD pathogenesis and give opinion on the clinical treatment of CCD patient.
Materials and Methods Genomic DNA extracted from peripheral venous blood was taken from the proband and three unaffected family members. Analysis of their respective RUNX2 gene sequences was performed by PCR amplification and Sanger sequencing. The function of the mutant RUNX2 was studied by bioinformatics, real-time PCR, western blotting, and subcellular localization analysis. Clinically, we made a highly organized treatment plan, such as extraction of the supernumerary teeth, partial resection of alveolar bone, distraction of impacted teeth, and orthodontic surgery.
Results Sanger sequencing identified a novel, single base deletion (c.132delG or c.133delG) in RUNX2 gene in a Chinese patient with CCD. In vitro functional studies showed altered protein localization and increased mRNA and protein expression level of mutant RUNX2. And the Clinical orthodontic-surgical therapy obtained the good clinical treatment result.
Conclusions We identified a sporadic CCD patient carrying a novel deletion/frameshift mutation of RUNX2 and performed screening and functional analyses to determine the cause of the CCD phenotype.
Clinical Relevance An individualized treatment protocol was offered, based on the needs and demand of the patient, the age at diagnosis, and social and economic circumstances. This study helped the family members to understand the disease progression and provided new insights into the pathogenesis of CCD.

Gene4HL：一站式耳聋基因变异知识库

袁永一[1] 黄莎莎[1] 赵贵虎[2] 李津臣[2] 戴朴[1]
1.解放军总医院耳鼻咽喉头颈外科医学部
2.中南大学湘雅医院

耳聋是常见的出生缺陷之一，是最常见的感官出生缺陷，其中60%由遗传因素导致。新一代测序助力了遗传性耳聋患者致病基因及致病变异的鉴定。目前公开的数据库中，针对遗传性耳聋的主要有两个：Hereditary Hearing Loss Homepage 和 Deafness Variation Database（DVD）。前者主要提供耳聋相关座位、已鉴定的致病基因及相关文献，未包含变异信息。后者聚焦基于指南及遗传性耳聋专家再评定的变异致病性分级，DVD 目前应用较广，但未能呈现每个变异的表型信息。此外，ClinVar 数据库合并了表型和变异对应的信息，但该数据库由研究者及研究机构自愿提交数据，尚存在某些变异没被上传及变异致病性和表型尚存在争议等问题。为此，我们搭建了一个一站式耳聋基因及变异知识库——Gene4HL (http://www.genemed.tech/gene4hl/)，兼具分类、检索、浏览及遗传数据分析功能。Gene4HL 整合了来自 Pubmed 上 1608 篇文献的 326 个耳聋相关基因的临床及遗传数据及 62 个公开的遗传信息数据库的信息。能支持使用者完成测序数据的注释、自定义条件下的分析和致病基因及变异的筛选。同时 Gene4HL 还呈现了耳聋相关基因的功能的变异的基因型表型相关性。

云南省德宏州和西双版纳州傣族人群 G6PD 缺乏症流行病学调查研究

张杰[1] 贺铭[2] 谢美娟[1] 张小来[1] 滕聪聪[1] 杨炬华[1] 龙岚[1] 倪俊学[1]
马丽[3] 玉尖香[3] 徐咏梅[4] 唐树萍[4] 朱宝生[1]
1.云南省第一人民医院 2.昆明医科大学
3.西双版纳州妇幼保健院
4.德宏州妇幼保健院

背景 葡萄糖-6-磷酸脱氢酶（Glucose-6-phosphate dehydrogenase; G6PD）缺乏症是一种最常见的伴 X 连锁不完全显性的遗传性疾病，云南省傣族人群是 G6PD 缺乏症高发群体，但是其流行病学特征的研究还较为缺乏。
目的 对云南省德宏州及西双版纳州傣族人群 G6PD 缺乏症流行病学进行调查及临床特征研究；对德宏州及西双版纳州傣族人群进行 LD block 及单体型构建，为阐明 G6PD 基因突变类型起源提供依据。
方法 1、二代基因测序技术对云南省德宏州及西双版纳州傣族人群 1596 份样本进行 G6PD 基因常见 14 个突变位点的检测；用一代基因测序技术对随机的 200 份样品进行验证。2、用荧光斑点法对德宏州及西双版纳州傣族人群 1596 份样本定量检测 G6PD 酶活性；采用 ROC 曲线对 G6PD 酶活性进行截断值分析。3、使用 SPSS 20.0 分别对 G6PD 基因突变样本进行基因型与临床表型的统计分析。4、用 Haploview 4.2 软件，对德宏州及西双版纳州傣族人群进行 SNP 位点连锁不平分析和 LD block 的构建。
结果 1、利用二代基因测序技术对德宏州及西双版纳州傣族人群进行 G6PD 缺乏症进行基因筛查，两地区 G6PD 基因突变类型携带率为 48.12%（男性 40.89%、女性 53.73%）。2、采用荧光斑点法对德宏州及西双版纳州傣族人群进行 G6PD 酶活性检测，结果提示阳性率为 14.53%。G6PD 酶活性截断值 2.25 U/gHb 时，特异性为 97%，敏感性为 27%。3、德宏州 4 种 G6PD 基因突变类型男性 G6PD 酶活性下降均较女性明显。西双版纳州两种 G6PD 基因突变类型男性酶活性下降较女性明显。4、14 个 SNP 位点进行 LD block 及单倍体型构建，提示 5 个突变位点具有强连锁性。
结论 1、云南省德宏州及西双版纳州傣族人群 G6PD 基因携带率为 48.12%，是目前国内报道的最高基因携带率，在世界范围内也属于较高值。2、傣族人群中男性阳性率明显高于女性；荧光斑点法对 G6PD 酶活性筛查敏感性较低。 3、不同基因突变类型的酶活性改变情况也不同；相同基因突变类型男性酶活性下降较女性明显；女性酶活性差异性较大。4、傣族人群五个 SNP 位点具有强连锁性。

46 个骨骼异常先证者及夫妻家系的遗传学研究

邬玲仟[1,2] 张丽[1,2]
1.中南大学生命科学学院医学遗传学研究中心
2.医学遗传学湖南省重点实验室

背景 骨骼发育不良（SDs）是一大类强临床异质性及遗传异质性的疾病，总体发生率高，目前国内鲜有针对骨骼系统的分子诊断研究。
目的 针对具有 SDs 表型的先证者或有 SDs 生育史的夫妻进行分子遗传学诊断；对部分可疑致病变异进行研究，明确变异致病性。
方法 收集具有 SDs 表型的先证者或妊娠史家系样本及临床资料；采集患者及家系成员外周血进行 Sanger 测序及全外显子测序等分子诊断；抽提患者外周血 RNA 行 RT-qPCR 实验，对剪接位点变异的转录水平进行研究。
结果 共收集到 46 个具有先证者或不良生育史的夫妻家系。1、34 个家系检测到致病/可能致病突变，诊断率为 73.91%；2、鉴定出 24 个基因的 42 个可疑变异，包括 27 个致病变异，13 个可能致病变异以及 2 个意义不明确变异，其中 26 个（61.90%,26/42）变异为首次报道的新突变。3、检测到

CEP152 基因的一个新的非经典剪接位点突变 c.1414-14A>G，RT-PCR 及 qPCR 实验结果显示突变会影响正常剪接，产生一种异常剪接产物，与正常对照相比，变异使基因的相对表达量显著降低。**结论** 研究中的高诊断率提示针对 SD 患者行分子诊断的必要性，丰富了遗传性骨病致病基因的突变谱，证实了 CEP152 基因的非经典剪接位点突变 c.1414-14A>G 能导致转录水平的异常剪接。

甲基丙二酸血症患儿表型和基因型分析

王朝[1,2,3] 刘洋[1] 张新杰[1,2,3] 王洪[1] 崔亚琼[1,2,3] 支秀芳[1,2,3]
郑洁[1,2,3] 王宁[1,2,3] 舒剑波[1,2,3] 李东[1] 蔡春泉[1,2,3]
1.天津市儿童医院（天津大学儿童医院） 2.天津市儿科研究所
3.天津市儿童出生缺陷防治重点实验室

目的 甲基丙二酸血症（Methylmalonic Acidemia, MMA）是一类由甲基丙二酰辅酶-A 缺陷或钴胺素代谢障碍引起的罕见的遗传性代谢病，主要以常染色体隐性方式遗传，根据是否合并同型半胱氨酸血症和致病基因可分为多种不同亚型。MMA 临床表型各异，轻重不一，早诊断早治疗可以明显改善预后。本研究对就诊于天津市儿童医院的 MMA 患儿的表型和基因型进行分析总结。
方法 搜集天津市儿童医院 2012 年至 2020 年期间确诊的 MMA 患儿。所有患儿均进行了全面的体格和实验室检查。以质谱法对患儿血液和尿液中的代谢产物进行筛查。利用 Sanger 测序法和高通量测序方法进行基因检测。对所有患儿的临床表型进行归纳总结。排除标准：维生素 B_{12} 缺乏所致 MMA。
结果 天津市儿童医院高危遗传代谢病患儿中 MMA 的检出率为 0.20%。84 例临床确诊的 MMA 患儿中男性 52 例，女性 32 例，年龄在 52 小时至 16 岁之间，年龄中位数为 8.5 个月。所有获得临床表型资料的 75 患儿中最常见的 3 种临床表型为呼吸性/代谢性酸中毒、精神运动发育落后和贫血，分别见于 36.00%（27/75）、33.33%（25/75）和 30.67%（23/75）的患儿中。单纯型 MMA 患儿血尿筛主要指标均高于合并型患儿（P<0.05），单纯型 MMA 患儿表型多于合并型患儿的有呼吸性/代谢性酸中毒、电解质紊乱、心脏疾病、高氨血症、血小板减少、血糖异常和高胆红素血症（P<0.05）。共 53 例患儿有明确基因检测结果，其中 cblC 型 44 例，mut 型 8 例，cblD 型 1 例。cblC 患儿 MMACHC 基因最常见突变为 c.609G>A、c.658-660delAAG 和 c.80A>G，出现频率分别为 34.09%（30/88）、13.64%（12/88）和 13.64%（12/88）。分别在 MMACHC 基因和 MMADHC 基因检测到一个新突变。
结论 本研究中 MMA 患儿最常见的临床表型为呼吸性/代谢性酸中毒、精神运动发育落后和贫血等，单纯型 MMA 患儿表型多重于合并型患儿。cblC 患儿的 MMACHC 突变谱与中国 cblC 患者整体突变谱基本一致。此研究拓展了中国人群 MMA 患儿表型和基因型研究，可为此病临床诊疗提供参考。

第三代测序技术在地中海贫血基因检测中的应用研究

黄婷 邹永毅 沈吟琴 阳彦 黄淑晖 杨必成 刘艳秋
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

目的 通过与传统地贫基因检测方法（Gap-PCR+PCR-RDB）以及与第二代测序技术（NGS）的对比，分析第三代测序技术在地贫基因检测中的临床应用价值。
方法 通过基于 PacBio 测序平台的第三代测序技术对 $HBA_{1/2}$ 和 HBB 基因同时进行检测，实现地贫等位基因的综合分析。以血液学筛查指标任意一项阳性为入组标准，随机选取我院 2020 年 4 月至 2021 年 4 月通过 Gap-PCR+PCR-RDB 进行常见 23 型（α+β）地中海贫血基因检测的 110 例样本，以及通过 PCR-NGS 的方法进行地中海贫血基因检测（α+β）508 型的 83 例样本，进行三代测序检测地贫基因。
结果 109 例行传统地贫基因检测的样本，在检测范围内（α-地贫的 3 种缺失型，3 种突变型以及 β-地贫的 17 种突变型）共检出 68 例样本变异，检出率 62.4%（68/109），对基因型与表型明显不符的样本进行罕见型分析，额外检出 8 例变异，阳性检出率提升至 69.7%（76/109）。利用第三代测

序技术检测上述标本，除 1 例样本降解未检测成功，其余 108 例样本中，所有阳性变异均准确检出，且额外检出 α 基因结构变异 2 例（ααα$^{anti3.7}$/αα 型和 ααα$^{anti4.2}$/αα 型各 1 例），以及 6 例 $HBA_{1/2}$ 和 HBB 单核苷酸变异，阳性检出率提高了 10.5%（8/76）；83 例行地中海贫血基因检测（α+β）508 型的样本中，阳性检出率为 60.2%（50/83），利用第三代测序技术检测上述标本，所有阳性变异均准确检出，且额外检出了 α 基因结构变异（ααα$^{anti3.7}$/αα 型）1 例以及 $HBA_{1/2}$ 和 HBB 单核苷酸变异 3 例，阳性检出率提高了 8%（4/50）。

结论 第三代测序技术在地贫基因检测的应用中，能准确检出通过传统方法以及 PCR-NGS 技术检出的所有变异，在检测范围内的准确性为 100%。通过与两种方法的比对，第三代测序技术在地贫基因的检测中具有更高的阳性检出率，具有检测范围广、准确性高、漏检率低等优势。

A novel LGI1 mutation causes autosomal dominant lateral temporal lobe epilepsy confirmed by a precise knock-in mouse model

Ping Hu Wu Dan Shi YunStone Zhengfeng Xu
Nanjing Maternity and Child Health care Hospital

Aims This study was to explore the pathogenic mechanism of the LGI1D51G mutation identified in a family of ADLTE using a precise knock-in mouse model.

Methods and Results A novel LGI1 mutation, c.152A>G; p. Asp51Gly, was identified by whole exome sequencing (WES) in a Chinese ADLTE family. The pathogenic mechanism of the mutation was explored by generation of Lgi1D51G knock-in mice which quite precisely phenocopied the epileptic symptoms in patients. Lgi1D51G/D51G mice showed spontaneous recurrent generalized seizures and premature death. Lgi1D51G/+ mice had partial epilepsy with half of them displaying epileptiform discharges in electroencephalogram (EEG). The Lgi1D51G/+mice also showed enhanced sensitivities to convulsant agent pentylenetetrazole (PTZ). Mechanistically, the D51G mutation disrupts Lgi1 secretion and drastically reduces Lgi1 level in mouse brain. In addition, the antiepileptic drugs, carbamazepine, oxcarbazepine and sodium valproate, could elongate the survival time of Lgi1D51G/D51G mice and oxcarbazepine appeared to be more effective.

Conclusions We identified a novel epilepsy-causing mutation of LGI1 in human. The Lgi1D51G/+epileptic mouse model precisely phenocopying patients would be a useful tool for future study on the pathogenesis and potential therapy for epilepsy.

The Mitochondrial DNA copy number acts as a biomarker in the pathological state

Tong Zhang[1,2] Fengxiang Wei[1,2] Guoqiang Zhao[1,2] Yanan Liu[1,2]
1.Longgang District Maternity&Child Healthcare Hospital of Shenzhen City
2.Jiamusi University

Mitochondria are vital organelles in cells. Mitochondrial DNA is the only genetic material that exists outside the nucleus, and there are hundreds to thousands of copies in each cell in a tissue-specific way. When mitochondrial DNA is subjected to oxidative damage and carcinogen attack, it causes overproduction of reactive oxygen species, damage to some large molecules, insufficient energy supply and production of essential molecules such as heme and nucleotides, and abnormal mitochondrial signaling function. It can easily lead to mutations in mitochondrial DNA, which can lead to abnormalities in energy metabolism and oxidative stress. This is also one of the important reasons leading to mitochondrial dysfunction. At present, the change of mitochondrial DNA copy number is very important in various pathological conditions in the body such as diabetes, cardiovascular disease, mental disease, cancer, and aging, and reflects the biomarkers of various pathological conditions in the human body. Therefore, the regulation and detection of mitochondrial DNA copy number is an important aspect of mitochondrial genetics and biogenesis. And it is helpful

for targeted disease prevention, early diagnosis and individualized treatment. It is of great significance for applications in clinical medicine, genetics, and life sciences. Nowadays, digital PCR technology can be used to identify diseases in the early stage of disease progression. Continue to track the existence, expansion and disappearance of pathogenic microorganisms and genetic variations in cancer, infectious diseases, and other human diseases. Nucleic acid detection with high resolution and low target level has a significant impact in the field of diagnosis, providing great advantages for diagnosis and preventive medicine. In short, changes in plasma mitochondrial DNA content have been associated with a variety of disease types, suggesting that the mitochondrial genome may be a key contributor to the occurrence of some diseases. It is necessary to further understand the relationship between the content of mitochondrial DNA in plasma and the clinicopathological characteristics of the disease and targeted treatment. Using a non-invasive and dynamic method to assess disease is a very promising method for cancer diagnosis and prognosis.

SMC3 Variants Contribute to Congenital Heart Disease by Targeting ETS2

Bowen Zhang[1] Jing Ma[1,3] Duan Ma[1,2]
1.Fudan University
2.Children's Hospital of Fudan University
3.ENT institute, Eye & ENT Hospital, Fudan University

Background and Objects Congenital heart disease (CHD) is the most common birth defect with high heritability. Although some susceptibility genes have been identified, they are still not enough to explain the genetic basis of all the CHD cases.
Methods and Results A total of 1146 unrelated CHD patients were enrolled in our study. Whole exome sequencing in 50 CHD patients was performed to identify the novel candidate gene, Structural maintenance of chromosomes 3 (SMC3), which was then validated by Sanger sequencing. SMC3 variants were investigated in another 1096 CHD patients by multiplex PCR-targeting sequencing. The roles of SMC3 in heart development were examined in conditional knockout (CKO) mouse models. The cell phenotypes of SMC3 deficiency and variants were tested in cardiomyocytes, and the molecular mechanisms were preliminarily explored by RNA-seq and 3C-HTGTS.
A total of 12 coding and 8 non-coding SMC3 variants were identified in 32 (2.80%) of CHD cases sequenced. Smc3 deficiency resulted in a series of heart defects including right ventricular hypoplasis, persistent truncus arteriosus, aortic riding and ventricular septal defect in Smc3-CKO mouse models. Cell cycle arrest and increased cells with multipolar spindles that inhibited proliferation were observed in cardiomyocytes with variants or knockdown of SMC3. The differentially expressed genes (DGDs) were enriched in the pathway related to heart development when SMC3 was deficient, in which myocardial development and coronary artery formation related gene ETS2 was downregulated. SMC3 deficiency reduced the interaction between the ETS2 promoter and super-enhancer(SE). Ets2 deficiency resulted in left ventricle hypoplasia and abnormal conus artery in Ets2-SE-CKO mouse models.
Conclusions SMC3 was identified as a novel susceptibility gene of CHD. SMC3 participated in the cardiac development by affecting the interaction between the ETS2 promoter and SE.

浙江省新生儿异戊酸血症筛查及临床分析

黄新文
浙江大学医学院附属儿童医院

目的 了解浙江省新生儿异戊酸血症(IVA)的患病率、临床特征及基因突变特点。
方法 采用串联质谱技术对 2009 年 1 月至 2019 年 12 月浙江省新生儿疾病筛查中心的 3510004 名新生儿进行遗传代谢病筛查，结合尿有机酸分析及 IVD 基因检测进行 IVA 诊断。IVA 确诊患儿进行饮食和生活管理，补充左卡尼汀和甘氨酸治疗，长期随访观察并评估患儿的生长和智能发育情况。

结果 共确诊 IVA 患儿 15 例，3 例为急性新生儿型，其余无临床症状，患病率为 1/234000。 所有患儿的血异戊酰基肉碱浓度均不同程度增加。12 例患儿进行尿有机酸分析，其中 11 例异戊酰甘氨酸升高，4 例伴 3-羟基异戊酸升高。11 例患儿进行基因检测，9 例为 IVD 基因复合杂合突变，1 例为 IVD 基因纯合突变，1 例只检测出一个 IVD 基因位点。 发现 IVD 基因突变 19 种(错义突变 14 种、内含子突变 3 种、移码突变 1 种、同义突变 1 种)，其中 11 种突变未见报道。15 例患儿中 1 例死亡，2 例在当地随访，其余暂未发现明显临床症状(随访时间 2~79 个月)，其中 3 例生长发育落后，其他患儿体格和智力发育均正常。
结论 IVA 临床表现无特异性，基因谱分散。使用串联质谱开展 IVA 新生儿筛查，实现早期诊断和治疗能纠正代谢缺陷及其引发的病理生理改变。

Genetic causes in neonates with congenital heart disease: a retrospective study from the China neonatal genomes project

Feifan Xiao Huijun Wang Yanyan Qian Bingbing Wu Xinran Dong Yulan Lu Guoqiang Cheng Laishuan Wang Kai Yan Xiaojing Ma Fang Liu Yun Cao Guoying Huang Wenhao Zhou
Children's Hospital of Fudan University

Backgrounds Congenital heart disease (CHD) is the most common birth defect. The genetic causes underlying CHD were involved in both monogenic and complex genetic mechanisms. The overall distribution of genetic causes in CHD patients from the neonate intensive care unit (NICU) needs to be studied.
Methods Individuals with CHD were extracted from the China neonatal genomes project (2016-2021). The clinical exome sequencing results and medical records were retrospectively evaluated to estimate the frequency of genetic diagnoses and patient outcomes.
Results ASD and VSD account for a large portion of the subtype of CHD (ASD: 58.8%, VSD: 11.7%, and ASD plus VSD: 8.6%, respectively). Co-occurring extracardiac anomalies (ECAs) were observed in 22% of patients and functional abnormalities were observed in 90.8%. In 1795 included CHD patients, 385 were genetically diagnosed, and 269 genetic diagnoses can explain the CHD phenotypes. The top five diseases with pathogenic CNVs (trisomy 21, 22q11 microdeletion/microduplication syndrome, trisomy 18, Williams syndrome and PWS) accounted for 57% (98/172) of diagnosed CNV patients. Cases with the top five genes variants accounted for more than half of the diagnosed monogenic disease cases (53.6%, 52/97). We found that CHD patients with ECAs had the highest genetic diagnostic rate compared with complex CHD cases and cases with isolated CHD and extracardiac functional abnormalities (22% vs. 15.8% or 11.6%).
Conclusions Our study may help characterize the genotypic and phenotypic spectrum for CHD patients in NICU and may benefit future work related to improving screening and genetic counseling in the genetics of CHDs in critically ill infants.

超级增强子介导肿瘤炎性微环境维持脊索瘤细胞干性表型的作用和机制

冀晨辰 韩骅
空军军医大学

目的 超级增强子（SEs）是特异性调节基因表达、参与细胞鉴定和人类疾病的一段基因组 DNA 区域。SEs 可以强力驱动细胞相关基因的表达；且其可通过表观遗传学、染色质三维结构和调控相分离复合物等方式，决定细胞功能和命运。最新研究显示，SEs 与肿瘤炎性微环境相关，但是尚不清楚其是否参与炎性微环境下细胞干性表型的维持。本研究通过观察炎性微环境下脊索瘤细胞干性表型的变化，探讨 SEs 参与调控细胞干性表型的作用及其分子机制。

方法 首先，通过脂多糖（LPS）刺激脊索瘤细胞系 U-CH1、UMChor1 细胞模拟体外细胞炎性微环境。随后，采用 CCK8、有限稀释法、免疫荧光染色及流式细胞分析等方法，观察细胞增殖、凋亡及细胞干性表型的变化。其次，采用 qRT-PCR 和免疫印迹检测基因表达，并通过 siRNA 转染进行基因表达的抑制。最后，通过全转录组 RNA-seq 观察基因表达谱改变。
结果 LPS 体外刺激抑制脊索瘤 U-CH1、UMChor1 细胞增殖，导致少部分细胞发生凋亡。并且，LPS 刺激促进脊索瘤细胞细胞干性表型的发生，表现为自我更新的能力增强，干性关键转录因子 Brachyury\SOX2\OCT4\TWIST2 及干性标志物蛋白 Brachyury\Nestin\ALDH1 的表达上调,并激活 NF-kb、STAT3 及 Notch 信号。随后研究发现，下调 SEs 相关转录因子 Brachyury 的表达后，LPS 刺激诱发的脊索瘤细胞干性表型变化消失。
结论 SEs 是维持脊索瘤细胞干性表型发生的关键区域，且参与肿瘤炎性微环境对细胞干性表型的调控。因此，特异性的干预 SEs 有望为靶向肿瘤细胞干性表型发生的治疗策略提供新的治疗靶点。

复杂基因组重排致罕见型 Xp21 邻近基因缺失综合征的家系研究

张家鹏 蓝丹
广西医科大学第一附属医院

目的 基于一个家系中两例同胞兄弟典型的 DMD 和先天性肾上腺皮质功能不全（AHC）的临床表现，以及基因检测结果阴性的事实，应用 WGS 重分析技术辨识 Xp21.2-3 区域由复杂的断裂和倒位引起的新的重排事件，为一个罕见型 Xp21 邻近基因缺失综合征的家系提供基因层面的诊断。
方法 1. 收集该家系临床资料、实验室检查结果及血液样本。2. 对患者进行骨骼肌 MRI、肌肉活检 HE 染色和 dystrophin 蛋白免疫组化染色、血清肌特异性 miRNAs、尿有机酸气相色谱-质谱分析（Gas chromatography-mass，GC-MS）、染色体微阵列分析（Chromosomal microarray analysis，CMA）、外周血染色体核型分析、MLPA 检测 DMD 基因、遗传性肌病 Panel 二代测序、高精度临床外显子组测序以及两次全基因组测序（Whole-genome sequencing，WGS）检测，第 2 次 WGS 在建库时将插入片段的大小控制在 350 bp 左右。3. 针对 WGS 筛选出的可疑阳性断裂点分析基因结构的改变，设计引物行 PCR 及 Sanger 测序验证，并分析对基因表达的影响，同时进行家系验证和共分离分析。
结果 1.两例患儿临床表现为 DMD 和 AHC，实验室结果提示钠和血浆皮质醇降低、ACTH、CK、CK-MB、ALT 和 AST 升高。母亲及两个姐姐的 CK 和 CK-MB 轻中度增高，父亲正常。2.两例患者的双下肢骨骼肌 MRI 提示脂肪浸润；腓肠肌 HE 染色显示肌营养不良，免疫组化显示肌膜 dystrophin 蛋白缺失；血清 miR-499 相对表达量增高；尿有机酸 GC-MS、CMA、外周血染色体核型分析、DMD 基因的 MLPA、遗传性肌病 Panel 二代测序、高精度临床外显子组测序以及第 1 次 WGS 结果均为阴性。3.第 2 次 WGS 结果显示先证者的 Xp21 染色体存在 3 个断裂点，分别位于无明确基因存在的基因间区、NR0B1 基因上游约 1.6 kb 以及 DMD 基因的第 43 号内含子。4.PCR 扩增显示两例患者仅有 3 处重排序列的扩增，两个姐姐和母亲存在 3 处重排序列的扩增和野生型序列的扩增，父亲仅有野生型序列的扩增。
结论 1.Xp21 染色体的复杂基因组重排（CGRs）事件导致了两例患者 DMD 和 AHC 的表型，他们是该 CGRs 事件的半合子患者，两个姐姐和母亲均为杂合子携带者，父亲是无突变的野生型，遵循 X-连锁隐性遗传模式，符合家系共分离。2.首次报告仅累及 DMD 和 NR0B1 基因，但不影响 GK 基因的 CGRs 事件，导致患者出现了 DMD 和 AHC 表型，但没有 GKD 表型的罕见型 Xp21 邻近基因缺失综合征。3.首次将 miR-499 应用于 DMD 患者及携带者的协助诊断，证明血清肌特异性 miRNAs 协助辨识 DMD 患者和携带者的潜能。4.对常规基因检测结果为阴性但有较强临床表现证据的疑诊患者应进行基因检测的重新分析，有助于发现既往检测的缺陷及提高诊断效能；临床表型是选择基因检测方法的重要指标，当多种表型同时存在时，WGS 可能是一种更经济有效的方法；改进 WGS 文库的插入片段大小可能有助于平衡结构变异的发现。

基于散发耳聋 Trio 核心家系测序的遗传特征研究

关静[1,2] 王秋菊[1,2]
1.中国人民解放军总医院耳鼻咽喉头颈外科学部
2.国家耳鼻咽喉疾病临床医学研究中心

目的 通过 trio 核心家系基因测序研究分析散发性双耳听力下降患者的遗传特征及表型谱。
方法 我们对 404 例散发性双耳听力下降患者的测序数据及临床特征进行了回顾性分析，利用 trio 核心家系全外显子组测序(trio-WES)、仅先证者 WES (p-WES)或靶向外显子组测序(p-TES)，以及所有先证者的听力正常 808 个双亲样本进行了后续基因变异的验证分析，基因变异分类标准参考 ACMG/AMP 指南。
结果 404 例散发性双耳听力下降患者中有 191 例(47.3%)明确致病基因，表现为多种遗传模式：包括常染色体隐性遗传(AR，82.7%)、常染色体显性遗传(AD)de novo 变异（13.1%）、拷贝数变异体(CNVs，5.8%)、X 连锁隐性遗传（3.1%）和双基因遗传（1.0%）。本研究中常见耳聋基因（GJB2 和 SLC26A4）的致病占比 56.5%（108/191），其次分别是 USH2A (5.2%, 10/191), MYO15A (4.7%, 9/191)和 OTOF (3.1%, 6/191)。其中常见耳聋基因 SLC26A4 的 CNV+SNV 致病基因型相对常见，临床检测中需要关注 CNV 的评估。
结论 我们通过 trio 核心家系基因测序研究明确了遗传因素对散发性双耳听力下降的重要贡献。以 trio 核心家系进行耳聋病因的分析可以最大限度地减少其他固有遗传变异对致病性判读的干扰，并能对基因型与耳聋表型关联性提供合理遗传模式的解释。也是首次明确隐性遗传和显性遗传新生变异在散发性双侧耳聋患者中的重要病因学贡献。

MALDI-TOF MS for rapid screening and typing of β-haemoglobinopathies through direct measurements of intact globin chains

Qianqian Zhang[1] Ge Wang[2] Dehui Sun[3] Wanying Lin[1] Tizhen Yan[4] Yuanjun Wu[5] Meiying Wu[6] Jianhong Chen[7] Shaomin Zou[1] Xiongda Liang[1] Lingling Hu[2] Yuxi Wang[3] Linlin He[8] Yanhui Liu[9] Zhenxiong Qiu[6] Jialong Li[1] Hongqiu Wu[2] Pengwei Sun[3] Tongtong Chen[1] Xiaoguang Zhou[3] Yan Li[10] Xiangmin Xu[1]
1.Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University
2.Clinical Laboratory & Zhuhai Institute of Medical Genetics, Zhuhai Center For Maternity and Child Healthcare & Zhuhai Women And Chidren's Hospital
3.Intelligene Biosystems (Qingdao) Co., Ltd
4.Department of Medical Genetics, Liuzhou Key Laboratory of Reproductive Medicine, Liuzhou Maternity and Child Healthcare Hospital
5.Transfusion Department, Dongguan maternal and child health centre
6.Laboratory Department of Huidong Women and Children Hospital
7.Department of Medical Genetics and Prenatal Diagnosis, Huizhou First Maternal and Child Health Care Hospital
8.Marriage and Childbirth Center, Liuzhou Maternity and Child Healthcare Hospital
9.Dongguan maternal and child health centre, Dongguan Institute of Reproductive and Genetic Research
10.Institute of Biophysics, Chinese Academy of Sciences

Backgrounds The traditional phenotypic approach in primary screening haemoglobinopathies consists of haematological parameters and haemoglobin (Hb) component analysis, which rely on complex turnaround of samples among multiplex detection system. The traditional strategy is laborious, time-consuming and cost-ineffective. We aim to develop a robust assay based on Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) platform with high sensitivity detection capability, which use alternative markers for preventive and clinical applications of it in β-haemoglobinopathies.
Methods We established a new MALDI-TOF MS platform by improving the hardware properties and optical system performance. On the basis of this, we proposed to qualitatively and quantitatively determine intact globin chains without enzymatic digestion that are served as indices

for testing β-haemoglobinopathies. We constructed a model of β-thalassemia traits, HPFH and haemoglobin variants using 217 subjects with various β-haemoglobinopathies. A further parallel and blind validation study was conducted on a cohort of 8090 premarital and antenatal screening couples from high incidence area of haemoglobinopathies to demonstrate the accuracy and transferability of this new top-down MS detection system

Findings The MALDI-TOF MS protocol for peptide mapping of four intact globin chains (α, β, γ and δ) were established, which is capable of identifying different forms of β-haemoglobinopathies in a single test based on the δ/β-globin, γ/α-globin ratios and/or the abnormal peptide patterns. Typing of the β-haemoglobinopathies can be offered to screen for carrier status of β-thalassemia, the coinheritance of β- and α-thalassemia, hereditary persistence of fetal haemoglobin (HPFH) or β-globin variants. In large-scale population screening, the new method shows an accuracy of 99.83%. The accuracy of MALDI-TOF MS assay on β-thalassemia was similar between premarital and antenatal samples, it performed higher sensitivity than traditional phenotype-based strategy on antenatal samples (97.64% vs 93.87%), which lead to more possibility of missed detection for the latter. In addition, 40 different types of haemoglobin variants including 6 novel ones were correctly characterized by peptide mapping.

Conclusion A novel MALDI-TOF MS platform is established for fast and reliable screening and typing of β-haemoglobinopathies using intact globin chains as specific markers. This innovative assay is a highly accurate and cost-effective predictive tool which offers a new standard for phenotypic screening of β-haemoglobinopathies and shows great potential to be a first-line screening assay and universal implementation.

不明原因遗传性眼底病患者的分层分子诊断策略

郭洪 王郡旖 龙艳玲 孟晓红 黄小勇 白云
陆军军医大学

研究目的 遗传性眼底病是致盲性眼病的重要病因，临床上难以鉴别和及时确诊。随着基因组技术的进展，探索建立一种流程化的分级诊断策略具有重要意义。

研究方法 本课题收集了 111 例不明原因的视力下降病人，首先通过眼科学检查和病史资料进行初级分诊。图形视觉诱发电位（PVEP）阳性的患者进行 Leber 遗传性视神经病（LHON）相关热点变异的筛查，全线粒体测序以及全外显子测序（WES），而光学相干断层扫描（OCT）阳性的患者则直接进行 WES。对所检测到的变异位点，采用 ACMG 指南进行致病性评价。

研究结果 通过以上诊断策略，一共确诊 37 例 LHON， 其中 m.11778 位点变异 22 例，m.3460 位点 3 例，m.14484 位点变异 2 例，线粒体罕见位点变异共 10 例，包括 m.4161，m.14459，m.11696，m.14502，m.3635，m.12811，m.3497 和 m.3316。确诊黄斑营养不良 10 例，视网膜色素变性 4 例，视锥视杆营养不良 3 例，视神经病 2 例，其它疾病 2 例，共发现新变异位点 14 个，包括 BEST1（c.1242G>A 和 c.313C>A），PRPH2（c.799G>A），IMPG1（c.710_727del），CERKL （ c.1319C>G ， c.313C>T ， c.239-2A>G 和 c.1642_1643insCTTT ） ， KCNV2（c.1408G>C 和 c.1500C>G），ACO2（c.1628C>T 和 c.1819C>T），MYO7A（c.845C>A 和 c.1669A>G）。

研究意义 本课题明确了本地区遗传性眼底病的病因学构成，丰富了基因变异谱，探索了一条有效的分级诊断方法，有利于提高阳性率，具有临床应用价值。

Clinical and Genetic Features of NPHS1 Variant-Related Nephrotic Syndrome in Chinese Children: A Multicenter, Retrospective Study

Liping Rong[1] Lizhi Chen[1] Jia Rao[2] Qian Shen[2] Guomin Li[2] Jialu Liu[2] Jianhua Mao[3] Chunyue Feng[3] Xiaowen Wang[4] Si Wang[4] Xinyu Kuang[5] Wenyan Huang[5] Qingshan Ma[6] Xiaorong Liu[7] Chen Ling[7] Rong Fu[8] Xiaojie Gao[9] Guixia Ding[10] Huandan Yang[11] Mei Han[12] Zhimin Huang[13] Qian Li[14]
Qiuye Zhang[15] Yi Lin[15] Xiaoyun Jiang[1] Hong Xu[2]
1.The First Affiliated Hospital, Sun Yat-sen University
2.Children's Hospital of Fudan University
3.The Children's Hospital, Zhejiang University School of Medicine
4.Wuhan Children's Hospital（Wuhan Maternal and Child Healthcare Hospital）, Tongji Medical College, Huazhong University of Science & Technology
5.Children's Hospital of Shanghai Jiaotong University
6.First Hospital, Jilin University
7.Bejing Children's Hospital Affiliated to Capital University of Medical Science
8.Puyang Oilfield General Hospital
9.Shenzhen Children's Hospital
10.Nanjing Children's Hospital Affiliated to Nanjing Medical University
11.Xuzhou Children's Hospital
12.Children's Hospital of Dalian Medical University
13.Affiliated Hospital of Guangdong Medical University
14.Provincial Hospital Affiliated to Shandong University
15.Affiliated Hospital of Qingdao University

Background Few studies have addressed the genetic spectrum of NPHS1 variants in Chinese children with nephrotic syndrome. In this multicenter study, the clinical manifestations and features of NPHS1 variants in Chinese children with nephrotic syndrome were researched.
Method Genotypical and phenotypical data from 30 children affected by NPHS1 variants were collected from a multicenter registration system in China and analyzed retrospectively.
Results Patients were divided into two groups: congenital nephrotic syndrome (CNS [n=24]); and non-CNS (early onset nephrotic syndrome [n=6]). Renal biopsy was performed on four patients in the non-CNS group, revealing minimal change disease in three and focal segmental glomerulosclerosis in one. A total of 61 NPHS1 variants were detected, involving 25 novel variants. The “hot variants” included c.928G>A (p.Asp310Asn) in eight patients with CNS, followed by c.616C>A(p.Pro206Thr) in four and c.2207T>C(p.Val736Ala) in three. Steroid treatment was applied in 29.2% (7/24）of the patients in the CNS group and 50% (3/6) of the patients in the non-CNS group. One patient in each group experienced complete remission but relapsed subsequently. Immunosuppressants were administered to three patients in the non-CNS group, eliciting an effective response. In the CNS group, three patients underwent renal transplantation and six died mainly from infection.
Conclusion Variants of NPHS1 gene cause CNS as well as early childhood-onset nephrotic syndrome. NPHS1 variants in Chinese individuals with NS were mainly compound heterozygous variants and c.928G>A(p.Asp310Asn) in exon 8 was a hot variant, followed by c.616C>A(p.Pro206Thr) in exon 6. Steroids and immunosuppressants may have effects in selected patients.

妊娠期糖尿病患者中葡萄糖激酶-青少年的成人型糖尿病合并妊娠的识别与管理

刘丽梅
上海交通大学附属第六人民医院

目的 准确识别妊娠期糖尿病（GDM）中的葡萄糖激酶-青少年的成人型糖尿病（GCK-MODY）合并妊娠，对于精准管理妊娠结局至关重要。本研究筛查 GCK-MODY 合并妊娠在中国 GDM 患者中的患病率，探讨新突变致病机制，评估患者的妊娠结局与管理。
方法 用 PCR-直接测序和 MLPA 技术，对 411 名 GDM 患者进行 GCK 基因突变筛查；比较 21 个 GCK-MODY 家族的 65 名孕妇妊娠结局和治疗管理；构建新突变体酶三维结构、进行生物信息学分析；检测突变体酶功能和热稳定性。
结果 本研究 1）共鉴定出 21 个 GCK 突变：15 个来自 411 名 GDM 患者；新发现 12 个突变：5 个（D78N、M87R、c.1019+20G>A、L451V 和 L451P）为国际首报、7 个为中国人群首次发现。2）c.1019+20G>A 突变产生异常剪接位点；4 个新错义突变导致 GCK 蛋白 3D 结构改变、酶活性和热稳定性均明显降低；3）GCK 突变母亲的非 GCK 突变后代，出生体重明显高于有 GCK 突变者（$p<0.001$）；4）接受胰岛素治疗的 21 名 GCK 突变母亲：10 名发生低血糖（47.6%）、7 名的后代发生围产期并发症（33.3%）；其 GCK 突变后代出生体重明显低于 20 名饮食控制者的后代（$p = 0.031$）。
结论 本研究 GDM 患者中，GCK-MODY 合并妊娠患病率为 3.6%（15/411）。GCK 突变导致蛋白结构和功能缺陷，是新突变患者高血糖的原因。胎儿出生体重受到母亲和胎儿 GCK 基因型相互作用的影响。对于 GCK-MODY 合并妊娠孕妇不建议使用胰岛素治疗。

POLR3A 基因复合杂合突变导致 HDL7 罕见病例一例报道

曹立 李玲 田沃土 朱泽宇
上海交通大学附属第六人民医院

目的 报道一例 POLR3A 基因复合杂合突变所致 HDL7 病例，并对遗传学检出的 POLR3A 基因突变进行致病性评估，进一步探讨总结该病的临床表型特点。
材料与方法 对一例患者的临床表现进行分析评估，完善影像学检查，并进行全外显子测序及家系共分离和一代测序验证。
结果 患者，女，53 岁，因“进行性走路困难 30 余年”就诊，18 岁时出现姿势不协调，走路时肩部摆动，左右转弯不能一次完成，跑步速度减慢。26 岁起逐渐出现走路不稳，走路困难进行性加重，鞋子磨损以双侧鞋底前侧较明显。于同年分娩后出现双下肢无法上抬。42 岁起，上下楼梯需扶扶手。44-46 岁期间，出现平地行走困难，需人搀扶，同时伴有尿急、尿失禁（2h/次），并出现情绪不稳定，夜间腿部疼痛导致睡眠较差。46 岁起，行动需依赖轮椅。53 岁起出现明显的入睡困难和早醒，伴有吐词欠清，但反应速度和记忆力尚可。患者目前推助行器可走几步，平躺时平移下肢可，上下移动不能。患者自述 4 岁学会走路，牙齿发育晚于同龄儿，牙齿稀疏。家族史：否认父母近亲婚配和阳性家族史。体格检查：一般检查及心、胸、腹部查体未见异常，神清对答可，吐词欠清，颅神经查体阴性，双上肢肌力 5 级，双上肢腱反射（+），双下肢肌张力增高；下肢肌力：左下肢：$4\text{-}3\text{-}5^{-}\text{-}4\text{-}4^{+}$，右下肢：$4\text{-}3\text{-}5^{-}\text{-}4\text{-}4^{+}$；双下肢内收 5 级，双下肢外展 4^{-}级。双侧腱反射亢进：膝反射（+++）踝反射（++++）。髌阵挛（-），双侧踝阵挛持续（+），双侧病理征（+），行走呈痉挛步态需搀扶，指鼻试验正常，跟膝胫试验略差，浅感觉检查未见异常，图形觉、位置觉差，双踝音叉振动觉减退。辅助检查： 46 岁时头 MRI：对称性白质异常，胼胝体变薄，小脑萎缩，顶叶欠饱满，胸颈髓 MRI 示胸髓变细。遗传学检查：该患者外周血样本行外显子测序结果提示 POLR3A 基因存在双杂合变异（c.928T＞A 和 c.3295C＞T）。家系共分离和一代测序结果显示 POLR3A 的双杂合变异分别来自患者父亲（c.928T＞A）和母亲（c.3295C＞T），故患者 POLR3A 为复合杂合突变，符合常染色体隐性遗传规律。

结论 本研究中，患者慢性起病，病程呈进行性加重，存在构音障碍，并伴运动功能和部分感觉功能受累，同时伴有运动里程碑发育延迟，牙齿发育异常等表现。结合临床表现、辅助检查结果与遗传学特点综合考虑诊断为 HDL7（hypomyelinating leukodystrophy type 7，低髓鞘性脑白质营养不良 7 型），属于髓鞘形成障碍综合征中的一种亚型。本病为常染色体隐性遗传性疾病，致病基因为 POLR3A。该基因发生双等位基因突变可导致 RNA 聚合酶 III 复合物缺陷，可能与疾病的发生发展有关。迄今，全球范围总计报道 60 余种 POLR3A 基因突变，包括错义、无义、剪接位点、微小插入和/或微小缺失突变。此外，髓鞘形成障碍综合征相关的其他致病基因还包括 PLP1、GJC2、TUBB4A、GLB1、HEXA、HEXB、ERCC2 和 RARS 等。

Evaluating the relationship between Clinical G6PD enzymatic and its mutation types

Xinyi Zhou
Zhuhai Municipal Maternity and Child Healthcare Hospital

Glucose-6-phosphate dehydrogenase deficiency is the most common genetic enzyme deficiency worldwide. In this study, we investigate the relationship between the distribution of G6PD enzyme activity values and different G6PD gene mutations. 510 peripheral blood samples from patients with suspected G6PD deficiency were collected for evaluation. Enzymatic test results showed that 424 samples had a G6PD/6GPD ratio of <1.0, and 15 types of G6PD gene mutations were detected using MMCA and DNA sequence methods. Among them, enzyme activities of the hemizygous G6PD gene mutations were all <5U/gHb, which was significantly lower than those of the heterozygous and double heterozygous mutations (P<0.0001), whose levels were more concentrated. The heterozygous enzyme activity values ranged from 6.5U/gHb~20.1U/gHb, and no significant difference in activity levels was observed between each group (P>0.05). The enzyme activity value of the double heterozygous mutation was mainly in the range of 1.7~3.8U/gHb, which was far lower than that of the heterozygous gene (P<0.001) and hemizygous mutations (P<0.05). We found that activity assays of the G6PD heterozygous and double heterozygous mutant enzymes does not differ depending on mutation type, but the G6PD hemizygous c.1024C>T mutation may affect the kinetic parameters of the G6PD enzyme and increase utilization of analogues, so that its enzyme activity can be higher than other mutation sites in the same β+α region. However, its specific mechanism of action remains to be further determined.

Single-cell RNA-seq highlights intra-tumoral heterogeneity in different R-ISS stages of multiple myeloma

Ling Zhong[1,2] Bo Gong[1,2] Huan Li[1,2] Jialing Xiao[1,2]
1.Department of Health Management, Sichuan Provincial People's Hospital
2.University of Electronic Science and Technology of China, Chengdu, Sichuan, China

Objective To examine molecular heterogeneity in multiple myeloma (MM) in different stages at the single cell level including myeloma cells and immune cells in bone marrow microenvironment.
Methods Single cell RNA sequencing was used to study the heterogeneity of 9 patients along the R-ISS progression spectrum, and 2 healthy controls. Specific regulon was predicted by SCENIC analysis. Biologically relevant interacting ligand-receptor partners identified to analysis the cell to cell communication. The novel markers found in single cell RNA sequencing were verified in 22 other MM patients and four kinds of myeloma cell lines by qPCR and Immunofluorescence.
Results Plasma cells from each patient clustered into six groups. High variability between 6 clusters explained by CNV levels and expression of known MM drivers and novel putative factors. IRE1- mediated unfolded protein response and tRNA aminoacylation for protein translation were identified. In R-ISS stage III, a striking feature of CNV exhibited extensive chromosomal aberrations. 12 signature genes were exclusively high-expressed. The remarkable enriched pathways were p53 signaling pathway, oxidative phosphorylation and C-type lectin receptor

signaling pathway. UQCRB was identified as specific and activate regulon. Comparisons of the tumor microenvironment revealed SEMA6B in monocytes exerted immune functions on cell movements. And NFKBIZ in neutrophils promoted IL-6. the CD4/CD8 ratio dropped with an increase in R-ISS stage. R-ISS stage associated with an activated state of Th17 cell and an exhausted state in CD8+ T cells. We found several dysregulated expression of receptor-ligand pairs contributing to migration, angiogenesis, and attenuation of phagocytic killing effect.
Conclusions we provide not only a single-cell atlas of myeloma cells and immune cells in different R-ISS stages of MM but also the complex interplay of them. Based on that, additional putative factors and regulons were identified, and thus may prove important biomarkers when considering heterogeneity and therapeutic strategies for prevention of progression in MM.

1338 个中国 X 连锁肌营养不良家系 DMD 基因突变分析

包旭东[1] 邱正庆[1] 袁裕衡[1] 姚凤霞[2]
1.中国医学科学院 北京协和医学院 北京协和医院 儿科
2.中国医学科学院 北京协和医学院 临床遗传学实验室 产前诊断中心

目的 假性肥大型肌营养不良（Duchenne/Becker muscular dystrophy，DMD/BMD）为 X 连锁隐性遗传性肌肉病，由 DMD 基因突变所致。本研究总结北京协和医院 10 余年来确诊 DMD/BMD 患者的 DMD 基因突变谱，为遗传咨询和产前诊断提供依据。
方法 回顾 2006-09 至 2017-03 在北京协和医院临床遗传学实验室进行 DMD 基因检测的先证者或亲属 1338 人，共来自 1338 个家系。应用 MLPA、STR 连锁分析技术检测外周血外显子缺失或重复，部分检测结果阴性者使用 Sanger 测序明确有无点突变。
结果 本研究纳入 1328 例 DMD，10 例 BMD。共检出大片段缺失 1149 例（85.8%），其中多外显子缺失 902 例（78.5%），外显子 45～52 是 DMD 基因缺失突变热区，最常见基因型为 e48-50del；检出大片段重复 172 例（12.9%），其中多外显子重复 133 例（77.3%），外显子 8～18 是 DMD 基因重复突变热区，最常见基因型为 e2dup；此外检出缺失合并重复 5 例（0.4%），微小突变 12 例（0.9%）。10 例 BMD 患者中检出 9 种基因型，其中 8 种基在 DMD 患者中检出。
结论 在本研究中，DMD 基因最常见突变类型为大片段缺失或重复，外显子 45～52 和外显子 8～18 分别为 DMD 基因缺失和重复突变热区。尚无法根据基因型预测患者为 DMD 或 BMD。

Molecular diagnosis of hepatic glycogen storage diseasesby a custom-designed panel sequencing:Results in 134Chinese patients from a single center

Zhixing Sun Mingsheng Ma Zhengqing Qiu
Peking Union Medical College Hospital

Purpose Glycogen Storage Disease (GSD) is a group of disorders caused by alteration of the enzymes involved in glycogen metabolism, of which the liver is the top organ to be affected. The accurate diagnosis of hepatic GSD is no easy task though, due to genetic heterogeneity and clinical heterogeneity. This study aimed to evaluate the results of molecular diagnosis for hepatic GSD of large sample volume using a custom-designed panel.
Methods Genomic DNA was extracted from peripheral leukocytes of patients with clinical diagnosis of GSD from Peking Union Medical College Hospital between March 2014 and March 2018.Next-generation sequencing was performed using a targeted, custom-designed exome sequencing panel of 32 genes involved in metabolic disorders was designed, including all the 21 genes that had been proven causing GSD.
Results Altogether 134Chinese pediatric patients from 11 province clinically diagnosed with hepatic GSD were enrolled in the study, with the ages of initial diagnosis ranged from 2 months to 17 years. Common presenting symptoms included hepatomegaly (100%), increased serum transaminases (100%), hypoglycemia (83%), and growth retardation (72%).Among the 134cases

from 134 families, 119 were found to have causative variations (SNVs and indels) or large deletions, involved 7 GSD-associated genes. The most common related genes were AGL (GSD type III), PHKA2 (GSD type IXa), G6PC (GSD type Ia), and PYGL (GSD type VI), accounting for more than70% of those genetically diagnosed. The molecular diagnosis rate for NGS was 88.8% (119/134) in total. 168 variations were detected, the majority of which had previously been associated with the phenotype of the disease. Prevalent examples include: a missense mutation (c.648G>T, p.L216L) in G6PC, occurred in 56.3% (18/32) of GSD type Ia alleles; a splicing-site mutation (c.1735+1G>T) in AGL, accounted for 5.6% (4/72)of GSD type III alleles; and a missense mutation (c.884G>A, p.R295H) in PHKA2, made up nearly11.1% (3/27) of GSD type IXa alleles. Furthermore, we detected 69 variations that have never been reported before. Several atypical cases were also recorded.

Conclusion The present work shows the utilizing of a gene panel-based NGS in diagnosing liver-affected GSD in a large cohort. Our results clearly indicate that diagnosis of GSD can be based on clinical and biochemical abnormalities combined with mutation analysis instead of enzymatic diagnosis that requires liver biopsy.

Before NGS testing, precise phenotyping based on clinical features and biochemical results would be most important, and help improve the diagnosis rate.

The making of a single-gene transcriptome: alternative splicing of human FMR1 gene in peripheral blood

Fenghua Lan
PLA 900th Hospital of Joint Logistics Support Force

Fragile X syndrome (FXS) is a common inherited mental retardation disorder, the disease-determining gene of which is fragile X mental retardation 1 gene (FMR1), encoding fragile X mental retardation protein (FMRP). To investigate the alternative splicing of FMR1 gene in human peripheral blood, RT-PCR and clone-sequencing technology was employed to detect the types of alternatively spliced products in 10 normal individuals and their expression abundance was analyzed. The results showed that a total of 50 alternatively spliced products, including 27 novel ones, were identified from 505 recombinant plasmids of PCR product. The alternatively spliced products with the highest abundance are ISO 17 and ISO 7, both of which involve exon 12 skipping, followed by ISO 1 (containing the full-length sequence of the coding region) and ISO 13 (using the second acceptor site of exon 17), while the frequency of other types of spliced products is less than 5.0%.The novel alternatively spliced variants identified in this study involved skipping of exons 3, 4, and 11, insertion of 30bp and 87bp sequences from the middle of intron 7, and 46 bp and 140bp sequences from the middle of intron 9. Bioinformatics analysis of the splice sites was performed, justifying the splicing of these vatiants. A specific antibody against the C-terminal amino acid sequence was used in immunoblotting and showed that an FMRP isoform encoded by the novel transcript containing the 140bp sequence insertion spliced from the middle of intron 9 was detectable in adult peripheral blood. Furthermore, two structure models of the human FMRPs encoded by full-length coding sequence and the transcript sequence of novel spliced isoform ISO51-ISO53 were constructed by I-TASSER server, respectively, and part of functions were predicted, showing that the intracellular location of FMRP truncated protein encoded by the novel transcript has been altered. This study not only enriched our understanding of the complexity and diversity of alternative splicing of FMR1 gene, but also laid the foundation for exploring the effects of alternative splicing on the function of FMRP and the pathogenesis of FXS.

基于 Myd88-p38/MAPK 的氧化应激在 IV 型胶原突变引起足细胞损伤中的机制研究

余舒文 靳远萌 蔡一恺 仝君 方正滢 方正滢 杨明鑫 潘晓霞 任红 谢静远
上海交通大学医学院附属瑞金医院

目的 IV 型胶原的编码基因 COL4A3-A5 突变是引起慢性肾脏病（CKD）最常见致病基因之一。本研究旨在探讨 IV 型胶原分子突变引起肾损伤的致病机制，以及探讨抗氧化应激药物-熊去氧胆酸（TUDCA）对 IV 型胶原突变所致小鼠肾脏损伤的保护机制。

方法 本课题组前期研究发现，COL4A3 p.G801R 杂合突变是一个常染色体显性遗传 FSGS 家系致病性突变，突变位于保守区域，该家系中一共 6 位肾脏病患者，均有该突变，患者起病年龄 28-62 岁，临床表现为不同程度的 eGFR 下降及蛋白尿，其中 2 名患者行肾穿刺病理检查，光镜下表现为局灶性节段性肾小球硬化（FSGS），电镜下肾小球基底膜局灶变薄。为探究 COL4A3 突变的肾损伤机制，我们构建 COL4A3 p.G799R 点突变小鼠，观察突变组小鼠肾脏病理、相关基因和蛋白表达情况。在 8 周龄时给予小鼠 TUDCA（抗氧化应激药物）进行干预，连续使用 8 周后观察 TUDCA 对 IV 胶原突变小鼠肾脏的保护作用。

结果 COL4A3 p.G799R 纯合突变小鼠在 8 周龄时已出现足细胞足突融合，24 周龄时可观察到部分肾小球毛细血管袢开放不良、肾小管间质纤维化、肾小球基底膜出现厚薄不均，血肌酐、蛋白尿水平显著高于同组野生型小鼠。进一步分离突变组和野生组小鼠肾小球进行 RNA-seq 分析以及 Western blot、Real-time PCR 等验证。结果提示，COL4A3 p.G799R 纯合突变小鼠肾小球内氧化应激相关 Myd88-pP38/MAPK 信号通路明显激活，氧化应激抑制因子 SOD3、GSH-Px 表达下调。并随着小鼠年龄增长, 自噬相关蛋白激活（LC3BII/I 比值升高、P62 水平明显降低），凋亡相关蛋白（Cleaved casp3、BAX）增高，下游炎症相关因子（IL-6、IL-1β、TGF-β）生成增加，24 周小鼠肾间质纤维化相关蛋白（aSMA、Fibronectin）显著增高。TUDCA 能有效抑制 Myd88-pP38/MAPK 信号通路活化，减低自噬和凋亡水平，抑制炎症因子分泌，减轻肾脏纤维化，改善小鼠肾脏病变。

结论 COL4A3 突变可导致氧化应激相关 Myd88-P38/MAPK 通路激活，继而诱发肾组织自噬、炎症水平增高，导致肾脏纤维化等病理损害。抗氧化应激药物 TUDCA 能通过抑制 Myd88-P38/MAPK 通路活化，改善上述肾脏损伤，可能成为 IV 型胶原突变相关肾病的有效治疗药物。

Neuropathy-associated Fars2 deficiency affect neuronal development and cause neuron apoptosis by impairing mitochondria function

Xihui Chen
Air Force Medical University

Background and purpose Neurodegenerative diseases encompass an extensive and heterogeneous group of nervous system disorders which are characterized by progressive degeneration and death of neurons. Many lines of evidence suggest the participation of mitochondria dysfunction in these diseases. Mutations in mitochondrial aminoacyl-tRNA synthetase (mt-aaRSs) genes including DARS2, EARS2, MARS2 and RARS2 are reported to cause human mitochondrial disorders with dramatically affected central nervous system. As a member of mt-aaRSs genes, FARS2 missense homozygous mutation c.424G>T (p.D142Y) found in a Chinese consanguineous family first built the relationship between pure hereditary spastic paraplegia (HSP) and FARS2 gene. More FARS2 variations were subsequently found to cause heterogeneous group of neurologic disorders presenting three main phenotypic manifestations: infantile-onset epileptic mitochondrial encephalopathy, later-onset spastic paraplegia and juvenile onset refractory epilepsy. Reduced or absent mtPheRS aminoacylation activity is commonly detected in these cases which indicates a loss-of-function mechanism in FARS2 mutant patients.

While the underlying pathogenesis of neuropathy-associated Fars2 deficiency needs further research.

Methods Global and neurological conditional Fars2 knockout mouse was established by using CRISPR-Cas 9. Morphology of the embryos were recorded under a stereomicroscope. The structural changes of embryo brain were detected by Nissl staining and immunofluorescent staining. In vitro experiments were carried out by transferring Fars2-targeted shRNA lentivirus into primary cultured mouse neurons. Immunofluorescent staining was used to observe the outgrowth of neurites. Mitochondrial ultrastructure changes were observed under a transmission electron microscope. Mitochondrial membrane potential, ATP, ROS and NAD^+ level were measured to indicate mitochondrial function. The level of respiratory chain complexes were measured by western blot. Morpholinos were injected into fertilized zebrafish ova to obtain fars2 knockdown zebrafish and behavioral assays were carried out to assess the locomotor capacity.

Results Early-gestation lethality of global Fars2 knockout mouse were observed before neurogenesis. The neurological conditional Fars2 knockout mouse put off the lethal time to late-gestation and thinner cortex and enlarged ventricle were observed, which is consist with the MRI results revealing cortical atrophy and reduced cerebral white matter volume in human patients. Delayed and disrupted development of neurite outgrowth and neuron apoptosis were then confirmed in Fars2 deficient neurons both in vivo and in vitro. Interrupted integration of phenylalanine and $tRNA^{Phe}$, and disrupt mitochondrial protein synthesis were found in Fars2 deficient organisms. Reduced ATP and NAD^+ level among with increased ROS production revealed dysfunction of mitochondria both in vivo and in vitro. Disrupt motor neuron and reduced locomotor capacity of fars2 knockdown zebrafish were observed which is consist with the spastic paraplegia phenotype in human patients.

Conclusion This study provides valuable genetic models for investigating neuropathy-associated Fars2 deficiency, and clarifies neuropathy-associated Fars2 deficiency affect neuronal development by damaging mitochondrial respiratory chain and impairing mitochondrial function, and finally lead to neuron apoptosis.

神经遗传病样本库的建设及特点

林珉婷[1,2] 陈龙[1,2] 曾一恒[1,2] 林毅[1,2] 付莹[3] 陈万金[1,2] 王柠[1,2]
1.福建医科大学附属第一医院
2.福建省神经病学研究所
3.福建医科大学神经科学研究院

目的 为了提高福建省神经病学研究所神经遗传病生物样本库的样本质量，发挥遗传病家系病例的临床价值，促进样本的共享应用，为发现新基因、研究新的致病机制，并为临床提供精准的遗传咨询服务，我们建立了神经遗传病样本库管理及质控方案，并总结本样本库的特点。

方法 基于国内外标准化组织等机构制定的标准，参考本研究所正在开展的临床队列研究项目规范，建立适合的管理模式。针对不同研究项目样本的需求，制定了相应的样本收集操作流程，包括血液、脑脊液、肌肉组织以及骨髓组织等；相应的还有样本保藏方案、样本质控方案，并配置必需的仪器设备。

结果 神经遗传病生物样本库是依托于福建医科大学附属第一医院神经内科，目前初步建成生物样本库质量管理体系在前期积累的研究基础上，近年来样本库累计收集 3 万余例患者及 6000 余个家系，各种类型样本约 8 万余管，涵盖 90 余种神经系统疾病，其中包括神经遗传病、神经系统罕见病，部分为进入研究队列的神经系统非遗传病样本。

根据我国人类遗传资源管理的相关法规，知情同意，医院伦理委员会的审核通过。依据研究项目的不同，划分出相应的神经遗传病专病库，建立共享应用机制，通过各级权限管理，各专病库之间可互相申请访问样本库和数据库，提高样本利用率。针对不同的研究项目制定了相应的样品组的标准操作流程（SOP）。

总结，本神经遗传病生物样本库有着重要的三方面特点：（1）样本中除了病人样本之外，大量收集家系样本，这为后续发现神经遗传病新基因的研究奠定基础。（2）样本的维度和质量要求高：如遗传性神经肌肉疾病，除常规血样保藏外，肌肉样本的保藏要求至关重要，要求肌肉活检样本经

液氮-异戊烷快速处理，长期液氮保存；而对于面肩肱型肌营养不良症（FSHD）这类疾病，其基因诊断需要进行脉冲场电泳检测，其 DNA 制备需要适应低熔点胶包埋的要求，流程有别于常规流程；目前，我们针对神经遗传疾病的机制研究，已深入到免疫水平，部份还要求保藏骨髓样本。（3）大部分神经遗传病需要在基因、转录及蛋白水平上进行研究分析，除了能更好地为众多患者及其亲属提供基因诊断和遗传咨询外，还可通过分析家系数据资料揭示不明原因神经遗传病的发病机制。其借助于单细胞测序、二代测序、三代测序的检测方法还常需通过不同的组织进行相关验证，故对相应特定组织样本类型、核酸制备等要求更高，从而需要更细致精准的标准操作流程（SOP)。

结论 神经遗传病样本库的建立以及质量管理体系初步形成，可以为神经遗传病的临床和基础研究提供高质量生物样本。前期的努力也取得一定成果，这也为正在申请人类遗传资源保藏提供了前提保证。

基于三代测序探索 Turner 综合征患者甲基化谱特点

范歆[1,2] 巩纯秀[1]
1.首都医科大学附属北京儿童医院
2.广西医科大学第二附属医院

背景 特纳综合征（Turner Syndrome, TS）是人类最常见的性染色体非整倍体。研究发现，TS 的表型具有高度的异质性，基因型与表型的关系尚不明确，可能与表观遗传效应相关，TS 患者 X 染色体甲基化水平低于正常女性。本研究通过纳米孔测序技术对 TS 患者的全基因组甲基化模式进行更全面的探索。

方法 本研究对 13 例外周血染色体核型为 45,XO 的患者，所有患者进行病例资料的采集。收集 8 例（男/女，4/4）年龄相匹配的正常对照组。对 TS 病例组进行家系全外显子测序分析，对数据进行单基因变异分析，基因组拷贝数分析，排除已知致病基因的致病性/可疑致病性变异后，对病例组及对照组采用纳米孔测序方法（Oxford Nanopore Technologies 平台）进行测序分析。

结果

1、13 例 TS 患者的年龄 8.4±3.3 岁，其中心血管系统异常（4/13），泌尿系统异常（4/13），骨骼畸形（6/13）,甲状腺功能异常（2/12），智力障碍（3/13），听力障碍（2/13）。家系全外测序分析检测提示 9 例为 Xp 缺失，4 例为 Xm 缺失；未检测到整条 X 染色体缺失外，其他致病性染色体拷贝数变异；未检测到与 TS 特异表型相关基因的明确致病性变异。

2、45,X0 全基因组甲基化水平分析：45,X0 个体全基因组甲基化平均水平高于 46,XX 及 46，XY 个体，其中常染色体甲基化水平及模式与对照组无显著差异，但 X 染色体的平均甲基化水平高于正常女性，与正常男性相似。在 X 染色体的 Promoter 区域，45,X0 个体发生明显的去甲基化现象；但在 Genebody 区域则相反，超甲基化现象更显著；在 CGI 与 CGI_shore 区域，45,XO 都存在去甲基化现象，仅在 CGI_shore 有超甲基化现象；在还原转座子长散落元件(L1/L2)、还原转座子短散落元件以及转座子区域，都存在显著的超甲基化现象。

讨论 本研究发现 45,X0 个体的 X 染色体呈现高甲基化水平，与以往研究结论相反，进一步研究发现存在差异的原因在于：基于检测方法的局限，以往的研究主要针对 CpG 岛的甲基化进行检测，仅揭示了主要区域的情况，而不能反应整条染色体平均甲基化水平。而本研究的方法为三代测序检测法，所获取的 CpG 位点数量是现有甲基化芯片的 50 倍，因此造成了评估的差异。

45,X0 个体在 X 染色体上不同功能区域的差异性甲基化倾向，与基因的剂量补偿效应相符。即在 Promoter 区域呈现去甲基化倾向，与提高基因表达水平有关，而 Genebody 区域的超甲基化可维持转录稳定，其结果是提高基因表达效率，推测与个体为达到平衡缺失一条 X 染色体的剂量效应有关。同样，在 CGI 与 CGI_shore 区域的去甲基化现象，以及仅在 CGI_shore 有的超甲基化现象也是达到类似的目的。这是由于 CGI_shore 作为 CGI 与基因间区、Genebody 区间的区域，当临近 CGI 的区域发生去甲基化，基因间区和 Genebody 区的发生超甲基化，从而提高转录代谢因子与酶、DNA 上结合位点的效率，达到提高转录水平的效应。在转座子及相关区域的超甲基化，使得转座子元件的功能被抑制作用，增加 X 染色体内部 DNA 片段漂移、或与其他染色体重组的难度，间接提高染色体的稳定性。

综上，本研究发现 TS 个体中 X 染色体为显著的高甲基化，不同功能区域甲基化趋势，可能与提高基因表达效应有关。

遗传性共济失调一家系临床表型及基因突变分析

李虹雨[1] 马晴雯[1,2] 任兆瑞[1,2] 理查德.芬内尔[1,2] 曾凡一[1,2,3]
1.上海交通大学附属儿童医院，上海医学遗传研究所
2.上海市胚胎与生殖工程重点实验室，国家卫健委医学胚胎分子生物学重点实验室
3.上海交通大学基础医学院组织胚胎学与遗传发育学系

目的 遗传性共济失调是一类遗传异质性神经退行性疾病，累及小脑、脑干、周围神经、视神经等区域，主要临床表现为全身性共济失调，眼球运动受损，步态障碍等。遗传性共济失调已知有多种遗传方式，分型复杂，涉及超过 100 个致病基因。这里，我们报道一例 AFG3L2 引起的新发复合杂合突变导致的较为罕见的遗传性痉挛共济失调 SPAX5 (Spastic ataxia-5) ，并描述患者的临床特点和检查方法。
方法 对患者进行病史资料收集，体格检查，家系遗传病史调查。已进行的辅助检查包括，眼底照相和光学相干断层扫描、脑部和胸椎腰椎 MRI、双髋关节 MR、X-ray 射线检查、EMG 肌电图检查，并进行了全基因组二代测序和 Trio 全外显子测序。针对已有临床信息和检查结果进行总结并分析。
结果 患者现为 13 岁女童，父母健康，否认近亲结婚，否认家族中有类似患者，否认家族性遗传病史。病史资料显示，患者 3 月龄时发现臀纹不对称，2010 年时发现独立行走步态异常，2012 年起出现视力模糊，2014 年双髋关节 MR 检查发现双髋发育不良伴双髋关节腔积液，眼底照相和光学相干断层扫描结果显示双侧视盘颞侧苍白，伴缺少血管，视神经萎缩。2017 年脑部 MRI 显示在左基底节区有异常信号，2017 年双髋关节 MR 检查发现双髋关节腔积液增多，X-ray 射线检查结果为先天性髋关节发育不良。EMG 肌电图检查结果显示神经性损伤。全基因组二代测序和 Trio 全外显子测序并经 Sanger 测序验证发现患者携带 AFG3L2 基因新发复合杂合突变，突变位点位于 AFG3L2 基因的 1 号外显子和 15 号外显子上，分别来自患者父亲和母亲，HGMD、ExAC 和 1000 Genomes 数据库中均没有关于这两个位点的报道。通过突变分析软件预测两位点均为可能致病的突变位点，根据人类孟德尔遗传数据库 OMIM (Online Mendelian Inheritance in Man) 记录，提示携带 AFG3L2 基因复合杂合突变的患者应患有常染色体隐性遗传的痉挛共济失调 SPAX5。
结论 本文报道了两个 AFG3L2 的新发突变位点，临床诊断患者为 SPAX5 患者，遗传模式显示常染色体隐性遗传，其父母为无症状携带者。眼部光学相干断层扫描、脑部 MRI、双髋关节 MR、X-ray 射线检查和 EMG 肌电图检查有助于遗传性痉挛共济失调的临床诊断。在进行影像学辅助检查时，患者进行性的病灶区域病变或可成为 SPAX5 诊断的临床特征。该例患者扩大了遗传性共济失调的临床和遗传谱。

全基因组测序技术在胎儿结构异常产前诊断中的应用初探

周佳
上海市第一妇婴保健院

目的 初步探讨及评价全基因组测序(WGS)与序贯检测（胎儿染色体微阵列检测(CMA)阴性后进行全外显子组测序(WES)）在胎儿结构异常产前诊断中的应用价值。
方法 本研究为前瞻性研究，研究对象为 2019 年 11 月至 2020 年 1 月至同济大学附属第一妇婴保健院胎儿医学部的进行产前检查的孕妇，发现胎儿结构及生长异常的病例，其中胎儿样本 111 例及其父母外周血样本 209 例（包括 4 对双胎样本），同时进行 trio WGS(40X)检测及序贯检测(CMA + WES)，并用相应的生物信息学软件和数据库对数据进行分析。WGS 检测需 100 ng DNA，周转时间（TAT）为 18 ± 6 天；序贯检测需 350ng DNA，周转时间（TAT）为 CMA（10± 2 天）+ WES（21 ± 6 天）。

结果 WGS 不仅在 22 例序贯检测诊断阳性的病例中检出了所有致病变异，包括 6 例非整倍体异常，3 例致病性和可能致病性的拷贝数变异及 13 例致病性和可能致病性的单基因变异，检出率为 19.8%(22/110)；而且还提供了 CMA 或 WES 可能无法检测到的额外的、具有临床意义的信息：包括 1 例父母平衡易位和 1 例胎儿宫内巨细胞病毒感染。
结论 与序贯检测相比，WGS 提供了 CMA + WES 检测范围外的信息，快速周转时间和更少的 DNA 量的需求，WGS 可以作为为产前诊断胎儿结构异常的选择。

Early warning of low maternal free estriol level by prenatal screening for fetus with X-linked ichthyosis

Jia Huang[1] Xi Li[1] Congmin Li[1] Jiahuan He[1] Yue Wang[2] Hongyan Liu[1]
1.1. Dept. of Medical Genetics center, People's Hospital of Zhengzhou University
2.2. Dept. of Gynaecology and Obstetrics, People's Hospital of Zhengzhou University

Objective To analyze the prenatal serological screening characteristics of fetus with X-linked ichthyosis (XLI) and explored the association between free estriol (uE3) levels and XLI.
Methods The prenatal screening medical records and family history was collected, respectively. After informed consent was obtained, blood samples and amniotic fluid samples of the family members were collected. The next generation sequencing was used for pathogenic gene screening and prenatal diagnosis. The phenotype co-segregated analysis was carried out by Sanger sequencing for point mutation.
Results The Xp22.31 microdeletion was detected in eight of the nine families, and the deletion region encompassing STS gene. A frameshift mutation c.1230-1239del (p.a411pfs*13) in the STS gene was detected in one family. All the affected individuals were male, and family history of X-linked ichthyosis was found in five family. The result of Down's screened was abnormal for all seven pregnant women whom are from the above families, of which six pregnant women showed a significant low uE3 levels. Four infants were born during the follow-up period, of which three male infants developed scaly skin changes at 3 months of age and one female infant was normal at 8 months of follow-up.
Conclusion A novel hemizygous mutation c.1230-1239del (p.a411pfs*13) in the STS gene and an Xp22.31 microdeletion involving the STS gene are responsible for XLI in the family of this study. For pregnant women with unexplained low uE3 detected by Down syndrome screening, XLI should be suspected for the fetus when the pregnant women has a family history of ichthyosis.

单体型连锁分析在基因大片段缺失及重复致病案例中的产前诊断应用

肖敏
复旦大学附属妇产科医院集爱遗传与不育诊疗中心

目的 对缺乏 MLPA 探针以及分子诊断金标准的基因内大片段缺失及重复家系，进行基于 SNP 芯片的单体型连锁分析联合常规分子诊断方法，为其家庭提供产前分子诊断并评估再生育风险。
背景 随着全外显子组测序技术在单基因遗传病领域的广泛应用，越来越多的孟德尔遗传基因变异位点被发现，为后续采用 sanger 测序进行产前诊断提供了诊断依据。但除了 SNV 和 Indel 变异致病外，基因内外显子缺失或重复型，基因内大片段缺失或重复型，随着全外显子组测序分析技术的日新月异而不断被发现。
但基于二代测序数据的大片段拷贝数变异分析，无法确认拷贝数变异的准确边界以及大小，亦不排除基因组上实际拷贝数变异大于或小于上述染色体位置所示区域，因此对于全外显子组测序检出的基因大片段变化，需要经独立的拷贝数分析实验进行确认。目前常用的基因大片段缺失、重复检测方法存在操作繁琐、成本高、无 MLPA 探针、需要 PCR(Polymerase Chain Reaction)后处理等不足，且无金标准方法的分子诊断技术运用于产前基因诊断存在一定的风险。

方法 利用目标序列捕获、高通量测序和高级生物信息学分析技术、定量 PCR 或者 long-range PCR 等技术进行常规大片段拷贝数变异检测，同时针对变异位点涉及基因及基因的上下游区域内选择高密度紧密连锁的单核苷酸多态(SNP)作为遗传标记进行单体型连锁分析相结合的方法，进行产前诊断。

结果 目标序列捕获高通量测序、定量 PCR 或者 long-range PCR 可对基因内大片段拷贝数变异进行诊断，联合基于 SNP 芯片的单体型连锁分析方法能够进一步验证产前基因诊断的准确性，同时排除母源性污染，并同步进行产前羊水全基因组拷贝数变异（CMA）检测。

结论 单体型连锁分析在基因大片段缺失及重复致病案例中的产前诊断应用，能够提高产前基因诊断的准确性，并进一步降低遗传病家系的生育风险。

19 个先天性无痛无汗症家系的产前基因诊断

李双[1] 赵飞跃[1] 耿兴柱[1] 高劲松[2] 赵秀丽[1]
1.中国医学科学院基础医学研究所&北京协和医学院基础学院医学遗传学系
2.中国医学科学院北京协和医院妇产科

目的 无痛无汗症（congenital insensitivity to pain with anhidrosis，CIPA）是一种由 NTRK1 突变导致的以痛觉不敏感、皮肤干燥、自残和骨折等为主要特征的常染色体隐性遗传病。本项目在鉴定先证者致病基因型的基础上，对 19 个先天性无痛无汗症家系中进行致病突变鉴定，并在此基础上为先证者家庭提供遗传咨询和产前基因诊断。

方法 采集先证者及其父母周静脉外周血 4 mL/人份；采集妊娠 11-13 周胎儿绒毛组织或妊娠 18-22 周胎儿羊水细胞；采用酚-氯仿法从先证者与其父母的外周血及高风险胎儿的绒毛组织或羊水细胞中提取基因组 DNA，通过候选基因 panel 测序和 Sanger 测序的方法鉴定先证者致病突变，针对先证者致病突变，通过聚合酶链式反应（PCR）- Sanger DNA 测序的方法对先证者父母及家系中的高风险胎儿进行基因型鉴定；通过微卫星标记等位基因分析的方法排除母源 DNA 的污染，鉴定单亲二体；基因型与先证者相同的胎儿为患儿。

结果 本研究共对 19 个 CIPA 家系中的 20 例胎儿进行产前基因诊断，共检出 NTRK1 致病突变纯合或复合杂合子 5 例，NTRK1 致病突变携带者 11 例，基因型正常的胎儿 4 例，患儿检出率为 25%，携带者检出率为 55%，正常胎儿检出率为 20%。

结论 本研究 CIPA 家系提供了精准遗传咨询和产前基因诊断，为 CIPA 家系健康生育提供了重要保障，有效地预防了患儿的出生。

运用 SNP-array 对 NIPT 筛查高风险孕妇进行验证 提示胎儿纯合区域 ROH 的高检出率

刘维强 胡亮 罗小金 魏凤香
龙岗区妇幼保健院

目的 对 NIPT 筛查高风险孕妇进行验证，针对染色体数目、嵌合、拷贝数异常（Copy number variants,CNV）及纯合区域（Region of homozygosity,ROH）等指标分析，明确胎儿是否存在遗传物质异常。

方法 676 名本院及外院筛查 NIPT 高风险孕妇，其中 T21 高风险 173 例，T18 高风险 54 例，T13 高风险 47 例，其他常染色体高风险 109 例，性染色体高风险 177 例，CNV 高风险 116 例。对所有高风险孕妇穿刺抽取 10ml 羊水，提取 DNA，运用 SNP-array 对染色体数目、嵌合、CNV 及 ROH 等指标进行分析。

结果 （1）检出染色体数目异常率以 T21 高风险最高 74.57%（129/173），T18 高风险病例为 46.30%(25/54)，T13 高风险病例为 17.02%(8/47)。性染色体高风险病例检出染色体数目异常率为 37.29%（66/177），其他常染色体高风险检出染色体数目异常率仅为 3.67%(4/109)；（2）共检出染色体三体/二体嵌合体 15 例（2.22%，15/676），其中其他常染色体高风险验证后存在嵌合的比

例为 4.59%（5/109），T21 高风险验证存在嵌合比例为 2.89%（5/173）；（3）CNV 高风险的阳性预测值（PPV）为 30.17%，其他筛查高风险均可检出 CNV，检出率为 2.86%（16/560）；（4）在所有 NIPT 高风险病例中，ROH 的检出率为 1.78%（12/676），其中常染色体高风险的 ROH 检出率达 7.34%（8/109），NIPT 提示 CNV 高风险病例中的 ROH 检出率达 2.59%（3/116）。

结论 对 NIPT 筛查高风险建议使用 SNP-array 进行验证。对 NIPT 高风险孕妇验证时除了分析非整倍体异常外，还需关注嵌合以及 CNV。其他常染色体 NIPT 高风险常发生三体自救，其 ROH 的比例可高达 7.34%，存在印记疾病或常染色体隐性遗传疾病风险。

基于游离 DNA 和母亲白细胞 DNA 的无创产前诊断在单基因病结节性硬化症中的临床应用

杨孝燕 邹丽萍
解放军总医院儿科医学部；解放军总医院第一医学中心儿科

目的 结节性硬化症（TSC）是一种由 TSC1 或 TSC2 基因突变导致全身多系统形成错构瘤的常染色体显性遗传病。基于游离 DNA 对单基因病的无创产前诊断是目前研究热点，但尚无在 TSC 中的应用报道。本研究探讨通过游离 DNA 对 TSC 进行无创产前诊断的可行性。

方法 于 2016—2021 就诊我院的 TSC 患儿家系中招募了 17 个先证患儿母亲再次怀孕的家系，明确家系 TSC1/2 基因致病突变位点基础上，通过对孕母血浆游离 DNA 和血白细胞 DNA 进行基因扩增、基因捕获等靶向高通量测序判断胎儿是否携带家系致病变异。通过羊膜腔穿刺行羊水胎儿 DNA 检测、出生儿童健康随访验证 NIPD 结果。

结果 纳入家系的先证者突变来源有 13 例新发突变、2 例父源突变、2 例母源突变。检测的 TSC 基因突变类型有错义突变、无义突变、移码突变、剪切位点突变及大片段缺失。NIPD 平均孕周为 16.95±5.65 周，最小孕周为 8 周。17 例 NIPD 结果经羊水胎儿 DNA 检测和出生孩子的健康随访验证均准确。但有 1 例女性胎儿在出生后双下肢肌张力高，生后全外显子测序并没有发现明确致病突变。

结论 通过胎儿游离 DNA 对单基因病 TSC 进行无创产前诊断是可行的，具有无创、早期、准确的特点。而且我们的研究可以扩展到其他常染色体显性遗传病中，因为 TSC 无突变热点、包含各种常见的基因变异类型。

基于单倍型的无创产前诊断技术在甲型血友病临床检测中的应用

赵振华[1] 吴镝[2] 李少军[2] 冯俊[2] 孔祥东[1]
1.郑州大学第一附属医院 2.赛雷纳（中国）医疗科技有限公司

目的 探讨基于单倍型的无创产前诊断技术在甲型血友病临床检测中的准确度、时间、成本等指标，评估其临床实用性。

方法 收集 4 例由父母及先证者患儿组成的甲型血友病（Hemophilia A，HA）核心家系，于孕 8-11 周采集孕妇外周血。使用杂交捕获探针富集家系样本基因组 DNA（gDNA）及孕妇游离 DNA（cfDNA）F8 基因和其两侧 1Mb 范围内 405 个高频 SNP 位点区域 DNA 序列并进行高通量测序。基于先证者 gDNA 测序结果得到致病变异所在单倍型，使用贝叶斯因子结合相对单倍型剂量（RHDO）预测胎儿是否继承母亲致病单倍型。无创产前诊断结果均通过后期侵入性产前诊断予以验证。以上所有检测均在郑州大学第一附属医院产前诊断中心实验室完成。

结果 4 例 HA 家系均在样本采集后一周内完成检测并出具报告，共检出 1 例男胎患儿、 1 例正常男胎及 2 例正常女胎，均与侵入性产前诊断结果一致，准确度为 100%。每个家系平均总 reads 数为 3182012，测序深度 385，测序成本小于 3500 元，与临床开展的高通量测序项目相近。

结论 基于单倍型的无创产前诊断检测方法在 4 例 HA 临床案例的诊断中表现出高度准确性，并且在报告周期和检测成本方面与临床已开展的其他高通量测序项目相近，满足开展临床常规检测的需求。

壁报交流

Tmem138, a photoreceptor connecting cilium (CC) protein, is required for rhodopsin transport across the cilium and outer segment (OS) biogenesis

Chunqiao Liu
Zhongshan Ophthalmic Center, Sun Yat-sen University

Photoreceptor connecting cilium (CC) is structurally analogous to the transition zone (TZ) of primary cilia and gates the molecular trafficking between the inner and the outer segment (OS). Retinal dystrophies with underlying CC defects are manifested in a broad array of syndromic conditions known as ciliopathies as well as non-syndromic retinal degenerations. Despite extensive studies, protein trafficking across the photoreceptor CC is largely unknown. Here we genetically inactivated mouse *Tmem138*, a gene encoding a ciliary membrane protein localized to the ciliary TZ and linked to Joubert syndrome (JBTS). Germline deletion of *Tmem138* abolished OS morphogenesis followed by rapid photoreceptor degeneration. Tmem138 was found localized to the photoreceptor CC and, accordingly, the molecular compartments of the CC and axoneme of the mutant photoreceptors were altered despite ciliogenesis proceeding normally at the early stage of photoreceptor development. To gain further insights into Tmem138 function in OS biogenesis, we focused on trafficking of rhodopsin, the most abundant protein of the OS. Mislocalization of rhodopsin was readily observed as early as P5 in the mutant photoreceptors prior to growth of the OS. Ablation of *Tmem138* in mature rods recapitulated the molecular changes in the germline mutants, causing well-formed outer segment discs to disintegrate accompanied by mislocalization of rhodopsin in the cell body. Furthermore, Tmem138 interacted with rhodopsin, and two additional CC compartment proteins Ahi1 and Tmem231, which were both altered in the mutant photoreceptors. Taken together, these results suggest that Tmem138 has a distinct role in gating the transport of rhodopsin and likely other OS bound proteins through formation of CC transport complex(es).

Allele-specific methylation-mediated phenotypic variations in monozygotic twins discordant for schizophrenia

Qiyang Li Cunyou Zhao Zhongju Wang Lu Zong Linyan Ye
Department of Medical Genetics, Southern Medical University

Background The non-Mendelian features of phenotypic variations within psychiatric disorder-discordant monozygotic twins are likely complicated by environmental modifiers of genetic effects that have yet to be elucidated.
Methods We performed methylome and genome analyses of blood DNA from psychiatric disorder-discordant monozygotic twins to study how allele-specific methylation (ASM) mediates phenotypic variations.
Results We identified that thousands of genetic variants with ASM imbalances exhibit phenotypic variation-associated switching at regulatory loci **(Figure 1)**. These ASMs have plausible causal associations with psychiatric disorders through effects on interactions between transcription factors, DNA methylations, and other epigenomic markers and then contribute to dysregulated gene expression, which eventually increases disease susceptibility **(Figure 2)**. We also experimentally validated the model that the rs4854158 alternative C allele at an ASM switching regulatory locus of *EIPR1* encoding endosome-associated recycling protein interacting protein 1, is associated with demethylation and higher RNA expression and shows lower TF binding affinities in unaffected controls **(Figure 3)**. An epigenetic ASM switching induces C allele hypermethylation and then recruits repressive Polycomb repressive complex 2 (PRC2), reinforces trimethylation of lysine 27 on histone 3 and inhibits its transcriptional activity, thus leading to downregulation of *EIPR1* in schizophrenia **(Figure 3)**. Moreover, disruption of rs4854158 induces gain of EIPR1 function and promotes neural development and vesicle trafficking **(Figure 4)**.

Conclusions Our study provides a powerful framework for identifying regulatory risk variants and contributes to our understanding of the interplay between genetic and epigenetic variants in mediating psychiatric disorder susceptibility.

14 种功能性 KIR 基因同步测序分型技术的建立

邓志辉 甄建新 张国彬 杨智超
深圳市血液中心

目的 杀伤细胞免疫球蛋白样受体（KIR）与 HLA I 类分子配位，共同调节 NK 细胞的活性，在肿瘤免疫、机体抗感染中发挥重要作用；但迄今国际上尚无商品化 KIR 基因测序分型试剂盒。本文致力于建立 KIR 基因家族中全部 14 种功能性 KIR 基因同步测序分型技术。
方法 基于 KIR 基因全长序列的结构特点以及外显子两翼的内含子的长度，设计退火温度相近的 KIR 基因特异性 PCR 引物 56 对，每种功能性 KIR 基因的编码区序列采用 3~5 对特异性引物进行 PCR 扩增；设计使用测序引物 230 条，对扩增产物所包含的每一外显子进行双向测序，测序反应产物于 ABI3730 测序仪上电泳、Assign 4.7 软件判定分型结果。
结果 在同一 PCR 扩增条件下，可对全部 14 种 KIR 基因的编码区进行同步扩增和测序；测序分型涵盖了每种功能性 KIR 基因的全部编码区；所获得的序列中无背景信号和杂峰，易于识别和结果判读，已获得中国、美国发明专利授权（专利号分别为：ZL 201710284545.3、US 10266877 B2），为该技术的产业化奠定了基础。
结论 所建立的高通量化、高分辨水平的 14 种功能性 KIR 基因同步测序分型专利技术，可用于 KIR 群体遗传学、骨髓移植组织配型、疾病关联研究等领域。

一组 miRNAs 介导 Notch 信号调控血管内皮细胞表型中的作用和机制

晏贤春 韩骅 孙嘉星 王若楠 车波 梁亮 杨子岩 张家玉林 张沛然 丰星星
中国人民解放军空军军医大学

目的：血管发育涉及内皮细胞增殖、分化、迁移、凋亡等多种细胞行为改变。以往研究证实 Notch 信号在血管形成中决定顶细胞和茎细胞的分化；顶细胞增殖能力弱而迁移能力强、茎细胞则增殖能力强而迁移能力弱。Notch 信号如何调控在血管形成中两种内皮细胞的行为尚不明确。本研究鉴定受 Notch 调控的 miRNAs，并研究其在 Notch 调控内皮细胞分化这的作用和机制。
方法：采用条件性基因敲除在内皮细胞中敲除或激活 Notch 信号。采用小 RNA 测序等方法鉴定 Notch 下游 miRNAs。采用内皮细胞培养、结合细胞和分子生物学方法探讨 miRNAs 对内皮细胞的调控作用及其与 Notch 信号的关系。
结果：内皮细胞特异性激活 Notch 后，通过小 RNA 测序鉴定到 Notch 信号可在内皮细胞中上调一组 miRNAs。进一步功能研究现实，miR-342-5p 可以靶向 Endoglin 而抑制 SMAD1/5 的磷酸化，进而抑制 TGF-β 信号；此外，miR-342-5p 还可调控神经干细胞的增殖和分化。我们进而发现，miR-218 可以在 Notch 信号下游抑制内皮细胞增殖，其作用机制在于 miR-218 可以靶向 MYC 表达的多个环节，包括 mRNA 水平、翻译、翻译后修饰和蛋白质稳定性等，下调 MYC 蛋白水平。此外，我们还发现 miR-223-3p 可以在 Notch 下游抑制内皮细胞迁移。
结论：内皮细胞 Notch 信号在决定顶细胞/茎细胞分化时，通过一组 miRNAs 调控内皮细胞增殖、迁移等细胞行为，促进内皮细胞的茎细胞样表型。

miRNA-203 在中枢神经系统中的功能及其影响记忆认知的分子机制

梁晓昇
暨南大学

近来研究表明 miRNA-203 调节的靶基因参与调控包括凋亡，增殖和炎症反应在内的细胞活动，从而影响中枢神经系统中神经元的功能和小胶质细胞的活性。已有研究提示 miR-203 在包括阿尔兹海默症在内的神经退行性疾病的病理发生中扮演重要作用，其下游靶基因 14-3-3θ 是参与阿尔兹海默症 tau 蛋白缠结的关键蛋白。另外，miR-203 可能也通过下调抗凋亡基因 Bcl2l2 的表达，在小鼠额颞叶痴呆的模型中诱导额叶皮质神经元的凋亡。我们实验室的早期研究发现，吸入性麻醉药七氟醚可以诱导 miR-203 在中枢神经系统中的表达，因此猜测其可能与术后认知功能障碍发生有关。
为进一步明确 miR-203 在中枢神经系统中的分子功能，探索其作为不同原因导致的认知功能障碍的潜在治疗靶点的可能性，我们通过脑定位注射慢病毒载体构建了在中枢神经系统的不同部位（包括海马和下丘脑）的过表达 miR-203 的小鼠模型，研究过表达 miR-203 对认知功能和神经内分泌的可能影响，并进一步通过 Target Scan 等软件预测，并通过双荧光素酶报告基因验证和 western blot 等体内外实验发现了几个 miR-203 的新的靶基因，其中包括 AF4 转录因子家族成员 AFF4。AFF4 参与了小鼠皮质神经元的发育，编码该蛋白的基因突变后会出现智力下降等症状，并且在小脑共济失调、急性白血病等病症发展中起到了不容忽视的作用和影响。我们通过水迷宫、Y 迷宫、旷场、恐惧测试等行为学实验，研究了过表达 miR-203 对记忆和认知功能的影响，并进一步通过原位杂交和免疫荧光检测了 miR-203 在中枢神经系统中的表达，及其对神经元凋亡和神经炎症反应的调节作用和分子机制，为明确 miR-203 的分子功能和作为治疗靶点的可能性奠定了基础。

MID1 基因缺陷对颌面部早期胚胎发育的影响

宋超 邹奕
暨南大学生命科学与技术国家级实验教学示范中心

颜面部的形态发生起源于胚胎发育早期头部神经管的神经嵴细胞（neural crest cells），NCC 向胚胎头面部腹侧移行，不段填充到头面部外胚层下的间充质并在局部增生，最终形成颜面部的五大始基：头部中线上的额鼻突，左右上颌突和左右下颌突。这五大始基生长，靠拢并最终同对侧融合，形成鼻，上唇，硬腭和软腭的结构。从细胞水平上来看，这是一个融合了包括细胞增殖，识别，凋亡和上皮细胞向间充质细胞转化（epithilial-mesencymaltransition, EMT）的复杂过程。任何因素影响了上述过程则会造成临床上常见的先天畸形--唇腭裂（Clefts of the lip and/or palate）。唇腭裂根据是否合并其他脏器畸形而分为综合征型和单纯型，MID1 是综合征型唇腭裂（Opitz 综合征）的致病基因, 有研究表明 MID1 具有 E3 泛素连接酶活性，通过结合细胞内磷酸酶 2A（PP2A）的调节亚基 alpha4，形成 MID1-alpha4-PP2A 复合物。我们的研究结果显示，MID1 的基因功能缺陷可以促进 PP2A 的去磷酸化激活，从而抑制了细胞内 Wnt 信号通路的活性，并进一步促进了胚胎神经嵴细胞的移行。我们进一步构建了在胚胎神经嵴细胞中 MID1 基因条件敲除的小鼠模型，通过对 P0 期 MID1 基因条件敲除小鼠的头部 360.旋转 micro-CT 扫描并三维重构后的颅骨模型进行形态学鉴定，对颅骨及颌面部的 94 个骨性标志进行定位，通过 Python 包 spicy 计算各个样本标志点两两之间的 4371 个欧式距离，并与野生型小鼠对比揭示，MID1 基因缺陷导致雄性 *Mid1* 基因缺陷新生鼠的三维结构明显异于非敲除对照小鼠，反映额鼻突和上颌突胚胎发育状态的鼻骨前端至上颌牙槽骨的距离，反应腭突发育的腭孔前后距离，以及反映侧鼻突胚胎发育状态的鼻骨后外侧点至颧骨与上颌颧突交叉点的距离在 *Mid1* 基因缺陷鼠都有显著下降。我们推测 *MID1* 基因可能通过 Wnt 信号通路，影响早期胚胎神经嵴细胞的移形，从而导致了颌面部发育的异常。

KCTD7 突变阻碍溶酶体酶的运输导致神经元蜡样脂褐质沉积症

王亚兰
复旦大学附属妇产科医院

目的：神经元蜡样脂褐质沉积症(Neuronal Ceroid Lipofuscinoses, NCL) 是一类以细胞内脂褐质异常累积为特征、主要表现为渐进性失明、癫痫、运动失调及早夭的早发性神经退行性疾病，病因尚未明确。文献报道 KCTD7 基因功能缺失性突变会导致 NCL 的重要亚型 CLN14，但致病机理不明。
方法：通过基因敲入构建含有内源标签的 KCTD7 细胞株，结合亲和纯化偶连的质谱，鉴定 KCTD7 的潜在互作蛋白。构建 KCTD7 缺失细胞株以及突变回复细胞株，结合酶活检测、IP、免疫印迹、免疫荧光、RUSH 等生化手段观察 KCTD7 的功能。
结果：细胞水平的研究发现 KCTD7 缺失导致溶酶体物质的异常积累、溶酶体酶运输受损、细胞自噬缺陷、以及溶酶体细胞死亡(LCD) 增加。功能学研究显示，KCTD7 能够靶向 CLN5 发生泛素-蛋白酶体降解。而患者来源的 KCTD7 突变打破了 KCTD7 对 CLN5 的调控，并导致 CLN5 异常累积。累积的 CLN5 扰乱了 CLN6 和溶酶体酶之间的相互作用，进而阻碍了溶酶体酶的正常运输。
结论： KCTD7 参与维持溶酶体稳态，KCTD7 和 CLN5 的互作打破参与了 NCL 疾病的发生。

人体表征分子 SNP 位点在群体个体识别方面的初步研究

赖力
福建省立医院

摘要：
目的 通过对 DNA 遗传信息和表型特征进行关联分析，在人体外貌特征（EVC）的特定表型与第三代遗传标记单核苷酸多态性(Single nucleotide polymorphisms，SNPs)位点之间建立对应关系，评价分子遗传标记在人体表征鉴定识方面应用价值。筛选与特定群体虹膜颜色、发色等人体表征具有高度相关性的 SNPs 位点，为构建针对群体的 EVC 鉴识体系提供依据。
方法 以 100 名福建地区汉族无血缘关系个体为研究对象，采集研究对象个人头面像及虹膜照片，由人工读取 2D 照片并对色素表型进行分类的方法来提取色素特征。同时采集研究对象血样并提取基因组 DNA，构建 EVC 中与虹膜及毛发颜色相关的 24 个 SNPs 复合检测体系，来源于 11 个不同的基因：MClR， HERC2，OCA2，SLC24A4，SLC45A2，IRF4，EXOC2， TRYPl，TYR，KITLG 和 PIGU / ASIP。通过 PCR 复合扩增、产物消化、电泳体系纯化、毛细管电泳和荧光检测基因分型等方法获得 24 个 SNPs 位点的基因分型。将 SNPs 分型结果上传色素表型在线推断模型（https://HIrisPlex.erasmusmc.nl/）进行表型分析，计算后可得到眼睛颜色（中间色、棕色）和头发颜色（棕色、黑色、深色）的推断概率。依据推断模型使用说明及相关文献对眼睛头发颜色进行判读。判读结果与人工图片判读结果进行比较。
结果 福建地区汉族人群的虹膜和毛发颜色为棕色瞳孔和深色头发，体系预测的平均准确度为深色头发 93.3％和棕色瞳孔 95.8%，基于 SNP 位点基因型的色素表型推断结果与人工判断结果基本一致。
结论 24 个虹膜与毛发颜色相关的 SNP 位点构建的色素表征推断体系具有较高的可靠性，具有一定的适用性，能够在群体个体识别尤其是眼睛和毛发颜色预测中有重要作用。

衰老非人灵长类模型的角膜上皮细胞图谱分析

肖玉华 钟嘉纬 胡星 张淑尧 刘旭 胡友金
中山大学中山眼科中心

目的 衰老是许多疾病的主要危险因素，据估计超过 10% 的老年人会患有角膜疾病。老年人群中角膜缘的隐窝面积减少，提示衰老会降低角膜的自我更新能力。然而，衰老影响角膜再生能力的分子机制目前仍不清楚。单细胞转录组测序可测定单个细胞的表达谱，为研究衰老影响角膜再生障碍的分子机制提供强有力的手段。因此，本研究利用单细胞转录组测序阐明衰老对角膜上皮自我更新的影响及其分子机制研究，为衰老诱导的角膜病变的研究提供基础。
方法 我们对年轻食蟹猴（4 岁）和老年食蟹猴角膜缘（19 岁）上皮组织进行取材，消化为单细胞悬液后，利用 10X Genomics Chromium 进行单细胞转录组测序分析。通过构建基因调控网络分析鉴定衰老对角膜细胞转录的影响。通过体外细胞增殖、迁移等实验验证关键转录因子在角膜细胞衰老过程中的作用。
结果 我们分别检测到了 5734 和 7560 个来自年轻和老年食蟹猴的角膜上皮细胞。通过细胞聚类分析鉴定到 8 种细胞类型，包括角膜缘祖/干细胞、瞬时放大细胞、角膜上皮细胞等。GO 富集分析发现年龄上调差异表达基因主要和细胞凋亡相关，下调基因主要和葡萄糖代谢、细胞迁移等相关，进一步分析发现衰老导致氧化磷酸化和 TCA 循环基因在角膜缘祖/干细胞中下调，基因调控网络分析确认 ZNF281 衰老过程中的重要调控基因。为了验证 ZNF281 在角膜上皮的功能，我们在角膜上皮细胞系中敲低 ZNF281，发现角膜上皮细胞的增殖、迁移速率下降。
结论 衰老导致角膜细胞中细胞凋亡相关基因上调以及糖代谢水平水平降低。我们证实了 ZNF281 调控角膜上皮增殖、迁移。我们的研究为认识衰老对角膜的影响提供宝贵的数据资源，也为衰老引起的角膜病变的干预和治疗提供新思路。

Rare variants in N6 are associated with essential tremor

Zhangqi Yuan[1] Jing Yu Liu[2]
1.College of Life Science and Technology, Huazhong University of Science and Technology
2.Institute of Neuroscience, State Key Laboratory of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences,

Object Essential tremor (ET) is one of the most common adult-onset neurodegenerative movement disorder characterized by 4-12Hz kinetic tremor. Many suspicious genes and loci are associated with ET. But the exact pathophysiology mechanism of ET is unclear yet.

Methods 290 ET/ET-PD families and 164 sporadic individuals were recruited from Tianjin province, Hubei province and Xiangya Hospital Central South University. We performed whole exome sequencing, Sanger sequencing, *n6* knockout mice generation and genotyping, frozen and paraffin sections of tissues, HE and Golgi staining, immunohistochemistry, Purkinje cell (PC) linear density assessment and quantification of the empty basket, plasmid construction, protein extraction, Western blotting and cell immunofluorescence et al.

Results Here, we identified two variants in same allele of *N6*, c.T>C/p.M>T and c. G>A/p.G>S in a large six-generation Chinese family with ET (16 affected and 7 unaffected family members). Additionally, we also identified 13 different rare heterozygous variants and one homozygous variant from 11 families and 9 sporadic patients by Sanger sequencing. We found the *n6* knockout mice had ET-like tremor from 2 months after birth. The *n6* was expressed in all the brain regions of mice, with high expression in PCs. Furthermore, n6 knockout mice displayed similar dysplasia in PCs (PC body morphological changes, heterotopias, PC loss, and 'empty basket'; PC dendritic complexity reduced and CF-PC synaptic density decreased; subtle morphometric changes in the PCs axonal compantment, such as tickened axonal profiles, topedoes and swelling, axonal recurrent collaterals and axonal branching) as ET patients of the postmortem studies. Importantly, Purkinje cell-specific n6 knockout mice also developed like tremor.

Conclusion we identified *N6* as a new ET candidate gene from a cohort of ET affected individuals and generated *n6* knockout mice. Our research suggested that the $n6^{-/-}$ mice

simulated both the natural course and neuropathological alternations of disease in ET patients, providing an ideal system to further investigate the intrinsic factors that link *N6* function, PCs degeneration, and tremor generation. Besides, it can be used as a platform for developing the therapeutic approach and medicine of ET.

The Decrease of MtDNA Copy Number Affects Mitochondrial Function and Involves in the Pathological Consequences of Ischemic Stroke

He Ying[1] ying he[1] Baixue Zhou[1] Yingying Luan[1] Shangdong Yang[1] Zhihao Li[1] Jing Jia[1] Yan Xu[1] Guohui Shang[1] Tianyi Han[1] Yue Peng[1] Aifan Li[2] Hong Zheng[1]
1.Zhengzhou university
2.The First People's Hospital of Zhengzhou

Purpose MtDNA copy number is the number of mtDNA in the mitochondrial genome. The change of mtDNA copy number can affect the function of mitochondria and play an important role in the occurrence and development of diseases. However, there are few studies on the mechanism of mtDNA copy number variation and its follow-up effects in patients with IS. The specific mechanism of mtDNA copy number variation is still unclear.
Methods Firstly, mtDNA copy number levels of 101 IS patients and 101 normal controls were detected by quantitative real-time PCR and the effect of mitochondrial genome D loop variation on mtDNA copy number of IS patients was explored. Then, the OGD/R PC12 cell model was induced to seek genes that regulate mtDNA copy number changes in IS. Finally, a *TFAM* gene knockdown-overexpression PC12 cell model was constructed to explore the effect of mtDNA copy number variation on mitochondrial function by detecting the enzyme activity of the mitochondrial respiratory chain complex, mitochondrial membrane potential, and ATP production.
Results The mtDNA copy number level of the IS group was significantly lower than that of the normal control group (P<0.05). The relative expression of *TFAM* gene mRNA in the cells of the OGD/R treatment group was significantly lower than that of the control group (P<0.05). In addition, after *TFAM* gene knockdown and overexpression plasmids were transfected into HEK 293T cells, mtDNA copy number and ATP production level of Sh-TFAM transfection group was significantly decreased (P<0.05), while mtDNA copy number and ATP production level of OE-TFAM transfected group was significantly higher than that of blank control group and OE-ctrl negative control group (P<0.01).
Conclusion Our study demonstrated that mitochondrial D-loop mutation and *TFAM* gene dysfunction can cause the decrease of mtDNA copy number, thus affecting the mitochondrial metabolism and function of nerve cells, participating in the pathological damage mechanism of IS.

RNA 结合蛋白 SPEN 在血管内皮细胞发育中的作用和机制

杨子岩 晏贤春 梁亮 张家玉林 张沛然 韩骅
空军军医大学

目的 SPEN 是包含 3500 余氨基酸残基的核蛋白，具有 N 末端 RNA 结合结构域、C 末端 SPOC 结构域、以及位于二者之间的转录因子结合位点，可结合 Notch 下游转录因子 RBPj 等，发挥转录抑制作用。以往研究表明 SPEN 在 X 染色体灭活中发挥关键作用，通过 Notch 通路等调控神经发育、淋巴细胞发育，并参与基因组重复序列的调控。本研究探讨 SPEN 在血管发育中的作用和机制。
方法 采用条件性基因敲除在内皮细胞中敲除 SPEN。采用视网膜血管网发育和肿瘤模型观察生理性和病理性血管发育。采用细胞培养和分子生物学方法探讨 SPEN 调控内皮细胞的作用机制。
结果 内皮细胞特异性 SPEN 基因敲除抑制视网膜血管发育。在内皮细胞中敲除 SPEN 后接种肿瘤，可促进肿瘤血管正常化，即减少血管生成、增加周细胞覆盖、促进血液灌流而减少血管渗漏、

降低肿瘤组织缺氧，这些效应抑制肿瘤生长、降低肿瘤转移、增加化疗药物敏感性。通过体外内皮细胞培养和转录组测序，提示 SPEN 敲除引起内皮细胞 p53 信号激活；而在 SPEN 敲除基础上引入 p53 基因的杂合突变，可取消 SPEN 敲除造成的肿瘤血管正常化效应。
结论 内皮细胞 SPEN 是生理性和病理性血管发育的必须基因。SPEN 缺陷可激活内皮细胞 p53 应答，促进肿瘤血管正常化，因此 SPEN 及其相关蛋白是肿瘤血管正常化治疗的新靶点。

Microenvironment sequencing from stem cells to cancers at single-cell resolution

Xinghua Pan[1,2]
1.Southern Medical University
2.Guangdong Provincial Key Laboratory of Single Cell Technology and Application

We report our recent studies on cellular microenvironments in cancers and stem cells analyzed at single cell resolution to elucidate the development of the two interesting targets related to each other in life science and medicine, cancers and stem /progenitor cells. We particularly analyzed the cellular constitutions, interactions and fynamics basing on transcriptomic profiles for colorectal cancer (CRC) and osteosarcoma (OS), and hematopoietic stem cell (HSC) and a progeny of HSC (erythroid). For CRC, we found the 2 subpopulations of CRC stem cells that share a set of common markers, the “true” cancer stem cells and candidate tumor initiation cells (TICs), using simultaneous analysis of telomere length and full length RNAs in single cells, and combining with high-throughput scRNA-seq. For OS, we sequenced the transcriptome for over 100k single cells from primary, recurrent and lung metastatic lesions, and identified the major cell clusters including stromal cells and immune cells with their subtypes from progenitor to progeny, which constitute the tumor microenvironments (TME) interacting with the subtypes of malignant OS cells. For HSC, we revealed the heterogeneity of mouse HSCs, and built the niche architecture, particularly the cell-cell communication, of HSC in mouse fetal liver with the niche cells, using a single-cell spatial transcriptomic approach, MERFISH. For erythroid we dissected the gene expression dynamics of erythroblast from ProE to OrthoE of late stages isolated from human cord blood and bone marrow, and disclosed the continuum of erythroid differentiation and putative regulators. We will discuss our discoveries and lessons from these researches.

AUTS2 基因杂合缺失及其在 AUTS2 综合征发病机制中的研究

李子龙 杨小萌 李悦 张海燕 关景云 盖中涛 刘毅
济南市儿童医院

目的 AUTS2 基因在神经发育中发挥重要作用。我们在 1 名 AUTS2 综合征患儿中发现了 AUTS2 新发的杂合缺失，并对其功能作用进行了研究。
方法 采集患儿及其家系病史，应用 Gesell 发育观察校订量表、实验室检查、全基因组芯片技术进行临床和遗传学分析并使用 qRT-PCR 验证。将患儿尿细胞诱导为多能干细胞，并在此基础上诱导为神经干细胞和神经元。研究正常和 AUTS2 杂合缺失神经元的表型变化并转录组测序，探究 AUTS2 对下游靶基因的调控。
结果 患儿，男，语言发育迟缓，具有重复刻板行为和社交障碍，语言/认知能力、运动技巧等发育显著延迟。全基因组 SNP 分析表明染色体 7q11.22 区域有一个 830 Kb 的新发远端缺失，其位于 AUTS2 基因上游并包含其 1 号外显子，预测影响了 AUTS2 的转录调控区域、起始位点和转录本，破坏了蛋白的核定位功能域而导致功能丧失。qRT-PCR 验证了这一杂合缺失。结合临床表型和实验室结果诊断患儿为 AUTS2 综合征。诱导的 AUTS2 杂合缺失的神经元突触数量较少、长度较短且较细，且膜片钳电生理结果明显异于对照组。分析神经元转录组测序结果发现 RAC1 的表达随 AUTS2 的杂合缺失而降低。双荧光素酶报告载体实验表明 AUTS2 结合 RAC1 启动子而促进其表达。

结论 我们确定了一个新的 AUTS2 基因的杂合缺失，发现其基因剂量不足会导致 AUTS2 综合征。AUTS2 通过结合启动子区域促进下游 RAC1 表达，进而在神经发育过程中发挥功能。

8 例 46，XY 性发育不全患者 AR 基因变异的鉴定及功能分析

姜薇 曹莉 杨季云 李佳楠
四川省人民医院

目的 明确散发型 46,XY DSD 患者的遗传病因，为家系的遗传咨询和产前诊断提供理论依据。
方法 应用 MLPA 方法检测 *SOX9*，*NR5A1*，*WNT4*，*CXorf21*，*NROB1* 基因拷贝数变异；芯片靶向性捕获高通量测序检测性发育相关基因；Sanger 测序对变异位点进行家系验证，并通过体外实验对变异位点进行了功能研究。
结果 在 14 个不相关家系的 46，XY DSD 患者中鉴定出了 8 例 AR 基因的新发错义变异，分别为 c.967G>A（p.E323K）、c.1889G>A（p.R630Q）、c.2182A>G（p.N728D）、c.2242T>C（p.F748L）、c.2302G>C（p.D768H）、c.2581A>T（p.T861S）、c.2606C>T （p.P869L）、c.2659A>G（p.M887V）；WB 结果显示，与野生型相比，AR 基因的 c.967G>A（p.E323K）、c.2606C>T （p.P869L）变异显著降低了 AR 基因的蛋白表达量（P<0.01）。
结论 明确了 8 例散发型 46，XY DSD 患者的遗传病因，为家系的遗传咨询和产前诊断提供了理论依据，新变异位点的鉴定丰富了 AR 基因的变异谱。

RGCC balances self-renewal and neuronal differentiation of neural stem cells in the developing mammalian neocortex

Zhenming Guo Guang He
Shanghai Jiao Tong University, Bio-X institute

During neocortical development, neural stem cells (NSCs) divide symmetrically to self-renew at the early stage and then divide asymmetrically to generate post-mitotic neurons. The molecular mechanisms regulating the balance between NSC self-renewal and neurogenesis are not fully understood. Using mouse in utero electroporation (IUE) technique and in vitro human NSC differentiation models including cerebral organoids (hCOs), we show here that regulator of cell cycle (RGCC) modulates NSC self-renewal and neuronal differentiation by affecting cell cycle regulation and spindle orientation. RGCC deficiency hampers normal cell cycle process and dysregulates the mitotic spindle, thus driving more cells to divide asymmetrically. These modulations diminish the NSC population and cause NSC pre-differentiation that eventually leads to brain developmental malformation in hCOs. We further show that RGCC might regulate NSC spindle orientation by affecting the organization of centrosome and microtubules. Our results demonstrate that RGCC is essential to maintain the NSC pool during cortical development and suggest that RGCC defects could have etiological roles in human brain malformations.

Deletion of TMEM24/C2CD2L leads to retinal photoreceptor degeneration in mice

Yeming Yang Xianjun Zhu
University of Electronic Science and Technology of China

Purpose C2CD2L/TMEM24, an endoplasmic reticulum (ER)-localized phospholipid transporter, maintains lipid transport between ER and plasma membrane (PM). The lipid transport function of TMEM24 is essential for sustaining the intracellular Ca^{2+} oscillations, supporting a key role of TMEM24 in the coordination of Ca^{2+} and phosphoinositide signaling. C2CD2L is enriched in neuroendocrine cells and previously suggested to be required for a normal secretory response.

However, little is known about the roles of this protein in retina. To this end, we investigated the effect of genetic deletion of *C2cd2l* in retinal rods on the visual function and on pathological changes in mouse.
Methods Rho-Cre mice was crossed with *C2cd2l* transgenic mice to yield *C2cd2l* Rod-KO (RKO) progenies. Electroretinograms (ERGs) were firstly recorded from wild-type (WT) and RKO mice to evaluate the visual function. H&E staining was carried out to verify the loss of rod cells in outer nuclear layer (ONL). Immunofluorescent labeling of several antibodies was performed on WT and RKO retina to reveal pathological alterations caused by *C2cd2l* deficiency. Finally, RNA-seq and qPCR were used to investigate the underlying functional mechanisms behind the retinal pathologies.
Results C2CD2L is broadly expressed in the mouse retina. Cre-mediated recombination in Rho-Cre line led to C2CD2L depletion in retinal rods. ERG recordings manifested a reduction in the amplitudes of a- and b-waves in RKO mice. Both H&E staining and immunohistochemistry of retinas sections from 4-month-old mice revealed the loss of rod cells and shortened photoreceptor outer segments in RKO retina. Besides, activated astrocytes detected in RKO retinas by immunostaining with GFAP suggested severe glial reaction. Mechanistically, RNA-seq results indicated that the expression levels of several key genes were reduced in RKO retinas, which were involved in multiple biological process, such as voltage-gated calcium channel activity (*Cacna1f, Cacng7, Cacna2d2*), postsynaptic membrane regulation (*Dlg4, Ptprs, Adnp, Cux2, Dnm1*) and visual perception (*Reep6, Rho, Aipl1, Rpgrip1, Fam161a*). These results were further verified by qPCR. Thus, in retinal rods, TMEM24 should participate in these processes to maintain normal visual function.
Conclusions Our data demonstrated that C2CD2L plays essential roles in photoreceptor function and survival.

罕见 DNMT1 天然错义突变通过去甲基化途径介导的 γ-珠蛋白基因重启可在 β 地贫中升高胎儿血红蛋白水平

龚艺
南方医科大学南方医院

目的 DNA 甲基转移酶 1 (DNMT1) 通过与红系转录因子结合形成蛋白多聚复合物被招募致 γ-珠蛋白基因（*HBG*），维持 *HBG* 启动子的高甲基化水平，从而参与成人期 γ-珠蛋白的表达抑制调控。既往研究报道了一系列位于红系转录因子中的 SNP 与升高的 Hb F 水平密切相关，可修饰 β-地贫表型。然而，目前缺乏 *DNMT1* 遗传多态性与 β-地贫表型相关性的报道。本课题将对此展开研究。
方法 运用目标区域捕获结合二代测序技术系统地研究了 *DNMT1* 多态性与 β-地贫人群表型间的关联，并对突变修饰地贫表型的分子机制进行研究。
结果 本研究首先在对 1,142 例 β-地贫人群的基因型—表型相关性分析中发现 *DNMT1* 的新发天然错义突变（c.2633G＞A, S878F）与较轻的 β-地贫表型密切相关。随后通过在患者来源的 $CD34^+$ 细胞及 HuDEP-2 细胞中的功能实验证实：突变消除了 DNMT1 蛋白原本在第 878 位丝氨酸位点的磷酸化修饰，显著降低 DNMT1 稳定性及催化活性；此外，突变减弱了 DNMT1 与互作蛋白 BCL11A、GATA1 和 HDAC1/2 的结合能力，影响其在 *HBG* 启动子的富集进而降低了 *HBG* 甲基化水平，最终缓解对 γ-珠蛋白的表达抑制。我们进一步通过 CRISPR-Cas9 技术将 S878F 突变引入 HuDEP-2 细胞，重现了 *HBG* 的再激活。
结论 本研究证实该天然 *DNMT1* 突变通过介导 *HBG* 启动子去甲基化，重新开放 *HBG* 表达，缓解地贫表型，将为 β-地贫的精确诊断及治疗提供科学依据。

NLRP3 attenuates inflammation by inhibiting AIM2 mediated pyroptosis through SIK1/SREBF1 in experimental autoimmune uveitis

侯胜平
重庆医科大学附属第一医院

PURPOSE NLRP3 inflammasome was involved in the development of uveitis, but the exact mechanism remains elusive. Here, we explored the role of NLRP3 in the development of EAU.
METHODS AND RESULTS Our results show that NLRP3 plays an anti-inflammatory role in EAU and reduces macrophages infiltration. Additionally, macrophages show an increased pyroptosis in Nlrp3-/- mice. Further experiments indicate that this pyroptosis of macrophages was mediated by the upregulated transcription of Aim2 as a result of Nlrp3 deficiency. In mechanistic studies, Nlrp3 deficiency was implicated in downregulation of p-SIK1 and subsequently the upregulation of SREBF1, which binds to Aim2 and then promotes the latter's transcription.
CONCLUSION In summary, our data show that NLRP3 inhibits AIM2 inflammasome mediated EAU by regulating the expression of SREBF1, highlighting the therapeutic potential of targeting Nlrp3.

Inactivation of ERF via methylation reactivates γ-globin expression in β-thalassemia

Xiuqin Bao
Southern Medical University

Objection The fetal-to-adult hemoglobin switch is regulated in a developmental stage-specific manner and reactivation of fetal hemoglobin (HbF) has therapeutic implications for treatment of β-thalassemia and sickle cell anemia, two major global health problems. While significant progress has been made in our understanding of the molecular mechanism of fetal-to-adult hemoglobin switch, the mechanism of epigenetic regulation of fetal hemoglobin silencing remains to be fully defined.
Methods We recruited 6 β-thalassemia individuals with widely varying levels of HbF groups (HbF ≥ 95th percentile or ≤ 5th percentile) and performed whole genome bisulfite sequencing and RNA sequencing analysis of the bone marrow-derived $GYPA^+$ erythroid cells to screen novel epigenetic modulators of HbF and phenotypic diversity of β-thalassemia.
Results We identified an ETS2 repressor factor encoded by *ERF* gene, whose promoter hypermethylation and mRNA downregulation are associated with high HbF levels in β-thalassemia. We further observed that hypermethylation of *ERF* promoter mediated by enrichment of DNMT3A leads to demethylation of γ-globin gene and attenuation of binding of ERF on *HBG* promoter and eventually re-activation of HbF in β-thalassemia. We demonstrated that *ERF* depletion markedly increased HbF production in human $CD34^+$ erythroid progenitor cells, in HUDEP-2 cell line and in transplanted NCG-Kit-V831M mice. ERF represses γ-globin expression by directly binding to two consensus motifs regulating γ-globin gene expression. Importantly, *ERF* depletion did not affect maturation of erythroid cells.
Conclusions In this study, we identified alterations in DNA methylation of *ERF* gene as a novel modulator of HbF synthesis opens new therapeutic targets for β-hemoglobinopathies.

A study of negative life events driven depressive symptoms and academic engagement in Chinese college students

Lei Ji[1,2] Changfeng Chen[3] Binyin Hou[1,2] Decheng Ren[1,2] Fan Yuan[1,2] Liangjie Liu[1,2] Yan Bi[1,2] Zhengming Guo[1,2] Fengping Yang[1,2] Qian Wu[1,2] Fujun Chen[1,2] Xingwang Li[1,2] Chuanxin Liu[3] Zhen Zuo[3] Rong Zhang[4] Zhenghui Yi[2] Yifeng Xu[2] Lin He[1,2] Yi Shi[1,2] Tao Yu[1,4] Guang He[1,2]

1.Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Shanghai Jiao Tong University

2.Shanghai Key Laboratory of Psychotic Disorders, and Brain Science and Technology Research Center, Shanghai Jiao Tong University

3.Jining Medical University

4.Shanghai Center for Women and Children's Health

Aim Negative life events (NLEs) are an important predictor of depressive symptoms (DS). College students experiencing NLEs are at risk of developing DS that could further weaken their academic engagement (AE), while social supports may assuage such negative effect. The aim of this study was to examine the relationship between negative life events, depressive symptoms, and academic engagement, and how the NLE-DS-AE relationship is affected by the level of social support among Chinese college students.

Methods To test this hypothesis, we applied data from the Decoding Happiness Gene Cohort Study (DHGCS). Baseline depressive symptoms and academic engagement were measured at the beginning of the first academic year. Approximately 12 months later, negative life events and social support over the past year were assessed retrospectively along with current depressive symptoms and academic engagement. A total of 3629 college students (Age=18.67±0.82) were included in the study.

Results The prevalence of depressive symptoms was 26.7% and 36.7% in college students at the beginning of the first and second academic year, respectively. Depressive symptoms predicted subsequent academic engagement rather than the reverse based on cross-lagged analyses. Using structural equation modeling analyses, findings revealed a partial mediation effect of social support between negative life events and the development of depressive symptoms, and a partial mediation effect between negative life events and academic engagement.

Conclusions The findings presented negative life events jeopardize the academic engagement via depressive symptoms, while social supports are able to cancel such negative effect among college students under the Chinese cultural context.

性类固醇激素相关基因单核苷酸多态性与人类指长比的关联性研究

张静[1,2] 杨梦怡[1,2] 李帆[1,2] 马占兵[1,2] 党洁[1,2] 霍正浩[1,2]

1.宁夏医科大学医学遗传学与细胞生物学系

2.宁夏医科大学 生育力保持教育部重点实验室

目的 分析 34 个性类固醇激素代谢通路相关基因 SNP 位点与人类指长比的关联性。

方法 以 808 例宁夏汉族大学生群体作为研究对象，利用生物信息学和文献检索方法，综合应用 DAVID、METASCAPE、STRING 等基因数据库筛选与指长比可能有关的性类固醇激素相关基因；采用多重 PCR 法进行基因分型；采用 SNPstats 分析等位基因与基因频率的性别间差异；通过单因素方差分析比较不同基因型个体指长比的分布特征；采用多因素回归方法，分析不同单倍型与 2D:4D 的关联性；采用广义多维因子降维法，分析基因间互作对指长比的影响。

结果 rs12702047（*GPER1*）的基因型频率（*P*=0.047）和等位基因频率（*P*=0.043）分布在不同性别间均有显著性差异，男性携带等位基因 A 的频率高于女性。rs12529 (*AKR1C3*)的基因型频率分布存在性别差异（*P*=0.014），男性中 CG 基因型比例高于女性。rs2236903（*HSD11B1*）的各

基因型频率在男女间的差异具有统计学显著性（*P*=0.014），男性的 AA 基因型比例大于 AT 型，但女性 AT 基因型比例要高于 AA 型。*AKR1C3* 基因的 rs1937845-rs12529，*SHBG* 基因的 rs3760213-rs6259-rs727428，CYP19A1 基因的 rs2255192-rs4275794-rs4646，*ESR2* 基因的 rs8006145-rs928554-rs944459 ， *CYP17A1* 基因的 rs1004467-rs10786712-rs2486758， *HSD11B1* 基因的 rs1000283-rs2236903 存在较强关联。总人群 rs12702047（*GPER1*）不同基因型间 L2D:4D 有显著差异（*P*=0.048），A/A 基因型的 L2D:4D 显著低于 G/G-A/G 基因型（*P*=0.021）。男性群体中 rs1042839（*PGR*）不同基因型间 L2D:4D 有显著差异（*P*=0.026），携带 GG 基因型的群体 L2D:4D 显著低于 A/G 基因型。男性群体中 rs1004467（*CYP17A1*）不同基因型间 L2D:4D 有显著差别（*P*=0.029），含有等位基因 G 的基因型 A/G-G/G 的 L2D:4D 低于 A/A 基因型（*P*=0.040）。rs2486758（*CYP17A1*）不同基因型的 L2D:4D（*P*=0.013）和 R2D:4D（*P*=0.012）在男性群体中均有统计学差异。女性群体的 L2D:4D 在 rs4646（*CYP19A1*）不同基因型之间的差异有统计学意义（*P*=0.042）。CYP17A1 的 rs1004467-rs10786712-rs2486758 构成单倍型与 2D:4D 显著相关，L2D:4D 和 R2D:4D 在 A-C-T 和 A-T-T 中均高于主单倍型 G-T-T。MMP9 的 rs3918249-rs17576 构成的单倍型 T-A 的 R2D:4D 高于 C-G 单倍型，说明该单倍型与右手 2D:4D 显著相关。交互分析显示， rs2236903(*HSD11B1*)-rs1004467 (*HSD17B3*)–rs4646 (*CYP19A1*) 模型与 L2D:4D 有相关性（*P*=0.0010）； rs2242442(*TBX3*)-rs3809346 (*COL4A2*)互作模型与 r2D:4D 有相关性（*P*= 0.0107）。

结论 性类固醇激素相关基因单核苷酸多态性与人类指长比存在显著相关性，可能与指长比及其性别差异性的形成有关。

EMC3 controls retinal angiogenesis through WNT signaling

Mu Yang
Sichuan Provincial People's Hospital

目的 The ER membrane protein complex **(**EMC) regulates the synthesis and quality control of membrane proteins with multiple transmembrane domains. One of the membrane spanning subunits, EMC3, is a core member of the EMC complex that provides essential hydrophilic vestibule for substrate insertion. We aimed to elucidate the role of EMC3 in the mammalian angiogenesis.

方法 We generated endothelial specific *Emc3* knockout mouse model (*Emc3*$^{loxp/loxp}$; *Pdgfb-iCre-ER* mice) by breeding *Pdgfb-iCre-ER* mice with *Emc3*$^{loxp/loxp}$ mice. The defective vascular development of flat-mount and frozen section was detected using immunofluorescence. RNA-seq, western blotting, and RT-qPCR were applied to detect differentially expressed genes in primary human retinal microvascular endothelial cells (HRECs). *In vitro* matrigel tube formation, EdU cell proliferation and rescue assays were applied to study the role of *EMC3* in the Wnt signaling.

结果 Postnatal endothelial cell (EC)-specific deletion of *Emc3* led to retarded retinal vascular development with a hyperpruned vascular network, the appearance of blunt-ended, aneurysm-like tip endothelial cells (ECs) with reduced numbers of filopodia and leakage of erythrocytes at the vascular front, which recapitulated the typical phenotypes of familial exudative vitreoretinopathy (FEVR), a severe inherited disorder characterized by the incomplete development of the retinal vasculature. Diminished tube formation and cell proliferation were also observed in *EMC3* depleted human retinal endothelial cells (HRECs). We then discovered a critical role for EMC3 in expression of FZD4 receptor of β-catenin signaling using RNA sequencing, real-time quantitative PCR (RT-qPCR) and luciferase reporter assay. Moreover, augmentation of Wnt activity via lithium chloride (LiCl) treatment remarkably enhanced β-catenin signaling and cell proliferation of HRECs. Additionally, LiCl partially reversed the angiogenesis defects in *Emc3*-cKO mice.

结论 Here, we show that the EMC subunit EMC3 plays critical roles in the retinal vascular angiogenesis by regulating Norrin/β-catenin signaling and shed light on a potential therapeutic target for diseases involving FEVR and other vascular diseases.

IVF-ET 对其子代血管功能的影响及表观遗传机制的研究

施亚君[1] 张梦书[2] 孙淼[1]
1.江苏省苏州大学附属第一医院
2.南京医科大学附属苏州医院，苏州市立医院

目的 流行病学研究表明辅助生殖技术与后代患心血管疾病、肥胖、血脂升高等风险增高有关，本研究探讨体外受精-胚胎移植技术（IVF-ET）对胎儿脐静脉血管功能的影响，并探讨表观遗传在其中的作用机制。
方法 将单胎、无并发症、20 岁≤孕妇年龄≤37 岁、足月、剖宫产分娩的产妇分为自然受孕组（Con）和 IVF-ET 受孕组，收集两组新生儿的脐带，立即分离出脐静脉用于检测对血管紧张素 II（Ang II)、乙酰胆碱（ACh）的收缩反应，通过孵育特异性受体阻滞剂来探讨与血管收缩相关的毒蕈碱样受体（CHRMs）及 Ang II 受体的改变。采用 qRT-PCR 和 Western blot 检测脐静脉中相关受体的表达；用甲基化-亚硫酸氢盐修饰后测序法检测两组脐静脉中相关基因的甲基化水平；A7r5 细胞用 5-氮杂-2'-脱氧胞苷（5-Aza）孵育 48 小时后检验相应受体的变化。
结果 与 Con 组相比，IVF-ET 组脐静脉对 Ang II 的收缩明显增强，而对 ACh 的收缩明显减弱；IVF-ET 组 Ang II 受体的表达升高及 CHRMs 下降；同时，胎儿脐静脉甲基化测序结果示在 IVF-ET 组中 Ang II 受体的甲基化下调、相关 CHRMs 甲基化上调，细胞实验证明 Ang II 受体及 CHRMs 的表达受甲基化调控。
结论 本研究表明 IVF-ET 通过影响胎儿脐静脉血管中基因启动子区域的甲基化，进而影响相关受体的表达，使胎儿脐静脉收缩反应异常，并对心血管系统产生长远影响。

Studying pathogenesis of inherited retinal ciliopathy caused by Sdccag8-E451GfsX16 mutation

Zhilin Ren[1,2]
1.School of Medicine UESTC
2. Sichuan Provincial People's Hospital

Purpose Recently, it has been verified that *SDCCAG8 (NPHP10)* gene mutations cause two autosomal recessive ciliary-diseases, SeniorL Ken syndrome (SLS) and Bardet-Biedl syndrome (BBS). The affected patients all share progressive retinal degenerations in early childhood, which includes Leber congenital amaurosis (LCA) or infantile Retinitis pigmentosa (RP). In photoreceptor, SDCCAG8 protein was found to localize at the transition zone (TZ), but its function remains unknown. Our study is aim to identify the function of *SDCCAG8* gene in photoreceptors and to provide insights into the pathogenesis of retinal ciliopathies caused by *SDCCAG8* gene mutations and lead to a potential therapy to preserve retinal function for the infants and children suffering from retinal ciliopathies.
Methods: We generated *Sdccag8- E451GfsX16* global knock-in mice by CRISPR/Cas9 to analysis the form and function of photoreceptors and the outer segment (OS) protein transporting and targeting in *Sdccag8-E451GfsX16* mice and to reveal the pathogenesis of related retinal ciliopathy caused by Sdccag8 gene mutations. Electroretinogram (ERG) and immunofluorescence (IHC) were used to study the function and phenotypes of the retina of the *Sdccag8- E451GfsX16* mice respectively. HE staining was utilized to research the phenotypes of retina and kidney of the *Sdccag8- E451GfsX16* mice.
Results: As results, we found that homozygous *Sdccag8-E451GfsX16* mice exhibited retinal degeneration (since the 1 month of age) that was associated with rhodopsin reduced and outer nuclear layer (ONL) and OS degenerated in the photoreceptors and result in progressive loss of vision, and retinas of these mice were almost completely degenerated at 6 months and lead to blind. The renal histologic changes of these mice were observed at 6 months. And the *Sdccag8-E451GfsX16* mice have a phenotype with polydactyly after birth.
Conclusion: Our study indicates that SDCCAG8 is required for photoreceptor OS development, and SDCCAG8 plays a vital role in the protein transportation in photoreceptors.

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Tecrl deficiency results in aberrant mitochondrial function in cardiomyocytes

Cuilan Hou Xunwei Jiang Wei Liu Tingting Xiao
Shanghai Children's Hospital, Shanghai Jiaotong University, Shanghai

Aims Sudden cardiac death (SCD) due to ventricular arrhythmias is a leading cause of mortality of cardiovascular disease. Mutation in TECRL, an endoplasmic reticulum protein, was first reported in catecholaminergic polymorphic ventricular tachycardia (CPVT) which patient succumb to SCD. The TECRL protein function with CPVT has been rarely reported.
Methods Using loss- and gain-of-function approaches, we investigated the role of TECRL in murine and human cardiomyocytes. Transmission electron microscopy (TEM) was used to analyse mitochondria morphology and Agilent Seahorse XF Cell Mito Stress Test Kits to test mitochondria function.
Results Tecrl KO mice showed significantly aggravated cardiac dysfunction evidenced by the decrease of ejection fraction and fractional shortening. Mechanistically, TECRL deficiency impaired mitochondrial respiration characterized by reduced adenosine triphosphate production, increased fatty acid synthase (FAS) and reactive oxygen species production, decreased of MFN2, p-AKT (Ser473), and NRF2. Overexpression of TECRL induced mitochondria respiration and this induction is PI3K/AKT dependent. TECRL regulates mitochondrial function mainly through PI3K/AKT signaling and mitochondrial fusion.
Conclusions We propose a previously unrecognized mechanism of TECRL and provide support for therapeutic targeting of TECRL in treating CPVT.

I 型干扰素调节 IFI44L 参与系统性红斑狼疮(SLE)发病的机制初探

王媛[1,2] 贾维[1,2] 李帆[1,2] 杨梦怡[1,2] 马茜[1,2] 蒲静[1,2] 马占兵[1,2] 霍正浩[1,2] 党洁[1,2]
1.宁夏医科大学基础医学院医学遗传学与细胞生物学系
2.宁夏医科大学 生育力保持教育部重点实验室

目的 探讨人类干扰素刺激蛋白 44 样基因(*IFI44L*)在系统性红斑狼疮(SLE)发病中的作用。
方法 通过全基因组测序及生物信息学分析，确定人类 *IFI44L* 基因作为研究对象后，检测 24 例 SLE 患者及 24 例健康对照外周血单核细胞（PBMCs）中 *IFI44L* 基因的表达水平，分析其与 SLE 患者实验室相关检查指标的相关性；同时在 Pristane 诱导狼疮小鼠淋巴细胞中验证 *IFI44L* 的表达水平；体外构建过表达 *IFI44L* 的 HEK293T 细胞系，检测 *IFI44L* 对细胞增殖、凋亡及细胞活性的影响；检测不同时间点干扰素（IFN-α）刺激下 *IFI44L* 在 Raji 和 HEK293T 细胞中的表达水平。
结果 ⑴SLE 患者 *IFI44L* 的表达水平显著高于健康对照 (*P*<0.001)，且男性高于女性(*P*=0.0265)，狼疮鼠的验证结果与之相一致；⑵SLE 患者 *IFI44L* 表达水平与血小板计数呈负相关（r_s=-0.45，P=0.027），与红细胞分布宽度/血小板比值（RPR）呈正相关（r_s=0.476，P=0.019）。男性患者 *IFI44L* 表达水平与血小板平均体积（MPV）呈正相关（r_s=0.703，P=0.035），女性患者 *IFI44L* 表达水平与补体 C3（r_s=0. 622，P=0.013）、CRP（r_s=0.619，P=0.018）呈正相关，其余临床指标在 case-control 及性别间均无明显相关性；⑶ROC 曲线显示 *IFI44L* 对于 SLE 的诊断具有良好的灵敏度（Sensitivity=75%）与准确度（AUC=0.915）；⑷HEK293T 细胞中 *IFI44L* 过表达组与对照组间，细胞活力、细胞周期及细胞凋亡水平均无显著变化，然而在 IFN-α 刺激下，过表达 *IFI44L* 能够有效抑制细胞凋亡水平；⑸干扰素 IFN-α 能显著促进 Raji 及 HEK293T 细胞中 *IFI44L* 的表达。
结论 *IFI44L* 可能在 I 型干扰素的调节下参与 SLE 发病，是 SLE 致病的重要效应分子，可作为潜在 SLE 诊断标志物。

Stard3nl inhibits the osteogenic differentiation of C3H10T1/2 and C2C12 cells by inactivating the Wnt/beta-catenin pathway via binding to Annexin A2

Yuexin Xu[1] Jing Ma[1,2] Guohua Xu[3] Duan Ma[1]
1.Fudan University
2.ENT Institute, Eye & ENT Hospital, Fudan University
3.Changzheng Hospital, Second Military Medical University

Background and Objects Osteoporosis is one of the leading forms of systemic diseases related with bone metabolism in the world. This study aimed to investigate the role of STARD3 N-terminal like (Stard3nl) in osteoporosis and the osteogenic differentiation of cell line C3H10T1/2 and C2C12.
Methods and Results Real-time PCR was performed to detect the Stard3nl level in bone tissues from osteoporotic patients and OVX-induced osteoporotic mice. Cell line C3H10T1/2 and C2C12 were transfected with lentivirus to repress Stard3nl expression or overexpress Stard3nl and vector controls. The effect of Stard3nl on cell proliferation abilities were examined adopting the CCK8 assay and the EdU assay. The effect of Stard3nl on cell migration was evaluated by the transwell migration assay and the wound-healing assay. The activity of osteogenic differentiation was detected with alkaline phosphatase activity assay, alizarin red staining, and real-time PCR and western blot assay of osteoblast marker genes. Transcriptomic and bioinformatic methods were applied to identify canonical Wnt signaling involved in Stard3nl-mediated osteogenic differentiation. Wnt/β-catenin signaling activities were compared among groups by TOPFlash/FOPFlash assay, immunofluorescence staining, and western blot assay of beta-catenin. Coimmunoprecipitation mass spectrometry was also carried out to identify proteins binding with Stard3nl.
Here, we demonstrate that Stard3nl expression in the osteoporotic patients' and OVX-induced osteoporotic mice' bone tissues was markedly upregulated than that from the normal counterparts. We identified Stard3nl as a potent factor that negatively regulates osteoblast differentiation in mice. Enforced expression of Stard3nl resulted in diminished osteogenic differentiation, while decreased Stard3nl expression enhanced mouse osteoblast differentiation. Canonical Wnt signaling was found potentially important in Stard3nl-mediated osteogenic differentiation. Furthermore, inhibition of Stard3nl induced β-catenin gene expression as well as Wnt signaling activities in the C3H10T1/2 and C2C12 cells, contributing to the activation of the canonical Wnt/beta-catenin signaling, which is essential for osteogenic differentiation. Mechanistic studies revealed that Stard3nl bound with Annexin A2 (Anxa2) to suppress β-catenin expression, resulting into the suppression of Wnt signaling and downstream osteogenic differentiation.
Conclusions Collectively, our study revealed that Stard3nl suppressed osteogenesis via binding with Anxa2. It also highlights the preventive and therapeutic potential of Stard3nl as a specific and novel target for osteoporotic patients.

干扰素相关 lncRNA LINC01410 参与系统性红斑狼疮发病的初步研究

马茜[1,2,3] 杨梦怡[1,2] 周少岚[1,2] 王媛[1,2] 蒲静[1,2] 王延锋[1,2] 党洁[1,2] 霍正浩[1,2] 马占兵[1,2]
1.宁夏医科大学基础医学院医学遗传学与细胞生物学系
2.宁夏医科大学生育力保持教育部重点实验室
3.宁夏大学生命科学学院

目的 研究长链非编码 RNA LINC01410 对细胞周期、凋亡及增殖活力的 影 响，探究其参与 SLE 发病的潜在机制。
方法 运用高通量测序技术检测 IFN-α 诱 导细胞模型 lncRNA 的表达谱，并结合前期临床样本测序结果筛选出既受 IFN 诱 导调控又与 SLE 发病相关的 lncRNA 分子 LINC01410；通过 RT-qPCR 检

测 LINC01410 在 SLE 患者与健康对照外周血单个核细胞（PBMCs ）中的表达量及 其在 Raji 、Jurkat 、THP- 1、HEK293T 及 PBMCs 中受 IFN-α 的诱导调控作用； 构 建 LINC01410 过表达慢病毒转染 THP- 1 细胞，流式细胞术检测其对细胞周期及 凋亡的影响，western blot 检测 BCL-2、Cyclin B 及 CDK1 蛋白的表达量； CCK-8 法检测过表达 LINC01410 后对细胞增殖活力的影响。
结果 高通量测序技术发现 在 SLE 患者 PBMCs 中 LINC01410 高表达（FC=2.09，P<0.05），同时在 IFN 诱 导细胞模型中 116 个表达上调的 lncRNAs 中 LINC01410 的表达量最高（FC=4.32, P<0.05）；RT-qPCR 验证发现与健康对照相比 LINC01410 在 SLE 患者 PBMCs 中 显著高表达（P<0.01），并且不论在细胞系或 PBMCs 中 IFN-α 均可上调 LINC01410 的表达（P<0.001）；过表达 LINC01410 后，可提高 THP- 1 细胞的增 殖能力，抑制其凋亡，上调 BCL-2、Cyclin B 及 CDK1 蛋白的表达，并使 THP- 1 的 S 期细胞数量显著降低。
结论 LINC01410 在 SLE 患者 PBMCs 中表达上调， 并 可被 IFN-α 诱导，初步研究发现其可通过抑制细胞凋亡促进增殖参与 SLE 的发病 。

联合二代测序和全基因组关联研究鉴定新的肺结核易感性位点

李沫[1] 秦胜营[1] 胡屹[2] 陈鸾[1]
1.上海交通大学
2.复旦大学

目的 肺结核（TB）是由结核分枝杆菌感染引起的一种常见的高经济负担疾病。尽管对肺结核易感性的研究已经开展了几十年，但是我们对个体间的肺结核易感性差异的宿主因素和分子机制了解仍然十分有限。双胞胎和连锁研究表明，人类基因变异在肺结核易感性中发挥着重要作用。因此，本研究旨在挖掘新的肺结核遗传易感性位点。
方法 我们通过联合二代测序和全基因组关联研究的方法对 616 名肺结核患者和 709 名健康对照进行了一项两阶段的遗传学研究。在肺结核易感性位点发现阶段中使用的二代测序技术包括全外显子测序和靶向人类白细胞抗原（HLA）基因区域富集测序。为了进一步探索我们在验证阶段确认的基因变异功能，我们使用多种生物信息学分析方法来研究其靶基因的生物学特性。
结果 在发现阶段，我们鉴定出 93 个单核苷酸多态性（SNP）和 3 个 HLA-Ⅱ等位基因位点可能与肺结核易感性有关。在验证阶段，我们进一步确认了 6 个名义上差异显著的 SNPs，包括 *RAB17* 和 *DCTN4* 基因上的 2 个新的错义变异（比值比（OR）= 1.40, P = 0.00498 和 OR = 2.30, P = 0.0317）与肺结核易感性相关。在这项研究中，我们还重复验证出 1 个之前报道的与结核病易感性相关的 SNP rs2269497（P = 0.00108, OR = 1.81, 95% 置信区间（CI）= 1.26 - 2.60）。在 eQTL 分析中，最显著的 eQTL 位点为 SNP rs7607671，并显著影响 *RAB17* 基因在肺部的表达($P = 9.1 \times 10^{-6}$)。通过 DAVID 软件基因通路和基因本体（GO）富集分析，我们发现 16 条途径表现出显著富集(Fisher s exact test, $P < 0.05$)，包括防御反应和活化 T 细胞增殖的正调控。此外，我们的研究首次发现 HLA 等位基因 DQA1*05:05（P = 0.0011, OR = 1.44, 95%CI = 1.15 - 1.77）是一个肺结核易感性潜在位点。
结论 本研究揭示了多个与肺结核易感性相关的遗传位点，为将来进一步探究肺结核易感性机制提供了新思路。

Robo2/Gen1 通过激活 MAPK/ERK 信号通路共同调节小鼠输尿管芽萌出过程

李雅欣[1,2] 余明惠[1,2] 薛珊珊[1,2] 陈径[1,2] 吴晓晖[2,3] 徐虹[1,2] 沈茜[1,2]
1.复旦大学附属儿童医院肾内科
2.上海市肾脏发育和儿童肾脏病研究中心
3.复旦大学发育生物学研究所

目的 先天性肾脏和尿路畸形（CAKUT）是常见的出生缺陷，约占总出生缺陷的 20%-30%。为明确 *ROBO2* 与 *GEN1* 在 CAKUT 中的突变，并进一步探索 *ROBO2* 与 *GEN1* 的叠加效应，本实验建立了双敲除小鼠模型，以明确两基因叠加效应对小鼠后肾发育的影响，并探讨两基因调控输尿管芽（UB）生长和分支的潜在机制。

方法 通过带 Hoxb7-mVnus 荧光标记的 *Gen1* 与 *Robo2* 突变小鼠杂交，获得带荧光标记的 *Gen1*、*Robo2* 基因双敲背景小鼠。观察小鼠新生及胚胎期表型，检测 E11.5 输尿管芽组织相关基因进行差异表达并分析。

结果 （1）$Robo2^{PB/+}Gen1^{PB/+}$ 小鼠中，PB 插入使全胚 *Robo2*、*Gen1* 表达量均下降。E12.5 $Robo2^{PB/+}Gen1^{PB/+}$小鼠全胚 *Gen1* 表达量较野生型（WT）下降 53%，与 $Gen1^{PB/+}$小鼠相比 *Gen1* 表达无差别；$Robo2^{PB/+}Gen1^{PB/+}$小鼠全胚 *Robo2* 表达量较 WT 下降 41%，与 $Robo2^{PB/+}$小鼠相比 *Robo2* 表达无差别。（2）$Robo2^{PB/+}Gen1^{PB/+}$较 $Gen1^{PB/+}$、$Robo2^{PB/+}$新生子鼠 CAKUT 发生率增加（32.3% VS 17.3%，P=0.038；32.3% VS 13.6%，P=0.01），其中，以重复肾的表型增多为主。观察 $Robo2^{PB/+}Gen1^{PB/+}$表型发现，重复肾 30.2%，肾积水合并重复肾表型 2.1%。（3）$Robo2^{PB/+}Gen1^{PB/+}$新生期小鼠重复肾 HE 染色肾脏皮质生肾区凹陷，免疫组化 WT1 染色肾小球形态及肾小球足细胞数量无变化。（4）$Robo2^{PB/+}Gen1^{PB/+}$组表现为 E11-E11.5 重复输尿管芽萌出，与 $Robo2^{PB/+}$（10/31 VS 0/14，P=0.01）及 $Gen1^{PB/+}$（10/31 vs 1/24，P=0.02）组相比有统计学差异。（5）在 E11.5 胚肾组织中，$Robo2^{PB/+}Gen1^{PB/+}$突变小鼠 *Gen1* 表达量较 WT 小鼠明显降低（P=0.004），与 $Gen1^{PB/+}$突变小鼠相比 *Gen1* 表达量亦有明显下降（P=0.03）；在 $Robo2^{PB/+}Gen1^{PB/+}$突变小鼠中 *Robo2* 明显降低（P＜0.0001），与 $Robo2^{PB/+}$突变小鼠相比，*Robo2* 表达量亦有明显下降（P=0.002）。（6）对 E11.5 小鼠胚肾组织进行 RT-PCR 检测，$Gen1^{PB/+}$突变小鼠比 WT 组 Gdnf 表达量降低（P=0.03），Grem1 表达增高（P＜0.001），Ret 表达量增高（P＜0.001）；$Robo2^{PB/+}$突变小鼠比 WT 小鼠 Gdnf 表达量增高（P＜0.001），Ret 表达增高（P＜0.001）；$Robo2^{PB/+}Gen1^{PB/+}$突变小鼠 E11.5 胚肾中 Gdnf（P＜0.001）、Ret（P＜0.001）及 Grem1（P=0.04）表达较 WT 组小鼠均增高，Bmp4（P＜0.01）、Bmp2（P＜0.01）表达降低。（7）免疫荧光验证 E11.5 胚肾组织，$Robo2^{PB/+}Gen1^{PB/+}$突变小鼠 Ret 下游 pERK1/2 表达增高，pAKT 表达无差异，$Robo2^{PB/+}Gen1^{PB/+}$突变小鼠反应细胞增殖情况的分子 PHH3 表达量增高。

结论 在 $Robo2^{PB/+}Gen1^{PB/+}$突变小鼠中，*Robo2* 及 *Gen1* 两基因在后肾发育过程中 存在协同作用，两者通过共同影响 GDNF/RET 信号通路发挥作用，并进一步影响细胞内级联效应 MAPK/ERK 通路，调节细胞周期，致使细胞增殖增多，后肾输尿管芽分支重复萌出，进而导致重复肾生成。

Variants in X gene are associated with high myopia in human being and ocular coloboma in zebrafish

Jiamin Ouyang
Zhongshan Ophthalmic Center

Purpose High myopia is one of the most common causes for blindness due to continuous elongation of the eyeball and its associated complications. Genetic factor has been considered as the major cause for early-onset high myopia (eoHM), but the exact genetic defects for most eoHM are yet to be identified.

Methods Whole exome sequencing (WES) on genomic DNA was performed as described in our previous studies, including 5280 individuals previously mentioned and 30 new cases. Variants were filtered by multi-step bioinformatics analysis and screened based on significantly higher frequencies of variants in probands with eoHM compared by controls with othereye conditions. The variants incandidate gene were further validated by Sanger sequencing. Expression analysis and knockdown zebrafish model were performed to confirm the relationship between the candidate gene and eoHM.

Results Based on comparative analysis of in-house WES data, loss-of-function (LoF) variants in *X* gene were identified in two of 653 probands with eoHM but in none of the 4657 probands with other eye condition (P = 0.015, Fisher's Exact Test). LoF variants in *X* gene were extremely rare and intolerant (pLI = 1.0), while the two LoF variants in 653 eoHM were statistically higher than their frequency in gnomAD ($P = 1.6\times10^{-4}$, Fisher's Exact Test). These two LoF variants were absent from existing database. Variants in *X* gene have not been associated with any inherited eye disease before. Expression of *X* gene was enriched in the retinal ganglion cell and the inner nuclear layer in human being. Knockdown of *x* gene in zebrafish embryos resulted in ocular coloboma. Ocular coloboma in *x* gene morphants represents a novel finding. Such effect in eye morphology development might not affect the major retinal cell types development and some coloboma related genes expression in *x* gene knockdown zebrafish.

Conclusion Expression profile and *x* gene knockdown zebrafish suggest that *X* gene play roles in eye development and support its potential contribution to eoHM when mutated.

SIAH1 suppresses apoptosis and promotes bladder cancer progression by targeting proteasomal degradation of Caspase-3

Hao Dou Huili Hu
Shandong University

Goal Seven in absentia homolog (SIAH) proteins are evolutionary conserved E3 ubiquitin ligases that have been reported to play important roles in different types of cancer. Unlike its homolog SIAH2, SIAH1 were mostly indicated as a tumor suppressor. However, its role in the bladder cancer has not been understood clearly.

Method and Result Here, we report that SIAH1 was upregulated in bladder cancer based on TCGA database and tissue microarrays. In addition, knockdown of *SIAH1* significantly reduced the cell growth and impaired the migration and invasion abilities of T24 and 253J cells. The subcutaneous tumorigenesis model also suggested that SIAH1-deficient groups displayed much smaller tumor size than control groups. Consistently, SIAH1 overexpression enhanced proliferation, migration and invasion of bladder cancer cells. Using comparative proteomic analysis, we identified Caspase-3 as the ubiquitination substrate of SIAH1. Depletion of SIAH1 enhanced the protein level of Caspase-3 and induced cell apoptosis. We also found that SIAH1 promoted cell invasion dependent on its E3 activity.

Conclusion Together, our results showed an oncogenic role of SIAH1 in bladder cancer cells and SIAH1 knockdown could enhance the drug sensitivity to cisplatin, providing a new direction in treatment for bladder cancer.

Genome-wide copy number variation analysis of congenital kidney anomalies

Huihui Du Cong Huai Shengying Qin
Shanghai Jiao Tong University

Background Congenital anomalies of the kidney and urinary tract (CAKUT) constitute one of the most common birth defects and represent the leading cause of end-stage renal disease (ESRD)

in children. Although dozens of monogenic causes of CAKUT have been identified, the genetic etiology of congenital kidney anomalies (KA) remains unknown in most patients. This study aimed to identify novel genetic drivers of KA for guiding prenatal diagnosis and genetic counseling in clinical practice.
Methods We performed a genome-wide investigation of copy number variations (CNVs) in 62 fetuses and children with KA using high-resolution array-based comparative genomic hybridization (aCGH). For CNV analysis, we performed a systematic in silico analysis based on bioinformatic resources and a novel integrated approach for small CNVs and conducted qPCR experiments for validation.
Results We identified 10 known or novel genomic imbalances in 9 of 62(14.5%) cases, of which three were known genomic disorders and seven were novel rare CNVs. One of the known genomic disorders was 17q12 deletion, a known genomic disorder of renal cyst and diabetes (RCAD) syndrome, with *HNF1B* mutation being the cause of KA at this locus. Of the seven novel rare CNVs, four were likely pathogenic CNVs and three were variants of uncertain clinical significance (VUS). Significantly, two of the ten identified CNVs were integrated CNVs, 17p11.2 deletion and 11q13.4 deletion, both of which had small homozygous deletions harboring the initiating codons of genes before integrated.
Conclusions The identification of CNVs in KA cases implies a possible causative role for CNV in the etiology of congenital kidney anomalies.

SMN2 启动子区反义寡核苷酸提升 SMA 病人细胞系中 SMN 蛋白表达

欧阳世佳 王嘉 白晋丽 彭晓音 焦辉 金煜炜 王红 瞿宇晋 宋昉
首都儿科研究所

目的 应用反义寡核苷酸（ASO）靶向屏蔽 *SMN2* 基因启动子区，明确其对 SMA 患者成纤维细胞系中 *SMN2* 基因转录水平及 SMN 蛋白表达水平的影响，以初步探索 *SMN2* 启动子区作为新的治疗靶点的意义，筛选有治疗价值的 ASO。
方法 设计并合成 MOE 修饰的靶向 *SMN2* 启动子区的 ASOs，筛选有最佳提升效果的 ASOs；获得的最佳提升效果 ASOs 和阳性对照 ASO-NUS（同 nusinersen 序列），在 SMA 患者成纤维细胞系中评估其干预效果；每次实验均重复 3 次，计量资料均采用均数±SD 表示，组间差异采用 t 检验进行比较。以 P<0.05 为差异有统计学意义，数据分析均采用 GraphPad Prism 8.0 软件进行分析。
结果 靶向屏蔽 *SMN2* 基因启动子区（-372~-43）的 13 条的 ASOs 均可以不同程度地提升细胞系中 SMN 蛋白的表达水平，其中 ASO-P1（-300~-276）和 ASO-P2（-177~-148）的提升效果更好；SMA 患者成纤维细胞系经 ASO-P1 和 ASO-P2 处理后，fl-*SMN2* 和 Δ7-*SMN2* 的整体转录水平、SMN 蛋白表达的水平和 gems 小体的数量均得到显著提升。两条 ASOs 对 SMN 蛋白提升效应在两者之间、以及与 ASO-NUS 之间差异均没有统计学意义（P>0.05），但是与 ASO-NUS 仅提升 fl-*SMN2* 转录水平不同，ASO-P1 和 ASO-P2 对 *SMN2* 转录水平是整体提升。
结论 靶向 *SMN2* 基因启动子区关键甲基化位点的 ASOs 可以提升 SMA 患者细胞系中 *SMN2* 的转录水平和 SMN 蛋白的表达水平，作用机制与 nusinersen 存在差异，*SMN2* 启动子区（-372~-43）可以作为 SMA 治疗干预的新靶点。

CABE-RY: a PAM-flexible dual-mutation base editor for efficient simulating multi-nucleotide variants

liu qing
Southern Medical University

Objective Multi-nucleotide variants (MNVs) represent an important type of genetic variation and have biological and clinical significance. To simulate MNVs, we designed a dual-mutation base editor with minimal PAM restriction, which can make simultaneous A/C conversions.
Methods (1) To construct four base editor expression plasmids, human codon-optimized DNA sequences of hA3A(Y130F), TadA8e(V106W) and UGI were synthesized and cloned into the pCMV-SpRY(D10A) backbone containing C-terminal-fused EGFP and BSD. (2) To construct gRNA expression vectors, synthesized oligos were annealed and ligated into a BsaI-digested sgRNA expression vector (pGL3-U6-sgRNA-mCherry). (3) To transfect plasmids, the base editor expression plasmids (1000 ng) and corresponding sgRNA plasmids (500 ng) were cotransfected using Lipofectamine 2000 (Life Technologies) as the manufacturer's protocol recommended. (4) To analyze the on-target editing and RNA off-target editing after sanger and deep sequencing.
Result (1) The selected cytosine and adenine base editor-SpRY (CABE-RY), one of the four base editors, had the best editing performance. (2) Characterization and comparison showed that CABE-RY had a smaller DNA editing window and lower RNA off-target edits than the corresponding single base editors. (3) CABE-RY can efficiently simulate MNVs and is a versatile tool for dissection of the functions of MNVs.
Conclusion we have established a versatile tool (CABE-RY) to efficiently simulate MNVs over the genome, which could be very useful for functional studies on MNVs in humans.

Nocturnin 在糖尿病近端肾小管损伤中的作用及其机制研究

邵小青 刘文娟 王蒙 杨叶萍 王熠 谢丽杰 李益明 龚伟 何敏 张朝云
复旦大学附属华山医院

背景 Nocturnin（简称 Noct）在多个代谢性疾病中发挥重要作用，然而，Noct 在糖尿病肾脏疾病（Diabetic kidney disease，DKD）中的作用尚不清楚。我们发现 Noct 主要表达于肾小管，在糖尿病小鼠和人的肾脏组织，Noct 表达显著高于非糖尿病组。因此，我们研究了 Noct 在 DKD 发生中的作用及其可能机制。
方法 我们利用 Cre-loxp 系统构建了近端肾小管 Noct 敲除（$Noct^{flox/flox}$/Cad16-cre^{+}，PT-Noct-KO）小鼠，$Noct^{flox/flox}$/Cad16-cre^{-}作为野生型对照。选取 8 周龄小鼠，分为 4 组：野生型非糖尿病组（WT-NDM），野生型糖尿病组（WT-DM），敲除型非糖尿病组（KO-NDM）和敲除型糖尿病组（KO-DM）。糖尿病诱导采用 STZ 腹腔注射。小鼠连续饲养 12 周，饲养结束时收集小鼠尿液、血清和肾脏组织进行后续的研究。
结果 与 WT-NDM 组相比，WT-DM 小鼠 HbA1c（8.68 ± 1.07% vs. 19.24 ± 0.31%，P < 0.001）、尿糖/肌酐（2.15 ± 0.25μM/mg vs. 4599 ± 659.5μM/mg，P < 0.0001）、血清肌酐（1.30 ± 0.08mg/dL vs. 2.15 ± 0.18mg/dL，P < 0.01）、尿白蛋白/肌酐（UAlb/Cr，30.56 ± 4.46mg/g vs. 64.88 ± 8.13mg/g，P< 0.01）、尿 NGAL/肌酐（1.74 ± 0.22ng/mg vs. 9.00 ± 0.71ng/mg，P < 0.0001）显著升高；同时，WT-DM 小鼠肾脏 KIM-1 和 NGAL 表达显著升高，电镜显示肾小球基底膜增厚，足突融合明显，近端肾小管线粒体明显肿胀。近端肾小管糖原和胶原纤维沉积明显，炎症、纤维化、上皮-间质转分化和氧化应激明显加重。与 WT-DM 组相比，KO-DM 小鼠 HbA1c、血清肌酐、UAlb/Cr、尿 NGAL/肌酐水平显著降低，而尿糖/肌酐进一步增加；同时，KO-DM 小鼠肾脏 KIM-1 和 NGAL 表达显著降低，肾脏超微结构明显改善，近端肾小管糖原和间质胶原纤维沉积明显减轻，炎症、纤维化、上皮-间质转分化和氧化应激减轻。为了进一步研究 Noct 敲除减轻肾脏病变的机制，我们发现，与 WT-NDM 组相比，WT-DM 小鼠肾脏 NADPH 水平降低，SGLT2 表达明显升高；而在 KO-DM 小鼠肾脏中 NADPH 水平升高，SGLT2 表达明显降低。体外培养人近端肾小管上皮（HK-2）细胞，在高糖条件下抑制 Noct，近端肾小管上皮细胞损

伤、炎症、纤维化和氧化应激指标显著改善，SGLT2 表达显著降低，NADPH 水平升高，$NADP^+$/NADPH 显著降低；同时，NADPH 合成关键酶 ME1 的 mRNA 水平显著升高。
结论 糖尿病状态下，Noct 可能通过上调 SGLT2 表达、降低 NADPH 合成及增加 NADPH 降解而诱导氧化应激失衡，导致近端肾小管损伤。

A nonsense variant in PTGFR causing developmental dysplasia of the hip by inducing abnormal development of cartilage

Dan Yang
Shanghai Children's Hospital

Objectives Developmental dysplasia of the hip (DDH) is a debilitating condition that affects 1-7% of newborns. There are no key accurate diagnostic or prognostic molecular markers for DDH. Thus, the purpose of this study is to further screen and identify the genetic variation of DDH and clarify its pathogenesis.
Methods The genetic variation of DDH was tested by whole-exome analysis, and verified by Sanger test. The expression of PTGFR, COL2A1 and COL10A1 in clinical specimens were analyzed. ATDC5 cells with PTGFR variant and overexpression were constructed by gene editing technology. The proliferation of cells was analyzed by CCK assay, the development of cartilage of cells were analyzed by Alcian blue staining.
Results This variant was found to be present in 4/4 of the affected family members, in 4/15 of the healthy relatives in the family, in 0/7 of normal persons without consanguinity. 300 sporadic DDH patients showed that 21 cases were positive for PTGFR variant, and no variant was found in 300 normal individuals.The expression of PTGFR significantly lower in articular capsule and ligamentum teres of hip joint tissue in DDH patients. PTGFR variant in DDH patients significantly reduced the expression of COL2A1 and COL10A1. Mechanically, PTGFR variant didn't affect the proliferation of ATDC5 cells but decreased the expression of COL2A1 and COL10A1 and inhibited the differentiation and development of cells.
Conclusion Our study provided strong evidence for the role of PTGFR variants in DDH and elucidated the mechanism of PTGFR in the pathogenesis of DDH.

血管内皮细胞过表达 Twist1 促进小鼠病理性视网膜血管生成

王开放 [1,2]
1.四川省人类疾病基因研究重点实验室，四川省人民医院 2.电子科技大学

视网膜血管生成是视网膜正常功能的关键过程，而不加控制的血管生成会导致病理性新生血管(PNV)，而 PNV 与大多数不可逆的致盲视网膜疾病密切相关。目前，治疗视网膜新生血管病的药物和靶点相对有限，且对病理性新生血管无特异性。了解病理性 PNV 背后的分子基础对相关疾病的治疗具有重要意义。
为了进一步研究 TWIST1 在病理性视网膜 PNV 中的作用，寻找抗病理性 PNV 的特异性分子靶点，我们建立了可诱导的血管内皮细胞特异性 Twist1 转基因小鼠模型(*Tg-Twist1*$^{iEC+}$)。*Tg-Twist1*$^{iEC+}$小鼠的整体视网膜在生长的视网膜血管前端显示血管进展缓慢，血管密度增加，并观察到动脉瘤样的病理性视网膜新生血管。
进一步的研究表明，*Twist1* 在内皮细胞中的过表达促进了内皮细胞的增殖，但扰乱了内皮细胞的极性，从而导致视网膜血管生成失控。我们还发现 TWIST1 通过增强 Wnt/β-catenin 信号转导和诱导一组血管形成相关基因的表达来促进 PNV 的发生。本研究明确了 Twist1 在视网膜病理性 NV 中的重要作用，为病理性 NV 提供了一个潜在的治疗靶点。我们还建立了一种新的小鼠模型，可用于与 PNV 相关的视网膜疾病的治疗研究。

HMGCS2 上调致 β-羟基丁酸堆积损伤糖尿病近端肾小管的机制研究

杨叶萍[1] 邵小青[2] 王蒙[2] 俞一飞[2] 刘文娟[2] 李琴[3] 曾芳芳[2] 王熠[2] 何敏[2] 龚伟[2] 郝传明[2] 李益明[2] Robert C. Stanton[4] 张朝云[2]
1.复旦大学附属中山医院
2.复旦大学附属华山医院
3.上海交通大学医学院附属第九人民医院
4.Joslin 糖尿病中心

目的 研究酮体在糖尿病近端肾小管损伤中的作用并探索生酮限速酶 HMGCS2 的调控机制
方法 取 8 周的 db/db 2 型糖尿病小鼠及同窝非糖尿病小鼠做对照。检测小鼠的血糖、血压、尿白蛋白/肌酐比值，糖尿病 12 周后留取肾脏组织。根据 microarray RNA 筛选出与酮体生成相关基因 HMGCS2，在小鼠模型和肾小管上皮细胞中验证 HMGCS2 表达并利用化学发光试剂盒检测肾脏局部 β-羟基丁酸含量。检测正常人和糖尿病人的肾脏组织切片的 HMGCS2 表达差异。对 HK-2 细胞进行干预，进一步检测 β-羟基丁酸对肾小管上皮细胞的影响。在小鼠近端肾小管特异性敲除 HMGCS2 并诱导糖尿病，检测肾脏转分化、炎症、纤维化、氧化应激指标。使用醛固酮皮下注射 C57 小鼠 1 周后，留取血、尿、肾脏组织并检测 β-羟基丁酸含量及 HMGCS2 的表达。利用荧光素酶报告实验检测盐皮质激素受体是否调控 HMGCS2 的基因转录。
结果 与非糖尿病对照小鼠相比，糖尿病小鼠肾脏中酮体生成限速酶 HMGCS2 显著升高，免疫组化结果显示其主要表达在肾小管中，同时肾脏局部的酮体（β-羟基丁酸）显著升高；与非糖尿病对照相比，糖尿病病人的肾小管中 HMGSC2 显著升高；给予近端肾小管上皮细胞 β-羟基丁酸培养，可导致肾小管 E-cadherin 表达降低，α-SMA 表达升高；同时 TGF-β1、Fibronectin 表达增加；IKB-α 表达降低、MCP-1、TNF-α 表达升高；肾小管上皮细胞内 ROS 堆积增加；在 HK-2 细胞抑制 HMGCS2 表达及在糖尿病小鼠近端肾小管特异性敲除 HMGCS2 后可改善高糖（糖尿病）诱导的上皮功能失衡、纤维化、炎症以及氧化应激。使用醛固酮干预小鼠后，小鼠的肾脏 HMGCS2 表达增加且肾脏局部 β-羟基丁酸含量增加。体外使用荧光素酶报告实验发现盐皮质激素受体能上调 HMGCS2 的基因转录。
结论 醛固酮能通过盐皮质激素受体上调 HMGCS2 的表达，导致肾脏 β-羟基丁酸堆积，造成小管细胞的损伤，从而促进 DKD 的发生与进展。

NEIL3 contributes to the Fanconi Anemia/BRCA pathway by promoting the downstream double-strand break repair step

Niu Li Yufei Xu Hongzhu Chen Jing Chen Lina Chen Yi Zhang Tingting Yu Ruen Yao Qihua Fu Jian Wang
Shanghai Children's Medical Center

Unhooking of interstrand crosslinks (ICLs) by the canonical Fanconi anemia (FA) pathway generates double-strand breaks (DSBs), which are subsequently resected and repaired by the homologous recombination pathway (HR) during S phase. Recent studies show the NEIL3 DNA glycosylase can repair psoralen-ICLs through a direct unhooking mechanism. However, whether NEIL3 is also involved in repair process of MMC and cisplatin-ICLs following DSB generation remains unknown. Here we show that NEIL3 participates in the downstream process of DSB repair, promoting the HR pathway. Mechanistically, NEIL3 is rapidly recruited to the DSB sites through its GRF-zinc finger motifs, and the recruitment is independent of the glycosylase domain. NEIL3 physically interacts with the DSB resection machinery, including CtIP and the MRE11-RAD50-NBS1 (MRN) complex. NEIL3 is necessary for the stability of CtIP and the chromatin recruitment of CtIP and MRN at DSBs. Accordingly, depletion of NEIL3 decreases DSB end resection, compromises HR repair, and causes PARP inhibitor sensitivity in cells. Taken together, our results demonstrate that NEIL3 functions in ICL repair at two distinct steps. It participates not

only in the upstream unhooking of an ICL crosslink but also in the repair of DSBs generated by the FA/BRCA pathway.

STXBP1 新发无义突变导致的早发性癫痫性脑病

索桂海[1,2] 曹幸[1] 郑玉芹[1] 李海英[1] 张琦[3] 汤继宏[2] 吴尤佳[1]
1.南通大学附属医院
2.苏州大学附属儿童医院
3.南通大学

STXBP1 突变与多种神经发育性疾病相关，包括早发性癫痫性脑病。在一名生后 17 天诊断为早发性癫痫性脑病的婴儿中发现了 *STXBP1 的一种新的无义突变* c. 863G>A, p. W288X，脑电图 (EEG) 显示尖波和尖峰，而脑部 MRI 正常。为了进一步了解 W288X 突变在癫痫发生中的机制，我们通过过表达 *STXBP1(W288X)*突变体建立斑马鱼早发性癫痫性脑病模型，并研究其行为变化。此外，在斑马鱼模型中筛选有效的抗癫痫药物。斑马鱼 *STXBP1* 同源基因高度保守，在斑马鱼幼鱼大脑中显著表达。与野生型对照相比，Tg(hSTXBP1W288X)斑马鱼幼鱼表现出亢奋。在斑马鱼发育过程（1 ~ 5 dpf）中，STXBP1 的表达逐渐减少。斑马鱼突变体幼鱼中可见自发癫痫发作和 c-fos 表达增加。Tg(hSTXBP1W288X) 斑马鱼对 PTZ 的敏感性也显著增加。左乙拉西坦(LEV)、氯硝西泮(CZP)和托吡酯(TPM)对 Tg(hSTXBP1W288X)突变体幼鱼均有不同程度的抗癫痫作用。我们在新建立的斑马鱼突变系中的发现表明，斑马鱼重现了与人类 *STXBP1* 突变相关的临床表型，这为癫痫研究提供了合适的体内模型。

基于核心家系的全基因组拷贝数变异研究揭示汉族人群的多个精神分裂症风险新位点

怀聪[1] 吴茜[1] 沈陆[1] 李沫[1] 杨超[1] 张娟[1] 陈鸾[1] 朱文礼[2] 樊凌姿[3] 周伟[1] 邢清和[4] 贺林[1] 万春玲[1] 秦胜营[1]
1.上海交通大学
2.芜湖市第四人民医院
3.驻马店市精神病院
4.复旦大学

研究目的 精神分裂症（schizophrenia，SCZ）是一种严重的神经精神疾病，影响全球约 1%的人群，我国也有超过 1000 万的精神分裂症患病人口。遗传学研究表明，拷贝数变异（Copy，number variations, CNVs）在精神分裂症的发生发展过程中起着关键作用，然而尚未有基于家系的中国人群全基因组易感 CNV 研究，因此本研究拟通过家系分析的方法寻找与中国汉族人群相关的 CNV。

研究方法 本研究入组了 100 个中国汉族精神分裂症核心家系（含患有 SCZ 的子女及其父母的三口之家），使用 Agilent 1×1M SurePrint G3 aCGH microarray 高密度芯片开展了全基因组 CNV 检测和分析。

结果与结论 CNV 负担测试表明，与健康父母和无亲缘关系的健康对照者相比，SCZ 先证者们（家系中的患病子女）携带更多的染色体重复突变，特别是新发（*de novo*）的长、罕见 CNV 突变。通过传递不平衡检验分析，我们也发现了 4 个存在显著传递不平衡的新区段，即 3p22.2 重复、7p13 重复的低传递及 11p15.1 缺失、12p13.2 缺失的高传递。新发突变分析也富集出了一个位于 6p12.1 的高频的 CNV 缺失突变。即上述五个 CNV 区段为新发现的中国人群相关 SCZ 易感区段。此外，基于 PsychENCODE 数据库中 11 688 个样本的共表达网络分析，我们发现上述 CNV 中，*CTDSPL* 和 *MGAM* 基因在表达水平上表现出显著的 SCZ 相关性。我们的发现支持 CNVs 在 SCZ 病因中的关键作用，并为 SCZ 发病机制的潜在机制提供了新的见解。

唐氏综合症的非编码 RNA 网络构建和潜在调控轴分析

赵慧茹 廖世秀
河南省人民医院

目的 越来越多的证据表明长链非编码 RNA (lncRNAs)和环状 RNA (circRNAs)在唐氏综合症胚胎期神经系统发育中发挥重要作用。然而，这种机制在很大程度上仍是未知的。
方法 为了探索 lncRNA 和 circRNA 在唐氏综合症胚胎期神经系统发育中的表达及其生物学功能，我们使用高通量测序的方法对 5 例孕中期流产胎儿的大脑海马组织进行了 lncRNA/circRNA 和 mRNA 表达谱的研究。通过 GO 和 KEGG 途径富集分析，确定显著失调基因的主要功能。利用生物信息学方法构建了包括编码-非编码共表达(CNC)、内源性竞争 RNA (ceRNA)、Protein-Protein-Interaction(PPI)在内的相关表达网络。通过实时荧光定量 PCR 对样本中显著异常的 lncRNA 和 mRNA 进行验证。
结果 数千个显著变化的 lncRNA 和 mRNA 以及数百个 circRNA 被鉴定出来。通过实时荧光定量 PCR 对样本中 5 个异常 lncRNA 和 4 个 mRNA 检测。富集分析显示 basal cell carcinoma, wnt signaling pathway, focal adhesion 在唐氏综合症胚胎期神经系统的进展中起重要作用。CeRNA network 推测出 lincRNA C21orf62 和 circRNA Has_circ_0002485 可与 miRNA-730-5p 竞争性结合，增加靶基因 PPP1R17 和 SENP3-EIF4A1 的表达。此外，蛋白质相互作用网络表明 ERBB2 和 PENK 参与唐氏综合症胚胎期神经系统的进展。
结论 综上所述，这些结果提示 lncRNA 和 circRNA 可能参与唐氏综合症胚胎期神经系统的发病和发展。我们的发现为 lncRNA 和 circRNA 的研究提供了一个新的视角，为 lncRNA 和 circRNA 在唐氏综合症中的潜在作用进一步研究奠定了基础。

维甲酸相关孤儿受体 α（Rorα）低表达促进紫外线诱导的皮肤鳞状细胞癌进展

张国龙[1] 严国荣[1] 伏智亮[2] 吴煜昊[1] 刘业强[1] 王秀丽[1] 朱嗣博[2]
1.同济大学附属皮肤病医院
2.复旦大学生命科学学院

目的 针对皮肤鳞状细胞癌（cSCC）关键发病机制不明的现状，本研究旨在为进一步探索 cSCC 发病机制提供更加可靠的实验依据，并最终为 cSCC 的早期诊断和有效防治提供更加精准的新靶点。
方法 建立紫外线诱导的 SKH-1 无毛小鼠原发 cSCC 模型后，收集 4 只经病理诊断为正常皮肤（NS）、光线性角化病（AK）和 cSCC 的小鼠背部皮肤组织及 4 只未照光小鼠的正常皮肤组织进行转录组测序。原始数据下机后，利用 StringTie 构建表达矩阵，使用 R 语言进行皮尔逊相关系数的计算、层次聚类分析及差异基因的鉴定。同时，对基因表达矩阵进行基因集变异分析、拟时分析、免疫微环境的推断及共表达调控网络等分析。基于前期分析结果，收集临床标本分别进行 Q-PCR 和免疫组化染色验证人 cSCC 组织中 Rorα 的表达；构建 Rorα 基因的 SiRNA 干扰质粒，转染人源皮肤鳞癌细胞系 A431、HaCaT 细胞系和小鼠鳞癌细胞系 PECA，同步 Rorα 激动剂 SR1078 作对照，CCK8 检测细胞凋亡、划痕实验检测有效干预后细胞迁移能力的变化；最后通过应用 Rorα 激动剂 SR1078 进行小鼠在体实验，验证 Rorα 功能的改变对 cSCC 小鼠种植瘤的成瘤影响。
结果 基因表达结果显示 AK 与 NS 组织类似，cSCC 与 NS、AK 显著不同。在 AK *vs.*NS，cSCC *vs.*NS 和 cSCC *vs.*AK 中，分别鉴定了 2,022、2,031 和 1,617 个差异表达基因。S100 家族、Sprr 家族、Cxcl 家族、Ccl 家族、Mmp 家族成员等基因在 cSCC 中均显著上调。GSVA 分析显示 AK 中 $CD4^+/CD25^+T$ 增殖信号，IFN-α，IFN-β 等信号显著上调；在 cSCC *vs.*NS 中，VEGF 受体信号传导，肥大细胞趋化性，对缺氧的反应，巨核细胞分化和 T 细胞凋亡途径显著上调。Rorα 在 cSCC 中显著低表达，且其低表达与患者生存率呈负相关；共表达网络分析揭示 Rorα 调控多个与 cSCC 相关基因如 S100 家族和 SPRR 家族，暗示其可能是调控 cSCC 进展的关键基因。

体外细胞实验证实 Rorα 可以抑制肿瘤细胞的增殖、迁移；体内动物实验证实 Rorα 激活可以抑制肿瘤生长。
结论 Rorα 可作为抑癌基因，其激活可显著抑制肿瘤生长，或将成为 cSCC 治疗的潜在靶点。

fnPheno: classifying the human disease phenotypes based on their molecular function

Jinmeng Jia Tieliu Shi
East China Normal University

Connecting disease-related phenotypes to their underlying molecular mechanisms is crucial for a better understanding of complex human diseases. The Human Phenotype Ontology (HPO) is widely used in classifying and modeling clinical features. However, HPO clusters phenotypes by their semantic similarities, which is hard to explore the underlying functional mechanisms among them. Here, we present fnPheno, a tool for quantifying the similarities of disease phenotypes and exploring the correlations among them at the molecular level. fnPheno classifies phenotypes based on their enriched GO terms and offers a flexible classification of disease phenotypes that considers their molecular underpinnings. We analyzed the relationships among 2922 phenotypes from HPO using fnPheno and found that phenotypes with higher similarity score tend to occur in the same disease and may highly co-morbid in one patient. We demonstrate that fnPheno identifies phenotype clusters sharing the similar underlying mechanism, which will further help investigating the molecular pathogenesis for human diseases.

scCODE: a platform for personalized differentially expressed gene identification for single-cell data

Jiawei Zou[1] Jie Hao[2]
1.Shanghai JiaoTong University
2.Institute of Clinical Science, Zhongshan Hospital, Fudan University

Purpose Differentially expressed (DE) gene detection in single-cell RNA-seq data is a key step to understand the biological problem. DE methods together with filtering genes have profound impact on the DE results. Different scRNA-seq datasets require personalized analysis strategy for DE gene detection. Although there exist some platforms to evaluate different DE methods, the influence of gene filtering was not considered, furthermore, there is still lack of evaluation for optimal analysis strategy for the specific experimental dataset. Here, taking both gene filtering methods and DE methods into consideration, we propose scCODE (Consensus Optimization of Differentially Expressed gene detection for single cell) to optimize the DE gene identification performances on scRNA-seq data. To achieve it, we propose two new metrics, which for the first time can provide subjective evaluation of different methods without a priori knowledge of the dataset studied.
Methods In this article, we first produced a systematic evaluation of various combinations of methods based on the metrics used in conquer[1]. The DE detection of each data was resulted through two steps. Step 1, each data was first processed by 3 different gene filtering methods. Step 2, DE gene detection by DE methods. Then we applied multiple DE methods on the data filtered and the origin data (without filtering). The DE results were compared in the metrics exhibited. After the evaluation, we proposed two novel metrics AUCC and COD to evaluate the performance of DE gene detection of scRNA-seq data without a prior knowledge of true DE genes. The platform scCODE provides with optimal analytical strategy based on AUCC and CDO.
Results We exhibit the results from the aspects of FPR, FDP, SNR and AUROC. Without considering the influence of gene filtering, we got results in agreement with previous reasearches[1,2]. Even though, the performances with gene filtering methods are divergent, and the improvement it brings is significant. Gene filtering methods do help DE gene identification in all

aspects. OGFSC seems to help detect less false positive genes, while conquer and scmap could improve the sensitivity and AUROC significantly.
We verified our metrics on multiple simulated datasets, and a significant correlation between our metrics and the reference-AUROC value was found. The new metrics are closely correlated with the true performance of different methods, and we have shown that they are able to provide a personalized evaluation on individual experimental dataset. Furthermore, we present a platform scCODE based on these metrics. scCODE is able to provide personalized suggestion of which method is appropriate for the scRNA-seq dataset. It was tested on an experimental dataset, and the DE results of the combinations recommended by scCODE fits better with experimental design and biological explanation.
Conclusion 1. The performance of DE gene identification depends on both gene filtering and DE processing. 2. Personalized analytical strategy is needed for DE gene identification, but existing tools and metrics are not suit for scRNA-seq data without true DE genes known. 3. We evaluate the performance of various combinations of gene filtering methods and DE methods. 4. We propose two novel metrics applicable on real data, and provide a platform scCODE for optimizing DE gene detection of scRNA-seq dataset. 5. The two novel metrics are significantly correlated with AUROC value, and the DE results from the strategy suggested by scCODE best match the test experimental data.
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穿心莲内酯通过 Nrf2 信号通路保护骨髓间充质干细胞抵抗缺氧条件下葡萄糖和血清剥夺诱导的细胞损伤

孙艳婷 朱静
重庆医科大学附属儿童医院儿科研究所

背景 骨髓间充质干细胞（BMSCs）是重要的细胞治疗手段，在再生医学领域中起到重要作用，但是很多疾病的损伤部位存在血流减少（营养耗竭）以及缺氧等不良微环境使得移植后的 BMSCs 处于氧化应激状态下而存活率低下，这限制了 BMSCs 的应用，因此，提高不良微环境中 BMSCs 的抗氧化应激能力是提高 BMSCs 再生治疗效果的关键。越来越多的证据表明穿心莲内酯（Andr）具有抗氧化、抗炎、抗肿瘤等多种药理活性,但它对 BMSCs 的影响尚未得到验证。
目的 揭示低氧（1%O_2）、低糖及血清剥夺(GSDH)致 BMSCs 细胞损伤的机制，探讨穿心莲内酯对损伤微环境中 BMSCs 的保护作用以提高其应用价值。
方法 为探讨 Andr 对不良微环境中 BMSCs 的作用及其分子机制，在体外通过低氧（1%O_2）、低糖及血清剥夺(GSDH)的方式建立 BMSCs 细胞损伤模型。采用 MTT、结晶紫染色以及流式细胞术检测细胞周期分析 Andr 对 BMSCs 增殖的影响，通过 DCFH-DA 染色评估 ROS 水平，QPCR 和 WB 检测抗氧化应激相关基因及蛋白变化，采用 JC-1 法测定线粒体膜电位(ΔΨm)，Annexin V-FITC/PI 检测试剂盒检测细胞凋亡，通过激光共聚焦显微镜分析线粒体形态、数量以及钙离子数目的改变，QPCR 检测糖酵解、磷酸戊糖途径以及三羧酸循环中关键酶的表达，并检测 ATP 产能改变。WB 进一步检测 AKT 通路、STAT3 通路及 NRF2 通路中蛋白表达的影响。
结果 我们利用 GSDH 成功诱导体外 BMSCs 细胞损伤，在此模型基础上验证穿心莲内酯对 BMSCs 的保护作用。研究发现，Andr 对 GSDH 条件下的 BMSCs 具有促增殖、抵抗凋亡及氧化应激保护作用，同时我们发现线粒体膜电位(ΔΨm)有所增加，在这一过程中 BMSCs 线粒体形态、数量以及合成 ATP 功能均有增加，此外，我们发现 BMSCs 的代谢方式由糖酵解转向为产能更多的氧化磷酸化。Andr 显著增加核内核因子 E2 相关因子(NRF2)信号通路中 NRF2、HO-1、NQO-1 的蛋白表达，而 AKT 通路以及 STAT3 通路中相关蛋白表达没有变化，这些数据强烈表明了 NRF2 通路的参与。此外，我们的结果提示加入 NRF2 通路特异性抑制剂 ML385 可阻断 NRF2 表达和 Andr 的抗凋亡和抗氧化应激保护作用。

结论 Andr 改善 GSDH 诱导的 BMSCs 细胞凋亡及氧化应激损伤，同时将 BMSCs 代谢方式由糖酵解转为氧化磷酸化以合成更多的 ATP 供细胞生命活动，并提示 NRF2 信号通路在这一过程中起重要作用。我们的研究结果表明 Andr 是提高 BMSCs 细胞治疗效果的一种有前景的候选药物，为间充质干细胞细胞疗法提供了实验依据。

ERLIN2 基因杂合变异导致常显遗传性痉挛性截瘫的新机制

朱芯潼 戴礼猛 李嘉 谭小音 白云 郭洪
陆军军医大学

目的 遗传性痉挛性截瘫（Hereditary Spastic Paraplegia，HSP）又称家族性痉挛性截瘫，是一种神经系统退行性变性疾病，具有显著的临床和遗传异质性。本项目拟对一个常显遗传性痉挛性截瘫家系进行分子遗传学研究，以明确其发病原因与致病机制。
方法 通过临床特征分析和辅助检查明确家系患者的临床诊断，通过全外显子组测序（WES）对该家系中的患者与正常对照进行测序分析以明确致病基因及其变异，通过诱导重编程技术获得家系患者与正常对照的 iPS 细胞系，并进行定向诱导神经分化和转录组测序（RNASeq）。
结果 家系患者发病年龄在 10-35 岁之间，表现为单纯型痉挛性截瘫，主要为双下肢进行性萎缩、肌力下降、肌张力增强，呈钢管样强直，伴不自主震颤，独立行走不能，查体腱反射亢进，病理征阳性，无感觉障碍，WES 未检测到已知神经肌肉病相关基因存在致病性变异。结合 iPS 来源的 RNASeq 结果，发现 *ERLIN2* 基因的杂合变异 c.212T>C（p.V71A）与家系患者的疾病表型共分离，且生物信息学预测其具有致病性。iPS 来源的神经干细胞分析也显示，患者细胞因影响 Cyclin B1/Cdk 1 复合物的稳定性而表现出明显的细胞周期阻滞和增殖能力降低；同时，iPS 来源的运动神经元细胞分析显示，患者细胞中存在钙超载而导致其功能损害。
结论 既往研究已报道 *ERLIN2* 基因的双等位变异会导致常隐遗传性 HSP18，但本研究在一例 HSP 家系中首次明确了其存在杂合变异致病的机制，进一步丰富了 *ERLIN2* 基因变异通过功能获得导致 HSP 的新机制，研究结果有利于 HSP 的基因诊断和防治手段的研究。

A missense mutation in Pitx2 leads to early-onset glaucoma via NRF2-YAP1 axis

Xianjun Zhu Yeming Yang
Sichuan Provincial People's Hospital

Purpose Glaucoma is a leading cause of blindness, affecting 70 million people worldwide. Due to the similarity in anatomy and physiology between human and mouse eyes and the ability to genetically manipulate mice, mouse models are an invaluable resource for studying mechanisms underlying disease phenotypes and for developing therapeutic strategies. Here, we report the discovery of a new mouse model of early-onset glaucoma that bears a transversion substitution c. G344T, which results in a missense mutation, p. R115L in PITX2.
Method Intraocular pressure (IOP) was measured and death of retinal ganglion cells (RGC) was analyzed. Oxidative stress was assessed using retinal extract of Pitx2 mutant mice. Transcriptional analysis was performed to evaluate dowdstream target genes affected in mutant retina. Rescue experiment was performed by treatment with N-Acetyl-L-cysteine for neuroprotective effect.
Results The mutation causes an elevation in intraocular pressure (IOP) and progressive death of retinal ganglion cells (RGC). These ocular phenotypes recapitulate features of pathologies observed in human glaucoma. Increased oxidative stress was evident in the inner retina. We demonstrate that the mutant PITX2 protein was not capable of binding to Nuclear factor-like 2 (NRF2), which regulates *Pitx2* expression and nuclear localization, and to YAP1, which is necessary for co-initiation of transcription of downstream targets. PITX2-mediated transcription of several antioxidant genes were also impaired. Treatment with N-Acetyl-L-cysteine exerted a

profound neuroprotective effect on glaucoma associated neuropathies, presumably through inhibition of oxidative stress.
Conclusion Our study demonstrates an essential role of PITX2 in glaucoma optic pathogenesis and provides a novel early-onset glaucoma model to enable further elucidation of mechanisms underlying the disease as well as a resource to test new therapeutic strategies.

Single-cell transcriptomics reveals dysfunction of maternal engrafted T, NKT, and NK cells in human X-linked severe combined immunodeficiency

Xia Wu[1] Wei Dong[1] Wenyan Li[2] Xian Zeng[1] Huifeng Fan[2] Gen Lu[2] Zhonghui Tang[1]
1. Zhongshan School of Medicine, Sun Yat-sen University
2.Department of Respiratory Infection, Guangzhou Women and Children's Medical Center

Objective Maternal engraftment is frequently present in human X-linked severe combined immunodeficiency (X-SCID) caused by pathogenic mutations in *IL2GR*. However, the functional status of the engrafted maternal cells remains unclear due to the difficulty of separating maternal cells from the autologous ones. This study aims to discriminate and characterize the maternal and autologous lymphocyte cells with single-cell resolution, respectively, in the X-SCID patient.
Methods Single-cell RNA-seq was performed with bone marrow mononuclear cells (BMMCs) from an X-SCID patient. Maternal and autologous cells were distinguished using a novel bioinformatics analysis strategy, and the gene expression profiles of those cells were characterized in comparison with healthy donors.
Results Maternal cells were discriminated from autologous ones in the BMMCs derived from an X-SCID patient, which primarily consisted of T, NKT, and NK cells. The patient also harboured these cell types of autologous origin. The maternal T, NKT, and NK cells exhibited a similar cell status to their autologous counterparts. When compared with healthy donors, this X-SCID patient dramatically decreased the expression of transcription factors (*FOS*, *JUN*, *MYC*, *TCF7*, and *LEF1*) related to lymphocyte activation, proliferation, and differentiation, but increased the transcription of genes involving antigen presentation, inflammatory and type I interferon responses in T, NKT, and NK cells. Notably, the expression levels of multiple inhibitory factors (*LAG3*, *CTLA4*, and *HACVR2*) were substantially enhanced in T, NKT, and NK cells irrespective of their originations.
Conclusion Both the maternal and autologous T, NKT, and NK cells in the X-SCID patient were at an exhausted-like dysfunction status.

m6A Demethylase FTO Improves Cardiac Function via Regulating Glucose Uptake and Glycolysis in Mice with Pressure Overload-induced Heart Failure

Zhang Beijian Yun Cai Wei Luo Tingwen Gao Aijun Sun Junbo Ge
Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China

Background N^6-Methyladenosine (m6A) is the most common internal post-transcriptional modification of mammalian mRNA and plays critical roles in multiple biological processes and many diseases. However, the role of m6A in heart failure (HF), especially in cardiac energy metabolism, remains elusive. Here, we explored the role of fat mass and obesity-associated protein (FTO), a m6A demethylase, in cardiac glucose metabolism in pressure overload-induced HF.
Methods To test the function and related mechanism of m6A and FTO in HF, preclinical mouse model of pressure overload (TAC) and isolated adult mouse cardiomyocytes (CMs) were used. And Gene Expression Omnibus (GEO) data set (GDS2206) was used to determine the differently expressed FTO in non-failing hearts and patients with HF. m6A RNA immunoprecipitation

sequencing (MeRIP-seq) was also performed to map transcriptome-wide m6A modification. Expression of FTO was modulated using AAV9 (*in vivo*) and adenovirus (*in vitro*) to study its role in regulating CM's m6A, heart function, glucose uptake, ATP production and glycolysis. MeRIP-qPCR was used to identify the target of FTO.
Results The global level of m6A was increased and FTO was decreased in TAC mice. Knockdown of FTO enhanced cardiac hypertrophy, aggravated cardiac dysfunction, reduced glucose uptake, ATP production and glycolysis, and overexpression of FTO could rescued these phenotypes both *in vitro* and *in vivo*. Mechanically, FTO controlled glucose glycolysis by regulating the m6A modification of glycolysis-related gene *phosphoglycerate mutase 2* (*Pgam2)* and its mRNA stability and protein level. Moreover, FTO regulated cardiac glucose uptake through FTO-Akt-GLUT4 axis. Forced expression of FTO by AAV9 delayed the development of HF.
Conclusions FTO improves heart function by promoting glycolysis through up-regulating Pgam2 in a m6A-dependent manner and improving glucose uptake by activating FTO-Akt-GLUT4 axis in HF. Our study results demonstrate that FTO or FTO mimic could be used as a potential therapeutic agent in pressure overload-induced HF.

Pink1 介导的线粒体动力学在 hiPSCs 衍生心肌细胞成熟过程中的作用

刘蕙文
重庆医科大学附属儿童医院

目的 探讨 Pink1 介导的线粒体动力学在人诱导多能干细胞（hiPSCs）衍生心肌细胞（hiPSC-CMs）成熟过程中的作用。
方法 时序性调控 Wnt 信号使 hiPSCs 分化为 hiPSC-CMs，在分化 D28 采用 siPink1 处理，6h 后换液，并持续培养 48h；免疫荧光和 Western Blot 检测 hiPSCs 中干性因子和 hiPSC-CMs 心肌标志物的表达；Mitotracker 染色与 Lysotracker 染色检测 siPink1 后线粒体形态以及线粒体自噬程度；Western Blot 和 RT-qPCR 检测 siPink1 后 Pink1、线粒体融合分裂、生物发生、能量代谢和心肌标志物的表达；提取全细胞 DNA 检测线粒体 DNA 拷贝数；JC-1 检测线粒体膜电位；ATP 提取试剂盒检测 ATP 含量；DCF 检测细胞内活性氧；EDU 检测细胞增殖。
结果 hiPSCs 表达干性标志物 NANOG、SOX2、OCT4；hiPSC-CMs 表达心肌标志物 α-Actinin、cTnI、CX43；siPink1 48h 后 Pink1 的表达降低，线粒体碎裂程度增加，线粒体自噬以及线粒体生物发生受阻；JC-1 结果显示 siPink1 后线粒体膜电位显著降低，细胞内 ATP 含量减少，能量代谢相关基因表达降低；DCF 结果显示 siPink1 未引起 hiPSC-CMs 的氧化应激；siPink1 使 hiPSC-CMs 细胞面积以及周长减小、肌节缩短、形态趋近圆形，且心肌标志物表达降低；EDU 结果显示 siPink1 细胞增殖率增加。
结论 hiPSC-CMs 成熟过程中，敲低 Pink1 抑制线粒体融合、线粒体自噬和生物发生，并降低线粒体膜电位从而抑制线粒体功能，线粒体功能不全导致 hiPSC-CMs 结构功能受损。

CircINSR 对胰岛 β 细胞增殖的作用及其机制探讨

庄景燊 贾世奇
暨南大学附属第一医院

目的 验证胰岛素受体（Insulin receptor, INSR）形成的 circRNA（circINSR）在胰岛 β 细胞中的表达、功能及相关分子机制。
方法 通过 FISH，PCR 和 qPCR 检测 circINSR 在胰岛 β 细胞的表达及其丰度。细胞增殖曲线、CCK-8、Ki_67 染色和 EdU 染色检测细胞增殖变化。RNA pull down、Western blot 等分子生物学手段检测 circINSR 促进 β 细胞增殖的机制。

结果 1.CircINSR 在胰岛 β 细胞系中表达。Snager 测序检测“背对背”扩增出来的条带可见序列与已报道接口序列一致。FISH 检测 circINSR 在 β 细胞细胞质中表达。2.过表达 circINSR 可以促进胰岛 β 细胞增殖，敲低 circINSR 可以抑制胰岛 β 细胞增殖。过表达 circINSR 可以促进胰岛 β 细胞增殖曲线右移，Ki_67 阳性细胞和 EdU 阳性细胞比例增加。敲低可见相反的效应。3.过表达 circINSR 后转录组测序，对差异基因进行 KEGG 信号通路富集可见 PI3K/AKT 被富集。WB 结果进一步证实 CircINSR 促进下游的 PI3K 表达，激活 PI3K 同时诱导了 AKT 和 mToR 磷酸化增加，这两条通路同时激活了细胞周期蛋白 Cycling D1 表达。

结论 INSR 形成的 circRNA 通过激活 INSR 信号通路促进胰岛 β 细胞增殖，调控胰岛 β 细胞中 circINSR 表达水平可以精确操纵 β 细胞增殖率。

Prevention of acquired sensorineural hearing loss in mice by in vivo Htra2 gene editing

Xi Gu[1,2] Daqi Wang[1] Zhijiao Xu[1] Jinghan Wang[1] Luo Guo[1] Renjie Chai[3] Genglin Li[1] Yilai Shu[1] Huawei Li[1]
1.Eye & ENT Hospital, Fudan University, Shanghai
2.the First Affiliated Hospital of Fujian Medical University, Fuzhou
3.Southeast University, Nanjing

objective Aging, noise, infection, and ototoxic drugs are the major causes of human acquired sensorineural hearing loss, but treatment options are limited. CRISPR/Cas9 technology has tremendous potential to become a new therapeutic modality for acquired non-inherited sensorineural hearing loss. This study was designed to investigate the possibility of preventing ototoxic deafness, one of the most common types of acquired non-inherited sensorineural hearing loss, via disrupting an apoptosis-related gene with CRISPR/Cas9 technology.
Methods We selected *Htra2* as the target gene and developed two CRISPR/Cas9 systems, SpCas9 and SaCas9. The indel frequency of each gRNA for SpCas9 or SaCas9 system was measured in HEI-OC1 cells by high-throughput sequencing (HTS). AAV2/Anc80L65 was used to deliver CRISPR/Cas9 systems *in vitro* and *in vivo*. To identify whether disrupting the *Htra2* gene could protect cochlear hair cells against neomycin-induced ototoxicity, we performed the *in vitro* experiment in the cochlear explants firstly, measuring the hair cell survival and apoptosis by immunohistochemistry and confocal microscopy. The AAV-CRISPR/Cas9 systems were injected into the inner ear of wild type mice at P1, and the editing efficiency *in vivo* was evaluated by HTS. The protective effect *in vivo* was evaluated using immunohistochemical analysis and measurement of ABR thresholds, peak amplitudes, and latencies of ABR wave 1. Non-injected ears served as controls. Ears of both sides were randomly assigned to injected and non-injected groups, and wild type mice were randomized into neomycin-treated and neomycin-untreated experiments without regard to gender.
Results The results indicate that adeno-associated virus (AAV)-mediated delivery of CRISPR/SpCas9 system ameliorates neomycin-induced apoptosis, promotes hair cell survival, and significantly improves hearing function in neomycin-treated mice. The protective effect of the AAV–CRISPR/Cas9 system *in vivo* is sustained up to 8 weeks after neomycin exposure. For more efficient delivery of the whole CRISPR/Cas9 system, we also explore the AAV–CRISPR/SaCas9 system to prevent neomycin-induced deafness. The *in vivo* editing efficiency of the SaCas9 system is 1.73% on average. We observed significant improvement in auditory brainstem response thresholds in the injected ears compared with the non-injected ears. At 4 weeks after neomycin exposure, the protective effect of the AAV–CRISPR/SaCas9 system is still obvious, with the improvement in auditory brainstem response threshold up to 50 dB at 8 kHz.
Conclusion These findings demonstrate the safe and effective prevention of aminoglycoside-induced deafness via *Htra2* gene editing and support further development of the CRISPR/Cas9 technology in the treatment of non-inherited hearing loss as well as other non-inherited diseases.

妊高症胎盘中的 RNA 编辑

杨小雪[1] 杨静[1] 梁小珍[1] 杨新平[1,2,3]
1.南方医科大学南方医院，妇产科，遗传发育系统生物学研究中心
2.南方医科大学，教育部精神卫生重点实验室
3.南方医科大学，基础医学院，生物信息学系

目的 RNA 编辑是一种仅发生在 RNA 水平的碱基改变现象，主要包括腺嘌呤-次黄嘌呤（A-I）编辑和胞嘧啶-尿嘧啶（C-U）编辑。现有研究已证实 RNA 编辑参与神经退行性疾病、癌症、心血管疾病等多种疾病的发病过程。胎盘滋养细胞某些特征与癌细胞高度相似，鉴于 RNA 编辑现象参与癌症发生的多种调控过程，我们好奇胎盘源性疾病的发病中是否也存在 RNA 编辑的作用。妊高症作为一种胎盘源性疾病，对其中的 RNA 编辑现象研究较少，故进行妊高症胎盘中 RNA 编辑事件研究可为妊高症发病机制探索提供新思路。
方法 我们收集了 9 个妊高症病人和 32 个正常对照胎盘，进行转录组测序后结合生物信息学分析手段，筛选出胎盘中与妊高症发病可能相关的 RNA 编辑事件及相关生物学功能及机制；挑选具有代表性的 RNA 编辑事件，进一步通过 qPCR、过表达及荧光素酶报告体系在 HTR-8 细胞系中进行验证。
结果 我们在 41 个胎盘样本中筛选得到 236569 个 RNA 编辑事件，其中绝大部分 RNA 编辑事件为 A-I 编辑，约 2/3 的 RNA 编辑事件发生在 Alu 转座子区域内，超过 15 万个 RNA 编辑事件发生在基因的内含子区域。在此基础上，我们对妊高症胎盘和正常胎盘中的 RNA 编辑效率进行统计学检验，挑选出 2920 个在两组胎盘中存在显著差异的 RNA 编辑事件。这些事件显著富集在子痫前期的候选基因或差异表达基因中，证明差异 RNA 编辑事件与妊高症发病存在潜在相关性。不同区域的 RNA 编辑事件可能通过参与不同的生物学过程影响妊高症的发病。其中 *LEP* 基因的 3'UTR 区域中有两个差异 RNA 编辑位点位于 *miR-9-5p* 的靶向结合区域，这两个位点发生的编辑事件可影响 m*iR-9-5p* 与 *LEP* 的结合，降低其对 *LEP* 表达的抑制作用，最终引起 *LEP* 表达上升。
结论 本研究证明胎盘中的异常 RNA 编辑事件与妊高症发病存在相关性，并为后续研究提供了可靠的数据集。

Scorpion venom inhibits the voltage-gated proton channel using a Zn2+-like long-range conformational coupling mechanism

jiahui xu[1] Zhonghua Liu[2]
1.南方医科大学南方医院
2.生命科学学院

Blocking the voltage-gated proton channel HV1 is a promising strategy for the treatment of diseases like ischaemia stroke and cancer. However, few HV1 channel antagonists have been reported. Here, we have identified a novel HV1 channel antagonist from scorpion venom and have elucidated its action mechanism. HV1 channels were heterologously expressed inmammalian cell lines and their currents recorded using whole-cell patch clamp. Sitedirected mutagenesis was used to generate mutants. Toxins were recombinantly produced in Escherichia coli. AGAP/W38F-HV1 interaction was modelled by molecular dynamics simulations。Our results indicate that scorpion toxin AGAP (anti-tumour analgesic peptide) potently inhibited HV1 currents. One AGAP mutant has reduced NaV channel activity but intact HV1 activity (AGAP/W38F). AGAP/W38F inhibited HV1 channel activation by trapping its S4 voltage sensor in a deactivated state and inhibited HV1 currents with less pH dependence than Zn2+. Mutation analysis showed that the binding pockets of AGAP/W38F and Zn2+ in HV1 channel partly overlapped (common sites are His140 and His193). The E153A mutation at the intracellular Coulombic network (ICN) in HV1 channel markedly reduced AGAP/W38F inhibition, as observed for Zn2+. Experimental data

and MD simulations suggested that AGAP/W38F inhibited HV1 channel using a Zn2+-like long-range conformational coupling mechanism.
Our results suggest that the Zn2+ binding pocket in HV1 channel might be a hotspot for modulators and valuable for designing HV1 channel ligands. Moreover, AGAP/W38F is a useful molecular probe to study HV1 channel and a lead compound for drug development.

neuroCNVscore：一种量化 ASD 中 CNV 致病性的组织特异性工具

刘玄石 李巍 张鹏 徐文剑 冷菲 郝婵娟
北京儿童医院

目的 孤独症谱系障碍（ASD）是一类具有遗传基础的致残性精神疾患，北京地区患病率为 1%。ASD 起病早，越早发现，预后效果越好。目前诊断基于观察量表打分，确诊时间偏晚，容易出现漏诊。基因检测作为遗传疾病的临床筛查和诊断方法已经得到广泛认可，但现有工具和模型多聚焦在点突变，较少涉及拷贝数变异。拷贝数变异（CNV）已被证明在 ASD 的遗传病因学中起着关键作用，它通过破坏基因、影响基因剂量或通过调节机制影响基因表达。由于 CNV 数量巨大，且其影响基因组的方式多种多样，因此系统鉴定与疾病相关的 CNV 及其生物学后果具有挑战性。
方法 为了评估 CNVs 在 ASD 中的致病作用，我们以神经发育类疾病的公开 CNV 作为输入数据,通过整合基因组序列、基因和功能/基因组分割三个层面的综合特征（N=189），开发了监督学习模型 neuroCNVscore。
结果 NeuroCNVscore 模型在这些特征上实现了高预测性能（AUC=0.85）。NeuroCNVscore 在 ClinVar 和 GnomAD 的独立数据集以及现有的参考方法中表现出色。
结论 因此，NeuroCNVscore 可作为 ASD 中 CNV 致病性打分的重要工具，以支持临床诊断和破译 ASD 的发病机制。

SNAG 结构域对胰腺内分泌细胞分化的调节作用及机制研究

毛亚辉 贾世奇
暨南大学附属第一医院

目的 探究胰岛素瘤相关蛋白 1（Insm1）的 SNAG 结构域在胰腺内分泌细胞分化调节中的特异性功能和相关机制。
方法 以 Insm1 全突变以及 SNAG 突变和对照胚胎小鼠作为研究对象，通过免疫荧光、基因表达分析（RT-qRCR，RNAseq）、co-IP 以及 ChIP-PCR 方法,对 SNAG 结构域特异性功能及其机制进行研究。
结果 与对照小鼠相比，Insm1SNAG 突变体中的 δ 细胞数量增加，但 Insm1 全突变体中的 δ 细胞数量没有增加。与 Insm1 全突变体相比，Insm1delSNAG 突变体中 β 细胞数量的减少程度较低。此外，在 Insm1delSNAG 突变体和 Insm1 全突变体的 α、PP 和 ε-细胞中也观察到类似的缺陷。我们证实了 Insm1SNAG 突变体 δ 细胞数量的增加是由于 β 细胞转分化为 δ 细胞所致。在机制上，SNAG 结构域与 Lsd1 相互作用，Lsd1 是 H3K4me1/2 的去甲基化酶。SNAG 结构域的突变导致 Lsd1 的募集受损，并且在与 Insm1 结合的造血表达同源框（Hhex）基因座上 H3K4me1/2 水平增加，从而促进了 δ 细胞特异性基因 Hhex 的转录活性。
结论 SNAG 结构域调节胰腺内分泌细胞分化并抑制 β 细胞向 δ 细胞的转分化。

Genetic variants associated with response to antidepressant treatment in Han Chinese: a genome-wide association study

Chuyi Zhang Ming Li
Kunming Institute of Zoology

Rationale About two-thirds of patients with major depressive disorder (MDD) fail to achieve symptom remission after the initial antidepressant treatment, which is likely influenced by genetic variation. Though several genome-wide association studies (GWAS) of antidepressant efficacy were conducted in European population, the genetic basis of antidepressant response in Han Chinese individuals is not fully understood.
Objective The purpose of this study was to investigate the genetic variation contributing to inter-individual differences in antidepressant efficacy in Han Chinese population.
Methods and Results We performed a genome-wide association study of drug response in 636 MDD patients collected from the second Affiliated Hospital of Kunming Medical University with 2-week antidepressant treatment. The imputed common single nucleotide polymorphisms (SNPs) were tested for association with continuous and categorical outcome (response and remission) measurements after correcting for population stratification and other covariates. No individual association met the genome-wide significance threshold in each analyze. To further investigate the genetic architecture of antidepressant response, we explored whether polygenic risk scores (PRS) of drug response in other population and other traits could predict drug response in our sample. We found higher PRSs of good cognitive performance and two subtypes of neuroticism (loneliness and fed-up) were associated with better antidepressant efficacy whereas the PRSs of antidepressant response in European population were not able to predict drug response in Han Chinese.
Conclusions Although the findings reported here do not meet a genome-wide threshold for significance, our study firstly identified genetic regions possibly underlying antidepressant response in Han Chinese population which could be regarded as targets for following independent replication. The cross-trait PRS results indicate that there might exist share genetic roots between antidepressant response with cognitive performance and neuroticism. The cross-population PRS results of drug response might suggest considerable genetic heterogeneity in different ethnic groups.

MMP-9 介导的 NOTCH3 基因 R544C 点突变小鼠血脑屏障损伤机制研究

汤莹莹 蔡斌 康明霞 谢玮杰 范梦婷 胡芳炜 黄惠清
福建医科大学附属第一医院

目的 目前认为血脑屏障（blood brain barrier，BBB）损伤是影响脑小血管病发生和发展重要因素，如何防控 BBB 损伤也成为治疗的焦点。前期我们团队构建了 *NOTCH3* 基因 R544C 点突变模型鼠（R544C 小鼠），发现其 BBB 结构破坏，基质金属蛋白酶-9（Matrix metalloproteinase-9，MMP-9）表达增加。本研究探究 CADASIL 中 MMP-9 增多的作用及 BBB 破坏机制，以期为 CSVD 的发生机制提供新的理论依据，为治疗提供新的靶点。
方法 通过伊文思蓝渗漏实验检测伊文思蓝的渗出量及渗出部位，同时用 Western blot 和免疫荧光染色观察白蛋白的渗漏情况，反映血脑屏障通透性。Western blot 和免疫荧光染色观察 MMP-9 和 TIMP-1 表达情况及其细胞定位。利用 q-PCR 和 Western blot 检测 NF-κB、c-Jun 和 AKT 等信号通路指标。
结果 同 WT 小鼠相比，R544C 小鼠大脑和小脑的伊文思蓝渗漏量分别增加 96.11±33.83%（P<0.05）和 61.91±13.95%（P<0.001），白蛋白含量增加 30.13±9.26%（P<0.001）。R544C 小鼠皮层和海马 MMP-9 含量较 WT 小鼠增加，增多的 MMP-9 与神经元存在共定位，与星形胶质

细胞及小胶质细胞无共定位。R544C 小鼠的 TIMP-1 水平较 WT 小鼠降低 11.22±4.90%（P<0.05），MMP-9/TIMP-1 比值增加 50.45±22.25%（P<0.05）。R544C 小鼠 NF-κB（P65）mRNA 增加 52.72±19.29%（P<0.05）、c-Jun mRNA 增加 42.3 ± 17.94%（P<0.05），但免疫荧光未见 NF-κB（P65）入核，NF-κB、c-Jun 和 AKT 蛋白含量有减少趋势，均无统计学差异。
结论 R544C 小鼠 BBB 通透性增加，可能是神经元中 MMP-9 增加引起神经元损伤，通过神经血管单元，引起 BBB 通透性增加；也可能是 MMP-9/TIMP-1 表达失衡引起 BBB 破坏。R544C 小鼠中增多的 MMP-9 并非由 Notch3/NF-κB 和 Notch3 /AKT/c-Jun 信号通路调控。

Insm1 调控胸腺髓质上皮细胞关键转录因子和组织限制性抗原表达

魏怡秋
暨南大学附属第一医院华侨医院

目的 Aire 和 Fezf2 是迄今为止被鉴定的两个可以直接调控组织限制性抗原表达的基因。我们发现神经内分泌特异性因子 Insm1 在胸腺髓质细胞中与 Aire/Fezf2 共表达，因此，我们将探索 Insm1 在胸腺中枢免疫耐受调控中的作用和分子机制。
方法 我们拟采用 RNAseq、Western blot、qRT-PCR 等方法分析 Insm1 突变小鼠胸腺髓质基因表达改变；采用 ChIP、Co-IP 实验研究 Insm1 在转录水平调控 Aire、Fezf2 和组织限制性抗原基因表达的分子机制；采用胸腺移植裸鼠模型、条件性 Insm1 突变小鼠模型分析自身免疫反应表型，通过免疫组化和流式细胞分析技术分析 Insm1 突变胸腺中各细胞类型的比例。
结果 移植突变型胸腺裸鼠及条件性敲除小鼠胰岛、肝脏发生淋巴细胞浸润，免疫荧光染色显示突变小鼠中存在针对自身组织限制性抗原的抗体；qRT-PCR 结果显示 Insm1 突变小鼠髓质胸腺上皮细胞中 Aire、Fezf2 和多个依赖与不依赖 Aire/Fezf2 的组织限制性抗原基因表达水平降低。
结论 Insm1 直接调控组织限制性抗原基因的表达，Insm1 突变导致自身免疫耐受异常。

中国不同民族群体 KIR 及其 HLA 配体的多态性研究

边成 桑国鑫 黄小琴 王晓辉 孙浩 褚嘉祐 杨昭庆
中国医学科学院 北京协和医学院医学生物学研究所

目的 杀伤细胞免疫球蛋白样受体 (Killer cell immuoglobulin-like receptors, KIR) 及其配体人类白细胞抗原 (Human leukocyte antigen, HLA) 是具有丰富多态性的关键免疫系统基因, 在自身免疫疾病、感染性疾病及肿瘤相关疾病的生理过程中的作用有重要作用。我国不同地区、不同民族群体间 KIR 和 HLA 的等位基因多态性存在较大差异, 本研究旨在丰富和完善各民族群体 KIR 及其 HLA 配体多态性分型, 从地理及民族源流等方面探究 KIR 及其 HLA 受体多态性的进化特征, 并挖掘其受体配体关系。
方法 本研究基于中华民族永生细胞库遗传资源, 利用全外显子组测序 (Whole-exome sequencing, WES) 和序列特异引物 PCR (Sequence specific primer PCR, PCR-SSP) 的方法, 对云贵等 8 个地区的 18 个民族群体共计 1029 例样本进行了 KIR 和 HLA-I 类基因的等位基因分型, 并进行等位基因频率分布、进化关系及配体相关性等分析。
结果 在研究群体中共鉴定到了 123 种 KIR 基因型, 构建了各群体内 AB 两种 KIR 单倍型, 观察到不同民族群体中单倍型种类和频率的差异, 同时发现部分激活性 KIR 基因的频率要远小于抑制性 KIR 基因频率；鉴定到了大量在不同群体间存在频率分布差异的 KIR 和 HLA 等位基因, 其中, 云南地区的四个民族中鉴定到了 25 种 HLA-A 等位基因、52 种 HLA-B 等位基因、24 种 HLA-C 等位基因, 群体间高频等位基因种类及顺位均存在显著差异, 但 HLA 表位分布无统计学差异, 这表明云南西南地区 HLA 等位基因的多态性可能主要影响 HLA 配体与 KIR 受体结合的强度, 而对其结合的 KIR 受体种类无显著影响；在与既往国内外研究中的 20 个其他群体共同构建了 KIR 基因的进化关系后, 将其与民族源流和地理等因素进行了关联分析, 表明这些因素可能导致了免疫基因的多态；此外, 本研

究中的 4 个民族群体和既往研究报道的 10 个民族群体共 14 个民族群体的 KIR 和 HLA 携带者频率进行相关性分析时, 发现 2DL1 和 C2 之间出现显著的负相关。

结论 本研究探究了中国不同地区的多个民族 KIR 和 HLA 的分布特征, 进一步丰富了关键免疫系统基因的多态性数据, 揭示了免疫系统关键基因多态性可能与民族源流和疾病选择压力有关, 为进一步探究免疫基因及其配体的共进化特征、挖掘免疫基因多态性和疾病之间的关联等研究奠定了重要基础。

HDAC4 突变导致 Van der Woude 综合征中腭裂发生的作用机制研究

乌丹旦
上海交通大学医学院附属第九人民医院

唇腭裂是人类最常见的颅颌面出生缺陷，其发生率在所有先天缺陷畸形中居前三位。范德-伍德综合征（VWS）是最常见的一种综合征型唇腭裂，约占所有唇腭裂患者的 2%,发病率在 1/35000-1/100000 之间，已报告的致病基因有 IRF6 和 GRHL3，但仍有 25%的患者致病基因不明。我们发现一个 VWS 家系，4 代 20 人，共有 6 位患者（每代都有），全外显子测序发现所有 6 位患者的 HDAC4 基因的一个错义突变(p.Val831Met）。HDAC4 在骨骼发育中起重要作用，主要表达于增殖软骨细胞与前肥大软骨细胞，通过与组蛋白及其他转录因子相互作用调控软骨细胞增殖、分化、肥大化及软骨内骨化。但在颅颌面膜内成骨中的作用机制仍不明确。我们正通过构建 Hdac4 敲除/点突变小鼠模型和细胞实验研究 Hdac4 变异引起腭部发育缺陷的分子机制，为唇腭裂的防治提出新的分子靶标，为 VWS 的遗传诊断和分子机制提供新的依据。

AAV 介导的基因治疗 C1orf194 敲除导致的腓骨肌萎缩症模型鼠研究

沈宗锐[1] 黎美怡[1] 黄呈[1] 郑颖纯[1] 王志奎[1] 马顺飞[1] 郑卉（通讯）[2] 熊符[1]
1.南方医科大学基础医学院医学遗传学教研室
2.南方医院

目的 腓骨肌萎缩症 (Charcot-Marie-Tooth (CMT)) 是常见的遗传周围神经病，发病率约为 1/2500。目前尚无逆转腓骨肌萎缩症病程的治疗方案，主要是对症支持治疗。前期研究中发现了一个新的 CMT 致病基因 *C1orf194*，*C1orf194* 基因敲入（I121N）和基因敲除小鼠均出现与患者相似的临床表型。本研究拟通过体外注射腺相关病毒（adeno-associated virus, AAV）至全身性 *C1orf194* 敲除小鼠，对比野生型组、纯合安慰剂组和纯合治疗组小鼠的行为学、生理学指标，并观察组织形态学变化，以延缓病程，提高小鼠独立活动能力及生活质量。

方法 构建 AAV 载体、包装含 *C1orf194* 基因病毒；通过尾静脉向 6 周龄纯合敲除型 *C1orf194* 小鼠注射 AAV 病毒，以 PBS 作为安慰剂。待小鼠生长至 4-6 月龄时，进行行为学、生理学及组织形态学的检测。

结果 我们成功构建以 AAV 载体为骨架，以 C1orf194 为目的基因的表达载体，并成功包装血清型为 AAV9 的病毒。4 月龄时，与安慰剂组相比，治疗组小鼠在抓力与滚轴的实验中指标均有显著性上升，表现出 AAV 基因治疗具有一定的治疗效果。6 月龄时，安慰剂组表现出更为严重的运动和感觉能力减退，滚轴、抓力、痛阈等指标都显著下降。但与安慰剂组相比，治疗组小鼠表现出相对较轻的运动和感觉能力减退，滚轴、抓力、痛阈等指标都显著提高。电生理测定发现，治疗组的小鼠复合动作电位显著高于纯合安慰剂组。治疗组的小鼠尼氏染色的脊髓前角运动神经元数量与野生型小鼠无显著性差异。HE 染色的腓肠肌纤维萎缩现象有所改善。电镜观察治疗组小鼠坐骨神经细胞异常髓鞘减少，轴突变性得到改善。

结论 本研究成功构建以 AAV 载体为骨架，C1orf194 基因为目的基因的表达载体，并成功包装病毒。对全身性 *C1orf194* 敲除小鼠，以体外注射 AAV 病毒的方式进行基因治疗，能有效改善小鼠运动和感觉能力，从而促进小鼠独立生活，提高小鼠生活质量。此研究为进一步研究 CMT 患者的治疗提供了新的切入点。

miR-582 Negatively Regulates pre-B Cell Proliferation and Survival through Targeting Hif1a and Rictor

Xinxin Li[1,2,3]
1.Northwestern Polytechnical University
2.Fourth Military Medical University
3.Research & Development Institute of Northwestern Polytechnical University in Shenzhen

B cell development in bone marrow (BM) is a multi-staged process involving pro-B, pre-B, immature B and mature B cells, among which pre-B cells undergo vigorous proliferation, differentiation, apoptosis and gene rearrangement. While several signaling pathways participate in pre-B cell development have been clarified, detailed intrinsic mechanisms regulating pre-B cell proliferation and survival have not been fully understood. In the current study, we report that miR-582 regulates pre-B cell proliferation and survival. miR-582 is enriched in pre-B cells. Deletion of miR-582 in mice expanded the BM pre-B cell population in a cell-autonomous manner as shown by competitive BM transplantation. We show that forced miR-582 overexpression inhibited pre-B cell proliferation and survival, whereas downregulation of miR-582 by siRNA significantly promoted pre-B cell proliferation and survival in vitro. We identified that Hif1α and Rictor are authentic targets of miR-582 in pre-B cells as shown by reporter assays. Moreover, miR-582 overexpression reduced the expression of Hif1α and its downstream molecule Glut1, as well as Rictor and mTORC2 activity as shown by attenuated AKT and FoxO1 phosphorylation, while miR-582 knockdown showed opposite effects. miR-582 knockdown-induced increases in pre-B proliferation and survival was abrogated by Hif1α and Rictor inhibitors. Together, miR-582 functions as a negative regulator of pre-B cell proliferation and survival by simultaneously targeting Hif1α and mTORC2 signaling that regulates metabolism in early B cell development.

长链非编码 RNA lnc-H2AFV-1 通过调控 m6A RNA 甲基化促进头颈鳞癌细胞的增殖

陈曦[1] 蒋英英[1,2]
1.潍坊医学院口腔医学院
2.潍坊医学院附属医院口腔科

目的 探讨长链非编码 RNA lnc-H2AFV-1 通过调控 m6A RNA 甲基化修饰对头颈鳞状细胞癌细胞增殖的作用及分子机制。
材料与方法 qRT-PCR 检测 lnc-H2AFV-1 在头颈鳞状细胞癌组织及细胞系中的表达情况；RNA 核质分离和 FISH 检测 lnc-H2AFV-1 在头颈鳞癌细胞中的定位；转染 lnc-H2AFV-1 smart silencer 沉默 lnc-H2AFV-1 的表达；将 lnc-H2AFV-1 慢病毒过表达载体感染细胞建立 lnc-H2AFV-1 过表达稳转株；CCK-8 细胞增殖实验、克隆形成实验、EdU 细胞增殖实验检测细胞增殖能力；裸鼠皮下移植瘤模型实验研究体内功能。m6A RNA 甲基化定量分析、斑点印迹实验检测总 m6A 甲基化水平；Western Blot 检测 m6A 甲基化酶表达情况；MeRIP-seq、GO/KEGG 功能富集分析、MeRIP-qPCR 等筛选和验证 m6A 甲基化异常基因的表达情况。
结果 lnc-H2AFV-1 在头颈鳞癌组织及细胞系中均高表达且主要位于细胞的胞核内。敲低 lnc-H2AFV-1 表达后细胞的增殖能力减弱（P<0.05）；过表达 lnc-H2AFV-1 后增殖能力则增强（P<0.05）；体内实验亦发现 lnc-H2AFV-1 促进细胞皮下移植瘤的增殖能力。进一步研究发现头颈鳞癌细胞的总 m6A 甲基化水平与 lnc-H2AFV-1 的表达变化一致；甲基化转移酶 METTL3、

METTL14 的表达与 lnc-H2AFV-1 的表达变化一致，而去甲基化酶 FTO 的表达与 lnc-H2AFV-1 表达变化相反；与 lnc-H2AFV-1 表达一致的多个富集到细胞增殖相关通路基因的 m6A 甲基化水平显著升高。

结论 长链非编码 RNA lnc-H2AFV-1 通过调控 m6A RNA 甲基化促进头颈鳞癌细胞增殖，在头颈鳞癌发生进展中发挥重要作用。

CRISPR/Cas9 基因编辑治疗 Myo6 基因突变导致的显性遗传性耳聋

舒易来[1,2] 薛媛媛[1,2]
1.复旦大学附属眼耳鼻喉科医院
2.国家卫健委听觉医学重点实验室

目的 以模拟遗传性耳聋患者的 Myo6（c.1325G>A ，p.C442Y）耳聋小鼠为实验模型，通过 CRISPR/Cas9 基因编辑系统特异性靶向并敲除 Myo6 C442Y 突变基因，保留野生型链，从而治疗由 Myo6 C442Y 突变基因导致的显性遗传性聋。

方法 针对突变的 Myo6 C442Y 等位基因设计 sgRNA。取 Myo6 C442Y 突变小鼠的胚胎构建胚胎干细胞系（mESC），将 SaCas9-KKH-sgRNA-GFP 质粒导入到 mESC 中表达，随后收集荧光细胞并提取基因组 DNA，进行深度测序，分析比较不同 sgRNA 对突变位点的编辑效率，筛选出效率高、特异性高的 sgRNA2；同时使用 Cas-OFFinder 软件检测 Myo6-g2 的脱靶情况，以评估其安全性。使用 SaCas9-KKH-Myo6-g2 系统进行体内基因组编辑效率验证：以腺相关病毒（AAV）在新生鼠中运载基因编辑体系（AAV-SaCas9-KKH-Myo6-g2）。以 Myo6WT/C442Y 杂合新生鼠为实验对象，显微注入 AAV-SaCas9-KKH-Myo6-g2 治疗系统。通过听力学检测，比较 AAV-SaCas9-KKH-Myo6-g2 对治疗耳和非治疗耳听力的影响。通过免疫荧光染色并在激光共聚焦显微镜下拍照，并计数毛细胞数量，比较经 AAV-SaCas9-KKH-Myo6-g2 治疗前后毛细胞存活的差异。通过电镜检测毛细胞纤毛形态观察经 AAV-SaCas9-KKH-Myo6-g2 治疗后毛细胞纤毛形态的异同。通过电生理检测经 AAV-SaCas9-KKH-Myo6-g2 治疗后内毛细胞钙电流和膜电容的变化情况。

结果 AAV-SaCas9-KKH-Myo6-g2 系统在体外和体内均能特异性地敲除 Myo6WT/C442Y 小鼠中的 Myo6C442Y 突变等位基因，不影响野生型的等位基因链；Myo6WT/C442Y 小鼠中注射 AAV-SaCas9-KKH-Myo6-g2 后可在长达 5 个月的时间内，观察到听觉功能的恢复，同时，还观察到 ABR I 波潜伏期变短；5 个月时，中圈和底圈的外毛细胞数量同对照组相比得到显著提高，具有显著性差异；10 个月时，中圈和底圈的内毛细胞数量，中圈的外毛细胞数量同对照组相比都有显著的提高，具有统计学差异；10 周时，检测到治疗后纤毛形态变规则；第 15-16 天取材，观察到内毛细胞的钙电流恢复到正常水平。

结论 该研究证实了 AAV-SaCas9-KKH-Myo6-g2 基因编辑系统对 Myo6 C442Y 突变基因导致的显性遗传感音神经性聋的治疗作用，为显性遗传性聋和其他疾病的基因治疗的临床转化提供了科学依据。

A humanized mouse model, demonstrating progressive hearing loss caused by a novel KCNQ4 p.G228D from a large Chinese deaf family

Chong Cui Yilai Shu
Eye and ENT Hospital of Fudan University

Objectives *KCNQ4* is a voltage-gated potassium channel protein whose pathogenic mutation causes non-syndromic autosomal dominant deafness DFNA2. To study the pathogenetic characteristics, pathogenic mechanism and treatment of a noval *KCNQ4* mutation (c.683G>A, p.G228D)

Methods A novel *KCNQ4* mutation (p.G228D) in a large Chinese genetic family of deafness was identified by whole-exome sequencing, and a humanized mutant mouse model was constructed using CRISPR technology. The hearing characteristics and cellular physiological functions of mice were studied by ABR/DPOAE, immunohistochemistry and scanning electron microscopy.
Results We identified a novel *KCNQ4* mutation (p.G228D) in a genetic family of deafness whose heterozygotes showed delayed, progressive hearing loss, preceded by high-frequency hearing loss, which was more severe in homozygous. Subsequently, we investigated the hearing characteristics of this mutant mouse model, where heterozygotes first showed mid- and high-frequency hearing loss at 4 weeks of age and developed full-frequency profound deafness by week 12, and homozygous were completely deaf by 8 weeks, which are consistent with the hearing characteristics of the patients. Meanwhile, we observed hair cell loss starting from basal turn of basilar membrane only in the outer hair cells, but not in the inner hair cells, and curiously there were no significant changes in the cilia morphology of the hair cells.
Conclusions We have successfully constructed a noval *KCNQ4* mutation(p.G228D) mouse model, which mimics the human pathogenic features and provides a platform for studying the pathogenic mechanism and treatment of this mutation.

二代测序全基因组体细胞突变检测算法性能评测与应用

张弓[1] 杜红丽[2] 陈子曦[2]
1.暨南大学
2.华南理工大学

二代测序当前被用在越来越多的临床诊断上，尤其是使用 panel/全外显子组/全基因组的方式进行大范围的突变检测，例如肿瘤靶向用药就需要对肿瘤体细胞突变进行精准检测。然而肿瘤体细胞突变具有各种不同的突变率，虽然在实验中测得了良好质量的数据，但各种算法的结果却大相径庭，给临床诊断带来了极大困扰，甚至由于突变检测不准确可能导致临床上错误用药。因此，构建一个标准数据集，用于评测二代全基因组突变检测算法，以及在商业实践环境中进行测试各种算法的准确性和稳健性，显得十分重要。
将两个个体的高质量全外显子组数据集，进行一定比例的混合，产生不同突变率的“体细胞突变”标准测试数据集。采用了两个个体基因组中同一位置不同的纯合突变位点，总共约 3000 多个突变位点作为评价真集。用这一标准数据集评价业界常用的 Mutect2, Strelka2 和纯国产的 FANSe 突变检测流程。同时，也将测试数据集分发给国内 6 家知名的测序服务商，检验各自商业流程的准确性。业界常用的 Mutect2 和 Strelka2 对 20%以上突变率的变异可做到有效检出。对较低的突变率，提高测序深度可以提高检测效果，但对 5%突变率，需 800x 以上的深度，这将造成较高的测序成本；而对于 1%突变率，800x 深度都无法提供可用的检测结果。国产 FANSe 算法流程则在低频突变下大幅度超越其他算法，1%突变率 100~300x 深度下灵敏度是 Mutect2 的 6 倍，而准确率也一直保持在接近 100%的水平上。运行速度上，FANSe 流程的突变搜寻仅需 1 分钟，而 Mutect2 则需要 10 小时以上，FANSe 有着巨大的速度优势。在对 6 家知名的测序服务商的评测中，各服务商均基于自身优化过的算法流程，仅有承启生物（FANSe 流程）在灵敏度和准确度两项指标上同时合格。
构建了国际上第一个基于真实测序数据的不同突变频率的测试数据集和评价真集。基于二代测序的体细胞突变检测准确性受到突变频率、测序深度和算法的显著影响。本研究测试表明，全自主研发的 FANSe 算法流程在低频突变检测上具有速度和准确度优势，可有效降低测序通量需求，降低成本。因此，在实际应用中，需重视算法流程的选择，以达到体细胞突变更精准的检测结果。

从表观遗传学角度构建铁死亡相关长链非编码 RNA 模型预测子宫内膜癌患者预后及免疫环境

张瑜[1,2] 赵乐[1] 陈丽宏[2] 陈茜[3]
1.西安交通大学第一附属医院转化医学中心
2.陕西省人民医院妇产科
3.西安交通大学第二附属医院妇产科

目的 从表观遗传学角度出发，构建一个可预测子宫内膜癌患者预后的铁死亡相关长链非编码 RNA（long non-coding RNA, lncRNA）模型，并探讨不同危险人群的免疫特征及 m6A 相关基因的差异表达。
方法 从 TCGA 数据库下载子宫内膜癌组织 mRNA 表达谱和相应的临床数据，从 FerrDb 数据库下载铁死亡相关基因，鉴定铁死亡相关差异表达 lncRNA，对差异表达 lncRNA 通过单变量 Cox 分析和多变量 Cox 回归分析，构建铁死亡相关 lncRNA 预后模型。根据 RiskScore 的中位值将子宫内膜癌患者分为高危组及低危组，并进行 GSEA 分析。结合临床病理资料（年龄、BMI 指数、组织类型、临床分期和病例分级）绘制 1、3、5 年 ROC 曲线，同时绘制 nomogram *图*。对不同组别的生存状态、肿瘤浸润免疫细胞、免疫检查点抑制（immune checkpoints inhibition，ICI）相关免疫标志物和 m6A 相关基因进行分析。
结果 共下载 248 个铁死亡相关基因，根据相关性分析鉴定出 1007 个铁死亡相关 lncRNA,其中有 216 个铁死亡相关差异表达 lncRNA，并构建出一个由 9 个 lncRNA 构成的预后模型。根据中位值将患者分成两个风险组。1、3、5 年预后模型的 ROC 曲线下面积分别为 0.684、0.693、0.750。与低危组患者相比，高危组患者的生存时间明显缩短（P<0.001）。多因素分析提示该预后模型是子宫内膜癌患者总生存的独立预测因素（HR=1.164，95%CI=1.102~1.230，P<0.001）。GSEA 分析提示低危人群中，免疫相关途径显著富集。低危组和高危组的 T 细胞功能包括溶细胞活性、HLA、炎症调节、共刺激、共抑制和协调 I、II 型干扰素反应均有显著差异。免疫检查点（如 PDCD1(PD1)、CD274(PD-L1)、CTLA4、PDCD1LG2、CD80）和 m6A 相关基因（HNRNPC、YTHDF2、YTHDF1、YTHDC1、WTAP、FTO、RBM15）在两个风险组中的表达也显著不同。
结论 基于铁死亡相关差异表达 lncRNA 的预后模型，可预测子宫内膜癌患者的预后和免疫状态及 m6A 相关基因表达，该预测模型将有助于临床预后判断和个体化治疗。

A novel mutation of p.G46E in the GJA8 gene in a Chinese family with congenital cataracts

Ting Wang[1] Fangyuan Zhen[2]
1.School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan Province, China
2.The First Affiliated Hospital of Zhengzhou University

Purpose Congenital cataracts is the most common cause of visual impairment and blindness in children worldwide. To detect the disease-causing mutations in a nonconsanguineous Chinese family with congenital cataracts, and analyze the molecular consequence of the identified mutation.
Methods Comprehensive ophthalmic examinations were carried out in the affected and unaffected family members. Genomic DNA was extracted from peripheral blood. Whole exome sequencing was conducted with the affected individual. Candidate disease-causing mutations were amplified by polymerase chain reaction, and direct Sanger sequencing was performed to verify the mutations in the family and 400 ethnicity matched healthy controls. The plasmids including wild-type and mutant of GJA8 were constructed and expressed in 293T cells. Recombinant protein expression and cellular localization of CX50 were evaluated by western blotting, and confocal microscopy.
Results The affected individual showed the classically clinical symptoms of congenital cataracts. A novel homozygous mutation, c.G137A(p. G46E) in the gap junction protein alpha 8 (GJA8)

gene was identified by Whole Exome Sequencing. The pathogenic mutation was validated by direct Sanger sequencing. This mutation was absent from other unaffected family members and 400 ethnicity matched healthy controls. Compared with wild-type plasmid, mutation of GJA8 plasmid causes severe reduction in protein expression and mislocates of mutant Cx50 protein.
Conclusions A novel mutation in p.G46E was detected in a Chinese family with congenital cataracts. The mutation was reported for the first time, expanding the spectrum of GJA8 mutations with cataract. The mutation of p.G46E in GJA8 effects on protein function.

Baicalein inhibits SARS-CoV-2/VSV replication with interfering mitochondrial oxidative phosphorylation in a mPTP dependent manner

Yue Liu
TONGJI UNIVERSITY

Scutellaria Baicalensis Georgi extract and its key components have been widely used for treating viral infection, including the infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but the underline mechanism for its broad antiviral effect remains elusive. Here, we show Baicalein, a key component in *Scutellaria B.* Georgi extract, potently inhibits replication of SARS-CoV-2 and another RNA virus, vesicular stomatitis virus (VSV) at similar half maximal inhibitory concentration (IC50). Baicalein is identified as an oxygen consumption inhibitor in our screen. We found Baicalein interferes mitochondrial oxidative phosphorylation (OXPHOS) by reducing its oxygen consumption activity and inducing inner mitochondria membrane leakage. Baicalein OXPHOS interference is enhanced when activity of mitochondria permeability transition pore (mPTP) is reduced. Interestingly, virus infection blunts mPTPs in host cells to facilitate its replication. Interfering mitochondrial OXPHOS activity attenuates virus production. Thus, our study for the first time provides clear evidence showing quick and robust inhibitory effect of Baicalein on mitochondrial OXPHOS, and suggests targeting mitochondrial OXPHOS/mPTP is a novel strategy for developing drugs to treat virial infection including the SARS-CoV-2.

CRISPR/Cas9-HPV-liposome enhances antitumor immunity in cervical cancer models

Shuai Zhen
Northwest Women's and children's Hospital

Objectives Increasing evidence has demonstrated that the deletion HPV E6/E7 in cervical cancer cells may correlate with an immunosuppressive tumor microenvironment (TME) and poor response or resistance to immune checkpoint blockade (ICB) therapy.
Methods Here, we demonstrate that CRISPR/Cas9 delivery by liposome can effectively knockout HPV, which in turn induces autophagy and triggers cell death–associated immune activation via release of damage-associated molecular patterns.
Results In vivo results illustrated that gRNA targeted HPV-liposome can reverse the immunosuppressive TME by promoting CD8+ T cell infiltration of the tumor tissue, enhancing the expression of proinflammatory cytokines, such as interleukin-12, tumor necrosis factor– , and interferon- , and reducing regulatory T cells and myeloid-derived suppressor cells.
Conclusion The combination of gRNA targeted HPV-liposome with an immune checkpoint inhibitor, anti–programmed death–1 antibody, results in a highly potent antitumor effect. Moreover, the combinatorial treatment elicits immunological memory in the cervical cancer model.

clusterProfiler: A universal enrichment tool for interpreting omics data

Guangchuang Yu
Southern Medical University

Functional enrichment analysis is pivotal for interpreting high-throughput omics data in life science. It is crucial for this type of tool to use the latest annotation databases for as many organisms as possible. To meet these requirements, we present here an updated version of our popular Bioconductor package, clusterProfiler 4.0. This package has been enhanced considerably compared with its original version published 9 years ago. The new version provides a universal interface for functional enrichment analysis in thousands of organisms based on internally supported ontologies and pathways as well as annotation data provided by users or derived from online databases. It also extends the dplyr and ggplot2 packages to offer tidy interfaces for data operation and visualization. Other new features include gene set enrichment analysis and comparison of enrichment results from multiple gene lists. We anticipate that clusterProfiler 4.0 will be applied to a wide range of scenarios across diverse organisms.

Generation of an enhanced photoactivatable Cre mouse model for spatiotemporal genome manipulation in vivo

Huiying Li
East China Normal University

The Cre-loxP system is essential for understanding the gene function as well as cell behavior during organ development and disease progression. However, highly efficient genetic manipulation tool, which could achieve high spatiotemporal resolution with non- or low-level leaky phenomenon remains elusive *in vivo*. Here, we reported an enhanced version of photoactivatable Cre recombinase (ePA-Cre) and established an ePA-Cre mouse model which triggered strong-induction activity (up to 175-fold) upon blue light illumination. We systematically followed up the characterization of ePA-Cre mice by crossing them with Cre-reporter mice, demonstrating the tight regulation of recombination. In addition, we validated the feasibilty of *in vivo* specific cell ablation using the ePA-Cre mouse model we established, providing a powerful approach for studying cell origin, fate, and function. In conclusion, ePA-Cre mice offers a tightly inducible, highly efficient, and spatiotemporal-specific tool for developmental biology.

RNA 修饰在眼部病理性血管新生中的调控作用研究

颜标
复旦大学附属眼耳鼻喉科医院

目的 m6A 是真核生物中最常见的一类化学修饰,能够在多种生物过程和疾病发生过程中发挥重要的调控作用。然而关于其在眼科病理性血管新生中的调控作用仍然未知。
方法 通过高通量筛查，明确病理性血管新生和内皮活化中的 m6A 的关键调控分子；通过氧诱导的视网膜血管新生模型和角膜新生血管模型，明确关键调控分子在病理性血管新生中的调控作用；通过内皮细胞实验，采用 MTT、Ki67 染色、Transwell 技术等，研究该调控分子对血管内皮细胞功能影响；通过生物信息、RNA-SEQ、免疫共沉淀等技术，明确该调控分子参与病理性血管新生的分子机制。
结果 通过高通量筛选，发现 m6A 的关键调控分子, METTL3, 参与病理性血管新生和内皮活化；其介导的 m6A 修饰水平明显地在病理性血管新生中上调；METTL3 表达沉默抑制内皮细胞的活力、增殖、分化和迁移；动物实验发现，METTL3 表达沉默可以抑制视网膜血管的新生和角膜血管的新

生； METTL3 通过影响 Wnt 信号通路，调控该通路关键分子的 m6A 修饰水平最终影响病理性血管新生的进程。

结论 本研究发现了眼科病理性血管新生的调控新分子，从表观遗传角度阐明了血管新生的调控新机制，有望该类疾病的治疗提供新思路。

Knockdown of NRAGE induce enamel hypoplasia by activating autophagy in ameloblast

Xueqin Zhu[3] Shengcai Qi[1,2] Yanhong Yan[4] Chao Yao[1,2,5] Yu Wang[1,2] Yan Wang[1,2]
1.Department of Restoration, Shanghai Stomatological Hospital, Fudan University
2.Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases, Fudan University
3.Department of Stomatology, Shanghai Ninth People's Hospital
4.Department of Stomatology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, 200072, P.R. China
5.Medical College of Anhui University of Science and Technology, Huainan, 232000, P.R. China

Purpose: Neurotrophin receptor-interacting MAGE homologue (NRAGE) plays important roles in organ development. Our previous study showed NRAGE regulated the differentiation of dental pulp cells. However, the potential roles of NRAGE in regulationg tooth development are unknown. The aim of this research was to reveal the influence of NRAGE on tooth development.

Materials and methods: The NRAGE knockout mice was constructed. The tooth phenotype in NRAGE-/- mices was analyzed by gross appearance, micro-CT, TEM and HE staining. Autophagy related proteins, such as ATG5 and ATG7, were assessed in ameloblast cell *in vivo* by immunohistochemical method. In an *in vitro* experiment, NRAGE was knockdown in ameloblast-lineage cell line (ALC). Then, mineralization was detected by alizarin red S staining and ALPase activity. The enamel mineralization related genes were evaluated by real time PCR. In addition, cell proliferation, cell apoptosis and antophagy were detected in NRAGE-/- ALC cells. Meantime, mineralization was evaluated after CQ (chloroquine diphosphate salt) was used to block autophagy.

Results: Knockdown of NRAGE could cause enamel hypoplasia in mice. Moreover, high expression of autophage related proteins were detected in ameloblast of NRAGE-/- mices, which might be enrolled in this process. NRAGE knockdown significantly inhibited mineralized nodule formation and ALPase activity of ALC cells. But it was reversed by autophagy inhibitor CQ. Furthermore, after NRAGE konckdown in ALCs, cell cycle was promoted and cell apoptosis was decreased.

Conclusion: Knockdown of NRAGE could cause enamel hypoplasia in mice. NRAGE plays an important role in enamel development in mice by activating autophagy-related pathway.

RPanel: 基于大数据的基因组水平器官遗传疾病关键调控区集合研究

张雅雯 王凤 桂永浩 李强
国家儿童医学中心，复旦大学附属儿科医院，上海市出生缺陷重点实验室，儿科研究所

目的 通过 WES 可检测到遗传疾病的半数病因，其余致病因素包括调控区/其它因素。人类组织器官关键调控区的鉴定和研究对于临床遗传疾病的筛查诊断和病因学分析具有重要意义。本研究基于大数据在全基因组水平分析构建新型的调控区研究筛查和功能分析策略，以高效量化和筛选不同器官的重要性和特异性的功能调控区，并建立全新的可用于遗传疾病筛查、诊断和研究的 Regulatory Panel (RPanel)。

方法 本研究对人类心肝肾脑等重要器官的 500 多个 ChIP-seq 数据集进行大数据整合分析，在全基因组水平对每个调控区每个碱基进行量化评估其器官重要性和特异性；基于此，选择部分潜在关键区域，于细胞、动物和分子水平研究其对器官发育和功能的影响，并分析其与遗传疾病的相关性。

结果 通过对大数据的整合分析，本研究高效筛选到分别与人类心肝肾脑等重要器官密切相关的调控区（约占整个调控区的 1.5%），其中重要性和特异性的调控区分别占 1.1%和 0.4%。功能研究表明约 50%的关键区域具有增强子活性；细胞水平构建数个增强子敲除的人类细胞系后，发现细胞的增殖凋亡以及多条信号通路受到显著影响；此外，本研究鉴定发现多个功能性 SNP 位于以上增强子区，说明这些增强子与遗传疾病存在强相关性。
结论 本研究首次基于大数据分析在全基因组水平构建了一套高效的调控区研究筛查和功能分析策略；基于此，已定制出不同器官的 RPanel，可用于遗传疾病的筛查，这尤其对于编码区无异常病例的遗传病因诊断和研究具有重要指导意义。

Whole-transcriptome analysis of serum L1CAM-captured extracellular vesicles reveals specific signature for autism spectrum disorder

Yannan Qin[1] Li Cao[1] Haiqing Zhang[2] Shuang Cai[1] Jinyuan Zhang[1] Yanni Chen[2] Chen Huang[1]
1.Xi'an Jiaotong University Health Science Center
2.Xi'an Children's Hospital

The pathophysiology of autistic spectrum disorder (ASD) is not fully understood and there are no diagnostic or predictive biomarkers. Extracellular vesicles (EVs) are cell-derived nano-sized vesicles, carrying nucleic acids, proteins, lipids and other bioactive substances. As reported, L1CAM-captured EVs (LCEVs) can provide reliable and accurate biomarkers for neurological diseases due to the characteristic expression of L1CAM on neuron-derived EVs; however, little is known aboutthe LCEVs in children with ASD. In this study, serum samples were collected from 100 ASD children and 60 age-matched typically developed (TD) children, and were pooled into 5 ASD subgroups and 3 TD subgroups (n=20). LCEVs from each subgroup were isolated using L1CAM antibody mediated immunosorbent assay and characterized by nanoparticle tracking analysis, transmission electron microscopy and western blot. Whole-transcriptome of LCEVs was analyzed by lncRNA microarray and RNA-Sequencing. RNAs expressed differently in LCEVs from ASD sera vs. TD sera were screened, analyzed, and validated in individual samples. A total of 1418 mRNAs, 1745 lncRNAs and 11 miRNAs were identified to be differentially expressed, and most of them were down-regulated in ASD. The differentially expressed RNAs were more distributed on chromosome 17. A large portion of RNAs were involved in neuron- and glycan-related networks implicated in ASD. qRT-PCR identified that the levels of EDNRA, SLC17A6, HTR3A, OSTC, TMEM165, PC-5p-139289_26, and hsa-miR-193a-5p changedsignificantly in ASD, indicating them as potential biomarkers for the disease. In conclusion, whole-transcriptome analysis of serum LCEVs reveals specific signature for ASD in Chinese children, which may help detect predictive biomarkers and molecular mechanisms of ASD, and provide reference for diagnoses and therapeutic management of the disease.

Transmembrane protein 215：a novel gene regulating endothelial cell death in angiogenesis

Peiran Zhang Yuan Liu Liang Liang Hua Han
Fourth Military Medical University

Objective Many pathways necessary for regulating angiogenesis have been identified; however, those responsible for endothelial cells (ECs) survival during angiogenesis remain elusive. A better understanding of these processes may lead to the design of novel therapeutic strategies complementary to current angiogenesis inhibitors.
Methods and results Transmembrane protein 215 (TMEM215) was expressed in ECs derived from different tissues that we examined including mouse retina, brain, liver and tumor. We noticed that knockdown of TMEM215 in ECs induced strong cell death of ECs without affecting cell

proliferation and migration, suggesting that TMEM215 was required for ECs survival. To further investigate the role of endothelial TMEM215 in angiogenesis, we conditionally knocked out TMEM215 by crossing CDH5-CreERT mice with $TMEM215^{flox}$ mice to acquire $TMEM215^{iEC\text{-}KO}$ mice. As compared to control mice, EC-specific TMEM215 deletion led to delayed tumor progression with strongly impaired blood vessel density. Similar to the effects observed in primary tumors, $TMEM215^{iEC\text{-}KO}$ mice conferred longer survival and a drastic reduction in lung metastasis. Mechanistically, knockdown of TMEM215 resulted in ECs death with characteristics of both apoptosis and necrosis, which could be rescued by caspase inhibitor Z-VAD-FMK and necroptosis inhibitor necrostatin-1. Moreover, TMEM215 was predicted to interact with a series of proteins involving in unfold protein response (UPR). Considering VEGF signaling engages UPR sensors in an unconventional manner to promote endothelial cell survival and angiogenesis, the molecular mechanism underlying TMEM215-mediated ECs survival may be involved.
Conclusion Our research identified TMEM215 as a novel molecule involved in angiogenesis by regulating the survival of ECs and suggested the use of TMEM215-inhibitor as potent anti-angiogenic drug complementary to VEGF(R)-targeted therapies.

Endothelial TMEM215 may regulate abnormal angiogenesis in diabetic complications

Yuan Liu
Northwest Women and Children Hospital

Topic Endothelial TMEM215 may regulate abnormal angiogenesis in diabetic complications
Objective Human chromosome 9p21 mutation is a fragment highly correlated with the pathogenesis of human diabetes and its vascular lesions. Continued Endoplasmic reticulum stress (ER stress) in endothelial cells(ECs) caused by hyperglycemia and accumulation of glycosylation end products(AGEs) damage endothelial function and angiogenesis. In this study, we found a new vascular regulator, transmembrane protein 215(TMEM215) on 9p21 locus. We intend to study regulation of endothelial ER stress and angiogenic capacity by TMEM215 which may explain the chorangiosis in diabetes.
Methods Expression of TMEM215 was measured by chips of diabetes samples. The effect of TMEM215 on angiogenesis was studied by models in vitro and in vivo., such as retinal plexus, microbeads, tube formation, aortic rings and hindlimb ischemia. The effects of TMEM215 on endoplasmic reticulum homeostasis and stress were studied by transmission electron microscopy, qRT-PCR and RNA-Seq. Finally, the improvement of TMEM215 on diabetic angiogenesis was verified in DB/DB mouse models.
Conclusion The microarray data of multiple diabetes samples showed that the expression of TMEM215 was down-regulated in diabetes samples. Upregulation of TMEM215 improved synthesis function of endoplasmic reticulum and alleviated ER stress. Inadequate TMEM215 increased endothelial apoptosis and number of tips cells, leading to redundant plexus and impaired blood perfusion. Elevated expression of TMEM215 ameliorated the structure of pathological neovascularization and reduced the necrotic area of surrounding tissues. Therefore, expression changes of TMEM215 caused by mutation or high glucose may result in diabetic chorangiosis.

Combining analysis expression pattern of enzymes for m6A and m5C in hepatocellular carcinoma

Hongmeng Su[1,2] Chuqian Zheng[1,2] Xinxiu Li[1,2] Hong Fan[1,2]
1.Department of Genetics & Developmental Biology, Medical School of Southeast University
2.The Key Laboratory of Developmental Genes and Human Diseases, Ministry of Education

Hepatocellular carcinoma (HCC) is one of the common malignant tumors around world. RNA methylation is an important epigenetic regulation and plays an important role in tumorigenesis,

progression and prognosis. M6A and m5C are the main sites of RNA methylation. In order to explore the role of abnormal RNA methylation modification in HCC, this study analyzed the expression patterns of related modification enzymes of RNA methylation m6A and m5C with the pathological characteristics of HCC patients. Thirteen m6A and 11 m5C methylation enzymes were analyzed in HCC data from the Cancer Genome Atlas (TCGA) database. The expression levels of 21 in 24 genes were significantly up-regulated in tumor tissues compared with peri-cancer tissues. Cox regression analysis showed that 18 genes were associated with the prognosis of HCC patients. Nine genes including METTL3, VIRMA, YTHDF1, YTHDF2, NOP2, NSUN4, NSUN5, DNMT3A and ALYREF were identified function as important player in the regulation of patient prognosis by LASSO regression. Correlation analysis also confirmed that the 9 genes were highly correlated. Patients were divided into the high-risk group and the medium-low risk group according to the risk score. The prognostic differences and clinicopathological characteristics of patients in the two groups were analyzed, and it was found that there were significant differences in overall survival, tumor size, stage and grade, and patients in the high-risk group had worse prognosis and some clinicopathological characteristics were worse. Univariate and multivariate Cox regression analysis of risk score and clinicopathological characteristics of patients showed that the risk score based on the risk model constructed by 9 genes could be an independent risk factor for prognosis of patients with hepatocellular carcinoma. In conclusion, this study found that the abnormal expression of 9 RNA methylation related enzymes can be used as prognostic indicators of HCC patients.

Gpr126 调控身高和骨量的机理研究

何亮
同济大学

身材矮小是青少年群体中的一种常见病症，一直困扰着众多家庭。在诸多影响青少年身高的因素中，基因遗传是主要原因之一。但是，目前影响人体身高的基因及其作用机制尚不清楚。我们通过总结大量人类身材矮小的全基因组关联分析（GWAS）结果，发现 Gpr126 可能与人类的身高发育有着密切的关系。为了研究该基因是如何影响身高的，我们利用不同骨细胞特异性 Gpr126 基因敲除小鼠模型进行研究，发现仅在成骨细胞特异性敲除 Gpr126 的小鼠在胚胎发育和出生后的体长显著变短。除此之外，我们发现成骨细胞特异性敲除 Gpr126 不仅会影响小鼠的骨骼发育，还会影响出生后的骨质。分子机制方面，我们发现 Gpr126 在成骨细胞中主要是通过 cAMP-CREB 信号通路实现对骨代谢的调控，并阐明其在成骨细胞功能中的配体为细胞外基质 IV 型胶原。同时，研究还发现目前治疗骨质疏松的上市药物——特立帕肽（甲状旁腺素 PTH），能够有效改善因 Gpr126 缺失而引起小鼠短小以及骨量低下的表型。这一成果有望为该基因突变而引起的青少年身高矮小的世界科学难题，提供精准医疗的解决方案。（Sci Adv. 2020 Mar 20;6(12):eaaz0368.）

RunX1 upregulation causes mitochondrial dysfunction via regulating the PI3K-Akt pathway in iPSC from patients with Down syndrome

Yanna Liu[1] Zhaorui Ren[1,2] Jingbin Yan[1,2] Fanyi Zeng[1,2,3]
1.Shanghai Children's Hospital, Institute of Medical Genetics, Shanghai Jiao Tong University
2.NHC Key Laboratory of Medical Embryogenesis and Developmental Molecular Biology, Shanghai Key Laboratory of Embryo and Reproduction Engineering
3.Department of Histoembryology, Genetics & Development, Shanghai Jiao Tong University School of Medicine

Object Down Syndrome (DS) is the most common autosomal aneuploidy caused by trisomy of chromosome 21. Previous studies demonstrated that DS affected mitochondrial functions, which may be related to abnormal development of the nervous system in DS. Runt-related transcription factor 1 (RunX1), an encoding gene located on chromosomal 21, is an important transcriptional

regulator. It was reported that abnormal expression of RunX1 might affect cell apoptosis via the mitochondrial pathway. This study investigated whether RunX1 may play a critical role in the mitochondrial dysfunction of DS and how RunX1 affected mitochondrial functions.
Methods Induced pluripotent stem cells of DS patients (DS-iPSCs) were established from patient blood samples. The expression of *RunX1* was identified in DS-iPSCs and normal iPSCs by qRT-PCR, and the mitochondria functions were also investigated. Then, normal iPSCs were transfected with the *RunX1* expression vector, and DS-iPSCs were transfected with the *RunX1* shRNA vector, respectively. The mitochondrial functions were investigated thoroughly, including ROS levels, mitochondrial membrane potential, ATP content, and lysosomal activity. Finally, RNA-seq was used to explore the global expression pattern changes paying particular interest to the signaling pathways.
Results The expression level of *RunX1* in DS-iPSCs was significantly higher than that in normal controls. Impaired mitochondrial functions were readily observed in DS-iPSCs. Significant changes, including damage of mitochondrial membrane potential, increased reactive oxygen species, and reduced ATP synthesis, were apparent. Interestingly, overexpression of *RunX1* in normal iPSCs also resulted in mitochondrial dysfunction, while inhibition of *RunX1* expression can improve the mitochondrial function in DS-iPSCs. Global gene expression study showed that overexpression of RunX1 might promote apoptosis in DS-iPSCs by affecting the PI3K/Akt pathway.
Conclusion The abnormal expression of RunX1 may play a critical factor in mitochondrial dysfunction in DS-iPSCs.

GPCR在多能干细胞中的功能研究

樊莎莎[1] 薛燕[1,2] 马姬[1] 周一叶[1,2] 曾凡一[1,2]
1.上海交通大学医学院
2.上海交通大学附属儿童医院

目的 G蛋白偶联受体(G protein-coupled receptors，GPCRs)是细胞膜表面最大的受体家族，介导了多种疾病如肿瘤、代谢性疾病、中枢神经系统疾病和遗传病，市场上有超过50%的药物都是以GPCRs为靶标设计的，但是仍有大量的GPCRs作用机制还不明确。我们课题组前期研究发现GPCR中的一个受体在小鼠胚胎干细胞（ESCs）中高度表达，本研究目的是解析其在ESCs中的功能及作用机制，为将来药物研发和临床治疗提供理论基础。
方法 运用RNA-seq、IP/LC-MS、诱导分化和各种分子生物学手段研究该基因在ESCs中的作用和功能。
结果 诱导ESCs向EB分化，发现该基因随EB分化表达下降，敲低该基因后ESCs中多能因子表达下降，相应的分化基因表达上调，克隆形成能力下降，此外，通过RNA-seq发现该基因可参与JAK/STAT信号通路，进一步应用IP/LC-MS，鉴定到该基因表达的蛋白可以与JAK1相互作用，进而影响JAK1/STAT3的信号通路。
结论 我们的结果初步表明该基因在ESCs多能性和自我更新方面发挥重要作用，可介导 JAK1/STAT3信号通路决定ESCs的命运，这将对干细胞的筛选及其大规模应用提供有价值的参考。

Sema4D promotes trophoblast invasion via the Met/PI3K/Akt pathway in recurrent implantation failure

Xian Chen
Department of Regenerative Medicine, Tongji University School of Medicine

Objective The inadequate trophoblast invasion is associated with embryo implantation. Considering that semaphorin4D (sema4D) enhances tumor invasion, we aimed to explore the functional role of sema4D in trophoblast cells and to examine the underlying mechanism.
Methods Endometrium tissue samples were observed from January 2019 to April 2019 from two groups of women who had undergone IVF (RIF group, 10 women who underwent ≥ 3 ETs including a total of 4 good-quality embryo without pregnancy, control group, 12 women who conceived in their first treatment cycle). Endometrial gene expression profiling in were compared between the two groups. Sema4D expression in the endometrium of RIF patients was analyzed using qPCR and immunohistochemistry. Cell proliferation, invasion, and migration were determined using a CCK8 assay, Transwell assay, respectively. The expression levels of matrix metalloproteinase (MMP)-2，MMP-9, the total and phosphorylated of Met, PI3K and Akt were detected by Western blotting.
Results Database retrieval and literature review screened several novel cell adhesion-related genes that might participate in embryo implantation, which include Sema4D, ITGA7, LMO7 and EPHB4. Among these targets, the mRNA and protein levels of Sema4D were significantly lower in the RIF group than those in the control group. In human trophoblast HTR8/SVneo cell line, sema4D could promote Met, PI3K and Akt phosphorylation as well as enhance trophoblast cell invasion and migration. Moreover, the effect of sema4D on HTR8/ SVneo could be blocked by knocking down Met with specific siRNA.
Conclusion The crosstalk between sema4D and Met could transactivate Met to promote trophoblast cell invasion and migration, and decreased expression of sema4D and Plexin-B1 may be responsible for the deficiency in Met signalling and the development of RIF.

妇科肿瘤诊疗中遗传咨询开展现状的问卷调查

石月 王超
复旦大学附属妇产科医院

目的 评估患者对妇科肿瘤遗传咨询的认知、态度及其影响因素，以提高遗传咨询效率、推动遗传咨询工作的开展。
方法 以 2020 年 3 月 25 日至 2021 年 3 月 26 日期间就诊于复旦大学附属妇产科医院妇科肿瘤遗传咨询门诊的患者为研究对象，基于临床诊疗、患者反馈及文献阅读设计调查问卷，调查患者的一般情况、对遗传咨询的认知和态度。根据患者一般情况进行分组，分析影响患者对妇科肿瘤遗传咨询认知和态度的因素。
结果 本次调查共回收有效问卷 104 份。36 例（34.6%）患者表示在就诊前“没有顾虑，坦然面对”，患有恶性肿瘤和接受根治性手术治疗的患者更能坦然面对遗传咨询（*P*=0.048、0.008）。其余患者均对遗传咨询存在顾虑，无个人肿瘤病史的患者比有个人肿瘤史的患者更害怕检出遗传性突变（*P*=0.017），来自较发达地区的患者比来自欠发达地区的患者对可能罹患遗传性疾病有更多的焦虑情绪（*P*=0.013），已生育的患者比未生育的患者更担心自己患其他肿瘤的风险增加（*P*=0.008）。74 例（71.1%）患者希望通过遗传咨询明确所患疾病是否为家族遗传性，文化程度较高的患者比文化程度较低的患者、有肿瘤家族史的患者比无肿瘤家族史的患者更希望明确所患疾病是否为家族遗传性（*P*=0.024、0.009）。52 例（50.0%）患者希望了解如果有遗传性疾病是否可以对自己的后代进行有效预防，文化程度较高的患者比文化程度较低的患者、接受保育治疗的患者比接受手术治疗的患者、有生育要求的患者比无生育要求的患者更希望了解如有遗传性疾病是否可对后代进行有效预防（*P*=0.002、0.018、0.003）。共 25 位患者检测出携带胚系基因致病或可疑致病突变，经过门诊的报告解读后，19 例（76.0%）患者表示了解“其他系统发生肿瘤的风险会增加，应早期筛查”，14 例（56.0%）患者认同检测出基因突变可针对性地早期干预，10 例

（40.0%）患者认同有生育意愿者可通过第三代试管进行遗传阻断，13 例（52.0%）患者认同基因检测结果能提示预后及靶向治疗方案，仅 7 例（28.0%）患者表示“知道如何进行其他系统肿瘤的早期筛查”。

结论 文化程度、地区、疾病类型、治疗方法、家族史、个人肿瘤史、是否生育和是否有生育要求是影响患者对遗传咨询态度的重要因素。研究结果提示患者的接受度和依从性与其对遗传咨询及受益的了解程度密切相关，临床医师应在开具检查或推荐转诊时充分告知遗传咨询的目的，提高患者接受遗传咨询和进一步行基因检测的依从性。在一次遗传咨询后，存在胚系致病或可疑致病突变的患者对于疾病的了解及相关系统筛查和家族遗传风险管理上的理解并不满意。临床医师在诊疗过程中除了常规的叙述性解释说明，还可能需要借助通俗易懂的科普宣传手册、形象生动的宣教视频，以及医患互动的患者教育会等多种患者教育模式加深患者对疾病诊治及其预后的理解，以提高医患沟通效率，共同参与医疗决策。研究显示遗传咨询的可及性及就诊距离是影响患者遗传咨询门诊就诊的主要因素之一，地区欠发达、门诊可及性差等因素均可能导致患者家属延缓或拒绝进行检测。我们认为可以通过在全国各级城市、地区普遍设立遗传咨询门诊，将遗传咨询深入到临床一线，增加患者就医的可及性，有利于识别高危人群，推动肿瘤预防和诊治工作。

Genetic Testing Enable a Precision Medicine Approach for Nephrolithiasis and Nephrocalcinosis in Pediatrics: a single centre cohort

Lin Huang
Wuhan Children's Hospital

Objective The etiology of nephrolithiasis (NL) and nephrocalcinosis (NC) is heterogeneous, this article aims at summarizing the genotype-phenotype correlation of hereditary NL and NC in our center and conducted to assess the capability of genetic testing.

Methods The clinical data of 32 patients who were suspected of being diagnosed with hereditary NL/NC from May 2017 to August 2020 were retrospectively analyzed. The trio-whole exome sequencing as the main genetic testing, followed by Sanger sequencing and pathogenicity analysis by proteins.

Results There were 25 cases with positive detection rate of molecular diagnostic testing, including 24 with monogenic disorders and 1 with CNV, 20 (80%) with significant degree of growth retardation, 9 (36%) with psychomotor retardation, 13 (52%) with significantly increased urinary excretion of low-molecular weight protein (LMWP), 8 (32%) with hypercalciuria, and 9 (36%) cases who experienced electrolyte imbalances. Besides, 3 patients had abnormal renal function (12%, stage 2 chronic kidney disease (CKD)). The most frequent disease was distal renal tubular acidosis (dRTA)(with inclusion of *SLC4A1, ATP6V1B1,* and *ATP6VOA4* genes), followed by Dent disease (*CLCN5* and *OCRL1* genes), hyperoxaluria(*AGXT* and *HOGA1* genes), cystinuria (*SLC7A9* and *SLC3A1* genes), andKabuki syndrome (*KMT2D* gene). These patients mainly had NC, which is characterized by growth retardation, and is likely to merge with a specific biochemical phenotype, osteoporosis. Patients (median age 10.5 months (5.5 months, 29.5 months)) with abnormal urinary oxalate, cysteine, excretion of amino acids, such as cystinuria and primary hyperoxaluria, mostly had multiple recurrent stones. In children (median age 9 months (3 months, 58 months)), some genetic abnormalities, such as Kabuki syndrome or CNV can also be combined with kidney stone, often with special facial features or congenital abnormalities of the urinary system.

Conclusion NL/NC is a group of rare disorders, their prognosis is extremely variable from trivial to end-stage kidney disease, and their etiology is complicated. Genetic testing can provide a diagnosis for a genetic condition, especially for patients with a specific biochemical phenotype, osteoporosis, growth retardation, psychomotor retardation, special facial features, congenital abnormalities of the urinary system, and consanguineous family history. Genetic testing enables precision medicine approach for hereditary NL/NC.

应用转录组测序技术提高常染色体隐性多囊性肾脏疾病的诊断率

梁磊 赵建荣
内蒙古医科大学附属医院

高通量基因测序技术已经越来越多的应用于临床疾病的分子诊断中，目前利用外显子组/全基因组测序等手段进行单基因遗传疾病的序列分析，仅能达到约 25%的检出率，更多的问题存在于如何分析解读变异的功能及临床的意义。
目的 为了提高人类常染色体隐性多囊性肾脏疾病的诊断率。
方法 本课题组首先对入组患者的肾脏组织采用外显子组测序的方法进行 DNA 诊断，然后对外显子组测序结果为阴性的样本进行转录组测序，同时与 GTEx 数据库中的肾脏转录组数据进行对照。**结果** 在经外显子测序未确诊的常染色体隐性多囊性肾脏疾患者中发现了多个异常剪接。
结论 转录组测序可以提高常染色体隐性多囊性肾脏疾病的诊断率，对于应用于人类孟德尔遗传病诊断具有重要意义。

中国 Prader-Willi 综合征 226 例围生期特点分析

周煜 马明圣 李谷雨 张朕杰 丁娟 徐艺文 邱正庆 宋红梅
北京协和医院

目的 分析 Prader-Willi 综合征（PWS）患儿在围生期的临床特点，提高对本病的早期识别。
方法 横断面研究。2019 年 9 月至 2020 年 3 月在全国范围内入组经分子遗传学诊断明确的 PWS 患儿 226 例（男 120 例、女 106 例），收集临床资料包括胎龄、出生体重、胎动情况、胎位情况、羊水情况、分娩方式、哭声、肌张力、喂养以及男性患儿是否存在隐睾等，分析中国 PWS 患儿围生期的临床特点，并根据分娩方式、是否小于胎龄儿以及基因型进行亚组分析。对不同亚型的临床表现通过 *t* 检验、χ^2 检验和 Mann-Whitney *U* 检验进行统计学分析。
结果 226 例 PWS 患儿中，小于胎龄儿有 100 例（44.3%）。最常见宫内表现为孕期胎动减少 202 例（89.4%），其他表现包括羊水增多 71 例（31.4%）、胎位异常 58 例（25.9%），共有 185 例（81.9%）患儿经剖宫产娩出，且剖宫产娩出的患儿更常伴有胎位异常表现[30.8%(57/185) 比 2.4%（1/41），χ^2=14.161，p＜0.001]。患儿出生后的异常表现则包括肌张力低下 221 例（97.8%）、哭声弱 220 例（97.3%）、男性隐睾 116 例（占全部 120 例男性患者的 96.7%）及喂养困难 206 例（91.2%）。父源缺失型有 184 例（81%），非缺失型患儿的母亲怀孕年龄相较于父源染色体缺失型的患儿母亲更大[（35±5）比（29±5）岁，t=-6.591, p＜0.001]，也更易在孕期出现羊水过多[47.6%(20/42)比 27.7%(51/184），χ^2=6.286，p=0.012]的表现，差异均有统计学意义。
结论 PWS 患儿在围生期的主要表现为肌张力低、哭声小、喂养困难、宫内胎动减少以及男性隐睾，并且很有可能经剖宫产娩出。对有以上特征的新生儿，儿科医生应注意到 PWS 的可能性。 基因型与表型关系方面，非缺失型 PWS 患儿更容易有羊水过多的的表现。

A Novel COL1A1 Missense Mutation Associated with Dentineogenesis Imperfecta Type I

Yuhua Pan[1,2] Xiong Fu[1] Yuting Zeng[2] Wenjuan Yan[2]
1.Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University
2.Department of Stomatology, Southern Medical University,

Background Osteogenesis imperfecta (OI) is a clinical and genetic disorder that results in bone fragility, blue sclerae and dentineogenesis imperfecta (DGI), which is mainly caused by a mutation in the COL1A1 or COL1A2 genes, which encode type I procollagen.

Methods The ultrastructure of dentin was analyzed by micro-CT, scanning electron microscopy, energy-dispersive spectroscopy analysis, nanoindentation test and Toluidine Blue Staining. Whole-exome sequencing (WES) was performed to identify the pathogenic gene. The function of the mutant COL1A1 was studied by real-time PCR, western blotting, subcellular localization. Functional analysis in dental pulp stem cells (DPSCs) was also performed to explore the impact of the identified mutation on this phenotype.
Results A missense mutation (c.1463G > C) in exon 22 of the COL1A1 gene was found using whole-exome sequencing. However, the cases reported herein only exhibited a clinical DGI-I phenotype. There were no cases of bone disease or any other common abnormal symptom caused by a COL1A1 mutation. In addition, the ultrastructural analysis of the tooth affected with non-syndromic DGI-I showed that the abnormal dentine was accompanied by the disruption of odontoblast polarization, a reduced number of odontoblasts, a reduction in hardness and elasticity, and the loss of dentinal tubules, suggesting a severe developmental disorder. We also investigated the odontoblast differentiation ability using dental pulp stem cells (DPSCs) that were isolated from a patient with DGI-I and cultured. Stem cells isolated from patients with DGI-I are important to elucidate their pathogenesis and underlying mechanisms to develop regenerative therapies.
Conclusion This study can provide new insights into the phenotype-genotype association in collagen-associated diseases and improve the clinical diagnosis of OI/DGI-I.

Lack of MECP2 gene transcription on the duplicated alleles of two related assympomatic females with Xq28 duplications and opposite X chromosome inactivation skewing

Yixi Sun Yuqin Luo Min Chen Liya Wang Yingzhi Huang Yanmei Yang Minyue Dong
Women's Hospital, School of Medicine, Zhejiang University

Objective To explore the correlation between Xq28 (involving *MECP2*) duplication females' phenotype and X-chromosome inactivation (XCI) detected by androgen receptor (*AR*) assay and RNA sequencing
Methods We detected two asymptomatic female carriers II.2 (mother) and I.2 (grandmother) in a Xq28 duplication family by SNP array, qRT-PCR, and FISH analyses. Then we analyzed the XCI of the two females by androgen receptor (*AR*) and retinitis pigmentosa 2 (*RP2*) assays in DNA methylation level. Meanwhile, we performed whole-exome sequencing and RNA sequencing to quantify allelic read counts and allele-specific expression in transcriptional level. For important informative SNPs of *XIST* and *MECP2*, PCR-sequencing was performed on genomic DNA and cDNA to verify the parental origin of the active X chromosome
Results Xq28 intrachromosomal duplications were identified in female II.2 (mother) and I.2 (grandmother) by SNP array, qRT-PCR, and FISH analyses. *AR* and *RP2* assays showed that both had extreme skewed XCI, the Xq28 duplicated chromosome was inactivated in the mother, but surprisingly, it was activated in the grandmother. Interestingly, by combining RNA sequencing and whole-exome sequencing, we confirmed that *XIST* only expressed in the Xq28 duplication chromosomes of the two females, indicating that the Xq28 duplication chromosomes were inactive. Meanwhile, *MECP2* and most XCI genes in the duplicated X-chromosomes were not transcriptionally expressed or upregulated, precluding major clinical phenotypes in the two females, especially the grandmother.
Conclusions We showed that XCI status detected by RNA sequencing was more relevant for establishing the clinical phenotype of *MECP2* duplication females. It suggest there are other factors maintaining the XCI status in addition to DNA methylation, a possible additional inhibition mechanism occurs at the transcriptional level in the unmethylated X-chromosome, counter balancing the *MECP2* duplication's detrimental phenotype effects.

一例假阴性的遗传性乳腺癌卵巢癌家系检测结果引发的思考

何佳雪 姜艳芳 陈立国 胡欣彤
吉林大学第一医院

目的 探讨 PCR、高通量测序、MLPA 等技术在遗传性乳腺癌/卵巢癌基因检测中的应用价值。
方法 患者，女，78 岁，临床诊断为乳腺癌。其女儿卵巢癌患者，基因检测检出 BRCA1 胚系突变，使用奥拉帕利治疗有效。为确认患者是否携带遗传性基因变异，是否适合使用 PARP 抑制剂，在某检测机构对患者进行了基因检测。使用的方法为目标区域捕获和高通量测序技术，检测 BRCA 基因结果为阴性。后在我院对患者进行全面的基因检测，结果为 BRCA 基因 EX1-EX2 缺失，经验证后确认该变异与其女儿携带的变异一致。通过更精密的高通量测序和 MLPA 技术，结合生物信息学分析，明确了患者及其女儿的致病原因，并为家族其他成员提供了遗传咨询。
结论 高通量测序在遗传性肿瘤基因检测中具有重要意义，将高通量测序与其他技术相结合，可降低假阴性的检出，为患者和家属提供更精准的基因检测结果和精准诊疗方案。

Haploinsufficiency of PSMD12 causes proteasome dysfunction and autoinflammation

Kai Yan[1] Minyue Dong[1] Qing Zhou[1,2] Jiahui Zhang[2]
1.Women's hospital, School of medicine, Zhejiang University
2.The MOE Key Laboratory of Biosystems Homeostasis & Protection, Life Sciences Institute, Zhejiang University

Objective Proteasome-associated autoinflammatory syndrome (PRAAS) is caused by mutations affecting components of the proteasome and activation of the type I interferon pathway. We aim to study the pathogenic mechanism of caused by defects in the proteasome 19S regulatory subunit Rpn5 encoded by *PSMD12*.
Methods Whole exome sequencing (WES) was analyzed in a family with skin rash, congenital ophthalmia and developmental delay. We performed mechanistic studies to assess proteasome function and single cell RNA sequencing (scRNA-seq) to further explore the spectrum of immune cell activation.
Results We identified a novel nonsense variant in *PSMD12* in two patients. We confirmed impaired proteasome assembly and decreased proteasome activity in cells from the patients. We defined the inflammatory signatures in *PSMD12* haploinsufficiency and identified elevated inflammatory signals especially in monocytes by scRNA-seq. Interferon stimulated-genes (ISGs) were upregulated in various cell types, most prominently in monocytes.
Conclusion Our study identified haploinsufficiency of *PSMD12* as novel autoinflammatory syndrome associated with impaired proteasome function and type I interferon up regulation. This work expands the genotype and phenotype spectrum of PRAAS.

Loss of SPACA1 function causes autosomal recessive globozoospermia by damaging the acrosome-acroplaxome complex

Pingping Chen[1] Yu Sun[2]
1.Department of Reproduction, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, 200092, Shanghai, China.
2.Molecular Genetics Group, Shanghai Institute for Paediatric Research, 200092, Shanghai, China.

STUDY QUESTION
Is the sperm acrosome membrane-associated protein 1 (*SPACA1*) gene critical to human globozoospermia?

SUMMARY ANSWER
The biallelic loss-of-function (variant of *SPACA1* causes globozoospermia as a result of acrosome-acroplaxome complex damage.
WHAT IS KNOWN ALREADY
SPACA1 expression decreases in patients with globozoospermia. *Spaca1* gene-disrupted mice have abnormally shaped sperm heads that resemble those of human globozoospermia.
STUDY DESIGN, SIZE, DURATION
We recruited a consanguineous family with two brothers affected by infertility as a consequence of globozoospermia. The semen analysis data and ART outcomes were collected. Exome sequencing (ES) was used to identify potential pathogenic variants. Protein-protein interaction (PPI) technologies and proteomic analysis were utilized to explore the pathogenic mechanism.
PARTICIPANTS/MATERIALS, SETTING, METHODS
Two globozoospermic brothers and their consanguineous parents were recruited to identify the potential pathogenic variant through ES. A homozygous nonsense variant in the *SPACA1* gene in both brothers inherited from the heterozygous parents was identified. Twenty normal fertile males were recruited as controls. Sperm ultrastructure was observed with transmission electron microscopy. Western blotting was performed to measure SPACA1 expression level in the sperm from the patients. Mass spectrometry (MS) analyses were used to identify differentially expressed proteins and to investigate proteins that interact with SPACA1. Co-immunoprecipitation (co-IP), yeast two-hybrid (Y2H) and immunofluorescence colocalization assays were used to confirm the PPI.
MAIN RESULTS AND THE ROLE OF CHANCE
A nonsense variant (NM_030960.2:c.53G>A; p. Trp18*) in the *SPACA1* gene was identified as the pathogenic variant in a family with globozoospermia. Patient IV:1 and patient IV:2 had a phenotype very similar to that of *Spaca1* gene-disrupted mice. The nonsense variant in *SPACA1* led to premature transcriptional termination in the signal peptide, which was confirmed by western blotting. MS-based proteomics analysis showed that eight interactors of SPACA1 were differentially expressed in the patients' sperm, including actin-like protein 7A (ACTL7A), an important component of the acrosome-acroplaxome complex. The PPI of SPACA1 and ACTL7A was confirmed via co-IP and Y2H assays. Immunofluorescence showed that SPACA1 and ACTL7A colocalized in mature sperm, revealing that these proteins were coexpressed spatially.
LIMITATIONS, REASONS FOR CAUTION
Given the rarity of globozoospermia, only two patients from one family harbouring the *SPACA1* variant were found. Future studies should evaluate *SPACA1* variants in larger cohorts to corroborate this finding.
WIDER IMPLICATIONS OF THE FINDINGS
This study revealed that the *SPACA1* gene was critical for globozoospermia, which expanded the spectrum of causative genes for globozoospermia. This study also provided evidence for intracytoplasmic sperm injection (ICSI) clinical outcomes for patients with SPACA1-deficient globozoospermia, which may guide clinical treatment strategies. Furthermore, this study explored the pathogenesis of globozoospermia caused by SPACA1 deficiency.

The Value of Single Molecule Real- Time Technology in the Diagnosis of Rare Thalassemia and the Molecular Characteristics and Phenotype Analyses of Its Gene Variants

Shiqiang Luo[1] Xingyuan Chen[2] Dingyuan Ceng[1] Ning Tang[1] Dejian Yuan[1] Qingyan Zhong[1] Aiping Mao[3] Ruofan Xu[3] Tizhen Yan[1]
1.Liuzhou Maternity and Child Healthcare Hospital
2.The People's Hospital of Guangxi Zhuang Autonomous Region
3.5. Berry Genomics Corporation, Beijing

To compare single molecule real- time technology (SMRT) and traditional genetic diagnostic technology of rare types of thalassemia genes, and to analyze the molecular characteristics and

phenotypes of rare thalassemia gene variants. We used 434 cases with positive hematology screening as the cohort, then, using SMRT technology (research group) and traditional gene diagnosis technology (control group) for thalassemia gene screening. A total of 361 cases from genetic testing were confirmed as positive (83.18%). Among them, 318 cases (73.27%) were detected in the control group and 361 cases (83.18%) were detected in the research group. The results of testing 353 cases (81.34%) of conventional thalassaemia genes in the research group were essentially the same as those in the control group. However, the research group detected 76 more cases of 30 gene mutation types that were not detected in the control group, which were consistent with the verification results of Sanger sequencing or Gap-PCR. In addition, there were five rare cases, which were not in the detection range of SMRT. The differences in hematological phenotypic parameters of 81 cases among 33 rare type cases were also analyzed. SMRT technology increased the detection of thalassemia genes, and detected rare thalassemia cases with multiple phenotypes, which were conducive to clinical thalassemia gene screening.

Application of copy number variation sequencing in genetic detection of miscarriages in early and middle pregnancy

Shiqiang Luo[1] Xingyuan Chen[2] Tizhen Yan[1] Jiaolian Ya[1] Zehui Xu[1] Pengfei Cai[1] Dejian Yuan[1] Ning Tang[1]
1.Liuzhou Maternity and Child Healthcare Hospital
2.The People's Hospital of Guangxi Zhuang Autonomous Region

High-throughput sequencing based on copy number variation (CNV-seq) is commonly used to detect chromosomal abnormalities. This study identifies chromosomal abnormalities in aborted embryos in early and middle pregnancy and explores the application value of CNV-seq in embryo termination. High-throughput sequencing was used to detect chromosome copy number variations (CNVs) in 116 embryos in early and middle pregnancy that were discontinued. The detection data were compared with the database of genomic variants (DGV), the database of chromosomal imbalance and phenotype in humans using ensemble resources (DECIPHER), and the online Mendelian inheritance database (OMIM) to determine the CNV type and the clinical significance. High-throughput sequencing results were successfully obtained in 109 out of 116 specimens, with a detection success rate of 93.97%. In brief, there were 64 cases of abnormal chromosome number and 23 cases of copy number variation, in which ten were pathogenic mutations and 13 were variants of uncertain significance (VOUS). The abnormal chromosome number is the most important reason for embryo termination in early and middle pregnancy, followed by the pathogenic chromosome copy number variation. CNV-seq can quickly and accurately detect conventional chromosomal abnormalities and identify microdeletions and microduplicate chromosome copy number variations that cannot be detected by conventional chromosome karyotype analysis, which is convenient and efficient for genetic etiology diagnosis miscarriage.

液相色谱-串联质谱法在 21-羟化酶缺乏症随访中应用的探索

兰天
武汉儿童医院

目的 探讨如何将液相色谱-串联质谱（LC-MS/MS）以最经济、高效的方法应用于 21-羟化酶缺乏症（21-OHD）患者的随访。
方法 实验组为 109 例接受规范治疗的经典型 21-OHD 患者，对照组为 65 例正常儿童。同时用免疫法和 LC-MS/MS 法检测 17-羟孕酮（17-OHP）、雄烯二酮（Δ4-A）、睾酮（T）和皮质醇。LC-MS/MS 法同时还检测另外 15 种肾上腺类固醇激素。实验组分为过度治疗、控制良好、控制欠佳三组。进行以下研究：（1）分析免疫法与 LC-MS/MS 结果的一致性；（2）比较 21-OHD 患者与对

照组 LC-MS/MS 血清多种类固醇浓度差异，发掘 21-OHD 患者肾上腺激素改变的特点；（3）比较不同疗效 21-OHD 患者 20 种类固醇浓度差异，筛选更有价值的随访监测指标。
结果（1）同时用 LC-MS/MS 与免疫法检测的 4 项指标中，T、17-OHP 的一致性高。免疫法测定的皮质醇和青春发育前 Δ4-A 的浓度高于 LC-MS/MS。（2）LC-MS/MS 检测的肾上腺分泌的 20 种类固醇激素中 21-OHD 患者较对照组有 6 种激素明显偏高，6 种激素明显偏低，8 种没有统计学差异。（3）抑制过度组 17-OHP 降低、11-脱氧皮质醇升高；控制欠佳组 17-OHP、孕烯醇酮、孕酮、17-羟孕烯醇酮、21-脱氧皮质醇、Δ4-A、雌酮升高，皮质酮降低。
结论 LC-MS/MS 一次性检测多种低浓度的血清肾上腺类固醇激素,可替代免疫法用于 21-OHD 患者的随访，准确性更高，评价维度更多面。随访中 20 种激素中仅 9 种与患者控制状态密切相关，可减少不必要的消耗。LC-MS/MS 在 21-OHD 随访中的具体应用方案尚需结合患儿生长情况、骨龄进展情况等进行更大样本的研究。

Genetic and Phenotypic Characteristics of 107 Patients with Mucopolysaccharidosis Type II: A Retrospective Observational Study in China

Zhenjie Zhang
Peking Union Medical College Hospital

Background: Mucopolysaccharidosis Type II (MPS II) is a rare, progressive and ultimately fatal X-linked lysosomal storage disorder caused by mutations in the iduronate-2-sulfatase (IDS) gene. MPS II has a relatively high prevalence in Eastern Asian countries but there are few reports on patients in China. This report represents one of the largest studies of MPS II and is based on a retrospective, single-center analysis of medical records between 2008 and 2020. Data analyses were descriptive.
Methods and Results: A total of 107 patients (all male) were enrolled, including 11 with a family history of MPS II. Of 40 patients with gene sequencing data, 33 unique IDS mutations were identified, including eight previously unreported mutations. Mean age at diagnosis was 5 years (range: 2 months to 22 years) and onset of MPS II symptoms was predominantly recorded between 2 and 6 years of age. Musculoskeletal and dermatologic abnormalities were the most common clinical manifestations. Treatment was generally supportive and palliative with 38 patients undergoing ≥1 surgical treatment. One patient underwent a bone marrow stem cell transplant. Morbidity and mortality: Two patients, aged 11 years and 15 years, respectively, were wheelchair-bound and one 11-year-old was unable to eat independently. Three patients are now known to have died, aged 10, 11 and 13 years, respectively.
Conclusions: This study re-emphasized the clinical value as one of the largest analyses of an MPS II population and briefly summarize the key findings. It noted that the importance of early MPS II diagnosis and the importance of early initiation of enzyme replacement therapy to maximize clinical benefit.

Whole Exome Sequencing Identifies Three Novel Gene Mutations in Patients with the Triad of Diabetic Ketoacidosis, Hypertriglyceridemia and Acute Pancreatitis

Zixi Huang[1] Zhenyan Xu[1] Ruoqing Xu[2] Xiaoyang Lai[1]
1.the Second Affiliated Hospital of Nanchang University
2.Tongji Medical College, Huazhong University of Science and Technology

Abstract
Background: This study aimed to analyze the genetics and treatments of the patients with the triad of diabetic ketoacidosis (DKA), hypertriglyceridemia and acute pancreatitis (AP).

Methods: We conducted a retrospective study of six patients with the triad of AP, hypertriglyceridemia and DKA at our hospital. All patients underwent plasmapheresis as part of their treatment. The clinical characteristics of the patients were obtained from the hospital information system and analyzed. Whole exome sequencing was performed using samples of one patient (case 6) and his family members.
Results: The average triglyceride level before plasmapheresis was 3282.17 ± 2975.43 mg/dL (range: 1646-9332 mg/dL). The triglyceride levels dropped by approximately 80% after plasmapheresis. None of the patients developed complications related from plasmapheresis. During follow-up, patients 5 and 6 developed recurrent pancreatitis for several times, and showed the formation of pancreatic pseudocysts. We identified three novel heterozygous missense mutations in the family of patient 6, including c.12614C>T (p.Pro4205Leu) in *APOB*, c.160G>C (p.Glu54Gln) in *CILP2*, and c.1199C>A (p.Ala400Glu) in *PEPD*.
Conclusions: Three novel heterozygous missense mutations, including c.12614C>T (p.Pro4205Leu) in *APOB*, c.160G>C (p.Glu54Gln) in *CILP2*, and c.1199C>A (p.Ala400Glu) in *PEPD* were first identified in a patient with the triad of DKA, hypertriglyceridemia and AP. The combination of plasmapheresis, hydration and insulin therapy may have the greatest clinical benefits for these patients.
Highlights
1. Three novel heterozygous missense mutations were identified in a patient with the triad of diabetic ketoacidosis, hypertriglyceridemia and acute pancreatitis.
2. Plasmapheresis is effective and safe in reducing triglycerides levels.

Features of Chinese patients with Sitosterolemia and literature review

Zhizi Zhou Xiuzhen LI Xueying Su Yanna Cai Xiaodan Chen Yunting Lin Xiaojian Mao Chunhua Ceng Wen Zhang Li Liu
Guangzhou Women and Children's Medical Center

Background: Sitosterolemia is a lipid disorder characterized by the accumulation of xenosterols in plasma and tissues caused by mutations in ABCG5 and/or ABCG8 genes. The disease is commonly misdiagnosed and mistreated as familial hypercholesterolemia. In order to deepen the understanding of the disease, this study investigate the current status of diagnosis and treatment in Chinese patients with sitosterolemia.
Method: We searched the relevant literature in the electronic English database "PubMed" and Chinese database "CNKI and Wan Fang". We reviewed the clinical presentation, molecular characteristics of 56 Chinese patients, and evaluated four children with sitosterolemia from our center by analyzing their natural history and following-up.
Results: Fifty-six cases with sitosterolemia have been identified in China, among whom 30 were female and 26 were male. These patients were aged from 3 months to 67 years with a median age of 8 years at the time of diagnosis. The mean age at onset of sympotoms in our case series was 2.2 years, and the mean age of diagnosis was 6.4 years. Xanthomas occurred in 48 cases (86%), thrombocytopenia in 17 cases (30%), and anemia in 14 cases (25%), cardiovascular damage in 12 cases (21%). Forty cases (71%) mutations in ABCG5 and 15 cases (27%) had mutations in ABCG8. One case had mutations in both ABCG5 and ABCG8 genes (2%). We also reported a case suffered from sitosterolemia and GSD VI, combining two clinical rarities to yield a first for the literature. Our patients were treated with low cholesterol and plant sterol restriction diet alone or combined with cholestyramine. Total plasma cholesterol（TG）and low-density-lipoprotein cholesterol (LDL-C) of patients decreased to normal after combined treatment, but levels of plant sterols remained elevated in these patients. However, levels of TC, LDL-C and plant sterols remained high in patients under diet control alone.
Conclusions: This study summarized the clinical presentation, molecular characteristics of Chinese patients with sitosterolemia. We found that misdiagnosis and mistreatment of sitosterolemia were still frequently ocur in China. Our statistics also prompted that ABCG8 gene mutations are more common in the Chinese population than previously reported.

Our survey made recommendations on the clinical indications for plant sterol assay and provided clinical data to standardize sitosterolemia diagnosis and treatment.

A systematic study of mosaicism in heritable thoracic aortic aneurysm and dissection

Guoyan Zhu[1] Zhou Zhou[1] Hang Yang[1] Weizhen Zhou[1] Mingyao Luo[2] Yinhui Zhang[1] Yujing Zhang[1] Chang Shu[2]

1.State Key Laboratory of Cardiovascular Disease, Beijing Key Laboratory for Molecular Diagnostics of Cardiovascular Diseases, Diagnostic Laboratory Service, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China
2.State Key Laboratory of Cardiovascular Disease, Center of Vascular Surgery, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China

Purpose: Mosaicisms are often overlooked in routine molecular diagnosis. Although not common, it is of great significance for accurate diagnosis and genetic counseling. Recent studies suggested that mosaicisms in heritable thoracic aortic aneurysm and dissection (TAAD) may be underestimated, not only in asymptomatic parents, but also in affected patients. In this study, we aimed to systematically evaluate the frequency of mosaicisms in TAAD patients and parental mosaicisms.
Methods: 1085 patients with suspected inheritable TAAD who had been performed a targeted next generation sequencing (NGS) were included in our study. We reanalyzed the sequencing data and retrieved the variants with low allele frequencies. Deep sequencing of the specific amplicon (>5000×) was conducted to confirm the mosaicisms. Besides, there were 80 probands who was identified a causative mutation and had both parental samples. In these families, parental mosaicisms were investigated with the amplicon deep sequencing method too.
Results: A total of three symptomatic patients were identified with a mosaic variant, c.2607_2608insGAGCC, c.3284G>A in *FBN1* gene and c.631C>A in *TGFB2* gene. Notably, the low-level mosaic mutation in *TGFB2* was detected combined with a causative *FBN1* truncating mutation in patient AD2001, which might partially explain his skeletal deformities that his father did not have. Three parental mosaic mutations were detected in the trio-families, including one *TGFBR2* mosaic mutation that had been previously reported by our group. Besides, we firstly explored the proportion of mutated cells in diseased aorta and found it was not significantly higher than that in blood sample.
Conclusion: Mosaicisms could be a more common phenomenon in TAAD than it had been realized so far. It was necessary and feasible to implement mosaicism analysis in routine molecular diagnosis via adapting the bioinformatic parameters. Amplicon-based deep sequencing was an easy and cost-effective method to confirm the suspected mosaic mutations.

FBN2 新生嵌合剪切位点突变致马凡综合征病例报道

张悦妮[1] 石磊[1] 谭建强[2]
1.哈尔滨医科大学 2.柳州市妇幼保健院

目的 鉴定马凡综合征患者中新的致病突变，并结合已报道患者的临床表型资料，探索基因型与临床表型的相关性，提高对马凡综合征的认识，为临床诊断、遗传咨询，以及产前诊断等提供分子依据。
方法 收集患者病史并描述其特殊体征；采集患者及其父母的外周血，进行高精度临床外显子测序分析，过滤和筛查常见变异位点，并应用生信工具预测罕见变异的致病性。
结果 患者临床表现为手指、足趾细长，手足腕关节内翻畸形。外显子测序发现患者的 *FBN2* 存在新生嵌合剪切位点突变 c.3725-1G>C（NM_001999.4, Hg19, Chr5: 127671270）,嵌合比例约为20.4%，未检索到其人群频率数据，且其临床表现正常的双亲均未检出该突变。c.3725-1G>C 位于

FBN2 第 28 号内含子的经典剪切受体位点（GT-AG），经 Human Splicing Finder、MaxEntScan 和 MutationTaster 软件分析，预测为致病性变异。
结论 *FBN2* 的 c.3725-1G>C 新生嵌合突变可能为该患者致病突变。本研究结果丰富了马凡综合征的突变谱；结合已知病例的文献综述，为马凡综合征临床诊疗提供了分子标记。

二代测序在胚胎植入前遗传学检测染色体异常家系中的应用

张志宏 刘睿智
吉林大学第一医院

目的 探讨基于二代测序(next generation sequencing, NGS) 的胚胎植入前遗传学检测(preimplantation genetic test, PGT) 对于染色体易位携带者实现正常生育的意义。
方法 对 69 对染色体易位携带者夫妇，75 个周期（43 个周期为平衡易位，20 周期为罗氏易位，12 周期为倒位）行 PGT 周期的卵母细胞浆内单精子显微注射，进行胚胎培养至囊胚阶段，检出囊胚滋养外胚层细胞行全基因组扩增，用 NGS 技术对扩增产物进行基因组测序分析，选择正常或平衡易位胚胎移植，分析胚胎检测结果、妊娠、胚胎着床情况。成功妊娠的患者于孕中期进行羊膜腔穿刺后，基因芯片检测分析。
结果 共活检 456 枚胚胎，456 枚囊胚活检成功，成功诊断 449 个，诊断成功率为 98.46%（449/456），获得可供移植的整倍体胚胎共 137 个（30.51%），遗传所致胚胎染色体异常 176 个（39.20%），非遗传所致胚胎染色体异常 71 个（15.81%），嵌合体胚胎 65 个（14.48%），其中 16 个周期无可用胚胎，周期取消率为 21.33%。平衡易位组获得整倍体胚胎 67 个，罗氏易位组获得整倍体胚胎 44 个，倒位组获得整倍体胚胎 23 个。PGT 后 HCG 阳性率 72.50%（29/40），胚胎着床率为 62.50%（25/40），早期流产率为 2.50%（1/40）。产前诊断结果与 PGT 结果一致。
结论 基于 NGS 的 PGT 可准确的对胚胎进行染色体病诊断，避免反复流产和非意愿性终止妊娠，并获得理想的临床妊娠率。

在中国西南地区夫妇中与不良妊娠相关的染色体异常核型及其断点研究

吴伊恬 赖怡
四川大学华西第二医院

目的 通过研究有不良妊娠史的夫妻双方核型结果的结构异常及数目异常，为该类患者夫妇后续生育的诊疗提供新的思路。
方法 通过纳入 2020 年全年于四川大学华西第二医院咨询辅助生殖，且有过不良妊娠史的夫妻共 786 对，对其 550 条带染色体核型结果进行分析。通过 spss 19.0 进行统计学分析，对夫妻双方的染色体结构重排及数目异常率进行比较，进一步探索研究男性及女性具体染色体异常的结果，通过与现有发表文献比较，探究最可能的致病性结构异常。
结果 在有不良妊娠史的夫妻中，女性核型结果异常率（10.43%）高于男性（7.51%）且具有统计学意义。在染色体结构重排的异常结果中，男性与女性最多见的结构异常均为易位，分别为 1.78% 和 4.45%且差异具有统计学意义；男性结构异常最多发生于 7 号和 18 号染色体，7 号最常见的断点在 q22，18 号最常见断点在 p11；女性结构性异常最常见与 14 号染色体最常见的断点除 p10q10（罗伯逊易位）外，为 q13。在染色体数目异常结果中，女性均显示为多中 X 染色体核型嵌合。
结论 在有过不良妊娠史的夫妻中，男性的 7 号染色体和 18 号染色体的断点，以及女性 14 号染色体的断点可能与不良妊娠相关。因此，建议以上染色体易位的携带者应进行移植前诊断以提高正常生育的概率。

三代测序 CATSA 技术用于地中海贫血基因检测效果分析

宋琪玲
川北医学院附属医院

目的 对比传统基因检测技术 PCR-导流杂交技术与三代测序 CATSA 技术在地中海贫血基因检测的效果。
方法 从 2019 年 1 月到 2020 年 12 月川北医学院附属医院进行血常规和血红蛋白电泳患者出现检测结果异常的病例 134 例，双盲平行进行地贫基因检测，分别采用 PCR-导流杂交法和三代测序 CATSA 法检测。
结果 两种方法在 125 例样本中检测结果一致，占比 93.28%（125/134）。其中包括 99 例地贫基因检测未见异常，11 例 α 基因 3.7 位点杂合缺失，10 例 α 基因 SEA 杂合缺失，4 例 α 基因 4.2 位点杂合缺失,1 例 SEA 杂合缺失合并 4.2 位点杂合缺失。在 9 例样本中两种方法检测结果不一致，对比导流杂交法，CATSA 技术额外检出突变位点，包括 3.7 三联体 2 例、4.2 三联体 1 例、3.7 三联体合并罕见 β 突变 1 例、罕见 β 突变 3 例、核心 β 突变 1 例、α 结构变异 2 例。并且 9 例样本均用 Sanger 测序等方法进行验证。
结论 CATSA 技术较传统的导流杂交法，能额外检出地贫基因突变位点。特别在患者血常规和血红蛋白电泳结果不一致时，应采用检测范围更广的技术检测地贫基因，避免漏诊。

Health economic evaluation of noninvasive prenatal testing and serum screening for Down syndrome

Gefei Xiao
Zhuhai Center for Maternal and Child Healthcare

Background Down syndrome (DS), also known as trisomy 21 (T21), is the most common genetic disorder associated with intellectual disability. There are two methods commonly used for prenatal testing of DS: serum screening (SS) for biomarkers in maternal serum and noninvasive prenatal testing (NIPT) for aneuploidy by cell-free DNA (cfDNA) in maternal plasma. However, cost-effectiveness analyses of these two methods are mostly based on data derived from simulations with various models, with theoretical values calculated. In this study, we statistically analyzed clinical DS screening data and pregnancy outcomes during the follow-up of pregnant women in Zhuhai City, China. The economics of the two mainstream prenatal DS screening methods was evaluated from a public health perspective.
Methods A retrospective analysis was performed on the data of 17,363 pregnant women who received SS and NIPT during gestation in Zhuhai from 2018 to 2019, and a cost-effectiveness analysis was performed with four screening strategies. In strategy I, all pregnant women received SS, and those with T21 risk ≥1/270 had invasive prenatal diagnosis (IPD). In strategy II, all pregnant women received SS, those with T21 risk ≥ 1/270 had IPD, and those with 1/270 > T21 risk ≥ 1/1,000 had NIPT; then, women at high risk based on NIPT also had IPD. In strategy III, all pregnant women received SS, and those with T21 risk ≥1,000 had NIPT; then, women at high risk based on NIPT results had IPD. In strategy IV, all pregnant women received NIPT and those at high risk based on NIPT results had IPD. Finally, to assess the cost and effectiveness of DS screening, the total costs were calculated as the sum of screening and diagnosis as well as the direct and indirect economic burden during the average life cycle of DS patients.
Results A total of 22 of the 17,363 (1/789) pregnant women had DS, of which only one woman was over 35 years of age. SS detected 1,024 cases at high risk of T21 (≥1/270), 8 cases were true positive, with a positive predictive value of 0.78% and a detection rate of 36.4%. NIPT detected 27 cases at high risk of T21 (Z ≥ 3) and 22 cases of DS, with a positive predictive value of 81.5% and a detection rate of 100%. Strategy I had the largest total cost of 65.54 million CNY, strategy II and III had similar total costs of 40 million CNY, and strategy IV had the lowest total cost of 14.91 million CNY. By comparison, the screening strategy with NIPT alone had the highest health economic value for DS.

Conclusions SS was greatly affected by nuchal translucency and the accuracy of gestational age measured by ultrasonography. Unstandardized ultrasonography was an important reason for the low DS detection rate with SS. The influence of interfering factors on NIPT was much lower than in SS. NIPT can be used as an alternative to SS and as a primary screening strategy of prenatal DS screening for secondary prevention and control of birth defects. NIPT greatly decreased the frequency of IPD and the miscarriages associated with IPD, saved the limited medical and health resources, and greatly increased DS detection rate. Therefore, NIPT has great social and economic benefits.

Sex-specific difference in phenotype of Kabuki syndrome type 2 patients: a matched case-control study

wang yirou
上海儿童医学中心

Background Kabuki syndrome (KS) is a monogenic disorder leading to special facial features, mental retardation, and multiple system malformations. *KDM6A* (MIM*300128) is the pathogenic gene of Kabuki syndrome type 2 (KS2, MIM#300867), which accounts for only 5%–8% of KS. Previous studies suggested that female patients with KS2 may have a milder phenotype. Thus, we summarized the phenotype and genotype of KS2 patients who were diagnosed in Shanghai Children's Medical Center since July 2017 and conducted a 1:3 matched case-control study according to age and sex to investigate sex-specific differences between patients with and without KS2.
Results There were 12 KS2 cases in this study, and 8 of them matched with 24 controls. The intelligence quotient (IQ) score of the case group was significantly lower than that of the control group (P <0.001). In addition, both the incidence of intellectual disability (ID) (IQ <70) and moderate-to-severe ID (IQ <55) were significantly higher in the case group than those in the control group (P <0.05). No sex-specific difference was found in the incidence of ID or moderate-to-severe ID between the female cases and female controls (P>0.05), whereas there was a significant difference between male cases and male controls (P <0.01). Furthermore, the rate of moderate-to-severe ID and congenital heart disease (CHD) was significantly higher in the male group than that in the female group (P <0.05).
Conclusions Our results showed that a sex-specific difference was exhibited in the clinical phenotypes of KS2 patients. The incidence of CHD was higher in male patients, and mental retardation was significantly impaired. However, the female patients' phenotype was mild.

中国儿童发育障碍的拷贝数变异图谱

刘彦慧
东莞市妇幼保健院

目的 了解中国儿童发育障碍患者基因组拷贝数变异情况。
方法 收集 10,026 例儿童发育障碍患者的未鉴定染色体微阵列(cma)数据，重新评价不同医疗条件下致病性 CNV 产率，比较中西方患者基因组疾病的发生频率和表型变异性。
结果 中国儿童发育障碍 pCNVs 总阳性率为 21.37% ，不同疾病的 pCNVs 阳性率不同。多数疾病的 pCNVs 产率与表型复杂性和智力残疾/发育迟缓(ID/DD)共病呈正相关。神经发育障碍的基因组负担和 pCNVs 产率支持女性的保护作用。然而，分层分析显示，它只出现在非综合征型 ID/DD 中，而不是在非综合征型孤独症谱系障碍或癫痫中。此外，15 种已知基因组疾病在中国和西方的病人群中显示出显著的不同频率，15 种已知基因组疾病的参考临床特征在两个群体中也显著不同。
结论 我们定义了不同医疗条件的中国儿科患者的 pCNVs 产率和基因型谱，揭示了中西方儿童基因组疾病发生频率和表型多样性的差异。

The first report effective treatment of Tofacitinib in Chinese Pediatric patients with Blau syndrome

Song Zhang Huasong Zeng
Guangzhou Women and Children's Medical Center

Objective Blau syndrome (BS) is a rare autosomal dominant, autoinflammatory syndrome characterized by the clinical triad of granulomatous recurrent uveitis, dermatitis and symmetric arthritis. associated with mutations in the nucleotide-binding oligomerization domain containing 2 (NOD2) gene. The aim of this study was to assess the efficacy of Tofacitinib in patients with BS.
Methods Tofacitinib was given to 3 patients with BS regularly， patient 1,2 and 3 received 1.7mg/day,2.5mg/day and 2.5mg/day. Patients' characteristics, clinical manifestations, magnetic resonance (MR) imaging, lab findings, and therapeutic measures were reviewed and treatment outcomes were described.
Results three patients showed dramatic improvement of their clinical symptoms and laboratory findings. Three BS patients were all Chinese Han, and were men. three patients received tofacitinib, and all achieved clinical remission of polyarthritis rapidly, as well as normalization of erythrocyte sedimentation rate and C-reactive protein and improvements in inflammatory cytokines.
Conclusion JAK inhibitors such as Tofacitinib may be a promising approach for BS patients who have unsatisfactory response to corticosteroids, traditional disease-modifying antirheumatic drugs and biological agents

Incorporation of exome-based CNV analysis makes trio-WES a more powerful tool for clinical diagnosis in neurodevelopmental disorders: a retrospective study

Yiwen Zhai Xiangdong Kong
The First Affiliated Hospital of Zhengzhou University

Object: Neurodevelopmental disorders (NDDs), a genetically heterogeneous setting, affect 1-3% of children. Genetic factors such as pathogenic variants in single genes and chromosomal structural variants or copy number variants (CNVs) have been identified as etiology of NDDs. To evaluate the clinical yields of combined SNV/Indel analysis and exome-based CNV analysis from a single trio-WES test in the diagnosis of NDDs.
Method: Trio-WES was performed on a cohort of 74 pedigrees with NDDs and then proceeded to SNV/Indel analysis and exome-based CNV analysis. The diagnostic SNV/Indel variants were validated by Sanger sequencing. The suspected CNVs>100kb were validated by CNV-seq, and CNVs<100Kb were validated by real time-qPCR, respectively.
Results: An overall positive diagnostic yield of 54.05% (40/74) was obtained in the pipeline of combined SNV/Indel and CNV analysis, including 35.13% (26/74) from SNV/Indel analysis and 18.92% (14/74) from exome-based CNV analysis, respectively. In total, SNV/Indel analysis identified 38 variants in 28 different genes, of which 24 variants were novel; exome-based CNV analysis identified 14 CNVs, including 2 duplications and 12 deletions, which ranged from 440 bp (single exon) to 16.86 Mb (large fragment) in size.
Our findings facilitated the clinical diagnosis, treatment and prenatal diagnosis. The trio-exome-based CNV analysis revealed a single-exon deletion in *SLC16A2*, in a setting of normal karyotype, CMA and SNV/Indel analysis of WES data, leading to a diagnosis of Allan-Herndon-Dudley syndrome for an affected boy. In the cohort, we identified the heterozygous variants in guanidinoacetate N-methyltransferase (*GAMT*) gene: c.158_181+7del (r.spl?) and c.181G>A (p.G61R) in two affected individuals from the same family by SNV/Indel analysis. Both of the variants were novel. Based on the diagnosis of cerebral creatine deficiency syndrome 2 (CCDS2, OMIM: #612736), two affected boys were treated with oral creatine. The follow-up study after 18-

months treatment showed that the symptoms of NDDs in the 4 years old boy was improved, however the elder boy (14 years old) did not benefit from the treatment. With the diagnosis, the family also benefited from the prenatal diagnosis, obtaining an unaffected, healthy baby.
Conclusion: The incorporation of CNV detection into the typical SNV/Indel analysis pipeline for trio-WES significantly improved diagnostic yields on NDDs (54.05% vs 35.13%), making WES as a more powerful, practical and cost-effective tool in clinical diagnosis.

全外显子组测序技术在 361 例智力落后患儿中的应用

覃再隆 谌飞 阳奇 张强 易升 周训钊 苏家荪 张淑杰 张钦乐 李萌 江蕙芸 邹林霞 阮毅燕 罗静思
广西壮族自治区妇幼保健院

目的 应用全外显子组测序技术（whole exome sequencing，WES）分析智力落后患儿的遗传学病因，评估其诊断价值，分析智力落后患儿的基因突变谱。
方法 对 2016 年 3 月至 2020 年 7 月间，广西壮族自治区妇幼保健院儿科门诊和病房收治的 361 例智力落后/发育迟缓患儿进行全外显子组测序，通过生物信息学分析，结合患儿临床表型寻找致病变异，经 Sanger 测序家系验证，并根据美国医学遗传学与基因组学学会（ACMG）的基因变异解读指南完成致病性评估。
结果 （1）在 361 例患儿中检出阳性病例 187 例，阳性率为 51.8%。其中常染色体显性遗传 35.29%（66/187），常染色体隐性遗传 20.32%（38/187），X 连锁遗传 14.44%（27/187）。共检测到点突变 162 个，其中致病性变异 53.70%（87/162），可能致病性 36.42%（59/162），临床意义不明 9.88%（16/162）。染色体片段拷贝数异常 49 例，共检出拷贝数变异 60 个，其中拷贝数减少 88.46%（44/60），拷贝数增加 23.33%（14/60），拷贝数变异中致病性 91.67%（55/60），临床意义不明 8.33%（5/60）。（2）按变异类型分类，错义变异 48.77%（79/162），无义变异 15.43%（25/162），移码变异 22.22%（36/162），剪切位点变异 9.88%（16/162），外显子拷贝数缺失 1.85%（3/162），inframe indel 0.62%（1/162）。（3）未报道变异位点 51.23%（83/162），de novo 变异位点 41.36%（67/162）。（4）检出的致病变异主要涉及 IDS、MECP2、KMT2C、MYT1L、SMARCC2 等基因，另外还检测到染色体拷贝数变异 49 例，包括 15q11.2 微缺失 6 例，18p11.32 微缺失 3 例。
结论 导致智力落后的原因较为复杂，涉及的基因变异较多，WES 能检出 SNV 和 CNV，可作为智力落后的一线分子诊断方法。本研究发现的新致病性变异扩大了智力落后患儿的基因突变谱，为遗传咨询、产前诊断、疾病再发风险评估提供理论依据。

以神经系统损害为主要表型的甲基丙二酸血症患儿临床和遗传学分析

王朝[1,2,3] 舒剑波[1,2,3] 张培元[1] 李东[1] 张玉琴[1]
1.天津市儿童医院（天津大学儿童医院）
2.天津市儿科研究所
3.天津市儿童出生缺陷防治重点实验室

【目的】探讨以神经系统损害为主要特点的甲基丙二酸血症（MMA）患儿的临床表现和致病基因突变特征，为 MMA 患儿的诊疗和遗传咨询提供参考。

【方法】搜集天津市儿童医院 2013 年至 2020 年确诊的以神经系统损害为主要临床表现的 MMA 患儿。所有患儿均进行了全面的体格和实验室检查。利用 Sanger 测序法和高通量测序方法进行基因检测。

【结果】共 44 例 MMA 患儿有精神运动发育落后、癫痫、脑病和硬膜下积液中一种或多种诊断。患儿中男性 28 例，女性 16 例，年龄在 52 小时至 16 岁之间，年龄中位数为 1 岁。所有患者尿甲基丙二酸均值为 930.46（正常值<1），甲基枸橼酸均值为 23.79（正常值<1）。根据血清总同型半胱氨酸检测结果，判定 33 例患儿为合并型，8 例为单纯型，3 例未分型。所有患儿的神经损

害中精神运动发育落后最多，见于 56.82%（25/44）的患儿中。其次为癫痫、脑病和硬膜下积液分别见于 40.91%（18/44）、18.18%（8/44）和 9.09%（4/44）的患儿。几乎所有患儿有多种其他临床表型，其中呼吸性/代谢性酸中毒见于 34.09%（15/44）的患儿，电解质紊乱见于 22.73%（10/44）的患儿，贫血见于 18.18%（8/44）的患儿，粒细胞减少或缺乏见于 15.91% （7/44）的患儿，脏器衰竭见于 13.64% （6/44）的患儿。个别患儿并发有先天性心脏缺陷、高氨血症、血糖水平异常、血小板减少等。此外呼吸道感染或炎症见于 50.00%（22/44）的患儿，可能与免疫功能低下有关。31 例患儿进行了基因诊断，其中 cblC 型 25 例，mut 型 4 例，cblD 型 1 例。共发现 *MMACHC* 基因突变 14 种，其中错义突变 5 种，无义突变 4 种，重复突变 3 种，缺失突变 2 种。最常见突变为 c.609G>A、c.658-660delAAG 和 c.394C>T，出现频率分别为 42.00%（21/50）、18.00%（9/50）和 10.00% （5/50）。*MUT* 突变共 7 种，其中错义突变 3 种，剪接位点突变 2 种，重复突变 1 种，插入突变 1 种。cblD 患儿 *MMADHC* 基因存在纯合突变 c.24-25delAG。

【结论】所有类型 MMA 患儿的神经损害中以精神运动发育落后最多见，其次为癫痫、脑病和硬膜下积液。以神经系统损害为主的 cblC 患儿的 *MMACHC* 突变谱与中国 cblC 患者整体突变谱基本一致。

NLRP7 突变导致常染色体隐性遗传复发性葡萄胎三例

沈鉴东 孙雪萍 高彦 吴畏 刘金勇 彭雅文 谢佳孜 汪道武 崔毓桂 刘嘉茵 刁飞扬
南京医科大学第一附属医院（江苏省人民医院）

目的 分析复发性葡萄胎分子遗传学病因。
方法 收集 6 个家系的 7 个具有复发性葡萄胎病史的女性患者外周血，常规方法提取 gDNA，其中 2 个家系采用 PCR 结合 Sanger 测序技术检测 NLRP7 和/或 KHDC3L 外显子编码区及外显子和内含子交界区域序列变异，另外 4 个家系采用外显子组测序（ES）分析筛查 NLRP7、KHDC3L、PADI6、MEI1、REC114、TOP6BL 等复发性葡萄胎相关基因变异情况。
结果 在 3 个家系 4 个患者中发现 NLRP7 基因纯合或者复合杂合突变，其中患者 P1 和 P2 均为 NLRP7 exon 1-4 纯合缺失，患者 P5 为 NLRP7 c.939delG (p.Gln314SerfsTer6) pat 和 c.1533delG(p.Asn512ThrfsTer4) mat 复合杂合突变，患者 P6 为 NLRP7 c.2389_2390delTC(p.A798Qfs*6) pat 和 c.2165A>G(p.D722G) mat 复合杂合突变，所有变异根据 ACMG 致病性标准判读为致病性或者疑似致病性变异。
结论 NLRP7 基因突变是导致复发性葡萄胎的重要分子基础，明确分子诊断，有利于提供准确的遗传咨询；此外，本研究丰富了复发性葡萄胎相关的 NLRP7 基因突变谱。

唐氏综合症患儿外周血 miRNA 谱分析及鉴定 miR-29a-3p 参与神经退行性病变的 Aβ 降解途径的研究

李书香 宋萃 石宇 江伟 张云 吴瑞 吴莉婷 桂俊峰
重庆医科大学附属儿童医院

本研究旨在阐明唐氏综合征(Down syndrome, DS)患儿中 miRNA 的差异表达谱，并探讨靶 miRNA 是否参与了 DS 患者 β 淀粉样肽(amyloid β peptide, Aβ)的生成调控。采用 miRNA 芯片分析 DS 患者血清中的 microRNA 表达谱。通过 qRT-PCR 进一步验证感兴趣 mirna 的差异表达。采用双抗体夹心酶联免疫吸附法检测病例组和健康对照组血浆 Aβ40、Aβ42 水平，采用 RT-PCR 检测胰岛素降解酶(Insulin degradation enzyme,IDE)表达水平。在病例组和健康对照组中进行 miR-29a-3p 与 IDE 的相关性分析，并通过 Targetscan 预测其结合位点。研究发现，病例组和健康组共发现 167 种不同的 miRNAs，与健康组相比，其中病例组有 81 种 miRNAs 明显上调，86 种 miRNAs 下调。感兴趣 miRNA 的 qRT-PCR 结果与基因芯片数据一致。病例组的 Aβ40、Aβ42 和 IDE 表达水平显著高于健康组。此外，我们发现差异性表达的 miR-29a-3p 的水平与 IDE 呈负相关。Targetscan 预测 IDE 的 3 ' UTR 有 miR-29a-3p 的结合位点。总之，我们的研究结果表明，miR-29a-3p 及其靶点

IDE 的调节可能参与了神经退行性病变的 Aβ 的产生过程。我们的研究有望为唐氏综合症患者的发病机制提供潜在分子机制，特别是为与 Aβ 代谢相关的神经退行性病变的发展提供了线索。

Retrospective analysis of the risk factors associated with failure in obtaining effective noninvasive prenatal test results and pregnancy outcomes: a case-control study

Yanmei Lu
Department of Genetic Eugenics, Changsha Maternity and Child Health Hospital

Objective To explore the pregnancy outcomes of women who could not obtain effective results from noninvasive prenatal testing (NIPT) and examine the factors leading to test failure.
Methods From April 2017 to December 2019, 120,041 pregnant women enrolled for voluntary NIPT. The case group comprised of 274 (274/120,041) women who failed to obtain effective NIPT results, and the control group (n=540) was from the same population who obtained effective NIPT results and matched by age at a 1:2 ratio. Abnormal pregnancy rates between the two groups were analyzed using Chi-square analysis. NIPT failure risk factors were analyzed using logistic regression analysis.
Results Logistic regression analysis showed that increased maternal age (OR=0.988; 95% CI = 0.982-0.994), increased pregnancy age (OR=0.989; 95%CI = 0.988–0.991), and decreased cell-free fetal DNA concentration (OR=1.050; 95%CI=1.043–1.058) were independent risk factors for NIPT failure. 15 cases showed adverse pregnancy outcomes in case of NIPT failure. There was a significant difference in abnormal pregnancy rate between the NIPT success and failure groups ($\chi 2 = 50.943$, $P < 0.05$).
Conclusion There was an increased risk of adverse pregnancy outcomes in case of pregnant women who failed to obtain effective NIPT results.

Expression of CYB5D2 is associated with epithelial-mesenchymal transition and survival rates in patients with cervical cancer

Yanan Sun[1,2] Fengxiang Wei[1,2] Jinjiang Su[1]
1.Longgang District Maternity&Child Healthcare Hospital of Shenzhen City
2.Anhui Medical University

Abstract: objective A case of congenital central hypopnea syndrome (CCHS) was analyzed by whole exon sequencing to explain the phenotypic pathogenicity variation of CCHS at the gene level. Methods Whole-exome sequencing was employed to explore the potential causative genes in a 37+2-week-old patient. We used the Sanger sequencing method to detect the mutated genes. The pathogenic variation was compared with the database and the previous experimental methods to determine the mutant gene's pathogenicity.
Results Family members showed that heterozygous variation :741-758 dupCGCGGCAGCGGCGGCGGC(insertion variation) existed at the PHOX2B of congenital central hypopnea syndrome gene, which resulted in amino acid change p. A260-G261insAAAAAA (insertion variation), but neither of their parents carried this variation. A chromosome of congenital central hypopnea patients inserted six alanine in the region, resulting in 26 repeats, genotype: 20/26.
Conclusion A 758-759 insertion of exon 3 of the PHOX2B gene in this patient into six alanine, a typical polyalanine repeated extended mutant heterozygote, phenotype: 20/26. Combined with typical clinical phenotypic sleep can not be fully ventilated, lack of spontaneous regulation of respiratory rhythm, normal respiratory frequency and reduced tidal volume are identified as congenital central low-throughput syndrome and can explain the pathogenicity of the patient's phenotype.

国人先天性晶状体脱位的突变频谱及基因型—临床表型的关联研究

郭东炜[1] 郑丹莹[1] 靳光明[1] 郭奕斌[2]
1.中山大学中山眼科中心
2.中山大学医学院医学遗传学教研室

目的 探究国人先天性晶状体脱位(Congenital ectopia lentis, CEL)的基因突变频谱，明确 CEL 患者基因型与眼部临床表型之间的关联。
方法 对 2017 年 3 月至 2020 年 4 月就诊于中山眼科中心的 93 名 CEL 患者进行详细的眼科及全身系统检查，通过裂隙灯显微镜、主觉验光、IOL Master 等检查采集患者的最佳校正视力、眼轴、角膜曲率及角膜散光、晶状体脱位程度等眼部参数。通过提取患者 DNA 进行全外显子测序，依据所检测突变的类型、突变区域、氨基酸改变等进行亚组分析，比较不同基因型与眼部临床表型之间的关联。
结果 在 93 名 CEL 患者中,65 人携带 *FBN1* 基因突变，53 人可诊断为马方综合征。错义突变在 *FBN1* 突变中占 75.4%，主要集中在基因的 5'区。携带错义突变的患者的角膜散光(*P*=0.046)和晶状体脱位的程度(*P*=0.006)均显著高于截断突变的患者。
结论 本研究显示，以错义突变为主的 *FBN1* 基因突变是我国 CEL 患者最常见的基因突变类型。在携带 *FBN1* 突变的患者中，错义突变患者的眼部临床表型如角膜散光、晶状体的脱位程度，相较截断突变患者而言更为严重。

Application of fetal cell-free DNA enrichment in non-invasive prenatal screening: experience from a single center in Eastern China

Ying Lin Dong Liang Ping Hu Hang Li Chunyu Luo Zhengfeng Xu
Nanjing Maternity and Child Health Care Hospital

Background The fetal cell-free DNA (cfDNA) in the maternal plasma can be enrichment for NIPS using size-selection method. Here, we set out to assess the feasibility and efficacy of the NIPS with fetal cfDNA enrichment in a clinical setting.
Methods A total of 3599 women with a singleton pregnancy were enrolled in this study. Plasma samples were aliquoted and tested with both original NIPS and NIPS with fetal cfDNA enrichment in parallel. The test metrics, including sensitivity, specificity, from the two methods were analyzed and compared. In addition, we evaluated the efficacy of fetal fraction elevation and its relationship with maternal BMI and gestational age.
Results NIPS with fetal cfDNA enrichment showed a sensitivity of 100% and a specificity of 99.95% for common trisomies, and the 'no call' rate was significantly reduced (0.06% vs 0.47%, P < 0.001). The level of fetal fraction increase was significantly higher in 14.1-21.0 weeks group than that in 12.0-14.0 weeks group (P=0.016) and 21.1-26.4 weeks group (P<0.001). Furthermore, the level of fetal fraction increase in overweight women was found to be significantly higher than that in women with low weight and normal weight (P<0.01).
Conclusions The advantages of NIPS with fetal cfDNA enrichment were revealed in a clinical setting. Furthermore, we uncovered the relationship between the major fetal fraction associating factors and the efficacy of fetal fraction increase during the size-selection procedure.

Application of karyotype analysis combined with CMA technique in prenatal diagnosis of balanced translocation carriers

Liping Li Yongyi Zou Tingting Huang Shuhui Huang Bicheng Yang Yanqiu Liu
Medical Genetic Center; Jiangxi Provincial Key Laboratory of Birth Defect for Prevention and Control,Jiangxi Maternal and Child health Hospital

Objective To explore the reproductive risk and the application of chromosome karyotype analysis combined with chromosome microarray analysis (CMA) in balanced translocation carriers in the second trimester of pregnancy.
Methods Interventional amniocentesis was performed on pregnant women when one partner has a balanced chromosomal translocation, and chromosome karyotype analysis and CMA detection were performed to analyze the results. What's more, the early pregnancy abortion, pregnancy of abnormal fetus and birth of normal children in 56 couples with balanced translocation carriers was analyzed when combined with the childbearing history.
Results Among 56 couples with balanced translocation carriers collected in this study, there were 168 pregnancies except this one, among which the total number of abortions and embryo damage occurred in the early trimester was 107, accounting for 63.69%. There were 1 induced labor due to fetal chromosomal imbalance and translocation, 3 induced labor due to fetal malformation, and 2 stillbirths in utero during the second trimester. The total fetal abnormality rate was 67.26%. There were 32 fetuses with normal phenotype, accounting for 19.05%. In the prenatal diagnosis, a total of 21 cases (37.5%) of fetuses were detected without abnormal chromosomal karyotype and CMA, 23 cases (41.07%) with balanced chromosomal karyotype translocation and no abnormal CMA results, 5 cases (8.93%) with unbalanced chromosomal karyotype translocation and CMA showed partial deletion and duplication of fetal chromosomes. In 5 cases (8.93%), fetal chromosome was completely normal or balanced translocation, and CMA showed microdeletion or microduplication of fetal chromosome. There were 2 cases (3.57%) of fetal chromosome aneuploidy.
Conclusions 1.The proportion of early pregnancy abortion, termination, large-month stillbirth or malformation and abnormal birth of fetus in natural pregnancy of balanced translocation carriers is higher than that in normal population. 2. Chromosome karyotype analysis combined with CMA detection was more comprehensively and accurately detect fetal chromosomal abnormalities in prenatal diagnosis of balanced translocation carriers. The two technologies complement and verify each other, which can effectively prevent the birth of fetus with chromosomal abnormality.

钠通道 SCN5A 基因 V1951L 突变致短 QT 综合征 机制及相关研究

朱鑫
南昌大学第二附属医院

本团队发现编码 SCN5A 基因 R689H 突变致钠通道功能缺陷可能引起心脏兴奋性和电传导速度降低、心室动作电位的缩短，导致 QT 间期短。本研究发现一名反复晕厥患者，经过严格的诊断为 SQTS，基因测序发现存在 SCN5A 基因 V1951L 突变，钠通道基因突变是否是导致 SQTS 的病因还需进一步研究。SCN5A 基因编码的 Nav1.5 蛋白是构成钠通道的重要组成蛋白，其表达数量与功能直接影响钠通道功能。MOG1 是在酵母中发现的一种 Ran 结合蛋白，能在调控核蛋白的运输中发挥重要作用，广泛参与核质转运，微管装配，核装配等过程。研究显示 MOG1 能与 Nav1.5 结合，协助 Nav1.5 向细胞膜靶向转运，提高 Nav1.5 在细胞膜上表达。MOG1 蛋白在 SCN5A 基因 V1951L 突变相关短 QT 综合征中作用尚不明确，能否发挥拯救作用还需要进一步研究。使用抗心律失常药物胺碘酮灌洗细胞，探究药物对通道功能的影响。

Genetic landscape of DNA repair defects in human monogenic disorders

Niu Li Yufei Xu Ruen Yao Tingting Yu Guoqiang Li Lei Yin Yong Yin Xiumin Wang Jian Wang
Shanghai Children's Medical Center

DNA repair plays an important role in maintaining genome stability and homeostasis, defects of which may lead to various human genetic diseases. However, the contribution of DNA repair defect (DRD) in monogenic diseases is poorly understood. Here, we retrospectively analyzed a cohort of 9,107 unrelated patients of suspected inherited origin, and obtained an overall diagnostic rate of 33.5% (3,052/9,107). We assigned causal germ line variation in 384 patients from 95 candidate DNA repair genes, including 22 canonical and 73 non-canonical genes. Compared to other repair pathways, genes attributed to double-strand break repair account for the largest proportion. We proposed that DRDs account for 15.4% (2.9% in canonical, and 12.5% in non-canonical) of monogenic diseases. Patients with multiple system involvement were the most common (44.3%, 170/384), and often presented with neurological features. The incidence of cardiac, facial, and genital features in non-canonical group was twice that of canonical group. Our study is the first comprehensive study on the clinical and molecular characterization of DRD, also the first map of the DNA repair genes from the perspective of monogenic diseases, which provides a rich resource for further molecular research, and has implications for individualized management of patients with DRD.

全外显子组测序鉴定一个家系的 DMD 基因突变

黄盛文
贵州省人民医院

目的 对于一个疑似 Duchenne 肌营养不良（DMD）家系的致病基因进行检测和分析，为该家系提供遗传咨询依据。
方法 先证者，男，7 岁。临床表现有：走路呈摇摆状，鸭形步态，易倾倒，爬楼困难，腰部肌肉萎缩。CT 检查提示：双髋关节后缘软组织及双侧股骨上段周围软组织密度减低。家族中另有 7 名男性有类似症状，发病年龄均在 3 岁左右，症状逐渐加重。其中 2 人已死亡，死亡年龄分别为 17 岁和 20 岁，4 人已瘫痪在床。4 个已瘫痪的患者均进行了神经电生理检查，结果提示进行性肌营养不良。家族中的女性无类似症状。采集该家系三代共 21 人外周血样本，其中男性患者 6 例，无症状男性 3 例，女性 12 例。提取基因组 DNA，先后采用多重连接探针扩增（MLPA）和家系全外显子组测序（Trio-WES）检测先证者致病基因及突变位点。采用 Sanger 测序对家系其他成员进行致病位点验证。
结果 MLPA 未检出先证者 X 染色体上 *DMD* 基因缺失突变。Trio-WES 发现先证者 *DMD* 基因的 48 号外显子有一半合子变异：NM_004006.2:c.6963delA（p.Asp2322ThrfsTer16），母亲为该位点的杂合子，父亲为野生型。家系验证结果：其余 5 个患者均为该突变位点的半合子，无症状男性未检出该突变位点，12 名女性中有 7 例为该位点的杂合子携带者。此次检测到的 *DMD* 基因 NM_004006.2:c.6963delA（p.Asp2322ThrfsTer16）因 c.6963 缺失了一个 A 碱基，导致移码变异（frameshift variant），产生无功能的截短蛋白。在千人基因组、ExAC 和 gnomAD 外显子数据库中均未收录该变异，ClinVar 及 HGMD 专业版数据库中未见报道。*DMD* 基因缺陷导致的 Duchenne 肌营养不良症（DMD）与该家系中患者的表型一致，符合家系共分离，遗传方式为 X 连锁隐性遗传。根据 ACMG 变异分类指南，该变异的致病性分级为致病，证据包括 PVS1、PM2_Supporting 和 PP4。
结论 经 Trio-WES 和 Sanger 测序，确诊先证者及家系中其他患者为点突变型 DMD，致病位点 c.6963delA 为首次发现的 *DMD* 基因突变位点，丰富了 *DMD* 基因突变谱。检测结果为患者及家属遗传咨询提供了依据。

串联质谱技术结合目的基因捕获测序进行遗传代谢病基因诊断

王锦 易丹英 秦胜芳 尹雁 叶梦玲 张卓 席娜 宋筱 欧明才 汪雪雁
四川省妇幼保健院

目的 遗传代谢病是由于基因变异导致机体生化代谢紊乱，通常累及多系统多器官，包括氨基酸病、有机酸血症、过氧化酶体病、溶酶体病等，总体发病率高达 1/5000~1/1400。遗传代谢病的临床和遗传异质性以及串联质谱检测假阳性等，有必要结合基因诊断对常见的代谢性疾病进行鉴别诊断。

方法 采用 GenCap® 遗传代谢疾病基因捕获探针 V5.0 自定义探针捕获试剂盒，包含常见遗传代谢病相关 481 个基因的外显子区域，以及 HGMD 数据库报道的深度内含子区域致病位点，对 GCH1、OTC、PAH 基因增加探针覆盖密度，一次性分析点突变+大片段缺失重复。目标区域测序覆盖度>95%，测序平均深度>300x，20x 覆盖度>97%。测序数据经 TGex、dbNSFP 等软件进行生物信息分析。结合临床症状，相关疾病数据库与文献查阅，候选基因变异家系 Sanger 测序验证，并根据 ACMG/AMP 基因变异解读指南进行致病性评估。

结果 串联质谱筛查异常病例明确基因诊断率为 46.03%（87/189 例，致病性及可能致病性基因变异），均为隐性遗传性疾病，其中复合杂合 73 例，纯合/半合 16 例，合并外显子缺失的病例 6 例。另外在 15 例样本中仅检测到一个隐性遗传病的致病性杂合变异位点，以及非临床症状相关的致病性基因变异 2 例，尚未报道的基因变异占比 29.41%（35/119 个）。氨基酸代谢异常基因诊断率为 63.48%（73/115），脂肪酸氧化代谢异常基因诊断率为 53.13%（17/32），有机酸代谢异常基因诊断率为 34.62%（9/26），其中最多的是苯丙酮尿症/高苯丙氨酸血症 56 例，其次是原发性肉碱缺乏症 9 例。

结论 遗传代谢病临床症状复杂、遗传异质性高，高通量测序技术的应用推动了遗传代谢病的鉴别诊断和精准治疗，改善预后，也为家庭再生育提供遗传学证据。

Novel variants of SMARCA4 gene revealed autistic features rather than typical Coffin-Siris syndrome in eight Chinese pediatric patients

Yanyan Qian Huijun Wang Yuanfeng Zhou Bingbing Wu Huiyao Chen Suzhen Xu Yao Wang Ping Zhang Gang Li Qiong Xu Wenhao Zhou Xiu Xu
Children's Hospital of Fudan University

Autism spectrum disorders (ASDs) were a group of neurodevelopmental-related disorders with a high genetic risk. Recently, chromatin remodeling factors have been found to relate to ASDs. SMARCA4 is such a catalytic subunit of chromatin-remodeling complex. In this report, we identified seven novel missense variants in *SMARCA4* gene from eight pediatric patients. All eight patients had moderate to severe intellect disability and seven showed autistic/ likely autistic features. Compared with the patients reported in literature, our patients were less likely to show craniofacial anomalies, or finger/toe anomalies. We also compare the phenotypes of the patients carrying variants in different protein domains. Although the pathogenic variants in *SMARCA4* distracted in the protein domains, they were clustered in the catalytic core region. In addition, some clinical features, like motor delay, brain or heart anomalies, and frequent infection, were more frequent showed in the patients with pathogenic variants in the catalytic core region. Our finding further supported that *SMARCA4* is associated with ASDs. We suggest that individuals with those phenotypes take genetic testing into account, since a genetic diagnosis would better the patients' clinical assessments and treatments.

Study on the pathogenicity of FOXK2 in congenital ptosis

Peixuan Wu[1] Jing Ma[1,3] Tianyu Zhang[3] Duan Ma[1,2]
1.Fudan University
2.Children's Hospital of Fudan University
3.ENT institute, Eye & ENT Hospital, Fudan University

Background and Objects Congenital ptosis, also known as blepharoptosis, is defined as congenital maldevelopment of the levator palpebrae superioris or as lid ptosis present since birth. The estimated prevalence varies between 0.79 and 1.99 in 10,000 people among different populations. It is considered to be a complex disease resulting from the genetic and environmental factors, while the susceptibility genes have not be discovered. Abnormal mitochondrial morphology has been found in eyelid samples from congenital ptosis patients, while its mechanisms is still unclear. Our study was to explore the pathogenicity of the new candidate susceptibility gene *FOXK2* in congenital ptosis.
Material and methods Blood samples from a pedigree with congenital ptosis were collected for whole exome sequencing and deep bioinformatics analysis. The eyelid muscle samples from eight sporadic congenital ptosis patients and six normal control were collected for detecting the expression level of *FOXK2* expression,. *Foxk2*-knockout (*Foxk2*-KO), *Foxk2*-overexpressed (*Foxk2*-OE) of mouse C2C12 myoblast cell line were constructed. Then, cell migration was investigated by wound healing assay. The function of *Foxk2* on myoblast differentiation were detected by qPCR, western blot and immunofluorescence. The expression of mitochondria and autophagy related genes, the ATP content, mitochondrial membrane potential and ROS content in cells were detected to explore the effect of *Foxk2* on mitochondria and autophagy. The *Foxk2* knockout mouse models were consctructed for observing the role of *Foxk2* on muscle development.
Results *FOXK2* gene with point mutation c.643C>T was screened out in the pedigree to be as the the new candidate susceptibility for congenital ptosis, the downregulation of FOXK2 in the eyelid muscle tissue was also found in congenital ptosis. *Foxk2*-KO inhibited the migration and differentiation of C2C12 cells. The decreased expression of mitochondrial related genes, the increased expression of autophagy related genes, the reduced ATP production, the lower mitochondrial membrane potential, and the increase in ROS content were observed in *Foxk2*-KO cell line. Compared with wildtye, the rescue effect of c.643C>T on the phenotypes above were much weaker . The ptosis, weight loss, the decease in the mass and volume of gastrocnemius and tibialis anterior muscle, and hudding of hind limbs were observed in *Foxk2* knockout mouse.
Conclusions FOXK2 deficiency inhibited myoblast migration and differentiation due to mitochondrial dysfunction and increased autophagy, affecting muscle development related to the pathogenesis of congenital ptosis**.**

Comparative exome sequencing reveals novel candidate genes for retinitis pigmentosa

Zhen Yi Jiamin Ouyang Wenmin Sun Shiqiang Li Xueshan Xiao Qingjiong Zhang
Zhongshan Ophthalmic Center, Sun Yat-sen University

Purpose Retinitis pigmentosa (RP) is the most common form of inherited retinal degeneration, but genetic defects in nearly half of families remain unresolved. This study aims to identify novel genes associated with RP based on whole exome sequencing (WES) data from 552 probands with RP.
Methods Biallelic loss-of-function (LoF) variants were selected from the WES data of 552 probands with RP and compared with that of 4728 in-house controls and the gnomAD database. Expression analysis and knockout mice model or knockdown zebrafish model were performed to confirm the association of a few candidate genes with RP.
Results Unique biallelic LoF variants in *ENSA*, *DACT2*, *DDR1*, and *CCDC188* were identified in four probands with RP, but were absent in 4728 in-house controls and were extremely rare in the

gnomAD database. The expression of ENSA was enriched in the rod outer segments of human retina, and significant reduced responses of rod and cone were detected in *Ensa* knockout mice compared to wild-type mice by electroretinogram. The *DACT2* transcript showed the highest expression in human retina and knockdown of *dact2* in zebrafish resulted in photoreceptor disc membrane disarrangement.
Conclusions This study suggests that *ENSA* is likely a novel gene for RP and *DACT2* is a potentially candidate gene for RP. Further studies are expected to evaluate the association between mutations in the other two genes and RP. To our knowledge, mutations in these genes have not been reported to be associated with RP before.

CACNA1F 基因的致病变异和相关表型特征

孙文敏 黎仕强 王攀峰 贾小云 肖学珊 张清炯
中山大学中山眼科中心

目的 *CACNA1F* 基因变异是遗传性视网膜变性的常见原因之一，可导致不同的疾病，如先天性静止性夜盲、锥杆细胞营养不良、Aland Island 眼病等。本研究的目的是基于课题组大样本量的外显子组测序数据，分析 *CACNA1F* 基因的致病变异和表型特点。
方法 从课题组已有的外显子组测序数据中选择 *CACNA1F* 基因的变异，通过生物信息学方法评估变异的致病性，对携带致病变异的病人，详细分析和总结其临床表现的特点。
结果 通过生物信息学对课题组的大样本量外显子组测序数据分析显示，*CACNA1F* 基因的致病变异均为半合子，绝大多数为截断变异，少数为错义变异，个别为非移码缺失变异。携带致病变异的先证者表现出一定的共性，包括：起病早；视网膜电流图显示重度的视锥细胞反应振幅降低，视杆细胞反应呈现负波；后极部眼底表现为视盘黄斑间后巩膜葡萄肿和环视乳头的后巩膜葡萄肿。
结论 生物信息学分析可较为有效的评估 *CACNA1F* 基因变异的致病性。本组携带该基因致病变异的患者，未表现出三种不同疾病的区分，而是表现为共性的具有特征 ERG 和眼底表现的锥杆细胞营养不良。本研究扩展了对 *CACNA1F* 基因致病变异以及表型特征的认识，有助于对携带该基因变异患者的临床诊疗。

全外显子测序与 RNA 测序双组学揭示 ATM 基因中的复合杂合变异

顾春钰[1] 王洪[2,3] 舒剑波[3,4] 郑洁[3] 李东[2,3] 张培元[2,3] 蔡春泉[3,4,5]
1.天津医科大学研究生院
2.天津市儿童医院神经内科
3.天津市儿童医院（天津大学儿童医院）
4.天津市儿童医院（天津大学儿童医院）天津市儿科研究所，天津市儿童出生缺陷防治重点实验室
5.天津市儿童医院神经外科

目的 共济失调毛细血管扩张症(ataxia-telangiectasia, A-T)是一种罕见的常染色体隐性遗传性疾病，临床特征为进行性小脑共济失调，球结膜毛细血管扩张，肿瘤易感性，放射敏感和免疫缺陷等。疾病表型具有异质性，误诊或漏诊较为多见，本文探讨 1 例具有非典型临床症状患者的临床诊断及遗传学病因。
方法 签署知情同意书后，采集患者、姐姐及父母外周静脉血，提取基因组 DNA 和 RNA。应用 WES 对先证者进行致病变异筛查，使用 Sanger 测序法对先证者及其家系成员进行验证。利用 RNA 测序技术对先证者外周血转录组谱进行序列分析。
结果 WES 结果显示先证者 *ATM* 基因存在第 40 号外显子 c.5939_5948del 杂合缺失变异，是新变异，该变异遗传自父亲。RNA 测序检出 *ATM* 基因存在两个杂合变异，其一与 WES 结果一致，其二为第 17 号内含子发生碱基置换 c.2639-384A>G，引起邻近区域剪接水平改变，该变异遗传自健康携带者母亲。

结论 *ATM* 基因第 40 号外显子 c.5939_5948del 与第 17 号内含子 c.2639-384A>G 构成的复合杂合变异为本例患者发病的遗传学病因，结合患者临床表现、免疫学检测等检查结果，考虑诊断为共济失调毛细血管扩张。该变异丰富了 *ATM* 致病基因变异谱，为 A-T 临床诊断及遗传咨询提供依据。对于通过 WES 只检测到一种变异的临床怀疑常染色体隐性遗传疾病，我们建议使用 WES 与 RNA 测序相结合的双组学进行研究。

Alport 综合征致病基因 COL4A5 基因胶原区新发移码突变疾病动物模型的建立

匡新宇[1] 龚秀丽[2,3] 蔡勤[2,3] 孙蕾[2,3] 冯丹[1] 吴滢[1] 张静[1] 曾凡一[2,3] 黄文彦[1]
1.上海交通大学附属儿童医院，肾脏风湿科
2.上海交通大学附属儿童医院，上海医学遗传研究所
3.上海市胚胎与生殖工程重点实验室，国家卫健委医学胚胎分子生物学重点实验室

目的 X 连锁显性遗传 Alport 综合征（XLAS）是 *COL4A5* 基因突变所致的儿童罕见肾脏疾病，临床表现为进行性肾功能减退，最终只能依赖透析和肾移植。胶原区是 *COL4A5* 基因最重要的功能区，但由于该基因突变众多、缺乏热点突变，给突变的致病性判定造成了很大的困扰。目前仅有 2 种 *COL4A5* 基因无义突变小鼠模型，但尚未有胶原区移码变异的小鼠模型。为了研究 *COL4A5* 基因胶原区突变致病的机制，本研究拟构建 *COL4A5* 基因胶原区新发移码突变小鼠模型，并探索其致病功能性。
方法 临床诊断一例肾功能衰竭的 XLAS 患儿，并通过全外显子测序鉴定患儿及其父母的突变位点。应用 CRISPR/Cas9 技术，以此位点为编辑靶点构建突变小鼠模型并繁育种群。对点突变小鼠模型，自 6 周龄至 24 周龄每周/次进行尿液蛋白和肌酐水平测定；同时在 8 周、12 周、20 周、24 周进行血肌酐、尿素氮和白蛋白水平测定。在 8W 和 25W 分别进行半合子和杂合子小鼠肾脏电镜检测。
结果 临床诊断的一例 XLAS 患儿，16 岁男性，表现为肉眼血尿、大量蛋白尿、双侧感音神经性耳聋，同时伴有肾功能进行性下降，现血液透析治疗中。该患儿父母及亲属无相关临床表现。全外显子测序提示患儿存在 *COL4A5* 基因胶原区移码突变 c.2440delG（p.Gly814fs）。生物信息学分析显示该变异可导致 COL4A5 蛋白截短，尚未见该变异的相关报道。患儿父母基因检测未检出该基因突变，提示该变异为患儿自发的 *COL4A5* 基因新发突变。利用 CRISPR/Cas9 技术，成功构建了 *COL4A5* 基因移码突变 c.2440delG 定点突变小鼠，并繁育成系。与野生型小鼠相比，半合子（$X^{mut}Y$）和杂合子（$X^{mut}X$）小鼠均从 8 周龄起出现尿蛋白/肌酐的显著升高，且 $X^{mut}Y$ 小鼠尿蛋白/肌酐水平明显高于 $X^{mut}X$ 小鼠，与患儿临床大量蛋白尿表现相符。血检结果提示 $X^{mut}Y$ 小鼠自 8 周龄起即出现了血肌酐、尿素氮的明显升高及白蛋白的显著降低，且呈现快速增长模式，这与突变患儿肾功能进展相一致。而 $X^{mut}X$ 小鼠肾功能变化则较为平缓，未出现明显的肾功能异常。电镜检测可见 $X^{mut}Y$ 小鼠在 8 周龄出现肾小球基底膜厚薄不均，$X^{mut}X$ 小鼠在 25W 出现部分基底膜厚薄不均的表现，提示该变异可导致肾小球基底膜出现异常改变。
结论 本研究首次发现一例 *COL4A5* 基因胶原区新发移码突变 Gly814fs 致 XLAS 患儿，并成功构建了 *COL4A5* 基因移码突变小鼠模型，其表型和该患儿临床表现相符，为后续的精准治疗和机制探讨提供了良好的研究基础。

中国汉族人群华法林稳定剂量与基因型的关联研究

徐青青 秦胜营
上海交通大学

目的 华法林是瓣膜性心脏病的常用抗凝剂，在预防血栓形成事件的临床管理中起着重要作用。在本研究中我们对 211 名心脏瓣膜病患者进行全面系统的遗传学分析，旨在挖掘更多影响中国汉族人群华法林稳定剂量的基因标记。

方法 根据华法林药物在人体内参与发挥凝血和抗凝作用途径的 10 个重要基因（CYP2C9、VKORC1、ABCB1、CYP4F2、APOE、PROC、GGCX、EPHX1、CALU 和 SETD1A）作为候选基因，相应的共筛选到 40 个单核苷酸多态性（SNP）。我们应用 MassARRAY 技术对这些瓣膜性心脏病患者的 40 个 SNP 进行基因分型。
结果 我们的结果表明，6 个基因（CYP2C9、VKORC1、ABCB1、PROC、EPHX1 和 SETD1A）上的 13 个 SNP 与个体华法林稳定剂量相关，其中 2 个 VKORC1 SNP（rs9934438 和 rs2359612）是决定华法林稳定剂量存在个体差异的最强关联的基因变异（分别为 P = 8 × 10−6 和 9 × 10−6）。在我们的研究中，首次报道 SETD1A 中 rs4889599 与华法林剂量相关，经过 Bonferroni 校正后的 P= 0.040，具有统计学意义。
结论 我们发现 CYP2C9、VKORC1、ABCB1、PROC、EPHX1 和 SETD1A 的遗传变异可能影响中国汉族人群瓣膜病患者对华法林稳定剂量的影响。这些潜在遗传标记的发现将促进中国瓣膜性心脏病患者个性化抗凝治疗的发展。

Genetic and clinical landscape of high myopia in preschool children

Qingjiong Zhang
Zhongshan Ophthalmic Center, Sun Yat-sen University

High myopia presenting in preschool children, or early-onset high myopia (eoHM), is generally believed to be determined mostly by genetic factors. A significant proportion of high myopia may actually belong to or progress to pathologic myopia due to its frequent association with degenerative changes in the retina, choroid, vitreous, sclera, and optic nerve. This subgroup of high myopia is a major cause of preventable blindness in Children. A great number of progress has been made on genetic study of high myopia, especially in the identification of genes responsible for it when mutated. Based on exome sequencing nearly ten thousand of individuals with different eye conditions, including about one tenth of eoHM, we could get a brief view on the genetic landscape of currently known genes contributed to eoHM. Subsequent genotype-based phenotype analysis revealed some of the clues that can be used to monitor the risk of blindness consequence. Understanding genetic defects and associated ocular changes may greatly facilitate the prevention and management of this common vision-threating condition in children.

Risk Factors associated with End-Stage Kidney Disease (ESKD) in children with Congenital Anomalies of the Kidneys and Urinary Tracts (CAKUT): A comparative cohort study of the Chinese Children Genetic Kidney Disease Database

Jialu Liu[1] Cuihua Liu[2] Xiaowen Wang[3] Xiaojie Gao[4] Bingbing Wu[5] Jia Rao[1] Duan Ma[6] Qian Shen[1] Hong Xu[1]
1.Department of Nephrology, Children’s Hospital of Fudan University, National Children’s Medical Center
2.Department of Nephrology and Rheumatology, Children's Hospital Affiliated to Zhengzhou University
3.Department of Nephrology and Rheumatology, Wuhan Children's Hospital
4.Department of Nephrology, Shenzhen children's hospital
5.Clinical Genetic Center, Children’s Hospital of Fudan University, National Children’s Medical Center
6.Key Laboratory of Metabolism and Molecular Medicine, Ministry of Education, Department of Biochemistry and Molecular Biology, Institutes of Biomedical Sciences, School of Basic Medical Sciences, Fudan University

Background Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of end-stage kidney disease (ESKD) in children. The aim of this study was to evaluate factors associated with ESKD and underlying genetic abnormalities in children and adolescents

with CAKUT. Focusing on the severe end of the CAKUT may help identify modifiable or disease predictive factors.
Methods The genotype and phenotype of 568 CAKUT patients were collected and analyzed based on a national multicenter registration network (Chinese Children Genetic Kidney Disease Database, CCGKDD, www. ccgkdd.com.cn) covering 27 different provinces/regions in China from 2014 to 2020. The rate of gene mutations between different clinical feature were analyzed. The renal survival was established by Kaplan-Meier curves. The risk factors for ESKD were examined via Cox proportional hazards models.
Results We identified a CAKUT gene mutation in 46 patients (8.1%), an abnormal copy number variation (CNV) in 19 patients (3.4 %) and a chromosomal abnormality in 4 patients (0.7%). No gene mutations were observed in patients with isolated MCDK (five patients), renal ectopia (one patient), PUJO (one patient), horseshoe kidney (three patients), and megalobladder (two patients). Patients with positive family history, extrarenal phenotype and renal hypoplasia/dysplasia (RHD) exhibited higher rates of genetic risk factors than those without (29% vs. 11%, P < 0.01; 28% vs. 6%, P < 0.01 and 20% vs. 7%, P < 0.01). Moreover, 512 patients did micturating cystourethrogram (MCU) examination, more frequently genetic risk factors were found in bilateral CAKUT patients than in unilateral CAKUT patients (12% vs. 5%, P < 0.01), and in vesicoureteral reflux (VUR) with other CAKUT than in isolated CAKUT (9% vs. 5%, P =0.08). Furthermore, there were no significant differences in concordant or discordant CAKUT, VUR grade and bilateral or unilateral VUR.
ESKD occurred in 75 (13.2%) patients during the follow-up period. Prognostic analyses with the Cox proportional hazards regression model and Kaplan-Meier survival curves further identified that RHD (HR = 2.33, 95% CI: 1.19-4.56), prenatal diagnosis (HR =2.28, 95% CI: 1.30-4.00), and Genetic factors **(***EYA1, GATA3, HNFB1, PAX2*) (HR =2.18, 95% CI: 1.18-4.04) as an independent risk factor for the prognosis of kidney survival time.
Conclusions CAKUT patients with positive family, RHD, and extrarenal manifestations were significantly related to gene mutations. We recommend that CAKUT- related gene analysis be considered in cases of these patients. The present study identified that genetic factors, RHD, and prenatal diagnosis as useful prognostic factors for the kidney survival time.

The investigation of genetic and clinical features in patients with X-linked hypohidrotic ectodermal dysplasia

Yupei Wang
Gansu Provincial Maternity Child-care Hospital

Aim Hypohidrotic ectodermal dysplasia (HED) is the most common ectodermal dysplasia (ED) featured by hypotrichosis, hypohidrosis, cranial abnormalities, hypodontia and other oral characterization. Ectodysplasin A (EDA) mutation is the main pathogenic factor for HED. This research aims to investigate genetic and clinical features in patients with X-linked hypohidrotic ectodermal dysplasia in northwest China.
Methods We recruited three HED families. The clinical symptoms of patients and pedigree charts were presented. Using next-generation sequencing (NGS), the molecular genetic defects were analyzed. Variants in the *EDA* gene were identified by bioinformatics analysis and confirmed by Sanger sequencing. The pathogenicity of all the mutations was evaluated by guidelines of the American College of Medical Genetics and Genomics (ACMG). The effect of the splicing mutation was further verified by *EDA* minigene *in vitro*.
Results Three variants of *EDA* gene in the small cohort were identified, two variants (c.396+1 G>C and c.171-173 del GTT) had not been reported previously, and one variants of entire deletion of exon 1 (Del exon 1) was firstly reported in China. Minigene analysis of splicing mutation (c.396+1 G>C) showed a prolonged EDA-A1 transcript containing extra 699 bp of intron 1 after exon 1, demonstrated a functional cryptic splice site formation caused by splicing donor site mutation of *EDA* gene. Three mutations all affected exon 1 and were responsible for X-linked hypohidrotic ectodermal dysplasia (XLHED) with varying degrees of phenotype.

Conclusion We identified two novel mutations and investigated the pathogenic mechanism of splicing mutation in *EDA* gene, which will be a positive supplement to mutation spectrum of *EDA* gene, in favor of the clinical diagnosis, genetic counseling, and prenatal diagnosis of HED.

SERAC1 突变诱发青少年发作的复杂遗传性痉挛性截瘫的基因分析

闫单单[1,2,3] 支秀芳[1] 舒剑波[1,2,3] 蔡春泉[1,2,3] 张培元[1,4] 李东[1,4] 张玉琴[1,4]
1.天津市儿童医院（天津大学儿童医院）
2.天津市儿科研究所
3.天津市儿童出生缺陷防治重点实验室
4.天津市儿童医院神经科

目的 *SERAC1* 双等位基因突变可引起 MEGDEL 综合征（3-甲基戊烯二酸尿症，伴耳聋、脑病及 leigh 样综合征），临床特征是尿液中 3-甲基戊烯二酸尿症排泄增加，肌张力减退，锥体外系症状，行走不能， 语言发育不良或无，基底节病变等，然而导致这种疾病的机制是尚不清楚。 在这项研究中，我们介绍了一个中国家庭患儿因 *SERAC1* 突变而引起的代谢和肌张力障碍，但先证者的临床表型与之前报道的 MEGDEL 不同，结合相关症状初步认为先证者因 *SERAC1* 突变导致了青少年发作的复杂遗传性痉挛性截瘫（cHSP：uvenile-onset complicated hereditary spastic paraplegia），为了更好地研究 *SERAC1* 突变与 cHSP 之间的关系，探究患儿病因及相关遗传学机制，我们阐述了患儿的基因变异情况。
方法 在这项研究中，通过全外显子组测序（WES）发现了患儿携带两个新的突变；对该患者进行了临床和影像学表型分析；通过 Sanger 测序对新突变进行验证；利用各种软件预测新突变的致病性。
结果 WES 测序结果显示患儿携带 *SERAC1* 基因第 14 外显子的错义突变 c.1495A> G（p.Met499Val），该变异临床意义不明；携带 *SERAC1* 基因第 8 外显子的移码突变 c.721_722del（p .Leu242fs），该变异可疑致病，并且会导致蛋白质翻译提前终止； Sanger 测序结果证明，错义突变 c.1495A> G（p.Met499Val）来自于父亲，移码突变 c.721_722del（p .Leu242fs）来自于母亲，符合孟德尔遗传模式；临床检查中，尿液中的 3-甲基戊烯二酸增加 T2WI 及 FLAIR 序列见双侧基底节区对称性小片状高信号影； 先证者表现出青少年发作的复杂遗传性痉挛性截瘫症状。
结论 本研究表明，患儿表现出的时轻时重的跛行症状可能与携带 *SERAC1* 突变基因有关，而且该研究进一步扩大了 *SERAC1* 基因的变异谱和 SERAC1 缺乏症的表型谱，这些均有助于产前诊断和遗传咨询。

关于总蛋白水平和血糖异常对 CYP2C19 基因突变的脑动脉狭窄患者的氯吡格雷疗效影响的研究

郝思嘉 胡馨元 姜艳芳
吉林大学第一医院

研究背景 *CYP2C19* 多态性与脑血管病和冠心病中主要不良心脑血管事件(MACCEs)的风险增加有关。
目的 研究 *C*YP2C19 多态性与 MACCEs 的发生率的关系，并探讨肝功能、肾功能、血糖水平对 MACCEs 发生率的影响，评估脑动脉狭窄患者 MACCEs 发生率的预测因子。
方法:收集 2016 年 10 月至 2019 年 12 月在吉林大学第一医院基因诊断进行 CYP2C19 基因多态性检测的 1406 例患者信息。其中 362 例经我院神经外科诊断为脑动脉狭窄，164 例患者接受脑动脉支架手术，138 例患者接受保守治疗。计算 CYP2C19 各基因型、等位基因和表现型分布频率。比

较基因多态性、肝功能、肾功能、血糖水平与 MACCEs 发生率的相关性。采用 Cox 比例风险模型和 Kaplan-Meier 分析评估脑动脉狭窄患者 MACCEs 发生率的预测因子。
结果 CYP2C19 *1/*1 是人群中最主要的基因型(41.96%)。接受保守治疗的患者，血糖 > 6.5 mmol/L 发生 MACCEs 的机率更大(p = 0.022)。放支架组的患者，CYP2C19 LOF 等位基因变异(p = 0.020)、ALT 水平(p = 0.022)、总蛋白水平(p = 0.020)和血糖水平(p = 0.019)与脑动脉支架患者 MACCEs 风险增加相关。并在多变量 Cox 分析中，CYP2C19 基因型(p = 0.032)，总蛋白< 65 g/L (p = 0.017); 血糖 > 6.5 mmol/L (p = 0.028)与 MACCEs 显著相关。
结论 CYP2C19 LOF 等位基因变异、总蛋白水平和血糖异常协同影响脑动脉支架患者 MACCEs 的风险。

多种羧化酶缺乏症的筛查、诊断与治疗专家共识

黄新文
浙江大学医学院附属儿童医院

多种羧化酶缺乏症（MCD）包括常染色体隐性遗传的全羧化酶合成酶(HLCS)缺乏症和生物素酶(BTD)缺乏症，分别因 *HLCS* 及 *BTD* 基因变异所致，表现为神经皮肤综合征和有机酸尿症，但在起病年龄、神经症状和代谢失代偿等方面有所不同，须与获得性生物素缺乏或其他遗传代谢病鉴别，确诊需结合血尿生化特点、酶活性和基因检测。新生儿筛查 HLCS 缺乏症基于干血滤纸片 3-羟基异戊酰基肉碱等指标，BTD 缺乏症基于 BTD 活性检测。大部分 MCD 常规生物素剂量 5-20mg/d 疗效显著，少数 HLCS 缺乏症需要大剂量生物素 100-200mg/d 治疗，与其 *HLCS* 基因变异位于 N 端底物结合区有关。

NYS7 位点内非编码区结构变异导致先天性眼球震颤

孙文敏 黎仕强 贾小云 王攀峰 肖学珊 张清炯
中山大学中山眼科中心

目的 基于课题组前期在两个先天性眼球震颤大家系中连锁定位在 1q32.1 的 NYS7 位点，鉴定致病变异。
方法 在两个家系中分别选择一例先天性眼球震颤病人，对两例病人的基因组 DNA 进行短读长和长读长全基因组测序分析，对其中一个家系的一例患者和一例正常同胞的基因组 DNA 进行比较基因组杂交分析，在连锁定位区域中筛选致病变异，并通过 Sanger 测序在全部家系成员中验证。
结果 通过短读长测序分析排除了连锁区域内的蛋白编码基因的变异，而是提示可能是非编码区的大片段缺失变异。进一步比较基因组杂交分析提示连锁区域内约 0.89Mb 的缺失。长读长测序分析进一步明确两个家系中分别有 914,377 bp 和 794,505 bp 的缺失变异，通过 Sanger 测序证实这两个结构变异分别在两个大家系中与先天性眼球震颤共分离。这两个变异重叠的缺失区域为 0.78Mb，其中未包含任何已知蛋白编码基因，根据已知 Hi-C 数据库预测该该区域包含 TAD 边界，可能通过影响基因组三维结构而致病。
结论 本研究结果进一步证实基因组非编码区结构变异可通过影响三维基因组结构而导致人类遗传病，也为探索先天性眼球震颤发生的分子机制提供线索。

吉林省 APOE 基因多态性与血脂水平分布的研究

胡馨元 郝思嘉 姜艳芳
吉林大学第一医院

目的 研究报告 APOE 基因多态性与血脂水平分布相关，本研究纳入脑血管病和冠心病患者的 ApoE 基因多态性的分布特点,并探讨基因多态性与个体血脂水平的关系.

方法 收集 2018 年 1 月至 2021 年 5 月于吉林大学第一医院就诊的脑血管病和冠心病患者 836 例,用荧光 PCR 法检测 ApoE 基因多态性，并通过统计分析方法 One-Way ANOVA 分析其与血脂水平的相关性。
结果 ApoE 等位基因 E3 所占比例最多为 83.13%（695/836），其次为 E4 9.1%（76/836）, E2 7.77%（65/836）；APOE E3/E3 基因型占比最高 68.18 %（285/836），依次为 E3/E4 16.03%（67/836），E2/E313.87 %（58/836），E2/E41.19%（5/836），E4/E4 0.4%（2/836），E2/E 20.2%（1/836）。ApoE E4 等位基因 LDL 水平 为 2.74mmol/L，显著高于基因型为 E3（2.69 mmol/L）及 E2（2.38 mmol/L）的患者（P=0.019）。ApoE E4 等位基因 APOA1 水平为 1.15 g/L，显著高于基因型为 E2（1.12g/L）及 E3（1.09 g/L）的患者（P=0.019）。
结论 吉林省脑血管病和冠心病患者中，ApoE 基因型为 E4 的患者 LDL 及 APOA1 显著升高，ApoE 基因多态性与高脂血症有关，对他汀类药物治疗高脂血症的临床疗效也有一定影响。

46，XY 外生殖器畸形 220 例临床和分子遗传学分析

罗静思 覃再隆 谌飞 阳奇 张强 易升 易赏 钱家乐 张晓菲 唐晴 沈亦平
广西壮族自治区妇幼保健院

目的 应用全外显子组测序技术（whole exome sequencing，WES）分析 46，XY DSD 患儿的遗传学病因，评估其诊断价值，分析广西地区 46，XY DSD 基因突变谱。
方法 对广西壮族自治区妇幼保健院儿科门诊和病房收治的 220 例 46，XY DSD 患儿（年龄 4d ~ 18y）进行全外显子组测序，利用生物信息分析测序数据，结合临床表型寻找致病变异，经 Sanger 测序、基因芯片等家系验证，并根据美国医学遗传学与基因组学学会（ACMG）的基因变异解读指南完成致病性评估。
结果 （1）220 例患儿中检出阳性病例 81 例，检出率为 36.82%，检测到变异位点 127 个，其中致病性 66.14%，可能致病性 22.83%，临床意义不明 11.02%。（2）按变异类型分类，错义变异 80.32%，无义变异 5.51%，移码变异 3.15%，剪切位点变异 3.15%, CNV 变异 7.87%。（3）经软件预测及 ACMG 评估，发现 25 个未报道的变异，致病性 9 个，可能致病性 6 个，临床意义不明 10 个，其中 7 个为新发变异。（4）按照临床表型分组，尿道下裂（A, n=67），阴茎短小（B, n=161），隐睾/睾丸发育不良（C, n=122），阴囊发育差（D, n=48），检出阳性率分别为 46.27%，38.51%，34.43%，35.42%，差异无统计学意义(p=0.432)。临床表型合并组：A+B（n=48）、B+C(n=79)、A+B+C(n=16)，A+B+C+D（n=5）检出阳性率分别为 54.17%，35.44%，56.25%，60%，差异无统计学意义（p=0.122）。（5）发现 5α 还原酶缺乏症 40 例，占 49.38%，SRD5A2 热点突变为 c.680G>A，c.677G>A，c.16C>T，分别 57.50%，22.50%，5%，发现 1 个新致病位点 c.696-1G>A。其次低促性腺激素功能减退症 8 例，占 9.88%（8/81），涉及 FGFR1、KISS1R、PROKR2 基因。（6）发现 10 例与性发育不良相关综合征，其中 CHARGE 综合征 3 例，Kallmann 综合征 2 例，雄激素不敏感综合症、Prader-Willi 综合征、3M 综合征、类努南样综合征、努南综合征 8 型各 1 例。
结论 46，XY DSD 涉及的基因变异较多, WES 可作为一线分子诊断方法。广西地区最常见突变基因为 SRD5A2，尿道下裂患儿基因突变检出率相对高。本研究发现的新致病性变异扩大了 46，XYDSD 患儿的基因突变谱，为遗传咨询与产前诊断提供理论依据。

全外显子组测序技术在 152 例骨骼异常患儿中的应用

罗静思 覃再隆 谌飞 张强 阳奇 易升 周训钊 张晓菲 钱家乐 沈亦平
广西壮族自治区妇幼保健院

目的 应用全外显子组测序技术分析骨骼异常患儿的遗传学病因，评估其诊断价值，分析骨骼异常患儿基因突变谱。

方法 对 2016 年 3 月至 2020 年 6 月，广西壮族自治区妇幼保健院儿科及优生遗传科收治的 152 例骨骼异常患儿进行全外显子组测序，通过生物信息学分析，结合患儿临床表型寻找致病变异，经 Sanger 测序家系验证，并根据 ACMG/AMP 的基因变异解读指南完成致病性评估。
结果 （1）在 152 例患儿中检出阳性病例 86 例，阳性率为 56.58%。其中常染色体显性遗传 61.63%，常染色体隐性遗传 22.09%，X 连锁显/隐性遗传均为 8.14%。共检测到 104 个变异，致病性变异 66.35%，可能致病性 30.77%，临床意义不明 28.85%。（2）按变异类型分类，错义变异 45.19%，无义变异 18.27%，移码变异 12.50%，剪切位点变异、外显子缺失均为 5.77%，inframe del 1.92%，CNV loss 7.69%，CNVgain 2.88%。（3）未报道变异 38 个（44.19%），其中新发变异 17 个。（4）产前骨骼异常相关的致病变异主要涉及 ALPL、COL1A1、COL1A2、FGFR3、DYNC2H1 等基因，产后主要涉及 PHEX、RUNX2、GALNS、IDS 等基因。（5）发现 8 例罕见综合征，其中 Ellis-van Creveld 综合症、3M 综合征各 2 例,歌舞伎综合征、德朗热综合征 1 型、Schaaf-Yang 综合征、Ayme-Gripp 综合征各 1 例。
结论 涉及骨骼异常的基因变异较多，且以常染色体显性遗传的新发变异为主，WES 可作为一线分子诊断方法。新致病性变异扩大了本地区骨骼异常患儿的基因突变谱，为遗传咨询与产前诊断提供理论依据。

PLCG2 基因新突变致 APLAID 的临床表型和基因分析

彭琪 陆小梅 马达 姚志广 雒东 饶春宝
东莞市第八人民医院（东莞市儿童医院）

目的 自身炎症、磷脂酶 Cγ2(PLCγ2)相关抗体缺乏和免疫失调(APLAID)是一种常染色体显性遗传的自身炎症性疾病。本文旨在分析一位临床表现为 APLAID 患儿的遗传学病因，探索其分子发病机制。
方法 收集患儿及家系成员临床资料，利用全外显子测序（WES）技术对患儿及父母进行测序, 筛选致病基因突变, 并进行 Sanger 测序验证。进一步利用 PolyPhen-2 等预测软件对筛选出来的突变的致病性进行预测；采用流式细胞术对患儿外周血免疫细胞进行全面分析。采用 RayBiotech 芯片技术对患者及与其年龄性别相匹配的健康儿童外周血浆中 40 种细胞因子进行检测。
结果 测序结果显示患儿 PLCG2 基因存在 c.2534T>C 突变，该突变为错义突变，可导致其编码蛋白 PLCγ2 第 845 位氨基酸由亮氨酸变为丝氨酸(p.Leu845Ser)，多种生物信息学软件预测为致病性。该突变为未报道过的新突变，而患儿家系正常成员均未检出该突变。患儿外周血中循环记忆性 B 细胞显著减少，符合 APLAID 的典型特征。此外，患儿外周血浆中 IL-12、IL-2 等细胞因子同样明显减少（$p<0.05$）。
结论 PLCG2 基因的新突变 c.2534T>C 为该 APLAID 患儿的致病原因，本研究拓宽了 PLCG2 基因的突变谱，有助于加深对 ALPAID 发病机制的认识，并进一步为临床精准医疗提供一定的理论基础。

Molecular genetic, biochemical, and clinical characterization in three Chinese with Carbamoyl Phosphate Synthetase 1 Deficiency

Wei Ji Xiaofen Zhang Yanmin Wang Zhuo Zhou Guoli Tian
Department Neonatal Screening Center, Children's Hospital of Shanghai, Shanghai Jiao Tong University

Background Carbamoyl phosphate synthetase I (CPS1) deficiency (CPS1D)is a rare autosomal recessive genetic disordercharacterized by life-threatening hyperammonemia.CPS1D can develop at any age, with extremely variable clinical manifestations and rapid disease progression. Currently, biochemical testing is difficult to make a clear diagnosis, so based on biochemical testing, genetic testing is essential for the accurate diagnosis of CPS1D.

Methods A retrospective analysis of the Clinical features,Biochemical date,disease outcome and molecular genetic characteristics of 3 CPS1D patients from 3 unrelated families diagnosed by whole exome sequencing (WES) in Shanghai Children's Hospital from January 1, 2016 to December 1, 2020.This article used bioinformatics tools to conservatively analyze and predict the pathogenicity of the identified mutants.
Results Two patients with onset in the neonatal period, the disease progressed rapidly, the clinical symptoms were severe, and one case had an insidious disease.Both biochemical analysis and amino acid profile were abnormal. Genetic analysis revealed seven pathogenic variants in the CPS1 gene,fourof which were novel, includingthree missense mutations(c.1927A>G,c.2375T>G ,c.1784T>G) ,and one nonsense mutation(c.338A>T).Multiple online tools were used to predict that the four new mutations were pathogenic, and these four related amino acids were highly conserved in evolution.
Conclusions New mutations expand the mutation spectrum of CPS1, and the results of bioinformatics analysis help to better understand the clinical course and genetic characteristics of patients with urea cycle disorders.

CPAMD8 双等位基因变异导致原发性开角型青光眼及原发性闭角型青光眼

李雪晴 孙文敏 肖学珊 方蕾 黎仕强 刘杏 张清炯
中山大学中山眼科中心

目的 本研究旨在基于外显子组测序的系统性分析，评估 *CPAMD8* 双等位基因变异在青光眼亚群，尤其是原发性开角型青光眼（POAG）及原发性闭角型青光眼（PACG）的贡献。
方法 对收集的不同眼遗传病患者的全外显子组测序进行多重生物信息学分析，挑选出 *CPAMD8* 的可疑致病变异。*CPAMD8* 的基因型-表型分析在本研究的数据分析及对既往文献报道的系统性回顾的基础上进行。本研究同时检测 *CPAMD8* 的 mRNA 及蛋白质水平在人体组织的表达情况。
结果 7 个 *CPAMD8* 致病双等位基因变异，包括 1 个移码突变和 6 和错义突变，在 5 位青光眼患者中显著富集，而在对照组未检测到（$p<0.001$）。这 5 位青光眼患者包含 1 名青少年型青光眼（JOAG）患者，2 名 POAG 患者及两名 PACG 患者。*CPAMD8* 的双等位基因变异在以上 5 名青光眼患者中的表型相对眼前段发育不良或先天性青光眼轻微。在 mRNA 水平，*CPAMD8* 的表达在视神经、睫状体、视网膜及虹膜组织中高表达。相应地，蛋白质水平上，通过免疫荧光组织染色发现 CPAMD8 在虹膜和睫状突的非色素上皮细胞高表达。
结论 本研究不仅仅证实了 *CPAMD8* 的双等位基因致病变异导致 JOAG，而且将表型谱拓展到 POAG 及 PACG。

FOXI3 突变在外中耳发育异常中的致病性研究

马竞[1,3] 陈鑫[1,3] 陈颖[3] 李辰龙[3] 张天宇[3] 马端[1,2]
1.复旦大学
2.复旦大学附属儿科医院 3.复旦大学附属眼耳鼻喉科医院

背景 先天性小耳畸形是由于胚胎期第一、二鳃弓以及神经嵴细胞分化发育不良而导致外中耳形态结构及功能的异常。根据有无合并其他器官结构或功能异常，综合征型小耳畸形往往是单基因疾病，大多数已经发现了明确的致病基因。而非综合征型小耳畸形，在先天性小耳畸形中的占比最高可达 85%，在我国约为 73.41%。它是一种多基因疾病，受环境、遗传和表观遗传因素共同影响，其中遗传变异在疾病的发生发展中起重要作用。目前研究尽管发现了其少数几个较明确的易感基因，但远不足以解释非综合征型小耳畸形，而且很多遗传变异的和疾病的关系没有得到验证，分子机制也不明确。
材料与方法 为了深入研究先天性非综合征型小耳畸形的遗传学病因，我们对 47 个非综合征型小耳畸形家系全血样本进行全外显子组测序（whole-exome sequencing，WES）和生物信息学分析，

对筛选出来的新的候选易感基因叉头框 I3（ forkhead box I3，*FOXI3* ）基因的变异进行了 Sanger 测序验证以及致病性预测。在体内应用 CRISPR/Cas9 技术构建同源基因 *foxi3a/b* 敲降的荧光标记斑马鱼模型，在共聚焦显微镜下观察神经嵴细胞以及人类中耳骨的同源结构下颌软骨神经嵴细胞的变化情况，利用 TMR red 和 BrdU 分别原位检测神经嵴细胞凋亡和增殖的情况。通过对胎鼠耳廓组织进行免疫组化确定 FOXI3 表达部位，qPCR 检测不同软骨及皮肤相关细胞系 *FOXI3* 表达水平选择适合体外实验的细胞系；收集表皮细胞 A431 上清进行细胞因子芯片检测，并构建 FOXI3 过表达及敲低细胞稳转株，通过 Western blot、Elisa 等方法检测细胞内外细胞因子的变化；利用 CoIP-MS 检测 FOXI3 的互作蛋白。

结果 我们在 5 个非综合征型小耳畸形家系中发现 *FOXI3* 基因分别存在 5 个突变，包括 4 个错义突变和 1 个缺失移码突变，其中 1 个错义突变位于核心 DNA 结合结构域，可能影响了 FOXI3 与靶基因的结合，另外 3 个错义突变靠近核定位序列，提示这些突变很可能影响 FOXI3 入核；缺失移码突变导致蛋白截短，丧失 C 末端反式激活域，从而可能影响了 FOXI3 的转录活化。这 5 个突变在不同物种间高度保守，且预测均有致病性。应用 Sanger 测序进行验证，基因突变和表型在每个家系里均共分离。在斑马鱼模型中，我们发现 foxi3a/b 在胚胎发育早期表达逐渐上调，在 96hpf-120hpf 表达最高。下调 foxi3a/b 的斑马鱼整体发育无明显异常，24hpf 以及 48hpf 时神经嵴细胞数均显著减少，凋亡增加，增殖减少；72 和 120hpf 时下颌软骨发育延迟。FOXI3 主要表达于胎鼠耳廓的表皮，而在耳软骨中不表达；在软骨细胞系和间充质干细胞中 *FOXI3* 也均不表达，但在表皮细胞系中高表达，故选择表皮细胞系 A431 进行体外研究。A431 的细胞培养上清富集了软骨发育相关的细胞因子（PDGF-AA、 PDGF-AB、 TGF-α、TGF-β），而且在 A431 细胞中上调 FOXI3 后发现这些细胞因子的含量在细胞内和细胞外都增加，下调后都减少；根据 MS 分析的结果，筛选出与 FOXI3 可能结合的影响软骨发育的蛋白 NME1 和 PPP2A2R。

结论 *FOXI3* 的突变可能通过影响 PPP2R2A、NME1 的表达或功能，导致表皮细胞分泌软骨发育相关因子异常，从而影响软骨细胞的增殖和分化，最终导致先天性小耳畸形的形成。

串联质谱技术在过氧化物酶体病筛查中应用的研究

王燕敏 田国力
上海市儿童医院

目的 探讨串联质谱（MS/MS）检测极长链酰基肉碱（VLCAC）和溶血磷脂酰胆碱（LPC）在过氧化物酶体病诊断价值，了解疾病的临床特征及基因变异特点。

方法 选取以发育迟缓等神经系统异常就诊 205 例小儿，组成 X-连锁肾上腺脑白质营养不良组（X-ALD 组,14 例），Zellweger 综合征组（ZS 组，4 例）和发育迟缓组（187 例），同期同年龄 200 例体检小儿为正常对照组。收集所有对象的滤纸干血片样本，使用含稳定同位素内标[二十六碳酰基肉碱（^{2}H3-C26）和二十六碳溶血磷脂酰胆碱（^{2}H4-C26：0-LPC）]的溶剂萃取滤纸干血片样本中的 VLCAC 和 LPC（非衍生化法），直接采用 MS/MS 检测二十碳酰基肉碱（C20）、二十二碳酰基肉碱（C22）、二十四碳酰基肉碱（C24）、二十六碳酰基肉碱（C26）、二十碳溶血磷脂酰胆碱（C20：0-LPC）、二十二碳溶血磷脂酰胆碱（C22：0-LPC）、二十四碳溶血磷脂酰胆碱（C24：0-LPC）和二十六碳溶血磷脂酰胆碱（C26：0-LPC），对 8 个指标和相应 8 个比值在各组间比较；采用受试者工作特征（ROC）曲线评估各项指标诊断过氧化物酶体病的效能；分析 X-ALD 和 ZS 的临床和基因特征。**结果** 所有指标和比值在各组间差异均有统计学意义；两两组间比较显示各指标有不同程度的差异，但 X-ALD 组和 ZS 组间无差异；ROC 曲线分析显示曲线下面积(AUC)大于 0.9 有 7 个指标，依次为 C26、C24、C24:0-LPC、C26:0-LPC、C24/C22、C24/C20、 C26/C22，其中 C26 的 AUC 为 1.0；18 例患儿均有 VLCAC 和 LPC 不同程度增高，基因结果显示，*ABCD1* 基因的半合突变 14 例，*PEX1* 基因复合杂合突变 3 例和 *PEX10* 纯合突变 1 例；临床表现与 VLCAC 和 LPC 结果以及基因突变类型无关联性。

结论 MS/MS 检测 VLCAC 和 LPC 可作为过氧化物酶体病筛查的方法，其中 C26 或可作为诊断敏感指标；基因检测是过氧化物酶体病分型和治疗的标准。

PARD3 基因在腭裂中的突变及机制研究

李娜[1] 崔人婕[1] 胡颖熹[1] 葛润生[1] 郭珈妮[1] 姜楠[1] 张进[1] 马端[1,2]
1.复旦大学
2.复旦大学附属儿科医院

背景 非综合征型腭裂 (NSCP) 是一种常见的先天性畸形。本研究发现一中国汉族腭裂家系，家系图谱分析显示，该家系的遗传模式呈常染色体显性遗传。通过对该家系患病成员进行全外显子测序分析，结果显示 PARD3 基因编码区 1012 位点存在 G 单碱基插入 c.1012dupG，形成 p.E338Gfs*26 移码突变。本文旨在研究 PARD3 该突变位点的分子机制以及 PARD3 在腭裂中的突变频率。
材料方法和结果 PARD3 基因在斑马鱼中的同源基因有 pard3aa 和 pard3ab，针对其设计特异性 sgRNA，通过 CRISPR-CAS9 技术进行敲除，观察表型，进一步用细胞模型对 PARD3 突变体的功能进行探索与验证。并通过 Sanger 测序在腭裂散发病例中检测 PARD3 编码区 DNA 序列。
对 pard3aa 和 pard3ab 进行敲除后观察到斑马鱼上腭中筛板的发育形态出现异常，在表达突变体 PARD3 的三维培养模型中，内源 PARD3 的定位发生了改变，由细胞的紧密连接处改变至基底面。另外，在散发性单纯性腭裂家系中，PARD3 也表现出了较高的突变频率。
结论 我们推测 PARD3（c.1012dupG）突变是一个新的非综合征型腭裂突变致病候选基因。

Which type of chromosomal mosaicism is compatible for embryo transfer: a systematical review and meta-analysis

Yuanlin Ma
Reproductive Medicine Center, the First Affiliated Hospital, Sun Yat-sun University

Objectives To study which features of chromosomal mosaicism identified during preimplantation genetic testing for aneuploidy (PGT-A) is compatible for embryo transfer.
Design Systematic review and meta-analysis.
Setting Not applicable.
Patient(s) Patients who had a mosaic embryo transferred in PGT-A.
Intervention(s) Summary odds ratios (ORs) were calculated using fixed- or random-effects models.
Outcome measure(s): Implantation rate (gestational sac) (IR), miscarriage rate (MR), and ongoing pregnancy/live birth rate (OP/LBR).
Result(s): A total of six studies with 1,086 cycles that fulfilled the selection criteria were included in this meta-analysis. Comparable IR, MR and OP/LBR were observed when comparing embryos with mosaicism level < 50% and ≥ 50% [OR 1.42, 95% CI (1.06, 1.89); OR 0.45, 95% CI (0.27, 0.75); OR 1.74, 95% CI (1.28, 2.37)], embryos with mosaicism only involving whole chromosome(s) and only affecting segmental chromosome(s) [OR 0.76, 95% CI (0.58, 0.99); OR 1.69, 95% CI (1.05, 2.72); OR 0.66, 95% CI (0.50, 0.87)]. In addition, pooled results of the limited studies comparing embryos with only mosaic gains or losses had significant higher IR and OP/LBR than with complex mosaicism (embryos mosaic for combined losses and gains) [gains *vs* complex: OR 1.75, 95% CI (1.20, 2.54); OR 1.73, 95% CI (1.16, 2.58). losses *vs* complex: OR 1.90, 95% CI (1.34, 2.71); OR 2.10, 95% CI (1.44, 3.07)]. We also found that mosaic embryos with only one chromosome involved had significant favorable outcomes of IR and OP/LBR than with more than three chromosomes involved [OR 1.76, 95% CI (1.23, 2.52); OR 1.86, 95% CI (1.25,2.78)].
Conclusion(s) This pooled analysis provided evidence to support the ranking of transfer priority among embryos with mosaicism. Embryos with mosaicism level ≥ 50%, with mosaicism involving whole chromosome(s), with multiple mosaic abnormalities, and with more than three chromosomes involved were likely to have less priority in the ranking of transfer.

Genetic diagnosis spectrum and multigenic burden of exome-level rare variants in a childhood epilepsy cohort

Ruen Yao
Shanghai Children's Medical Center

Objective Childhood epilepsy is a considerably heterogeneous neurological condition with a high worldwide incidence. Genetic diagnosis of childhood epilepsy provides the most accurate pathogenetic evidence; however, a large proportion of highly suspected cases remain undiagnosed. Accumulation of rare variants at the exome level as a multigenic burden contributing to childhood epilepsy should be further evaluated.
Methods In this retrospective analysis, exome-level sequencing was used to depict the mutation spectra of 294 childhood epilepsy patients from Shanghai Children's Medical Center, Department of Neurology. Furthermore, variant information from exome sequencing data was analyzed apart from monogenic diagnostic purposes to elucidate the possible multigenic burden of rare variants related to epilepsy pathogenesis.
Results Exome sequencing reached a diagnostic rate of 30.61% and identified six genes not currently listed in the epilepsy-associated gene list. A multigenic burden study revealed a three-fold possibility that deleterious missense mutations in ion channel and synaptic genes in the undiagnosed cohort may contribute to genetic risk of childhood epilepsy, whereas variants in the gene categories of cell growth, metabolic, and regulatory function showed no significant difference.
Significance Our study provides a comprehensive overview of the genetic diagnosis of a Chinese childhood epilepsy cohort and provides novel insights into the genetic background of these patients. Harmful missense mutations in genes related to ion channels and synapses are most likely to produce multigenic burden in childhood epilepsy.

MYRF 基因截短变异导致常染色体显性遗传的高度远视合并闭角型青光眼

肖学珊 孙文敏 欧阳嘉敏 黎仕强 贾小云 张清炯
中山大学中山眼科中心

目的 高度远视合并闭角型青光眼可导致严重的视功能损害，甚至致盲，其发生与遗传有关，但绝大多数病人的致病基因不明。本研究目的是基于一个常染色体显性遗传高度远视合并闭角型青光眼的大家系，鉴定其致病基因及变异。
方法 首先对来自这个家系的共 14 例患者和 5 例正常成员的基因组 DNA，进行全基因组连锁定位分析明确致病位点，后通过对家系患者进行全外显子组测序分析，在连锁定位区域内，通过生物信息学方法，筛选致病基因及变异。进一步对 121 例高度远视先证者的全外显子组测序数据中筛查是否有该基因致病变异，并构建候选基因敲低斑马鱼模型，验证表型。
结果 通过全基因组连锁分析，明确导致该家系高度远视及闭角型青光眼的致病位点位于 11p12-q13.3，通过对该家系中 4 例患者的全外显子组测序分析数据的生物信息学分析，筛选出 *MYRF* 基因杂合变异， Sanger 测序分析确定该变异与疾病共分离。在其他 121 例高度远视先证者的全外显子组测序数据中发现有两例先证者携带 *MYRF* 基因杂合截短变异，也均位于该基因 C-末端，证实该基因 C-末端的截短变异与高度远视的相关性。Myrf 基因敲降的斑马鱼表现出小眼表现，与高度远视病人眼轴短的表型相符。
结论 *MYRF* 基因截短变异可导致常染色体显性遗传的高度远视合并闭角型青光眼，为高度远视合并闭角型青光眼发生的分子机制提供了线索 。

新发 SARS2 基因变异致 HUPRA 综合征的疾病表型与功能学分析

张仪 王剑 郁婷婷 韩聪 朱佳谊 卿彦荣
上海儿童医学中心

目的 报道 1 例新发罕见线粒体丝氨酰-tRNA 合成酶基因（seryl-tRNA synthethase 2, *SARS2*）变异导致大运动发育迟缓、肺动脉高压、突发性全身瘫痪以及癫痫反复发作的患儿，结合已有病例报道，阐明 *SARS2* 突变导致 HUPRA 综合征的表型特点及发病机理，形成此类疾病功能研究体系。
方法 提取患儿及父母外周血 DNA，行高通量测序检测变异，并经 Sanger 测序验证变异的亲本来源。构建 *SARS2* 野生型及突变型表达载体，通过免疫印迹、免疫荧光及免疫共沉淀实验，分析突变对 SARS2 稳态水平、稳定性、二聚化、入线粒体效率等的影响。通过 Octet 分子相互作用技术平台，分析突变对 SARS2 与线粒体 $tRNA^{Ser}$(AGY)和 $tRNA^{Ser}$(UCN)结合能力的影响。通过体外酶反应分析法，测定酶促反应动力学参数，分析突变对 SARS2 丝氨酰化功能的影响。
结果 该患儿表型与已报道病例表型存在交叉，同时又有明显差异。患儿存在 *SARS2* c.654-14T>A（父源）及 c.1519dupC（母源）复合杂合变异。c.654-14T>A 导致异常 mRNA 剪接，并在酶活性位点附近插入了 4 个氨基酸。c.1519dupC 导致 SARS2 的 C 末端序列改变和异常延伸。突变型 SARS2 蛋白的稳态水平显著下降，与野生型相比，c.1519dupC 变异蛋白下降约 50%，c.654-14T>A 变异蛋白则下降约 75%。变异严重损害了 SARS2 与线粒体 $tRNA^{Ser}$(AGY)和 $tRNA^{Ser}$(UCN)的结合能力，突变型蛋白质结合 $tRNA^{Ser}$(AGY)和 $tRNA^{Ser}$(UCN)的 kd 值可达野生型的 3-10 倍。突变型 SARS2 丝氨酰化能力显著损伤，c.654-14T>A 导致 SARS2 丝氨酰化能力几乎完全受损，c.1519dupC 导致 SARS2 对 $tRNA^{Ser}$(AGY)和 $tRNA^{Ser}$(UCN)的丝氨酰化能力分别下降至野生型的 5%和 30%。
结论 SARS2 参与线粒体内蛋白质合成，对维持线粒体及细胞正常功能至关重要，其突变会导致 HUPRA 综合征，但其临床表型和机制研究尚待补充完善。本文报道国内首例 *SARS2* 基因新发变异患儿，补充了疾病表型谱，并通过功能学实验证明变异导致 SARS2 稳态水平下调，且不能正常行使丝氨酰化功能，从而可能影响线粒体蛋白质合成，造成线粒体及细胞生命活动的异常。本文建立的功能学实验体系可为 SARS2 及其他氨基酰 tRNA 合成酶基因变异的解读、诊断和出生缺陷防治提供经验。

To evaluate the application value of various molecular detection techniques in diagnosing polysomic 9p of mosaicism

Sufen Zhang
Department of Clinical Laboratory & Medical Genetics of Zhuhai Municipality Maternal and Child Healthcare Hospital

Objective Advantages and limitations of various techniques were compared to evaluate the application value in diagnosis process of two cases of polysomic 9p of mosaicism.
Materials and methods Noninvasive prenatal testing (NIPT), chromosomal microarray analysis (CMA), karyotype analysis, fluorescence in situ hybridization (FISH) were used to diagnose two cases of polysomic 9p of mosaicism and the mosaic levels with different methods were compared at this study.
Results Chromosome 9 was duplicated to varying degrees in both two cases according to NIPT in the first trimester. The case one showed the levels of mosaicism of chromosome 9p were 2.2, 2.43 and 2.5 copies with traditional karyotype analysis, CMA and FISH, respectively. The case two presented a complex mosaicism containing three cell lines, with 2.96 copies of 9p and 2.82 copies of 9q based on karyotype analysis, 3 copies of 9p and 2.5 copies of 9q according to smooth signal and whole genome view (WGV) diagram of CMA.

Conclusion These two cases all provided evidence for the discrepancy in the levels of mosaic of 9p between various molecular detection techniques. Different detection technologies have their own advantages and limitations in the prenatal diagnosis, combined use of molecular diagnostic techniques based on needs may be could complement each other to increase the detection rate and accuracy.

Pin1-CaMKII-AMPAR 轴调节癫痫的易感性

刘合焜 侯晓君 杨帆 李昂成 赵得豹
福建医科大学

Pin1 是一种独特的异构酶，可调节磷酸化后的蛋白质构象和功能。 Pin1 突变会导致某些神经系统疾病，尤其是阿尔茨海默氏病，但其在癫痫中的作用尚未完全了解。我们发现，Pin1 缺陷型小鼠在多种化学诱导模型中均明显增加了癫痫发作的易感性，并且可出现年龄依赖性的自发性癫痫。电生理上，Pin1 敲除可增强前额叶皮层锥体神经元的兴奋性突触传递，而不影响其内在的兴奋性。蛋白水平上，Pin1 敲除作用于磷酸化的 CaMKII，从而上调了 AMPA 受体和磷酸化的 GluA1 的表达水平。临床上，癫痫患者大脑皮层的 Pin1 显著降低，而磷酸化的 CaMKII 和 GluA1 升高。更为重要的是，利用腺相关病毒在 Pin1 敲除小鼠的前额叶皮层中部分恢复 Pin1 的表达，可显著降低磷酸化的 CaMKII 和 GluA1 的蛋白水平，并有效抑制其癫痫发作的易感性。因此，Pin1-CaMKII-AMPAR 轴参与调控癫痫的易感性，可望发展新的有吸引力的治疗策略。

Bi-allelic variants of the TOE1 gene cause neurologic developmental disorder distinct from the phenotype of previous patients

Hongzhu Chen Yufei Xu Guoqiang Li Ruen Yao Tingting Yu Jian Wang Niu Li
Shanghai Children's Medical Center

The target of EGR1 protein 1 (TOE1) is a 3′-exonuclease which belongs to the DEDD (Asp-Glu-Asp-Asp) deadenylase family that plays a vital role in the maturation of a variety of of small nuclear RNAs (snRNAs). Bi-allelic deleterious variants in *TOE1* cause a rare and severe neurodegenerative syndrome, pontocerebellar hypoplasia type 7 (PCH7) (OMIM # 614969), which is characterized by progressive neurodegeneration, developmental delay, and ambiguous genitalia. To date, a total of 14 TOE1-related patients from 11 families have been described by 2 research groups. Here, we describe a 5-year-6-month-old Chinese female patient who mainly presented with cerebral dysplasia, moderate intellectual disability, developmental delay, and dystonia. Whole-exome sequencing revealed a previously unreported compound heterozygous variant of *TOE1* (c.255-2A>G and c.551G>T, p. Arg184Leu) in the patient. Most of the clinical features of the patient are concordant with those previously reported. However, the deformities of the brain (enlarged lateral ventricle and deepened cerebellum sulcus without microcephaly and reduced cerebellar volume) in our patient were less severe than PCH7 patients. Moreover, the patient had no gonadal malformation, which are common and variable in patients with PCH7. In summary, we reported a Chinese patient with atypical PCH7 caused by *TOE1* gene variation. Our work suggests that variation in the *TOE1* gene can lead to highly variable clinical phenotypes.

Downregulation of SHANK-associated RH domain-interacting protein elevates interleukin-33 expression by stimulating the Janus kinase 2/signal transducer and activator of transcription signalling pathway in HaCaT cells

Yanhua Liang
Shenzhen Hospital, Southern Medical University

Background Atopic dermatitis (AD) is a chronic inflammatory skin disease in which T-helper type 2 (Th2) immune responses are dominant. SH3 and multiple ankyrin repeat domains (SHANK)-associated RH domain-interacting protein (SHARPIN) is expressed at low levels in AD, resulting in the upregulation of the signal transducer and activator of transcription (STAT)3 protein and the Th2 cytokine, interleukin (IL)-33. However, the roles of SHARPIN in AD are not yet fully elucidated.
Aim To evaluate the signalling interactions of SHARPIN and IL-33 in order to improve understanding of AD pathogenesis.
Methods Western blotting was used to detect the Janus kinase (JAK)/STAT signalling proteins and IL-33 protein in HaCaT cells to determine the key proteins mediating the interaction between SHARPIN and IL-33. The findings were validated by immunofluorescence and immunohistochemical staining. Chromatin immunoprecipitation assays were used to evaluate the activity of STAT3 at the *IL-33* promoter.
Results We found that phosphorylated (phospho)-JAK2 and phospho-STAT3 were upregulated in SHARPIN-knockdown HaCaT cells. Subsequent chromatin immunoprecipitation assays revealed that STAT3 binds to the *IL-33* promoter to mediate IL-33 expression. Moreover, SHARPIN-mediated expression of IL-33 was reduced after treatment of HaCaT cells with the JAK/STAT inhibitor ruxolitinib. STAT3 and IL-33 expression levels were higher in AD skin lesion tissues than in normal skin tissues.
Conclusion These findings suggest that SHARPIN modulates inflammation in HaCaT cells by inhibiting JAK/STAT signalling, supporting the application of SHARPIN as a potential therapeutic target for AD.

Decreased expression of CPEB3 predicts a poor prognosis in patients with melanoma: A study based on TCGA data

Yanhua Liang
Shenzhen Hospital, Southern Medical University

Aim Cytoplasmic polyadenylation element binding protein 3 (CPEB3) has been acknowledged as a tumor suppressive gene in several cancers, however, there are few reports on the clinical significance of CPEB3 in melanoma. The purpose of this study was to explore the role of CPEB3 in predicting the prognosis of melanoma patients.
Methods The association of CPEB3 expression and clinical pathologic features was performed using The Cancer Genome Atlas (TCGA) data set. The role of CPEB3 expression in prognostic was also analyzed. In addition, Gene set enrichment analysis (GSEA) was used to enrich the pathway related to CPEB3 expression. Association analysis of CPEB3 gene expression and immune infiltration was performed by ssGSEA.
Results The mRNA was significantly less in melanoma than in normal tissues ($p< 0.001$). Reduced CPEB3 expression in melanoma was significantly associated with high T staging ($p< 0.001$), clinical staging ($p=0.029$), melanoma clark level ($p=0.014$) and melanoma ulceration ($p=0.003$), while it was marginally significant in N staging ($p=0.089$). Melanoma with CPEB3-low was associated with worse OS, disease-specific survival (DSS) and poorer progression-free survival (PFS) than in those with high expression. In univariate analysis, T stage, N stage, clinical

stage, melanoma clark level, age, melanoma ulceration and expression of CPEB3 were associated with OS ($p < 0.05$). Further analysis by multivariate Cox regression showed that N stage (P =0.029), melanoma ulceration (P=0.004) and CPEB3 expression (P <0.001) were independent prognostic factors of OS in melanoma. Moreover, GSEA showed that several pathways were enriched in CPEB3, such as PD1 signaling, CTLA4 pathway, CTCF pathway, CHEMOKIN signaling, VEGF signaling and JAK-STAT pathway. CPEB3 was significantly correlated with the infiltration level of B cells(P<0.001), T cells(P<0.001), T helper cells (P<0.001) and Central memory T (Tcm) cells(P<0.001).
Conclusion CPEB3 may be a potential prognostic marker in melenoma with poor survival. Moreover, PD1 signaling, CTLA4 pathway, CTCF pathway, CHEMOKIN signaling, VEGF signaling and JAK-STAT pathway. may be the key pathway regulated by CPEB3. Moreover, CPEB3 expression is correlated with immune infiltration level in melanoma.

外显子测序在复发性胎儿非免疫性水肿中的应用价值研究：一项回顾性研究

周鑫垚 孙路明
上海市第一妇婴保健院

我们的研究目的是为了探索复发性非免疫性水肿的单基因病谱以及评估遗传诊断对于产前管理和妊娠结局的价值。研究排除了免疫性水肿胎儿，非遗传因素导致的水肿（如感染等），核型异常，拷贝数异常的胎儿，纳入 2012 年 1 月至 2018 年 10 月在我们中心就诊的 28 例复发性非免疫性水肿胎儿，进行家系外显子测序。检测到变异运用 ACMG/AMP 指南进行致病性注释。并且针对其中的 7 例非免疫性水肿胎儿进行了宫内治疗。在 28 例胎儿中，10 例（36%）明确诊断，在 8 个基因（*GBA, GUSB, GBE1, RAPSN, FOXC2, PIEZO1, LZTR1* 和 *FOXP3*）上发现了致病性/可能致病变异。另有 5 例发现临床意义不明变异。在这 10 例明确诊断的胎儿中，5 例（50%）为代谢病。在 7 例接受宫内治疗的胎儿中，2 例在随后的外显子测序中被明确分子诊断并且发生了新生儿死亡。剩余的 5 例为阴性结果，4 例新生儿存活，1 例发生胎死宫内。家系外显子测序可提高复发性胎儿非免疫性水肿的遗传诊断率，能够帮助产前管理和妊娠结局。

G6PD 酶法与 G6PD/6PGD 比值法在葡萄糖-6-磷酸脱氢酶缺乏症诊断中的临床价值及基因突变分析

张潇分 田国力
上海市儿童医院

目的 探讨 G6PD 酶法与 G6PD/6PGD 比值法在葡萄糖-6-磷酸脱氢酶（G6PD）缺乏症诊断的临床价值并对其进行基因突变类型分析。
方法 选择 2018 年 6 月至 2021 年 3 月就诊于上海市儿童医院疑似 G6PD 缺乏症的患儿并采用 G6PD 酶法、G6PD/6PGD 比值法和多色荧光熔解曲线法对 G6PD 酶活性和基因突变类型进行检测。将 G6PD 酶法和 G6PD/6PGD 比值法的结果与基因突变结果对比分析，评价其诊断效能。采用 MannWhitneyU 检验或 KruskalWallis H 检验比较各组差异，分析 G6PD 酶活性和 G6PD/6PGD 比值法与基因突变类型的关系。
结果 1.共完成 1331 例（1208 例患儿，123 例患儿父母）疑似患者相关指标测定。确诊患儿 163 例，G6PD 酶法确诊 156 例，阳性率 95.71%，比值法确诊 140 例，阳性率 85.89%。163 例患儿中（男 135 例，女 28 例），G6PD 酶活性及 G6PD/6PGD 比值法男性患儿和女性患儿之间，差异均具有统计学意义（U=642.5，P<0.0001；U=734.5，P<0.0001）。家系（父母）中，G6PD 酶法与 G6PD/6PGD 比值法差异均具有统计学意义（U=14.00，P=0.0003；U=18.00，P=0.0003）。2. 112 例患儿接受基因检测，共检出基因突变 92 例，包括 7 个突变位点，分别为 c.1388G>A、c.1376G>T、c.871G>A、c.1024C>T、c.95A>G、c.487G>A、c.392G>T。其中男

性半合子突变 74 个，女性纯合子突变 1 个（c.1376G>T 位点纯合子突变），杂合突变 17 个及 2 例复合杂合突变(c.1024C>T 和 c.1376G>T ，c.1388G>A 和 c.392G>T)。不同突变类型的 G6PD 酶活性之间 c.1376G>T 和 c.1024C>T （*P*=0.020），c.1376G>T 和 c.487G>A（*P*=0.009）差异有统计学意义；不同突变类型的 G6PD/6PGD 比值法之间 c.1388G>A 和 c.1024C>T（*P*=0.014），c.1376G>T 和 c.1024C>T（*P*=0.0001），c.871G>A 和 c.1024C>T（*P*=0.010），c.1024C>T 和 c.95A>G（*P*=0.016）差异均有统计学意义。3. 对 G6PD 酶法和 G6PD/6PGD 比值法分别作 ROC 曲线分析，发现 G6PD 酶法灵敏度 100%，特异度 95.65%，曲线下面积 AUC 0.9723，符合率 93.75%，诊断误差率 6.25%。G6PD/6PGD 法灵敏度 100%，特异度 94.57%，曲线下面积 0.9793。符合率 79.46%。对于 17 个女性患儿杂合子，G6PD/6PGD 检出 4 个，检出率 23.53%。

结论 G6PD/6PGD 比值法可能无法有效检测女性杂合子；G6PD 酶活性结合 G6PD 比值法检测有利于减少漏诊，结合基因突变检测，可能提高 G6PD 患儿诊断率。

Clinical exome sequencing identified 12 critically ill infants with Schaaf-Yang syndrome from the China Neonatal Genomes Project

Zhongwen Huang
Children's Hospital of Fudan University

Objectives Schaaf-Yang syndrome (SYS) is a recently identified rare neurodevelopmental disorder characterized by neonatal hypotonia, feeding difficulty, joint contractures, intellectual disability/development delay and autism spectrum disorder. SYS is mainly caused by truncating variants in maternally imprinted gene *MAGEL2*. Clinical diagnosis of SYS is difficult for a physician due to its rarity and highly variable phenotypes. This study aims to raise the awareness of SYS in critically ill infants and to promote accurate early diagnosis and comprehensive treatments with better benefits.

Methods We retrospectively investigated the mutation spectrum and phenotypic features in a cohort of critically ill infants from the China neonatal genomes project (CNGP). Genetic tests were performed by clinical exome sequencing (CES)/exome sequencing (ES), and the clinical medical records were reviewed retrospectively.

Results Twelve unrelated Chinese infants were diagnosed with SYS based on genetic testing. All these patients carried truncating variants on paternal *MAGEL2* allele with six previously unreported mutations: p. Met1195Cysfs*4, p.Gln339*, p.Thr217Hisfs*22, p.Ser950Alafs*6, p.Gly883Alafs*21 and p.Trp368*. Notably, we found that 11 of our patients presented with congenital heart diseases especially atrial septal defect.

Conclusion Our findings expand the genotype spectrum of SYS. Congenital heart disease may be a common phenotype of critically ill infants with SYS in China. This study could provide a new insight into SYS.

误诊为心肌病的婴幼儿囊性纤维化一例及新发复合杂合突变分析

王凤 钱翠萍
复旦大学附属儿科医院

目的 报道一例外院误诊为心肌病的婴幼儿囊性纤维化（cystic fibrosis，CF）的临床特征及基因突变特点，提高临床医师对 CF 疾病的认识，减少误诊及漏诊。

方法 采用回顾性分析的方法总结复旦大学附属儿科医院 2021 年 4 月收治的 1 例囊性纤维化患儿的临床资料，分享其诊治过程，并进行基因检测分析。

结果 1 岁 10 月男童，因“反复浮肿伴气促 5 月余，加重 20 天”收入我院。外院考虑右室心肌病可能。患儿既往辅食添加困难，10 月龄起体重不增；1 岁起反复咳嗽，大便有时呈油状稀糊样。体格

检查：身材瘦小，营养不良，吸凹（+），辅检提示低蛋白血症、脂溶性维生素降低，粪便弹力蛋白酶 1＜0.5ug/g（参考值＞200）。汗液氯离子浓度显著升高。肝硬化指标升高，肝功能及心肌酶轻度升高。痰培养阴性。CT 示两肺炎症，鼻窦炎，肺潮气呼吸功能异常，存在重度阻塞性通气功能障碍。肝脏 B 超示肝脏肿大、质地差。胰腺 MR 示胰腺小，肝脏、胰腺脂肪浸润。基因检测显示 CFTR 的两处复合杂合突变：c.1209+1G>C 剪接突变（母源）和 c.2475_2478dupCGAA 移码突变（父源），均为致病性变异，前者在我国先天性输精管缺如患者中报道为隐性遗传致病突变，后者为本次新发现移码突变位点。经抗感染、雾化、输注白蛋白、补充脂溶性维生素及胰酶等处理后，患儿咳嗽好转，呼吸平稳，无浮肿反复，体重增长满意。

结论 囊性纤维化为常染色体隐性遗传性疾病，国内 CF 发病率或被低估，临床上对于反复呼吸道感染合并胰腺外分泌功能不全的多系统累及的患儿需考虑 CF 可能，早期行汗液氯离子测定及胰腺功能检查可提示诊断，基因检测有助于确诊疾病及新发突变位点，提高临床医生对该疾病的识别。

De Novel CSNK2B variants in four cases of Poirier-Bienvenu neurodevelopmental syndrome

Qi Yang
Genetic and Metabolic Central Laboratory, Guangxi Maternal and Child Health Hospital

Poirier-Bienvenu neurodevelopmental syndrome is an autosomal dominant disorder characterized by mental retardation and epilepsy. The disease is caused by a mutation in the *CSNK2B* gene, encoding the beta subunits of casein kinase II (CK2), plays an important role in neuron morphology and synaptic transmission. In this study, five additional Chinese patients were diagnosed as Poirier-Bienvenu neurodevelopmental syndrome with CSNK2B variants by whole exome sequencing. We detected four de novo variants in *CSNK2B* in these five unrelated Chinese patients, two novel de novo variants c.100delT (p.Phe34fs*16) and c.158_159insA(p.Asp55fs*4), and two recurrent variants c.1A>G (p.Met1?) and c.332 G >C (p.R111P). All of 5 patients showed mild to profound intellectual disabilities, developmental delays, with or without seizures. Although ID/DD and epilepsy are the most common phenotypes of CSNK2B deficiency, the clinical phenotypes of probands are highly variable, and there is no significant correlation between genotype and phenotype. In addition, abnormal linear height may be another common manifestation of CSNK2B deficiency. We also report the effect of growth hormone therapy on the patient's linear height. In conclusion, Poirier Bienvenu neurodevelopmental syndrome is a highly heterogeneous disease caused by CSNK2B mutation. Short stature patients with CSNK2B deficiency may benefit from growth hormone therapy. The novel variants will expands the mutation spectrum of Poirier-Bienvenu neurodevelopmental syndrome.

The bi-allelic p.V37I variant in GJB2 is associated with increasing penetrance and expressivity for hearing loss in the life span

Tao Yang
Ninth People's Hospital, Shanghai Jiaotong University School of Medicine

Background Over 10 million people in Asia are estimated to carry the bi-allelic p.V37I variant in *GJB2*, which is associated with mild to moderate hearing loss. Its penetrance, expressivity and progressiveness, however, have not been quantitatively assessed during the lifespan.
Methods Genetic screening of the bi-allelic p.V37I variant was performed in 30122 individuals from the general population in Shanghai between age 0 and 97 years. Hearing thresholds of the 159 carriers and 279 age-matched controls were determined by click auditory brainstem response for newborns and pure tone audiometry for others.

Results The bi-allelic p.V37I variant was detected in 0·528% (159/30122) of the subjects. In newborns, 85·37% (35/41) of the carriers passed their newborn hearing screening. The older carriers, however, have steadily elevated hearing thresholds that average 23·04 [95% CI, 18·64 to 27·43] dB HL between age 7 and 15 years, 27·34 [95% CI, 23·75 to 30·93] dB HL between 20 and 40 years, 36·91 [95% CI, 32·79 to 41·04] dB HL between 40 and 60 years and 44·75 [95% CI, 40·76 to 48·74] dB HL between 60 and 85 years, with increasing penetrance of 9·52%, 23·08%, 59·38% and 80·00% for moderate or higher grade of hearing loss in respective age groups. Non-categorizing analysis for the age showed that the hearing of the carriers deteriorates at a slow but steady rate of 0·40 dB HL per year on average, is more susceptible in males and at higher sound frequencies.
Conclusions Our cross-sectional study suggested that the bi-allelic p.V37I variant in *GJB2* is associated with steadily progressive hearing loss with increasing penetrance and expressivity in the life span. The majority of the carriers may develop significant hearing loss in adulthood, who can be benefited from early diagnosis and intervention through wide-spread genetic screening.

Twin pregnancy give birth to a girl with partial trisomy 21 mosaicism after in vitro fertilization and embryo transfer

Zhenglong Guo
Henan Provincial People's Hospital

Objective To report a rare case in which an IVF-ET twin pregnancy give birth to a partial trisomy 21 chimera girl.
Design Case report.
Setting University hospital.
Patient A 28-year-old man and a 26-year-old woman assisted with *in vitro* fertilization and embryo transfer in 2019, the live births of twin sisters.
Interventions *In vitro* fertilization (IVF) and embryo transfer (ET) was utilized.
Main Outcome Measure Karyotype analysis, Copy Number Variation sequencing (CNV-seq), stLFR-WGS, and Short Tandem Repeat (STR) analysis.
Results Being assisted with IVF and EF technology, the couple successfully gave birth to twin sisters at 37 weeks of gestational age. During the period, the NonInvasive Prenatal Testing (NIPT) and Nuchal Translucency (NT) examination results showed no detectable genetic abnormal. However, after birth, the younger infant had growth retardation and feeding difficulties, which was not observed in her twin sister. Further genetic counseling and diagnosis indicated that she is a Chimera of complex partial trisomy 21. Consistently, stLFR-WGS results showed multiple CNV variations in the Chr21, and STR analysis confirmed the paternal origin of the additional fragments.
Conclusion(s): It is a rare case that IVF-ET assistance twin pregnancy gave birth to a girl with a complex combination of abnormal Chr21, suggesting that *in vitro* fertilization increases the risk of chromosomal defects. Therefore, preimplantation genetic screening (PGS) is necessary for couples with no genetic family history or chromosome defects.

Clinical and molecular characterization of a novel LMX1A frameshift mutation identified in patients with familial non-syndromic severe-to-profound sensorineural hearing loss

Min Xiao[1,2]
1.Shanghai Ji Ai Genetics & IVF Institute, the Obstetrics & Gynecology Hospital of Fudan University
2.Genetics Center of Obstetrics and Gynecology of Fudan University

Hereditary hearing loss (HHL) is a group of genetically heterogeneous condition with broad phenotypic heterogeneity. There is, at present, no curative treatment for genetic hearing loss. To

date, only four *LMX1A* variants, all of which were missense mutations, have been reported from three previously studies linked to autosomal dominant or recessive HHL. In the present study, we identified a novel rare frameshift variant in exon 8 of *LMX1A* (c.915dup, p.Val306Cysfs*32). This C-terminal frameshift mutation co-segregated with autosomal dominant non-syndromic hearing loss (ADNSHL) in a three-generation Chinese family. In this family, affected individuals exhibited clinically variable auditory phenotypes ranging from profound congenital deafness at birth or late-onset hearing loss to mild/moderate hearing loss. Flow cytometry exhibited that compared with *LMX1A* wide-type (WT), the overexpression of c.915dup mutant decreased the rate of apoptosis[X1] . We therefore investigated the global gene expression patterns of the c.915dup variant by RNA-seq[X2] . To investigate the molecular mechanism, we performed luciferase assay to evaluate transcriptional activity of LMX1A C-terminal variants. Resultantly, the truncation of the highly conservative C-termination showed significantly reduction of transcriptional activity in contrast with *LMX1A* WT, proposing a genotype-phenotype correlation. An electrophoretic mobility shift assay (EMSA) further demonstrated that the DNA-binding activity of c.915dup variant is decreased. This is the first report involving a Chinese who harbored *LMX1A* mutation. To the best of our knowledge, the results firstly support the notion that the C-terminal domain of *LMX1A* gene is also an important functional region that affects the binding of the transcription factor to DNA in addition to the LIM- and homeodomain. Our work not only expands the mutant spectrum of the *LMX1A* gene but also provides new insights on its resulting phenotype.

[X1]待修改
[X2]待增加描述结果

BVVLS2 overlooked for 3 years in a pediatric patient caused by novel compound heterozygous mutations in SLC52A2 gene

Xiaomei Lu Ziqiang Liu Qi Peng
Dongguan Children's Hospital

Background Brown-Vialetto-Van Laere syndrome-2 (BVVLS2) is a rare autosomal recessive neurological disorder caused by mutations in the SLC52A2 gene, which is characterized by early childhood onset of sensorineural hearing loss, bulbar palsy, peripheral neuropathy, and respiratory insufficiency. We aimed to investigate the genetic cause of a 4-year-old boy who suffered from BVVLS2 whose initial presentation was severe normocytic anemia and had been overlooked for three years in a local hospital. He was misdiagnosed with pure red cell aplasia (PRCA) and treated with hormones and chemotherapy drugs, but there was no obvious effect.
Methods The targeted capture of 927 genes associated with neuromuscular disorders and next-generation sequencing were performed. Sanger sequencing was employed to verify the variant mutations.
Results The proband was found to be heterozygous for c.350 T >C (p.L117P) in exon 3 and c.1135_1137delTGG (p.W379del) in exon 5 of SLC52A2 gene. His anemia and neurological symptoms improved significantly after treatment with low dose oral riboflavin.
Conclusions This study expands the mutational spectrum of SLC52A2 and phenotypic spectrum of BVVLS2, which provides a foundation for further investigations elucidating the SLC52A2 related mechanisms of BVVLS2. A low-dosage of riboflavin supplementation was used to obtain good curative effect, which provides further future references for the clinical treatments of BVVLS.

Progressive Cholestasis：Severe Phenotype of MEGDEL Syndrome with SATB2-associated Syndrome

Yajie Su[1,2] Hui Zhang[2] Huijun Wang[1] Bingbing Wu[1] Jiao Yang[2] Wenhao Zhou[1] Long Li[2]
1.Children's Hospital of Fudan University
2.Children's Hospital of Xinjiang Uygur Autonomous Region

Objective We describe a rare disease progression and a severe phenotype of progressive cholestasis of a girl from birth to 15 months, who was compound heterozygous for *SERAC1* of MEGDEL syndrome and had a mutation in *SATB2* of *SATB2*-associated syndrome.
Methods We present the case of a 2-day-old girl with an unexplained abnormal liver function, feeding problem, and dystonia. Using next-generation sequencing.
Results We identified two novel mutations in *SERAC1* and a mutation in *SATB2*. Now, she is 15 months old and has the characteristics of SAS, such as downslanting palpebral fissures and delayed primary dentition. Besides the typical phenotypes of MEGDEL syndrome, such as hypertonia, failure to thrive, deafness, and motor regression, she has progressive cholestasis and is prone to high serum lactate after rehabilitation training and hypoglycemia with low ketone under starving conditions.
Conclusion These phenotypes substantially differ from the transient liver function abnormalities and hypoglycemia reported in the literature.

COL4A5 基因新发突变所致 X 连锁显性遗传 Alport 综合征基因及临床分析

胡玉杰 黄文彦
上海交通大学附属儿童医院

目的 通过全外显子测序、肾活检以及皮肤活检，为一例临床表现为血尿的 Alport 综合征患儿明确诊断。
方法 应用全外显子测序技术进行基因检测，应用 sanger 测序对候选致病 COL4A5 基因新发突变进行验证。通过患儿肾组织及皮肤 a5 链免疫荧光学检查，对候选致病 COL4A5 基因新发突变进行功能验证，明确致病性。
结果 患儿男性，3 岁 5 个月，因体检发现镜下血尿 1 周入院，入院查尿红细胞均>100/HP,尿红细胞畸形率 78%，尿蛋白-，肝肾功能、体液免疫、补体、自身抗体、T-spot、乙丙肝、HIV、TPPA 等均阴性，眼睛、听力均正常。基因检测提示：与 Alport 综合征相关的 COL4A5 基因有位点发生嵌合变异。该突变在 X 染色体 chrX:107869502 位置发生碱基 G＞A 的变异，导致编码的第 1057 号氨基酸由甘氨酸变异为精氨酸，该位点变异频率在千人基因组、ExAC 以及 gnomAD 等数据库中未收录，根据 ACMG 判定标准为临床意义未明变异。家系验证结果显示：受检者母亲及其父亲该位点均为野生型。肾穿刺病理提示：肾小球轻微病变。IV 型胶原 a5 链肾小球基底膜、包曼氏囊壁及远曲小管基膜连续分布。皮肤 IV 型胶原 a5 链免疫荧光染色提示：基底膜不连续分布，可见多处小片段缺失，局部小片段淡染色。
结论 基因检测有助于确诊 Alport 综合征, 染色体 chrX:107869502 位置发生碱基 G＞A 的变异为新发的 Alport 综合征致病突变位点。

基于靶向测序的新生儿疾病筛查体系的建立及其临床应用研究

郝婵娟 郭若兰 胡旭昀 齐展 郭琦 刘玄石 倪鑫 李巍
首都医科大学附属北京儿童医院

自 20 世纪 60 年代以来，许多国家实施了不同的新生儿疾病筛查计划。随着二代测序技术的发展，该技术是否适用于新生儿疾病筛查成为众多研究人员关注的问题。我们在基于靶向测序的新生儿疾病筛查（Newborn Screening with Targeted Sequencing, NESTS）项目中，开发了一组包含 465 个致病基因的测序 panel，用于筛查 596 种早发、相对高发病率和潜在可干预的严重遗传病，对中国 8 家妇幼医院的 11484 名婴儿进行回顾性筛查。NESTS 初筛阳性率为 7.85%（902/11484）。对初筛阳性病例进行随访（随访率为 45.89%，414/902），随访人群中单基因疾病的总体临床确诊率为 12.07%（50/414），估计平均临床诊断率为 0.95%（7.85%×12.07%），表明单基因疾病占出生缺陷较大比例。同时，研究发现中国不同地区的疾病谱/基因谱各不相同。进一步在单中心 3923 名新生儿中进行靶向基因筛查和遗传咨询来评估 NESTS 的临床应用。通过我们自主建立的自动化分析/数据解读流程，报告的周转时间（包括不到 7 天的测序周期）可缩短至 11 天之内。我们的研究结果表明，对于缺乏传统筛查手段的疾病，NESTS 作为一线新生儿疾病筛查检测手段是可行的，并且具有成本效益，这将改变目前中国新生儿疾病筛查临床实践的现状。

CNV-Seq technique reveals a new mutation of X-linked recessive deafness gene POU3F4

Rong Yu Hongqun Jiang Yuanping Xiong
Department of Otolaryngology, The First Affiliated Hospital of Nanchang University

A 3.92 Mb was deleted in the Xq21.1 region of the X chromosome, which is very rare. Here we described a patient with an interstitial deletion of the Xq21.1 chromosome, *POU3F4* (mutated inX-linked deafness),determined through Copy number variation sequencing(CNV-Seq).*POU3F4* mutations can cause hearing loss. Hearing can be improved with cochlear implants. Different mutation sites have different postoperative CI effects, with certain mutation sites leading to poor operative outcomes in patients.We sought to explain the postoperative CI effects based on genotypephenotype correlation.In the patient studied,we found that sensorineural hearing loss was present and the temporal bone computed tomography showed a bilateral incomplete cochlear partition deformity(IP-III).Q21.1(79.40Mb-83.32Mb) of the patient's chromosome X had a copy number deletion with a fragment size of about 3.92Mb,which was identified as a newly developed mutation through pedigree analysis.CAP scores and SIR scores of the cochlea in this child with an IP-III malformation all improved after surgery. In conclusion, through the analysis of *POU3F4*,a novel mutation site with clear pathogenic significance was found in this study. It provided guidance for gene diagnosis of deafness in cochlear implantation.

Genetics and clinical analysis of three Chinese families with Nicolaides-Baraitser

Gao Min Zaifen Gao Yujie Guo Kaihui Zhang Yuqiang Lv Xuxia Luo Dong Wang Jian Ma Yi Liu
Qilu Children's Hospital of Shandong University

Objective Nicolaides-Baraitser syndrome (NBS; MIM 601358) is a rare childhood syndrome, characterized by sparse hair, typical facial morphology, short stature, microcephaly, brachydactyly, interphalangeal joint swellings, epilepsy, intellectual disability and marked language impairment.To date,only less than one hundred patients have been reported.Here we reported one novel SMARCA2 mutation in three Chinese families with Nicolaides-Baraitser.

Methods In this study,the phenotype and genotype of the proband was studied. Clinical and laboratory tests were performed for the patient. The peripheral venous blood from the neonate and his parents were extracted respectively. Whole exome sequencing was applied and PCR Sanger sequencing was designed to verify the mutations.Pathogenicity assessment of genetic variation was following the Sequence Variation Interpretation Standards and Guidelines published by the American Society of Medical Genetics and Genomics (ACMG) in 2015.
Results All patients had developmental delay, seizures, sparse hair and thinness, controlled seizures.three missense variants, including two reported variants were c.C2563G and c.3386G>A and one novel c.G3592A, was identified in SMARCA2.We noted that mutations of single nucleotide reported in the SMARCA2 gene focused on exon 18-25 (account for 47/58) specially on exon18, 24 and 25 and the patient with a nonsense variant showed more severe intellectual disability than who harboring a missense variant,the weak ability of walking may be not relevant with age, but due to the severity of disease itself.
Conclusion In summary, this was the first report of Chinese NBS patients with one novel mutation in SMARCA2. We not only expanded the spectrum of NCBRS, but also described and contrasted the phenotype, and further clarificated phenotypic differences.

WES 结合 HPO 在神经发育障碍诊断中的应用

王青青
河南省人民医院

背景 神经发育障碍（Neurodevelopmental disorders, NDDs）影响约 2~5%的儿童，其临床表型主要为智力障碍、注意力缺陷多动障碍、自闭症谱系障碍、交流障碍、运动障碍和特定的学习障碍。NDDs 病因的鉴别诊断相对耗时且昂贵，通常没有明确的诊断结果。传统方法包括染色体核型、全基因组拷贝数变异（Copy number variations ,CNVs）等，对 NDDs 患者的诊断率不到 30%。既往研究报道 NDDs 患者存在明显的临床和遗传异质性，导致病因鉴定困难。虽然全外显子测序（Whole-exome sequencing,WES）、全基因组测序（Whole-genome sequencing,WGS）已用来诊断 NDDs 患者，但其临床和成本效益尚不清楚。尽管临床全外显子组测序越来越多地被用于罕见孟德尔病的诊断，但在建立基因型-表型相关以解决致病基因或突变的计算分析方面仍然存在差距。人类表型本体论（Human Phenotype Ontology,HPO）为深入表型分析提供了最全面的生物信息学资源，是基因组生物学向临床医学转化的桥梁，正逐步被用于罕见疾病的表型分析与鉴别诊断。Exomiser 使用临床数据、模型生物表型数据以及蛋白质相互作用组数据的随机游走分析来执行优先级排序。
目的 本研究拟利用 HPO 标准化患者表型信息，结合 WES 测序数据及 exomiser 应用程序对候选变异进行优先排序，以识别潜在的致病基因及突变或对孟德尔遗传病进行鉴别诊断，有助于识别遗传性疾病病因，为描述基因型-表型的相关提供更准确的信息，为确定合适的治疗措施和临床管理策略提供依据。
方法 招募 45 个传统诊断方法不能确诊的 NDDs 核心家系。通过对先证者的病史及体格检查获得每个核心家系的临床表型。使用 HPO 对表型进行标准化，然后对 45 个核心家系进行 WES 测序，测序数据使用 exomiser 结合 HPO 标准的异常表型对候选变异进行优先排序。
结果 （1） 45 个 NDDs 核心家系的诊断率为 49%；（2） 对 NDDs 家系深度表型分析发现患者异常表型以神经系统异常为主，同时伴有多系统异常。（3） exomiser 对候选基因优先化排序筛选出多个 NDDs 相关基因的新突变。（4） 利用蛋白质-蛋白质游走分析发现 3 个基因 *FOXO4*、*DSCAML1*、*TREX2* 变异通过蛋白质-蛋白质相互作用可能与 NDDs 相关。
结论（1） WES 结合 HPO 表型分析及 exomiser 分析软件可以提高 NDDs 患儿的诊断率，该方法用于解决临床患者的表型没有系统的整理及标准化，建立基因型与表型相关性具有重要的意义。（2） 首次报道了 NDDs 相关基因的可能致病性突变，扩展了这些基因的突变谱并有助于家系进行遗传咨询和产前诊断。（3） exomiser 对候选基因优先化排序，以及利用蛋白质-蛋白质游走分析疑似能筛选出新的致病基因。

中国人 MODY 家系首个 NEUROD1 基因 E59Q 突变的遗传、致病机制与临床特点

蒋燕燕[1] 陈亚婷[1] 张娟[1] 葛晓旭[1] 张荣[1] 蒋伏松[1] 李鸣[1] 于淼[2] 贾伟平[1] 刘丽梅[1]
1.上海交通大学附属第六人民医院
2.中国协和医科大学附属协和医院

目的 在青少年成人型糖尿病（MODY）13 种致病基因中，与较常见的 MODY2、MODY3 和 MODY5 不同，NEUROD1/MODY6 亚型少见。我们在 MODY 家系中筛查 *NEUROD1* 突变，研究其遗传、致病机制与临床特点。
方法 用 PCR-直接测序法，筛查 32 个中国人 MODY 家系（MODY2、3 和 5 基因突变阴性）先证者 NEUROD1 基因突变；通过基因型-临床表型、MIN6 细胞突变-转染蛋白转录活性检测、3D 模型构建与生物信息学分析。
结果 1）在中国典型 MODY 家系中，首次发现 NEUROD1 基因杂合错义突变 E59Q (c.175G>C, p.Glu59Gln)，Glu59 氨基酸残基在哺乳动物物种的 NEUROD1 蛋白中高度保守；2）该家系 5 名突变携带者，其中 4 名突变与高血糖呈遗传共分离，空腹和餐后 2 小时的胰岛素与血糖比值，与家系的非携带者（n=4）相比显著降低（p<0.005）；但 1 名（先证者父亲）虽携带突变但无糖耐量异常；3）3D 研究显示 E59Q 突变后，带负电荷的 Glu59 氨基酸被不带电的 Gln59 取代，导致侧链两个盐桥键消失，而与 Arg54 形成新的氢键。4）E59Q 突变体的转录活性下降 36.8%(vs.WT，p<0.01)；5）201 个“超正常”葡萄糖耐量的对照受试者中未检测到 E59Q 突变。
结论 本研究表明 NEUROD1-E59Q 突变通过改变与其周围氨基酸的相互作用，改变了 N 端 3D 分子构象，阻碍突变体 E59Q 与胰岛素启动子的结合，降低其转录活性，导致胰岛素分泌缺陷的 MODY6 发生。提示 E59Q 突变引起的 MODY6 呈不完全外显。

四个非综合征性耳聋家系的遗传学分析

王莉
河南省人民医院

目的 对 4 个不相关的耳聋家系进行基因检测，明确其致病机制，为家系遗传咨询及产前诊断提供依据。
方法 搜集 4 个家系的详细资料，包括临床表现、听力学检查、影像学检查等，绘制遗传图谱。家系 1、2、3、4 分别为 X 连锁显性、常染色体显性、常染色体隐性、X 连锁隐性遗传。同时采集 4 个家系先证者及相关成员的 DNA 样本行全外显子组测序及外显子缺失检测，并进行致病性分析。
结果 家系 1 先证者测序结果显示 *PRPS1* 基因存在 c. 46 T>C 变异。家系 2 先证者测序结果显示 *OSBPL2* 基因存在 c. 564 _ 565 ins G 变异，未见文献报道。家系 3 先证者测序结果显示 *SLC26A4* 基因存在 c.919-2 A＞G 变异、第 5 外显子杂合缺失。家系 4 先证者测序结果显示 *POU3F4* 基因存在 c. 520G>T 变异，未见文献报道。以上 4 个家系均符合基因型-表型共分离，且根据 ACMG 指南，上述突变均为致病性突变。
结论 全外显子组测序技术已成为遗传性耳聋分子诊断和遗传学研究的重要手段之一，突变基因为上述四个家系遗传咨询及产前诊断提供了有力依据，其中首次报道的突变丰富了人类基因突变数据库。

Correlation between steroid levels in follicular fluid and mitochondrial abnormalities in its exosomes and embryonic development in women undergoing assisted reproductive technology

Li Yu[1] Miao Liu[3] Zhenxin Wang[1] Te Liu[2] Suying Liu[3] Baishen Pan[1] Beili Wang[1] Xi Dong[3] Wei Guo[1]
1.Department of Laboratory Medicine, Zhongshan Hospital, Fudan University, Shanghai, China
2.Shanghai Geriatric Institute of Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China
3. Reproductive Medicine Center, Zhongshan Hospital, Fudan University, Shanghai, China.

Purpose Human follicular fluid is a complex biological fluid that contributes to the microenvironment of developing oocyte. There is increasing evidence that sex hormones present in follicular fluid (FF) may play an important role in regulating the developmental potential of oocyte. The aim of this study was to evaluate the role of sex hormones in embryo development during the in vitro fertilization cycles.

Methods This was a cohort study of 138 women undergoing IVF/ICSI, including 136 FF samples from 109 infertile women. The corresponding oocyte was individually cultured in order to track its developmental outcome. FF AMH, FSH, LH, PRL and hCG levels were measured by immunoassays. Another 20 steroid levels in FF were tested by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Meanwhile, the mRNA expression levels of mitochondrial electron transport chain (ETC) complex genes from exosomes of FF were detected by qPCR.

Results An analysis of these individual FF concentrations revealed that LH and FSH concentrations were higher in follicles in which the oocyte developed into a top quality (TQ) blastocyst (LH: 9.44±2.32mIU/ml, FSH: 9.32±1.01mIU/ml) than those in which there was a failure of fertilization (LH: 5.30±0.84mIU/ml, FSH: 6.91±0.62mIU/ml). In contrast, follicular cortisone concentrations were the lower for oocytes that resulted in a TQ blastocyst (12.20±0.82mIU/ml) than for oocytes that failed to fertilise (15.37±0.87mIU/ml). The receiver operating characteristic analysis showed that FF LH and FSH levels predicted TQ blastocyst with excellent AUC value of 0.711 and 0.747. The mRNA levels of mitochondrial ETC complex I and III were increased in the FF exosomes of TQ blastocyst. Correlation analysis showed that mRNA levels of ETC complex I was positively correlated with LH and FSH levels in FF.

Conclusion FF LH and FSH levels from individual follicles can accurately predetermine subsequent embryonic development. Combining follicular fluid analysis with routine morphological assessment, could allow for a more accurate and sensitive method of determining embryonic developmental competence. Furthermore, impaired exosome mitochondrial dysfunction is a potiential event that causes hormone change in embryo development.

全十号染色体父源单亲二体致 COL17A1 突变纯合引发交界型大疱性表皮松解症一例报道

王瑶[1] 喻东[2] 毕新岭[1] 颜宏利[1]
1.中国人民解放军海军军医大学第一附属医院
2.中国人民解放军海军军医大学

目的 报道一例因父源 10 号染色体全染色体单亲二体致胶原蛋白 COL17A1 基因第 23 号外显子突变纯合（患儿父亲为杂合子，母亲为野生型）引发患儿遗传性交界型大疱性表皮松解症（JEB）病例。

方法 四岁女童，智力正常，从出生起，全身复发性水泡破溃，肢体发育异常，发育迟缓。经家系全外显子组测序（trio-WES）分析致病突变，并排除拷贝数变异区域的突变，通过 UPDio 算法分析单亲二体事件，突变位点经一代测序验证。对病变组织活检，并进行免疫组化、免疫荧光以及投射电镜检测。

结果 患儿致病突变为 COL17A1 (NM_000494.4): c.1880(exon23)delG (p.G627Afs*56)，相关联的疾病为交界型大疱性表皮松解症（OMIM: 226650），该突变之前未经文献报道，为新检出突变。患儿 10 号染色体杂合缺失，并排除拷贝数异常，通过 UPDio 分析表明患儿 10 号染色体为全染色体父源单亲二体，从而，父源杂合突变 COL17A1 (NM_000494.4): c.1880(exon23)delG 发生纯合导致疾病发生。病理结果与分子检测结果相符。

结论 本文报道了一例因 10 号染色体全染色体父源单亲二体导致的 COL17A1 纯合突变引发交界型大疱性表皮松解症病例。该突变位点以及 10 号染色体全染色体父源单亲二体未有文献报道。由于 trio-WES 与病理活检相比相对无创且易于实施，我们推荐将 trio-WES 作为大疱性表皮松解症检测的首选方案，并且，在 WES 数据分析时将单亲二体纳入常规分析范畴。

Application of chromosomal microarray analysis in autism spectrum disorder, intellectual disability and developmental delay

Yuqiang Lv Yi Liu
Qilu Children's Hospital of Shandong University

Objective Copy number variants (CNVs) are recognized as a crucial genetic cause of neurodevelopmental disorders (NDDs). Chromosomal microarray analysis (CMA), the first-tier diagnostic test for individuals with NDDs, has been utilized to detect CNVs in clinical practice, but most reports are still from populations of European ancestry. Here we investigated the genetic etiology of 410 Han Chinese patients with NDDs (151 with autism and 259 with unexplained intellectual disability (ID) and developmental delay (DD)) using CMA (Affymetrix) after G-banding karyotyping.

Methods A total of 410 probands with ASD or unexplained ID/DD with or without other anomalies referred for genetic services in our institute between January 2014 and December 2018 and their parents were enrolled in this study. Genomic DNA was extracted from peripheral blood samples of the probands and their parents, and genotyped using CMA. The data were analyzed with Chromosome Analysis Suite (ChAS). qPCR with SYBR Green chemistry were utilized to verify the potentially clinically relevant CNVs in the cases and their parents.

Results Among all the NDD patients, 109 (26.6%) carried clinically relevant CNVs or uniparental disomies (UPDs), and 8 (2.0%) had aneuploidies (6 with trisomy 21 syndrome, 1 with 47,XXY, 1 with 47,XYY). In total, we found 129 clinically relevant CNVs and UPDs, including 32 CNVs in 30 ASD patients, and 92 CNVs and 5 UPDs in 79 ID/DD cases. When excluding the eight patients with aneuploidies, the diagnostic yield of pathogenic and likely pathogenic CNVs and UPDs was 20.9% for all NDDs (84/402), 3.3% in ASD (5/151), and 31.5% in ID/DD (79/251). When aneuploidies were included, the diagnostic yield increased to 22.4% for all NDDs (92/410), and 33.6% for ID/DD (87/259). We identified a de novo CNV in 14.9% (60/402) of subjects with NDDs. Interestingly, a higher diagnostic yield was observed in females (31.3%, 40/128) compared to males (16.1%, 44/274) for all NDDs (P=4.8×10-4), suggesting that a female protective mechanism exists for deleterious CNVs and UPDs.

Conclusion In this study, the higher diagnostic yield was observed in the ID/DD group which might be influenced by the clinical experience of the referring pediatricians, the phenotypic severity of the cohort, gender, and age.

羟氯喹治疗 X 连锁 Alport 综合征疗效及安全性研究

孙蕾[1] 匡新宇[1] 龚秀丽[2] 蔡勤[2] 张静[1] 郝胜[1] 康郁林[1] 曾凡一[2] 黄文彦[1]
1.上海交通大学附属儿童医院
2.上海医学遗传研究所

目的 X 连锁 Alport 综合征(XLAS)是一种罕见的遗传进展性肾脏病，由编码 IV 型胶原 α5 链的 *COL4A5* 基因突变引起，是儿童及青少年终末期肾脏病主要原因之一。XLAS 目前尚无有效治疗手段，常规 RAAS 系统抑制剂治疗效果差，基因治疗的可行性尚不确定，本研究首次探讨硫酸羟氯喹（HCQ）对 XLAS 治疗的疗效及安全性。

方法 （1）HCQ 治疗 XLAS 疗效初步观察：分析 8 例 XLAS 患儿使用 HCQ 治疗（6.5mg/kg.d，分 2 次口服，持续 6 个月），获上海市儿童医院伦理委员会（编号：2019R063-E02）批准。治疗期间监测患儿尿红细胞计数、尿蛋白定性、24 小时尿蛋白定量及肝肾功能、眼科检查等；（2）HCQ 对 XLAS 小鼠（COL4A5 p.G5X）肾脏保护作用。实验分组如下：X^{G5X}/X^{w} 羟氯喹治疗组及对照组（各 4 只），X^{G5X}/Y 羟氯喹治疗组及对照组（各 4 只），野生型羟氯喹治疗组及对照组（各 4 只），于 8 周龄起接受 HCQ 灌胃治疗（150mg/kg.d）。治疗期间监测小鼠尿蛋白/肌酐、肝肾功能等，治疗 8 周结束后行肾组织病理检查等，各组间进行组间单因素方差分析，以 $P<0.05$ 为差异有统计学意义。

结果 （1）HCQ 治疗 XLAS 临床疗效：治疗 1 个月 4 例患儿(患儿 1、2、3、4)血尿程度较前好转(表 1，$P>0.05$)，其中 2 例表现为肉眼血尿患儿(患儿 1、3)肉眼血尿消失。治疗 6 个月，8 例患儿血尿程度均明显下降，尿红细胞计数均明显小于基线值(表 1，$P<0.05$)。观察期 6 个月 8 例患儿尿蛋白水平下降但无统计学意义(表 1)。HCQ 治疗期间，所有患儿同时接受贝那普利口服，无严重不良事件发生。（2）HCQ 治疗 XLAS 小鼠 8 周，X^{G5X}/X^{w} 小鼠尿蛋白/肌酐水平在治疗第 8 周较对照组明显降低，X^{G5X}/Y 小鼠尿蛋白/肌酐水平在第 4 周治疗较对照组明显降低，结果具有统计学意义(图 1、2，$P<0.05$）。治疗组 XLAS 小鼠监测肝肾功能较对照组无明显异常。

结论 首次报道 HCQ 能够明显改善 XLAS 患儿病情并明显改善 XLAS 小鼠蛋白尿水平且安全性良好，其确切长期疗效有待进一步大样本随机对照研究及机制探讨。

G6PD 缺乏症，从新生儿筛查到治疗新策略的实验研究

张虹洋[1,2] 彭单伊[3] 余朝文[3] 何晓燕[3] 王冬娟[3] 刘之岱[3] 舒逸[3] 王治国[4] 邹琳[1,2,3]
1.上海市儿童医院临床研究中心
2.上海交通大学医学院儿童感染免疫与重症医学研究院
3.重庆医科大学附属儿童医院临床分子医学中心/新生儿筛查中心
4.国家卫健委临床检验中心

目的 葡萄糖-6-磷酸脱氢酶（G6PD）缺乏症是我国南方省市常见的遗传性血液病，自 2010 年开始，逐渐成为我国新生儿筛查（新筛）的主要病种之一，但全国的新筛现状未知。本研究旨在探索我国 G6PD 缺乏症新筛现状、基因突变谱与可能筛查新策略。

方法 汇总全国 G6PD 缺乏症 5 年新筛数据，分析全国筛查状况；收集其中 1 年的多中心筛查血片，利用 PCR 和测序方法，检测全国 *G6PD* 基因突变谱，发现的可能新位点，验证其位点致病性。

结果 汇总我国 2013-2017 年全国 G6PD 缺乏症新筛数据，发现筛查量/机构 5 年逐年递增，G6PD 缺乏发病率主要呈现南高北低趋势，以海南、广东、广西最多；收集我国 12 省 29 新筛中心 2016 年 10,357 个新生儿血片，发现 *G6PD* 基因突变主要位点包括 1376G>T、c.1388G>A、c.95A>G、c.1024C>T 和 c.871G>A，突变位点存在地区与民族差异；发现 4 个新发位点 （c.152C>T, c.290A>T, c.697G>C, c.1285A>G）；进一步利用 CRISPR/Cas9 技术在 HEK293 和 K562 细胞中证明其致病性，发现 c.697 G>C 突变后，造成 G6PD 酶热稳定性下降；在中国南方 9 省市中 G6PD 酶活性正常的 7400 女婴血片中，发现 371 例（约 5%）*G6PD* 基因呈现杂合突变，后续建议中国新筛南方省市的可能新策略。

结论 中国开展 G6PD 缺乏症新筛逐渐增多，疾病南高北低，基因突变有地域差异，*G6PD* 基因新位点 c.697G>C 有致病性，可为中国未来新筛新策略提供依据。

514 例新生儿消化道畸形的遗传变异谱分析

王瑶 吴冰冰 卢宇蓝 董欣然 张萍 刘仁超 程国强 曹云 沈淳 王慧君 周文浩
复旦大学附属儿科医院

目的 消化道畸形（gastrointestinal malformation, GIM）是新生儿期最常见的出生缺陷之一。GIM 在产前难以通过超声明确诊断，出生后往往病情危重，需要紧急外科干预，且预后不良。GIM 的遗传背景尚不明确，通过大样本的二代测序数据分析其遗传变异谱将有助于辅助临床病因诊断，改善治疗，判断预后。
方法 采用回顾性分析研究方法，纳入 2014 年 1 月-2021 年 6 月期间，在复旦大学附属儿科医院分子医学中心进行二代测序的消化道畸形患儿。纳入标准包括从食管至肛门的消化道各段的畸形，以及肝、胆、胰腺的畸形。排除口腔、腭部畸形、腹外疝等异常。对纳入病例的二代测序结果（包括临床外显子测序和全外显子组测序）进行基因变异分析和染色体拷贝数变异分析，并结合患儿的临床表型、影像学表现，总结 GIM 患儿的临床与遗传学特征。
结果 共纳入 514 例病例，70 例获得明确的遗传诊断，阳性诊断率约 13.5%。其中，检测到基因位点变异 47 例（9.1%），染色体拷贝数变异 23 例（4.4%）。其中，复杂型 GIM 组（并发其他畸形或功能障碍）的诊断阳性率明显高于单纯型 GIM 组（16.4%vs 8.4%，p= 0.0002382）。本研究中，常见的突变基因包括 *ACTG2*（8 例），*CHD7*（3 例），*EFTUD2*（3 例），*JAG1*（3 例），MNX1（3 例），*EDNRB*（2 例），*RET*（2 例），*ZEB2*（2 例），占阳性基因突变的 55.3%。在 8 例 *ACTG2* 基因突变导致的内脏肌病（Visceral myopathy）[MIM: 155310]患儿中，均检测到基因上存在新发致病变异（*De novo*），其中 6 例为外显子 7 的 c.769C>T (p. Arg257Cys) 变异。最常见的染色体拷贝数变异是 22q11.21 的缺失（4 例）和 16p13.11 重复（2 例），占阳性染色体异常的 26.0%。
结论 我们首次报告了大样本的基于二代测序数据的消化道畸形的遗传研究结果。通过二代测序同时分析基因变异和染色体变异，有助于更为全面地了解 GIM 的遗传变异谱。同时，本研究发现的上述 8 个基因和 2 个染色体区段可作为 GIM 遗传筛查的首要考虑因素。

Nrg4 突变在非酒精性脂肪肝中的作用机制

Yangyang Li
Shanghai Jiao Tong University Affiliated Sixth People's Hospital

Aims Neuregulin 4 (Nrg4), as an adipose tissue–enriched endocrine factor, participates in adipocyte-to-hepatocyte communication, and elicits beneficial metabolic effects in non-alcoholic fatty liver disease (NAFLD). Here, we evaluate the physiological roles of Nrg4 in humans and unravel the role of NRG4 variants in the pathogenesis of NAFLD and related metabolic disorders.
Methods We performed whole exome sequencing in 224 severely obese subjects and exome array in a community-based population of 2388 subjects to screen for mutations of *NRG4* in Chinese population. High-fat diet mice were used to construct NRG4 over-expression animal models through AAV9-mediated delivery. Then we explore the mechanism of mutant Nrg4 on lipid metabolism in primary hepatocytes. Surface plasmon resonance and imaging flow cytometry experiments were performed to measure the interaction between different versions of purified Nrg4 and the receptor ErbB4.
Results We identified two rare missense mutations—p. R44H and p.E47Q— in the NRG4 EGFL domain by whole exome sequencing and exome genotyping from Shanghai Obesity Study. The over-expression animal models showed Nrg4 WT could attenuate HFD-induced hepatic lipogenesis and improve energy metabolism. Nrg4 E47Q enhanced the protective effect, however Nrg4 R44H had no significantly positive effects. We then found that Nrg4 WT activated

phosphorylation of ErbB4 and negatively regulated *de novo* lipogenesis mediated by SREBP1c. Nrg4 R44H purified protein didn't showed the same activation as Nrg4 WT, however Nrg4 E47Q enhanced the activation. We performed surface plasmon resonance experiments and proved that the receptor of Nrg4 was ErbB4 with a affinity of 2.20uM. Nrg4 E47Q showed a higher binding affinity of 1.66 μM, while R44H showed no binding. Imaging flow cytometry experiments also showed, compared with WT Nrg4, the combining capacity of E47Q Nrg4 was evidently increasing; however, R44H Nrg4 almost lost its combining capacity (18.12% for WT vs. 0.85% for R44H vs. 27.21% for E47Q).
Conclusions In conclusion, these results suggest that Nrg4 WT interact with its receptor ErbB4 to prevent HFD-induced NAFLD and alleviate insulin resistance, and demonstrate Nrg4 R44H and E47Q lose or enhance the ability to bind to ErbB4, thus altering physiological function, suggesting Nrg4 enhancement may be a new therapeutic strategy to treat NAFLD.

RTN2 杂合突变致痉挛性截瘫 12 型三例报道

曹立 田沃土 朱泽宇
上海交通大学附属第六人民医院

目的 报道三例 *RTN2* 基因突变所致痉挛性截瘫 12 型（SPG12）病例，并对遗传学检出的 *RTN2* 突变进行功能学验证，探讨该病的表型以及评估相应突变的致病性。
材料和方法 对三例患者的临床表现进行分析评估，并进行全外显子测序；体外构建 RTN2 基因真核表达载体（野生型和突变体），转染 HEK 293T 细胞系，进行细胞免疫荧光检测。
结果 病例一：女，31 岁，因"双下肢发硬 13 年，行走不利 5 年"就诊，18 岁起出现行走时双下肢肌肉发硬、紧张感，但尚未影响行走；近 5 年出现行走速度慢、易摔倒，同时伴有视物成双、偶有小便失禁。体格检查：吐词清，双眼远视时有复视。四肢肌力 5 级，四肢肌张力增高，双上肢腱反射（+++），膝反射（++++），髌阵挛、踝阵挛（-），Babinski 征（+），行走呈剪刀步态，共济可。**病例二：**男，36 岁，因"进行性行走困难 19 年"就诊，17 岁起出现行走时双下肢乏力，休息数分钟后好转；随后下肢乏力进行性加重，约行走 10 分钟即需要休息，但仍可缓慢行走，伴双下肢肌肉僵硬、紧绷和肿胀感，偶有摔倒。随后上肢肌肉也出现僵硬、肿胀感。无肌痛、肌萎缩、吞咽困难、饮水呛咳、构音障碍等。体格检查：双下肢肌张力轻度增高，四肢肌力 5 级，四肢腱反射（+++），右侧踝阵挛（+），共济和轮替动作可，为外八字步态。**病例三：**男，50 岁，因"进行性行走困难 26 年余"就诊，24 岁起发现自己行走姿势与他人不同，右下肢僵硬；逐渐出现行走时双下肢易乏力，抬腿费力。起病 16 年后需扶拐杖行走，并出现排尿困难、便秘，逐渐发展为无法独立行走。自幼视力较差，8 岁确诊双眼白内障。体格检查：双眼视力<0.8，双上肢肌力 5 级，双下肢肌张力增高，下肢腱反射（+++），剪刀步态，行走需要扶墙，双侧 Babinski 征（+）、踝阵挛（+）。全外显子测序结果提示三位患者分别存在 RTN2 基因 c.103C>T（p.R35X）、c.230G>A（p.G77D）和 c.337C>A（p.P113T）杂合突变。体外功能实验结果显示野生型 RTN2 蛋白在细胞内与内质网共标，无义突变 p.R35X 呈均质弥漫分布于胞浆中，而错义突变 p.G77D 和 p.P113T 仍与内质网存在共定位，但其内质网形态结构发生异常聚集呈团块状。根据 ACMG 评估和分级指南，该位点可评为"可能致病"。
结论 本研究中，一例患者仅有运动功能受累，表现为单纯型 HSP；另两例还伴有视力、排尿功能障碍，表现为复杂型 HSP。结合临床与遗传学特点综合考虑诊断为 SPG12。本病为常染色体显性遗传性疾病，据文献报道其起病年龄自 5 岁至 39 岁不等。同时本研究发现三个新的 *RTN2* 致病性突变，其可能通过 RTN2 在细胞内的定位或影响内质网的稳定性，从而导致疾病的发生。

基于转录组的分子分型对胶质瘤临床病理分型的辅助作用

李聪
广州市驰跃科技有限公司

目的 胶质瘤的病理诊断中，组织病理学和分子特征相结合可使神经外科医师更精准地评估肿瘤级别和预后。然而目前对胶质瘤，尤其是将病理形态结合分子遗传学信息整合的研究报道偏少。
方法 我们对 105 份胶质瘤（WHO II~IV 级）冰冻组织和对应的癌旁组织做了两套组学分析：全转录组和非靶向代谢组学。转录组数据中我们以 log2FoldChange > 1，BH-adjusted P < 0.05 和 AUC > 0.8 为标准挑选了一系列标签基因，基于标签基因的表达水平将全部肿瘤分为 5 组：RNAS1~5。
结果 5 组肿瘤的总生存 OS 和无进展生存 PFS 存在显著差异，在驱动基因的突变负荷层面上 RNAS4 的 IDH1 突变显著少于其他 4 组，且 OS 和 PFS 最短。5 组肿瘤的代谢富集通路也存在明显差异，从差异代谢物中我们鉴别出甘氨酸，甘油磷脂等小分子代谢物在 RNAS1 组中显著上调（adjusted P < 0.05），而谷胱甘肽、花生四烯酸在 RNAS3 组中显著上调（adjusted P < 10^{-3}），葡萄糖-6-磷酸在 RNA4 组中显著上调（adjusted P < 0.05），甲酰甲硫氨酸在 RNA5 组中显著上调（adjusted P < 0.05）。我们将这个系列的标签基因用于 TCGA-LGG 和 TCGA-GBM 数据，结果发现分成 5 组后生存曲线也存在显著差异。
结论 我们的结果显示，基于基因表达谱的分子分型可以将我们的胶质瘤（包括低级别胶质瘤和胶质母细胞瘤）分为预后显著不同的 5 组，而且 5 组胶质瘤的代谢特征也具有显著差异。建议临床的分子病理可以对胶质瘤组织做辅助转录组测序，检测上述标签基因，以进一步整合诊断并为临床提供预后相关的分子遗传学因素。

DCTN1 突变所致 Perry 综合征一例及功能学研究

田沃土 栾兴华 曹立
上海交通大学附属第六人民医院

目的 报道一例由 DCTN1 剪切位点突变所致 Perry 综合征患者，探讨 DCTN1 相关疾病谱系的临床表现与功能学特点。
材料与方法 对该患者的临床表现进行分析评估和遗传学检测；进一步构建 Minigene 系统载体，探索 DCTN1 剪切位点突变对该基因转录翻译的影响。
结果 患者，女，65 岁，因“进行性加重的失眠、抑郁、帕金森样症状 4 年，通气功能障碍伴反复呼吸道感染 1 年”就诊，患者 4 年前起开始出现入睡困难，并伴有情绪不稳定和性格改变，就诊精神科考虑“抑郁症”并予以抗抑郁药物治疗，同时伴有双上肢静止性震颤和步态异常；近 1 年反复因中枢性通气功能障碍、呼吸道感染住院治疗。近一年体重减轻 10 斤。家族史：否认父母近亲婚配；患者的两个姐姐和母亲生前均有相似症状，均在 60-70 岁之间因呼吸道感染去世，未获得查体资料和外周血样本。体格检查：身高 160cm，体重 41kg，卧床吸氧中；神清，对答切题，言语含糊，偶表达出放弃生命的悲观愿望。四肢僵硬、肌张力增加，四肢肌肉废用性萎缩，双上肢静止性震颤，四肢肌腱反射（+++），双侧髌阵挛阳性，病理征检查不配合。辅助检查：2020 年于 ICU 住院期间动脉血气分析提示电解质紊乱，PaO2=15.73kpa，PaCO2=8.06kpa，剩余碱（9.1mmol/L）和标准碳酸氢根浓度（32.0mmol/L）均升高。（2019 年）头颅磁共振：双侧侧脑室旁和额顶叶多发腔隙性病灶，脑萎缩，白质轻度变性。（2019 年）多导睡眠监测：中度阻塞性呼吸暂停，低通气伴严重睡眠低氧血症。（2019 年）全外显子测序和一代测序验证：DCTN1 基因 c.279+1G>T 杂合突变；先证者儿子无此突变，目前表型正常。功能能学研究：通过构建野生型和突变体的 Minigene 体系质粒，在 HEK 293T 细胞中野生型呈正常转录加工方式，而突变体在第 2 号外显子末端缺失 108bp。
结论 DCTN1 基因不同突变可以导致不同的临床表型，包括遗传性远端运动神经病 7B 型（dHMN7B）、肌萎缩侧索硬化症（ALS）以及 Perry 综合征。结合本例患者的临床表现、辅助检查和基因检测结果以及功能学验证结果，综合考虑诊断为 Perry 综合征。综上，我们报告了一种导

致 Perry 综合征的新 DCTN1 剪切突变，通过功能学实验证实 c.279+1G>T 可导致 DCTN1 基因 mRNA 剪接异常。c.279+1G>T 通过破坏并替换原剪接供体位点，导致 DCTN1-RNA 2 号外显子-2 号内含子剪接方式异常，从而导致 Perry 综合征。

鳃-耳综合征相关 EYA1 基因隐匿性基因组变异的发现与鉴定

庞秀红
江苏省泰州市人民医院

目的 鳃-耳综合征（BOS）以耳聋合并耳畸形、鳃弓发育异常为特征的较为常见的综合征耳聋。*EYA1* 基因为其最常见的遗传性病因。前期收集 1 例 BOS 散发患者及其父母样本，二代测序发现 *EYA1* 基因可疑杂合大片段缺失。本研究旨在利用多种遗传学检测技术探索该杂合缺失确切断点，从而为隐匿性基因组变异的发现及鉴定提供方法学流程。
方法 利用 Real-time PCR 技术验证靶向捕获二代测序所发现可疑杂合大片段缺失是否真实存在，全基因组测序技术寻找确切断点，一代测序技术跨大片段扩增验证。
结果 Real-time PCR 证实了 *EYA1* 基因大片段缺失真实存在，全基因组测序发现杂合大片段缺失位点，一代测序验证发现该杂合缺失突变实为杂合缺失-插入突变 GRCh38/hg38:chr8:g.71318554-_71374171delinsTGCC。先证者正常表型父母未发现携带该杂合突变。先证者良性位点变异父母来源提示先证者与父母亲生关系，因此该大片段缺失-插入突变为 *de novo* 突变。
结论 本研究利用多种遗传性检测技术最终在散发 BOS 患者中发现 *EYA1* 基因未报道 *de novo* 大片段缺失-插入突变，该突变很可能为患者遗传性病因。本研究丰富了鳃-耳-肾谱系疾病基因谱，为临床咨询进一步提供理论依据。本研究以 *EYA1* 基因大片段缺失-插入突变发现与鉴定为例，为隐匿性杂合基因组变异的探寻提供了方法学技术流程。

Hedgehog signaling pathway negatively affects development in Drosophila melanogaster PheRS-m mutants

mo lidangzhi Yuanming Wu
Air Force Medical University

Hereditary spastic paraplegia (HSP) is one of the neurodegeneration diseases which can be sporatic and genetic. The degeneration of corticospinal tract is the reason that cause HSP. The characterization of HSP is spastic paraplegia of lower limbs and progressively decreased extremity weakness. We had previously found in a Chinese family has genetic autosomal recessive HSP that caused by missense mutation of karyogene encodes phenylalanyl-tRNA synthetase 2, mitochondrial (*FARS2* c.424 G>T). However, there is a little study about the molecular mechanisms about *FARS2* and HSP. *FARS2* is a conservative gene that has 50% identity with Drosophila *FARS2* gene (*PheRS-m*). We used CRISPR/Cas 9 to construct a Drosophila HSP missense mutation disease model and *PheRS-m* knock out model. We noticed some interesting phenotypes in the fly models, including developmental delay, shorten lifespan ($P<0.05$), abnormal wing structure ($P<0.05$) and so on. Then RNA-seq technique was applied to investigate molecular mechanisms which combined with phenotypes focused on the hedgehog signaling pathway. By using qRT-PCR experiments to determine in different developmental stages of Drosophila (including 3 different larval stages, pupa and adult stage), we noticed that *PheRS-m* cause dysfunction of development process through hedgehog signaling pathway. Some important gene relative expression level changed obviously in this process like hib, Hh, ptc, slmb etc ($P<0.05$). Overall, we proposed that hedgehog signaling is negative regulated by *PheRS-m* and is part of the reason that cause the body dysplasia phenomenon of the *PheRS-m* mutants.

FSHR 基因复合杂合新变异导致高促性腺激素闭经而不孕

肖敏 陈小琴 雷彩霞 奚燕萍
复旦大学附属妇产科医院集爱遗传与不育诊疗中心

目的 为探讨 1 例高促性腺激素闭经同时卵巢功能正常的不孕患者的遗传学病因，同时也为遗传咨询以及生育指导提供依据。
方法 应用全外显子组测序技术对患者临床表征相关的基因进行生物信息学分析及诊断，对患者及其姐姐、弟弟与父母的 FSHR 基因进行变异位点 Sanger 测序。
结果 检出患者 FSHR 基因第 5 外显子 c.392G>A（p.Gly131Asp）及第 4 外显子 c.310A>G（p.Lys104Glu）的复合杂合变异，母亲携带 c.392G>A（p.Gly131Asp）杂合变异，父亲携带 c.310A>G（p.Lys104Glu）的杂合变异。姐姐和弟弟检出与患者相同的 FSHR 基因复合杂合变异。通过家系分析及依据美国医学遗传学与基因组学学会（ACMG）指南对变异进行分类得出，2 个错义突变均为可能致病性突变，临床数据以及文献回顾显示该患者应为卵巢抵抗综合征（ROS）而非卵巢早衰（POF）。
结论 本研究发现 FSHR 基因复合杂合变异是导致患者及其姐姐原发性闭经以及不孕的可能遗传学病因。不孕不育是遗传异质性非常高的一类疾病，临床很难通过常规检测来对疾病进行区分，基因检测对这类疾病的检测具有重要意义。同时 FSHR 基因中国人群已报道的致病性变异较少，本文卵巢抵抗综合征家系中 FSHR 基因两个新变异位点的检出，丰富了 FSHR 基因突变谱，对于未来该疾病的诊断具有重要的参考意义。

CCDC151 基因新无义变异导致 Kartagener 综合征伴无精症表型

肖敏 雷彩霞 奚燕萍
复旦大学附属妇产科医院集爱遗传与不育诊疗中心

目的 Kartagener 综合征是原发性纤毛运动障碍（primary ciliary dyskinesia，PCD）的一种亚型，是一种罕见先天性的以常染色体隐性遗传为主的疾病，以纤毛运动障碍为特征。为探索 1 例 PCD 伴无精子症患者不孕的遗传学病因，同时也为其生殖遗传咨询包括后代发生遗传病风险提供指导。
方法 应用全外显子组测序技术对 PCD 以及不孕不育相关基因进行生物信息学分析及诊断，发现患者 CCDC151 基因第 8 外显子 c.1059C>A（p.Tyr353*）纯合突变，可导致原发性纤毛运动障碍 30 型。
结果 依据美国医学遗传学与基因组学学会（American college of medical genetics and genomics，ACMG）指南分类，该无义突变为致病性变异。该病患者相关临床表征有反复发作型中耳炎、慢性支气管炎、鼻塞、纤毛清除缺陷所致呼吸功能不全、哮喘、咳嗽、反复呼吸道感染、鼻息肉、纤毛运动异常、支气管扩张，约 50%的患者有完全性内脏反位。目前未见 CCDC151 基因变异导致男性不育及无精子症表型的报道。
结论 本研究发现一个导致原发性纤毛运动障碍的 CCDC151 基因新突变，丰富了 PCD 罕见病以及 CCDC151 基因突变谱，同时首次报道了 CCDC151 基因突变可导致男性无精子症的不育表型。

一例 TBCK 基因突变导致 IHPRF3 综合征的临床和遗传学分析

张开慧
山东大学齐鲁儿童医院

目的 婴儿期肌张力减退-伴精神运动迟滞-特殊面容 3 型(Hypotonia, infantile, with psychomotor retardation and characteristic facies 3，IHPRF3)是一种罕见的伴有独特先天性多发畸形的常染色体隐性遗传病，其主要特征为出生时或婴儿早期的神经发育障碍性疾病，如大头畸形、精神运动迟

缓、语言障碍、脑室扩大、侧脑室白质异常等。2016 年 Chong 等人发现 TBCK 基因突变导致 IHPRF3，目前只发现了 29 个 TBCK 基因突变。本研究旨在分析一例发育迟缓、脑积水、特殊面容、肌无力患儿的临床表现与遗传学病因。
方法 对 2019 年 6 月山东大学齐鲁儿童医院神经外科接诊的一例患儿的临床表现进行回顾性分析，并采集患儿及其父母哥哥外周血，应用染色体芯片微阵列（CMA）和全外显子组测序技术进行检测，对突变位点进行患儿及其父母的 Sanger 测序验证和致病性分析。
结果 （1）患儿，男，1 岁 7 月，发育迟缓、脑积水、特殊面容、肌无力、双手通贯掌、肌无力，单侧隐睾，不会说话。MRI 大脑髓质发育不良，室旁白质软化，部分脑外腔隙较宽。CMA 检测正常，无家族史。（2）测序发现该患儿 TBCK 基因 c.244_263del (p.Leu82fs)纯合变异，父母分别为杂合携带该突变；致病性分析示 c.244_263del 为未报道的截断突变，根据 ACMG 2015 年指南分析为致病性变异。
结论 该患儿最终诊断为 TBCK 基因突变所致 IHPRF3 综合征，这是国内第一例 IHPRF3 综合征的报道；为临床诊疗和遗传咨询提供了依据。

上海市溶酶体贮积症新生儿筛查及基因突变分析

张惠文
上海交通大学医学院附属新华医院

目的 分析上海市 6 种溶酶体贮积症（lysosomal storage disorders，LSD）酶活性及基因突变情况，为 LSD 发病率、早期诊断及治疗提供依据。
方法 利用串联质谱技术（Tandem Mass Spectrometry，MS/MS）对 2020~2021 年上海交通大学医学院附属新华医院新生儿筛查中心新生儿干血滤纸片样本进行戈谢病、尼曼匹克病 A/B 型、克拉伯病、黏多糖贮积症 I 型、法布里病及庞贝病 6 种 LSD 酶活性检测， LSD 指标分别为酸性 β-葡萄糖脑苷脂酶（ABG）、酸性鞘磷脂酶（ASM）、β-半乳糖脑苷酯酶（GALC）、α-L-艾杜糖苷酸酶（IDUA）、α-半乳糖苷酶（GLA）和酸性 α-葡糖苷酶（GAA）。通过检测 NeoLSD 试剂盒质控品来评估 MS/MS 检测 LSD 的性能。对酶活性降低的新生儿进行基因检测，分析 LSD 基因突变情况。
结果 7995 例新生儿 6 种 LSD 酶活性分布中位数值分别为 ABG：7.43（1.42-67.28）μmol/L/h、ASM：3.71（0.26-26.88）μmol/L/h、GALC：3.12（0.31-32.68）μmol/L/h、IDUA：5.17（0.81-17.96）μmol/L/h、GLA：8.58（0.34-75.46）μmol/L/h、GAA：9.52（0.34-34.38）μmol/L/h。试剂盒质控品检测结果均处于靶值±1SD 范围内，准确度好。目前共检出 6 例新生儿 LSD 酶活性均显著降低，2 例为克拉伯病阳性患儿，*GALC* 基因上均检出 1 个纯合错义突变 c.1901T>C（p.L634S）；1 例为庞贝病疑似患儿，*GAA* 基因上检出两个杂合变异，c.2238G>C（p.W746C）变异为致病突变，c.2189+22G>A 变异临床意义不明；3 例新生儿基因结果暂未知。
结论 MS/MS 技术可用于 LSD 的新生儿筛查，酶活性结果与基因检测一致性较好，2 例克拉伯病阳性患儿突变位点均为 c.1901T>C（p.L634S），提示该位点可能为中国人群的热点变异。

应用三代测序技术检测一例 KNO 综合征家系 COL18A1 基因大片段缺失

李泳榆 张清炯
中山大学中山眼科中心

目的 以往通过 RNA 测序在一名 Knobloch（KNO）综合征患者发现 *COL18A1* 基因的 32-36 号外显子发生缺失，但断点不清。应用 Nanopore 三代测序技术（TGS）明确该 KNO 综合征患者的分子病因。
方法 对一名 KNO 综合征患者及其家系进行临床研究和系谱分析。采集该患者及其家系成员的外周血标本，采用 LR-PCR 方法扩增覆盖 *COL1A81* 基因包含断点的区域，长约 12.8kb。应用基于纳

米孔测序技术的 TGS 平台（Oxford Nanopore）对扩增长片段进行测序。对于检测到的基因组拷贝数缺失应用 Sanger 测序进行家系验证。

结果 该家系共 2 代 5 名成员。先证者（II1）及其妹妹（II2）携带 chr21:46925244_46925278 纯合缺失，其父亲（I1）在该位点为杂合缺失。TGS 检测提示先证者（II1）及其母亲（I2）、妹妹(II2)在 chr21:46921287-46926478 区域存在长约 5.2kb，包含 *COL1A81* 基因 33-36 号外显子的缺失变异，确定了准确的断点位置。父亲（I1）和弟弟（II3）未见该突变。Sanger 测序结果证实该缺失突变位点存在。结果符合家系遗传共分离。

结论 TGS 能够有效提供基因拷贝数变异信息及精确定位断点，可为 KNO 综合征诊断及进一步遗传咨询提供更有价值的信息，对 KNO 综合征出生缺陷的预防具有临床指导意义。

Linear Darier’s Disease Combined with Nagashima-type Palmoplantar Keratosis: a case report

Zijun Zhao
Shanghai Skin Disease Hospital

Linear Darier's disease is an uncommon chronic dermatosis with a mutation in the ATP2A2 gene. It showed linear multiple hyperkeratotic papules predominantly in seborrheic areas on the head, neck, and trunk. Nagashima-type palmoplantar keratosis is the most common type in the Asian population with well-demarcated, mild, nonprogressive diffuse hyperkeratosis. It is an autosomal recessive skin disease caused by mutations in the SERPINB7 gene. There have been few reports ofNagashima-type palmoplantar keratosis combined with Darier's disease. Here we report the case of a 34-year-old female who had a history of palmoplantar hyperkeratosis since she was born. The patient also presented with multiple linear brown wart-like papules on the left frontal occipital, left limbs for 4 years. The genomic DNA of the patient's both blood and tissue were analyzed using a gene probe. The result showed that she has the mutation of ATP2A2 and SERPINB7 genes. These findings suggest that the linear DD can coexist with NPPK. In addition, the patient's skin tissue genetic test suggested a mutation in the ATP2A2 gene, while the blood test suggested another mutation in the SERPINB7 gene. The choice of specimen type is critical to the results of genetic testing.

线粒体 3-羟基-3-甲基戊二酰辅酶 A 合成酶-2 缺乏症 10 例临床及遗传学分析

毋盛楠 卫海燕 沈凌花 陈琼 陈永兴
郑州大学附属儿童医院、河南省儿童医院、郑州儿童医院 内分泌遗传代谢科

目的 线粒体 3-羟基-3-甲基戊二酰辅酶 A 合成酶-2 缺乏症（HMGCS2D）是一种影响酮体生成的罕见常染色体隐性遗传疾病，临床表现及常规生化检查结果缺乏特异性，诊断较困难，国内关于该病仅数例个案报道。我们回顾性分析了 10 例线粒体 HMGCS2D 患儿的临床及遗传学特点，以期提高临床医师对该病的认识。

方法 选取本院确诊来自 10 个不同家系的 10 例患儿，收集详细临床资料。

结果 10 例患者中男性 3 例，女性 7 例，均 1 岁以内发病，最常见表现为厌食、发热起病，随后 2～7 天内进展为呕吐、呼吸困难和意识障碍。病程中均有厌食、呼吸困难和意识障碍、肝大，发热呕吐 8 例，咳嗽 4 例，腹泻 3 例。实验室检查均有严重代谢性酸中毒、转氨酶升高，乳酸均正常；7 例低酮性低血糖，3 例无低血糖；CK-MB 升高 7 例，高氨血症、低钙血症各 4 例，高甘油三酯血症 3 例。急性期头颅 MRI 检查 3 例脑沟及额颞部蛛网膜下腔增宽，1 例基底节异常信号，1 例白质髓鞘形成延迟，4 例正常。急性期尿中均检出大量二羧酸，6 例血游离肉碱降低，同时乙酰肉碱增高；9 例乙酰肉碱/游离肉碱比值增高；2 例血游离肉碱正常，乙酰肉碱增高。1 例患者死于急性期难以纠正的代谢性酸中毒、多脏器功能衰竭，其余 9 例随访 1-4 年预后均良好，生长发育正

常。10 例患者均在 HMGCS2 基因上检出复合杂合变异，共 15 种，其中已报道的变异 5 种，新变异 10 种，包括 c.220G>A/p.E74K，c.407A>G/p.D136G，c.422T>A/p.V141D，c.719A>c/p.D240A，c.821G>A/p.R274H，c.39dupA/p.Leu14fs，c.1394delA/p.N465Tfs*10，c.788delT/p.L263Cfs*36，c.717T>G / p.Y239*，c.1017-2A>G。既往已报道的中国患者 11 例，结合本研究 10 例，21 例患者中，7 例 HMGCS2 基因上检出 c.1201G>T/p.E401*，提示该突变可能是中国线粒体 HMGCS2D 患者的热点突变。

结论 线粒体 HMGCS2D 多于婴儿期因感染、进食差为诱因急性起病，短时间可进展至昏迷甚至致死，主要表现为严重代谢性酸中毒、低酮性低血糖、尿中排除大量二羧酸，血乙酰肉碱/游离肉碱比值增高。稳定期多无异常表现，各项生化指标可正常，多数预后良好。基因检测为该病的及时诊断提供帮助，c.1201G>T/p.E401*可能为中国患者 HMGCS2 基因的热点突变。

Genetic variants affect the efficacy of resistant starch on NAFLD

Xiaoxue Long Weiping Jia
Shanghai Jiao Tong University Affiliated Sixth People's Hospital

Resistant starch, a kind of dietary fiber, has been implicated as a promising nutritional intervention to metabolism disorders including NAFLD, while genetic factor is one of the determinants of response to treatment in NAFLD. We aimed to investigate the effect of genetic variants on the response to resistant starch in NAFLD patients. This study was conducted in a randomized controlled trial of resistant starch on non-alcoholic fatty liver disease among Chinese subjects. Genomic DNA from 88 subjects who completed a 4-month supplementation with type 2 resistant starch (RS2) was genotyped on Infinium Asian Screening Array-24 v1.0 BeadChip. We investigated the effects of these single nucleotide polymorphisms (SNP) on the relative change of intrahepatic triglyceride content (IHTC) as measured by proton magnetic resonance spectroscopy (MRS). 14 loci were associated with relative change of IHTC ($P < 1 \times 10^{-5}$), including SNPs in or near KLRK1, NAV2, NXPH1, GRIN2A, LINC01081, EYA2, ZMYND8, GRID1, and LOC105377885 genes. A genetic risk score (GRS) was constructed by summing the number of risk alleles and can predict the response of patients with NAFLD to RS2 supplementation (AUC: 0.98; 95% CI: 0.95 - 1.00). Taken together, supplementation of RS alleviated NAFLD and the efficacy is associated with genetic variants. A genetic risk score can prospectively evaluate the responses and may further serve as a promising tool for personalized treatment.

先天性心脏病合并心外畸形中 RHOB 基因突变的致病机制研究

王金鑫
复旦大学附属儿科医院

目的：研究 RHOB 基因在先天性心脏病合并心外畸形中的致病机制。

方法：前期通过临床普筛，将先心患儿 1155 名进行全外显子测序，我们发现了其中有一名患儿为完全性肺静脉异位引流合并神经发育迟滞，后续对其父母进行基因测序，确认该患儿为新发突变。后续对该基因突变进行体外细胞实验，验证其对于细胞功能的影响。

结果：细胞实验结果表明，RHOB 有抑制细胞迁移及增殖的作用，而在点突变后，此抑制作用被一定程度的抵消。

结论：RHOB 基因点突变的体外实验结果表明，此点突变或许造成了患儿患先天性心脏病合并神经系统发育迟滞。

基于 SMA 注册队列人群的基因诊断技术应用调查分析

白晋丽 宋昉 瞿宇晋 曹延延 贾妮 金煜炜 王红
首都儿科研究所

目的 调查分析基于中国罕见病注册系统中脊髓性肌萎缩症（SMA）队列人群相关基因诊断技术的应用现况和发展趋势。
方法 本项横断面调查研究以 2016 年 7 月至 2018 年 12 月在首都儿科研究所注册登记的 200 例 SMA 患儿为研究对象，通过查阅注册信息、基因检测报告以及电话随访等方式获得患儿基本信息、疾病分型、基因型、基因诊断相关信息等。按照检测时间分层后，分别统计采用不同基因诊断技术的人数和构成比，采用 Pearson 相关分析基因诊断技术的应用与时间的相关性。
结果 除 3 例资料不全的病例，共纳入 197 例 SMA 病例。SMAⅠ、Ⅱ和Ⅲ型的患儿分别为 37（18.8%）、115（58.4%）和 45 例（22.8%），SMN1 纯合缺失和复合杂合变异病例分别为 185（93.9%）和 12 例（6.1%）。2004—2017 年 SMA 基因诊断技术有 7 种：以多重连接探针扩增技术（MLPA）为主，占 54.1%（100/185），其次是聚合酶链式反应‐限制性片段长度多态性（PCR‐RFLP）和一代测序，分别为 22.7%（42/185）和 10.3%（19/185），等位基因特异性 PCR（AS‐PCR）、实时定量 PCR（qPCR）、全外显子组测序（WES）及变性高效液相色谱分析（DHPLC）分别 9、6、5 和 4 例，占 2.2%~4.9%。MLPA 的应用从 2010 年开始逐步增加（r=0.95，P<0.05），而 PCR‐RFLP 从 2004 年开始逐步下降（r=-0.99，P<0.05），其他检测方法应用与时间暂未发现相关性（P>0.05）。定量检测技术（MLPA、qPCR 和 DHPLC）的应用从 2010 年开始逐渐增高（r=0.94，P<0.05），定性检测技术（PCR‐RFLP、一代测序、AS‐PCR 和 WES）从 2004 年开始逐渐下降（r=-0.94，P<0.05）。纯合缺失与复合杂合变异的基因重复检测率分别为 12.4% （23/185）和 41.7%（5/12），差异有统计学意义（χ^2=5.86，P<0.05）。基因检测结果显示，同时提供 SMN1、SMN2 基因定量分析报告的构成比在 2008—2015 年为 56.8%（21/37），2016—2017 年上升至 69.1%（56/81）。
结论 SMA 基因检测技术从定性检测技术逐步发展为以 MLPA 和 qPCR 为主的定量检测技术。SMA 定量检测报告不仅提供了 SMN1 致病基因的定量结果，也提供了 SMN2 修饰基因的定量结果。
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TRNT1 基因突变导致先天性铁粒细胞性贫血伴免疫缺陷、发热和发育迟缓综合征

李妍 毛华伟 韩彤昕 孙菲 莫文秀
北京儿童医院

目的 通过对先天性铁粒细胞性贫血伴免疫缺陷、发热和发育迟缓综合征（congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay，SIFD）临床表现及辅助检查的研究，了解该疾病的特点，提高对本疾病的认识。
方法 回顾性分析我院在 2021 年 6 月收治的一例 TRNT1 基因突变所致 SIFD 患儿的症状、体征及辅助检查，总结其临床特点以及诊治经过，并对本病进行文献回顾。
结果 患儿生后出现周期性发热，体温最高 39.5℃，每日热峰 3-4 次，每次发热 5 天，体温正常 7 天再次出现发热，体温正常与否与抗感染治疗无相关性。发热时查白细胞升高，中性粒细胞为主，CRP 明显升高，体温正常时，白细胞及 CRP 较发热时下降，但仍高于正常。发热时伴腹泻，呕吐，体温正常时症状消失。病程中曾出现颜面部淡红色圆形皮疹，皮疹中央可见白色丘疹，压之褪色，部分可见破溃，渐波及全身，外院予丙种球蛋白及地塞米松治疗后皮疹消退。伴有中重度贫血（小细胞低色素），病程中出现一次血小板减少。此外，患儿存在发育迟缓，3 月会抬头，1 岁会翻身、爬，1 岁 6 月会坐，2 岁会站，3 岁会扶走，4 岁会独走约 5-10 米，4 岁会说叠词。完善 CD 系列提示 T 细胞绝对值明显升高，B 细胞绝对值冥想降低，Ig 系列提示 IgG、IgA、IgM 明显降

低，细胞因子提示 γ-IFN 明显升高，IL-6 及 IL-8 升高，全外显子基因检查示 TRNT1，chr3:3189238，NM_182916；exon7，c.907C＞G（母亲来源）；chr3:3170812，NM_181916;exon2，c.88A＞G（父亲来源)，根据患儿症状、体征及辅助检查，最终诊断为先天性铁粒细胞性贫血伴免疫缺陷、发热和发育迟缓综合征。患儿于我院行丙种球蛋白冲击治疗，并于发热第 2 天予阿达木单抗皮下注射治疗，发热 3 天体温即恢复正常，复测细胞因子均降至正常范围。
结论 TRNT1 是编码 tRNA 核苷酸基转移酶的核基因，tRNA 核苷酸基是成熟 tRNA 氨基酰化和参与蛋白质生物合成的基本先决条件。TRNT1 基因的突变导致线粒体和细胞质的代谢异常，表现为 SIFD 综合征。SIFD 是一种常染色体隐性疾病，伴有严重的多脏器受累，可表现为铁粒细胞性贫血、B 细胞免疫缺陷、周期性发热和发育迟缓。免疫球蛋白替代疗法主要用于 B 细胞缺陷患者，可以降低感染风险。本例患儿还应用 TNF 抑制剂（阿达木单抗）治疗，有效控制了周期性发热的热程，且降低了外周血异常细胞因子的水平，提示阿达木单抗对于治疗本疾病有效。对于本病的发病机制有待进一步研究。

DHX37 基因杂合变异——胚胎睾丸退化综合征新病因

潘丽丽 苏喆 深圳市儿童医院 DSD 多学科协作组
深圳市儿童医院

目的 总结胚胎睾丸退化综合征（Embryonic testicular regression syndrome，ETRS）的临床特点，并在国内首次报道 *DHX37* 基因杂合变异致 ETRS，提高临床医生对 *DHX37* 基因认识。
方法 收集深圳市儿童医院 ETRS 病例，对全外显子基因结果阴性患儿数据重新分析，关注 *DHX37* 基因，并对已报道的 *DHX37* 基因杂合变异病例进行复习。
结果 共收集 5 例 ETRS 患儿资料。初诊年龄 2 月～5 岁 5 月，社会性别 3 例男性，因男性化不全就诊，2 例女性，因阴蒂肥大就诊。超声检查均未显示子宫。5 例行腹腔探查见睾丸萎缩、发育不良。性腺活检：3 例条索性状腺，1 例一侧条索、另一侧发育不良睾丸并性腺母细胞瘤，另 1 例未行活检。全外显子基因重新分析：发现 2 例 *DHX37* 基因存在 c.923G＞A(p.R308Q)杂合变异，余 3 例未发现致病性变异。检索文献发现，2019 年首次报道 *DHX37* 基因致 ETRS 及 46，XY 性腺发育不良，共 40 例，ETRS21 例，以男性化不全表型常见，亦可见女性表型，睾丸组织消失为主要病理改变。国内未见报道。
结论 本文总结了 5 例 ERTS 的临床表现和全外显子检测结果，在国内首次检出 *DHX37* 杂合变异 2 例，占 2/5，并首次报道了 ERTS 合并性腺母细胞瘤。*DHX37* 杂合变异是 2019 年发现的 46,XY 性腺发育不良（含 ETRS）新病因，在该人群需注意筛查。

在中国神经发育障碍队列中确认 WASF1 R506 再发性变异的致病性的研究

Guanshaofang Shang
Capital of pediatrics

基于家系的全外显子测序（Whole exome sequencing，WES）所发现的新生变异（包括单核苷酸变异和拷贝数变异）是研究中到重度神经发育障碍遗传致病因素的重要手段。我们利用家系 WES，在 1000 人的中国神经发育障碍（neurodevelopmental disorders ,NDDs)队列中发现了 *WASF1* 基因[MIM: 605035]一例新生截断性变异 c.1516C>T (p.Arg506Ter)。这是中国报道的第一例和 NDDs 相关的再发性 *WASF1* 基因变异。该患者的主要表型包括智力发育障碍、癫痫和自闭症等，和欧洲报道的病例表型高度相似。我们还对患者的全血 RNA 进行了高通量转录组测序，经过通路分析后发现，*WASF1* 截断性变异可能通过影响线粒体动力学功能导致相应表型的发生。我们的研究支持 *WASF1* 截断性变异是造成 *NDDs* 发生的致病性因素，并将这一变异的种族范围扩大到亚洲人群。

NAA15 基因致病性突变导致的轻度智力发育落后及追赶生长

田宇[1] 谢华[2] 杨圣海[1] 上官少方[2] 王建红[1] 金春华[1] 张裕[2] 崔小岱[2] 吕岩玉[2] 陈晓丽[2] 王琳[1]
1.首都儿科研究所附属儿童医院
2.首都儿科研究所

NAA15 基因的突变和神经系统发育障碍（Neurodevelopmental disorders，NDD）的发生密切相关。在这项研究中，我们招募了 769 名中国 NDD 患者，并对队列中 *NAA15* 基因突变的测序结果及临床表型进行分析。通过全外显子组测序，从中检测出 4 例 *NAA15* 突变患者。这 4 例突变均未被报道，其中 3 例是新生突变，1 例母源突变。采用 Minigene 体外剪切分析技术对其中 1 例非经典剪切位点突变（c.1410+5G>C)进行功能验证，证实其导致 mRNA 剪切异常。所有患者均表现为轻度智力发育落后，通过对患者在不同年龄的发育评估，发现其中两名患者出现追赶生长。同时，文献回顾显示，一半的 *NAA15* 致病性变异患者出现轻度/中度发育迟缓或智力障碍，其中 3 名报告患者随着年龄的增长被描述为“好转”或“正常”。我们通过研究中国大陆的 NDD 患者扩大了致病性 *NAA15* 突变的变异谱系。所有患者均表现为轻度智力发育落后，并在一半患者中发现追赶生长。未来需要研究具有致病变异的 NDD 患者的自然神经发育轨迹及其从物理康复中的益处，以进行精确的遗传咨询和临床管理。

5 个 SMN1 基因 2+0 模式的脊髓性肌萎缩症家系的基因诊断与遗传咨询

高敏 张开慧 律玉强 马健 王东 刘毅
山东大学齐鲁儿童医院

目的 脊髓性肌萎缩症是一种因脊髓前角运动神经元退化变性导致肌肉无力的常染色体隐性遗传病，发病率约为 1/6000～10000 活产儿，中国人群 SMA 致病基因的携带者频率约为 1/42。SMA 患儿多呈 SMN1 基因 exon7 纯合缺失，患儿父母一般为 SMN1 基因 exon7 杂合缺失,部分患儿父母 SMN1 基因为 2+0 模式。目前 SMA 分子诊断采用的多重连接探针扩增技术进行检测仅能对拷贝数进行检测，不能检测 2+0 模式。本研究对 5 个 SMA 患儿父或母 SMN1 基因 exon7 拷贝数为 2 的 SMA 家系进一步分析，明确其遗传方式。
方法 抽取患儿及父母外周血，并提取其 DNA。应用荧光 PCR-毛细管电泳法对样本进行拷贝数检测，依据 SMN1 基因紧密连锁的多态性遗传标记基因分型结果。
结果 多态性遗传标记检测示 5 例家系样本亲缘关系正确，SMN 基因所在的 5 号染色体上多态性遗传标记符合孟德尔遗传规律。5 例家系患儿 SMN1 基因 exon7 纯合缺失,4 例患儿母亲提示 2+0，2 例患儿父亲提示 2+0，与 MLPA 检测结果一致。5 例家系自然生育，下一胎均有 25%风险患病，应及时进行产前诊断。
结论 MLPA 可以检测 SMN1 基因拷贝数，但不能识别 2+0 模式。荧光 PCR-毛细管电泳法可以利用多态性遗传标记识别 2+0 模式，为进一步明确家系的基因分型和 2+0 模式的遗传咨询起到了重要的作用。

大脑皮层发育不良患儿的临床及遗传学分析

赵培伟 彭雪华 张蕾 黄玉凤 郑楠楠 何学莲
武汉儿童医院

目的 探讨大脑皮层发育不良（MCD）患者的临床特点以及遗传学特点。
方法 利用全外显子测序技术（WES）以及染色体芯片技术（CMA）对大脑皮层发育不良的患者进行遗传学分析，并对 WES 检测阳性的患者进行 Sanger 测序验证。

结果 本研究纳入 33 例患者，存在癫痫、智力低下、发育落后等症状；MRI 发现巨脑回畸形 11 例，小头畸形 4 例，带状灰质异位/脑室旁灰质结节异位 5 例，局灶性皮质发育不良（FCD）2 例，多小脑回畸形 1 例，其他脑沟裂增宽、脑裂畸形等 10 例。11 例巨脑回畸形中 7 例患者检测阳性，包括 1 例 17p13.3 区域缺失（LIS1 基因）、3 例 LIS1 基因突变、DCX、DCHS1 以及 DYNC1H1 基因突变各一例。4 例小头畸形中发现 1 例由染色体微缺失所致（del11q23.3q25）；1 例极重度小头畸形患者是由 16p13.11 杂合缺失（包括 NDE1 基因）和另一拷贝 NDE1 点突变组成的复合变异所致；其余两例患者由 KIF11 以及 IQSEC2 所致。5 例灰质异位患者中 2 例存在缺失分别为 Xq22.3q23 缺失（包括 DCX 基因）和 Xq27.3q28 缺失，1 例患者（SBH）存在 17p13.3 嵌合缺失（比例约为 20%），1 例脑室旁灰质结节异位（BPNH）患者存在 FLNA 基因突变，另外一例患者未见明确致病基因。2 例局灶皮质增厚的患者中 1 例发现 WDR26 基因异常。1 例多小脑回畸形患者临床表现为巨头畸形，WES 发现其 PTEN 基因存在突变。其余的 10 例脑沟裂增宽、脑裂畸形的患者中发现 5 例存在 COG6、SON、EPG5 以及 del9p24.3 等异常。
结论 MCD 患者临床表型差异较大，WES 以及 CMA 技术科协助临床进行明确诊断。

AQP5 mutations induce palmoplantar keratoderma Bothnia type in two Chinese families

Yumeng Wang Ming Li
Xinhua Hospital, Shanghai Jiaotong University School of Medicine

Background: Palmoplantar keratoderma Bothnia type was caused by *AQP5* mutations. The mechanisms of this disease and the genotype-phenotype correlations are still not fully understood.
Objectives: Two pedigrees with palmoplantar keratoderma Bothnia type are reported here. To explore whether *AQP5* gene mutation affects differentiation or proliferation of keratinocytes and the genotype-phenotype correlations of palmoplantar keratoderma Bothnia type.
Materials and Methods: Blood sample from two Chinese families were collected. Next generation sequencing and Sanger sequencing were applied to identify the pathogenic gene according to clinical observation. Skin biopsy from one patient was conducted, and the expression of keratinocyte differentiation markers (KRT14, KRT10, LORICRIN) and co-localization of AQP5 and TRPV4 was investigated in the skin.
Results: A recurrent mutation c.367A>T and a novel mutation c.530T>A in the *AQP5* gene were identified. Histochemical analysis of skin sections revealed that keratinocytes with c.367A>T had abnormal expression of some specific proteins related to cornification. Besides, the co-localization of AQP5 and TRPV4 was apparent in sweat gland of patient.
Conclusion: We detected an unreported *AQP5* mutation in one Chinese family and considered c.367A>T (p.Asn123Tyr) as a hotspot mutation in Chinese patients. We also noticed that epidermis of the patient have lower differentiation potential. Moreover, we summarized the cases with *AQP5* variants identified and found there seemed to be no significant genotype-phenotype correlations of this disease.

广西中北部地区新生儿与高危儿原发性肉碱缺乏症筛查、诊断及干预研究

谭建强 蔡稔 陈大宇 畅荣妮 严提珍 潘莉珍 袁德健 黄钧 韦笑宝 宁海萍 曾婷
柳州市妇幼保健院

目的 探讨广西中北部地区新生儿与高危儿原发性肉碱缺乏症（PCD）的筛查效率、检出率、人群致病基因突变携带率、SLC22A5 基因突变谱及随访干预情况。
方法 采用串联质谱技术，对本地区 2012 年 1 月～2019 年 12 月出生的 111986 例新生儿和 7461 例高危儿进行酰基肉碱谱筛查，对游离肉碱（C0）水平低于 10 umol/L 的初筛阳性标本再次采血复

查后仍然偏低者进行基因诊断确诊，对诊断为 PCD 的患儿予左卡尼汀治疗，定期随访评估治疗效果。同时，随机对 2093 例新生儿进行高通量测序，对 SLC22A5 基因突变进行筛查，了解本地区人群 SLC22A5 基因突变携带率。

结果 111986 例新生儿 PCD 初筛阳性 784 例，初筛阳性率 0.7%，召回 720 例，召回率 91.8%，结合基因诊断确诊 PCD 患儿 12 例，本地区新生儿 PCD 检出率为 1/9332，远远高于以往我国学者报道。7461 例高危儿确诊 PCD 患儿 2 例，高危儿 PCD 检出率为 1/3731。14 例患儿 SLC22A5 基因测序检测到 11 种 28 个突变位点，分别为为 c.51C>G、c.976C>T、c.1411C>T、c.1195C>T、c.760C>T、c.919delG、c.1400C>G、c.517delC、c.839C>T、c.505C>T、c.338G>A，其中 c.976C>T、c.919delG 两个变异为首次发现的新变异，查阅相关数据库未见收录，多个生物信息学软件分析均提示为有害变异。c.51C>G 突变在本地区人群中检出率最高，与以往我国各地区报道有所差异，可能属本地区 SLC22A5 基因热点突变。2093 例新生儿 SLC22A5 基因筛查检出已报道突变携带者 24 例，本地区人群 PCD 致病基因突变携带率约 1.1%（24/2093）。PCD 患儿治疗前血游离肉碱水平明显偏低，与正常对照组比较差异有统计学意义（$P < 0.05$）；治疗前血游离肉碱及其他酰基肉碱水平与治疗后比较差异有统计学意义（$P < 0.05$），治疗后血游离肉碱及其他酰基肉碱水平恢复正常水平与正常对照组比较差异无统计学意义（$P > 0.05$）。目前 14 例患儿均在门诊随访，生长、智力及运动发育正常，血糖、血氨、肝功能、肌酸激酶以及心脏超声均未见异常。

结论 本地区新生儿与高危儿 PCD 检出率较国内其他地区偏高，SLC22A5 基因 c.51C>G 突变在本地区人群中检出率最高，可能属本地区热点突变。正常人群 PCD 致病基因突变携带率较高，建议在新生儿早期期进行遗传代谢病筛查，左卡尼汀早期干预对该病治疗效果显著预后良好。

R544C 突变 CADASIL 患者临床及影像特征分析

范梦婷 蔡斌 胡芳炜 黄惠清 汤莹莹 康明霞 谢玮杰
福建医科大学附属第一医院

目的 常染色体显性遗传性脑动脉病伴皮质下梗死和白质脑病（Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy，CADASIL）为最常见的单基因遗传性脑小血管病，其中 p.R544C 突变为东亚地区突变热点，本研究拟探讨 CADASIL 基因型与表型的相关性。

方法 收集 2014-2020 年就诊于我院，基因确诊为 CADASIL 患者的临床及影像学等信息，将其分为 R544C 突变组与非 R544C 突变组，进行组间临床及影像特征方面的比较。

结果

1.比较 R544C 突变组与非 R544C 突变组临床特征，发现两组在脑出血发生率（40.8% VS 3.2%，P＜0.001）、高血压患病率（50.7% VS 25.8%，P=0.02）、认知障碍发生率（73.2% VS 93.5%，P=0.02）及颞极受累率（31.0% VS 71.0%，P＜0.001）方面有统计学差异。

2．比较 R544C 突变组与非 R544C 突变组影像特征，发现两组在脑微出血数量（P=0.006）、微出血≥9 个（58.8% VS 23.1%,P=0.021）、基底节微出血（58.8% VS 15.4%,P=0.005）、丘脑微出血（80.4% VS 38.5%,P=0.008）方面进行性别、年龄校正后差异具有统计学意义。

3.高血压组与非高血压组 R544C 突变占比分别为 81.8%和 60.3%，存在统计学差异（P=0.02）；逻辑回归分析提示 R544C 突变为高血压病发生的独立危险因素（OR=2.870,95%可信区间:1.091-7.550，P=0.033）。

结论

1. 与非 R544C 突变组相比，R544C 突变组认知障碍发生率及颞极受累率较低，而微出血数量更多、负荷更重，基底节及丘脑微出血发生率更高。

2. R544C 突变为 CADASIL 患者发生高血压的独立危险因素。

遗传性鱼鳞病的基因诊断与治疗思路

潘超兰
上海交通大学医学院附属新华医院

目的 研究遗传性鱼鳞病的临床表现、遗传机制和治疗手段。
方法 文献检索收集遗传性鱼鳞病的分型、基因诊断及治疗方法，探究遗传性鱼鳞病与炎症因子之间的关系；同时收集严重皮炎、多种过敏、代谢消耗（SAM）综合征家系的血样，进行二代靶向测序、Sanger 测序和构建 minigene 模拟相关突变，明确患者的致病突变，研究其遗传致病机制；通过实时定量聚合酶链式反应（qRT-PCR）对患者的大片段缺失突变进行验证，同时对血液样本中炎症因子 mRNA 水平表达量进行检测，探究其炎症因子表达水平，并采取司库奇尤单抗皮下注射治疗 1 例 SAM 综合征。
结果 我们发现类似于特性性皮炎和银屑病患者，鱼鳞病患者体内同样有细胞因子的失调和屏障缺失、银屑病样免疫失调和脂质改变，数据支持对 IL-17/IL-36 靶向治疗的鱼鳞病患者；同时对于 2 例 SAM 综合征患者，在其中 1 例患者中找到了 DSG1 基因缺失突变 c.2437_2450delacctcccgg 和内含子突变 c.1688-30A>T，并发现内含子突变可导致外显子跳跃而致病；在另外 1 例患者中检测到了 DSP 基因的复合杂合突变，包括一个 37kb 的大片段缺失突变（chr6:7571617-7609106del）和一个错义突变（c.5014C>G），并在该患者血液样本中发现 Th17 炎症信号通路倾向，使用司库奇尤单抗后患者皮损状态好转，减少瘙痒状态、红皮病、鱼鳞病的发生，显著改善患者的心理健康及生活质量，同时减轻了患者家属对于其的日常护理的压力。
结论 我们发现免疫激活的潜在基础可使针对其他炎症性皮肤疾病的靶向抑制剂的重新利用成为可能；同时，我们首次发现了 DSG1 基因中 1 个致病的深部内含子突变，为未检测到外显子突变的患者提供了遗传学指导意义；首次发现 DSP 基因突变导致 SAM 综合征的常染色体隐性遗传模式，并且明确了司库奇尤单抗治疗 SAM 综合征在中国汉族人群中的有效性和安全性。

不同基因敲除小鼠模型揭示高度遗传异质性自闭症发病的共同分子机制

杨新平
南方医科大学

目前 已经发现数千自闭症候选基因，然而具有不同突变的自闭症患者却具有 共同的核心症状，提示高度遗传异质性自闭症具有发病的共同分子机制。我们对于小鼠两个 GABA 能受体(Gabrb1 和 Gabra4)和一个 5 羟色胺能受体（Htr3a）进行敲除，敲除小鼠表现出自闭症样表型，有记忆下降和抗癫痫表型，并且电生理显示兴奋/抑制突触传递失衡。海马组织转录组和分子网络分析揭示出一系列自闭症分子信号通路、学习记忆分子信号通路和癫痫相关的分子信号通路。三种基因敲除小鼠的 NMDAR 系统均上调，NMDAR 抑制剂可以逆转小鼠自闭症样行为和电生理兴奋/抑制突触传递失衡。这些结果提示，NMDAR 系统可能是自闭症发病的共同分子通路，是潜在的治疗靶标。

683 个耳聋家庭 Usher 综合征 1 型相关基因变异情况分析

严提珍[1] 卢宇[2] 袁德健[1] 黄钧[1] 韦笑宝[1] 罗世强[1] 袁慧军[3]
1.柳州市妇幼保健院 2.四川大学华西医院罕见病研究院
3.陆军军医大学第一附属医院医学遗传中心

目的 探讨 Usher 综合征 1 型（Usher syndrome type 1，USH1）相关基因在 683 例广西地区耳聋家庭中的变异情况。
方法 总结 2014 年至 2021 年 5 月在柳州市妇幼保健院医学遗传科遗传咨询门诊应用二代测序（next-generation sequencing，NGS）技术进行耳聋基因检测的 683 个耳聋家庭的临床资料和测

序数据，统计分析 USH1 相关基因（ *MYO7A*、*USH1C*、 *PCDH15*、*CDH23*、*USH1G*、*CIB2*）的变异情况。
结果 共有 26 个耳聋家庭检测到 USH1 相关基因的 35 个致病或可能致病变异，占所有耳聋家庭的 3.81%（26/683），其中 10 个耳聋家庭致病基因为 *MYO7A*，6 个耳聋家庭致病基因为 *USH1C*，5 个耳聋家庭致病基因为 *PCDH15*，3 个耳聋家庭致病基因为 *CIB2*，2 个耳聋家庭致病基因为 *CDH23*。35 个变异中的 16 个变异为首次报道，包括 *MYO7A* 基因的 c.523delC、c.3346_3347delCT、c.4485G>A、c.5309C>A、c.6049C>T 变异，*USH1C* 基因的 c.388-1G>A、c.579+2T>C、c.1414delG，*PCDH15* 基因的 c.1399C>T、c.3042_3045dupTGTG、c.4970_4971delCT，*CIB2* 基因的 c.383delC 变异，以及 *CDH23* 基因的 c.2746G>A、c.4696_4698delTAC、c.6613C>T、c.9433C>T。
结论 在广西地区耳聋患者中，*MYO7A* 为 USH1 相关基因中最常见的致病基因。应用 NGS 技术可以在视觉症状出现之前对 USH1 患者进行初步诊断。

cblC 型甲基丙二酸血症合并同型半胱氨酸血症、先天性心脏病及急性淋巴细胞白血病的 1 例报道并文献复习

朱俊 姜红堃 万水森
中国医科大学附属第一医院

目的 探讨甲基丙二酸血症（MMA）合并同型半胱氨酸血症、先天性心脏病及急性淋巴细胞白血病的遗传代谢机制、临床特征及诊疗。
方法 回顾性分析 2021 年 5 月于中国医科大学附属第一医院诊治的甲基丙二酸血症合并同型半胱氨酸血症、先天性心脏病及急性淋巴细胞白血病的 1 例患儿，对其实验室、影像检查，基因变异类型，治疗随访情况进行分析。
结果 该患儿主要临床表现为脑瘫、双下肢水肿、四肢无力及周身出血点。实验室检查：甲基丙二酸-2、乙酰肉碱（C2）、丙酰肉碱（C3）、C3/C2 及血同型半胱氨酸水平明显升高。颅脑 MRI 显示脑萎缩，右侧顶叶、岛叶异常信号。在 MMACHC 基因中检测到复合杂合突变：c.80A＞G（p.Q27R）和 c.609G＞A（p.W203X），证实为 CblC 型 MMA。骨穿、骨髓流式细胞术及骨髓基因学回报为急性 B 淋巴细胞白血病。心脏彩超提示卵圆孔未闭。经过氰钴胺肌肉注射、口服左卡尼汀治疗 2 个月，期间间断长春地辛及泼尼松化疗，患儿双下肢水肿、四肢无力及周身出血点逐渐好转。
结论 针对临床症状复杂的疾病，代谢病筛查及基因检测是非常必要的，同时需注意其遗传代谢机制的相关性。

Mechanisms of congenital myasthenia caused by three mutations in the COLQ gene

Xiaona Luo Yucai Chen
Shanghai Children's Hospital

The gene encoding collagen like tail subunit of asymmetric acetylcholinesterase (COLQ) is responsible for the transcription of three strands of collagen of acetylcholinesterase, which is attached to the endplate of neuromuscular junctions. Mutations in the *COLQ* gene are inherited in an autosomal-recessive manner and can lead to type V congenital myasthenia syndrome (CMS), which manifests as decreased muscle strength at birth or shortly after birth, respiratory failure, restricted eye movements, drooping of eyelids, and difficulty swallowing. Here we reported three variants within *COLQ* in two unrelated children with CMS. An intronic variant (c.393+1G>A) and a novel missense variant (p.Q381P) were identified as compound heterozygous in a 13-month-old boy, with the parents being carriers of each. An intragenic deletion including exons 14 and 15 was found in a homozygous state in a 12-year-old boy. We studied the relative expression of the

COLQ gene in the probands' families, performed three-dimensional protein structural analysis, and analyzed the conservation of the missense mutation c.1142A>C (p.Q381P). The splicing mutation c.393+1G>A was found to affect the normal splicing of *COLQ* exon 5, resulting in a 27-bp deletion. The missense mutation c.1142A>C (p.Q381P) was located in a conserved position in different species. We found that homozygous deletion of *COLQ* exons 14–15 resulted in a 241-bp deletion, which decreased the number of amino acids and caused a frameshift translation. *COLQ* expression was significantly lower in the probands than in the probands' parents and siblings. Moreover, the mutations were found to cause significant differences in the predicted three-dimensional structure of the protein. The splicing mutation c.393+1G>A, missense mutation c.1142A>C (p.Q381P), and *COLQ* exon 14–15 deletion could cause CMS.

CHD2 基因突变相关神经系统疾病 8 例临床研究和机制探索

罗晓娜 陈育才
上海市儿童医院

目的 探索 CHD2 基因（Chromodomain helicase DNA-binding protein 2）与神经系统疾病的关系。
方法 分析 CHD2 突变患者的临床资料，探讨其临床特点及可能的发病机制，通过实时荧光定量 PCR（qPCR），分析突变 CHD2 基因的表达量，并回顾了相关文献中报道的 CHD2 突变的病例的特点。
结果 共收集 8 例 CHD 基因突变，包括 6 个突变位点，其中 4 个为未报到的突变位点(c.670C>T, Arg224*; c4012A>C Lys1338Gln; c.2416dup, R806Kfs*20; c.1727-1728insAT, E576Efs*13)，另外两种已被报道（c5035C>T,Arg1679*,2 例；c4173dup,Gln1392Thr*17，2 例），其中 7 例为新发突变，1 例因父母未做基因检测，无法确定，临床表现为或轻或重的智力发育落后、癫痫、行为异常。qPCR 发现 CHD2 基因突变患者的表达量与其父母和正常人相比无明显变化.
结论 CHD2 基因突变可导致智力发育落后、癫痫、行为异常，同一位点突变可导致不同的临床表型，CHD2 基因突变并不会导致表达量下降，可能是其他机制影响 CHD2 的表达，其致病机制尚不清楚，需要进一步研究。

190 例肝豆状核变性患者临床特点及治疗分析

王伟 马明圣 邱正庆
北京协和医院

目的 总结肝豆状核变性（Wilson disease，WD）患者起病时临床表现，分析铜兰蛋白、24h 尿铜、K-F 环在儿童 WD 患者诊断中的意义；评估不同临床诊断方法在儿童 WD 患者的应用；明确基因诊断在儿童 WD 患者早期诊断中的意义。
方法 回顾性总结分析 1997 年至 2018 年就诊于北京协和医院儿科遗传门诊的 190 例肝豆状核变性患者的首诊症状、辅助检查、基因结果。
结果 190 例患者中，平均发病年龄为 8.05±6.04 岁（1.3-36 岁），男女比例为 1.6:1, 其中儿童 175/190 例。138/185 例（74.59%）初诊临床分型为肝脏型，其中无症状肝酶升高占 80.43%。185 例患者铜兰蛋白均＜0.2g/L,铜兰蛋白＜0.08g/L 在儿童 WD 中的检出率在 80%以上。24 小时尿铜＞40ug 在儿童 WD 中阳性率为 71.53-98.21%。K-F 在神经受累患者中阳性率更高。在家族史筛查阳性及部分无肝病表现的患者中，肝脏超声出现回声异常。2008 年肝豆状核变性诊疗临床诊断标准在 7 岁前临床诊断率仅为 20.36%，80%左右 7 岁前儿童患者需行 ATP7B 基因分析。
结论 本研究为单中心、回顾性研究，儿童患者为主；肝脏型肝豆状核变性患者占 74.59%；铜兰蛋白＜0.08g/L，24 小时尿铜＞40ug，肝脏超声异常在儿童肝豆状核变性患者中具有提示意义；ATP7B 基因检测在儿童肝豆早期诊断中具有重要意义。

RDH11 基因突变导致肌肉受累的视网膜色素变性综合征新表型

刘艺丹[1] 黄淑抒[2,3,4] 李梅[1] Monkol Lek[2] 宋丹羽[1] 谈丹丹[1] 陈晓瑜[1] 张弘[5] 刘洁玉[1] 常杏芝[1] 熊晖[1]
1.北京大学第一医院
2.耶鲁大学医学院
3.南通大学附属医院
4.南京医科大学
5.北京大学医学部

目的 视黄醇脱氢酶 11（RDH11）在视觉循环中具有特征性的辅助作用，可以氧化 11 顺式视黄醇到 11 顺式视黄醛。该基因突变导致疾病非常罕见，目前国际上仅报道了一个眼睛和智力的受累的家系，国内尚无相关报道。在这里，我们报道一例 RDH11 突变的中国患者的临床特征和遗传学发现。
方法 收集并分析患者的临床资料。取外周血进行家系全外显子测序（Trio-WES），对候选位点进行 Sanger 测序验证。分离外周血淋巴细胞，提取 RNA 并逆转录为 cDNA，cDNA 测序鉴定可能的剪接突变。使用 PSIPRED、SWISS-MODEL 和 RaptorX 预测蛋白结构。免疫荧光检测患者肌肉组织中 RDH11 的表达。
结果 临床资料：患儿，男，7 岁 6 个月，因“智力、运动发育落后，步态异常，肌无力”首次就诊于我院儿科。既往 5 岁时双眼白内障手术史。父母非近亲结婚，家族史（—）。体格检查发现四肢肌力下降，肌张力稍低，双侧跟腱挛缩，肌病步态，Gowers 征阳性。血清肌酸激酶 441U/L。肌活检示轻度肌肉病样病理改变，电镜下局灶肌丝破坏、部分肌纤维膜下和肌丝间线粒体数目轻度增多。15 岁时经全面眼科检查诊断为“视网膜色素变性”。遗传学发现：对患儿及父母进行全外显子测序，发现患儿 RDH11 基因复合杂合突变，c.938T>C（p.Leu313Pro），错义突变，来源于父亲；c.75-3C>A，来源于母亲。经 cDNA 测序证实 c.75-3C>A 为剪接突变，引起 Exon2 跳跃，导致蛋白翻译提前终止（p.Lys26Serfs*38）。蛋白结构预测：经突变体功能预测，两突变均导致蛋白二级结构、三级结构发生改变。免疫荧光：发现 RDH11 在患者骨骼肌细胞中的定位发生改变。
结论 本案例为国内首次报道的与 RDH11 基因突变有关的临床病例，揭示了肌肉受累的视网膜色素变性综合征新表型。c.938T>C 和 c.75-3C>A 为先前未经报道的新突变，扩大了 RDH11 基因的突变谱及与之相关的临床表型。

基于基因组拷贝数变异测序分析胚胎停育绒毛组织的染色体

石子佳[1,2] 高健[1]
1.河北省人民医院
2.河北医科大学

目的 应用基因组拷贝数变异测序（copy number variation sequencing，CNV-seq）分析停育胚胎的染色体变异情况，分析染色体异常与患者年龄、流产次数之间的相关性等。
方法 回顾性分析 240 例胚胎停育患者临床信息及其流产后绒毛样本的 CNV-seq 检测结果。
结果 （1） 胚胎停育绒毛组织染色体异常率为 75.4%（181/240），数目异常和结构异常分别占异常总数的 53.6%和 66.3%。（2）数目异常主要为三体（63.32%），发生频次较高的依次为 16-三体、22-三体、15-三体和 21-三 体。（3）按年龄分组比较，孕妇高龄与低龄者的绒毛染色体总异常率差异无统计学意义（$P > 0.05$），但常染色体三体在高龄组的异常占比高于低龄组（$P < 0.05$）；按停育次数分组比较，发生 1 次和≥2 次者异常率差异无统计学意义（$P > 0.05$）。（4）结构异常共有 120 例，多数同时发生两个或两个以上位点的 CNV，7 号染色体发生频次较高。其中 18 例（18/240，7.5%）致病，发生频次较高的染色体依次为 4、7、8 号染色体，2 例（2/240，0.8%）可能致病，发生在 6、7 号染色体，87 例（87/240，36.3%）临床意义不明，发生频次较高的为 7、16、17 号染色体，13 例（13/240，5.4%）可能良性，发生频次较高的为 1、4、10、7 号染色体。

结论 染色体异常是胚胎停育的主要原因，应用 CNV-seq 技术可提高染色体异常的检出率，更好地为胚胎停育患者再生育风险评估提供指导，同时 CNV-seq 分析结果的不确定性也增加了临床遗传咨询的难度，需结合多种产前诊断方法综合评估。

Uromodulin 相关遗传变异与 IgA 肾病进展相关

陈孜瑾 欧阳彦 杜雯 靳远萌 马骏 王朝晖 潘晓霞 任红 王伟铭 谢静远
上海交通大学医学院附属瑞金医院

目的 IgA 肾病(IgAN)是我国常见的肾小球肾炎，遗传因素与 IgAN 的发病和进展相关，探究与 IgAN 进展相关的遗传因素有助于增进对该病的认识。
方法 本研究入选 IgAN 队列：经肾活检确诊的由上海交通大学医学院附属瑞金医院肾脏科诊治的 IgAN 患者，年龄大于 18 周岁，且入选时 eGFR>15ml/min/1.73m2，收集患者的临床数据、肾活检病理资料、进展至 ESRD 的时间和血尿标本。健康队列：肾功能正常且微量白蛋白尿阴性的人群，收集其血尿标本。入选患者及健康人签署知情同意书。使用 SNapShot 法检测与 CKD 进展相关的 15 个 SNP。ELISA 法检测尿 Uromodulin 浓度。使用 STATA 进行统计分析，p<0.05 认为有统计学差异。
结果 961 例 IgAN 患者纳入本研究，其中男性 482 例(50.2%)，平均起病年龄为 35.3 岁，肾活检年龄 37.2 岁，肾活检时 eGFR 为 70.8(45.9，99.3) ml/min/1.73m2，蛋白尿 1.26(0.62-2.48)/24 小时，白蛋白 34.9±6.5g/L，血红蛋白 127.9±20.6g/L，626(71.6%)例患者使用血管紧张素系统抑制剂，532(60.9%)例患者接受激素治疗。961 例患者中位随访时间为 26.1(11.6-51.2)月，93(9.7%)例患者进展至终末期肾脏病。15 个 CKD 相关 SNP 均符合 Hardy-Weinberg Equilibrium 检验。采用逐步 Cox 回归分析，rs2490391[each C allele, HR=1.72（95%CI 1.20-2.47）] 和 rs77924615[each G allele, HR=1.88（95%CI 1.22-2.90）] 与 IgAN 患者进展至 ESRD 相关。通过 NephVS eQTL Browser 发现 rs77924615 与 UMOD 基因 mRNA 表达相关。随后，我们检测了 256 例健康人群和 68 例 IgAN 患者的尿液样本中 Uromodulin 的水平，结果显示 AA 基因型尿 Uromodulin 浓度为 3.732(1.716-4.745) ug/ml，AG 基因型 5.422(3.592-8.053) ug/ml，GG 基因型 5.266(3.532-7.577) ug/ml，AA 基因型患者尿 Uromodulin 浓度显著低于 AG 和 GG 基因型（p<0.05）。在 IgAN 人群和健康人群亚组中，AA 基因型的 uromodulin 均低于 AG 和 GG 基因型。最后，我们对 31 例 IgAN 患者的肾组织进行 UMOD 免疫组化染色，其中 AA 基因型 9 例，AG 基因型 12 例，GG 基因型 10 例。所有患者的肾小管上皮细胞内弥漫表达，顶端表达最明显，GG 基因型 AG 基因型肾小管上皮细胞中观察到不规则的 Uromodulin 聚集，而 AA 基因型患者中没有观察到此现象。
结论 CKD 相关遗传位点 rs2490391 和 rs77924615 与 IgAN 的进展相关，rs77924615 AA 的 IgAN 患者进展为 ESRD 的风险更低，可能与其尿液 Uromodulin 水平更低有关。

MAST3 基因突变导致神经系统发育性疾病

毛翛
湖南省妇幼保健院

目的 证实 MAST3 是神经系统发育性疾病新致病基因并提供其相关疾病表型
方法 通过对四个神经系统发育性疾病患者的 Trio-WES 发现其携带 MAST3 新发错义突变，并通过公开基因组及转录组数据数据分析及在体斑马鱼试验，证实 MAST3 突变在神经系统发育性疾病中的作用
结果 4 名患者分别携带位于 MAST3 基因的 c.302C>T、c.311C>T、c.1543G>A、c.1547T>C 新发错义突变，均表现为发育性癫痫脑病（DEE），突变分别位于 DUF 及 STK 结构域。通过应用发表公开的全外测序数据分析，我们发现神经系统发育性疾病群体所携带的 MAST3 DUFF 结构域变异

的 CADD 值明显高于 gnomAD 数据库正常对照组且具有统计学意义。在体斑马鱼 Mast3 敲减模型亦出现中枢神经系统相关表型。
结论 MAST3 是神经系统发育性疾病新致病基因

家族性 IgA 肾病致病基因研究

方正滢 欧阳彦 余舒文 杜雯 靳远萌 马骏 仝君 高琛妮 刘剑 王朝晖 任红 王伟铭 陈楠 谢静远
上海交通大学医学院附属瑞金医院

目的 家族性 IgA 肾病（IgAN）约占 IgAN 的 10~20%，提示可能存在单基因突变，目前尚无中国人家族性 IgAN 的大组研究。
方法 本研究共纳入 62 个独立的 IgAN 家系，IgAN 家系的定义为：1）家系中有 2 例或 2 例以上经肾活检确诊为 IgAN 的患者；2）家系中 1 例患者经肾活检确诊为 IgAN，另有至少一例家庭成员有不明原因的终末期肾衰和/或肾性血尿和/或蛋白尿（蛋白尿的定义为：尿常规示尿蛋白≥++和/或 24 小时尿蛋白定量≥150mg）。对所有先证者进行外周血全外显子测序（WES）。应用美国医学遗传学与基因组学学会 (The American College of Medical Genetics and Genomics, ACMG)制定的序列变异解读指南，对候选突变进行评分。评分结果为 Pathogenic（致病的）及 Likely Pathogenic（可能致病的）的突变为致病性突变。
结果 本研究共纳入 62 个 IgAN 家系，其中 48 个家系仅有 1 例肾活检确诊的 IgAN 患者，14 个家系存在 2 例或 2 例以上肾活检确诊的 IgAN 患者。共发现 8 个家系（12.9%）存在已知肾病基因致病性突变，突变类型均为杂合突变，突变在家系中符合疾病共分离。突变所在基因包括：*COL4A3*（3 例）、*COL4A5*（2 例）、*PAX2*（1 例）、*INF2*（1 例）、*UMOD*（1 例）。突变患者的平均起病年龄早于无突变的 IgAN 患者（26.4±18.0 vs 33.4±12.7 岁）；两组患者基线血肌酐水平未见明显差异[96.0（77.0，163.5）vs 98.0（77.5，129.5）umol/L]。与无突变患者比较，IV 型胶原突变 IgAN 患者，起病时尿蛋白更多[24 小时尿蛋白定量：3.3（0.8，2.2）vs 0.9（0.5，1.5）g]、血肌酐水平更高[125.5（84.0，162.8）vs 98.0（77.5，129.5）umol/L]。
结论 在家族性 IgAN 中，12.9% 的患者存在已知肾病相关基因单基因突变，其中 IV 型胶原突变最为常见，占 8.1%。因此有必要对家族性 IgAN 患者行已知肾病相关基因检测。

一例 4q 部分单体 6q 部分三体导致 Pierre Robin 序列征的遗传学分析

马俐[1] 孙婧婧[1,2,3] 张红专[1] 杨帆[2,3] 蔡成[1] 龚小慧[1]
1.上海交通大学附属儿童医院
2.上海交通大学医学遗传学研究所
3.上海市胚胎与生殖工程重点实验室

目的 对 1 例临床诊断为 Pierre Robin 序列征的患儿进行分子及细胞遗传学分析，寻找遗传学病因。
方法 应用家系全外显子测序技术（可同时行拷贝数变异分析）和外周血染色体核型分析，分别对 1 例表型为小下颌、舌后坠、上颚裂开、上呼吸道阻塞、先天性趾畸形的患儿及其正常表型的父母进行检测。
结果 家系全外显子测序结果表明：患儿全血基因组 DNA 中检测到在 4 号染色体 4q32.3q35.2 区域（chr4:167658597-190876326）约 23.218Mbp 的杂合缺失，父母检测结果表明，该变异为新发变异；同时从该患儿全血基因组 DNA 中检测到 6 号染色体 6q25.3q27 区域（chr6:160818990-170893800）约 10.075Mbp 的重复，父母检测结果表明该变异为新发变异。故于遗传咨询时建议父母进行染色体核型分析，结果表明母亲核型为：46，XX；父亲核型为：46，XY，t(4;6)(q33;q25.3)。父亲为染色体平衡易位携带者；故推测患儿的染色体异常来源于父亲结构重排的 4 号和 6 号染色体，导致 6q25.3q27 片段三体、1q32.3q35.2 片段单体。

结论 患儿的 4 号染色体片段缺失及 6 号染色体片段重复可能导致其 Pierre Robin 序列征相关表型。

Cockayne 综合征的临床表型及研究进展

王秋红
解放军总医院儿科医学部

目的 Cockayne 综合征是一种罕见的常染色体隐性遗传病，通过对 6 例 Cockayne 综合征患儿临床表型的描述，增加临床医师对 Cockayne 综合征的认识。
方法 回顾性分析 6 例 Cockayne 综合征患儿的临床特征，影像学资料及基因检测结果。
结果 6 例患儿临床特点相似，主要表现为早老面容，生长迟缓，发育落后，皮肤光敏感，踝关节挛缩及视力、听力下降等。患儿出生时均未发现异常，一般在 2 岁左右开始发病。头颅 CT 以基底节钙化常见，头颅 MRI 主要表现为白质脱髓鞘、脑室扩大及脑萎缩等。基因检测结果提示存在 ERCC6 或 ERCC8 基因突变。
结论 Cockayne 综合征具有典型的临床特征及明确的基因位点，患儿的加速衰老及出现的老年特征与疾病，可有助于人类自然衰老的研究。

COL4A1 突变相关的 West 综合征的表型特征

王秋红
解放军总医院儿科医学部

目的 通过对 3 例 IV 型胶原蛋白 α_1 (collagen, type IV, alpha-1, COL4A1)基因突变患儿临床表型的描述，增加临床医师对 COL4AI 基因突变相关疾病的认识。**方法**：回顾性分析 3 例 COL4A1 基因突变患儿的临床、脑电图和影像学资料。
结果 3 例患儿均表现为癫痫性痉挛，高峰失律，明显的精神运动发育迟缓，均伴有小头畸形及脑室周围白质软化，然而，他们均无早产及缺血缺氧性脑病的病史，其基因检测均为 COL4AI 基因杂合新发突变，其中，患儿 1 为剪切突变，c.3406+1(IVS39)G>T；患儿 2 及患儿 3 均为错义突变，c.4088G>A，p.(Gly1363Asp)；c.2441G>T. P. Gly814Val, (NM_001845)。
结论 COL4A1 基因突变患儿可表现为 West 综合征，早期基因检测对识别 COL4A1 基因突变相关疾病具有重要临床意义。

Long-Read RNA Sequencing and ATAC-Seq reveals novel molecular events, regulation effect on NPTN and oncogene FAM20C in glioma

Huan Li[1] Zongze He[2] Bo Gong[1]
1.The Key Laboratory for Human Disease Gene Study of Sichuan Province and Institute of Laboratory Medicine, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu610072, Sichuan, China
2.Department of Neurosurgery, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu 610072, Sichuan, China

Objective Gliomas are validated as the most prevalent and aggressive malignancies of the nervous system. Abnormal RNA molecular events are known to be involved in glioma progression, and the identification of more glioma-related RNA molecular events would clarify glioma pathogenesis, which is of prime clinical significance.
Methods A total of 18 glioma tissues and adjacent normal samples were used to this study.Moreover,This study pioneered the establishment of the full-length transcriptome, novel and

differential transcripts, alternative splicing, gene fusion, and alternative polyadenylation (APA) events in glioma samples. The subsequent analysis of differentially expressed genes (DEGs) highlights a potential link between neuron activity and glioma cells. The gene expression was subsequently interrogated with chromatin accessibility, TFs binding, and APA numbers.
Results The expression of Neuroplastin (NPTN) in glioma samples was significantly lower, whereas increased peak signals were observed in glioma. Moreover, the APA number of NPTN in glioma was significantly smaller than in control groups. The hypothesis that the APA number dominates transcriptional regulation for gene NPTN expression in glioma was thereby proposed. The clinical significance, in vitro function, and hub transportation factors of FAM20C were all ultimately established.
Conclusions This study first characterizes novel and differential RNA molecular events in glioma. Also, the genes involved in neuron-glioma cells interaction were identified. Gene expression was also interrogated with chromatin accessibility and APA numbers for gene NPTN. The clinical significance, cellular phenotype, and transcription activators of FAM20C in glioma were revealed, providing a deeper comprehension of glioma pathogenesis and providing another target for glioma therapy.

TCB1D8B 基因突变引起的局灶节段性肾小球硬化难治性肾综 1 例

陈婉婷
东莞市儿童医院

目的 难治性肾病综合征（nephrotie syndrome,NS）是原发肾病综合征中频繁依赖或者耐药病例的总称。本病例拟通过探讨 TCB1D8B 基因变异导致肾病综合征的临床表现及基因学特征，随访该基因突变引起难治性肾病综合征病例，追踪患儿治疗效果，提高对难治性肾综的认知水平、治疗水平和管理水平。
方法 回顾性分析 2021 年 8 月我院治疗的 1 例 TCB1D8B 基因变异导致难治性肾病综合征患儿的临床表现、病理类型、治疗效果以及预后。对 TCB1D8B 基因变异对疾病预后相关性进行分析。
结果 患儿，男，13 岁，8 月前因“全身水肿，解泡沫尿半月”住院治疗，查尿蛋白 4+，尿红细胞 1500/ml,24 小时尿蛋白定量 26g,总胆固醇 11.66mmol/L,尿蛋白/肌酐比值 2.47mg/mg,诊断肾病综合征,病理活检提示局灶节段性肾小球硬化改变，电镜下足突弥漫融合，有微绒毛变。全外显基因测序证实 TCB1D8B 基因突变。患儿予足量激素治疗,3 月后患儿复查尿常规蛋白 3+-4+，可见数十个红细胞不等，考虑激素不敏感。目前患儿进展至慢性肾脏病 5 期，查血清尿素 15.76mmol/L，血清肌酐 517.0umol/L，定期透析治疗。TCB1D8B 基因突变未曾被 ExaC、GNomAD 以及 1000 Genomes Project databases 报道。生物信息学蛋白功能综合性预测软件 REVEL 预测结果为潜在有害，SIFT、MutationTaster、GERP+预测结果均为有害。
结论 本研究扩展了 EDA-related disorders 的临床遗传谱。难治性肾病及早完善基因检查明确病因可提高病因认知，减少激素用量减少药物副作用，提前准备进一步治疗方案，为患者争取最大的康复程度。

采用目标基因组测序的方法鉴定 1027 例听力缺失患者的分子病因

吴婕[1] 戴朴[1] 曹宗富[2] 苏钰[1] 王杨[3] 蔡瑞坤[2] 陈继跃[1] 高搏[1] 韩明昱[1] 李晓红[4] 张德军[5] 高雪[6] 黄莎莎[1] 黄铨飞[3] 马旭[2] 袁永一[1]

1.1、 中国人民解放军总医院耳鼻咽喉头颈外科医学部

2.2、 国家人类遗传资源中心计划生育研究所

3.3、 东莞博奥木华基因科技有限公司

4.4、 北京市儿童医院耳鼻咽喉头颈外科

5.5、 吉林医科大学第二医院耳鼻咽喉头颈外科

6.6、 中国人民解放军火箭军特色医学中心耳鼻咽喉头颈外科

目的 遗传性听力缺失（hereditary hearing loss, HHL）的分子病因呈现高度异质性。此研究旨在采用病例对照研究，为 1027 例双侧听力缺失患者进行全面的分子病因诊断，从而促进对中国人群遗传性耳聋分子病因的认识。

方法 对双侧听力缺失患者 1027 例和正常听力对照人群 520 例进行目标基因组测序（targeted genome sequencing）（227 个耳聋基因）。

结果 在 1027 例听力缺失患者中，已诊断 588 例（57.25%），未诊断 391 例，以及诊断未明确 48 例（至少检测到一个意义未明变异）。

在已诊断的 588 例患者中，由常见耳聋基因 *SLC26A4*（278）、*GJB2*（207）、*MT-RNR1*（19）合计致病 503 例（85.54%）。其余 85 例（14.46%）为 31 个非常见耳聋基因变异引发，包括：*MYO15A*（18/85）、*MITF*（7/85）、*OTOF*（7/85）、*POU3F4*（5/85）、*PTPN11*（5/85），等。此外，534 例为常染色体隐性遗传，29 例为常染色体显性遗传，19 例患者为线粒体遗传，7 例为 X 连锁。鉴定到的综合征包括：Pendred、CHARGE、Alport、Branchio-Oto-Renal、Barakat, Perrault、Waardenburg、LEOPARD/Noonan、Deafness-Dystonia-Optic、Neuronopathy 综合征。

在 588 例已诊断及 48 例诊断未明确患者中，共计鉴定致病/可能致病变异 244 个，意义未明变异 63 个，其中新变异为 104 个。

结论 中国人群中遗传性耳聋最主要的分子病因为 *GJB2* 和 *SLC26A4*，同时，分子病因呈现高度的遗传异质性；对于意义未明变异的进一步分类，建立正常人群耳聋基因变异数据库和进行相关功能研究是非常必要的。

20 例轻中度感音神经性耳聋患者基因型与临床表型分析

俞莎 许政敏 王慧君

复旦大学附属儿科医院

目的 分析 20 例轻中度感音神经性耳聋患者的基因突变类型与临床表型。

方法 对 2019-2021 年于我院耳鼻咽喉头颈外科就诊的 20 例轻中度高度可疑遗传性耳聋患者及家属留取血样及临床资料，通过二代测序方法进行基因分析，并对先证者及亲属进行候选变异位点的 Sanger 验证。对于患儿临床表型进行归纳总结，并与国外文献比较，进行表型-基因型关联分析。

结果 在 20 例患者中，11 例（55%， 11/20）患者检测到可以解释表型的可疑致病变异。2 例患者 *TECTA* 基因发生 2 个新发变异，分别为 c.1891T>C[p.(Cys631Arg)], c.5999G>A[p.(Gly2000Glu)]，其中 c.1891T>C 来自患者父亲。1 例患者 *OTOG* 基因发生 2 个新发变异，分别为：c.1389C>A[p.(Phe463Leu)],c.7084G>T[p.(Glu2362*)]。1 例患者 *USH2A* 基因发生 2 个新发变异，分别为：c.14201C>T[p.(Pro4734Leu)]，c.10855G>A[p.(Val3619Ile)]。1 例患者 *USH2A* 基因发生 2 个已报道的变异，分别为：c.5581G>A[p.(Gly1861Ser)],c.8559-2A>G。1 例患者 *OTOF* 基因发生 2 个新发变异，分别为：c.1553G>T[p.(Arg518Leu)]，c.3748C>T[p.(Arg1250Cys)]。1 例患者 *OTOF* 基因发生 2 个已报道变异，分别为：c.5581G>A[p.(Gly1861Ser)],c.8559-2A>G。5 例

患者 *GJB2* 基因发生 2 个已报道变异，分别为 c.109G>A[p.(Val37Ile)],c.235del[p.(Leu79Cysfs*3)], c.299_300delAT[p.(His100Argfs*14)]。国外最常见的轻中度耳聋相关基因 *STRC* 基因未检测到变异。

结论 通过二代测序，55%(11/20)轻中度感音神经性耳聋患者检测到了致病变异，分别位于 *TECTA*,*OTOG*,*USH2A*,*OTOF*,*GJB2* 基因。对于轻中度耳聋患者，可通过二代测序早期发现 Usher 综合症这类早期仅有耳聋表型的综合征性耳聋，为后期疾病进展提供相关遗传咨询及防治方案。对于轻中度耳聋病因明确，仍需要更多的遗传学检测方法。

PTPN11 在先天性心脏病发病中的分子机制研究

徐子清 盛伟 黄国英
复旦大学附属儿科医院

目的 本研究旨在探讨 PTPN11 基因异常相关性先天性心脏病（CHD）的临床特点及其发病机制。

方法 在二代测序资料中，我们收集了 9 个携带 PTPN11 基因突变的 CHD 核心家系，进行 Sanger 靶向测序验证，分析突变位点的保守性和对空间结构的改变，通过生物信息学网站 Polyphen2、SIFT 和 Mutation Taster，结合 CADD 评分及 gnomeAD 数据库，进行致病性风险预测，总结突变与 CHD 表型的关系，初步判断 PTPN11 基因突变的致病性及与 CHD 的关系。然后，我们将测序范围扩大到 1154 个 CHD 患者和 400 个无关对照以进一步探究（过滤标准：MAF <0.1%和 CADD >20）。为进一步观察 PTPN11 基因异常在 CHD 中的致病作用，我们利用 Western Blot 和免疫荧光观察了突变对 SHP2 蛋白表达和定位的影响；同时构建 shRNA 靶向敲低 SHP2 的细胞系，运用 Western Blot 实验，分析野生组和突变组对 RAS-MAPK 信号通路中关键分子 ERK1/2 磷酸化水平的影响程度；通过增殖实验和划痕实验，探索对细胞增殖和迁移能力的改变，以期说明 PTPN11 基因异常导致 CHD 的可能致病机制。

结果 我们在 9 个 CHD 核心家系中检测到 8 种 PTPN11 致病变异，基因型-表型关联性分析显示 PTPN11 基因突变主要为散发性，且与房间隔缺损(ASD)密切相关。随后在 1154 例 CHD 散发病例中的进一步扩大测序也观察到了同样的结果。患者的临床信息、PTPN11 变异来源、突变所处关键功能结构域及影响氨基酸的保守性、致病性预测和 gnomeAD 数据库等结果均支持这些变异在 CHD 中的致病作用。实验结果显示，PTPN11 基因突变对 SHP2 蛋白的表达水平和亚细胞定位无明显影响，但 RAS-MAPK 信号通路活性发生变化，心肌细胞增殖和迁移能力也不同程度增强。

结论 我们的研究表明，中国人群中 PTPN11 基因变异患者最常见的 CHD 表型是 ASD。PTPN11 突变体通过不同程度改变 RAS-MAPK 信号通路的活性，增加心肌细胞的增殖和迁移能力，在 CHD 的致病中发挥重要作用。

Genome sequencing demonstrates high diagnostic yield in children with undiagnosed global developmental delay/intellectual disability: a prospective study

Yu Sun[1] Jing Peng[2] Desheng Liang[3] Xiantao Ye[1] Na Xu[1] Linlin Chen[1] Dan Yan[1] Huiwen Zhang[1] Bing Xiao[1] Wenjuan Qiu[1] Yiping Shen[5] Nan Pang[2] Yingdi Liu[3] Chen Liang[4] Zailong Tan[5] Jingsi Luo[5] Fei Chen[5] Jingmin Wang[6] Zhixin Zhang[7] Haiyan Wei[8] Juan Du[9] Huifang Yan[6] Ruoyu Duan[6] Junyu Wang[6] Yu Zhang[6] Shixiu Liao[10] Kun Sun[1] Lingqian Wu[3] Yongguo Yu[1]

1.Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University
2.Xiangya Hospital, Central South University
3.Central South University
4.Jiangmen Maternity and Child Health Care Hospital
5.Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region
6.Peking University First Hospital
7.China-Japan Friendship Hospital
8.Childen's Hospital affiliated Zhengzhou university
9.Reproductive and Genetic Hospital of CITIC-Xiangya
10.Henan Provincial People's Hospital

BACKGROUND Genome sequencing (GS) has been applied in the diagnosis of global developmental delay (GDD)/intellectual disability (ID). However, the performance of GS in those with inconclusive results from chromosomal microarray analysis (CMA) and exome sequencing (ES) is unknown. We initiated this study to determine the diagnostic yield and the clinical utility of GS in undiagnosed GDD/ID patients.

METHODS This prospective study included 100 pediatric patients with GDD/ID recruited from multiple sites in China from February 2018 to August 2020. Patients were required to have received at least one genomic diagnostic test prior to enrollment. Patients and family members received GS. Reanalysis of CMA and ES data was performed. The diagnostic yield of GS was calculated and explanations for missed diagnoses by CMA and/or ES were investigated. Clinical utility was assessed by interviewing the parents by phone during the follow-up period.

RESULTS The overall diagnostic yield of GS was 23% (23/100). Five types of disease-causing variants were detected including small variants, copy number variations (CNV), loss of heterozygosity, mitochondrial variants and trinucleotide repeats. Of the 23 patients with positive GS results, 30.4% (7/23) could have been solved with reanalysis of ES data. For the remaining 16 cases that were not solved with ES reanalysis, nine cases were CMA only and the causative mutations were small variants that could not be detected by CMA. Four underwent ES, however, the causative mutations were CNVs that were not detectable by ES. Finally, three that received prior CMA and ES remained unsolved after ES reanalysis due to allele dropout, complex mutations missed by ES, and a CNV in untranslated regions. Follow-up of the diagnosed families revealed that nine families experienced changes in clinical management, including identification of targeted treatments, cessation of unnecessary treatment, and considerations for family planning.

CONCLUSION GS demonstrated high diagnostic yield in this cohort of undiagnosed GDD/ID patients, detecting a wide range of variant types of different sizes in a single workflow. A precise molecular diagnosis can enable timely modifications to clinical care and medical management and positively impact patient outcomes.

Randomized Controlled Trial of Nerve Growth Factor in Children with Spinal Muscular Atrophy

Linyan Hu[1] Liping Zou[1] Xiaoyan Li[2] Fang Song[2]
1.The Seventh Medical Center of Chinese PLA General Hospital
2.Children's Hospital，Capital Institute of Pediatrics

Background The nerve growth factor (NGF) is effective in protecting and repairing injured or degenerative nerve system. This study aimed to investigate whether exogenous NGF could play a role in promoting motor function and improving the symptoms of childhood spinal muscular atrophy (SMA).
Methods This was a multicenter, self-controlled trial in children with SMA types II and III treated at three Chinese hospitals between October 1st, 2010 and December 31st, 2011 (ChiCTR-TRC-10001093). Patients were randomized 1:1 to Groups A (24 weeks of NGF 18μg/d intramuscular and 12 weeks without) and B (12 weeks without treatment and 24 weeks with NGF 18μg/d intramuscular). Primary outcomes after 24 weeks of treatment were the manual muscle testing and Pediatric Evaluation of Disability Inventory (PEDI). Secondary outcomes included the changes in electromyography (EMG).
Results After 24 weeks, the muscle strength of the proximal and distal extremities were remarkably increased compared to baseline in both groups (all P<0.05). At 12 and 24 weeks of NGF treatment, patients in Group A and B showed significant improvement in self-care and mobility (all P<0.05). After 24 weeks of treatment with NGF, there were increases in the EMG amplitudes in both groups. During the 24 weeks, 57 adverse events were reported in 24 patients, including upper respiratory infection and gastrointestinal symptoms. Three patients experienced long-term pain at the local injection sites.
Conclusion NGF improves muscle strength, self-care, and mobility of SMA patients, without serious adverse effect. It may be considered as a potential therapy for patients with SMA which connot afford nusinersen or other gene therapy or as an adjuvant therapy for the patient with SMA who received nusinersen threatment.

环状 RNA 分子作为糖尿病性视网膜血管病变的新型早期诊断物的研究

颜标
复旦大学附属眼耳鼻喉科医院

目的 糖尿病视网膜病变（DR）早期性状隐匿，未发生血管的器质性病变之前不易被发现；目前对 DR 诊断主要基于器质性的血管病变，缺少早期诊断的标记物。本研究期望以环状 RNA 作为研究对象，探究该类分子在 DR 诊断和风险评估中的潜力。
方法 收集临床样本，通过高通量筛查，寻找 DR 发病相关的标记物；并通过 MTT、Ki67 染色、Transwell 技术等，明确相关靶标在视网膜血管病变中调控作用；并涉及外源性的标准品，设计相关试剂盒，并对试剂盒的诊断性能以及灵敏度、特异地进行评估，探究该类环状分子用于 DR 诊断的可行性。
结果 通过芯片筛查共发现 529 个环状 RNA 在正常视网膜和糖尿病视网膜间异常表达，其中 cZBTB44、cZNF609 和 cZNF532 的表达与糖尿病视网膜病变的发生密切，且这些分子在 DR 诊断中具有较好的特异度、灵敏度和准确度；在此基础上，与广州吉赛生物公司合作，共同开发了基于房水和血清的环状 RNA 诊断试剂盒
结论 环状 RNA 因其表达稳定性和疾病特异性，有望成为 DR 诊断的新型标记物，用于该类疾病的风险评估和早期诊断。

江西地区 899 例胎儿脐带血穿刺结果分析

黄淑晖 潘璐 黄婷婷 肖惠 邹永毅 杨必成 刘艳秋
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

目的 染色体核型分析及染色体微阵列分析（CMA）技术及不同产前诊断指征在胎儿脐带血染色体异常的结果分析。
方法 对 899 例不同产前诊断指征的孕妇于孕中晚期行脐带血穿刺术，对胎儿脐血标本行染色体核型分析及 CMA 分析。
结果 利用染色体核型分析检出异常 55 例（6.12%），CMA 分析检出异常 78 例（8.68%），染色体核型分析联合 CMA 分析检出异常例数 89 例（9.90%），经过两两组之间进行比较发现，相对于传统对染色体核型分析，CMA 对染色体异常检出率明显提高，具有统计学意义（X^2=35.21，P＜0.05），而染色体核型分析联合 CMA 分析对染色体异常检出率最高且具有统计学意义（X^2=8.86，P＜0.05）。在产前诊断指征中高龄（生育年龄≥35 岁）112 例，非高龄 787 例，高龄检出染色体异常 18 例（16.07%），非高龄检出染色体异常 71 例（9.02%），差异有统计学意义（X^2=5.46，P＜0.05）。本研究因超声异常进行脐穿产前诊断 827 例（91.99%），其中单纯超声异常共 719 例，检出染色体异常 56 例（7.92%），超声异常合并其他指征（高龄、筛查高危、不良孕产史、夫妻染色体异常）共 108 例，检出染色体异常 17 例（15.74%），且两组比较差异具有统计学意义（X^2=7.38，P＜0.05）。
结论 胎儿脐带血产前诊断中，染色体核型分析联合 CMA 分析检出率最高；在产前诊断指征中，胎儿超声结构异常合并其他指征较单纯超声结构异常染色体异常的检出率更高。

NIPT 技术在胎儿染色体拷贝数变异中的应用

谭玲珑 黄婷婷 黎俏 邹永毅 刘艳秋
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

目的 探讨无创产前检测（NIPT）在除 21、18、13 号染色体及性染色体外其他染色体拷贝数变异中的应用。
方法 选取 2019 年 01 月至 2021 年 01 月 NIPT 结果提示除 21、18、13 号染色体及性染色体异常外其他染色体拷贝数变异(CNVs)的样本共 114 例，在知情同意原则下行羊膜腔穿刺术，同时行染色体核型分析及染色体微阵列分析(CMA)，并进行随访。
结果 NIPT 检测提示染色体拷贝数变异的 114 例孕妇中，共检出与 NIPT 结果较一致的 CNVs 37 例，阳性率达 32.46％(37/114)，其中临床意义不明确变异 12 例，占 32.43％(12/37)。随访数据显示，22 例选择终止妊娠，90 例正常出生，2 例正常妊娠。
结论 NIPT 对 CNVs 具有一定的预测价值，同时建议行产前诊断应用染色体核型分析联合 CMA 以明确诊断，根据结果必要时行父母比对，为临床遗传咨询提供意见及依据。

不同产前诊断指征与胎儿染色体异常的相关性及临床应用研究

肖惠 肖钧方 张刘洋 黄淑晖 杨必成 刘艳秋
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

目的 探讨在接受介入性产前诊断的孕妇中不同产前诊断指征与胎儿染色体异常的相关性及临床应用评价。
方法 选取 2020 年 1 月 1 日-2020 年 12 月 31 日在江西省妇幼保健院医学遗传中心行 NIPT 或 NIPT-PLUS，且无创 DNA 检测为阳性的孕妇都行介入性产前诊断。通过单因素和多因素 logistic 回归分析比较不同产前诊断指征与胎儿染色体异常的相关性，分析不同指征的孕妇需行产前诊断的需求量以及其阳性率。

结果 本研究的 1959 例孕妇平均年龄(33.24±3.12)岁，不同指征介入性产前诊断的阳性率为 12.66%。其中无创产前检测符合率达到了 96.27%（1886/1959）。单因素分析表明：高龄、B 超异常、血清学筛查异常、不良孕产史等因素与胎儿染色体异常具有相关性；经多因素 logistic 回归分析显示：在介入性产前诊断指征中，高龄、血清学筛查异常和 B 超异常与胎儿染色体异常存在相关性且具有统计学意义，而不良孕产史与胎儿染色体异常的相关性不具有统计学意义。单纯因高龄做无创 DNA 检测可以让 41.59%避免做产前诊断。

结论 高龄、血清学筛查异常和超声异常对胎儿染色异常具有显著相关性，且单纯高龄孕妇做无创 DNA 的检测可以一定程度上减少介入性产前诊断需求量，并提高产前诊断的效率。

X 连锁的 BCOR 基因突变在汉族人群先天性心脏病中的发病机制研究

索美姣 马晓静
复旦大学附属儿科医院

目的 先天性心脏病（（congenital heart disease，CHD）是最常见的出生缺陷。内脏异位（heterotaxy, HTX）是一种罕见的多发性先天性异常综合征，广泛累及心脏和其他心外器官，如肝脾等。近年来大量研究显示 CHD 发病与遗传因素（至少是 1/3 的比例）密切相关。许多复杂型 CHD 合并 HTX，术后并发症多、死亡率高且预后较差。随着二代测序技术的发展，越来越多的遗传性变异被发现。很多基因突变在各类动物模型中被证实与身体左右轴发育异常和 CHD 有关，比如 BCOR、ZIC3、DNAH8、DNAH11 基因等。本研究旨在研究 BCOR 基因突变在内脏异位合并先心病（heterotaxy with congenital heart disease，HTX-CHD）发生中的致病机制。

方法 本研究运用二代测序技术发现 BCOR 基因突变 c.C1448T（p.P483L）和 c.G2774A（p.C925Y），对其核心家系进行一代 Sanger 测序验证，然后结合一系列生物信息学预测，判断 BCOR 基因突变位点致病性，预测相关突变可能与内脏异位合并先心病的发生风险相关。在此基础上结合既往文献报道构建了 BCOR 野生型和突变型质粒，通过免疫印迹、免疫荧光定位与共定位、免疫共沉淀、双荧光素酶、细胞增殖实验（CCK8）和实时荧光定量实验对位于 BCL6 结合域附近的两个突变 c.C1448T(p.P483L)和 c.G1619A(p.R540Q)展开了一系列功能和机制研究。后期扩大先心病人群进行靶向测序并寻找致病性位点。

结果 BCOR 基因在小鼠心脏相关细胞中普遍表达，在小鼠胚胎时期身体左右模式的发育的过程中起着重要的作用。一代测序验证 c.C1448T（p.P483L）和 c.G2774A（p.C925Y）突变患儿的致病位点。在先心病人群中靶向测序扩大 BCOR 基因突变筛选，共筛选出 10 个家系携带 11 个致病性变异并进行了一代测序验证，发现变异大多集中在第四外显子上。突变位点 c.C1448T（p.P483L）、c.G1619A（p.R540Q）、c.G2774A（p.C925Y）的氨基酸序列在物种进化中相对保守，预测为致病性突变。突变 P483L 对 BCOR 蛋白在细胞核内的定位形态产生了影响；共定位结果显示突变 P483L 对 BCOR 蛋白与 BCL6 蛋白在细胞核内的共同定位情况产生影响。而突变 R540Q 在细胞核中定位及与 BCL6 蛋白在细胞核内的共定位情况均未见明显差异。免疫共沉淀实验显示突变 P483L 在蛋白水平影响了 BCOR 蛋白与 BCL6 蛋白的结合，而突变 R540Q 未见明显差异。双荧光素酶实验显示突变 P483L、R540Q 与 BCL6 结合形成的转录抑制复合体功能障碍，转录抑制活性降低，转录活性上升。细胞增殖 实验显示突变 P483L 和 R540Q 可以促进心肌细胞的增殖。实时荧光定量实验提示突变 P483L、R540Q 可以引起心肌细胞中 Notch 信号通路上 Hes1 基因的 mRNA 水平表达变化。

结论 本研究发现了 BCOR 基因突变可能与 CHD 的发生风险相关。发现了一种新的 X 连锁隐性遗传模式可能。通过基础实验揭示了 BCOR 基因突变与 CHD 的关系，拓展了 CHD 的基因谱。

Clinical and Genetic Spectra of 60 Chinese Patients with Sitosterolemia and the Efficacy of Targeted Treatments

Bing Xiao Yu Xia Ying Duan Wanqi Zheng Lili Liang Huiwen Zhang Xiaomei Luo Xuefan Gu Yu Sun Wenjuan Qiu Yongguo Yu
Department of Clinical Genetic Center, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University

Objective Sitosterolemia is a rare autosomal recessive disease with accumulation of phytosterols in the blood and tissues. However, the detailed clinical and genetic spectrum are lacking. We aim to describe the clinical, biochemical, genetic, therapeutic, and follow-up characteristics of patients with sitosterolemia.
Patients and Methods Clinical, genetic and therapeutic data from 60 patients at Xinhua Hospital from January 2016 to June 2021 were retrospectively collected.
Results The manifestations of sitosterolemia included xanthomas(92%), hematological disorders(33%), arthralgia(27%), premature atherosclerosis(19%), splenomegaly(15%). Polyclonal gammopathy and membranous nephropathy were observed in a 65-year-old patient. Elevated total cholesterol(TC, 96%), low-density lipoprotein cholesterol(LDL-C, 96%), and phytosterol(100%) levels were observed. TC and LDL-C levels were significantly higher in 50 patients with xanthomas occurring under 18 years of age than those in the remaining eight patients (both P<0.0001). Targeted treatments resulted in symptomatic remission(94%), and significantly decreased lipid and phytosterol levels(all P<0.05). In the dietary-therapy cohort(n=34), blood lipid levels decreased(all P<0.05). In the 13 patients out of the dietary-therapy cohort who switched from dietary to combination therapy with ezetimibe, dietary therapy decreased TC and LDL-C levels by 54% and 52%, and ezetimibe further decreased them by 18% and 20%. In 17 patients directly undergoing combination therapy with ezetimibe, both lipid and phytosterol levels also significantly decreased(all P<0.05). Further, we identified 16 novel variants in *ABCG5*/*ABCG8*.
Conclusions This study expands the clinical and genetic spectrum of sitosterolemia. The low-phytosterol diet is the cornerstone of sitosterolemia treatment. Ezetimibe can further decrease blood lipid levels and increase daily dietary phytosterol tolerance.

Baseline Data and Novel Genetic Insights for Ethnicity-specific Population with Inherited Eye Diseases

Ning Qu Liang Zhou Weiping Qian
Peking University Shenzhen Hospital

Ethnicity-specific population genetic data is necessary to ascertain aetiological variants or delineating genetic characteristics of the genome. Here, we used panel-based targeted exome sequencing to generate 86,852 distinct high-quality variants on 792 eye disease-associated genes for a large Chinese population with inherited eye diseases(IEDs). At least 1,896 distinct pathogenic or likely pathogenic mutations have been identified, including 455 were first identified in this study. 76 recurrent causative mutations were conformed, including 56 founder mutations and 20 hot spot mutations. Of these, 42 founder mutations and 10 hot spot mutations were first conformed in Chinese ethnicity. Trio-based analysis revealed 75 De novo mutations(DNMs) in a large IED trio populations, with a prevalence of 5.85%, and all DNMs were distributed on 30 IEDs-causative genes. Of these trios, the incidence of DNMs in Retinoblastoma(37%), Ectopia lentis(34%) and Aniridia(31%) all exceeds 30%. Furthermore, twelve digenic combinations families were identified for the first time. Our study systematically delineating the variations spectrum of IED-related genes and evaluated the frequency and pathogenicity of all 86,852 distinct high-quality variants in a large IED cohort, and also provide East Asian and other ethnicity with baseline data from a Chinese ethnic population-specific level.

探讨青少年型帕金森综合征的临床及遗传特点

卢曼
苏州大学附属第一医院

目的 探讨 1 例青少年型帕金森综合征的临床及遗传学特点
方法 回顾性分析 1 例青少年型帕金森综合征患者的临床资料及遗传特点。
结果 本例患者为青少年男性，14 岁起病，主要表现为进行性加重的行走不稳及运动迟缓，活动后易疲劳，在给予美多芭治疗后症状有明显缓解。随着病情进展，伴随有焦虑症状及睡眠障碍。Parkin 基因测序检出 PARK2 基因 4 号外显子区域发现缺失突变。父母近亲结婚，并验证其父母为该位点的杂合性缺失，为常染色体隐性遗传。根据临床症状及基因检测确诊为青少年型帕金森综合征。
结论 JP 是青少年起病，首发症状以运动迟缓多见，症状相对不典型，Parkin 基因突变的患者发病年龄较早，对左旋多巴反应较好，异动症出现比较早。

五例 KBG 综合征临床及遗传学特征分析

王诗琦 卫海燕 付东霞 刘晓景 沈凌花 毋盛楠 陈永兴
河南省儿童医院

目的 提高对罕见的遗传性疾病-KBG 综合征的诊治能力。
方法 回顾性分析本院 2018 年 11 月至 2020 年 9 月收治的 5 例 KBG 综合征患儿，对其临床特征、基因变异及治疗结果进行归纳总结，并进行系统性文献复习。
结果 5 例患儿均为男性，来自 4 个家系，全外显子基因组测序检测出 ANKRD11 基因杂合突变，变异位点依次为：c.6836_6837delTG，c.5866C>T，c.3770_3771delAA，c.6270delT，c.6270delT，有 3 个新发突变位点，均未发现父母携带突变变异。5 例均有三角脸、浓眉、薄上唇、前囟大或闭合延迟、骨骼发育异常，4 例有生长发育迟缓、中切牙大、大耳、耳唇厚、小指弯曲短小等表现，2 例有足跟及足弓发育异常，2 例伴先天性心脏病，1 例有皮肤白斑及蒙古斑，1 例有癫痫。病例 1 和病例 2 应用重组人生长激素治疗后实现身高追赶及认知能力的提高。基因型与表型之间无明显关联。
结论 KBG 综合征表型谱广，前囟大或闭合延迟、耳大耳唇厚也应纳入该病婴幼儿期的主要表现；ANKRD11 基因变异多见于自发突变，c.6836_6837delTG、c.5866C>T、c.6270delT 为新发变异位点，扩充了 KBG 综合征的基因突变谱；早期应用生长激素对实现身高追赶及提高认知能力有帮助。

Genetic and phenotypic spectrum of LMX1B mutations

HafizMuhammadJafar Hussain Shuwen Yu Jun Tong Yuanmeng Jin Qinjie Weng Zhengying Fang Xiaoxia Pan Hong Ren Nan Chen Xie Jingyuan
Department of Nephrology, Institute of Nephrology, Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China

Objective Nail patella syndrome (NPS) is a multisystemic autosomal dominant disease having clinical manifestations of tetrad of dysplastic nails and/or triangular lunula on fingers, presence of iliac horns in the pelvis, elbow deformities, hypoplastic patella, presence of ocular, renal, and neurological abnormalities in some cases. The clinical diagnosis of NPS involves physical examination as well as radiological imaging findings. Besides this, genetic testing and even renal biopsy can assist in diagnostic confirmation. Mostly patients present with variations of hematuria, proteinuria and can sometimes progress to renal failure. Mutations in LMX1B gene have been associated with NPS in different populations.

Methods Whole exome sequencing (WES) was performed in a Chinese family with familial NPS and kidney disease to detect causative mutation. The proband whose had a typical triangular lunula fingers, imaging diagnostic of hypoplastic patella and iliac horns, renal biopsy of FSGS. Besides, proband's mother with proteinuria and dysplastic nails. To find other mutations in the detected gene, WES data analysis was conducted on a large Chinese cohort that consisted of 40 families and 77 sporadic FSGS patients. Subsequently, Sanger sequencing was performed to check segregation of the identified variants. Additionally, to see the genotypic and phenotypic spectrum for the reported mutations in identified gene (LMX1B), an extensive literature review was conducted from HGMD and PubMed. Clinical and genetic analyses were implemented to correlate the phenotypes with genotypes.
Results A heterozygous deletion mutation of LMX1B (c.775_776del; p.S259fs) gene was identified in the family. By WES data analysis of Chinese cohort, we identified another known mutation (c.G746A; p.R249Q) in another family affected with isolated nephropathy. Sanger sequencing confirmed segregation of the detected mutations with the phenotypes in the families. Furthermore, by literature review, we curated 215 reported mutations of them 7 were from Chinese population totally. Interestingly, a study reported an autosomal recessive inheritance of a Saudi Arab family with NPS, which is very rare in LXM1B gene. Moreover, phenotypic spectrum of LMX1B has been extended to some other phenotypes including short stature & hypothyroidism, paroxysmal dyskinesia, IgA nephropathy, spontaneous coronary artery dissection, tuberous sclerosis and C-cell carcinoma in addition to NSP.
Conclusion Here, we report a heterozygous deletion mutation which causes a frameshift in LMX1B gene within a Chinese family affected with NPS and FSGS. Moreover, we found a wide spectrum of phenotypes associated with LMX1B gene. Thus, it can be helpful for nephrologists and clinical geneticists in making decisions for correct diagnosis, treatment and genetic counseling of such patients in future.

Distinct Non-Clock-Like Signatures in the Basal Cell Carcinomas from Three Sisters with Lethal Gorlin Syndrome.

Kexin Peng[1,2] Zhenghua Zhang[1]
1.Department of Dermatology, Huashan Hospital, Shanghai Medical College, Fudan University
2.Department of Dermatology, Haikou People's Hospital, Xiangya Medical College, Central South University

Purpose Gorlin Syndrome (GS), also called nevoid basal cell carcinoma syndrome, is an autosomal dominant disease characterized by predisposition to multiple basal cell carcinomas (BCCs) and developmental defects, whose casual genes have been identified in the Hedgehog (Hh) signaling pathway. Despite of its varied clinical manifestations, it does not significantly affect the life expectancy of patients if detected and treated early. A three-generation family was identified from Hainan province of China, in which there were two of four patients died of GS. This family is of great value since this is the first death from GS to be report in China. Our study is to investigate the pathogenic genes and the possible reason for the untimely death in the family.
Methods Whole exome sequencing and RNA-seq were used to investigate the candidate genes *PTCH1, Shh, SMO, GLI1* and other six genes engaged in the Hh pathway. Quantitative PCR was used to quantify the mRNA expression levels of *PTCH1* and *GLI1* in paired samples of BCC and adjacent non-cancerous tissue (ANCT).
Results One novel mutation, the c.1341dup in *PTCH1*, was identified by whole genome sequencing and displayed 100% cosegregation with BCCs phenotype in a three-generation Chinese family, which was the direct cause of death in two of four patients. Compared with ANCT, four second-hit mutations were detected in four of the six pairs of BCCs from the patients. Of note, somatic genomic alterations in all six BCC samples were mainly clustered into Signature 7 (ultraviolet mutagenesis) , as well as Signature 11 (related to certain alkylating agents). The mRNA levels of ten Hh pathway genes was measured, in which five genes exhibited substantially elevated levels and five genes reversed. Both RNA-seq and qRT-PCR showed the mRNA levels

of *PTCH1* and its effector *GLI1* were markedly up-regulated in BCC samples in contrast to ANCT. The evidence from this study suggests that primary concern of BCC should be restricted exposure to ultraviolet light.

Conclusion *PTCH1* (c.1341dup), a novel frame-shift mutation, underlies GS, resulting in the loss of *PTCH1* inhibitory function in the Shh signaling pathway and activating the downstream genes. The four somatic mutations we found, whose mutational signature were similar to Signature 7, indicate that ultraviolet mutagenesis plays the most important role in somatic secondary mutations.

Systematic functional interrogation of the Lynch Syndrome gene MLH1 by deep mutational scanning

Xiaoyan Jia Jacob Kitzman
University of Michigan Medical School, Department of Human Genetics

Aim Variant interpretation poses a key barrier to the clinical utility of genetic testing. Even intensively studied genes, such as the DNA mismatch repair factors that underlie Lynch Syndrome, have a heavy burden of variants of uncertain significance (VUS). Missense variants are particularly challenging to interpret, and ~87% of the Lynch Syndrome gene missense variants listed in the ClinVar database remain unclassified. This VUS burden severely impedes diagnosis, prevention and intervention for this highly prevalent (~1:300) and actionable familial cancer syndrome. To systematically generate functional evidence that can assist clinical variant interpretation, we performed a deep mutational scan of *MLH1,* one of four key genes underlying Lynch Syndrome.

Method We used saturation single-codon mutagenesis to generate libraries covering 99.6% of all *MLH1* missense mutations (N=14,364). These libraries were stably knocked in to *MLH1*-deficient human cell lines, and the resulting population of *MLH1* missense mutant cells was subjected to functional selection using 6-thioguanine treatment, an established assay for mismatch repair gene function. We deeply sequenced these *MLH1* libraries before and after selection, to generate loss-of-function (LoF) scores for >14,300 *MLH1* missense variants.

Results The LoF scores were bimodally distributed, with 22% (n=3,139) of all missense variants having a damaging effect on MLH1 function. Overlaying these LoF scores onto MLH1 protein structural domains, we observe damaging variants are strongly enriched in the N-terminal ATPase domain (in which 26.8% of missense variants are LoF) and C-terminal dimerization domain (24.6%). By contrast, the internal, intrinsically disordered linker domain is highly tolerant to single missense mutations (only 7.9% of variants are LoF).

Conclusions These scores showed strong concordance (AUC ROC=0.995) with expert reviewed classifications from ClinVar (N=103 missense variants), suggesting that they are highly predictive of pathogenicity and can extrapolate to unclassified and newly observed variants. This map, together with a recent scan of another key Lynch gene *MSH2* from our group (Jia et al, *AJHG*, 2021), demonstrates the promise of systematic functional characterization for enabling prospective early detection and intervention in Lynch Syndrome.

Novel CUL7 mutations and effect of growth hormone treatment in five Chinese patients with 3-M syndrome

Xin Fan Xianda Wei Baoheng Gui Bobo Xie Shaoke Chen Yujun Chen
The Second Affiliated Hopital of Guangxi Medical University

Objectives 3-M syndrome is a rare Mendelian disorder characterized by severe short stature, dysmorphic facial features and skeletal abnormalities. To date, only 251 variants in *CUL7*, the major causative gene of 3-M syndrome, were recorded in Clinvar database, which were primarily found in Western populations. We aim to report clinical features and novel *CUL7* mutations of five

patients with 3-M syndrome, and discuss genotype-phenotype correlations regarding to the effect of growth hormone treatment.
Methods We performed detailed clinical evaluations and Whole Exome Sequencing (WES) for a cohort of idiopathic or syndromic short stature patients. Variants were filtered with standard operations and interpreted according to the ACMG standards and guidelines for the interpretation of sequence variants. Variants classified as “pathogenic” and “likely pathogenic” was validated by Sanger sequencing. Patients diagnosed with 3-M syndrome used growth hormone therapy following our medical advice. We invited patients to return every month to perform longitudinal observation. Over each visit, height of the patients was measured and evaluated. Growth hormone, ACTH and IGF-1 levels were tested by Chemiluminescence method.
Results Seven different pathogenic/ likely pathogenic variants were detected in *CUL7* in the five patients, among which 5 had not been found in any patients with 3-M syndrome. Four in five of the cases were diagnosed by WES before two years of age. Our cases showed typical and heterozygous phenotypes of 3-M syndrome. All of them detected with short limbs (4 cases) or IUGR (1 case) during prenatal examination. Enlarged abdomen and pointed chin was observed in all of the cases. Four patients manifested typical triangular face. One patient had unique features including low hairline, broad short fingers but no obvious triangular face. Specially, delayed bone age was not observed in three patients.After receiving growth hormone treatment, a patient with compound heterozygous missense mutations gained a faster-than-average growing speed, while two patients with compound heterozygous loss-of-function mutations just retained normal growth.
Conclusions The detection and curation of the 5 novel causative variants in *CUL7* would broaden the mutational spectrum of this rare disease. Our findings may facilitate clinical and genetic diagnosis of 3-M syndrome and optimal design of therapeutics using growth hormone, especially for the Chinese patients.

Circle RNA circFOXP1 promote the progression of keloids through binding Galectin

Jing Zhang
Eye, Ear, Nose, and Throat Hospital, Fudan University

Background Keloids is difficult to be treated with high recurrence rate, and its pathogenesis is still unknown.
Objectives: The implementation of the project will clarify the molecular mechanism of circFOXP1 involved in keloids formation and provide a new target for its prevention and treatment.
Materials & Methods In this study, cell proliferation, cell migration, flow cytometry, western blotting, fluorescence in situ hybridization, dualluciferase activity, quantitative real-time polymerase chain reaction (QPCR), western-blot, RNA-pulldown, and immunohistochemistry assays were applied to explore the roles and mechanisms of the circFOXP1/ LGALS1 axis in the keloid.
Results We first found that hsa_circFOXP1 was significantly upregulated in keloids tissue by whole transcriptome sequencing and expanded sample verification Up-regulation of circFOXP1 promoted cell proliferationboth in vivo and in vitro. circFOXP1 was located in the cytoplasm of human skin fibroblasts and could bind to miR-574-5p and Galectin-1 (LGALS1). Based on the information above, we speculate that the upregulation of circFOXP1 may be involved in the formation of keloids by affecting cell proliferation.
Conclusions Collectively, the present study revealed that circFOXP1 functioned as competing endogenous RNA (ceRNA) by adsorbing miR-574-5p to release Smad4, which contributed to pathological hyperplasia of keloids through activating the TGF-b/Smad signaling pathway. In the other hand, circFOXP1 can binding to Galectin-1 to promoting keloid formation.

ACMG 功能实验证据(PS3/BS3)标准化操作流程的建立

李发科 王兴旺 丁红珂
广东省妇幼保健院

功能实验证据在临床意义未明（VUS）变异的再次评估方面具有巨大作用。美国医学遗传学与基因组学学会（ACMG）会同美国分子病理学协会（AMP）2015 年联合发布指南（即 2015 ACMG/AMP 指南）提出变异评级的功能实验证据（PS3/BS3），并且给了大致的使用建议。如应采用公认的功能实验数据，应重点考虑功能实验的有效性、重复性和稳定性，以及考虑是否反映变异发挥功能的生物学环境。但该指南并未明确 PS3/BS3 的使用细则。同时，选择适当的 PS3/BS3 通常需要准确获取、消化、理解和应用关于基因、疾病和机制研究等方面的知识背景和素质。因此，增加了日常变异评级工作中应用 PS3/BS3 的难度。2018 年我们国家临床检验中心举办的 NGS 遗传变异位点生物信息学室间质评活动，发现了我国临床遗传检测实验室（包括三方实验室）在应用 PS3/BS3 方面存在不一致性，多个实验室存在误用情况。而且包括美国在内的其他国家的临床实践也发现类似情况，不同临床实验室之间 PS3/BS3 证据的使用情况也不一致。因此，亟需规范指导 PS3/BS3 的临床应用。

临床基因组资源机构（ClinGen）建立了变异解读工作组（SVI）和多个专门的疾病变异解读专家组（VCEP），以优化细化 2015 ACMG/AMP 指南中的证据标准。2019 年 12 月 31 日发布最新 PS3/BS3 指南，提出了基于贝叶斯理论的致病风险判别指数（OddsPath），建立了 PS3/BS3 的判断及升降级标准，以及使用 PS3/BS3 的四步指导框架。该指南为 PS3/BS3 的应用等提供了结构化的指导。在 PS3/BS3 的新指南发布以来，PS3/BS3 在临床变异解读方面的应用并没有呈现出所预期的常态化，尤其鲜见使用 PS3 的升降级。很多同行反馈其使用难度太大。其原因可能包括：OddsPath 模型理解上的困难；功能实验数据的选择、评估和理解方面的专业壁垒；或变异本身缺乏功能实验数据。

为进一步推进 PS3/BS3 在临床变异解读中的应用，我们拟深入理解贝叶斯理论 OddsPath 模型，剖析四步临时指导框架各个部分的要点，设计 PS3/BS3 应用于临床变异评级的标准化操作流程。具体包括：（1）检索和获取变异位点相关功能研究文献的标准化流程：包括数据库、检索词、布尔逻辑运用规则等。（2）文献中功能研究相关信息获取的标准化流程：包括疾病机制、基因功能、研究方法、质量控制、对照信息、生物学重复等。（3）OddsPath 模型参数计算和结果评估的标准化流程：包括 OddsPath 模型适用性判断，先验概率 P1、后验概率 P2 以及 OddsPath 指数的计算等。（4）四步指导框架应用的标准化流程：包括决策树的流程化、功能实验模型适用性判断程序、功能实验有效性判断程序、OddsPath 模型的应用、PS3/BS3 的证据级别及升降级情况等。

然后，实操上述 PS3/BS3 的 SOP，评估常见耳聋基因变异（ClinGen 收录的 GJB2 基因的 24 个变异）的 PS3/BS3 级别及升降级情况。2019 年 ClinGen 耳聋疾病变异解读专家组（VCEP）制定了 GJB2 等耳聋基因变异的致病性评级，当时该 PS3/BS3 指南尚未发布。将本研究结果与 VCEP 的结果进行比对，探索一致性情况，分析不一致原因。

本工作把相对晦涩的理论模型转换为临床遗传学从业者可理解可操作的标准化操作流程，降低 PS3/BS3 在临床变异评级工作中的应用难度，为临床变异评级工作增加一件利器，可以更好的服务临床遗传检测和咨询。同时我们将收集在实际使用遇到的问题及良好建议，以期持续改进。

身材矮小症的遗传病因探究及新致病机制探讨：521 例多中心矮小症队列研究

桂宝恒[1,2,7] 于辰曦[3,4] 李孝鑫[5] 赵森[3,4] 陈少科[2,6] 范歆[2,6] 谢波波[1,2] 郑海洋[1,2] 魏贤达[1,2] 桂春绒[1,2] 李川[2,6] 吴南[3,4,7] 陈玉君[2,6]

1.广西医科大学第二附属医院遗传与基因组医学中心
2.广西卫健委医学遗传与基因组学研究重点实验室
3.中国医学科学院北京协和医院骨科
4.北京市骨骼畸形遗传学研究重点实验室
5.中国医学科学院北京协和医院医学研究中心
6.广西医科大学第二附属医院儿科
7.中国医学科学院脊柱畸形大数据研究与应用重点实验室

目的 探究身材矮小症的遗传致病因素并调查新致病基因突变谱及其引起身材矮小的分子机制。
方法 对全国多中心 521 例身材矮小症队列进行全外显子组测序分析明确遗传病因；对未明确基因诊断的病例，进一步挖掘病例数据及功能研究证据，通过体外实验探讨和验证身材矮小症新致病机制。
结果 521 例身材矮小症病例中，通过全外显子组测序为 125 例（24%）患者明确病因（已知矮小症致病基因）。对其余 426 例病因未明患者的测序数据进行重分析及变异筛选，在 21 例患者中鉴定出 ROR2 基因的 12 种变异，包括 10 种错义变异，1 种无义变异和 1 种移码变异。进一步对其中 4 种在不同病例家系中反复出现的错义变异进行体外功能验证发现，c.1675G>A[p.Gly559Ser]变异明显改变 ROR2 蛋白表达水平和细胞定位，并导致 Wnt5a-ROR2 信号通路下游 c-Jun 明显下调。
结论 全外显子组测序结合功能验证研究扩展了身材矮小症的致病基因谱及其变异谱。体外功能实验证实 ROR2 基因 c.1675G>A 变异可能通过扰乱 ROR2 蛋白表达水平及细胞定位调控 Wnt5a-ROR2 通路影响骨骼发育，提示 ROR2 基因功能缺失或异常可能是导致身材矮小的新机制。

婴儿神经轴索营养不良 3 例临床特点及基因变异分析

方雨[1] 刘丽琴[2] 麦嘉卉[2] 路新国[2] 张会婷[1] 廖建湘[1]

1.中国医科大学深圳市儿童医院
2.深圳市儿童医院

目的 婴儿神经轴索营养不良（INAD）是一种非常罕见的婴幼儿疾病。本文对 3 例 INAD 患儿临床特点及基因变异进行分析，旨在提高临床医生对该病的认识和诊断水平。
方法 对深圳市儿童医院神经肌肉病门诊既往诊断的 3 例 INAD 患儿的临床资料进行回顾性分析总结。
结果 例 1 是一个 3 岁 2 月女性患儿，例 2 例 3 是一对同卵双胎兄弟，目前 7 岁 8 个月。1、临床表现：例 1 在一岁以前精神运动发育尚可，一岁后开始出现倒退，现不能独坐，进食易呛咳，四肢肌张力低，膝反射活跃。例 2 例 3 的运动发育倒退出现在一岁半左右，现喂养困难，易呛咳，四肢关节明显挛缩，手脚严重变形，肌萎缩严重，膝反射弱。两兄弟在三岁半至四岁间出现全面强直阵挛癫痫发作。2、头颅 MR 改变：三例患儿均出现明显的小脑萎缩，双胎兄弟大脑萎缩也较明显。3、肌电图改变：均为神经源性损伤（轴索损伤为主）。4、脑电图改变：例 1 脑电图见清醒枕区节律慢，睡眠中可见稍多的慢波发放。双胎儿脑电图可见大量慢波发放，发作间期癫痫样波多导频繁发放。5、基因变异：例 1 为 PLA2G6 基因复合杂合突变（chr22:38508200, c.2389C>T, p.Gln797Ter, 无义突变，源于父亲；chr22:38522377，c.1427+1G>A, 剪切突变，源于母亲）。例 2 例 3 也为 PLA2G6 基因复合杂合突变（Exon4: c.496dupG;p.(Glu166fs)，源于父亲；Exon6: c.799T>C, p.(Cys267Arg)，源于母亲），目前这两个突变位点均未见报道。

结论 INAD 以精神运动发育倒退为主要表现，可有吞咽困难及癫痫发作；小脑萎缩多见，肌电图为神经源性损伤，PLA2G6 基因阳性可协助诊断。发现 PLA2G6 基因的新突变位点 c.496dupG，扩大了中国 INAD 患者的基因突变谱。

3 例德朗热综合征患儿不同致病基因的遗传学分析

赵磊[1,2] 惠玲[1] 张庆华[1] 周秉博[1] 郝胜菊[1] 张钏[1] 郑蕾[1] 杨蕊琼[1,2] 李嘉璇[1,2] 唐娇[1,2]
1.甘肃省妇幼保健院医学遗传中心
2.甘肃省中医药大学公共卫生学院

目的 通过对 3 例德朗热综合征（Cornelia de Lange syndrome）患儿的临床表型及基因检测结果进行分析，明确患儿的致病原因。
方法 收集患儿及父母的临床资料，采集外周血标本，全血基因组 DNA 提取，构建文库，靶向捕获、富集，全外显子组基因检测，Sanger 测序验证，将发现的致病基因变异位点在数据库中进行比对并对致病性作出评估。
结果 3 例患儿均为 2020 年来我院就诊的患儿，病例 1 为男孩，病例 2 和 3 均为女孩，来我院就诊时的年龄分别为 1 岁半，2 岁半，9 岁，临床主要表现为发育迟缓、智力低下、特殊面容和其它伴随症状。根据共识提出的标准，三名患儿疑似德朗热综合征。通过全外显子组基因检测明确了 3 例患儿的致病基因，例 1 为 NIPBL 基因 c.5567_5569delGAAinsTAT 错义突变，例 2 为 SMC1A 基因 c.607A＞G 错义突变，例 3 为 HDAC8 基因 c.628+1G>A 剪接突变。3 例患儿父母均未携带患儿致病变异位点，患儿的致病变异为新生突变。
结论 3 例患儿均发现了致病变异位点，其中 SMC1A 基因和 HDAC8 基因的变异位点未见文献报道和收录，丰富了德朗热综合征致病基因突变谱。

NR0B1 重复引起的 46，XY 性反转一家系研究

刘晓景 卫海燕
河南省儿童医院

目的：通过分析携带 NR0B1 基因重复社会性别为女性的姐妹及其家系的临床资料，探讨携带 NR0B1 基因重复引起的 46,XY 性反转患者的临床特点，并进行文献综述。方法：收集社会性别女性，染色体核型为 46,XY 的 2 人临床资料，并进行家系染色体核型、SRY 基因、基因全外显子测序、CNV-seq 检查、X 染色体失活检测。结果：“姐姐”15 岁，因未行经就诊，身高 164.5cm（75-90th） 体重 67kg（>97th）SRY 基因阳性，卵泡刺激素（FSH）、黄体生成素（LH）升高。彩超显示子宫位置正常，呈幼稚型，卵巢显示不清。“妹妹”4 岁 3 月，因生长发育迟缓就诊，身高 93.5cm（<3rd） 体重 13kg（3-5rd），FSH 增高，子宫呈幼稚型，双侧卵巢显示。CNV-seq 检测提示均 Xp21.2 存在 NR0B1、MAGEB 基因重复，来自于母亲。母亲 X 染色体失活检测提示存在偏倚失活。通过 Pubmed 检索结果，目前报道 NR0B1 基因重复引起的 46XY 性反转病例数 18 例，临床特征均无睾丸存在，卵巢不发育或发育不良。携带 NR0B1 基因重复的 46,XX 女性临床特征不受影响，可能与 X 染色体偏倚失活有关。结论：携带 NR0B1 重复可导致 46,XY 性反转。

河南地区 Turner 综合征染色体核型与临床表型相关性分析

刘晓景 卫海燕
河南省儿童医院

目的 通过回顾性分析河南省多中心 2019 年 01 月至 2021 年 01 月 348 例 Turner 综合征患者染色体核型及临床表型，总结河南省 Turner 综合征的临床特点，探讨染色体核型和临床特征相关性。

方法 348 名 Turner 综合征患者，诊断年龄 3 岁-42 岁，Turner 综合征核型 45，XO 人数为 145 例，占比 42.3%，45XO/46XX 人数 157 例，占比 45.9%，3 例为 46XY/45XO，45,X/46X,i（X）（q10）8 例，占比为 2.3%，46，X,i(X)(q10) 7 例， 占比 2.1%，45,X/46X,i（X）（q10）/47Xi(X)（q10）X2 2 例，占比 0.6%，45，X/46，X，？Del（Y）1 例，占比 0.3%，46，X,del(X) 2 例，占比 0.6%， 46，X，t（X；8）（q21：p23）1 例， 占比 0.3% ，46，X，del（X）（？q23）3 例，占比 1% ，45，X/46，X,r（X）p22.3q28 1 例。根据年龄分成两组，一组为<18 岁患者，一组为 18-42 岁患者；再分析不同核型组间临床表型及相同核型组内临床表型的不同。

结果 这些患儿表现为生长迟缓和终身高受损占 96.3%，大部分身高在 145cm 以下，染色体核型多为 45XO。随访到终身高患者中有 7 人身高在 151-160 之间，2 人在 161-170 之间，1 人身高 171.5cm，这例患者的染色体核型 46，X，？del（X）（q25q28），疑 X 染色体长臂缺失。高促性腺功能减退症 73%，这些患者中 3 例伴有自发月经初潮，染色体核型 1 例为与等长臂 X 染色体核型嵌合，1 例为 46XY/45XO，1 例为 45XO/XX/XXX。糖耐量异常 5%，染色体核型 2 例 45XO，1 例 46,X,i(q10)，1 例为 47,XXX/45XO/46,XX,1 例 45,X,i(q10)/45,XO。1 例 1 型糖尿病，占 0.3%，染色体核型为 46，Xi(X)(q10)。2 型糖尿病 3%，甲状腺疾病 3%，男性化表现 1%，性早熟 0.3%，自身免疫性疾病 0.3%，转氨酶升高 0.58%，炎症性肠病 0.3%，脂肪肝 3%，高腭弓 25%，牙齿发育异常 0.88%，小下颌 36%，中耳炎 1.5%，听力丧失 5.9%，发际线低 49.5%，颈蹼 50.5%，短颈 50.5%，盾状胸 25%， 乳距宽 38.5%， 色素痣 31%，白癜风 0.3%，脱发 0.6%， 神经纤维瘤 0.3%，骨龄延迟 32%，骨密度减低 26%，肘外翻 53%， 掌骨征阳性 16%，膝外翻 3%，脊柱侧弯 2.9%，马德龙畸形 0.3%， 通贯掌 2.9%，主动脉瓣发育畸形（四瓣畸形）0.6%，高血压 0.6%，马蹄肾 1%，肾盂/输尿管发育异常或重复 0.3%，肾脏发育不全 0.3%，学习障碍 3%，心理行为问题 2.4%，1 岁内发育迟缓 2.3%。

结论 河南省 348 例患者，以 45XO，及 45XO/46XX 核型最常见，X 染色体结构异常发生比率低，这些患者临床表型多样，其中 45XO 核型多发生矮身材、高促性性腺发育不良，或伴随有其它系统发育畸形。

Clinical and genetic features of 9 patients with KCNQ2 variants

Ning Liu
Qilu children's hospital of Shandong university

Objective Pathogenic variants in KCNQ2 gene caused the clinical phenotype range from self-limited neonatal epilepsy at the mild to neonatal epileptic encephalopathy at the severe. However, the correlation between phenotype and genotype of the *KCNQ2* variants are unclear. Here, we report on the variability of the phenotype and spectrum of *KCNQ2* variants in 9 nonconsanguineous patients.

Methods Patients with unknown cause of seizures were performed for Whole-exome sequencing or Epilepsy multi-gene panel testing. Sanger sequence and real-time qualitative PCR were performed to detect and verify the genetic variants. Pathogenicity of the variants were assessed by multiple in silico tools. Clinical data, electroclinical features, *KCNQ2* variants and response to the treatment were analyzed.

Results Age range of the nine patients were sent to our hospital for treatment was between 3 days and 1-month-16-day. The age onset of seizures range from 5 hours to the fourth day after birth. Tonic and clonic seizures were the major seizure types, and 2 patients showed epileptic spasms. Initial EEGs were burst suppression pattern in 5 patients, where the other 4 patients were multifocal discharge. Genetic analysis identified 9 variants in *KCNQ2,* 2 in-frame indels, 7 missense mutations. Of them, 7 variants arose de novo, 1 inherited from his healthy father, 1 inherited from his mother, and 4 variants were novel. The variants were distributed between exons 1 and 15 in the region of *KCNQ2*, and the changed amino acid located at the cytoplasmic N-terminal, voltage sensor S4, S5, pore-forming (H5) and cytoplasmic C-terminal region. The pathogenicity of the variant had been predicted to be pathogenic or likely pathogenic according to the American College of Medical Genetics and Genomics standards and guidelines. Two patients

had perinatal history, both were meconium-stained amniotic fluid. Phenobarbital and topiramate were the most common used medications.
Conclusion Patients carried missense variants in S5 and cytoplasmic C-terminal region were diagnosed with neonatal seizures, whereas the other variants caused neonatal epileptic encephalopathy. There was no clear correlation between the clinical phenotype and localization of the variants within *KCNQ2*.

儿童腺苷脱氨酶缺乏症——单中心及国内病例总结

张越 舒洲 李妍 孙菲 韩彤昕 毛华伟
首都医科大学附属北京儿童医院

目的 腺苷脱氨酶(Adenosine deaminase，ADA)是嘌呤代谢途径的关键酶，ADA 基因缺陷导致腺苷脱氨酶缺乏是致重症联合免疫缺陷病(severe combined immunodeficiency, SCID)的常见原因之一，约占所有 SCID 的 10-15%。目前国内相关病例报道很少。因此，该研究总结本中心及国内已知 ADA 缺乏症患儿表型、基因特征与治疗等，以期辅助临床管理。
方法 回顾性分析北京儿童医院免疫科诊断的 ADA 缺乏症患儿的临床资料，查阅 PubMed、CNKI、万方等数据库对国内已报到的 ADA 缺乏症病例进行复习，总结国内 ADA 缺乏症患儿的临床表现，实验室检查，治疗等。
结果 目前国内总共已知 8 例 ADA 缺乏症患儿，其中我中心 5 例，其他单位已报道 3 例。来自 6 个不同家庭，男女比例为 1:1。2 例患儿为临床诊断，6 例患儿 ADA 基因纯合或复合杂合突变，共包含 6 个 ADA 基因突变位点，其中有 2 个为新突变。所有患儿均有条件致病菌和/或真菌感染，7 例有呼吸道感染。6 例患儿有生长受限，5 例胸腺缩小或消失。非免疫系统表现包括肋骨影像学异常（2 例），双耳听觉传导通路受损（1 例）。1 例晚发型 ADA 缺陷患儿在随访过程中出现语言、右手精细运动障碍和双眼视力下降，完善颅脑血管造影提示脑动脉瘤。实验室检查提示所有患儿均存在细胞和体液免疫缺陷，4/6 例可见 NK 细胞计数降低，4/5 例患儿存在中性粒细胞缺乏。5 例患儿检测腺苷脱氨酶活性结果均低于正常，1 例检测脱氧核苷酸腺苷(dAXP)水平增高。7 例患儿予预防性应用抗生素及静脉注射免疫球蛋白治疗。3 例接受酶替代（ERT）治疗，其中 1 例随访 1 个月免疫功能部分恢复,1 例因严重生长发育落后放弃治疗,1 例死于感染。1 例接受新鲜辐照红细胞输注补充 ADA，6 个月时死于感染。晚发型 ADA 缺陷患儿生命体征相对稳定，拟进行造血干细胞移植(HSCT)。另 3 例死于感染。中位死亡年龄为 4 月(29 天~10 个月)。
结论 本研究是国内首个儿童腺苷脱氨酶缺乏症病例系列研究。早发感染，生长受限和胸腺发育不良是 ADA-SCID 患儿常见表现，晚发型 ADA 缺陷患儿临床感染症状相对较轻。本研究首次报道 ADA-SCID 合并颅内动脉瘤，具体机制不明，推测可能与腺苷异常代谢导致炎症反应增加相关，相关分子机制尚需进一步研究证实。

Identification of novel variants in COL2A1 causing rare spondyloepiphyseal dysplasia congenita in two Chinese families

Lihong Fan
Huzhou Maternity & Child Health Care Hospital

Objective To explore the genetic etiology of spondyloepiphyseal dysplasia congenital (SEDC) in two Chinese families.
Methods The next-generation sequencing was performed on two unrelated clinically confirmed SEDC patients and their family members using a gene panel comprising 2740 skeletal-specific genes. Moreover, prenatal diagnosis and counseling were completed in one of the families.
Results The two probands were diagnosed as SEDC based on the phenotypes of disproportionately short‐trunk stature and adduction deformity of hips. Radiographs showed

flattened bilateral femoral heads and shortened femoral neck. Two heterozygous missense variants (c.3392G>T, p. Gly1131Val; c.1115G>A, p.Gly372Glu) in *COL2A1* were detected in the two families, which would impair the structure of stable triple‐helical type II collagen.
Conclusions We identified two disease-causing variations in *COL2A1*, which expanded the genotypic spectrum and phenotypic spectrum of SEDC. In addition, prenatal diagnosis and genetic counseling should be carried out in a family with SEDC for better procreative management.

第三代环形测序在广东地区 40 例地中海贫血基因检测中的效果评价

李浩贤 冯建江 梁忱 张杨慧 孙铁兰 陆叶 李小敏 曾钦龙 李秋丽 孙淑湘
广东省江门市妇幼保健院

目的 地中海贫血是中国南方最为常见的遗传性疾病之一，广东地区常规进行孕期地中海贫血筛查，阳性者采用跨越断裂点 PCR（GAP-PCR）、反向点杂交（RDB）检测 *HBA*、*HBB* 基因常见突变，上述策略时常误诊常见基因突变，漏诊罕见、未知基因突变。本研究探讨应用第三代测序技术对 40 例样本进行地贫基因双盲检测，评估效果。
方法 收集已进行传统 GAP-PCR、RDB 检测的江门地区 35 例地贫筛查阳性及 5 例筛查阴性样本，双盲法 PacBio 第三代环形长片段测序。定制 6 对覆盖 *HBA*、*HBB* 基因引物，多重扩增产物接 PacBio 接头形成特殊的哑铃状文库，利用 PacBio Sequel II 平台进行环形一致性测序（Circular Consensus Sequencing, CCS），比对目标序列，分析基因突变，Sanger 测序验证点突变，评估两种检测方法的效果。
结果 第三代环形测序与 GAP-PCR、RDB 检测结果完全一致样本 18 例，额外检出点突变样本 12 例，结构突变 7 例，纠正错误结果 4 例。发现未报道 *HBB* 基因大片段缺失 1 例，详见附表。
结论 本研究中第三代环形测序较传统 GAP-PCR、RDB 检测的阳性病例检测准确性提高了 62.86%（22/35），准确性为 100%，能检测已知常见、罕见地贫基因突变，发现未报道的突变，更精准明确地贫基因型-表型。本研究样本为选择性样本，存在偏倚。

广西柳州地区 2014-2020 年 0-5 岁儿童外周血染色体异常结果及出生原因分析

徐玉婵 严提珍 王文丹 韦德宁 罗颖花 何萍 韦相 蔡稔
柳州市妇幼保健院

目的 分析柳州地区近年来 0-5 岁儿童外周血染色体异常结果及出生原因，为柳州地区染色体病出生缺陷的防控措施及防控策略的制定提供参考。
方法 回顾性分析我院 2014 年 1 月至 2020 年 10 月行外周血染色体核型分析的就诊者 69636 名，对其中 0-5 岁儿童外周血染色体异常者其母亲产前筛查、产前诊断情况，父母文化程度、职业、居住地等情况进行调查分析。
结果 69636 例 0-5 岁就诊者染色体异常 320 例，检出率 0.46%，其中数目异常 270 例，检出率 0.39%，21-三体综合征 241 例，占 75.31%；结构异常 50 例，检出率 0.07%。调查到 97 例确诊的 0-5 岁唐氏综合征患儿中，其母亲在孕期有 68 例未做血清学筛查，23 例筛查低风险，5 例血清学筛查高风险或临界风险，均未进行产前诊断。居住地偏远，到上级医院检查不便，患儿父母大多来自农村，文化程度普遍不高，对产前筛查的相关知识的认知程度不高是制约该地区产妇进行唐氏筛查及产前诊断的重要因素。
结论 柳州地区 0-5 岁儿童中以唐氏综合征的检出率最高，医务人员尤其是基层人员要加强遗传咨询工作，加大对孕妇夫妻双方的宣传力度，提高产前筛查的覆盖率，完善筛查技术和方法等可有效减少唐氏患儿的出生。

罗氏易位携带者囊胚期胚胎 PGT 相关遗传学分析

何萍
柳州市妇幼保健院柳东分院

目的 通过对罗氏易位携带者夫妇实施第三代试管婴儿辅助生殖术，对囊胚期胚胎行胚胎植入前遗传学检测（PGT），分析囊胚期胚胎染色体异常构成情况。
方法 选取自 2017 年 1 月起来我院行外周血染色体检查的不孕不育夫妇进行核型分析，筛选出罗氏易位携带者，并对罗氏易位携带者夫妇实施第三代试管婴儿辅助生殖技术，对囊胚期胚胎采用高通量测序技术进行胚胎植入前遗传学检测，比较分析囊胚期胚胎染色体异常构成情况及可移植胚胎实际获得率与理论值差异。
结果 通过染色体核型分析，共筛选出 30 余对染色体罗氏易位携带者夫妇，其中 25 对愿意接受第三代试管婴儿辅助生殖术，应用高通量测序行 PGT-SR 检测，共检测 197 个囊胚期胚胎，3 例检测失败，可分析胚胎数 194 个，获得可移植胚胎 72 个，获得率 37.11%，略高于理论值（33.33%），获得染色体异常胚胎 120 个，单纯性不平衡胚胎 10 个（12%），散发性异常胚胎 77 个（64.17%），复杂性异常胚胎 31 个（25.83%），染色体异常以散发性异常占大多数。
结论 罗氏易位携带者囊胚期胚胎行植入前遗传学检测获得可移植胚胎率略高于理论值，囊胚期胚胎染色体异常类型中散发性异常占多数，因罗氏易位引起的单纯性异常反而最少，遗传咨询时应充分考虑散发性异常对罗氏易位携带者囊胚胎胚胎染色体组构成的影响,并告知患者知情。

两例男性复杂性染色体重组伴生精功能障碍的个案报道及文献回顾

金晨曦[1,2] 王钰峰[1,2] 李敬[1,2] 李鸿昌[1,2] 颜军昊[1,2]
1.山东大学生殖医学研究中心
2.山东大学附属生殖医院

复杂性染色体重排（complex chromosomal rearrangement，CCR），是指一类涉及两条以上的染色体、包含三个及以上断裂点的染色体结构重组。其携带者相较普通平衡易位携带者更易发生早期流产。
案例报道 第一例患者男性婚后未避孕未孕 7 年，精液常规检查示无精子症，核型 46,XY,t(7;14;21)(q11.2;q21.1;q21.3)。于我院行 PGT-SR（携带者筛查）助孕 1 个周期，获囊胚 21 枚，经检测 5 枚为对位分离的平衡胚胎： 1 枚为不携带 CCR 的胚胎，2 枚为携带型胚胎，2 枚因新发突变不可移植。第二例患者婚后自然流产、生化妊娠流产各 1 次，精液常规检查示少弱精子症，核型 46,XY,t(4;11;9)(q13;q22;p22)。于我院行 PGT-SR2 个周期，获囊胚 13 枚，经检测示嵌合体可移植胚胎 2 枚。
结果 两对夫妇均已完成孕 12 周产检，B 超检查未见明显异常。
讨论 胚胎植入前染色体结构重排检测（PGT-SR）技术，可以检测并挑选染色体平衡的胚胎进行移植，避免染色体异常导致的不良妊娠结局。通过结合 SNP 连锁分析所衍生的 PGT-SR（携带者筛查）技术，可筛选出不携带 CCR 的胚胎进行移植，阻断 CCR 向子代的下传。CCR 携带者夫妇所获胚胎中可移植胚胎比例相对更低。故能否获得可移植的胚胎，更易受到女方卵巢储备情况的限制。其次，进行携带者筛查相比于 PGT-SR 技术会带来更大的经济负担，故患者家庭经济状况也是需要纳入考虑的因素之一。

49 个携带 SCN1A 基因变异相关癫痫家系的产前诊断研究

肖洋 张英 王松涛 裴珮 郑雪飞 马祎楠
北京大学第一医院

目的 总结携带 *SCN1A* 基因变异相关癫痫家系的基因变异及产前诊断特点，探讨产前诊断在预防 *SCN1A* 基因变异相关癫痫患儿出生中的应用价值。
方法 回顾性纳入 49 个携带 *SCN1A* 基因变异相关癫痫家系。收集先证者及其父母外周血 DNA,验证其 *SCN1A* 基因变异情况。随后收集其产前样本 DNA，验证分析胎儿携带先证者 *SCN1A* 基因变异情况。于胎儿出生或终止妊娠后进行基因变异点验证，随访妊娠结局和出生胎儿健康状况。
结果 1.49 个家系中先证者携带错义变异 24 例(49.0%),无义变异 11 例(22.4%),移码变异 9 例(18.4%),剪切位点变异 5 例(10.2%)。其中 1 例先证者母亲携带变异且为癫痫患者，1 例母体嵌合，其余未在父母外周血发现携带先证者变异。
2.上述家系共进行了 53 次产前诊断（4 家进行了两次）。其中先证者母亲为携带者的家系两次产前诊断均携带先证者 *SCN1A* 基因变异；一家系父母均未发现携带先证者变异，胎儿发现变异；其余胎儿未发现携带先证者变异。
结论 尽管 *SCN1A* 基因变异以新生变异为主，但嵌合仍比例较高（4.1%），因此进行产前诊断意义重大。

12970 例羊水染色体核型分析在产前诊断中的应用价值探讨

张美瑜 严提珍 韦小妮 韦朔峰 韦德宁 徐玉婵 罗颖花 王文丹
柳州市妇幼保健院

目的 探讨 12970 例妊娠中期孕妇羊水染色体核型类型及分布情况，为优生优育提供实验室诊断依据。
方法 统计 2018 年 3 月至 2020 年 12 月于柳州市妇幼保健院就诊的 12970 例孕妇羊水染色体核型结果，分析异常率、各种异常核型分布情况以及＜25、25-29、30-34、35-39 和≥40 岁各年龄组的阳性率。
结果 共分析染色体核型 12970 例，异常核型 859 例（异常率 6.62%）；其中数量异常 389 例（占 45.29%），检测率 3.0%：47,XN,+21 为 204 例（占 23.75%）、47,XN,+18 为 42 例（占 4.89%）、47,XN,+13 为 8 例（占 0.93%），性染色体数目异常 125 例（占 14.55%）；结构异常 470 例（占 54.71%）：易位 56 例（占 6.52%）、倒位 261 例（占 30.38%）、缺失 19 例（占 2.21%）、衍生染色体 16 例（占 1.86%）、标记染色体 10 例（占 1.16%），多态性 97 例（占 11.29%）。＜25、25-29、30-34、35-39 和≥40 岁组羊水标本染色体异常检出率分别为 5.75%、5.58%、6.42%、7.11%、9.09%。异常核型结果中，21-三体综合征发病率较高，＜25、25-29、30-34、35-39 和≥40 岁各年组 21 三体发病率分别为 0.1%、0.22%、0.35%、0.46%、0.44%，发病率随年龄的增大而增加。
结论 羊水染色体核型分析是产前诊断较好的染色体异常诊断方法，对孕妇进行羊水细胞染色体核型分析能有效的诊断胎儿染色体病，是减少染色体异常胎儿出生的重要手段。

Clinical application of noninvasive prenatal testing for sex chromosome aneuploidy in central china

Ganye Zhao
The First Affiliated Hospital of Zhengzhou University

Background: The relatively high incidences and their clinical symptoms of sex chromosome aneuploidy (SCA) make prenatal screening of SCAs an attractive option for pregnant

women. This study was performed to evaluate the clinical performance of noninvasive prenatal testing (NIPT) for SCAs in singleton pregnancies in central China.
Methods: NIPT was performed using next generation sequencing. Standard Z-score analysis was used to call fetal sex chromosome aneuploidy. NIPT positive results were confirmed by invasive prenatal diagnosis with karyotyping.
Results: After excluding the detected failure samples due to low fetal DNA fraction, 42164 singleton pregnant women were recruited in this study. They were divided into 5 groups with different clinical indications, including group with ultrasound abnormalities (9.23%, 3892/42164), group with advanced maternal age (22.14%, 9336/42164), group with high risk for maternal serum screening (18.35%, 7738/42164), group with intermediate risk for maternal serum screening (26.6%, 11215/42164) and group with low risk (23.68%, 9983/42164). 223 women had high risk for SCAs by NIPT with a positive rate of 0.53%. There was no significant difference associated with the five groups in positive rate. Of all of the positive results, 89 were 45, X (39.91%), 38 were 47, XXX (17.04%), 31 were 46, XY, del(X) (13.90%), 50 were 47, XXY (22.42%) and 15 were 47, XYY (6.73%). Finally, 147 participants (65.92%, 127/223) chose to undergo invasive prenatal diagnosis, and 38 cases were confirmed. The combined positive predictive value (PPV) of NIPT for SCA was 25.85% (38/147). PPV were high for 47, XYY (100%, 11/11), moderate for 47,XXX (33.33%, 7/21) and 47,XXY （42.42%，14/33）, but low for 45,X (9.68%, 6/62) and 46,XY (delX) (0%, 0/20). The termination rates of Turner syndrome and 47,XXY syndrome were higher than 47,XXX syndrome and 47,XYY syndrome.
Conclusion: This is a relatively large sample size to evaluate the value of NIPT for screening sex chromosome aneuploidy. Our data showed that with informed consent and the subsequent professional genetical consulting, NIPT can be a useful method to screen SCAs.

天津市胎儿无创产前检测的临床应用研究及卫生经济学评价

马瑞玉 张颖 李晓洲 史云芳
天津医科大学总医院

目的 探讨无创产前检测（non-invasive prenatal test, NIPT）技术应用于胎儿常见染色体非整倍体产前筛查的临床应用效能及卫生经济学价值。
方法 对天津市 10612 例妊娠妇女的 NIPT 检测结果及后续产前诊断或随访结局进行回顾性分析比较，同时选取先后两个时间段内 NIPT 检测数据，评估其作为二线/一线筛查手段对于诊断胎儿 21、18、13-三体综合征的卫生经济学效益。
结果 10612 例接受 NIPT 检测的孕妇中，检测成功率为 99.7%，混合风险人群胎儿 21、18、13-三体综合征筛查灵敏度分别为 100%、92.86%、100%，阳性预测值（positive predictive value, PPV）分别为 89.74%、61.90%、44.44%，血清学筛查高风险、高龄及合并胎儿超声软指标异常的孕妇，其 NIPT 检测高危率明显升高，NIPT 检测的 PPV 在各人群亚组间无统计学差异；2019 年为止，NIPT 作为传统筛查的二线筛查具有较高的卫生经济学效益，但其作为一线筛查的增量成本-效果比较 2015-2017 年有所下降。
结论 NIPT 对于混合风险人群 21、18、13-三体综合征的筛查效能明显优于传统血清学筛查，对于某些相对高风险人群，在进行充分的检测前/后遗传咨询情况下，NIPT 也可作为优选筛查方案；从卫生经济学角度来看，随着 NIPT 检测成本的不断降低，其取代传统血清学筛查（除外筛查开放性神经管缺陷）将有可能成为现实。

染色体微阵列分析技术在 3548 例孕早期自然流产遗传学病因诊断中的应用

朱丹 孔令蓉 邓林贝 熊诗诣 孙路明
上海市第一妇婴保健院

目的 应用染色体微阵列（chromosomal microarray analysis，CMA）技术在全基因组水平分析引起孕早期自然流产的胚胎染色体异常情况，探讨胚胎染色体异常与流产次数的关系。
方法 回顾性分析 2016 年 2 月-2020 年 5 月收集的 3548 例孕 12 周前（包含 12 周）自然流产女性的流产绒毛的 CMA 结果，归纳与流产密切相关的染色体数目及结构的异常，并探究其与流产次数的相关性。
结果 排除 8 例母源感染及 2 例因 DNA 降解导致的检测失败，共计纳入 3538 例流产绒毛 CMA 结果。CMA 异常病例占 63.99%（2264/3538），其中与流产密切相关的 CMA 异常占 97.75%（2213/2264），包括染色体数目异常 2055 例（92.86%），染色体结构异常 158 例（7.14%），其中传统核型分析难以检测的微缺失微重复（<10Mb）11 例（6.96%），全基因组杂合性丢失 7 例（4.43%）。暂无充分证据支持与流产相关的 CMA 异常有 51 例（2.25%），包括致病性/可能致病性的拷贝数变异(pathogenic，P /likely pathogenic，LP)44 例（86.27%）,临床意义不明的拷贝数变异(variants of uncertain significance ,VOUS)7 例（13.73%）。随着流产次数的增加，染色体数目异常的发生率下降（分别为 64.78%，60.34%，50.44%，42.92%，35.85%，33.33%，P＜0.001），染色体结构异常的发生率上升（分别为 3.75%，3.97%，5.13%，5.72%），但各组差异无统计学意义（*P*=0.229）。
结论 CMA 技术是进行流产物遗传病因诊断的重要手段。胚胎染色体数目及结构的异常是造成流产的主要原因。染色体数目的异常率随着流产次数的增加而降低。

Digital Polymerase Chain Reaction and its application in biological detection

Yanan Liu[1,2] Fengxiang Wei[1,2] Tong Zhang[1,2] Guoqiang Zhao[1,2]
1.Longgang District Maternity&Child Healthcare Hospital of Shenzhen City
2.JIAMUSI UNIVERSITY

Digital polymerase chain reaction is a high-sensitivity and high-specificity nucleic acid absolute quantitative analysis technology developed after real-time quantitative polymerase chain reaction, which does not depend on the standard curve. The reaction system is divided into a large number of independent reaction molecule pools for PCR amplification, and the number of nucleic acid copies is corrected according to the Poisson distribution. It can achieve absolute quantitative analysis of low-concentration samples. In recent years, based on the development of microfluidic technology, digital PCR is mainly divided into three types: microfluidic digital PCR, microdroplet digital PCR and chip digital PCR. Digital polymerase chain reaction detection technology is very suitable for the detection of circulating nucleic acid, circulating tumor cell DNA or microribonucleic acid in blood or other body fluids. It not only realizes detection and quantification, but also discovers new tumor markers and studies the function of nucleic acid And prognosis, such as: detecting early diagnosis markers of oral cancer in oral saliva samples to predict the risk of oral cancer. Simultaneously detect a variety of molecular aberrations, improve the early diagnosis rate of lung cancer, and improve the detection and quantification of copy number variation. In gynecological prenatal diagnosis, traditional prenatal diagnosis is carried out through amniocentesis and chorionic villus sampling. This invasive sampling method is likely to cause trauma to the fetus and increase the risk of miscarriage for pregnant women. dPCR can accurately analyze free fetal DNA in maternal plasma and is a safe, fast and accurate new technology for prenatal diagnosis. For example: It has strong applicability in the risk management of large gestational babies with singleton diabetes.The ddPCR method has high sensitivity and strong specificity, and is suitable for the screening of chromosomal genetic diseases such as

spinal muscular atrophy and the determination of carrier status. Digital polymerase chain reaction has excellent performance in virus detection and prognostic treatment. Digital PCR is more sensitive to the low viral load of SARS-CoV-2 clinical samples, and can accurately reflect changes in viral RNA copy number. dPCR also shows high specificity in the identification of SARS-CoV-2 from other respiratory pathogens such as common influenza virus or other human coronaviruses, and can be used as an important supplementary detection method for clinically difficult patients or difficult specimens. The paper introduces the principle of digital polymerase chain reaction technology in detail, and expounds its application status and technological development in tumor research, gynecological prenatal diagnosis, pediatric disease diagnosis, and prognosis of infectious diseases. dPCR has the characteristics of high specificity and high sensitivity. Compared with RT-qPCR, the main advantages of this technology are high quantitative analysis accuracy, strong reliability, and good reproducibility. Large-scale parallel single-molecule amplification of complex target sequences can be achieved. This technology can be used in clinical biology laboratories, clinical laboratory diagnosis and almost all disciplines, and is especially suitable for the quantitative detection of nucleotide sequences in low abundance or complex environments where inhibitors exist. dPCR technology can also be combined with NGS sequencing, mass spectrometry and other technologies. Through the continuous development and improvement of dPCR technology, its scope of application will gradually expand, and its integration with other detection technologies will be closer, and it is expected that it will play a greater role in basic research and application.

基于 Logistic 回归分析无创产前检查筛查失败因素

石杨 邵小光 姜海燕
大连市妇女儿童医疗中心（集团）

目的 通过多因素 Logistic 回归分析孕妇年龄、体重、BMI、胎儿游离 DNA 浓度(cffDNA)、孕周、妊娠类型（单胎/双胎）、是否经产、是否使用肝素治疗、受孕方式（自然/辅助生殖）等影响无创产前检查（non-invasive prenatal testing，NIPT）失败。
方法 回顾性分析 2019 年 7 月-2020 年 6 月就诊于大连市妇女儿童医疗中心经知情同意后进行 NIPT 检测的 3410 例孕妇，分为首次筛查失败组(A)和首次筛查成功组(B)，分析比较两组受试者临床资料的差异，进行 Logistic 分析影响 NIPT 失败因素。
结果 1）60 例未获得结果，首次筛查失败率 1.76%（60/3410）。重采血 41 例，其中 25 例获得 NIPT 结果，总失败率 1.0%（35/3410）。2)比较临床资料，结果显示孕周、cffDNA 浓度、妊娠状态（单/双胎）、是否经产、是否使用肝素治疗有统计学意义（P<0.05）；A 组平均孕周为 17.97±1.87 ， 平 均 BMI 23.17±3.49 kg/m2 ， B 组 平 均 孕 周 16.24±2.13 ， 平 均 BMI 22.86±3.72 kg/m2。3）孕周、胎儿游离 DNA 浓度及使用肝素治疗对于 NIPT 检测失败有统计学意义（P<0.05）。孕妇妊娠状态（单胎/双胎）、是否经产对于 NIPT 检测失败的影响差异无统计学意义。4）NIPT 筛查失败的回归方程为 Logit（P）=-9.867+0.319*孕周，截断值为 16.36 周；NIPT 筛查失败的回归方程为 Logit（P）=-0.405+0.517*cffDNA 浓度，截断值为 11.14%。
结论 孕周、cffDNA 浓度和使用肝素治疗是 NIPT 首次检测失败的影响因素。经过回归分析确定最佳取样孕周为 16.36 周和 cffDNA 浓度为 11.14%，为 NIPT 筛查时机提供参考依据。

应用多重荧光竞争性 PCR 进行脊髓性肌萎缩症携带者筛查

张菁菁[1,2] 王玉国[1,2] 胡平[1,2] 许争峰[1,2]
1.南京市妇幼保健院
2.南京医科大学附属妇产医院（南京市妇幼保健院）

目的 探讨多重荧光竞争性 PCR 应用于脊髓性肌萎缩症（spinal muscular atrophy，SMA）携带者筛查中的可行性，以建立起一种快速、准确、适于大规模人群筛查的技术，从而降低 SMA 患儿出生率。

方法 应用多重荧光竞争性 PCR 技术检测 12 例 SMA 患者及其父母 *SMN* 基因拷贝数，同时对江苏地区 120 例健康孕妇人群 *SMN* 基因进行拷贝数检测，并通过 MLPA 技术验证检测结果。
结果 多重荧光竞争性 PCR 结果与 MLPA 结果一致，显示 12 例 SMA 患者均为 *SMN1* 基因零拷贝，其父母的 *SMN1* 基因拷贝数均为单拷贝，120 例健康人群中检测出 *SMN1* 基因单拷贝 2 例（即 SMA 携带者），占 1.7%；*SMN1* 基因双拷贝 114 例，占 95%；*SMN1* 基因大于双拷贝 4 例，占 3.3%。
结论 多重荧光竞争性 PCR 技术是一种快速、简便和准确的 SMA 携带者检测技术，有潜力应用于人群中 SMA 的大规模筛查。

Uniparental Disomy of Chromosome 16 Aggravates Fetal Growth Restriction Caused by Trisomy 16 Mosaicism

Yiqing Chen Yanmin Luo
The First Affiliated Hospital of Sun Yat‐Sen University

Objective To investigate the effects of uniparental disomy of chromosome 16(UPD16) on fetal growth restriction(FGR) with placental trisomy 16(T16) mosaicism and the clinical management of UPD16.
Methods Chromosome microarray analysis were performed in 4 cases of FGR at our hospital. Furthermore, other cases with confirmed placental T16 mosaicism, UPD16 screening, and prenatal diagnosis published since 1992 were retrieved from PubMed, and the clinical features of these cases and 3 of the 4 cases we reported were analyzed.
Results Of the 89 cases, 58 cases had confined placental mosaicism(CPM); the remaining cases had true fetal mosaicism(TFM). UPD16 was present in 48 cases. The incidence rate of FGR was 71.6%. The incidence and severity of FGR significantly differed between cases with and without UPD16 in the CPM T16 group but not in the TFM group. Follow-up was done for 10 liveborn children with UPD16 and FGR, of which 7 showed catch-up growth; the remaining 3 children had TFM T16 and showed growth delay but normal psychomotor development.
Conclusion UPD16 was associated with the incidence and severity of FGR in cases of CPM T16. The prenatal management of UPD16 should be based on monitoring fetal intrauterine condition and assessing the probability of neonatal survival.

一例颅骨锁骨发育不全胎儿的影像学分析及产前诊断

郭梁洁
河南省人民医院

目的 探讨颅骨锁骨发育不全胎儿的围产期影像学特点及，为产前诊断提供理论依据，为家族再生育提供优生咨询。
方法 三维超声评估胎儿骨骼系统异常情况；提取胎儿羊水细胞及父母双方外周血 DNA。全外显子测序寻找胎儿可能致病基因，并利用 Sanger 测序进行验证。
结果 三维超声影像学显示胎儿颅骨钙化不良及骨缝增宽、鼻骨未显示、长骨短小。全外显子测序（WES）结果发现胎儿 **RUNX2** 基因 c.341C>A 无义杂合突变，胎儿为新发突变。
结论 颅骨钙化不良及骨缝增宽，鼻骨未显示、长骨短小可能是颅骨锁骨发育不全胎儿围产期常见影像学表现，RUNX2 基因变异是该颅骨锁骨发育不全胎儿的致病原因。临床影像学特征和全外显子测序技术有助于临床医生及时准确的诊断和治疗。

Whole exome sequencing discloses a pathogenic MTM1 gene mutation in a continuous polyhydramnios family in China: Case report and literature review

Neng Jin[1] YeTao Xu[2] Dong Xu[1] Xingmiao Li[1] Ying Jiang[1] Jingping Zhu[1] Juefei Lu[3] Hefeng Huang[1] Qiong Luo[1]
1.Women's Hospital, School of Medicine, Zhejiang University
2.The First Affiliated Hospital of Nanjing Medical Universtiy
3.Tong Xiang Maternaity and Child Health Care Hospital

Polyhydramnios can be caused by genetic defects at times. However, to establish an accurate diagnosis and provide a precise prenatal consultation in a given case is still a great challenge toward obstetricians. To uncover the genetic cause of polyhydramnios in the two consecutive pregnancies, we performed whole-exome sequencing of DNA for the second suffering fetuses, their parents, and targeted sanger sequencing of other members of this family. We discovered a hemizygous truncating variant in MTM1 gene, c.438_439 del (p. H146Q fs*10) in this Chinese family. In the light of the molecular discoveries, the fetus's clinical phenotype was considered to be a good fit for X-linked myotubular myopathy. There is no related research to the prenatal manifestations of MTM1-related XLMTM among Chinese population, and this is the first one to present. Though the etiology of polyhydramnios is complicated, WES may provide us with a creative avenue in prenatal diagnosis.

CMA 联合 ES 在 71 例足内翻的产前咨询与遗产咨询中的应用

孔令蓉
上海市第一妇婴保健院

目的 探究 CMA 和 ES 在足畸形产前咨询和诊断中的应用
方法 选取我院 16 年-21 年共 178 系统超声评估为足畸形的胎儿，其中 71 例进行了产前诊断。经过胎儿全身系统超声评估，根据是否合并其他结构畸形将足畸形分为孤立性和复杂性。在排除家族遗传性疾病后进行介入性产前诊断。胎儿首先进行全基因组 CMA 检查，部分阴性结果胎儿进一步进行 WES 检查。对所有胎儿进行随访，了解妊娠结局及产后诊治情况。
结果 71 例足畸形胎儿经 CMA 检查，共有 2 例染色体非整倍体异常，4 例染色体片段拷贝数变异。CMA 阴性胎儿中共有 14 例进行了 WES 检查，发现 2 例胎儿出现基因突变。分别为 FGFR2 新发突变突变和 NEB 基因杂合突变。CMA 检出率为 8.3%，CMA 同时检测 WES 的检出率为 11.1%。孤立性足内翻胎儿有 32 例，复杂性足内翻胎儿共有 39 例。孤立性足内翻中发生异常的比例为 12.5%，复杂性足内翻中发生异常的比例为 15.4%。
结论 数据表明，合并其他结构畸形的足内翻胎儿 CMA 与 ES 检出率更高。因此，复杂性足内翻胎儿建议进行产前诊断。孤立性足内翻仍建议进行产前诊断。复杂性足内翻应根据合并的结构异常及遗传问题的特殊性、个性化管理。而对孤立性足内翻胎儿进行产前咨询时，要讲明产前筛查/诊断的局限性。

X chromosome inactivation study in female carriers of pathogenic X-linked deletions

Yuanyin Zhao Jia Li Limeng Dai Yongyi Ma Yun Bai Hong Guo
Army Medical University

Objective To evaluate the prognostic value of the XCI pattern in heterozygous female carriers of X-linked microdeletions.

Methods Four pedigrees with a total of 11 female carriers of distinct pathogenic X-linked deletions were recruited. Three of them contain unborn fetuses. XCI assay using peripheral blood lymphocytes was performed in all female carriers. Prenatal XCI assay using uncultured amniocytes was firstly performed in a fetal female with a deletion containing whole *PCDH19* gene. The pregnancy outcomes were followed up.
Results Favorable XCI skewing occurs in all female carriers, while the correlation between the XCI pattern and the clinical outcome is not consistent, relying on the specific genomic contents of the deletion region. For the carriers who lost one copy of the XCI escapees enriched region, the gene dosage insufficiency on the deleted allele could be compensated by upregulating gene expression from the intact X chromosome. The prenatal XCI assay for the heterozygous *PCDH19*-deletion female suggested that the XCI pattern of uncultured amniocytes could be an effective indicator for prenatal risk prediction of this disorder.
Conclusions Prenatal XCI assay in combination with the analysis of specific genomic contents would provide an accurate interpretation for the clinical implication of X-linked microdeletions in heterozygous carriers.

478 例单胎妊娠羊水过多病例的染色体微阵列分析

李玲
广东省妇幼保健院

目的 采用染色体微阵列分析(chromosomal microarray analysis, CMA)研究单胎妊娠羊水过多的可能病因。
方法 收集 2015 年 6 月-2020 年 12 月在我院经 III 级超声诊断为羊水过多并行产前诊断的 478 例单胎病例，患者抽取羊水或脐静脉血行 CMA 检测，其中 392 例同时行染色体核型分析。478 例病例按照是否合并其他胎儿异常分为孤立性羊水过多和非孤立性羊水过多，按照羊水过多程度分为轻度羊水过多和中度羊水过多。
结果 478 例中共检出 56 例致病性拷贝数变异（copy number variations, CNVs）（11.7%）；186 孤立性羊水过多病例检出 4 例致病性 CNVs（2.2%），292 例非孤立性羊水过多病例检出 52 例致病性 CNVs（17.8%），两组致病性 CNVs 检出率差异有统计学意义；轻度羊水过多致病性 CNVs50 例（12%），中度羊水过多致病性 CNVs6 例（11.3），两组致病性 CNVs 检出率差异无统计学意义。
结论 非孤立性羊水过多明显增加胎儿致病性 CNVs 的风险，当超声诊断羊水过多时应仔细排查是否合并其他的胎儿异常，并及时行胎儿 CMA 检测。中度羊水过多致病性 CNVs 检出率并不比轻度羊水过多增加，中度羊水过多可能是随着孕周增加的病情进展。

Isolated absent or hypoplastic nasal bone: is chromosomal microarray analysis necessary?

Xiaomei Shi
Guangdong Women and Children Hospital

Objectives To summarize the results of prenatal diagnoses of fetuses with isolated absent or hypoplastic nasal bone in the first and second trimester.
Methods From January 2015 to April 2021, 229 pregnancies with fetal isolated absent or hypoplastic nasal bone who received invasive prenatal diagnosis were included. The results of chromosome microarray analysis (CMA) were analyzes.
Results All cases enrolled were divided into advanced maternal age (AMA) group (n=42) and non-AMA group (n=187). The overall diagnostic yield of CMA testing for fetuses with isolated absent or hypoplastic nasal bone was 8.7% (20/229). Aneuploidy were detected in 13 (5.7%, 13/229) fetuses. Among them, 10 (4.4%, 10/229) cases of Down syndrome, 2 (0.9%, 2/229) cases of Klinefelter's syndrome, and 1 (0.4%, 1/229) cases of trisomy 18 were identified.

Pathogenic copy number variations (CNVs) were detected in 7 fetuses (3.1%, 7/229). Compared to non-AMA group, AMA group was accompanied by an increased prevalence of chromosomal abnormalities (7.0% (13/187) vs.16.7%(7/42), χ^2=4.61, *P*=0.044, Chi-square test).
Conclusion Isolated absent or hypoplastic nasal bone is not only associated with a high risk of Down syndrome but also with other chromosomal abnormalities, including pathogenic CNVs. Our cohort study demonstrate that CMA should be recommended in case of isolated absent or hypoplastic nasal bone.

The Value of Exome Sequencing in Thoracoamniotic Shunt for Non-immune Hydrops Fetalis : a Retrospective Clinical Study

Xing Wei Jia Zhou Xinyao Zhou Yingjun Yang Jianping Chen Luming Sun
Shanghai First Maternity and Infant Hospital

Objective To study the value of exome sequencing (ES) in non-immune hydrops fetalis (NIHF) that underwent thoracoamniotic shunt (TAS).
Methods It was a retrospective study of NIHF that underwent TAS between 2012 and 2020 at Shanghai First Maternity and Infant Hospital. After detailed assessment, NIHF cases with aneuploidies, infections, and structural anomalies were excluded, and TAS was offered to cases with severe pleural effusion. Quantitative fluorescence polymerase chain reaction (QF-PCR) were conducted to exclude Trisomy 21, 18 and 13 before fetal therapy, and chromosomal microarray analysis (CMA) were offered to all the cases. Before 2019, ES was retrospectively performed using stored fetal DNA extracted from prenatal samples; from 2019 and onwards, ES was discussed and offered during genetic counseling before intrauterine therapies.
Results A total of 18 NIHF cases underwent TAS with negative CMA and going on pregnancy were included. Fetal hydrops were relieved in 16 cases (88.9%). All cases were born alive. The median gestational ages at intervention and at delivery were 31.2 (22.0~33.1) weeks and 34.3 (29.7~38.6) weeks, respectively. The neonatal survival rate was 72.2% (13/18) and no causative gene variants were identified from ES in all survivors. Pathogenic or likely pathogenic variants were detected in 3 of the 5 neonatal deaths. If rapid ES could have been available to guide fetal therapy, neonatal survival rate after TAS would have increased from 72% to 87%.
Conclusions Single gene disorders were associated with perinatal death of NIHF underwent fetal therapy. Prenatal rapid exome sequencing may be of good promise for NIHF to explore precise etiology and guide fetal therapy.

15q11.2BP1-BP2 微缺失(Burnside-Butler)综合征

崔玉
无锡市妇幼保健院

目的 通过分析 15q11.2 BP1-BP2 微缺失综合征(Burnside-Butler syndrome，BBS)的胎儿期表现及出生后生长发育情况，有助于 15q11.2BP1-BP2 微缺失及优生咨询。
方法 回顾性分析 24 例 BBS 胎儿的确诊过程及出生后情况，对确诊 BBS 的孕期血清学筛查、超声表现、出生情况及目前发育情况进行分析；
结果 24 例均在孕中期行羊水穿刺确诊：6 例孕中期血清学筛查高风险，12 例超声异常，5 例不良孕产史，1 例高龄；12 例超声异常病例中 6 例 NT 增厚，2 例唇裂伴腭裂/牙槽突裂，1 例多关节挛缩综合征，1 例胎儿右侧膈疝+单脐动脉，1 例胎儿十二指肠闭锁可能，1 例鼻骨缺失；5 例不良孕产史中有 2 例存在≥2 次自然流产史，1 例畸形引产史，2 例有发育迟缓儿分娩史，1 例高龄妊娠。21 例经亲本验证，1 例新发突变，6 例遗传自父亲，14 例遗传自母亲。最终结局：5 例孕中期终止妊娠，余 19 例病例分娩：13 例女孩（遗传自父亲 4 例，遗传自母亲 7 例，新发突变 1 例，未验证

1 例），6 例男孩（遗传自父亲 1 例，遗传自母亲 5 例）；目前发育情况：生长发育迟缓 6 例；生长发育迟缓+语言发育迟缓 1 例；生长发育迟缓+多动症 1 例；语言发育迟缓 1 例。

结论 BBS 是一种新的综合征，是目前临床研究的热点基因之一，可以导致智力障碍、自闭症谱系障碍及其他相关异常行为等临床表现，但存在表型差异性大及不完全外显率。产前确诊 BBS，通过亲本验证，结合目前 BBS 干预现状，通过专业遗传咨询师进行评估并给予详细的咨询及建议，可以有效的指导优生优育。

Research Progress of Prenatal Diagnosis of Hemophilia

Yijuan Gao
Shenzhen Longgang Maternity and Child Health Hospital

Hemophilia is an X-linked recessive hemorrhagic disorder located on the X chromosome in humans. It consists of hemophilia A(abnormal F.VII gene) and hemophilia B (abnormal F.VII gene). Hemophiliacs can attack throughout their lives from birth to death, and are prone to disability and death without standardized treatment.For hemophilia gene carriers to conduct pathogenic gene testing and their fetus's prenatal diagnosis is an effective way to reduce the birth rate of hemophilia patients, and also a pointer to take special care of hemophilia newborns. Currently, the diagnostic methods used include:Villus extraction, amniocentesis, umbilical cord blood puncture, noninvasive direct genetic diagnosis(LD-PCR, MLPA(Multiplex ligation-dependent Probe Amplification), DS (direct sequencing)), indirect gene diagnosis (RFLP (restriction fragmentlengthpo lymor phism), STR (short tandem repeat), VNTR (V ariable number o f tandem repeats)). The choice of prenatal diagnosis method mainly according to gestational age and whether there is safe, due to the traditional invasive detection have the risk of miscarriage, now mostly with noninvasive prenatal genetic testing. Hemophili not only have various types of genetic defects, but also gene mutation , that have makes hemophilia diagnosis rate is low, so the current clinical use a variety of genetic testing means more joint applied to diagnosis of hemophilia. In the future, with the continuous development of genetic diagnosis technology, the detection of prenatal diagnosis of hemophilia will be more accurate, fast and convenient. Prenatal genetic diagnosis has significant advantages in the future.

Performances of noninvasive prenatal detection for fetal chromosome aneuploidy based on Semiconductor Sequencing Platform of difference sequencing depths

Jiexia Yang
Guangdong Women and Children Hospital

Objective To evaluate the performance of non-invasive prenatal testing (NIPT) by the semiconductor sequencing platform for chromosome aneuploidy and analysis the postive predictive value (PPV) in different sequencing depths for all chromosome aneuploidies.

Methods A cohort of 61581 pregnancies were recruited to review the NIPT results. Cell‐free DNA from plasma samples were sequenced using the Ion Proton sequencer, NIPT sequencing depths included 0.15X (3 Mb sequencing datas) and 0.4X (8 Mb sequencing datas). All high risk cases of NIPT were recommended to undergo invasive prenatal diagnosis, and all pregnant women were followed up.

Results A total of 910 cases were high risk of chromosome aneuploidies predicted by 0.15x NIPT and 0.4x NIPT, in which 0.15x NIPT predicted 677 high risk of chromosome aneuploidies, and 0.4x NIPT predicted 233. A total of 757 cases accepted prenatal diagnosis with 550 cases of 0.15 x NIPT and 207 cases of 0.4x NIPT. The PPV of autosomal aneuploidies in 0.4x NIPT was slightly better than 0.15x NIPT, but the difference had no statistically significant. The PPV of sex chromosome aneuploidies in 0.4x NIPT was lower than 0.15x NIPT.

Conclusion This study had revealed that 0.4x NIPT had a better performance in detecting T21/T18/T13. The PPV of two sequencing depth for rare autosomes chromosome aneuploidy and sex chromosome aneuploidy had no obvious difference.

对不良孕产史嵌合病例的诊断及胚胎植入前遗传学检测的成功干预

吴畏 孙雪萍 高超 谢佳孜 蔡令波
南京医科大学第一附属医院（江苏省人民医院）

目的 探索 Tri-WES 在生殖腺嵌合特殊病例的诊断中的应用及子代再发风险的干预
方法 对 2 例不良孕产史夫妇，采用 Tri-WES 方法，检测出可能存在的生殖腺嵌合，并通过胚胎植入前遗传学检测（PGT-M）进行风险排除，获得健康子代。
案例 1：原发不孕 3 年，因女方输卵管因素，男方染色体 46,XY,inv(1)(p11;q21)，遗传咨询后选择行 PGT-SR，移植整倍体胚胎后孕 13+周超声检查发现“颈部淋巴水囊瘤，胎儿水肿，四肢长骨呈短骨样回声”，致死性骨发育不良可能。引产胎儿 Trio+WES 检测提示 COL2A1 基因 52 号外显子 c.3944G>A（p.Cys1315Tyr）杂合变异，进一步验证提示男方为该变异的嵌合携带。再次通过单体型分析对余下胚胎再次 PGT-M，选择正常胚胎移植，成功妊娠，羊水穿刺检查胎儿未检测到 COL2A1 基因 c.3944G>A 突变，成功分娩 1 健康男婴。
案例 2：婚后 5 年两次不良孕史， B 超均提示胎儿四肢短于相应孕周，胎儿全身皮肤层水肿，胎儿胸腹腔积液，均为女胎孕 24 周引产。引产胎儿 WES 检测均提示 STAG2 基因 12 号外显子 c.1099T>C（p.Phe367Leu）杂合变异，为可能致病性变异，该基因突变可导致 X 连锁隐性遗传神经发育障碍伴颅面异常，父母外周血均未检出该位点变异，生殖腺嵌合可能性大。通过 PGT-M 单体型分析风险排查，选择正常胚胎移植，目前持续妊娠中，产前超声检查未提示异常。
结果 对 2 例生殖腺嵌合案例，成功进行 PGT-M，获得正常胎儿。
结论 生殖腺嵌合的诊断、临床遗传咨询及处理困难，Tri-WES 有助于明确诊断，后续通过 PGT-M 能有效预防出生缺陷再次发生。

一例 18 号染色体与 X 染色体小片段平衡易位合并 DUOX2 基因突变的植入前遗传学检测

叶英辉 石碧炜
浙江大学医学院附属妇产科医院

目的 植入前遗传学检测（PGT）能够帮助单基因病（PGT-M）或染色体结构异常（PGT-SR）患者选择无遗传问题的胚胎植入宫腔，以出生表型正常的胎儿。本文报道 PGT-M 联合 PGT-SR 并行染色体易位携带检测后成功临床妊娠一例。
方法 先证者男性，9 个月大时因腭裂、甲状腺功能低下、发育迟缓就诊。经染色体拷贝数变异（CNV）检测提示其 18 号染色体长臂末端 q22.2-q23 存在 9.85Mb 的杂合缺失，X 染色体长臂末端 q28 存在 5.59Mb 的重复，父母双方 CNV 及染色体核型未见异常，经 FISH 检测母亲为 X 染色体及 18 号染色体的平衡易位携带者。对先证者及其父母进行单基因病全外显子组测序分析，提示先证者存在 *DUOX2*：c. 1588A>T 杂合无义突变和 c. 2654G>T 杂合错义突变，父亲存在 *DUOX2*: c.2654G>T 杂合错义突变，母亲存在 *DUOX2*：c. 1588A>T 杂合无义突变。与患者沟通后，决定行 PGT-M 联合 PGT-SR 并行染色体易位携带检测。经体外授精后获得 3 枚囊胚，采用高通量测序进行基因检测，SNP 连锁分析，染色体 CNV 及易位携带检测。
结果 1 号胚胎染色体 CNV 异常；2 号胚胎携带父源突变（*DUOX2*: c.2654G>T 杂合错义突变），染色体 CNV 检测未见异常且未携带 t (X;18) 相互易位；3 号胚胎携带母源突变，染色体 CNV 检测未见异常但携带 t (X;18) 相互易位。移植 2 号胚胎后并成功获得妊娠，羊水检测与胚胎结果完全吻合。

讨论 1）核型检测可能无法检出部分小片段平衡易位，先证者或流产物样本行 CNV 检测有助于确定平衡易位；2）不排除男性 X 染色体与常染色体相互易位可能会有表型，且子代若为易位携带者仍有生育风险，故在本病例中进行了易位携带检测；3）PGT 的应用可在染色体易位合并单基因突变的复杂情况下筛选出可移植胚胎并获得持续妊娠。

一例 CNV 变异与基因突变共同致病的产前超声异常病例的分析

张慧敏 何文智 陈兢思 黎青 孙筱放
广州医科大学附属第三医院

目的 拷贝数变异和基因点突变是遗传性疾病的两个主要致病机制。基因所在区域的拷贝数变异（CNV）与该基因点突变（SNV）的共同作用已逐步被人们认识到是遗传病的一种致病方式。
方法 孕妇，孕 26+周，超声提示胎儿双侧侧脑室扩张（左侧 11.5mm，右侧 10.9mm），双肾实质回声增强，接受羊膜腔穿刺术，抽取羊水，进行染色体微阵列分析（CMA）和全基因组外显子测序检测（WES），同时抽取父母的外周血进行 WES 检测。
结果 羊水样本的 CMA 结果提示为在 2q13 区域存在一段长约 482Kb，拷贝数为 1 的缺失，NPHP1 基因包含在这段缺失区域内；Trio-WES 结果提示羊水样本的 NPHP1 基因存在一个可能致病性变异（c.1937_1938delAA），来源于父亲。NPHP1 是一个与常染色体隐性遗传病（AR）相关的基因。单独 NPHP1 基因所在区域的杂合性缺失或 NPHP1 基因的点突变一般不致病。结合本病例 CMA 和 WES 的检测结果，认为 2q13 区域（包含 NPHP1 基因）的杂合缺失与 NPHP1 基因的点突变共同作用下的 NPHP1 基因复合杂合变异是导致常染色体隐性遗传病--青少年期肾单位肾痨 1 型（Nephro nophthisis 1, juvenile，MIM:256100）的致病方式，本病例肾脏实质回声增强的超声表现与之相关。
结论 CMA 联合 WES 检测能找到 CNV 与 SNV 共同作用致病的方式，特别对超声结构异常的产前病例的诊断与咨询能提供很大的帮助。

Prenatal diagnosis and pregnancy determination of sex chromosome aneuploidy screened by non-invasive prenatal testing from 91,453 unselected singleton pregnancies: a retrospective analysis of 5-year experience

Sheng Luo
Longgang District Maternity &Child Heathcare Hospital of Shenzhen City

Objective To estimate the positive predictive value (PPV) of fetal sex chromosome aneuploidy (SCA) screened in non-selective population and explore the rate of pregnancy termination and ultrasound findings for fetal SCA and the factors influencing parents' decisions in South China.
Methods This is a large-scale retrospective cohort of positive SCA screened from unselected singleton pregnancies by non-invasive prenatal testing (NIPT) from a single prenatal center of a tertiary hospital, from January 2016 to July 2021. Clinical information, indications, diagnostic results, ultrasound findings, pregnancy determinations, and follow-up were reviewed and analyzed.
Results 526 cases of SCA positive were screened out of 91,453, giving a positive detection rate of 0.58%. The majority of indications (42.8%) were low-risk pregnancies. After genetic counseling, 76 pregnancies (14.4%) declined to prenatal diagnosis, the rest of 450 cases (85.6%) conducted with amniocentesis to detect fetal chromosome, of which 216 were confirmed as true positive of SCA with PPV of 48.0% (216/450). The SCA consisted of 145 sex chromosomal trisomies (60 cases of 47,XXY, 44 cases of 47,XXX and 50 cases of 47,XYY), 37 cases of monosomy X (45,X), seven cases of 48,XXYY, eight cases of mosaicisms (45,X/46,XX), ten cases with sex chromosome structural abnormalities, included four cases of 46,X,del(Y)(q11.21), three cases of 46,X,del(X)(p11) and three cases of 46,X,i(X)(q10). Of the 216 cases confirmed as true positive

SCA, 98 cases (45.3%)chose to terminate the pregnancy (93.0%, 65.3%, 15.4% and 10.9% for 45,X, 47,XXY, 47,XXX and 47,XYY, respectively), 118 cases (54.6%) elected to continue the pregnancy.
Conclusions NIPT, as a first-tier routine method for screening autosomal aneuploidies, also could play an important role in screening SCA. Low-risk pregnant women are the main indication for the detection of SCA as NIPT test provides to non-selective population. The trend of overall termination rates of SCA-affected pregnancies is decreased. For 47,XXX and 47,XYY with mild phenotype, couples would like to continue the pregnancy. But for 45,X and 47,XXY, parents apt to terminate pregnancy no matter ultrasound abnormalities were found or not. pregnancy determinations are affected by types of SCA, sonographic findings, maternal age, and presence of infertility.

Retrospective and cost-effective analysis of Citywide Implementation of NIPT as a First-Tier Screening Test in Changsha, China

Shihao Zhou Mengyue Yang Siyi Ding Shaolan Liu Jun He
Prenatal Diagnostic Center, Changsha Hospital for Maternal & Child Health Care

Background Changsha launched a Healthy People's Livelihood Project which implemented NIPT as a first-tier screening test to all pregnant women in Changsha. This study aims to explore the clinical application and health economic value of NIPT in this project.
Methods We performed a retrospective analysis based on 222,116 cases on NIPT results and 140,274 cases on STSS (second trimester serum screening), from April 2018 to December 2020 in healthy people's livelihood project. For pregnant women with high risk of birth defects, prenatal diagnosis and follow-up of pregnancy outcomes were then conducted. The performance of NIPT and STSS was compared and the cost-effectiveness analysis for Down syndrome was implemented.
Results Among all Changsha's pregnant women during this project, 78 % (222116/283718) applied NIPT. For NIPT, the results were obtained from 221,903 samples (99.90%), and 622 cases (2.84%) were diagnosed as high risk. Among these, 571 cases (91.80%) had accepted amniocentesis, which led to the diagnosis of 310 cases of T21 (PPV: 84.70%), 56 cases of T18 (PPV: 45.90%) and 15 cases of T13 (PPV: 18.07%). The sensitivity and specificity of NIPT were (T21: 97.48%, 99.98%), (T18: 98.25%, 99.97%), (T13: 100%, 99.97%). 315 cases were diagnosed as sex chromosomal aneuploidies (PPV: 46.2%). By comparing the results of 140,274 pregnant women who were screened by NIPT and STSS at the same time, we found that NIPT had better detection performance in detecting T21 and T18, and identified more T21 and T18 births than STSS. The cost-effectiveness ratio of NIPT and STSS for T21 was $107,363 and $136,466, respectively.
Conclusion NIPT is a highly accurate screening test for T21, followed by the screening accuracy for T18 and sex chromosomal aneuploidies. NIPT screening is superior to STSS in terms of detection performance and health economic value.

产前超声诊断胎儿消化道梗阻的遗传结果和产后结局分析

倪梦瑶 朱湘玉 刘威 顾雷雷 曹培暄 李洁
南京大学医学院附属鼓楼医院

目的 回顾性分析 2014-2020 年因产前超声提示"胎儿消化道梗阻可能"于我院行 CMA 检查的 65 例单胎妊娠病例的 CMA 结果，电话随访其妊娠结局，为门诊咨询胎儿消化道梗阻提供佐证。
方法 根据产前超声提示胎儿消化道梗阻位置分为 3 组，A 组：上消化道梗阻组，B 组：下消化道梗阻组，C 组：梗阻位置不明确组。样本来源包括 62 例羊水和 3 例引产胎儿皮肤组织，根据不同样本类型选取不同试剂盒提取胎儿 DNA，进行母血污染鉴定试验。排除母血污染后，根据操作流

程，采用 Cyto Scan TM750K Array（Affymetrix，Thermo Fish，加州，美国）芯片行 CMA 检查。结合胎儿超声及其他临床资料，查找 Database of Genomic Variants、Decipher Database、PubMed 等相关数据库资料进行分析，出具 CMA 报告。对 62 例羊水穿刺孕妇电话随访妊娠结局及生长发育情况。

结果 （1）在纳入研究的 65 例病例中，发现 10 例染色体异常，染色体异常率 15.4%。10 例染色体异常包括 21-三体综合征 4 例、致病性 CNV4 例、可能致病性 CNV1 例和不平衡易位 1 例，另检出临床意义不明的变异（Variant of Uncertain Significance，VOUS）4 例。A 组 47 例，染色体异常率 21.3%（10/47）；B 组 14 例，染色体异常率 0；C 组 4 例，染色体异常率 0。（2）51 例 CMA 未见异常中，16 例产后诊断消化道梗阻、11 例未见异常、14 例引产和 10 例失访；4 例非整倍体、4 例致病性 CNV 和 1 例不平衡易位均引产；1 例可能致病性 CNV 胎儿宫内死亡引产；4 例 VOUS 中，2 例产后诊断消化道梗阻、1 例活产未见异常、1 例引产。（3）本研究 18 例产后消化道梗阻的新生儿中，1 例“食道闭锁”患儿家属放弃手术，1 例产后诊断十二指肠梗阻合并胆道梗阻，肠梗阻手术效果好，患儿后因肝硬化死亡，余 16 例消化道梗阻患儿均手术效果良好，生长发育未见异常。

结论 胎儿消化道梗阻与染色体异常相关，产前超声提示胎儿消化道梗阻，CMA 可作为一线产前诊断技术。在排除染色体异常情况下，单纯消化道梗阻胎儿出生后手术成功率高，术后恢复效果良好。

产前分子诊断中心变异验证与原始结果不一致的案例分析

林丽灵[1,2] 马祎楠[1] 潘虹[1] 戚豫[1] 王静敏[1] 张英[1]
1.北京大学第一医院 2.北京协和医院

研究背景和目的 国内测序市场蓬勃发展，NGS 已在各大城市和医院普及。遗传病诊断瓶颈从检测技术的不可及，转换为测序结果解读，尤其是临床表现与关键遗传变异的归因关联。产前分子诊断中心面临大量外单位检测报告，需重新验证方能决定能否继续产前诊断。多项国外研究表明，变异分级存在实验室间差异，不一致率在 10~30%左右，国内尚无产前分子诊断实验室与其他遗传诊断实验室变异解读差异相关数据。本研究对单中心产前分子诊断前变异验证结果与原始报告结果不一致的案例进行详尽解析和总结，分析不一致原因并提供优化方案。

研究方法 回顾性研究，纳入来自 2015 年到 2019 年间就诊于一家三级医院产前诊断中心的罕见单基因神经遗传病家系。变异分级依据 2015 年美国医学遗传学学会（American College of Medical Genetics，ACMG）测序变异解读指南。不一致类型包括变异检测、致病性分析和遗传方式不一致。SNVs 和小片段 indels 采用 PCR-Sanger 法验证，大片段的 indels 选择 qRCR、MLPA 或长片段 PCR 验证。变异分级一致性评估采用三分法比较，即为致病（P/LP），意义不明（VUS）和良性（LB/B）3 个类别间的比较。检测父母标本验证遗传方式和变异来源，必要时检测同胞/其他亲属标本明确共分离。

研究结果 共发现有 17/286（6%）个不一致家系。其中变异检测不一致的案例 4 例（23.5%），变异分级不一致 13 例（76.5%）及遗传方式不一致 1 例（6%）；有 1 例家系同时存在检测不一致和分级不一致。检测不一致原因包括假基因干扰、高 GC 序列和二代测序结果未经一代测序验证。对应的优化策略为二代测序检测机构在报告中标注假基因和高 GC 基因的变异，强调从业者在解读报告时重视测序质量和变异率，且需明确二代测序结果是否验证。13 个分级不一致案例包含 18 个变异，错义变异有 16/18 个。分级改变方向为 14 个变异从 LP 变为 VUS/LB/B、3 个变异由 VUS 变为 LP/P 和 1 个变异由 VUS 变为 LB/B。变异分级不一致原因包括分级体系差异（n=4）和分级证据使用差异（n=14）。分级证据使用差异包括临床表型评估差异（n=4）、频率证据评价差异（n=6）、共分离证据评价差异（n=8）、计算机预测证据评价差异（n=5）和文献分析差异（n=6）。对应的优化策略为加强从业者临床遗传学知识和变异分级指南使用规范化培训。遗传方式不一致的 1 例为母源性混合型单亲二体，核心家系呈现出先证者为纯合子，母亲为杂合子而父亲为野生型的非孟德尔遗传。单亲二体再发风险低于 1%，而 AR 遗传变异再发风险高达 25%，故对遗传咨询具有重要意义。结合测序技术新进展，本研究提出单亲二体鉴别诊断流程。

研究结论 首次全面总结国内产前分子诊断实践中面临的 3 种变异验证与原始结果不一致形式及具体原因。研究表明产前中心所采用评判标准较临床专科严格，重新变异验证是十分重要的。基于潜在的不一致可能，亦建议有再生育计划的单基因病受累家庭提前于产前机构遗传咨询和变异验证，以免因不一致而延误后续临床处理。针对不一致原因，亦提出针对性的优化方法。

肾脏回声增强合并羊水过少胎儿基因诊断及家系分析

朱娟
广东省妇幼保健院

目的 探索肾脏回声增强合并羊水过少胎儿的遗传学致病因素，并进行家系分析以评估遗传风险。
方法 选取产前超声筛查发现胎儿肾脏回声增强、从孕中期开始羊水进行性减少的两例胎儿，通过介入性产前诊断抽取羊水后进行全外显子组基因检测（whole exome sequencing,WES）,同时提取其父母静脉血 2mL，对发现的基因突变位点进行家系验证及分析。
结果 两例胎儿从孕 18 周开始出现羊水过少合并胎儿肾脏回声增强，其他结构未见明显异常。羊水检查发现其中 1 例胎儿 ACE 基因复合杂合变异 c.1028G>A(p.W343*)和 c.2948T>C(p.L983P),1 例胎儿 ACE 基因纯合变异 c.1028G>A(p.W343*)，均分别来源于父亲和母亲。c.1028G>A 变异可导致肽链合成提前终止，引起 ACE（血管紧张素 I 转换酶）编码异常导致肾素-血管紧张素系统（renin-angiotensin system,RAS）通路异常，与常染色体隐性遗传性肾小管发育不良（renal tubular dysgenesis，ARRTD）有关。ARRTD 是一种罕见的致死性疾病,大多数报告的病例是出生后通过肾脏近端小管缺乏或缺乏分化的组织病理学特征诊断,产前诊断困难。
结论 产前超声筛查提示胎儿羊水过少合并肾回声增强时，可能与 ACE 基因突变有关，通过全外显子检测有助于明确病因。

Noninvasive prenatal diagnosis of hereditary colorectal cancer syndromes using cell-free DNA in maternal plasma

Wang Yao[1] Suqing Li[2] Wu Di[2] Yan Hongli[1]
1.Changhai Hospital, Naval Medical University
2.Celula Medical Technology Co., Ltd

BACKGROUND Peutz-Jeghers syndrome (PJS) and familial adenomatous polyposis (FAP) are two classical types of hereditary colorectal cancer syndromes. Considering the characteristics of the diseases, a complete set of detection and analysis system is needed for these patients planning for children to execute prenatal diagnosis and genetic counseling for risk evaluation and whole-life monitoring. This study was to establish a practical protocol for early non-invasive prenatal diagnosis (NIPD) of fetuses at risk for PJS or FAP.
METHODS Targeted enrichment was done using hybridization probes coordinating the *STK11* gene region and *APC* gene region, with 1,458 highly heterozygous SNPs included. Semi-target amplification random sequencing was used for large fragment deletion detection. For RHDO analysis, haplotype construction was done by the software SHAPEIT, CBS algorithm was used for recombination event calculation and the determination of whether the fetus was affected was according to the Bayes Factor.
RESULTS Haplotypes were successfully constructed in the five recruited families with different pedigree characteristics, the results for the RHDO analysis were consistent with the amniocentesis sampling detection results. The cell-free fetal DNA fraction can be detected as low as 2% in maternal plasma.
CONCLUSIONS We report a NIPD assay for PJS and FAP using targeted sequencing on maternal cell-free DNA, which is the first NIPD report on hereditary colorectal cancer syndromes. Through our strategy, the fetal status can be determined without proband when the pathogenic mutation is large fragment deletion, and the pathogenic haplotype construction are not restricted to first-degree relatives.

A retrospective cohort analysis of the genetic assay outcomes of fetuses with umbilical cord cyst

Qian Liu Jing Wu
Guangdong Women and Children Hospital

Objective To analyze the risk of clinical chromosome abnormality in pregnancies with umbilical cord cyst.
Methods Data from all genetic assay performed due to umbilical cord cyst between October 2014 and June 2021 were retrospectively obtained in Guangdong Women and Children Hospital. Compare the difference of genetic assay findings in isolated and non-isolated umbilical cord cyst cohorts.
Results Total of 49 singleton pregnancies and 2 MCDA twin pregnancies total 51 fetus were enrolled into the cohort, including 20 fetus isolated and 31 fetus non-isolated umbilical cord cyst. One fetus (5%,1/20)in isolated umbilical cord cyst group showed chromosomal abnormality, 17p12 microduplication. 12 cases (38.7%,12/31) with chromosomal abnormalities were identified in the non-isolated umbilical cord cyst group, including seven cases trisomy 18, two cases trisomy 13 and three cases microdeletion. The incidences of chromosomal abnormalities between the two groups was significant different (1/20, 5% vs 13/31, 38.7%, p=0.003). There was no positive medical exon sequencing finding in the three fetus suffered from non-isolated umbilical cord cyst whose parents choose to accept CMA and medical exon sequencing.
Conclusion This historical cohort study evaluated the value of CMA in fetuses with umbilical cord cyst, suggested that CNVs may be the basic genetic etiologies which should be considered as the diagnostic evaluation. We recommended CMA as basic genetic evaluation in case of umbilical cord cyst.

Prenatal diagnosis of 17p11.2 copy number abnormalities associated with Smith–Magenis and Potocki–Lupsiki syndromes in fetuses

Meiying Cai[1] Na Lin[1] Xianguo Fu[2] Liangpu Xu[1] Hailong Huang[1]
1.Fujian Maternity and Child Health Hospital
2.Ningde Municipal Hospital

Objectives Smith-Magenis syndrome (SMS) and Potocki-Lupski syndrome (PTLS) are rare autosomal dominant diseases. Currently, clinical phenotypes of adults and children have been reported, while fetal ultrasonic phenotypes are rarely reported. We aimed to analyze the prenatal ultrasound phenotypes of 17p11.2 copy number abnormalities associated with SMS and PTLS in fetuses to improve the understanding, diagnosis, and monitoring of these diseases in fetuses.
Methods A retrospective analysis of 6200 pregnant women who received invasive prenatal diagnosis at Fujian Provincial Maternal and Child Health Hospital between October 2016 and January 2021 was performed. Amniotic fluid or umbilical cord blood was extracted for karyotype analysis and single nucleotide polymorphism array (SNP-array).
Results SNP-array revealed six fetuses with copy number variant (CNV) changes in region 17p11.2. Among them, one had CNV microdeletion in the 17p11.2 region, which was pathogenically analyzed and diagnosed as SMS. Five fetuses had CNV microduplication in the 17p11.2 region, which was pathogenically analyzed and diagnosed as PTLS. Prenatal ultrasound phenotypes of the six fetuses were varied, and one of the fetuses with SMS was characterized by cardiac malformations and polyhydramnios. Among the five fetuses with PTLS, two mainly presented cardiac malformations, one showed minor ultrasonographic markers, and the remaining two fetuses showed normal ultrasound phenotype, but their mothers had mental retardation. The parents of two fetuses with PTLS refused pedigree verification. One fetus with SMS and one fetus with PTLS were confirmed as de novo by pedigree. PTLS in two fetuses was confirmed to be from maternal inheritance. They were the first and second fetuses from the same

mother, and the mother had mental retardation. After genetic counseling, the parents of all six fetuses chose to terminate their pregnancies.
Conclusions Prenatal ultrasound phenotypes of SMS and PTLS in fetuses vary: SNP-array is a powerful diagnostic tool for these diseases. The ultrasonic phenotypes of these cases enrich the clinical database. In the future, detailed molecular genetic testing and prenatal ultrasonographic analysis of an increased number of SMS and fetuses with PTLS will aid in the identification of SMS and PTLS in fetuses, as well as the accurate localization of more potentially related genes.

The value of non-invasive prenatal testing in the diagnosis of birth defects: Insights from a large multicentre study in Southern China

Meiying Cai[1] Na Lin[1] Xuemei Chen[1] Ying Li[1] Min Lin[1] Xianguo Fu[2] Shuqiong He[1] Liangpu Xu[1] Hailong Huang[1]
1.Fujian Maternity and Child Health Hospital
2.Ningde Municipal Hospital

Objective Non-invasive prenatal testing (NIPT) is a fast, safe, and non-disruptive diagnostic method. At present, few studies have evaluated the screening efficiency of NIPT positive predictive value (PPV) in study subjects. Here, the results of NIPT in pregnant women were retrospectively analysed, and the detection rate, PPV and follow-up data were evaluated to determine its clinical value.
Methods A large multicentre study was conducted involving 52,855 pregnant women who received NIPT. Based on gestational age, amniotic fluid or umbilical cord blood were extracted for simultaneous karyotype and chromosome microarray analysis (CMA) in NIPT-positive patients.
Results Among the 52,855 cases, 754 were NIPT-positive, with a positivity rate of 1.4%. Karyotype analysis and/or CMA confirmed 323 cases of chromosomal abnormalities, with a PPV of 45.1%. PPV of Trisomy 21 (T21), Trisomy 18 (T18), Trisomy 13 (T13), sex chromosomal aneuploidies (SCA) and copy number variations (CNV) were 78.9%, 35.3%, 22.2%, 36.9% and 32.9%, respectively. The PPV of T21, T18, and T13 increased with age whereas, the PPV of SCA and CNVs had little correlation with age. The PPV was significantly high in patients with advanced age along with an abnormal ultrasound.
Conclusions NIPT had a high PPV for T21, and a low PPV for T13 and T18, while screening for SCA and CNVs showed clinical significance. However, in case of NIPT screening for SCA and CNVs, simultaneous karyotype and CMA should be performed to increase the detection rates. Interventional prenatal diagnosis is still required in NIPT-positive cases to avoid false positives or unnecessary termination of pregnancy.

两例 NIPS 提示微缺失综合征高风险病例的产前诊断及遗传分析

赵少志 彭莹莹 杜囡 苗晨 刘红卫 张欣文
西安市人民医院（西安市第四医院）

目的 为两个无创产前筛查（noninvasive prenatal screening，NIPS）提示微缺失综合征高风险病例进行产前诊断，并提供合适的遗传咨询。
方法 利用高通量测序对孕妇外周血胎儿游离 DNA 进行检测，检出两例微缺失综合征高风险病例，病例 1 提示为 Langer-Giedion 综合征，病例 2 提示为 22q11.2 微缺失综合征。经孕妇知情同意进行产前诊断，除常规核型分析外，采用产前 BACs-on-Beads（bacterial artificial chromosome on beads，BoBs）快速检测，进一步经染色体微阵列验证（Chromosomal Microarray，CMA）。
结果 病例 1，产前 BoBs 提示 Langer-Giedion 综合征区域探针部分缺失，CMA 提示 arr[GRCh37] 8q24.11q24.12(118777181_121045190)x1，仅为 Langer-Giedion 综合征常规缺失区域的一部分，该缺失为致病性拷贝数变异（copy number variants，CNV）；病例 2，产前 BoBs 提示未见

异常，CMA 提示 arr[GRCh37] 22q11.21(20734765_21460594)x1，为意义不明的 CNV，家系验证遗传自孕妇本人。
讨论 NIPS 除了最常见的假阳性及假阴性，非预期的 CNV 亦会对孕妇及家庭造成一定的困扰。临床医生或遗传咨询医师需要了解每种检测方法的特点及局限，在检测前后进行充分的知情告知，以减轻孕妇焦虑，结合家系进一步检测并分析其致病性，以帮助其做出合适的选择。

Feasibility and challenge of trio whole exome sequencing in prenatal diagnosis of central nervous system abnormalities

Xiaoying Lin
Guangdong Second Provincial General Hospital

Objective To evaluate the feasibility of trio whole exome sequencing(trio-WES) in fetuses with central nervous system (CNS) abnormalities and summarize our experiences in clinical implementation.
Method We adopted a retrospective approach to review the trio-WES data of 9 prenatal cases with CNS abnormalities from April 2019 to February 2021, whose karyotype was normal and chromosomal microarray analysis was negative.
Results 7 of 9 fetuses were found to have genetic variants associated with clinical abnormalities (a detection rate of 77.78%), of which 5 were definitively diagnosed with pathogenic and likely pathogenic variants (a diagnostic yield of 55.56%). Of the 12 variants identified in 8 genes, four variants (*OFD1* NM_003611.2: c.2305A>T; *CPLANE1* NM_023073.3: c.4781T>C; *TBCD* NM_005993.4: c.1543C>T and *STIL* NM_003035.2: c.515G>C) were not reported previously. The findings in some cases indicated that single gene variation might coexist with CNVs and multiple structural abnormalities might be caused by different gene variants. Additionally, antenatal symptoms with diagnostic variants in TBCD gene were firstly described.
Conclusion Trio-WES is feasible in prenatal diagnosis of fetuses with CNS abnormalities after karyotype and CMA were undiagnostic. To deal with the complexity of CNS abnormalities and the difficulty of genotype-phenotype analysis, a multidisciplinary team is essential.

遵义地区 3087 例孕妇无创产前检测结果回顾性分析

余江 万雪 刘娟 王钰莹 郑艺 余丽梅 章涛 范振海
遵义医科大学附属医院

目的 探讨孕妇外周血胎儿游离 DNA 无创产前检测（non-invasive prenatal testing，NIPT）在遵义地区胎儿染色体非整倍体产前筛查的临床应用价值。
方法 对 2019 年 11 月—2021 年 04 月遵义地区 3087 例孕妇外周血样本进行 DNA 无创产前检测，并对筛查高风险的孕妇行有创产前诊断，并对所有孕妇妊娠结局进行随访。
结果 孕妇年龄 29.34±4.97 岁，最小 15 岁，最大 46 岁，高龄孕妇 513 个，平均孕周 19.83±4.69 周，3087 例孕妇外周血共筛查出高风险 41（1.33%），其中 21-三体、18-三体及 13-三体高风险分别为 8 例、5 例、2 例，性染色体异常 9 例，其他常染色体异常 17 例。NIPT 对 21-三体、18-三体、13-三体、性染色体异常以及其他常染色体异常的阳性预测值分别为 85.71%（6/7）、40%（2/5）、0（0/2）、33.33%（3/9）、35.71（5/17），妊娠终止率分别为 87.50%、0、40%、33.33%、23.52%。
结论 采用无创产前检测技术筛查胎儿染色体非整倍体疾病，准确较高，可将其作为产前筛查染色体非整倍体疾病的首选方式，但针对高风险病例更应该加强遗传咨询、有创产前诊断及随访。

河南省重点民生实事工程-三门峡市 6997 例孕中期血清学唐氏筛查的临床应用现状分析

韦贞汁
三门峡市中心医院

目的 通过对三门峡市中心医院（三门峡市妇幼保健院）6997 例孕妇行河南省重点民生实事工程-孕中期血清学唐氏筛查，通过筛查现状分析，评估此民生事实工程技术在我市开展和推广的价值。
方法 选择 2018 年 1 月至 2020 年 12 月就诊于河南省三门峡市妇幼保健的河南省户籍或在本省居住 6 个月以上孕 15-20^{+6} 周单胎孕妇 6997 例，知情同意后进行孕中期血清学唐氏筛查，评估胎儿患 21-三体、18-三体的风险值，并对临界风险、高风险的孕妇进行 NIPT 无创产前筛查及羊膜腔穿刺产前诊断。
结果 通过孕中期血清学唐氏筛查，6997 例单胎孕妇中有 1371 例筛查出高危妊娠，总高风险率为 19.59% ，其中筛查出 21-三体高风险 382 例，临界风险 892 例；18-三体高风险 15 例，临界风险 37 例，神经管缺陷高风险 45 例。无创 DNA 筛查 929 人，137 例经羊膜腔穿刺产前诊断确诊后有 44 例发现异常染色体核型,其中 21-三体 31 例、18-三体 4 例、其他染色体异常 9 例。
结论 通过积极开展河南省重点民生实事工程-孕中期血清学唐氏筛查，能有效辅助产前诊断的异常检出，预防缺陷儿的产出，值得积极推广和应用。

A prenatally diagnosed case of postaxial polydactyly with a novel compound heterozygous variant in SMO

Lihong Fan
Huzhou Maternity & Child Health Care Hospital

Objective To explore the genetic etiology of postaxial polydactyly (PAP) in a Chinese family.
Methods We recruited a Chinese PAP family where the fetus was diagnosed with PAP by ultrasonography for a multi-platform laboratory survey, including chromosome microarray analysis (CMA), karyotype analysis, and Trio-based whole-exome sequencing (Trio-WES).
Results Trio-WES identified a compound heterozygous variation in the smoothened (SMO) gene with two variants, namely c.1619C>T (p. Ala540Val) and c.1219C>G (p. Pro407Ala). Then Sanger sequencing validated the two mutations were from the father and mother, respectively. The two missense variants reported here are predicted deleterious in silico by SIFT and Mutation Taster.
Conclusions Our findings expanded the variation spectrum of the SMO gene, and provided solid evidence for genetic counseling. It is likely to be the first report of prenatal diagnosis in SMO and will contribute to a better understanding of the complex genetic mechanism underlie PAP.

Prenatal diagnosis of Pallister-Killian syndrome and literature review

Xiaoqing Wu
Fujian Provincial Maternity and Child Hospital, Affiliated Hospital of Fujian Medical University

Background Pallister-Killian syndrome (PKS) is a rare sporadic genetic disorder usually caused by mosaicism of an extra isochromosome of 12p (i(12p)). It has no typical prenatal manifestation. Molecular methodology is always required for the confirmation due to the indistinguishable morphologically of i(12p) and variable mosaic level.
Objective This retrospective study analyzed the prenatal ultrasound manifestation and molecular as well as cytogenetic results of five PKS fetuses confirmed in prenatal diagnosis.

Methods Samples of amniotic fluid, and/or cord blood, skin biopsy, placenta were collected. Conventional karyotyping and single Nucleotide Polymorphism array (SNP array) were performed on all the amniotic fluid or cord blood. Copy Number Variants Sequencing (CNV seq) and fluorescence in situ hybridization (FISH) were also used for the validation for one fetus. The clinical features and detective results were compared with previously published cases.
Results All the five fetuses were from pregnancies with advanced parental age. Two fetuses involved structural abnormalities and one fetus had only soft markers, all of which included increased nuchal translucency (NT). The rest two fetuses had normal ultrasound in the second trimester. The karyotype revealed typical i(12p) in four cases and an small supernumerary marker chromosome consisting of 12p and 20p in the rest one, which was confirmed by SNP array. The proportion of cell with i(12p) ranged from 0% to 100% in cultural cells, while SNP array results suggested 2-4 copies of the whole short arm of chromosome 12. For one fetus, metaphase FISH showed normal results but the interphase FISH suggested that the proportion of cell with two copies, three copies and four copies of 12p in the amniotic fluid were 59%, 19% and 22%, respectively.
Conclusions Advanced parental age may be an important risk factor for PKS and there were no typical ultrasound manifestations related to PKS. The combination of karyotype analysis and molecular diagnosis is an effective method for the diagnosis of PKS.

染色体微阵列分析在双胎妊娠中的应用

朱湘玉 刘威 顾雷雷 朱雨捷 曹培暄 吴星 杨滢 李洁
南京大学医学院附属鼓楼医院

目的 分析不同类型双胎遗传学的一致性与不一致性，为双胎宫内治疗和检查方案提供依据。
方法 回顾 2014 年 6 月至 2021 年 2 月间，308 名双胎妊娠孕妇因发现胎儿超声异常在我中心行染色体微阵列芯片分析（chromosomal microarray analysis，CMA）的拷贝数分析结果，同时通过单核苷酸多态性位点（Single nuclear polymorphism，SNP）行一致性分析。CMA 实验及分析、验证流程按本中心常规操作流程进行。双胎绒毛膜性的确定通过 10-14 周时超声对“双胎峰”的识别完成。
结果 308 对双胎中，15 对胎儿因两胎儿所用芯片不一致或检测失败无法进行一致性分析。剩余 293 对中，101 对为双绒毛膜双胎（dichorionic twins, DCT），其中 56 对性别不同，SNP 一致性为 72.38-80.37%，提示均为双合子双胎（dizygotic twins, DZT）；45 对性别相同的 DCT 中，39 对为 DZT，6 对为单合子双胎（monozygotic twins, MZT）。29 对为单绒毛膜双胎（monochorionic twins，MCT），两胎儿性别均相同，且均为单合子双胎。163 对因错过检查时间，绒毛膜性不明确（uncertain chorionicity twins, UCT），通过 SNP 一致性分析，62 对（38.0%）不同性别胎儿均为 DZT，101（61.9%）对性别相同的胎儿中，67 对为 DZT，34 对为 MZT。拷贝数分析提示，224 对 DZT 中，阳性检出 58 对，其中 13 对(22.4%)结果相同，均为拷贝数变异，45 对两胎儿结果不一致，非整倍体占 51.1%（23 对），拷贝数变异占 48.9%（22 对）。69 对 MZT 中阳性检出 9 对，其中 8 对（88.9%）均相同，仅一对（11.1%）结果不一致，双胎之一为正常女性，另一为 Turner 综合征[arr (X)x1]。
结论 双胎类型复杂，结合遗传学和影像学信息有助于更好判断双胎风险，为胎儿宫内治疗方案选择提供可靠证据。

书面交流

核孔蛋白 37 对哺乳动物植入前胚胎发育的影响

彭雅文[1,2] 沈鉴东[1,2] 刁飞扬[1,2]
1.南京医科大学生殖医学国家重点实验室，江苏省，南京市
2.南京医科大学第一附属医院临床生殖中心，江苏省，南京市

目的 NUP37 是核孔蛋白家族的一员，是 NUP107-160 亚复合物重要成分，果蝇的 Nup37 基因表现了母源效应基因属性。本研究旨在探究核孔蛋白 37 在哺乳动物卵母细胞早期胚胎中的表达模式，定位分析，及其缺陷是否影响哺乳动物植入前胚胎的发育。
方法 1. 提取小鼠卵母细胞、早期胚胎及其他组织 RNA，采用实时荧光定量链式反应研究 Nup37 的 mRNA 表达水平。2. 采用免疫荧光法研究 NUP37 蛋白质在小鼠卵母细胞及早期胚胎中定位及半定量情况。3. 采用显微注射 Nup37 小干扰 RNA 的方法，干扰早期胚胎中 Nup37 基因的表达，观察其胚胎发育是否受到影响。
结果 1. Nup37 在卵母细胞及胚胎中的 mRNA 表达远高于其他组织；在受精卵从双原核到囊胚中的 mRNA 成逐渐减少的趋势。2. NUP37 蛋白在卵母细胞及早期胚胎中与 DNA 共定位；在受精卵中从双原核到囊胚中的蛋白表达成逐渐下降趋势。3. Nup37 表达干扰后囊胚率（64.81%）较空白组（92.04%）及阴性对照组（85.79%）均下降(P<0.01)。干扰组囊胚的总细胞数【（32.17±9.04）个 vs.（59.46±12.38）个】、滋养层细胞数【（26.30±8.14）个 vs.（46.71±11.53）个】及内细胞团细胞数【（5.87±3.60）个 vs.（12.75±3.33）个】较阴性对照组均下降（P<0.01）。
结论 Nup37 基因在哺乳动物早期胚胎的发育中起到关键性作用，Nup37 功能缺陷可能导致哺乳动物早期胚胎发育阻滞。

SLC38A4 通过调节 Wnt/β-catenin/MYC/HMGCS2 抑制肝癌

李洁 袁继行 刘永达
中国人民解放军海军军医大学

目的 肝癌具有许多与胎肝发育相似的分子特征-癌胚分子事件。癌胚分子的高表达往往伴随着更差的预后。因此，进一步解析肝癌发生发展过程中的重要癌胚分子事件，将为理解肝癌的发生发展和寻求治疗策略提供新的见解。
方法 通过 qRT-PCR、蛋白质免疫印迹、TCGA 和 GEO 数据集分析研究了 SLC38A4 和 HMGCS2 的表达水平与临床相关性。通过功能学实验研究了 SLC38A4 的生物学作用。通过 qRT-PCR、蛋白质免疫印迹、免疫荧光、荧光素酶报告基因系统、TCGA 和 GEO 数据集分析对 SLC38A4 下游信号通路进行了研究。
结果 SLC38A4 的下调表达被确定为癌胚分子事件。DNA 高甲基化导致胎肝和 HCC 中 Slc38a4/SLC38A4 的表达下调。 SLC38A4 的低表达与肝癌患者不良预后有关。功能实验结果显示 SLC38A4 的表达下调促进了 HCC 细胞在体外的增殖、干性和迁移能力，并抑制 HCC 细胞凋亡，从而进一步抑制体内 HCC 肿瘤发生。HMGCS2 被确定为 SLC38A4 的关键下游靶标。SLC38A4 通过上调 AXIN1 抑制 Wnt/β-catenin/MYC 轴的信号传递，促进 HMGCS2 的表达。功能性拯救实验表明 HMGCS2 过表达逆转了 SLC38A4 的表达下调在 HCC 中的致癌作用。
结论 SLC38A4 的下调表达被确定为一种新的癌胚分子事件，SLC38A4 被确定为一种新的 HCC 相关肿瘤抑制因子。

Notch 活化 IRE1α-XBP1 促进血管内皮细胞干细胞转变参与肿瘤血管异常

晏贤春 韩骅 梁亮 杨子岩 张家玉林 张沛然 王若楠 车波 丰星星
中国人民解放军空军军医大学

目的 肿瘤新生血管具有结构紊乱、功能异常的特征，在促进肿瘤恶性生长和转移中发挥特殊作用。Notch 信号在血管发育中调控血管内皮细胞的分化、增殖、迁移等表型，但其下游机制上不清楚。本研究探讨 Notch 信号对肿瘤血管内皮细胞的调控作用和机制。
方法 采用条件性基因修饰小鼠在内皮细胞中激活 Notch 信号或敲除 Notch 下游转录因子 RBPj；采用移植肿瘤模型观察肿瘤血管发育；单细胞测序和转录组测序观察内皮细胞命运转变；采用细胞培养和分子生物学方法探讨 Notch 调控内皮细胞的作用机制。
结果 内皮细胞特异性激活 Notch 信号并进行单细胞测序，发现 Notch 激活可以促进内皮细胞获得干细胞表型，表现为干细胞标志物和转录因子表达上升，集落性增殖能力和分化潜能增加。Notch 激活可以通过下游转录因子 Hes1 及 Hey1 下调分子伴侣蛋白 BiP，从而激活 IRE1α-XBP1 信号。XBP1 是内皮细胞向内皮干细胞转变的必要和充要条件。在培养的内皮细胞中，敲低 XBP1 或干细胞因子 Oct4，不仅抑制内皮干细胞，也降低内皮细胞向间充质相关细胞的转化。而敲除 RBPj 减少肿瘤内皮的干细胞特征。
结论 Notch 信号可以通过活化 IRE1α-XBP1 信号促进肿瘤内皮细胞转变为内皮干细胞，促进肿瘤内皮的异质性。

矮小症队列中 FBXW4 有害变异的遗传学研究

李红豆 王红艳
复旦大学附属妇产科医院

目的 矮小症是由基因变异等多种复杂原因导致的最常见的骨骼发育障碍疾病。本研究旨在从遗传学角度拓展对矮小症病因的理解，并探索其分子致病机理。
方法 建立矮小症与性别-年龄匹配的非矮小患者对照队列，进行全外显子组测序检测，对检出变异进行生物信息学分析和 Sanger 测序验证。对富集有害变异的候选目的基因进行细胞功能学验证。
结果 共募集 1046 例矮小症患者与性别年龄相匹配的对照组 592 例，在矮小症队列中富集到 5 个患者特有的 *FBXW4* 杂合错义突变（S356F, C328Y, R153H, V93M, D65E），5 个变异均使细胞内蛋白水平上调并发生堆积。使用双荧光素酶报告基因系统检测显示 *FBXW4* 为 BMP 通路靶基因，RNAseq 分析和 qPCR 验证结果显示了外源过表达 *FBXW4* 会降低Ⅸ型胶原蛋白 *COL9A2* 的表达水平，进而影响软骨发育。
结论 *FBXW4* 功能获得性有害变异可能是导致矮小症的致病原因。

先天性心脏病中 IRX4 变异位点的鉴定

彭瑞[1,2] 王红艳[1,2,3]
1.复旦大学附属妇产科医院 2.复旦大学生命科学学院 3.复旦大学代谢与整合生物学研究院

目的 先天性心脏病（Congenital heart disease, CHD）是新生儿最常见的发育异常。流行病学调查数据显示，我国 CHD 的发病率约为 8‰。 *IRX4* (*iroquois*-related homeobox)在心脏发育建立腔室的过程中发挥关键作用。本研究的目的，是在先天性心脏病病例中鉴定 *IRX4* 的变异位点。
方法 我们收集了 412 例来自山东的 CHD 病人样本和 213 例正常对照样本，使用二代测序技术对 IRX4 基因的 promoter 区、5’-UTR 区、外显子区、3’- UTR 区进行突变筛查。对于筛查到的变异位点，使用 Sanger 测序技术进行验证。后续，再进行扩大样本验证。

结果 我们在其中 6 个病例样本（其中一例 TOF）中同时鉴定到了 5 个变异位点 (deletionGCCCCCTTGCC, rs62335813, rs62335812, rs62335811, c.355C>T)，并用 Sanger 测序进行了验证。接下来，我们在 96 例样本中进行了扩大样本测序验证，结果显示，只有一例 TOF 样本同时出现了上述 5 个变异位点。因此接下来，我们在 126 例 TOF 样本中进行了 Sanger 测序验证，结果显示，没有样本同时出现上述 5 个变异。
结论 我们在 CHD 中鉴定到 *IRX4* 的 5 个变异位点，其中 4 个位于 promoter 区，1 个位于外显子区。通过扩大样本验证，这些变异位点属于稀有变异。我们的样本量不足，且这些变异位点的生物学功能还需进一步研究。

间断消融通过调控 S100A4/GDF15 表达对肝细胞癌增殖特性影响的研究

王恩铭扬
中国医科大学

目的 探究间断消融是否通过调控 S100A4/GDF15 表达影响肝细胞癌增殖特性。
方法 构建裸鼠肝癌移植瘤并应用射频消融处理肿瘤；体外加热处理肝癌 HCCLM3 细胞，转染 siRNA 或/和表达载体改变热处理细胞中 S100A4 和 GDF15 表达，CCK8 检测热处理后细胞增殖能力。Realtime-PCR 检测组织和细胞中 mRNA 表达，Western Blot 检测组织和细胞中蛋白表达。
结果 间断 60S 消融可以促进肿瘤生长，并使 S100A4 和 GDF15 表达显著增高；48℃加热处理 5min 使肝癌细胞 HCCLM3 增殖能力显著增强，细胞中 S100A4 和 GDF15 表达显著增高。沉默 S100A4 或 GDF15 可以抑制热处理细胞的过度增殖，而过表达 GDF15 可以有效逆转 S100A4 基因沉默所致的增殖抑制。
结论 不完全消融通过上调 S100A4/GDF15 表达显著促进肝癌细胞增殖。

MYORG 新突变与原发性家族性脑钙化相关

任雅琼[1] 石磊[2]
1.北京协和医学院基础医学研究所 2.哈尔滨医科大学附属第四医院

目的 原发性家族性脑钙化（Primary Familial Brain Calcification, PFBC）是一种以双侧对称性脑钙化为特征的神经退行性和神经精神疾病。本课题组收集到两例 PFBC 家系（F-01, F-02）和一例散发的患者（S），并对已知致病基因 *SLC20A2* 和 *MYORG* 进行突变筛查。
方法 采集患者以及影像学确认正常的直系血亲的外周血并提取基因组 DNA；利用 PCR 扩增 *SLC20A2* 和 *MYORG* 的全部外显子，非翻译区，以及内含子-外显子交界片段，进行 Sanger 测序分析。
结果 家系 F-01 中两个患者均携带 *MYORG* 复合杂合突变【NM_020702.5, c.877C>T, p.(His293Tyr)和 c.1270_1277delCGCTGGTG】。F-02 中先证者和散发 S，携带 *MYORG* 杂合插入突变（c.40insC）。
结论 *MYORG* 三例突变未见人群频率信息，且均为首次报道。大多 *MYORG* 突变以常染色体隐性模式遗传，但 *MYORG* 杂合突变也可导致 PFBC，提示 c.40insC 可能杂合致病。

翻译后修饰异常导致人源性 SMAD6 突变功能翻转

李铃
复旦大学

目的 SMAD6 是维持 TGF/BMP 信号通路平衡的关键负调控因子。SMAD6 在先天性心脏病、骨发育疾病和肿瘤中均被发现高频有害突变，但作用机制不明。我们从 SMAD6 的蛋白翻译后修饰入手，发现棕榈酰化等修饰对 smad6 的功能维持至关重要，，进一步阐明这些修饰异常导致 SMAD6 功能异常的机制，进而挖掘 SMAD6 突变的致病机理。
方法及结果 我们通过质谱以及生化实验检测到来源于病例（先天性心脏病，颅缝早闭等）的 SMAD6 突变蛋白较野生型发生棕榈酰化以及脱酰胺的异常。细胞实验验证修饰改变促使 SMAD6 功能翻转，从 BMP 信号通路抑制因子转变为激活因子。我们进一步发现突变 SMAD6 棕榈酰化降低，导致其细胞膜定位丧失，从而失去对 BMP 受体的结合抑制。另外，突变 SMAD6 蛋白会在进入细胞核形成三聚体形式的激活复合体，进一步激活 BMP 信号通路。
结论 我们实验证实来自先天性心脏病以及骨发育病病例的 SMAD6 突变蛋白通过调节自身的棕榈酰化修饰以及核内三聚体形成，发生功能翻转,最终导致 BMP 信号通路失衡。我们的发现解释了大量病例 smad6 突变的共同机理，对于其他遗传突变的机制研究也提供借鉴。

孤独症谱系障碍中突触相关基因 SHANK1 稀有突变的鉴定和致病性分析

秦越[1,2] 公晓红[1,2] 王红艳[1,2]
1.复旦大学附属妇产科医院 2.复旦大学生命科学学院

目的 遗传因素对孤独症谱系障碍（孤独症，ASD）发病的贡献度高达 90%，但是其遗传病因和潜在的机制尚未被完全揭示。突触异常是孤独症重要的病理生理学基础，探讨突触相关基因对于孤独症发生的贡献度有助于深入拓展对该病遗传学发生机制的理解。
方法 结合遗传分析和体外功能实验识别可解释孤独症的稀有变异，并建立基因敲入小鼠模型，通过从行为学表型到分子层面的分析来探索其潜在的致病机理。
结果 通过对 615 例病例和 503 例健康对照的基因编码区和剪切位点测序扫描， 我们首次在谷氨酸能突触相关基因 SHANK1 鉴定到 1 个孤独症病例特异的稀有（MAF < 1%）错义突变 X，导致氨基酸从脯氨酸变为赖氨酸，该突变为杂合突变，在多个人群数据库中频率小于 0.1%，分别在两个没有血缘关系的病例中出现。尽管在多个有害性预测工具中没有较高的打分，但基于原代神经元细胞的实验分析表明该突变对突触的发育有显著影响，构建了 KI 小鼠模型以进一步探索。对 X-KI 小鼠的行为学分析表明，X-KI HET 有孤独症两个核心症状，X-KI HOM 没有两个核心症状而是表现出空间学习和长期记忆受损。
结论 本研究首次在 SHANK1 基因中鉴定到一个孤独症的致病位点并证明其对核心表型有贡献。但其详细致病机制有待对脑区结构与功能以及分子基础的研究，并需进一步探索不同基因型导致不同表型的原因。

PRSS56 启动子区稀有突变导致遗传性高度近视

曾炜佳[1,2] 王红艳[1,2]
1.复旦大学附属妇产科医院 2.复旦大学生科院

目的 高度近视（HM）是一种严重的近视表型，其特征在于眼轴长度大于 26 mm 或屈光不正大于-6.00 屈光度。尽管目前已定位了 22 个近视基因座（MYP），但确切的致病基因仍有待研究。在这项研究中，我们旨在揭示 PRSS56 启动子区域突变对遗传性高度近视的影响。

方法 我们获得一个 XXX 的常染色体显性遗传的高度近视家系。通过连锁定位分析、全外显子、全基因组测序等技术确定该家系的致病位点，双荧光素酶报告基因检测突变对启动子活性的影响。进而通过 iPSC 细胞、基因编辑以及 AAV 病毒注射小鼠模型，分析突变对基因表达水平的影响以及与小鼠眼睛表型的相关性。酵母双杂交文库、蛋白质组学分析以及后续分子生物学实验揭示其潜在调节靶标。

结果 我们鉴定出位于染色体 XXX 的 PRSS56 启动子区域中的新型稀有突变。双荧光素酶报告基因检测揭示该突变可增强启动子活性。来自家系 HM 个体的 iPS 细胞系中 PRSS56 的 mRNA 水平更高。Prss56$^{KI/KI}$ 新生小鼠的 Prss56 表达水平显著上调。在第八周时，Prss56$^{KI/KI}$ 眼轴长度明显短于野生型。酵母双杂交文库的筛选和转录组分析也揭示了 PRSS56 对离子通道和微管组装方面具有潜在的调节作用。

结论 PRSS56 启动子区域中的罕见突变可能会导致常染色体显性高度近视的发生。

T 基因编码区 Q1#突变位点会导致中国人 CVM 的发生

陈淑霞 杨雪艳 王红艳
复旦大学

目的 我们此前在一个常染色体显性遗传的先天性脊柱畸形（Congenital Vertebral malformation, CVM）家系中通过连锁分析将致病区段定位于 *T* 基因，但 *T* 基因的致病机制尚待明确。本研究旨在确认 *T* 基因上 Q1#突变的致病性及明确其致病机理。

方法 采用免疫印迹实验、电泳迁移率实验、双荧光素酶报告基因系统等在细胞、分子水平进行功能验证，探究该突变是否为致病性位点。利用 CRISPR/Cas9 技术将小鼠基因组中 *T* 基因的相应位点编辑成为家系中出现的突变（Q1#），模拟疾病发生的过程。

结果 免疫印迹实验结果显示，Q1#突变不会影响 T 蛋白表达水平，但其核质比增加。电泳迁移率实验显示突变后的 T 蛋白与 NDA 的亲和力增强。双荧光素酶报告基因系统显示，与野生型的 T 蛋白相比，Q1#突变的 T 蛋白的转录活性下调。通过对 *T* 基因 Q1#突变小鼠模型的研究发现纯合突变小鼠胚胎呈现出 100%的脊柱发育异常。

结论 Q1#突变会导致 T 蛋白的功能异常，是人脊柱畸形的致病性位点。

Adenine base-editing-mediated exon skipping induces gene knockout in cultured pig cells

Xiangxing Zhu[1] Jiasheng Pan[1] Tao Lin[2] Yecheng Yang[1] Qiuyan Huang[1] Zisheng Lin[1] Jiancong Wen[1] Aifen Yan[1] Juan Feng[1] Lian Liu[1] Xiaoli Zhang[1] Jiahong Lu[3] Dongsheng Tang[1]
1.Foshan University 2.Hebei University of Engineering
3.University of Macau

Objective Gene-knockout pigs have important applications in agriculture and medicine. Compared with CRISPR/Cas9, Adenine base editor (ABE) convert single A·T pairs to G·C pairs in the genome without generating DNA double-strand breaks, and this method has higher accuracy and biosafety in pig genetic modification. However, the application of ABE in pig gene knockout is limited by protospacer-adjacent motif (PAM) sequences and the base-editing window. Alternative mRNA splicing is an important mechanism underlying the formation of proteins with diverse functions in eukaryotes. Spliceosome recognizes the conservative sequences of splice donors and acceptors in a precursor mRNA. Mutations in these conservative sequences induce exon skipping, leading to proteins with novel functions or to gene inactivation due to frameshift mutations. In this study, adenine base-editing-mediated exon skipping was used to expand the application of ABE in the generation of gene knockout pigs.

Methods and Results We first constructed a modified “all-in-one” ABE vector suitable for porcine somatic cell transfection that contained an ABE for single-base editing and an sgRNA expression cassette. The “all-in-one” ABE vector induced efficient sgRNA-dependent A-to-G conversions in

porcine cells during single base-editing of multiple endogenous gene loci. Subsequently, an ABE system was designed for single adenine editing of the conservative splice acceptor site (AG sequence at the 3' end of the intron 5) and splice donor site (GT sequence at the 5' end of the intron 6) in the porcine gene *GHR*; this method achieved highly efficient A-to-G conversion at the cellular level. Then, porcine single-cell colonies carrying a biallelic A-to-G conversion in the splice acceptor site in the intron 5 of *GHR* were generated. RT-PCR indicated exon 6 skipped at the mRNA level. Western blotting revealed GHR protein loss, and gene sequencing showed no sgRNA-dependent off-target effects. These results demonstrate accurate adenine base-editing-mediated exon skipping and gene knockout in porcine cells.
Conclusion This is the first proof-of-concept study of adenine base-editing-mediated exon skipping for gene regulation in pigs, and this work provides a new strategy for accurate and safe genetic modification of pigs for agricultural and medical applications.

采用基于学生自身体验的教学方法提高医学遗传学课堂教学质量

梁亮
空军军医大学

随着对人类基因组和人类复杂疾病的遗传机制的深入理解，越来越多的基因检测用于临床疾病的诊断、质粒和预防。这对医学遗传学课堂教学提出了新的挑战。如何让学生理解基因型和表型的关系对于医学遗传学学习至关重要。我们提出了基于学生自身体验的教学方法（student experience-based teaching, SEBT），并与基于讲座的传统教学（lecture-based teaching，LBT）在教学效果、学生反馈等多维度进行比较。结果表明：分别实施 SEBT 和 LBT 的两个五年制本科生班级虽然在多项选择题上表现出相似的结果，但在有关基因多态性和表型的简答题回答上，SEBT 班级表现出明显更好的表现。这说明在医学遗传学课堂教学实施 SEBT，可能会提高学生对基因型-表型关系的理解，从而提升医学遗传学课堂教学质量。

Insm1 基因：从功能研究到人群中突变和疾病鉴定

贾世奇
暨南大学

目的 Insulinoma associated 1 (Insm1)是一个在内分泌细胞发育和稳态维持以及神经细胞发育中特异性表达的基因。为了探讨 Insm1 对内分泌细胞功能的调控作用，我们采用 Insm1 突变小鼠（Jia et al, Dev Biol, 2015）、成体胰岛 β 细胞特异性 Insm1 突变小鼠（Jia et al, EMBO J, 2015）、Insm1 单倍体不足小鼠(Tao et al, Diabetes,2018)、Insm1 SNAG 结构域突变小鼠(Liang et al, Diabetes, 2021)等模型，开展了表型和调控机制分析；为了鉴定 INSM1 对人类疾病的贡献，我们与合作者对神经内分泌疾病患者进行了遗传筛查。
方法 采用基因敲除小鼠模型、ChIP-seq、RNAseq 以及经典细胞和分子生物学方法，对 Insm1 基因功能进行了分析；采用外显子测序方法，鉴定神经内分泌表型异常人群中 INSM1 基因突变；采用细胞、类器官以及构建人 INSM1 基因突变小鼠的方法，拟对人类 INSM1 突变基因的功能开展研究。
结果 1，Insm1 与 Neurod、Foxa2 等转录因子相互作用，结合并调控 β 细胞中重要调控序列，维持胰岛 β 细胞的成熟功能；2，Insm1 单倍体不足，导致出生后在 β 细胞基础 mass 建立期胰岛 β 细胞增殖周期延长，β 细胞基础数量减少；3，Insm1 SNAG 结构域在维持 β 细胞特性和抑制转分化发生中起调控作用；4，在德国、荷兰、土耳其裔患者中，发现了 3 种 INSM1 突变类型。
结论 我们对 Insm1 基因功能进行了深入研究，鉴定了 Insm1 是一个重要的调控神经内分泌细胞发育和功能的基因；在人群中初步鉴定了其突变可以导致人类神经内分泌疾病。

CD169+巨噬细胞在成红细胞岛中的作用和机制探讨

白健 高春辰 魏调霞 冯蕾 秦鸿雁
空军军医大学基础医学院遗传与发育生物学教研室

成红细胞岛(Erythroblastic islands, EBIs)，特指中央巨噬细胞被周围向红系终末阶段分化的成红细胞围绕成类似岛屿样的结构，是红系早期发育不可或缺的造血龛。CD169+骨髓定居的巨噬细胞对EBIs 的形成至关重要，但介导巨噬细胞与成红细胞粘附的机制尚不清楚。目前已知 EMP－EMP、VCAM-1－α4β1、αv－ICAM-4 在该过程中发挥作用，但是否还有其他粘附分子，如 CD169，参与其中有待探索。我们成功构建了 CD169-CreERT 小鼠，并利用其与 ROSA26tdTomato 小鼠交配，他莫昔芬诱导后可特异性示踪成红细胞岛中央巨噬细胞，同时骨髓定居的巨噬细胞和 BMDM 特异性表达 CD169；进一步在巨噬细胞与成红细胞体外共培养的成岛实验中观察到 CD169 抗体阻断和 CD169 敲除均可削弱体外 EBIs 的成岛能力；为了进一步探索 CD169 对应的受体，我们发现 CD169 重组蛋白可以粘附结合成红细胞，查阅文献发现 CD43 可能是 CD169 对应的受体，流式及 WB 结果证明成红细胞表达 CD43，其中 CD43 在早幼红细胞上表达最高，随着红系发育成熟的过程 CD43 表达逐渐降低，而成熟红细胞几乎不表达 CD43，进一步利用 CD43 抗体阻断成红细胞进行体外成岛观察到巨噬细胞与成红细胞的粘附发生减弱；然而，CD169 敲除小鼠静息态下骨髓中 EBIs 的形成并未受到影响，成红细胞发育以及血常规也未见明显异常，同时 CD169 敲除并不影响成红细胞岛中央巨噬细胞其他黏附分子 VCAM-1 和 αv 的表达；CD169 敲除小鼠在高海拔性红细胞增多症模型中 EBIs 形成未见减弱，血常规与对照小鼠相比也无明显差异，但骨髓中早幼红细胞和中幼红细胞的比例明显增多，而成熟红细胞的比例明显下降，提示 CD169 可能在红系应激状态下通过 CD43 促进成红细胞的分化。综上所述，巨噬细胞表达的 CD169 与成红细胞的受体 CD43 共同参与成红细胞岛的形成，同时 CD43 可作为成红细胞发育过程分群的标志物，虽然 CD169 在体内成红细胞岛形成中的作用并非必需，但 CD169 可能在红系应激状态下通过 CD43 促进成红细胞的分化。

PIGK 缺陷导致 IGD 的致病机制研究

邬玲仟[1,2] 陈新[1,2]
1.中南大学生命科学学院医学遗传学研究中心
2.医学遗传学湖南省重点实验室

目的 验证家系 PIGK 基因 c.610G>C（p.D204H）与 c.87dupT（p.I30Yfs*10）变异致病性，并进行基因型表型分析；利用斑马鱼和小鼠模型探究 PIGK 缺陷导致 GPI 缺陷病（IGD）神经系统症状的病理和分子机制。

方法 抽提家系建株淋巴细胞的总 mRNA 和总蛋白，行 qPCR 和 Wb，探究变异对转录和翻译的影响；行流式细胞术检测，分析变异对 GPI-APs 表达的影响；吗啡啉法构建 Pigk 敲降斑马鱼模型，观察 Pigk 水平与表型相关性，利用 tol-056:GFP 品系和 TUNEL 实验观察斑马鱼神经发育改变；构建 PigkWt/I30fs 和 PigkWt/D204H 小鼠模型，观察突变对子代小鼠发育的影响。

结果 PIGK 基因 c.610G>C 与 c.87dupT 杂合突变携带者 mRNA 无明显改变，蛋白分别出现不同程度下降。PIGK 基因双等位突变患者 mRNA 表达升高，蛋白较对照组下降了 50%以上。流式细胞术结果显示患者 GPI-APs 表达降低，表明 PIGK 双等位突变影响了 GPI-APs 在质膜上的锚定。Pigk 敲降斑马鱼胚胎出现严重发育缺陷，畸形率和致死率升高，并出现大量神经细胞凋亡，表明 Pigk 剂量不足影响了斑马鱼神经发育。PigkWt/I30fs 和 PigkWt/D204H 小鼠相互杂交后，纯合及复合杂合子代在 E13.5 前全部致死，表明 Pigk 对于胚胎发育必不可少。

结论 本研究首次构建了斑马鱼 Pigk 敲降和小鼠 Pigk 突变敲入疾病模型；PIGK 基因 p.D204H 变异导致与 p.I30Yfs*10 类似的功能丧失改变；斑马鱼 Pigk 剂量减少导致神经细胞凋亡；Pigk 双等位功能丧失变异导致小鼠胚胎致死。

Reduced cell invasion may be the characteristic of placental defect in pregnant women with advanced maternal age: at single-cell level

Bin Yu
Changzhou Maternal and Child Health Care Hospital affiliated to Nanjing Medical University

Background It remains unclear about the mechanisms of an increased risk of poor maternal and neonatal outcomes in advanced maternal age (AMA) women. Trophoblast cells are heterogeneous population of cells with different morphology and biological functions, and perform the distinct process essential for placentation and pregnancy. Here, we used single-cell RNA sequencing (scRNA-seq) to profile and compare the cellular signature and transcriptomes of human placeta in AMA, explored the new subtypes of trophoblast and their differentiation track. Based on the differentially expressed genes (DEGs), bioinformatic analysis and *in-vitro* experiments suggested that the decrease of cell invasion ability might be an important manifestation of placental defect. Overall, our data provides rich resource to reveal the molecular mechanism of pregnancy risk for AMA women.

Methods Four freshly cesarean section-delivered placenta tissues (2 AMA and 2 controls) were collected and dissociated into single-cell suspension. To investigate whether AMA women also have a decline in cell invasion, trophoblast cells were obtained from placentas of 6 pregnant women (3 cases of AMA and 3 of young women). 40 samples (20 AMA and 20 control) were used to further verify the specific expression of SERPINE1 in AMA women by western blot. The lentiviral vector of hSERPINE1 were constructed and transfected into HTR8-S/Vneo trophoblast cells. ScRNA-seq were loaded on the Chromium Single Cell Controller Instrument (10×Genomics) to generate single cell gel beads in emulsions (GEMs).

Results The high-quality transcriptomes of 27,607 cells (14,978 from AMA and 12,629 young) were dectected, and annotated cell clusters into nine main cell types. With the canonical marker genes, three types of trophoblast cells were detected, including VCT (7,258, 70.3%), EVT (2,333, 22.6%) and SCT (735, 7.1%). Furthermore, we classified eight subtypes of trophoblast by the differences of gene expression and Gene Ontology (GO) function, including four subtypes of VCT, two of EVT and two of SCT. These subtypes also perform different biological functions and have certain differentiation tracks. We suggested the hypothesis of trophoblast subtype differentiation trajectory. A total of 110 differentially expressed genes (DEGs) were identified (pvalue<0.05 and foldchange >2) in trophoblast cells between the AMA and control groups KEGG analysis suggested that the DEGs were enriched in multiple pathways related to cell invasion, such as ECM-receptor interaction, focal adhesion etc. After primary cell culture, *in-vitro* Transwell assay was conducted to observe the the ability of cell invasion. *SERPINE1*, an inhibitor of serine protease, is involved in cellular and replicative senescence. The results of scRNA-seq and immunohistochemistry showed that *SERPINE1* specifically expressed in trophoblast, especially in EVT. Compared with the normal prenant women, the expression of SERPINE1were increased in the placenta tissue of AMA women (P<0.05). Transfection with hSERPINE1 into HTR8-S/Vneo trophoblast cells showed that there were fewer invading cells in the hSERPINE1 group than NC group 24h after transfection.

Conclusion The understanding of placental dysfunction in AMA pregnant women is obviously insufficient. This study initially revealed the specific changes of placenta from the single cell level, found new trophoblast subtypes and development trajectory. It suggests that placental dysfunction may be the reason of increased risk of adverse pregnancy in AMA women, especially the lack of the cell invasion ability. It will contribute to provide new ideas for perinatal health management of AMA pregnant women.

初发与复发急性 B 淋巴细胞白血病儿童单核细胞 microRNA 表达谱差异

邱丽娟 世淑兰
昆明市儿童医院

为探明 B 淋巴细胞白血病（B-Acute Lymphocytic Leukemia, B-ALL）患儿初发和复发情况中单核细胞差异表达的 microRNA，本研究分离了初发 B-ALL 和复发 B-ALL 患儿及正常儿童外周血单核细胞，提取核酸进行 HiSeq 测序，获得了靶细胞的 microRNA 及 mRNA 表达水平结果。通过关联分析 microRNA 及其靶 mRNA 表达差异，筛选出在初发和复发共同出现且有别于正常组的 microRNA 和 mRNA 负相关组合，筛选出与 B-ALL 致病密切相关的 microRNA。在此基础上筛选复发组与初发组差异显著的 microRNA ，并预测与之相关的候选靶基因和信号通路。结果显示初发组 / 复发组共检出 20 个差异表达的 microRNA，其中 10 个下调，10 个上调。其中按矫正 P 值排序，差异前五位为 has-miR-30a-3p，has-miR-30a-5p，has-miR-30c-2-3p，has-miR-139-5p，has-miR-99b-5p。对候选靶基因功能富集，涉及到的蛋白功能为细胞质、细胞内组分、蛋白结合、细胞内、细胞质部分，主要为行使细胞成分和蛋白结合方面的蛋白。总的来说，针对复发是儿童急性淋巴细胞白血病（ALL）治疗难题，研究从 microRNA 水平研究儿童 ALL 在初发和复发之间的差异，为 ALL 的病理机制研究提供数据基础，以期为诊断、治疗和预后寻找新的靶点。

肿瘤微环境对胶质瘤干细胞表型的作用和机制

梁亮
空军军医大学

目的：脑胶质瘤是最常见的颅内恶性肿瘤。其中 IV 级胶质瘤、即胶质母细胞瘤恶性程度极高，缺乏有效的治疗手段，患者五年生存率极低。胶质母细胞瘤高度恶性的根本原因之一是肿瘤细胞中存在的干细胞样肿瘤细胞，即胶质瘤干细胞。既往研究提示胶质瘤干细胞可以来源于神经干细胞的基因突变；但近年来的研究也提示，肿瘤微环境因素也可以使肿瘤细胞获得干细胞表型而转变为胶质瘤干细胞。本研究探讨胶质瘤免疫微环境对胶质瘤干细胞表型的作用和机制。
方法：采用患者手术标本体外培养获得人胶质瘤细胞和胶质瘤干细胞；采用 RNA-seq 观察基因表达谱改变；用 qRT-PCR 和免疫印迹检测基因表达；采用 siRNA 转染进行基因表达的抑制；采用免疫缺陷小鼠颅内接种观察胶质瘤干细胞的体内生长。所有涉及人类标本的研究都经空军军医大学西京医院伦理委员会审查批准。
结果：来自胶质母细胞瘤患者的手术标本可在体外以原代细胞形式进行培养，并在干细胞培养条件下形成胶质瘤干细胞。用腺病毒感染培养的原代胶质瘤细胞，可促进胶质瘤干细胞的形成，表现为 tumorsphere 增多，干性标志物表达上升，干性相关转录因子上调，在免疫缺陷小鼠颅内成瘤能力增强。进一步研究发现腺病毒感染通过 TLR9 促进胶质瘤干细胞形成。TLR9 的活化促进 STAT3 磷酸化和活化，上调 NEAT1 长链非编码 RNA，促进了胶质瘤细胞的干性。此外，损伤相关分子模式（DAMP）HMGB1 也可通过 TLR2-NEAT1-Wnt 信号促进胶质瘤细胞干性，而抗胶质瘤药物替莫唑胺可以增加 HMGB1 释放促进胶质瘤干性，可能是替莫唑胺耐药的机制之一。
结论：肿瘤微环境这的固有免疫刺激物如病毒 DNA、DAMP 等，可以促进胶质瘤细胞的干性表型，参与胶质瘤的恶性进展和耐药及对其他治疗的抵抗。特异性阻断固有免疫信号可以靶向清除胶质瘤干细胞，有望成为胶质瘤治疗新靶点。

Epigenetic Age Acceleration Was Delayed in Schizophrenia

Xiaohui Wu
Southern Medical University

[Objective] Schizophrenia is a serious neuropsychiatric disorder with abnormal age-related neurodevelopmental (or neurodegenerative) trajectories. Although an accelerated aging hypothesis of schizophrenia has been proposed, the quantitative study of the disruption of the physiological trajectory caused by schizophrenia is inconclusive.
[Methods] In this study, we employed three “epigenetic clock” methods to quantify the epigenetic age of a large sample size of whole blood (1069 samples from patients with schizophrenia vs 1264 samples from unaffected controls) and brain tissues (500 samples from patients with schizophrenia vs 711 samples from unaffected controls).
[Results] We observed significant positive correlations between epigenetic age and chronological age in both blood and brain tissues from unaffected controls and patients with schizophrenia, as estimated by 3 methods. Furthermore, we observed that epigenetic age acceleration was significantly delayed in schizophrenia from the whole blood samples (aged 20–90 years) and brain frontal cortex tissues (aged 20–39 years). Intriguingly, the genes regulated by the epigenetic clock also contained schizophrenia associated genes, displaying differential expression and methylation in patients with schizophrenia and involving in the regulation of cell activation and development. These findings were further supported by the dysregulated leukocyte composition in patients with schizophrenia.
[Conclusion] Our study presents quantitative evidence for a neurodevelopmental model of schizophrenia from the perspective of a skewed “epigenetic clock.” Moreover, landmark changes in an easily accessible biological sample, blood, reveal the value of these epigenetic clock genes as peripheral biomarkers for schizophrenia

大规模遗传分析揭示女性生殖年龄与多种表型相关和预测中国女性早绝经风险

傅肖依
复旦大学

研究目的：
约 5%-10%的女性受早绝经影响，早绝经提示女性生殖期限缩短，且增加女性患心血管疾病、骨质疏松等的风险。本研究旨在发现早绝经风险位点和相关表型，探究其生物学意义，为临床甄别早绝经高风险女性提供指导。

研究方法：
基于英国及日本 Biobank 约 80,000 例已绝经女性的 SNP 基因分型芯片数据，进行绝经年龄的全基因组关联分析（GWAS）。利用孟德尔随机化模型，进一步明确绝经年龄与相关表型之间的因果关系。结合遗传与环境因素和运用机器学习方法，预测中国女性早绝经风险。

研究结果和结论：
我们分析得到了 50 个与绝经年龄显著相关的独立位点（P-Value 最高为 4.914E-81）。早绝经风险位点主要聚集在 DNA 损伤响应、DNA 修复通路中。女性绝经年龄与多项人体测量学表型，如体重、体脂、身高显著相关，且携带早绝经风险位点的个体身高偏矮及体重偏低。同时，环境因素如个体是否为母乳喂养、是否为多胞胎和母亲怀孕期间是否吸烟等指标也与绝经年龄密切相关，提示早绝经可以能是个体整体发育水平不佳所致结果之一，

LncRNA-AC006129.1 reactivates a SOCS3-mediated anti-inflammatory response through DNA methylation-mediated CIC downregulation in schizophrenia

Chaoying Ni
Southern Medical University

Objective
Schizophrenia is a complex genetic disorder, the non-Mendelian features of which are likely complicated by epigenetic factors yet to be elucidated.
Methods
we performed RNA sequencing of peripheral blood RNA from monozygotic twins discordant for schizophrenia.
Results
we identified a schizophrenia-associated upregulated long noncoding RNA (lncRNA, AC006129.1) that participates in the inflammatory response by enhancing SOCS3 and CASP1 expression in schizophrenia patients and further validated this finding in AC006129.1-overexpressing mice showing schizophrenia-related abnormal behaviors. We find that AC006129.1 binds to the promoter region of the transcriptional repressor Capicua (CIC), facilitates the interactions of DNA methyltransferases with the CIC promoter, and promotes DNA methylation-mediated CIC downregulation, thereby ameliorating CIC-induced SOCS3 and CASP1 repression. Derepression of SOCS3 enhances the anti-inflammatory response by inhibiting JAK/STAT-signaling activation.

MYCT1 通过 ADAM20 参与喉癌细胞增殖和迁移的分子机制研究

丁锶钰 孙媛媛 王悦 富伟能
中国医科大学

目的：探讨 MYCT1 通过 ADAM20 参与喉癌细胞增殖和迁移的分子机制。
方法：应用 Real-time PCR 及 Western Blot 技术检测相关基因表达水平；应用荧光素酶报告基因系统检测 miR-181a 对 ADAM20 的调控机制；应用 CCK8、克隆形成、Transwell 及细胞划痕愈合实验检测喉癌细胞增殖及迁移能力。
结果：在喉癌细胞中，MYCT1 显著上调 miR-181a 表达水平，而 MYCT1 和 miR-181a 均显著下调 ADAM20 表达水平（$p<0.05$）；miR-181a 可以与 ADAM20 的 3'UTR 直接结合；敲减 MYCT1 或 miR-181a 可以显著促进喉癌细胞增殖和迁移能力，且敲减 ADAM20 可以回复敲减 MYCT1 及 miR-181a 对喉癌增殖和迁移能力的影响（$p<0.05$）。
结论： MYCT1 通过上调 miR-181a 抑制 ADAM20 的表达水平，进而抑制喉癌细胞增殖和迁移。

基于大样本人群的汉族非综合征型唇腭裂表型分析

段世均 石冰 贾仲林
四川大学华西口腔医院

目的：了解非综合征型唇腭裂的临床表型，为其病因学研究提供理论依据。**方法：**对 2010 年 1 月至 2021 年 6 月期间在我院住院的 8399 例非综合征型唇腭裂患者临床资料进行分类整理和统计学分析。**结果：**唇裂患者 2541 例，腭裂患者 2617 例，唇裂伴腭裂患者 3241 例，男女性别比例分别为：1.27:1、1:1.67、2.19:1；唇裂患者左侧：右侧：双侧为 5.57:3.27:1，唇裂伴腭裂患者左侧：右侧：双侧为 1.62:0.94:1；在对唇部畸形亚型分析中，唇裂患者完全性：不完全性：微小型为 1:3.21:1.06，唇裂伴腭裂患者完全性：不完全性：微小型为 20.29:7.71:1；在对牙槽突裂分析中，唇裂合并牙槽突裂为 51.3%，唇裂伴腭裂合并牙槽突裂为 92.87%（P=0.000）；在对腭部畸形分

析中，腭裂患者完全性：硬软腭裂：软腭裂：腭隐裂为 1:8.13:1.19：1.08，唇裂伴腭裂患者完全性：硬软腭裂：软腭裂：腭隐裂为 93.56:7:1:4.75；在家族史分析中，唇裂伴腭裂多于唇裂及腭裂组（P=0.001）；唇裂及腭裂患者多出生于秋季，唇裂伴腭裂患者多出生于冬季（P=0.000）。结论：非综合征型唇裂及唇裂伴腭裂患者中，男性多于女性，而腭裂患者女性多于男性，唇部畸形中单侧多于双侧，以左侧为主；腭裂患者中以硬软腭裂为主，唇裂伴腭裂患者的腭部畸形中则以完全性腭裂为主；同时唇裂伴腭裂患者的牙槽突裂以及合并家族史也更为常见；非综合征型唇腭裂患者出生也存在季节差异。

Downregulation by CNNM2 of ATP5MD expression in the 10q24.32 schizophrenia-associated locus involved in impaired ATP production and neurodevelopment

Wang Zhongju Zhao Cunyou Hao Bingtao
Department of Medical Genetics, Southern Medical University

Genome-wide association studies (GWAS) have accelerated the discovery of numerous genetic variants associated with schizophrenia. However, most risk variants show a small effect size (odds ratio (OR)<1.2), suggesting that more functional risk variants remain to be identified.
We employed region-based multi-marker analysis of genomic annotation (MAGMA) to identify additional risk loci containing variants with large OR value from Psychiatry Genomics Consortium (PGC2) schizophrenia GWAS data and then employed summary-data-based mendelian randomization (SMR) to prioritize schizophrenia susceptibility genes.
The top-ranked susceptibility gene *ATP5MD*, encoding an ATP synthase membrane subunit, is observed to be downregulated in schizophrenia by the risk allele of *CNNM2*-rs1926032 in the schizophrenia-associated 10q24.32 locus. The *Atp5md* knockout in mice was associated with abnormal startle reflex and gait, and *ATP5MD* knockdown in human induced pluripotent stem cell-derived neurons disrupted the neural development and mitochondrial respiration and ATP production. Moreover, *CNNM2*-rs1926032 knockout could induce downregulation of *ATP5MD* expression and disruptions of mitochondrial respiration and ATP production.
This study constitutes an important mechanistic component that links schizophrenia-associated *CNNM2* regions to disruption in energy adenosine system modulation and neuronal function by long-distance chromatin domain downregulation of *ATP5MD*. This pathogenic mechanism provides therapeutic implications for schizophrenia.

46,XX,der(5)t(5;15)(p13.3;p11.1)dmat 生长发育落后一例

郑杰梅
四川大学华西第二医院

目的 父母是平衡易位携带者，在生育下一代时建议进一步做产前诊断。
方法 抽取患儿及父母外周血样本进行淋巴细胞培养，高分辨染色体制备，G 显带，分析 20 个中期分裂相，并对 5 个分裂相进行核型分析；患儿外周血染色体微阵列检测。
结果 患儿母亲细胞遗传学染色体核型结果为 46,XX,t(5;15)(p13.3;p11.1)，见图 1；父亲染色体核型结果为 46,XY。患儿染色体核型结果为：46,XX,der(5)t(5;15)(p13.3;p11.1)dmat，见图 2；患儿染色体微阵列检测结果为 arr[GRCh38]5p15.33p13.3（113462_31967280)x1 (31854kb)。
讨论 两条非同源染色体间的平衡易位是最常见的染色体结构畸变，平衡易位患者在生育下一代时容易导致生化妊娠、早期流产、死胎、死产、生育智力、体格低下患儿。该患儿母亲为 5 号与 15 号染色体平衡易位携带者，由于无遗传物质的丢失，其表型和智力正常。平衡易位携带者在减数分裂联会期间形成四射体结构，为了保证同源染色体的充分配对，将会发生多种分离形式，导致多种配子的产生。传统教科书上常写的是形成 18 种配子（远远不止），其中 1/18 为正常，1/18 为表型正常携带者，其余 16/18 为不平衡配子，不平衡配子与正常配子受精后，形成部分三体，部分单体

或单体并三体，不能正常发育，将会在妊娠早期流产。部分存活单体或三体患儿大多将会发生相应的临床表现。患儿母亲易位的 5 号染色体遗传给患儿，而另一条易位的 15 号染色体未遗传给患儿，导致患儿的染色体易位不平衡。从患儿的核型图可以看出，5 号染色体的短臂缺失，为部分单体，15 号染色体短臂 p11.1 至随体部分易位到 5 号染色体短臂处。由于染色体微阵列检测的探针不涉及随体部分，所以只检测出 5 号染色体短臂 p15.33 到 p13.3 的缺失。5 号染色体短臂的缺失部分涵盖猫叫综合征的关键区域[a1]，患儿的相关临床表现也符合猫叫综合征。平衡易位携带者在生育下一代时，建议进一步做产前诊断。

Rs1260326 associated with the risk of NAFLD through triglyceride levels in elderly Chinese Han population

Fan Yuan
Shanghai Jiao Tong University

Introduction and Aims Accumulated studies pointed out the strikingly associated between variants in or near *APOC3*, *GCKR*, *PNPLA3* and nonalcoholic fatty liver disease (NAFLD) at various different age from multiple ethnic groups. But it remained unclear in the Chinese Han elderly population, as well as whether this relationship correlated to some clinical parameters. In this study, we aim to decipher the complex relevance between gene polymorphisms, clinical parameters and NAFLD.
Methods Eight snps (rs2854116, rs2854117, rs780093, rs780094, rs1260362, rs738409, rs2294918 and rs2281135) within *APOC3*, *GCKR* and *PNPLA3* were genotyped in 733 eldery Chinese Han NAFLD patients and 824 age- and ethnic-matched controls. Association and mediation analysis were employed by R.
Results The genotypic frequencies of rs1260326 and rs780094 were significantly different between NAFLD and control (rs1260326: P=0.004, P_{corr}=0.020, OR [95%CI]= 0.69 [0.54-0.89]; rs780094: P=0.005, P_{corr}=0.025, OR [95%CI]= 0.70 [0.55-0.90]). Particularly, an increaesd triglyceride level was observed in carriers of rs1260326 T allele (1.94±1.19 mmol/L) compared with non-carriers (1.73±1.05 mmol/L). Notably, we highlighted that approximately 12.7% of the rs1260326 effect on NAFLD was mediated through triglyceride levels.
Conclusions Our results identified a relationship between *GCKR* rs1260326 and NAFLD, which may be mediated through triglyceride levels in the Chinese Han elderly.

氧化应激在男性不育病因中的遗传学特性

陈贺
南昌大学第二附属医院

尽管男性不育症的患病率很高，但对其病因知之甚少。然而，近年来，基因测序技术的进步使我们能够通过精子发生的内分泌调节到生殖细胞分化和精子功能，识别出大量罕见的单点突变，这些突变负责从胚胎起源阻碍男性生殖的各个方面。氧化应激也已成为男性生育的主要原因，至少 40%的患者表现出一些氧化还原攻击的证据，导致高水平的脂质过氧化和 8-羟基-2'-脱氧鸟苷形式的氧化性 DNA 损伤。8OHdG)。后者具有高度致突变性，可能导致我们物种的从头突变，其中 75%已知发生在雄性种系中。对人类精子基因组中 8OHdG 病变的检查显示，约有 9,000 个基因组区域容易受到精子氧化攻击。虽然这些氧化碱基通常广泛分布在整个基因组中，但 15 号染色体上的特定区域似乎是氧化攻击的热点。该基因座映射到一个遗传位置，该位置与男性不育、癌症、印迹障碍和各种行为状况（自闭症、双相情感障碍、自发性精神分裂症）有关，这些状况与受孕时父亲的年龄有关。我们提出了一个假设，即许多环境、生活方式和临床因素共同诱导雄性生殖系中的氧化性 DNA 损伤，然后触发从头突变的形成，这可能对后代的健康产生重大影响，包括随后的生育能力。

单基因病植入前遗传学检测阻断遗传性多发性骨软骨瘤垂直遗传

偶健
苏州市立医院本部

目的 遗传性多发性骨软骨瘤是以软骨化骨形成障碍、多发骨软骨瘤为特征的一种常染色体显性遗传病，12 岁前发病者约 96%-100%，需行手术进行肿瘤切除。多发性骨软骨瘤虽然多为良性，然而由于骨软骨瘤生长造成骨骼畸形，会导致躯体疼痛，给患者生理和心理产生很大负面影响。本文探讨采用二代测序技术（NGS）对遗传性多发性骨软骨瘤(HMO)家系行胚胎植入前遗传学检测(PGT)阻断其垂直遗传。
方法 针对突变位点涉及的 EXT1 基因及基因的上下游区域内选择高密度紧密连锁的单核苷酸多态（SNP）作为遗传标记。二代测序（NGS）后，选择若干有效位点进行单体型分析。最后使用单体型连锁分析技术进行单基因病植入前遗传学检测（PGT-M）。
结果 先证者携带 EXT1 基因（NM_000127.2）c.1645delC 杂合突变，先证者母亲、弟弟、舅舅及舅舅的儿子均为患者且有同样突变。通过单体型连锁分析先证者及其母亲之后行 PGT-M，形成 11 枚囊胚，检测结果显示未携带突变的整倍体囊胚 6 枚、携带突变的致病囊胚 3 枚、非整倍体囊胚 2 枚。将 1 枚未携带突变的整倍体囊胚行冻融胚胎移植后获得临床妊娠，产前诊断羊水结果显示未见基因和染色体异常，足月自然分娩一正常女婴，体重 3450g，健康状况良好。
结论 PGT-M 技术在该家系中成功阻断了由 EXT1 基因突变所致的 HMO 在家族中的传递，也为其他遗传性肿瘤家族中有生育需求的携带者提供了新的选择。

Healthy pregnancy from mosaic embryos with lower mtDNA content

Jian Ou
Suzhou Municipal Hospital

Background There is a risk of misdiagnosis during preimplantation genetic testing due to the presence of mosaicism in the embryo. The purpose of this study is to investigate whether the mitochondrial DNA (mtDNA) content can reflect the real state of mosaic embryos.
Materials and methods The study included 1669 blastocysts derived from 394 PGT-A cycles between January 2018 and December 2020 in which , preimplantation genetic testing for aneuploidy was performed and mtDNA content was determined. Standard deviation (SD) of whole genomic sequencing data were calculated for quality control. mtDNA content is measured as proportion of mtDNA in genomic DNA. 1558 blastocysts with SD value less than 4.0 and mtDNA value less than 0.4 were selected for statistical analysis.
Results It was found that the mtDNA content of PGT mosaic group was significantly higher than that of PGT normal group ($P < 0.05$). A total of 16 mosaic embryos were transferred, and the results are as follows: 2 out of 16 had undergone spontaneous abortion , 7 embryos were not pregnant, and 7 resulted in live birth. There was significant difference in mtDNA content between the miscarriage/non-pregnancy group and the live birth group ($P < 0.05$).
Conclusions Our study suggested that the mtDNA content could indicate the clinical outcomes of PGT-A cycle. The amount of mtDNA was lower in PGT normal group compared to PGT abnormal group. It is also indicated that the embryos with lower mtDNA content may be more likely to have real normal PGT-A results according to the pregnancy outcome of PGT mosaic embryos. Therefore, it can be considered as a supplementary method for the selection of mosaic embryos for transfer in the future.

Identification and interruption of cryptic translocation in families

Jian Ou
Suzhou Municipal Hospital

Background Cryptic translocation can be found in the genetic analysis of aborted tissues or malformed infants, but it is difficult to deduce the parent origin of the translocation. If the origin cannot be determined, it is hard to distinguish the translocated embryos from real normal embryos in preimplantation genetic testing, so as to block the transmission of translocation in the family. In this paper, a new method to detect cryptic translocation of chromosome and to block its transmission in the family is discussed.
Materials and methods The whole genome low coverage pairing sequencing (WGL-MPS) and crossover PCR were used to provide chromosome breakpoint sequence accurately, and then haplotype preimplantation genetic testing (PGH) was used to provide translocation blocking service for couples with cryptic translocation in the process of embryo selection.
Results The cryptic translocation was found in four families by WGL-MPS, and PGH was used to block the translocation embryos in two of them.
Conclusions WGL-MPS method combined with crossover PCR and PGH is a powerful and practical method, which can identify the source of cryptic translocation and block its transmission in the family.

miR-548ag promotes the occurrence and development of obesity-associated endometrial cancer by targeting inhibition of MOB1B

Huai Pang[1] Jun Zhang[2] Bingqi Yang[1] Zhongge Pan[1] Jianyu Xiong[1] Xiaolong Chu[1] Xin Yang[1] Chenggang Yuan[1] Cuizhe Wang[2]
1.Shihezi University School of Medicine
2.Department of Genetics, School of Medicine, Shihezi University

Objectives Obesity is a high risk factor for the development of Endometrial Cancer (EC). miR-548ag was significantly overexpressed in the serum of obese individuals, and bioinformatics analysis showed that the survival rate of EC patients with high miR-548ag expression was significantly reduced. Clarifying the role of miR-548ag overexpression in the occurrence and development of EC and its possible molecular mechanism will provide experimental data and theoretical basis for the early diagnosis of obesity-related EC and the screening of drug targets for clinical treatment.
Methods (1) qRT-PCR was applied to detect the expression of miR-548ag in serum of subjects. (2) The downstream target genes and binding sites of miR-548ag were predicted by bioinformatics, and verified by dual luciferase reporter assay. The protein expression levels of target genes and downstream factors in EC tissues were detected by immunohistochemistry. (3) miR-548ag mimic and miR-548ag inhibitor were constructed and transfected into EC cell line Ishikawa, then Cell Counting Kit-8 (CCK-8) assay, Colony Formation assay, Wound Healing assay and Transwell assay were used to detect cell proliferation, invasion and migration ability, respectively. The mRNA and protein expression levels of target genes and downstream factors were detected by qRT-PCR and Western blot. (4) The constructed overexpressed plasmid of downstream target gene was transfected into Ishikawa cells and the downstream target gene was up-regulated after transfection with miR-548ag mimic, then the proliferation, invasion and migration of Ishikawa cells were detected by CCK-8, Colony Formation assay, Wound Healing assay and Transwell assay.
Results (1) miR-548ag was highly expressed in the serum of the subjects, which was positively correlated with BMI and negatively correlated with the prognosis of the subjects; (2) Bioinformatics prediction and dual luciferase reporter gene assay indicated that the downstream

target gene of miR-548ag might be MOB1B; (3) The protein expression level of MOB1B was significantly decreased in the EC tissues of the subjects, and was significantly and positively correlated with the prognosis of the subjects. The up-regulation of miR-548ag significantly promoted the proliferation, invasion and migration ability of Ishikawa cells, while the down-regulation of miR-548ag significantly inhibited the proliferation, invasion and migration ability of Ishikawa cells. miR-548ag up-regulation significantly inhibited the mRNA and protein expression of MOB1B, while the mRNA and protein expression levels of CCND1 and XIAP were significantly increased. The down-regulation of miR-548ag significantly promoted the mRNA and protein expression of MOB1B, while the mRNA and protein expression levels of CCND1 and XIAP were significantly decreased. (4) The up-regulation of MOB1B in Ishikawa cells significantly inhibited the proliferation, invasion and migration of cells, and significantly reversed the carcinogenesis of miR-548ag. (5) miR-548ag can inactivate the Hippo pathway by inhibiting the expression of MOB1B, promoting the mRNA and protein expressions of CCND1 and XIAP.
Conclusion The increased expression of miR-548ag can promote the occurrence and development of obesity-related EC by inhibiting the expression of MOB1B.

赖氨酸巴豆酰化修饰的研究进展

王威 戴勇
深圳市人民医院

目的 赖氨酸巴豆酰化作为一种新型的蛋白质翻译后修饰方式，调控许多重要的生命活动。但目前缺乏一个全面的综述。
方法 本文对该修饰近年来相关的文献进行了全面的分析和讨论，梳理并总结了赖氨酸巴豆酰化修饰的研究进展。
结果 赖氨酸巴豆酰化修饰的功能和作用范围越来越广泛，已经突破了物种的局限，相关的科学研究也已从组蛋白上的发现及其调控作用，扩大到了众多疾病的研究报道。
结论 赖氨酸巴豆酰化修饰作为当下的研究热点，具有重要的科学意义。并且该修饰可以作为未来研究和治疗相关疾病等的重要方向。

Effect of curcumin on biological characteristics and EXPRESSION of YES related protein 1 in A549 lung cancer cells

Yao Xu[1,2] Fengxiang Wei[1,2]
1.Longgang District Maternal and child Healthy Care Hospital
2.Jiamusi University

Objective To investigate the effect of curcumin on the proliferation, apoptosis, migration and expression of YES related protein 1 (YAP1) in A549 lung cancer cells.
Methods CCK8 was used to detect IC50 concentration of curcumin on A549 cells.The A549 lung cancer cells were treated with curcumin at 10, 20 and 40 umol/L (Cur10, Cur20 and Cur40 groups), and the effects of curcumin on the proliferation, apoptosis and migration of A549 cells were detected by CCK-8, flow cytometry and Transwell assay.Western Blot was used to detect the effect of curcumin on YAP1 protein expression. **Results** After curcumin treatment, the proliferation ability of Cur10, Cur20 and Cur40 cells was significantly lower than that of BC group (P<0.05), the proliferation inhibition rate and apoptosis rate were gradually increased, and the migration ability was gradually decreased in a dose-dependent manner (P<0.05);Compared with the control group, the expression level of YAP1 protein in the Cur10, Cur20 and Cur40 groups was significantly lower than that in the Cur10 group and Cur40 was significantly lower than that in the Cur20 group, and the differences were statistically significant (P<0.05).

Conclusion Curcumin can inhibit the proliferation and migration of A549 lung cancer cells in a dose-dependent manner and promote their apoptosis, which may be related to the inhibition of YAP1 protein.

Effect of dihydroartemisinin synergistic knockdown of DSG2 gene on the biological characteristics of human cervical cancer (Hela) cell

Yanan Liu[1,2] Fengxiang Wei[1,2] Tong Zhang[1,2] Guoqiang Zhao[1,2]
1.Longgang District Maternity&Child Healthcare Hospital of Shenzhen City
2.JIAMUSI UNIVERSITY

Purpose The purpose of this study is to explore the effect of dihydroartemisinin synergistic knockdown of DSG2 gene on hela cells and the related molecular mechanism, provide new information for the clinical treatment of cervical cancer hela cell proliferation and growth, metastasis and invasion, etc. Potential therapeutic drugs, and provides new potential therapeutic drugs for the clinical treatment of cervical cancer hela cell proliferation, growth, metastasis and invasion, as well as provides theoretical support for basic research for follow-up animal experiments and pre-clinical research.
Methods Over-expressing hela cells, low-expressing hela cells, unloaded hela cells were treated with dihydroartemisinin (DHA).We design 6 experimental groups:
Experimental group 1: DSG2 overexpression + dihydroartemisinin
Experimental group 2: DSG2 knockdown + dihydroartemisinin
Experimental group 3: DSG2 blank control (no drug treatment) + dihydroartemisinin
Control group 1: DSG2 overexpression
Control group 2: DSG2 knockdown
Control group 3: DSG2 blank control (no drug treatment)
Cellular immunofluorescence experiment was used to identify the expression of DSG2 gene in each group of cells; the CCK8 method was used to detect the effects of DSG2 and dihydroartemisinin on the survival rate of hela cells; western blot was used to detect the correlation between DSG2 and dihydroartemisinin on hela cell apoptosis and EMT The influence of the pathway; cell cloning experiment to detect the influence of DSG2 and dihydroartemisinin on the proliferation of hela cells; monostratal wound healing test and transwell assay evaluate the effects of DSG2 and dihydroartemisinin on the migration and invasion ability of hela cells; flow cytometry measures the effects of DSG2 and dihydroartemisinin on the cell cycle of hela. In addition, all analyzed data uses chi-square test and Fisher's exact test, t-test or analysis of variance is used to evaluate the statistical significance of the difference between the experimental group and the control group. $P<0.05$ is considered to be statistically significant, and "*" represents $P<0.05$, "**" represents $P<0.01$, "***" represents $P<0.001$, and "****" represents $P<0.0001$.
Results Dihydroartemisinin (DHA) synergistically with low expression of DSG2 can inhibit the growth of hela cells and reduce the survival rate of cells. Further research found that dihydroartemisinin (DHA) can significantly induce apoptosis of hela cells. Through mechanism exploration, it is found that in hela cells, DHA can inhibit cell migration and invasion by regulating the expression of EMT-related proteins and DNA damage-related proteins. **Conclusion**: Dihydroartemisinin synergistically with low expression of DSG2 has a certain inhibitory effect on the occurrence and development of cervical cancer. It has broad clinical application prospects and can be used as a new prevention and treatment weapon for cervical cancer in the future.

BMI1 reduces ETOP-induced DSB damage in breast cancer cell line MCF7 by down-regulating VEGFA-VEGFR2-ERK signaling pathway

Yao Xu[1,2] Fengxiang Wei[1,2]
1.Longgang District Maternal and Child Health Care Hospital of Shenzhen City, Guangdong Province
2.Jiamusi University

Background Breast cancer is the most common aggressive tumor in women, and its incidence is increasing year by year. In breast cancer, genomic instability is a major feature, and tumor suppressor genes usually form an important anti-tumor barrier by regulating DNA damage response (DDR). In the DNA damage reaction, because of the double-stranded DNA breaks (DSBs) associated with the deletion of DNA fragments and the instability of the genome, it also became the most serious DNA damage in cells. At present, although studies have proved that the apoptosis of MCF7 breast cancer cells induced by etoposide (ETOP) is related to the down-regulation of BMI1 gene expression, the specific mechanism is still unclear.
Objective To investigate the BMI1 gene-related signaling pathway and its differential genes in DSB damage of MCF7 in breast cancer, and to find the specific binding site of BMI1 gene in this signaling pathway.
Methods MCF7 cell lines were constructed with BMI1 overexpression, P-Babe no-load, HT and NLS mutants knocked out. Cck-8 assay was used to detect IC50 of MCF7 cells induced by ETOP and DDR damage model. The ability of migration and proliferation of breast cancer cells was evaluated by Transwell migration and cell scratch assay. QPCR whole gene sequencing was used for differential gene screening and pathway enrichment analysis. Finally, vegfa-vegfr2-erk was qualitatively verified by westernblot.
Conclusion The results suggest that BMI1 can reduce ETOP-induced DSB damage in breast cancer cells MCF7 by down-regulating VEGFa/VEGFR2/ERK signaling pathway.

1 个遗传性掌趾角化病家系致病基因探索

魏彬 孙淼 鲁礼魁
苏州大学附属第一医院

目的 遗传性掌跖角化病是一种以手掌和脚掌角化过度增厚为特征的多种角化疾病，可以通过常染色体显性或隐性方式遗传。本研究通过连锁定位分析结合高通量测序技术，在遗传性掌趾角化家系中寻找致病基因。
方法 本研究收集了一 3 代以上的常染色体显性遗传的掌跖角化病家系，其中 6 名患者。提取家系成员外周血 DNA 和相关皮肤科临床资料；利用 Sanger 测序法验证已报道相关致病基因与遗传候选位点；Affymetrix 的 CytoScan HD 芯片检测患者 CNV；对家系成员样本进行全外显子组测序分析,获得的数据进行生物信息学分析,寻找可能的致病突变。
结果 临床分析提示该家系属于弥漫性非表皮松解性掌趾角化，未发现已知致病基因 KRT1、KRT9、KRT6C、AQP5、GJB2 编码区突变；未发现致病性 CNV；全外显子组测序结合患者共享区域分析，发现染色体 1、5、6、10、12 上可能存在新的候选基因位点，其中包括 Chr12 上大量 KRT 同源基因所在区域。
结论 遗传性掌趾角化可能存在新的致病基因或者与非编码调控有关。

Transcription factors, lncRNAs, and miRNAs associated with CYP3A gene expression in human liver and small intestine assessed with weighted gene co-expression network analysis

Huina Huang Xiaozhen Wen Siqi Zhang Siyao Yang Liang Li
Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University

Purpose CYP3A4, CYP3A5, and CYP3A7 play crucial roles in the metabolism of drugs in clinical use. To identify interactions between transcription factors (TFs), long noncoding RNAs (lncRNAs), and microRNAs (miRNAs) involved in the regulation of *CYP3A* expression in liver and small intestine.
Methods We used weighted gene co-expression network analysis (WGCNA) to analyze GTEx v8 RNA expression data, either mRNAs alone or including lncRNAs and microRNAs. GeneCards, JASPAR, PROMO, miRDB, TargetScan, and starBase databases served to predict TFs that potentially bind to promoter or enhancer regions of *CYP3A*s. A multiple stepwise regression analysis was performed between gene TPMs of TFs, lncRNAs and miRNAs and *CYP3A*s.
Results A series of TFs and lncRNAs were significantly associated with *CYP3A* expression in liver and small intestine. The regulatory mode of CYP3A expression in liver and small intestine may be different, and different TFs and ncRNAs are involved in this process.
Conclusion Our analyses provide a framework for future functional studies of possible CYP3A gene associated TFs, lncRNAs, and miRNAs.

一例因 CD40LG 基因半合子突变导致的 X-连锁高 IgM 综合征报道

王玉国 刘刚 马定远 许争峰
南京市妇幼保健院

目的 X-连锁高 IgM 综合征（X-linked hyper immunoglobulin M syndrome; XHIM）是由 Xq26 染色体上 CD40LG 基因突变引起的一种罕见的免疫缺陷病，其特征在于血清 IgM 水平正常或升高，并伴有 IgG，IgA 和 IgE 显着降低，从而导致对细菌感染的高度易感性和对机会性感染的易感性增加。XHIM 患者也倾向于中性粒细胞减少以及胃肠道和中枢神经系统感染的高发生率，通常导致严重的肝脏疾病和/或神经退行性变。CD40LG 基因位于 Xq26.3-27，长 13kb，由 5 个外显子和 4 个内含子组成。CD40LG 与 B 细胞上 CD40 结合产生记忆 B 细胞，促进 IgM 转化为 IgG, IgA 或 IgE。T 细胞通过 CD40LG 与巨噬细胞和树突状细胞 CD40 结合，可诱导其分泌 IL-12，形成对细胞内微生物的免疫应答。CD40LG 基因突变后，导致 T 细胞依赖抗原的再次免疫应答障碍。因此，患者易发生细菌、卡氏肺囊虫和隐孢子虫感染。本文描述了一例疑似 X-连锁高 IgM 综合征 3 岁男孩，该患者在 CD40LG 基因上被检出半合子突变而被诊断为 X-连锁高 IgM 综合征。
方法 针对该患者及其母亲的 CD40LG 基因，使用 WES 测序技术和 real time PCR 技术等进行分子研究。
结果 在该患者中检测到存在 NM_000074.3(CD40LG_v001):c.50_60del, p.Leu17Hisfs*28，半合子型突变。其母亲存在相同位点的突变，为杂合突变携带者。
结论 CD40LG 基因 c.50_60del, p.Leu17Hisfs*28 突变致使氨基酸发生了移码突变，可导致 CD40LG 基因不能正常编码功能蛋白。WES 检测可以提高患者突变的检出率，使检测结果更准确。

Mechanism research of neural crest cell migration involved in the pathogenesis of neural tube defects using 3D organoids

Haiqin Huo Xiaozuo Zhang Ping Hu Zhengfeng Xu
Women's Hospital of Nanjing Medical University

AIMS The detailed mechanism of human neural tube defects (NTDs) with polygenic inheritance still remains unknown in most cases. The neural crest cell migration deficit in the early neurulation was involved with neural tube closure failure and therefore played a role in NTDs.
METHOD Recently, a large body of work has been made to elicit tissue and organ biology in 3D organogenesis. The reconstitution of neural tube so far has been described as the generation of neuroepithelium in 3D culture from human pluripotent stem cells (hPSCs), which is often a mixture of several rosettes. Furthermore, the contribution of inhomogeneous neuroepithelium secreting signaling molecules could also not hardly be excluded in the present induction system. Here, we would like to present an optimized method that can induce neural tube formation from hPSCs by defined under certain conditions under induction system. Strikingly, neural tube reconstituted in vitro can pose the process of elongation, folding and closure.
In our study, neural tube organoids were generated from human pluripotent stem cells, facilitating a human model for researching NTDs. Morphometric analysis of NTDs organoids and neural tube organoids was performed to compare the developmental events, especially neural crest cell migration.
RESULTS We found a decreased migration capacity of the neural crest cells and neural tube closure failure in NTDs organoids. By using specific inhibitors, we show that the neural crest cells in early development is specified by signaling molecules including Rho-associated kinase (ROCK). And ROCK inhibitors could mitigate the neural crest cell migration deficit and neural tube closure failure in vitro.
CONCLUSION We proposed a reliable approach tohave induced hPSCs to neural tube-like structures, at least in the in vitro context. The dynamic developmental progress of the neural tube, shown here, was unanticipated at the begaining. Following the formation of the neuroepithelium layer, we found that the structure organoid tended to elongate, fold, and close in a manner mimicking in vivo development, termed as primary neurulation. Following After the closure, the neural tube was promoted to generate subdivisions of the early brain. So far, little is known about cellular and molecular mechanisms of neurulation in human. Thus, detailed studies are needed to determine discover the precise mechanisms that, if disrupted, would cause the neural tube to fail to close, an event that results in neural tube defects. Overall, our method provides novel insight into human early neurodevelopment.

一例巨轴索神经病家系的致病基因位点分析

曾华沙 马定远 罗春玉 张菁菁 刘安 李璃 胡平 许争峰
南京市妇幼保健院

目的 采集该巨轴索神经病患儿病史及临床资料，对其家系可能的致病基因突变进行检测，对基因突变位点的序列和致病性进行鉴定。
方法 提取患儿及父母外周血 DNA 样本， Sanger 测序验证家系成员的突变情况；生物信息学分析突变位点蛋白结构及功能的改变；评估基因突变位点的致病性。
结果 患儿表现为走路不稳，下蹲后自行站立较困难，肌电诱发电位示：多发性周围神经源性损害电生理改变（运动，感觉神经轴索损害伴轻度脱髓鞘改变，以双下肢为著）。外单位全外显子测序检测到巨轴突蛋白基因 *GAN*（NM_022041.3, c.809G>T,p.Gly270Val,het; c.1139G>A,p.Gly380Glu,het.）突变，这两个突变位点在数据库和文献中均未有记录，在相同的氨基酸位点，文献记录有 c.808G>A（Gly270Ser）突变。Sanger 测序显示：患儿母亲携带 c.809G>T 突变，杂合型，患儿父亲携带 c.1139G>A,p.Gly380Glu 突变，杂合型；生物信息学分析

发现，这两个突变位点均为致病性。根据 ACMG 标准，评估 c.809G>T 突变为可能致病性突变，评估 c.1139G>A 为临床意义未明的突变。
结论 *GAN* 基因（NM_022041.3）c.809G>T/c.1139G>A 复合杂合突变影响了巨轴突蛋白的结构及其功能可能是该患儿巨轴索神经病的发病原因。

A capillary electrophoresis-based multiplex PCR assay for expanded carrier screening in the eastern Han Chinese population

Jianxin Tan Binbin Shao Ping Hu Zhengfeng Xu
Nanjing Maternity and Child Health Care Hospital

Objectives Expanded carrier screening, a type of reproductive genetic testing for couples, has gained tremendous popularity for assessing the risk of passing on certain genetic conditions to offspring.
Methods Here, a carrier screening assay for 448 pathogenic variants was developed using capillary electrophoresis-based multiplex PCR technology.
Results The capillary electrophoresis-based multiplex PCR assay achieved a sensitivity, specificity, and accuracy of 97.4%, 100%, and 99.6%, respectively in detecting the specific variants. Among the 1,915 couples (3,830 individuals), 708 individuals (18.5%) were identified as carriers for at least one condition. Of the 708 carriers, 633 (89.4%) were heterozygous for one condition, 71 (10.0%) for two disorders, 3 (0.4%) for three disorders, and 1 (0.1%) for four disorders. Meanwhile, 30 (1.57%) couples were identified as at‐risk couples.
Conclusions This study describes an inexpensive and effective method for expanded carrier screening. The simplicity and accuracy of this approach will facilitate the clinical implementation of expanded carrier screening.

宁夏大学生瘦体组织成分与基础代谢率的相关性分析

党洁[1,2] 刘秋君[1,2] 张静[1,2] 杨梦怡[1,2] 贾维[1,2] 李帆[1,2] 马占兵[1,2] 霍正浩[1,2]
1.宁夏医科大学医学遗传学与细胞生物学系
2.宁夏医科大学 生育力保持教育部重点实验室

目的 分析宁夏大学生七项瘦体组织成分指标与基础代谢率（BMR）的相关性。
方法 随机选取 741 名在校大学生（男性 364 名，女性 377 名）作为研究对象，采用 InBody BSM370 体成分仪测试受试者体重、身高、身体总水分、细胞内液、细胞外液、蛋白含量、无机盐含量、骨骼肌含量、Inbody Score 及 BMR 值的分布。应用回归分析法研究各项瘦体组织成分指标与基础代谢率之间的相关关系，并计算出回归方程系数。
结果 男性大学生身高、体重及各项体成分指标均显著高于女大学生（P<0.05）；男性回族大学生除体重、Inbody Score 显著高于男性汉族大学生外，其他指标在两者间均无显著性差异；女性回族大学生仅有 Inbody Score 显著高于女性汉族大学生（P<0.05）；回归分析显示，七项瘦体组织指标在男、女大学生间均显示与 BMR 呈明显正相关（P<0.05）。
结论 宁夏大学生瘦体组织成分存在显著性别差异。各项体成分指标均与 BMR 呈正相关，体成分指标高者，BMR 更高。

3D Genome Contributes to MHC-II Neoantigen Prediction

Mofan Feng
Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Shanghai Jiao Tong University

Reliable and ultra-fast DNA and RNA sequencing have been achieved with the emergence of high-throughput sequencing technology. When combining the results of DNA and RNA sequencing for tumor cells of cancer patients, neoantigens that potentially stimulate the immune response of either $CD4^+$ or $CD8^+$ T cells can be identified. However, due to the abundance of somatic mutations and the high polymorphic nature of human leukocyte antigen (HLA) it is challenging to accurately predict the neoantigens. Moreover, comparing to HLA-I presented peptides, the HLA-II presented peptides are more variable in length, making the prediction of HLA-II loaded neoantigens even harder. A number of computational approaches have been proposed to address this issue but none of them considers the DNA origin of the neoantigens from the perspective of 3D genome. Here we investigate the DNA origins of the immune-positive and non-negative HLA-II neoantigens in the context of 3D genome and discovered that the chromatin 3D architecture plays an important role in more effective HLA-II neoantigen prediction. We believe that the 3D genome information will help to increase the precision of HLA-II neoantigen discovery and eventually benefit precision and personalized medicine in cancer immunotherapy.

Upregulation of DGCR8, a Candidate Predisposing to Schizophrenia in Han Chinese, Contributes to Phenotypic Deficits and Neuronal Migration Delay

Yan Bi
Shanghai Jiao Tong University

Objective Digeorge Syndrome Critical Region Gene 8 (*DGCR8*) is a key component of the microprocessor complex governing the maturation of most microRNAs, some of which participate in schizophrenia and neural development. Previous studies have found that the 22q11.2 locus, containing *DGCR8*, confers a risk of schizophrenia. However, the role of *DGCR8* in schizophrenia and the early stage of neural development has remained unknown. In the present study, we try to identify the role of *DGCR8* in schizophrenia from human samples and animal model.
Methods In this study, we attempted to determine the role of DGCR8 in schizophrenia from human sample association analysis as well as embryonic and adult animal models.
Results We found that the G allele and GG genotype of rs3757 in *DGCR8* conferred higher risk of schizophrenia, which likely resulted from higher expression of DGCR8 according to our test of dual-luciferase reporter system. Employed overexpression model in utero and adult mice, we also revealed that the aberrant increase of Dgcr8 delayed neuronal migration during embryological development and consequently triggered abnormal behaviors seen in human schizophrenia.
Conclusion Together, these results demonstrate that *DGCR8* may play a role in the etiology of schizophrenia through regulating neural development.

基于三代测序的原因不明发育迟缓患者全基因组结构变异系统分析

黄明涛 王亚 乔凤昌 王艳 季修庆 胡平 许争峰
南京市妇幼保健院

背景 结构变异是基因组变异的重要组成部分，众多遗传病是由染色体结构变异所引起。三代测序具有长读长和无 GC 偏好性的优势，能够有效克服二代测序鉴定结构变异的不足。本研究使用三代测序技术对原因不明发育迟缓患者进行分析，研究其结构变异整体情况，以期阐明结构变异在遗传病中的作用。
方法 本研究收集了四例原因不明发育迟缓患者外周血样本，采用牛津纳米孔技术进行全基因组三代测序。对患者测序数据进行结构变异鉴定，并筛选具有潜在致病性的结构变异。对潜在致病结构变异影响的基因进行功能注释和通路富集分析，探讨其可能发挥的功能。
结果 本研究中四例样本平均测序深度为 13.5×，平均测序读长为 14Kb，平均每个患者可以鉴定到 19,332 个结构变异。四例患者共发现 16,773 个非重复结构变异，仅 36.08%为已知的基因组结构变异。其中 5,862 个结构变异在至少两例患者中存在且在正常人数据库中未发现，定义为潜在致病结构变异。通路富集结果显示，潜在致病结构变异影响的基因显著富集于发育迟缓相关通路。
结论 本研究系统性地分析了原因不明发育迟缓患者中结构变异情况，并为结构变异在遗传病中的作用提供了新的见解，有助于促进遗传病筛查和诊断的发展。

Exercise and diet intervention altered DNA methylation of potassium voltage-gated channel subfamily Q member 1 in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Na Wu[1,3] Siran Yue[2] Fan Yuan[1,3] Fengyan Jiang[2] Decheng Ren[1,3] Liangjie Liu[1,3] Yan Bi[1,3] Zhenming Guo[1,3] Lei Ji[1,3] Ke Han[1,3] Xiao Yang[1,3] Mofan Feng[1,3] Kai Su[1,3] Fengping Yang[1,3] Xi Wu[1,3] Ruirui Wang[2] Shenglong Le[4] Baocheng Liu[2] Yi Shi[1,3] Guang He[1,3]
1.Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Shanghai Jiao Tong University, Shanghai, China
2.Shanghai Innovation Center of Traditional Chinese Medicine Health Service, Shanghai University of Traditional Chinese Medicine, Shanghai, China
3.Shanghai Key Laboratory of Psychotic Disorders, and Brain Science and Technology Research Center, Shanghai Jiao Tong University, Shanghai, China
4.Exercise Translational Medicine Center, Shanghai Center for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, China

Background Lifestyle interventions are cornerstones of nonalcoholic fatty liver disease (NAFLD) management, and differential DNA methylation of potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*) was involved in NAFLD-related diseases. However, little is known about DNA methylation mechanism of *KCNQ1* underling the effect of lifestyle interventions on the most common liver disease.
Objective This study aimed to investigate the role of DNA methylation of *KCNQ1* in NAFLD and nonalcoholic steatohepatitis (NASH) after lifestyle intervention.
Methods 32 NAFLD women aged 50–65 were selected and partitioned into four groups, i.e., exercise (Ex, n = 8), low carbohydrate diet (LCD, n = 8), exercise plus diet intervention (ELCD, n = 9) and no intervention groups (No, n = 7) according to the liver fat content change. EPIC assay was used to quantify the methylation of genomic DNA from blood in these NAFLD patients. *ChAMP* package in R program was used to select the cytosine-guanine dinucleotides locating in promoters for subsequent analyses (False discovery rate (FDR) < 0.05, $|\Delta\beta| \geq 0.1$). Differentially methylated genes according to 3D genome from human embryonic stem cell were further clustered with k-means clustering method and analyzed by Kyoto encyclopedia of genes and

genomes pathway enrichment to select the candidate genes responding to the intervention. EpiTYPER and quantitative real time polymerase chain reaction were used to quantify DNA methylation and mRNA expression of *KCNQ1* in NASH mice after exercise, low fat diet (LFD), and exercise plus low fat diet (ELFD) intervention.
Results Hypo-methylation in promoter region of *KCNQ1* was observed after LCD and ELCD intervention in blood of NAFLD patients (FDR < 0.05, $|\Delta\beta| \geq 0.1$). Low DNA methylation and high mRNA expression of *KCNQ1* were validated in liver of NASH mice in response to ELFD ($p < 0.05$).
Conclusions The study reinforced the role of DNA methylation in regulating gene expression of *KCNQ1* in response to ELFD intervention, and highlighted the DNA methylation of *KCNQ1* in NAFLD blood could be a biomarker to mimic epigenetic signature cross tissues, i.e., liver in NASH. All these results contribute to elucidate the molecular mechanisms underlying the activities of DNA methylation in NAFLD.

泛素结合酶 E2C 通过特异性结合 β-微管蛋白参与调控肝细胞癌进展

刘梦 黄金凤 肖邦 朱怡卿 陈美婷 王芳
海军军医大学

目的 筛选泛素结合酶 E2C（UBE2C）的底物蛋白，并探讨其在肝细胞癌进展中的作用。
方法 构建 带有 Halotag 标签的 UBE2C 过表达质粒，将 UBE2C 与 Halotag 在人高转移肝癌细胞系 HCCLM3 中融合表达，通过 Halolink 树脂沉淀 UBE2C 结合的底物蛋白，并联合 SDS-PAGE 和质谱对底物蛋白进行鉴定。在人肝癌细胞系 Huh7 中过表达 UBE2C，通过 qRT-PCR、蛋白质印迹分析和细胞免疫荧光实验检测 UBE2C 过表达对其底物蛋白表达的 影响，利用细胞核质分离结合蛋白质印迹分析及 TOP flash/FOP flash 荧光素酶报告基因实验检测 UBE2C 过表达对 Wnt 信号通路的影响，并进一步通过 qRT-PCR 和蛋白质印迹分析验证 UBE2C 过表达对 Wnt 信号通路下游基因表达 的影响。
结果 Halotag 共沉淀产物经 SDS-PAGE 和银染后所获得差异条带的质谱鉴定结果显示，β- 微管蛋白 是 UBE2C 结合的底物蛋白。与对照组相比，过表达 UBE2C 降低了 Huh7 细胞中 β- 微管蛋白在蛋白水平的表达 （P＜0.01），但对其在 mRNA 水平的表达没有影响（P＞0.05）。同时，过表达 UBE2C 促进了 β-链蛋白入核（P＜0.05）， 提高了 TOP flash/FOP flash 荧光素酶活性（P＜0.01），增强了 Wnt 信号通路下游基因 JNK、细胞周期蛋白 D1 和基质 金属蛋白酶 7 的表达（P 均＜0.05）。
结论 UBE2C 通过特异性结合 β- 微管蛋白降低肝癌细胞中 β- 微管蛋白水平， 从而提高 Wnt 信号通路活性，促进其下游基因表达，进而参与调控肝细胞癌的进展。

The Emerging Role of Fatty Acid Synthase in Hypoxia-induced Pulmonary Hypertensive Mouse Energy Metabolism

Cuilan Hou Sirui Song Tingting Xiao
Shanghai Children's Hospital, Shanghai Jiaotong University

Aims This study aimed to examine whether fatty acid synthase (*FAS*) can regulate mitochondrial function in hypoxia-induced pulmonary arterial hypertension (PAH) and its related mechanism.
Methods Chronic HyOA-induced PAH mice. Transmission electron microscopy (TEM) was used to analyse mitochondria morphology and Agilent Seahorse XF Cell Mito Stress Test Kits to test mitochondria function. Mitochondria were extracted to test its related mechanism.
Results The expression of *FAS* significantly increased in the lung tissue of mice with hypoxia-induced PAH, and its pharmacological inhibition by C75 ameliorated right ventricle cardiac

function as revealed by echocardiographic analysis. Based on transmission electron microscopy and Seahorse assays, the mitochondrial function of mice with hypoxia was abnormal but was partially reversed after C75 injection. *In vitro* studies also showed an increase in the expression of *FAS* in hypoxia-induced human pulmonary artery smooth muscle cells (HPASMCs), which could be attenuated by *FAS* shRNA as well as C75 treatment. Meanwhile, C75 treatment reversed hypoxia-induced oxidative stress and activated *PI3K/AKT* signaling. ShRNA-mediated inhibition of *FAS* reduced its expression and oxidative stress levels and improved mitochondrial respiratory capacity and ATP levels of hypoxia-induced HPASMCs.
Conclusions Inhibition of *FAS* plays a crucial role in shielding mice from hypoxia-induced PAH, which was partially achieved through the activation of *PI3K/AKT* signaling, indicating that the inhibition of *FAS* may provide a potential future direction for reversing PAH in humans.

miRNA-144-3p 在早发性卵巢功能不全中的作用和机制研究

刘梦 黄金凤 肖邦 朱怡卿 陈美婷 王芳
海军军医大学

目的 早发性卵巢功能不全（POI）或卵巢早衰（POF）是一种女性在青春期后、40 岁以前发生的以闭经、卵巢萎缩、性活动减退和生育能力下降为特征的卵巢功能障碍性疾病。POI 的病因尚未明确。
方法 我们利用顺铂诱导，构建了小鼠 POI 模型，通过分离、提取并鉴定 POI 组和对照组小鼠的卵巢颗粒细胞，进行 mRNA 表达谱和 miRNA 芯片检测，筛选 POI 小鼠颗粒细胞中差异表达的 miRNAs 和 mRNAs，并对这些差异 miRNAs 进行目的基因预测及通路分析。
结果 我们发现 POI 组小鼠较对照组体重显著减轻（$P<0.05$），卵巢体积减小，ELISA 结果显示 E2 水平显著降低（$P<0.05$），FSH 水平显著增高（$P<0.05$），HE 结果提示卵巢间质严重纤维化，免疫组化结果显示卵巢颗粒细胞凋亡增加，卵泡计数发现始基卵泡、初级卵泡、次级卵泡和窦卵泡数均显著减少（$P<0.05$），以上结果表明造模成功。芯片检测结果显示，miRNA-144-3p 在 POI 小鼠卵巢颗粒细胞中显著下调表达。
结论 成功构建了 POI 小鼠模型，筛选得到了在 POI 小鼠颗粒细胞中显著下调表达的 miRNA-144-3p，为进一步通过生物信息学分析研究其对 POI 发生发展过程的影响奠定了基础。

基于精神疾病新发变异知识库构建遗传解读方案

王卫娣[1] 郭思佳[2] 镇旭阳[2] 宋炜宸[1] 王晗[3] 林关宁[1,2]
1.上海市精神卫生中心
2.上海交通大学生物医学工程学院
3.东北师范大学信息科学与技术学院

目的 在众多的神经精神发育性疾病的遗传研究中，新发变异(*De novo* variants, DNVs)是导致严重精神障碍的关键遗传因素，而如何从遗传上充分解读新发变异则是一个重要研究。随着高通量测序技术渐趋成熟，基于家系研究已鉴定识别了大量的神经精神疾病新发变异，并已报道了相关的突变解析注释来了解这些变异在基因及生物体内的影响。课题组一直致力于构建完善的精神疾病新发变异知识库（NeuroPsychiatric Mutation Knowledge Base，PsyMuKB），并初步已完成了基于转录本水平的注解。注重从蛋白功能层面理解变异的生物学功能，可以实现对新发变异的遗传影响解读。
方法 基于前期完成的数据基础，我们进一步收集齐备更新的公开报道文献及数据库来源的神经精神疾病新发变异数据，通过双人互检核对方式进行临床信息校验，确保数据真实可靠；同步整合已发布的注释内容，集成大规模组学数据，保留前期构建的一个包含全方位解析转录和翻译注释信息，可识别可变剪接转录本特异性；针对未见报道的新发变异，增加突变的生物功能层面注释，同时聚焦在基因功能来解析变异可能造成的功能缺失；参考 ACMG/AMP 2015 对遗传性位点的致病

性解读，设定评分规范及标准；另外，纳入变异对基因编码蛋白的结构域及互作蛋白功能的深度预测模型评分，以实现在功能通路上检测异常。
结果 当前已发布的 PsyMuKB 是一个多层次、多维度探索新发变异的综合资源平台,可用于识别组织特异性相关的变异；本研究则更加侧重于进一步关联疾病风险基因注释、基因所在分子通路与发病机理探索的知识库。目前可通过 http://psymukb.net 免费访问知识库查看已发布信息。
结论 PsyMuKB 包含了多方位多层次注释的转录和翻译的新发突变集合，提供了功能齐全的可视化界面，能够识别有组织特异性转录本的新发突变。课题组正通过不断优化更新，并整合对用户更有帮助的组学数据，着重体现临床遗传解读时效，并不断提升和完善临床解读方案体系。

A novel heterozygous missense variant of ARID4A gene identified in Han Chinese patient-sibling schizophrenia families that interferes with DNA-binding activity

Decheng Ren
Shanghai Jiao Tong Univeristy

Schizophrenia is a severe psychiatric disorder that has a profound impact on the individual and society. The cause of schizophrenia is still unclear. In this study, Two patient-sibling SCZ families were selected from the mental disease Biobank of Bio-X institutes. Whole-exome sequencing was performed for two families. We found the *ARID4A* c.C1231G (NM_002892.4,) was associated with the SCZ. p.His411Asp is located at the C-terminal of the ARID4A ARID domain. Despite many functional studies of *ARID4A*, less structural data is available for the ARID domains, which is crucial to fully understand the structural mechanism of its repression activity. In order to study the function of the *ARID4A* p.His411Asp variant, we determined the crystal structure of the tandem PWWP-ARID domain of ARID4A. The result indicated that the structure of the p.His411Asp ARID domain was looser than that of wild type, and the loose structure affected the binding of double-stranded DNA. The p.His411Asp mutation reduced the cells arrested in G0-G1 phase and made more cells enter G2-M phase. In addition, the missense mutation promoted the proliferation of HEK293T cells and SH-SY5Y cells. In conclusion, we identified a possible pathogenic mutation on the *ARID4A* gene in schizophrenia families. And *ARID4A* p.His411Asp can cause conformational changes of the ARID domain, affect DNA binding function, and then interfere with cell cycle arrest in G1 phase. Our findings will contribute to an in-depth understanding of the role of *ARID4A* gene in SCZ.

紫外吸收剂和胎儿宫内生长发育及不良出生结局的研究进展

姚瑶 魏凤香
深圳市龙岗区妇幼保健院

孕妇妊娠期是极其敏感的时期，这一时期的环境暴露对胎儿的生长发育乃至成人以后的生长都有至关重要的影响。当前随着社会经济的发展，环境污染严重，环境内分泌干扰物暴露和胎儿窗口期的发展是当前的研究热点。当前，我国南方城市孕妇可能存在紫外吸收剂暴露要远高于我国其他地区孕妇的情况。因此，需要对南方孕妇紫外吸收剂暴露和其胎儿出生结局的相关性开展科学研究。本综述分析了近年来紫外吸收剂和胎儿宫内生长发育的国内外研究进展。综述引用文献 37 篇。

绝缘子 EACBE 对 Tcrd 基因 V(D)J 重排的影响

朱永常
郑州大学，郑州大学人民医院，河南省遗传性疾病功能基因组重点实验室，河南省医学遗传研究所

目的 T 和 B 淋巴细胞在发育过程中通过 V(D)J 重排产生高度多样的抗原受体，抗原受体的多样性是淋巴细胞识别外源病原体微生物的基础。染色质的空间组织调节抗原受体基因的重排，然而具体机制还不清楚。本研究旨在探讨 Tcra/d 基因座增强子 Eα 的 CTCF 和 cohesin 结合位点（EACBE）对 *Tcrd* 基因重排的影响及其机制。
方法 以 EACBE 敲除和野生型 C57/B6 小鼠为实验动物，通过 HTGTS 和 5'RACE 技术检测 *Tcrd* 和 *Tcra* 基因免疫组库的变化；通过 RT-qPCR 和非交联 ChIP 检测胸腺 DN 细胞中 EACBE 对 *Tcrd* 基因表观遗传的影响；通过 3C-HTGTS 技术检测胸腺 DN 细胞中 *Tcrd* 基因的空间相互作用的变化；通过 RT-qPCR 检测胸腺 DN 细胞中 EACBE 对其下游基因表达的影响。
结果 EACBE 对 Tcrd 的重排具有调控作用，促进近端 Vδ 的使用；EACBE 也通过影响 Tcrd 的重排而影响 Tcra 的重排；EACBE 敲除不影响 *Tcrd* 基因的表观遗传； EACBE 缺失使近端 Vδ 与 Dδ/Jδ 的相互作用减少， EACBE 上下游的相互作用增加；EACBE 敲除减少 Eα 与其下游基因的相互作用，但其下游基因的表达不受影响。
结论 EACBE 对维持 Tcrd 抗原受体基因免疫组库的多样性具有重要作用。EACBE 通过维持 Dδ 基因区与近端 Vδ 基因片段之间的相互作用，促进 Tcrd 的正常重排。

Developmental angiogenesis requires the mitochondrial phenylalanyl-tRNA synthetase

bowen li Yuanming Wu
Air Force Medical University

Background and aims Mitochondrial aminoacyl-tRNA synthetases (mtARSs) catalyze the binding of specific amino acids to their cognate tRNAs and play an essential role in the synthesis of proteins encoded by mitochondrial DNA. Defects in mtARSs have been linked to human diseases, but their tissue-specific pathophysiology remains elusive. Mitochondrial phenylalanyl-tRNA synthetase, encoded by the nuclear gene *FARS2*, catalyzes the recognition and binding of Phe and mt-tRNA^{Phe} in mitochondria. Mutations in the *FARS2* gene are associated with central nervous system diseases such as autosomal recessive spastic paraplegia, epileptic encephalopathy, and infantile mitochondrial Alpers encephalopathy. In addition, our group reported that a missense homozygous mutation (c.424 G>T (p.D142Y)) in the *FARS2* gene was the underlying cause of hereditary spastic paraplegia in a Chinese family. Because CNS disorders are recognized as the major manifestations of *FARS2* gene mutations, previous research into the potential molecular mechanisms involved in the pathogenicity of these mutations has focused on the CNS, and little is known about their effects on the cardiovascular system. Here, we examined the role of mitochondrial phenylalanyl-tRNA synthetase (FARS2) in developmental angiogenesis and its potential contribution to the pathogenesis of cardiovascular disease.
Methods Morpholinos were injected into fertilized zebrafish ova to establish an *in vivo fars2* knock-down model. Visualization of the vasculature was achieved by using *Tg (fli1: EGFP)* ^{y1} transgenic zebrafish. In addition, small interference RNAs (siRNAs) were transferred into human umbilical vein endothelial cells (HUVECs) to establish an *in vitro FARS2* knock-down model. Cell motility, proliferation, and tubulogenesis were determined using scratch-wound CCK8, transwell-based migration, and tube formation assays. In addition, mitochondria- and non-mitochondria-related respiration were evaluated using a Seahorse XF24 analyzer and flow cytometry assays. The expression levels of transcripts and proteins were performed using qRT-PCR and western blotting, respectively.
Results Knock-down of *fars2* hampered embryonic development in zebrafish and delayed formation of the vasculature in *Tg (fli1: EGFP)* ^{y1} transgenic zebrafish. In addition, siRNA-

mediated knock-down of *FARS2* impaired angiogenesis in HUVECs, as indicated by decreased cell motility and tube formation capacity. Knock-down of *FARS2* also produced variable decreases in mitochondrial- and non-mitochondrial respiration in HUVECs, and disrupted the regulatory pathways of angiogenesis in both HUVECs and zebrafish.
Conclusion Our current work offers novel insights into angiogenesis defects and cardiovascular diseases induced by *FARS2* deficiency.

姜黄素对电离辐射诱导的雄性小鼠生殖系统损伤的保护作用及其相关机制研究

黄金凤 朱怡卿 肖邦 陈美婷 王芳
中国人民解放军海军军医大学医学遗传学教研室

目的 男性生殖能力下降是导致不孕不育的重要因素，而电离辐射对男性生殖系统会造成损伤。研究证实氧化应激在电离辐射诱导的男性生殖系统损伤中起着关键作用。姜黄素，作为一种从传统中药中提取的化合物，已被证明具有抗肿瘤、抗炎症、抗氧化等多种生物活性。然而，姜黄素是否能够在电离辐射诱导的男性生殖系统损伤中发挥保护作用尚未有报道。在本课题中，我们主要研究了姜黄素在电离辐射诱导的雄性小鼠生殖损伤中的防护作用及其可能的机制。
方法 本课题使用 GC-2 小鼠精母细胞株作为细胞模型；8 周龄的 BALB/c 雄性小鼠作为动物模型，30 只小鼠随机分为正常对照组、羟甲基纤维素钠对照组、2Gy 电离辐射处理组、4Gy 电离辐射处理组、6Gy 电离辐射处理组、4Gy 电离辐射处理组+40mg/Kg 姜黄素组 6 组，采取灌胃的方式连续喂养小鼠姜黄素悬浮液 8 周后，进行不同剂量电离辐射一次性照射处理小鼠或细胞。然后分别对辐射后的细胞和小鼠睾丸组织，进行细胞活力、细胞凋亡、线粒体膜电位、ROS、MDA、GSH 检测，以及小鼠睾丸称重、精子计数、HE 染色组织切片、免疫组化等各种检测。
结果 与未辐射的正常小鼠对比，经电离辐射后的小鼠睾丸重量及附睾尾部精子浓度出现显著降低，HE 染色显示其睾丸组织正常结构受损。电离辐射处理后小鼠 GC-2 细胞活力下降、凋亡率增加。辐射后小鼠睾丸及小鼠精母细胞内 caspase-3 蛋白水平均升高。而口服姜黄素可显著提高辐射后小鼠睾丸附睾尾部精子浓度，降低睾丸组织内生精细胞的凋亡，改善线粒体膜电位及氧化应激损伤。进一步的研究表明，姜黄素预处理可以显著增加精母细胞及小鼠睾丸组织内的 Nrf2 蛋白水平，激活 Nrf-2/HO-1 信号通路，促进 Nrf2 从胞浆向胞核内的转移。而在 GC-2 细胞中对 Nrf2 基因进行干扰后显著降低了姜黄素对精母细胞的保护作用。
结论 姜黄素能够在电离辐射诱导的雄性小鼠生殖系统损伤中发挥保护作用，其作用机制可能是通过调控 Nrf-2/HO-1 抗氧化信号通路维持机体氧化应激状态平衡有关。

Research progress of correlation between premature rupture of membranes and MMPs gene polymorphism

Yingyao Tan Fengxiang Wei
Longgang Maternal and Child Health Hospital

Because of the influence of the social environmental factors, especially the opening of the two-child policy and the three-child policy, the elderly maternal also will increase, leading to the incidence of preterm birth also increased year by year. At the same time, perinatal morbidity, mortality and sequelae problem caused by preterm birth has also become a very serious medical and health problem. In perinatal death, 50%-70% is associated with preterm birth. With the development of medical technology, the survival rate of premature infants has increased, but the incidence of very low birth weight infants, cerebral palsy and other diseases has increased year by year, and some children can't walk independently, language development delay or hearing loss are even found in the later stage. These nervous system diseases caused by premature birth will cause heavy economic and social burden to the children’s families. Therefore, it is necessary to clarify the risk factors of preterm birth, and give early prevention, in order to improve the quality

of China's birth population, reduce the social and economic burden brought by the effective method.
Premature rupture of membranes (Premature rupture of membrane, PROM) refers to the naturally occurring membranes rupture before labor, and the incidence of the disease in recent years has a tendency to increase. The occurrence of PROM is related to many factors. The incidence of PROM in black is higher than whites. In addition, the prevalence of PROM was higher among people who smoked, has adverse pregnancy history, carried sexually transmitted diseases, and had lower socioeconomic status. At present, the etiology of PROM more tend to environmental and genetic interaction results. At the genetic level, it has been found in recent years that the polymorphism of matrix metalloproteinases (MMPs) genes involved in regulating the expression of inflammatory cytokines, fetal membrane surface lead to weakening membranes become thinner, resulting in the happening of the PROM. Therefore, the study of the etiology and pathogenesis of PROM helps to provide a scientific basis for the prevention, risk assessment and treatment of PROM.

Research on the Efficacy of Limonene Against Human Adenovirus Type 3

Yingyao Tan[1] Fengxiang Wei[1] Leon Lee Zhou[2] Chu nuo Chu[3]
1.Shenzhen Longgang Maternal and Child Health Hospital
2.Shenzhen Middle School
3.Shenzhen Foreign Languages School

Objective To explore the inhibitory effect of the anti-adenovirus drug Limonene on adenoviruses and the underlying mechanism.
Methods Cytopathogenic effect inhibition assay and MTT(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay were performed to assess the inhibitory effect of Limonene on Human Adenoviruses Type 3(ADV3). Morphological changes of ADV3 after directly interacting with Limonene were observed using an atomic force microscope. The effect of Limonene on ADV3 in the adsorption stage was assessed using a laser confocal microscope.
Results The results suggest that limonene functions by inhibiting it from entering cells, thus manifesting as the direct inactivation of the virus and the protective effect on cells.
Conclusion Limonene has an anti-adenovirus effect, which provides scientific references for developing natural, high-efficiency and low-toxic anti-adenovirus drugs.

P4-ATPase 的 β 亚基缺失影响骨骼肌再生

孙宽祥 [1,2]
1.电子科技大学
2.四川省人民医院

目的 卫星细胞又称为骨骼肌干细胞，是一类未分化并能够完成自我更新的单核细胞，正常情况下处于静息状态，当机体的肌肉组织出现损伤时，卫星细胞被激活并迅速增殖分化，形成新的肌纤维，最终完成肌肉组织的修复。磷脂酰丝氨酸（PS）不对称分布在真核细胞质膜中，该不对称分布是依靠磷脂酰丝氨酸翻转酶（P4-ATPase）完成的，P4-ATPase 能将 PS 从膜中脂质双层的外部小叶运输到内部小叶，以维持 PS 不对称性，这对于细胞的生物活性是至关重要的。P4-ATPase 能够发挥正常的功能，其 β 亚基 Tmem30a 是必不可少的。目前已有研究证明 *Tmem30a* 在体内多个组织中发挥着重要的作用，其中 *Tmem30a* 对视网膜的视锥细胞以及双极细胞的生存至关重要；在小鼠视网膜血管形成中，*Tmem30a* 的缺失抑制 VEGF 诱导的信号传导而导致内皮细胞增殖减少，最终导致视网膜血管发育受阻；*Tmem30a* 缺失导致小脑浦肯野细胞退化；在肝脏中，由于 BS 转运蛋白的定位错误，*Tmem30a* 缺乏导致肝内胆汁淤积。近期有日本科学家研究发现，

ATP11A 和 TMEM30A 组成的复合体是控制肌管形成的分子开关，但 *Tmem30a* 在骨骼肌再生过程中的机制尚缺乏研究。

方法 *Tmem30a*$^{LoxP/LoxP}$ 小鼠与 Pax7-Cre^{ER} 小鼠杂交，得到在卫星细胞中特异性敲除 *Tmem30a* 的小鼠。通过基因分型筛选小鼠，Tamoxifen 诱导 Cre 表达。小鼠出生后连续两个月记录小鼠的体重。取 10 周年龄的小鼠，$BaCl_2$ 注射胫骨前肌造成骨骼肌损伤，分别取损伤后 1、3、5、7、10、14、21 天不同时间的小鼠胫骨前肌进行实验，HE 染色和天狼星红染色观察骨骼肌再生过程的病理变化，免疫组化观察骨骼肌再生过程 Mark 蛋白的表达变化。

结果 本研究发现在卫星细胞特异性敲除 *Tmem30a*，小鼠出生后的两个月，cKO 和 WT 小鼠体重并无明显差异，从而间接排除在卫星细胞中敲除 *Tmem30a* 对肌肉发育的影响。但在骨骼肌损伤后，HE 结果显示 cKO 小鼠卫星细胞的数目和直接均少于小于 WT 小鼠。cKO 小鼠的 Mark 蛋白 Pax7、MYH3、MYOG、MYOD 的表达均少于 WT 小鼠。

结论 卫星细胞特异性敲除 *Tmem30a* 减缓了骨骼肌再生蛋白的表达，从而延迟了骨骼肌的再生速度，说明 *Tmem30a* 在骨骼肌再生过程卫星细胞的增殖和分化中扮演着重要的角色。

病毒来源小干扰 RNA 提供跨代免疫保护的遗传机制研究

任严新
河南省人民医院

目的 哺乳动物在抵抗病毒感染时所产生的免疫效应分子不仅可以为个体提供持久性的免疫保护，而且特定类型的分子还可以通过胎盘或者哺乳等方式传递给子代。已有研究显示 RNA 干扰在哺乳动物抗病毒感染中发挥免疫保护功效，但其是否同样可以跨代遗传介导免疫保护以及内在的分子机制尚不清楚。

方法 出生后 6-8 天 BALB/c 乳鼠经腹腔注射感染 NoV DB2（抗病毒 RNA 干扰抑制子蛋白 B2 缺陷的野田村病毒），同时设置无病毒注射组做对照。待性成熟后进行组内和组间交配。所产乳鼠设置正常哺乳组（产仔母鼠进行哺乳）和交叉哺乳组（非产仔母鼠进行哺乳），并在出生后 6-8 天进行致死剂量野生型 NoV 攻毒，记录乳鼠死亡情况。同时，对母鼠乳汁进行小 RNA 高通量测序，鉴定病毒来源小干扰 RNA 特征。

结果 无病毒注射组组内交配所产乳鼠经致死剂量野生型 NoV 攻毒后全部死亡；NoV DB2 注射组组内交配所产乳鼠则全部存活。组间交配结果显示，无论公鼠有无预先经 NoV DB2 暴露，只有当母鼠预先经 NoV DB2 暴露后，所产子代乳鼠才可豁免于致死剂量野生型 NoV 攻毒。此外，实验组母鼠所产子代经对照组母鼠哺乳后，经致死剂量野生型 NoV 攻毒后全部死亡；而对照组母鼠所产子代经实验组母鼠哺乳后，则全部存活。采集实验鼠母鼠乳汁，提取总 RNA 后进行小 RNA 高通量测序，发现有特征性的病毒来源小干扰 RNA 存在。

结论 病毒感染过程中产生的特征性病毒来源小干扰 RNA，可经哺乳进入子代体内并可能参与介导了子代的免疫保护功效。

河南汉族人群 22 个 STR 基因座的突变观察与分析

康冰
河南省人民医院

目的 观察和分析 22 个常染色体 STR 基因座在河南地区汉族人群亲子鉴定案例中的突变现象及规律，并探讨该复合扩增系统在亲子鉴定中的应用价值。

方法 应用直接扩增法对 22 个常染色体 STR 基因座进行荧光标记复核扩增 PCR，扩增产物用 3500Dx 遗传分析仪进行电泳分析，并用 Genemapper ID-X 软件进行基因分型。收集 1060 例亲子鉴定案件进行 STR 基因座突变规律的研究。

结果 1060 例亲子鉴定案例中三联体 539 例，二联体 521 例；排除 38 例（3.58%）；认定案例 1022 例（96.42%）。观察到 22 例突变案例共发生 23 次突变，其中一步突变占 95.7%，两步突变

占 4.3%；其中父源突变 17 例，母源突变 3 例，父母双向突变 2 例，父源突变与母源突变的比例约为 6：1。

结论 STR 基因座突变是一种较为常见的遗传现象，通过对突变案例的观察分析，能够为法医物证学亲子鉴定 STR 基因座的选择提供有效的理论支撑，避免突变对鉴定结论的干扰以保证鉴定结果的客观准确。22 个常染色体 STR 基因座复核扩增分型系统在河南汉族群体中具有较低的突变率，可满足日常亲子鉴定的需要以及河南汉族群体的亲子鉴定、个体识别以及 DNA 数据库建设。

Functional analysis of a novel RUNX2 gene variant identified in a patient with cleidocranial dysplasia

Jie Zheng[1] Yang Liu[1] Jianbo Shu[1,2,3] Xiaowei Xu[1,2,3] Chunquan Cai[1,2,3]
1.Tianjin Children's Hospital/ Tianjin University Children's Hospital
2.Tianjin Pediatric Research Institute
3.Tianjin Key Laboratory of Birth Defects for Prevention and Treatment

Background Cleidocranial Dysostosis (CCD) is a rare autosomal dominant hereditary disease caused by variants of Runt-related transcription factor 2 (*RUNX2*) gene. The main manifestations of CCD include open or delayed closure of the cranial sutures, dysplastic or aplastic clavicles and tooth dysplasia. In this study, we identified a novel variant of *RUNX2* in a CCD patient and explore the pathogenic nature of the novel variant.
Methods Proband underwent whole exome sequencing to identify potential variants. Sanger sequencing was performed to confirm the variant. In silico analysis were used to predict the pathogenicity of novel variant and the changes in protein structure. The effect of this variant on RUNX2 protein was studied by transient overexpression in HEK-293 cells. Subsequently, we performed the western blot to analyze the protein expression level, qRT-PCR assay for mRNA level of bone-related genes, cycloheximide chase assay for protein stability and immunofluorescence for protein subcellular localization.
Results A novel heterozygous variant of *RUNX2* c.539C>A (p.Ala180Glu) was identified in the proband but was absent from proband's parents. In silico analysis showed that the novel variant was putatively pathogenic. The results of qRT-PCR showed that mRNA expression of BMP2, BGLAP, COL1A1, OPN, SMAD1, SMAD8, WNT3A, IHH and MMP13 were decreased in the *RUNX2*-A180E group compared with the wild type, which suggested that the variant downregulated the associated markers of intramembranous and endochondral osteogenesis. The cycloheximide chase assay revealed that the novel variant decreased protein stability. The results of immunofluorescence showed that the novel variant altered nuclear localization of RUNX2, and ultimately reduced maturation and differentiation of osteoblasts.
Conclusions Our study identified a novel A180E variant of *RUNX2*, presented cellular evidence that the variant impairs RUNX2 protein function causing CCD, enriched the spectrum of *RUNX2* variants and validated its pathogenic effects.

The association of rs9362054 with diabetic retinopathy in Chinese population

Huijuan Xu[1] Huan Li[2]
1.chengdu biology of institute, chinese academy of science
2.Sichuan Academy of Medical Sciences & Sichuan Provincial People' S Hospital, University of Electronic Science and Technology of China

Purpose Identification the genetic susceptibility factors of diabetic retinopathy (DR) is of great significance to understand the pathogenesis of DR, and may help to identify the genetic risk factors for DR. This study aims to to identify DR susceptibility loci in Chinese Han population.
Methods A total of 381 patients with diabetic retinopathy (DR), and 476 patients with type 2 diabetic mellitus without retinopathy (DM) controls were recruited in this study. Single-nucleotide

polymorphisms (SNPs) for rs9362054 near the CEP162 gene were genotyped by Mass ARRAY MALDI-TOF system. The genotype and allele frequencies were evaluated using the χ2 tests. Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated for the risk of genotypes and alleles.

Results There was a statistically significant difference for SNPs rs9362054 near the CEP162 gene between DR cases and controls in the allelic model (P = 0.027, OR = 1.26, 95% CI = 1.03-1.54). The T allele frequency of this polymorphism was 0.360 in the DR cases, whereas it was 0.309 in controls, suggesting a risk effect for DR. SNP rs9362054 had a significant association with DR in the dominant model (P=0.031, OR=1.35, 95%CI = 1.03-1.77), indicating that the TT/TC genotype was more likely to suffer from DR.

Conclusions This study showed that the SNPs rs9362054 near the CEP162 gene was significantly associated with DR, CEP162 plays a critical role in ciliary transition zone formation before ciliogenesis. The present study raises the possibility that the dysregulation of ciliary-associated genes plays a role in susceptibility to DR.

Screening of diagnostic markers from plasma derived extracellular vesicles for ischemic stroke using RNA-seq

Shangdong Yang Jing Jia Zhihao Li Yang Liu Zhaojing Zhang Yuanli Wang Ying He Hong Zheng
Zhengzhou University

Objective To screen and identify biomarkers from plasma derived extracellular vesicles (EVs) for diagnosis of ischemic stroke (IS) and to investigate the feasibility as predictive markers for ischemic stroke.

Method Plasma samples were collected from IS patients (n=50) and healthy controls (n=47) in the present study. RNA-seq was performed on the 3 best-matched patients and healthy control pairs. Plasma EVs were isolated by chemical precipitation, and characterized by Transmission Electron Microscopy (TEM), Nanoparticle Tracking Analysis (NTA) and Western Blot (CD63, CD81). EV-RNA was extracted by TRIzol Reagent and precipitated with glycogen. After the preparation of EV-RNA library, Agilent 2100 Bioanalyzer and Agilent 4200 TapeStation were applied for quality control. Qubit 4 and qPCR were used for library quantification. Sequencing data was processed with FastQC and aligned with Bowtie2. DESeq2 was used for data normalization and differentially expressed transcripts were selected by fold change and adjusted *P* value. Heatmap and volcano plot were drawn based on the sequencing data. Principal Component Analysis (PCA) and t-Distributed Stochastic Neighbor Embedding (t-SNE) were used for visualizing clusters generated by the differentially expressed transcripts. Target gene prediction, GO enrichment and KEGG pathway analysis were performed. The selected transcripts were validated by RT-qPCR.

Result There was no difference in gender, age and blood lipid levels between the IS and healthy control group, but the blood glucose and hs-CRP in the case group were slightly higher than those in the control ($P < 0.05$). The cup-shaped structure of EVs was obviously seen using TEM. NTA showed that the main peak of EVs particle size was 100.1nm and the concentration was 1.3E+12 Particles/mL. Western blot results showed that bands of EVs markers CD63 and CD81 were clearly visible. The size of the library was about 140bp and the quantification was higher than 10nM. RNA-seq results showed that a variety of differentially expressed EV-miRNAs, such as hsa-miR-21-5p, hsa-miR-30a-3p, hsa-miR-124-5p and hsa-miR-9-5p, were closely related to the occurrence and progression of IS. We selected hsa-miR-21-5p and hsa-miR-30a-3p as potential diagnostic biomarkers by differential transcript expression profiles based on sequencing data. In validation cohort, RT-qPCR results showed that hsa-miR-21-5p ($P < 0.001$) and hsa-miR-30a-3p ($P=0.002$) had a significant statistical difference between the IS and healthy control group. Further, ROC curve showed that hsa-miR-21-5p (AUC=0.7553, $P < 0.001$) and hsa-miR-30a-3p (AUC=0.7284, $P=0.002$) had good diagnostic efficacy of IS. Interestingly, we aligned the sequencing data with tRNA reference. By differential expression analysis, we found that tRNA Glu-TTC showed significantly low expression in the IS group (fold change=2.37, $P=0.004$), suggesting it might be used as a novel potential marker for diagnosis of IS. Thus, this study

suggested that hsa-miR-21-5p and hsa-miR-30a-3p have potential clinical diagnostic value for ischemic stroke.

Conclusion The expression of plasma derived extracellular vesicles hsa-miR-21-5p and hsa-miR-30a-3p were significantly associated with the occurrence and progression of ischemic stroke. They might be used as potential biomarkers for the diagnosis of ischemic stroke. And this study provides a basis for further studies on the pathogenesis of IS.

DNA methylation patterns of β-globin cluster in β-thalassemia patients

Xiuqin Bao
Southern Medical University

Objection Reactivation of fetal hemoglobin (HbF, a_2g_2) holds a therapeutic target for b-thalassemia and sickle cell disease (SCD). Although many HbF regulators have been identified, the methylation patterns in b-globin cluster driving the fetal-to-adult hemoglobin switch remains to be determined.

Methods We evaluated DNA methylation patterns of the b-globin cluster from peripheral bloods (PB) of 105 b^0/b^0 thalassemia patients and 44 normal controls. We also recruited 15 bone marrows and 4 cord blood samples for further evaluation.

Results We identified that the CpG sites in the locus control region (LCR) DNase I hypersensitive site 4 and 3 (HS4-3) regions, and g- and b-globin promoters displayed hypomethylation in b^0/β^0-thalassemia patients, especially for the patients with high HbF level, as compared with normal controls. Furthermore, hypomethylations in most of CpG sites of the HS4-3 core regions were also observed in bone marrows (BM) of b^0/b^0-patients compared with normal controls; and methylation level of g-globin promoter -50 and +17 CpG sites showed lower methylation level in patients with high HbF level compared with those with low HbF level and a negative correlation with HbF level among β^0-thalassemia patients. Finally, g-globin promoter +17 and +50 CpG sites also displayed significant hypomethylation in cord blood tissues (n=4) compared with BM tissues from normal controls.

Conclusions Our findings revealed methylation patterns in b-globin cluster associated with b^0 thalassemia disease and g-globin expression, contributed to understand the epigenetic modification in b^0 thalassemia patients and provided candidate targets for the therapies of β-hemoglobinopathies.

23 个常染色体 STR 基因座在河南汉族人群中的遗传多态性分析

刘治佑
河南省人民医院

目的 调查河南汉族人群 24 个短串连重复序列（STR）基因座的遗传多态性分布，并对该 24 个 STR 基因座检测效能在亲权关系中的验证。

方法 选取 276 例河南籍贯汉族无关个体外周血 DNA，使用 PowerPlex^R Fusion System 系统身份认证系统 PPF24NC 对 D3S1358 等 23 个常染色体 STR 位点多态性进行检验，用 Genemapper ID-X 软件进行基因分型，统计各基因座遗传学参数。

结果 23 个常染色体 STR基因座的基因频率分布均符合 Hardy-Weinberg 平衡(P＞0.05) 。23 个 STR 基因座的 MAF、HoB、HeX、PD、PIC、TPI、PE，MP 分别介于：0.002~0.040，0.062~1, 0~0.938,0.208~0.982，0.334~0.91，0.5~8.06, 0~0.873，0.018~0.873。对二联体和存在突变位点的亲权鉴定利用 PowerPlex^R Fusion System 身份鉴定系统进行检测，均能得出明确的结论。

结论 PowerPlex^R Fusion System 身份鉴定系统 PPF24NC 扩增体系所包含的 23 个常染色体 STR在河南汉族人群中具有高度多态性，PPF24NC 系统为河南汉族群体的亲子鉴定、个体识别和 DNA 数据库建设提供新的鉴别位点。

多基因脑表型的自然选择压力图谱

宋炜宸 禹顺英 赵敏 林关宁
上海精神卫生中心

目的 理解脑表型与脑疾病的遗传结构对研究其生理、病理机制有重要意义，而自然选择在塑造其遗传结构中起到了关键作用。本研究旨在分析脑表型在不同时间尺度上受到的自然选择压力特点及其与其它性状所受压力的异同，以对自然选择在塑造脑表型遗传结构中的作用作出全面的理解。
方法 我们收集了包括 19 种脑疾病与 231 种脑表型在内的共 870 种人类性状的全基因组关联分析（GWAS）数据，并使用孟德尔随机化、SDS 分布、古人类多基因风险评分、连锁不平衡分数回归以及 GWAS 位点作用方向分布来衡量这些表型在当代、近两千年、新石器时代及更久远的时间尺度上受到的自然选择方向及强度。所得统计量经矫正后通过线性回归估算不同时间点的自然选择压力间的相互关系。
结果 从整体上看，脑表型均受到较强的负向选择，但其正向选择压力小于体型、色素、饮食等性状的选择压力，且在不同时间点受到的压力方向基本保持一致。精神分裂症的遗传度高度富集于受强烈负向选择作用的基因附近，而控制神经性厌食及饮酒量的遗传位点则在特定时间段受自然选择促进。与之相反，智商则在某些时间受自然选择的压制。此外，包括精神分裂症及脑卒中等在内的脑疾病富集于连锁不平衡水平较低、碱基多样性较低以及突变时间较晚的区域，而这些区域易于逃脱负向选择的作用。
结论 本研究绘制了人类表型组的自然选择压力图谱，并对脑疾病未被自然选择淘汰的原因找到了部分解释。

先天性心脏病相关 CNV-lncRNA 的筛选与鉴定

陆逸波 王波
上海儿童医学中心

目的 探讨先天性心脏病(CHD)相关拷贝数变异(CNV)区域中长链非编码 RNA(lncRNA)对心脏发育的调控作用。
方法 运用生物信息学分析方法，根据 CHDGKB 数据库收录的 370 例单纯性 CHD 病例（1998 年至 2020 年 5 月被报道）的遗传变异信息筛选得到 CHD 相关 CNV 位点；根据数据库中最新的人类 lncRNA 注释信息，筛选出映射至上述 CHD 相关 CNV 位点、在心脏发育过程中表达的 CNV-lncRNA；选取 EBI ArrayExpress 数据库中的 E-MTAB-6814 数据集（包含了来源于 314 个健康人群组织样本的基因转录组数据），对筛选出的 CNV-lncRNA 和 19957 个具有基因转录组数据的蛋白编码基因进行加权基因共表达网络分析（WGCNA）；使用 lncRNA 相关的 miRNA 海绵调控网络(LncmiRSRN)分析方法构建人类心脏发育相关 lncRNA 驱动的 ceRNA 调控网络。
结果 通过 WGCNA 共预测出 30 个与 CHD 相关蛋白编码基因共表达的 hub CNV-lncRNA,经鉴定认为其与 CHD 之间可能存在关联。通过 LncmiRSRN 分析共预测出 9 个能够作为 miRNA 海绵对 mRNA 起到因果调控作用的 hub CNV-lncRNA。结合 WGCNA 和 LncmiRSRN 分析的结果，发现其中 HSALNG0110244 与 CHD 相关蛋白编码基因 AKT3，HSALNG0104472 与 CHD 相关蛋白编码基因 GATA6、SMAD6 之间存在共表达关系，并可能通过 ceRNA 调控作用影响心脏发育。
结论 本研究共筛选出 39 个与 CHD 相关的 hub CNV-lncRNA，共分布于 14 个 CHD 相关 CNV 区域，能够为约 73.7%（14/19）的 CHD 相关 CNV 的致病机制提供解释，提示 lncRNA 在 CNV 导致 CHD 发生的过程中具有重要作用。

LncRNA FGD5-AS1 抑制 HAS2 表达影响心脏发育

祁明 方晴 张星玉 张小平 项盈 王波 傅启华
上海交通大学医学院附属上海儿童医学中心

目的 长链非编码 RNA（lncRNA）是长度大于 200 个核苷酸的非编码 RNA。研究表明 lncRNA 在胚胎心脏发育中发挥重要作用，其异常与先天性心脏病（CHD）的发生有关。在先前研究中，我们发现 *FGD5-AS1* 是法洛四联症患者心脏组织中竞争性内源 RNA 调控网络中的关键 lncRNA，对多个 CHD 相关基因有调控作用，可能在心脏发育中发挥抑制功能，其中尤为关注的下游基因是 *HAS2*。为了进一步探究 *FGD5-AS1* 在心脏发育中的功能，我们比较了 *FGD5-AS1* 敲减和过表达的人诱导多能干细胞（iPSC）中下游基因的表达变化及其向心肌细胞分化的情况。
方法 构建慢病毒载体将 *FGD5-AS1* 敲减和过表达元件分别转染入 iPSC，获得 *FGD5-AS1* 敲减及过表达细胞系。利用逆转录实时荧光定量 PCR 技术检测 *HAS2* 的转录水平。使用 CardioEasy 人心肌细胞分化试剂盒（赛贝生物）对 iPSC 进行心肌分化定向诱导。使用人透明质酸 ELISA 试剂盒检测细胞培养上清液中 HA 含量。
结果 *FGD5-AS1* 敲减 iPSC 与对照组相比，HAS2 转录显著增加，心肌分化能力增强，分化第 11 天到 14 天心肌细胞跳动频率更高，且细胞培养上清液中 HA 含量明显增加；*FGD5-AS1* 过表达 iPSC 则反之。此外，在敲减细胞中加入 HAS2 抑制剂可抑制 *FGD5-AS1* 敲减的效应；在过表达细胞中加入 HA 可回补 *FGD5-AS1* 过表达的效应。
结论 *FGD5-AS1* 可通过抑制 *HAS2* 表达降低细胞外基质中的 HA 分泌量，从而抑制心肌分化、影响心脏发育。

STAT3 is critical for skeletal development and bone homeostasis by regulating osteogenesis

Siru Zhou Qinggang Dai Xiangru Huang Anting Jin Lingyong Jiang
Shanghai Ninth People's Hospital , Shanghai Jiao Tong University School of Medicine

Objective Autosomal dominant hyper-immunoglobulin E syndrome (AD-HIES), also known as Job's syndrome, is a rare genetic disorder caused by heterozygous and loss-of-function mutations in Signal transducer and activator of transcription 3 (STAT3), characterized by immune dysfunction primarily along with comorbid skeleton developmental abnormalities including anomalies in craniofacial bone, severe osteoporosis, and recurrent minimal trauma fractures. So far, there is no definitive cure for the skeletal defects in AD-HIES, and treatments are limited. Hence, clarifying the underlying mechanisms of AD-HIES-related bone defects is important.
Methods We generated osteoclast-specific and osteobalst lineage-specific *Stat3* deletion mouse model separately, found inactivation of STAT3 in osteoblasts, but not osteoclasts, induced the AD-HIES-related bone defects. Then, Micro-CT was used to analysis skeletal elements isolated from Osx^{Cre};$Stat3^{fl/fl}$ mice and control littermates. Histological analysis osteoblastic and osteoclastic activity of Osx^{Cre};$Stat3^{fl/fl}$ mice and control littermates. Next, Osx^{Cre};$Stat3^{fl/fl}$ and Osx^{Cre} BMSCs were cultured and induced with osteogenic differentiation mediea .The relative mRNA levels of osteogenesis genes were quantified by RT-pcr. Then we performed RNA-seq with total RNA extracted from the calvaria of Osx^{Cre};$Stat3^{fl/fl}$ and Osx^{Cre} mice. Further analyzed found that STAT3 participated in osteoblast differentiation and ossification by controlling DLX5 expression. Next we used Chip-qpcr and Luciferase reporter assay to investigated the mechanisms by which STAT3 regulates DLX5 expression. We then used inducible osteoblast deletion of *Stat3* mouse model and heterozygous knockout mice to explore whether STAT3 could be a suitable pharmacological target to regulate bone metabolism and bone homeostasis.
Results Here we show that STAT3 deficiency in bone marrow mesenchymal stem cells (BMSCs) or pre-osteoblasts, but not in osteoclasts, induces craniofacial deformity, osteoporosis, and spontaneous bone fractures, resembling the cranial bone phenotypes of AD-HIES patients. Mechanistic analyses revealed that STAT3 in cooperation with Msh homeobox 1(MSX1) drove osteoblast differentiation by promoting Distal-less homeobox 5(*Dlx5)* transcription.

Furthermore, pharmacological activation of STAT3 partially rescued skeletal deformities in heterozygous knockout mice, while inhibition of STAT3 aggravated bone loss.
Conclusions STAT3 is critical for modulating skeletal development and maintaining bone homeostasis through STAT3-indcued osteogenesis. Meanwhile, inactivation in osteoblasts rather than osteoclasts, although does not genetically mimic the patients' *STAT3* mutations, can induce AD-HIES-related skeletal deformities by impairing osteogenesis, providing a potiential target for treatments.

TEAD4 通过直接结合 γ-珠蛋白基因启动子抑制胎儿血红蛋白表达

林佳琼 叶宇华 商璇 张燕霞 魏小凤 徐湘民
南方医科大学基础医学院医学遗传学教研室

目的 胎儿血红蛋白（HbF）的重新开放表达已被证实能改善 β-地中海贫血患者临床表型的严重程度。 因此，在本研究中我们结合生物信息学分析筛选潜在调节因子，以期为 HbF 重新开放表达提供新的治疗靶点。
方法 通过生物信息学分析筛选潜在调控因子，对 TEAD4 以及顺式作用原件采用慢病毒敲降以及 CRISPR/Cas9 敲除实验，利用 RT-qpcr、Western blot、流式细胞术等方法检测 HbF 含量以及红系细胞分化水平，通过染色质免疫共沉淀和凝胶迁移等实验进行结合位点验证。
结果 TEAD4 在不同测序数据集样本以及不同 HbF 水平 β-地贫患者中差异表达，且 TEAD4 可结合在 γ-珠蛋白基因启动子区。在原代及红系细胞中敲除 TEAD4 以及顺式作用原件后，HbF 表达水平明显增加且不影响红系分化。
结论 该研究发现 TEAD4 为一个新的 HbF 抑制因子，且 TEAD4 通过直接结合 γ-珠蛋白基因启动子抑制 HbF 表达，为血红蛋白疾病的治疗提供了潜在的治疗靶点。

FGD4 基因突变导致腓骨肌萎缩 4H 型的分子机制初探研究

串俊兰 何诗雨 杨正林
四川省人民医院

目的 FGD4 是 Rho 蛋白家族 GTP 酶的鸟嘌呤核苷酸交换因子（Guanosinenucleotide exchange factors, GEFs）的一员，有研究报道 *FGD4* 基因是腓骨肌萎缩（CMT）4H 的致病基因。因此研究 FGD4 蛋白野生型和突变型的 Rho 蛋白家族 CDC42 蛋白鸟苷酸交换活性，并从结构层面分析 FGD4 蛋白与 CDC42 蛋白的相互作用，对于了解 FGD4 蛋白的生物学功能和致病机制有着重要意义。
方法 本论文首先构建了 FGD4-DH 结构域野生型与突变型的表达载体，在原核表达系统中进行了表达与纯化，得到大量高纯度蛋白进行体外鸟嘌呤核苷酸交换活性研究，并将所得 FGD4-DH 蛋白野生型/突变型与 CDC42 蛋白共同孵育制备复合物，利用 X 射线晶体学解析 FGD4-DH 与 CDC42 的复合物结构，分析 FGD4 突变导致 CMT4H 的机制。
结果（1）FGD4-DH 结构域的表达和纯化：通过重组载体的构建，选用大肠杆菌原核表达系统对人源 FGD4 蛋白的 DH 结构域（第 206-408 位氨基酸）进行表达，并通过进一步的亲和层析、凝胶过滤层析纯化得到大量高纯度的 FGD4-DH 蛋白。同时，我们也通过点突变的手段，突变了 FGD4-DH 结构域的第 213 位、275 位、298 位、345 位氨基酸，并通过相同的方法表达纯化了突变体蛋白；（2）FGD4-DH 蛋白的鸟嘌呤核苷酸活性研究：将不同浓度的野生型 FGD4-DH 蛋白与荧光标记后的 CDC42 蛋白（mantGDP-CDC42）共同孵育，通过 1 小时后荧光强度的变化检测野生型和突变型 FGD4-DH 蛋白的鸟苷酸交换活性。结果发现，当蛋白浓度在 10 mM 以下时，其交换活性较弱，当浓度增加值 50 mM 时，表现出明显的鸟苷酸交换活性。当突变第 213 位、第 275 位（R275H）以及第 345 位氨基酸时，FGD4 的鸟苷酸交换活性明显降低，而另外两种突变型并没有改变蛋白的鸟苷酸交换活性。（3）解析了 FGD4-DH 蛋白与 CDC 蛋白复合物的三维结构，分辨

率为 2.2 埃，从三维结构可以看出，第 213 位氨基酸突变导致 FGD4-DH 与 CDC42 相互作用的三对氢键遭到破坏。
结论 通过鸟苷酸交换活性实验，FGD4-DH 蛋白野生型对 CDC42 表现出较强的鸟嘌呤核苷酸交换活性，通过复合物结构的解析，揭示了 FGD4 与 CDC42 相互作用的结构基础和致病突变导致 FGD4 活性改变的原因。

利用 CRISPRi 筛选在体外诱导心肌肥大模型中揭示 TOF 关键 lncRNA

张星
上海儿童医学中心

背景 CRISPR 干扰（Clustered Regularly Interspaced Short Palindromic Repeat interference, CRISPRi）技术因高效的基因干扰效率而成为研究长链非编码 RNA（long noncoding RNA, lncRNA）功能的重要工具。先天性心脏病（Congenital Heart Disease, CHD）是胎儿期心脏及大血管发育异常所致的先天性畸形，其中法洛氏四联症（Tetralogy of Fallot, TOF）是最常见的紫绀型 CHD，目前多为散发病例且病因尚未明确。目前关于 lncRNA 在心脏发育及 CHD 致病机制中的作用有着越来越多的发现，
目的 本研究利用 CRISPRi 技术进行高通量筛选，同时结合体外诱导心肌肥大模型，以期揭示 TOF 相关的功能 lncRNA。
方法 逐步构建能够稳定表达核酸酶 dCas9 及报告因子 NF-κB 的人心肌 AC16 细胞，分别用以配合后续筛选及指示细胞肥大程度。结合 TOF 患者右心室肥大表型，后续利用成功构建的心肌细胞系建立体外心肌肥大及激活 NF-κB 信号通路的最适条件。在此基础上，通过定制相关 lncRNA 筛选文库，完成 CRISPRi 高通量筛选。
结果 筛选出 TOF 致病机制中发挥作用的潜在功能 lncRNA 及共表达关系密切的蛋白编码基因，为 CHD 的防治提供理论基础。

Loss of phosphatidylserine flippase β-subunit Tmem30a in podocytes leads to albuminuria and glomerulosclerosis

Wenjing Liu
University of Electronic Science and Technology of China

Purpose The asymmetric distribution of phosphatidylserine (PS) in the cytoplasmic leaflet of eukaryotic cell plasma membranes is regulated by a group of P4-ATPases (named PS flippases) and the β-subunit TMEM30A. Podocytes in the glomerulus form a filtration barrier to prevent the traversing of large cellular elements and macromolecules from the blood into the urinary space. Damage to podocytes can disrupt the filtration barrier and lead to proteinuria and podocytopathy. We observed reduced TMEM30A expression in patients with minimal change disease and membranous nephropathy, indicating potential roles of TMEM30A in podocytopathy. To investigate the role of Tmem30a in the kidney, we generated a podocyte-specific Tmem30a knockout (KO) mouse model using the NPHS2-Cre line.
Methodes we generated a podocyte-specific Tmem30a knockout (KO) mouse model by Loxp-Cre system. Urine analysis with specific ELISA kits according to manufactures' instruction. Renal pathology was detected with PAS staining. Ultrastructure change of glomerulus was observed using TEM. Western bolt used to elucidate the mechanism underlying the glomerulosclerosis due to loss of *Tmem30a* in podocyte.
Results *Tmem30a* KO mice displayed albuminuria, podocyte degeneration, mesangial cell proliferation with prominent extracellular matrix accumulation and eventual progression to focal segmental glomerulosclerosis.

Conclution Our data demonstrate a critical role of *Tmem30a* in maintaining podocyte survival and glomerular filtration barrier integrity. Understanding the dynamic regulation of the PS distribution in the glomerulus provides a unique perspective to pinpointing the mechanism of podocyte damage and potential therapeutic targets.

SEPT9-v1 对人乳腺癌 MCF-7 细胞周期调控和细胞增殖的作用机制

李甜 肖莉凡 代荣阳 贾蔓 曾毅 余文静 王荣浩 曾永秋
西南医科大学 基础医学院

目的 研究 SEPT9-v1 的表达对人乳腺癌 MCF-7 细胞周期调控和细胞增殖的影响及相关分子机制。
方法 用慢病毒 shRNA 感染人乳腺癌 MCF-7 细胞，筛选获得 Sh-SEPT9 多克隆细胞株及阴性对照 Scramble 细胞株。进一步在 Sh-SEPT9 细胞中感染携带外源 SEPT9-v1-C3FLAG 基因的慢病毒载体，筛选得到 SEPT9-v1Rescue 细胞株；采用 CCK8、平板克隆形成实验检测三种细胞株的增殖能力；流式细胞术检测三种细胞株周期分布；Western Blot 检测三种细胞株 G2/M 期相关蛋白表达；质谱分析可能与 SEPT9-v1 作用的蛋白；运用免疫共沉淀实验和免疫荧光实验检测 SEPT9-v1 与 PUM1 的相互作用及共定位情况，qRT-RCR 及 Western Blot 检测三种细胞中 PUM1 的表达变化；用放线菌酮（Cycloheximide，CHX）处理三种细胞（0、1、2、4、8h），Western Blot 检测 PUM1 蛋白的降解情况；在乳腺癌细胞 MDA-MB-231 及 T47D 中分别转染 siNC 及 SEPT9siRNA，Western Blot 检测 PUM1 蛋白的表达；在 MCF-7 及 MDA-MB-231 细胞中转染 siNC 及 PUM1siRNA，Western Blot 检测 SEPT9、G2/M 期相关蛋白表达；在 Rescue 细胞株中干扰 PUM1 及在 Sh-SEPT9 细胞株中过表达 PUM1 后，Western Blot 检测 G2/M 期相关蛋白 cyclinB1、CDK1、p21、p27、肿瘤抑制因子 P53 及 MAPK 家族蛋白的表达。
结果 （1）CCK8、平板克隆形成实验结果显示，与 Scramble 组比较，Sh-SEPT9 组细胞增殖能力明显受到抑制，而 Rescue 组细胞增殖能力明显恢复；（2）流式细胞术检测细胞周期显示，Sh-SEPT9 组处于 G2/M 期的细胞分布明显增多,且 Western Blot 结果显示 Sh-SEPT9 组 G2/M 期相关蛋白 cyclinB1、CDK1 表达明显降低，而 Rescue 组与 Scramble 组差异不明显；（3）质谱检测发现 SEPT9-v1 与 PUM1 间可能存在蛋白相互作用，免疫共沉淀实验、免疫荧光实验和 Western Blot 证实了这一猜想，但 qRT-PCR 结果显示 PUM1 在 mRNA 水平的表达不受 SEPT9 的影响；（4）用 CHX 处理细胞后，Sh-SEPT9 组中 PUM1 蛋白在 1h 内开始降解，而 Scramble 组和 Rescue 组中 PUM1 蛋白 4h 后开始降解；（5）在乳腺癌细胞 MDA-MB-231 及 T47D 中干扰 SEPT9，PUM1 蛋白表达明显下调。在 MCF-7 及 MDA-MB-231 细胞中干扰 PUM1 表达后，G2/M 期相关蛋白 cyclinB1、CDK1 表达明显下降，而 SEPT9 表达不受影响；（6）在 Rescue 细胞株细胞中干扰 PUM1 表达，G2/M 期相关蛋白 cyclinB1、CDK1 表达明显下降，p21、p27、P53 蛋白表达明显升高，而在 Sh-SEPT9 细胞株过表达 PUM1，结果相反。同时，MAPK 家族蛋白如 p38、JNK、ERK 的磷酸化水平在干扰或过表达 PUM1 的实验中均不受影响。
结论 SEPT9-v1 通过在蛋白水平调控 PUM1 的表达来促进人乳腺癌细胞 MCF-7 增殖。敲低 SEPT9-v1 会降低 PUM1 蛋白的稳定性，同时激活肿瘤抑制因子 P53，进而阻滞人乳腺癌细胞 MCF-7 于 G2/M 期，此过程与 MAPK 信号通路无关。

CREBBP 基因突变导致骨骼畸形的致病机制研究

安莹 傅启华 项盈 方晴 刘展
上海儿童医学中心

目的 初步阐明 CREBBP 突变导致骨骼发育畸形的分子致病机制，为骨骼发育畸形的早期精准诊断、精准治疗、产前诊断和遗传咨询等提供理论依据。

方法 选用胚胎干细胞打靶策略，构建 *Crebbp* 点突变小鼠模型，通过分离骨髓间充质细胞（BMSC），诱导 BMSC 成骨分化、成软骨分化，免疫荧光、免疫共沉淀及 Western Blot 等细胞生物学实验，探讨 CREBBP 对骨骼发育调控及影响机制。
结果 通过分离骨髓间充质细胞（BMSC），我们发现该点突变不影响 BMSC 的细胞骨架，但显著降低了其细胞增殖能力；通过成骨细胞分化及成软骨细胞分化实验，我们证明该点突变影响了小鼠的成骨细胞分化能力，但不影响其成软骨细胞分化能力。
结论 本研究发现 CREBBP 基因变异与骨骼畸形相关，通过制备小鼠模型揭示了 CREBBP 点突变导致骨骼畸形发生的机制。本研究为骨骼畸形的分子诊断、分型及治疗提供了一定的理论依据，对降低我国出生缺陷发生率具有重要的社会意义。

以斑马鱼为模式动物研究 MVD 基因功能

黄永雄 张正华
华山医院

目的 甲羟戊酸焦磷酸脱羧酶基因(*mevalonate diphosphate decarboxylase, MVD)*是中国汗孔角化症患者的最常见致病基因，汗孔角化症是呈常染色体显性遗传的自身炎症性角化病。目前 *MVD* 基因的生物学功能仍然未知，本研究以斑马鱼为模式动物，对其直系同源的 *mvda* 基因进行功能研究。
方法 使用吗啉环反义寡核苷酸技术（morpholino antisense oligonucleotides）构建 *mvda* 沉默斑马鱼模型，并通过 RT-PCR 和 Sanger 测序证实斑马鱼 *mvda* 基因沉默有效性。我们接着通过扫描和透射电子显微镜分析斑马鱼表皮形态，使用了 *Tg(fli1a:EGFP)*^{y1} 转基因斑马鱼品系进行血管形成研究，此外，应用吖啶橙染色检测斑马鱼体内细胞凋亡状况。
结果 *mvda* 沉默斑马鱼在受精后 48 小时出现表皮形态异常，同时，我们在实验组斑马鱼观察到躯干血管的生成异常和尾静脉丛的形成受损。此外，在受精后 96 小时，我们在 *mvda* 沉默斑马鱼的尾部、心脏和眼睛中发现了细胞凋亡增加。
结论 本研究首次对斑马鱼 *mvda* 基因的功能进行了初步探索，我们的发现表明 *mvda* 基因在斑马鱼早期发育中的重要作用。这将有助于了解 *MVD* 基因的生物学功能，从而为汗孔角化症的发病机理提供研究线索。

精神分裂症和癌症的两样本孟德尔随机化研究

袁铠[1] 宋炜宸[1,2] 唐诗婕[3] 林关宁[1,2] 禹顺英[1]
1.上海市精神卫生中心 2.上海交通大学生物医学工程学院
3.中国科学院分子细胞科学卓越创新中心

精神分裂症与恶性肿瘤的关系一直存在争议，有研究报道在精神分裂症患者中恶性肿瘤发生率低于普通人群，精神分裂症的遗传易感性可能是恶性肿瘤的保护因素，也有相反报道。本研究目的是调查精神分裂症的风险是否与癌症患病风险存在因果关系。我们采用孟德尔随机化分析方法，对精神分裂症和常见的 13 种恶性肿瘤（包括乳腺癌，肺癌，胶质母细胞瘤等）的 GWAS 数据分别进行计算分析，以精神分裂症作为暴露因素，探讨精神分裂症的遗传易感性是否影响恶性肿瘤。并利用 TCGA 肿瘤 eQTL 数据，寻找精神分裂症易感位点对应癌症的相关基因，并对基因进行差异表达和预后分析。我们发现精神分裂症的遗传易感性会增加乳腺癌（随机效应模型，OR 值=1.041,95%置信区间：1.014 - 1.067, p = 0.0026），卵巢癌（OR 值=1.086，95%置信区间：1.031 - 1.143; P = 0.0018）和甲状腺癌（OR 值=1.559; 95% 置信区间：1.055 - 2.303; P = 0.0256）的患病风险。结合 eQTL 数据，找到了与精神分裂症相关的 rs11191418、rs7432375 位点对应的 eQTL genes（AS3MT，SFXN2 和 PCCB），通过基因下游分析发现这三个基因在肿瘤中表达存在差异且预后有显著差异。根据乳腺癌，卵巢癌和甲状腺癌的患病特征，进一步利用 MR 分析探究精神分裂症是否影响激素水平，发现精神分裂症会影响促甲状腺激素的水平（OR 值=1.095; 95% 置信区间：

1.006 - 1.191; P = 0.0354），可能和导致这三类癌症患病风险增加有关。通过该项研究，我们发现了精神分裂症会增加乳腺癌，卵巢癌和甲状腺癌的患病率，但导致癌症患病率增加的机制可能不同。同时 AS3MT，SFXN2 和 PCCB 未来可能可以作为精神分裂症患者乳腺癌，甲状腺癌预防的生物标志物。

GJA1 在肿瘤肝转移中发挥的作用及潜在机制

刘永达
海军军医大学

目的 通过人为构建 GJA1 高表达或低表达细胞株，探讨 GJA1 在肝转移中的作用、机制。
方法 利用脾脏注射、尾静脉注射、皮下荷瘤模型，检测 GJA1 在肿瘤肝定植、肺定植、体内生长中的作用。在临床肝癌、结直肠癌样本中分析 GJA1 的表达与肝转移、预后的相关性。
通过 RT-PCR、免疫荧光、流式分析、核质分离等实验探究 GJA1 在肿瘤肝定植过程中的作用机制。
结果 与肝血窦内皮细胞（LSEC）共培养时，高表达 GJA1 的肿瘤细胞增殖减缓，凋亡减少，呈现慢增殖状态。此种状态下的肿瘤细胞表面 NK 细胞杀伤相关表面配体表达下调，躲避 NK 杀伤，增强其存活能力和后期成瘤能力。
结论 过表达 GJA1 可使肿瘤细胞在肝脏内呈现慢增殖状态，下调肿瘤细胞表面 NK 杀伤相关配体的表达，增加肿瘤细胞肝定植能力。

Single-cell transcriptomic analysis reveals the critical molecular pattern of UV-induced cutaneous squamous cell carcinoma

Guolong Zhang Guorong Yan Xiuli Wang
Shanghai Skin Disease Hospital, School of Medicine, Tongji University

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer characterized by high invasiveness, heterogeneity,and mainly occurs in the ultraviolet (UV) exposed areas, but its pathogenesis is still unclear. Here, we generated single-cell transcriptome profiles for 350 cells from 6 primary UV-induced cSCC, together with matched normal adjacent skin samples, and 3 healthy control skin tissues by single-cell RNA-sequencing based on Smart-seq2 strategy. A series of bioinformatics analyses and *in vitro* experiments were used to decipher and validate the critical molecular pattern of cSCC. Results showed that cSCC cells and normal keratinocytes were significantly distinct in gene expression and chromosomal copy number variation. Furthermore, cSCC cells exhibited 18 hallmark pathways of cancer by gene set enrichment analysis. Differential expression analysis demonstrated many members belonging to S100 gene family, SPRR gene family, and *FABP5* were significantly up-regulated in cSCC cells. Further cell experiments confirmed their up-regulation and the effects of promoting cell proliferation and migration of *S100A9* and *FABP5*. Together, our study provides a valuable resource for deciphering the molecular pattern in UV-induced cSCC at a single-cell level and suggests that *S100A9* and *FABP5* may provide novel targets for therapeutic intervention in cSCC in the future.

DNA Hypermethylation Modification Promotes the Development of Hepatocellular Carcinoma by Depressing the Tumor Suppressor Gene ZNF334

Dapeng Sun[1] Fu Yang[2]
1. The Third Department of Hepatic Surgery, The Third Affiliated Hospital of Navel Medical University
2.The department of Medical Genetics, Naval Medical University

Background DNA methylation plays a pivotal role in the development and progression of tumors, but studies focused on the dynamic changes of DNA methylation in the development of hepatocellular carcinoma (HCC) are rare. This manuscript is aimed to construct pre- and early DNA methylation maps of liver cancer of the same genetic background, as well as to reveal the mechanism of epigenetics regulating gene expression during the development of liver cancer, thus providing new targets and clinical evidence for early diagnosis and shedding lights on the precise treatment for liver cancer.
Method The study includes 5 patients who were chronic hepatitis B virus infected, clinically diagnosed as primary liver cancer and pathologically diagnosed as early liver cancer with liver dysplastic nodules. Liver fibrosis tissues, dysplastic nodules and early HCC tissues from these patients have been used to measure DNA methylation.
Results We report significant differences in the DNA methylation spectrum of three types of tissues. In the early stage of HCC, DNA hypermethylation of tumor suppressor genes is predominant. Additionally, DNA hypermethylation in the early stage of HCC changes the binding of transcription factor P53 to the promoter of tumor suppressor gene ZNF334, and inhibits the expression of ZNF334 at the transcription level. Furthermore, through a series of in vivo and in vitro experiments, we have clarified the exacerbation effect of tumor suppressor gene ZNF334 deletion in the occurrence of HCC. Combined with clinical data, we found that the overall survival and disease-free survival of patients with high ZNF334 expression are longer than the lower one.
Conclusion We constructed a sequential map of DNA methylation modification during the occurrence of HCC, and clarified the biological function and regulatory mechanism of the tumor suppressor gene ZNF334, which is regulated by related DNA methylation sites, and also provide new targets and clinical evidence for the early diagnosis and precise treatment of liver cancer.

LncRNA RP5-998N21.4 通过调控 IFIT2 和 IFIT3 介导的抗病毒免疫通路参与精神分裂症的发病机制研究

郭波
南方医科大学

背景与目的 为研究表观遗传学因素 LncRNA 参与精神分裂症的发病机制，我们以单患精神分裂症同卵双生子对和健康同卵双生子对为研究对象，研究 lncRNA 对精神分裂症发生发展的影响。
方法 1.采用二代测序和生物信息学分析的方法结合，筛选出差异表达的 lncRNA 和与其共表达的基因；2.通过细胞实验来验证 lncRNA 通过调控与精神分裂症疾 病相关基因来影响疾病的发生发展；3.使用散发的临床样本验证 lncRNA 的表达情况。
结果和讨论 我们前期通过对单患精神分裂症同卵双胞胎进行转录组测序分析，确定了一个与精神分裂症有关的长非编码 RNA（lncRNA）RP5-998N21.4,尽管 RP5-998N21.4 的功能尚不清楚，但我们发现在人类外周血样本以及 RP5-998N21.4 过表达的 SK-N-SH 细胞系中与 RP5-998N21.4 共表达的基因富集在抗病毒防御相关的生物学通路中。然后，我们对过表达 RP5-998N21.4 的 SK-N-SH 中的差异表达基因和双生子样本中与精神分裂症相关的差异表达的基因进行了综合分析后，我们确定了两个 RP5-998N21.4 的潜在靶基因，分别是编码具有四三肽重复（IFIT）1 和 2 的干扰素诱导蛋白的两个基因，它们在宿主抗病毒防御中起着重要作用。接下来，我们证明 RP5-998N21.4 通过影响组蛋白修饰来正向调节 IFIT3 和 IFIT2 的转录。此外，确定了与 RP5-998N21.4 的相互作用的蛋白—RBM14，它可以编码 RNA 结合基序蛋白 14 作为一般的核共激活因子。最后，我们观

察到，RP5-998N21.4 的过表达可以通过激活 STAT1 的磷酸化来增强多聚 IC 诱导的 IFIT2 和 IFIT3 的表达。结论：我们的发现表明 lncRNA RP5-998N21.4 是抗病毒免疫反应的关键调节剂，为精神分裂症提供了病因学和治疗学意义。

Genetic analysis and generation of induced pluripotent stem cell lines from three patients with Alport syndrome

Yanyan Ma
Shandong University

Obejective Alport syndrome (AS) is a hereditary kidney disease caused by mutations in *COL4A3*, *COL4A4*, or *COL4A5* genes. The aim of this study is to explore the genetic causes of three patients who were suspected with Alport syndrome, and establish patient-specific induced pluripotent stem cell lines (iPSCs) for in vitro study.
Methods Patients and their relatives were identified and detected by Whole-exome sequencing. PBMCs from patients were reprogrammed to iPSCs by non-integrating episomal vector expressing OCT4, SOX2, KLF4, MYC and Lin28. The origination of iPSCs were confirmed by short tandem repeats (STRs). Exogenous gene was detected by PCR and karyotype was analysed by G-band chromosome analysis. Pluripotency markers and differentiation potential were detected by immunofluorescence staining and qRT-PCR.
Results Patient 1 was a 25-year-old Chinese woman, has a history of proteinuria and hematuria with cleft lip and palate, sequencing results revealed that she carried two heterozygous mutations (c.4243G>C, p.G1415R) in the *COL4A3* gene, which was inherited from her parents. Patient 2 and 3, two brothers that has a history of proteinuria, were heterozygous carriers for c.796C>T (p.R266X) in *COL4A5* gene. The patient-specific iPSCs were successfully established, STRs analysis data confirmed that our iPSCs were 100% identical to the parental PBMCs. All iPSCs expressed pluripotency markers TRA-1-81, TRA-1-60, SSEA-4, OCT4 and NANOG. The iPSCs displayed an excellent differentiation capacity. In vitro, iPSCs could form typical embryoid bodies (EBs) which demonstrated representative markers of three germ layers. After multiple passages, iPSCs were void of transgene expression and retained the original 46,XX or 46,XY karyotype.
Conclusions We identified novel *COL4A3* mutations and *COL4A5* mutation in three Alport syndrome patients, and generated the patient-specific iPSCs, providing a valuable in vitro model for studying disease mechanisms.

The mechanism and current concepts and future research direction of rare hereditary disease White Sponge Nevus

Wenping Cai
Tongji University School of Medicine

White sponge nevus (WSN) is an autosomal dominant rare hereditary disease. Keratin 4 (KRT4) and Keratin 13 (KRT13) gene mutations were involved in the WSN. In this study we will explore the pathogenesis of WSN. We recruited two WSN Chinese families, The mutations of KRT4 and KRT13 gene were detected by PCR and direct sequencing. The multiple alignments of KRT13 from 28 diverse species homology analysis were performed by the ClustalW program. The KRT13 expression was measured by Real-Time PCR and Western blot analysis. We revealed the pathological pathway of the WSN expression profile by RNA sequencing (RNA-seq). Sequencing analysis revealed two mutations of KRT13 gene: one mutation was 332T>C (Leu111Pro). Another mutation was 340C>T (Arg114Cys). The sequence of KRT13 was highly conserved. Real-Time PCR and Western blot analysis results show that KRT13 expression level is lower in patient but keep almost no change in mRNA level. When treat cells with MG132, KRT13 protein level was increased and kept almost the same in normal and patient cell. We identified two

heritable mutations in the KRT13 gene, which were associated with the development of WSN. The abnormal degradation of KRT13 protein of WSN may probably associate with abnormal ubiquitination process. Further RNA-seq analysis suggests that the abnormal degradation of KRT13 protein of WSN may probably associate with Keratin 7 (KRT7) and abnormal ubiquitination process. All the efforts may contribute to the molecular therapy for WSN. Gene-based diagnosis and gene therapy for WSN may become available in the near future while provide reference and instruction for treating other keratin associated diseases.

Breakpoint analysis of two large deletions at the 3'end of DMD gene

Zhujun Zhang
Nankai University School of Medicine

Objective Deletion of one or more exons is a common type of mutation in DMD gene, which cause Duchenne and Becker muscular dystrophy. Characterization of deletion breakpoints can give insight into the molecular mechanism of such genomic variations. In this study, we identified two large deletion mutations that missing the 3' end of DMD gene and analyzed the deletion junctions.
Methods Multiplex PCR or MLPA are used to screen 79 DMD exons for deletion and duplication. Intronic sequences are screened by primer walking approach to roughly map the deletion breakpoints. Junction fragments were amplified by long range-PCR and sequenced. Analysis of repetitive elements was performed by Repeat Masker program.
Results We identified two large deletions that missing the 3' end of DMD gene (exons 57-79, and exons 68-79) from 50 DMD/BMD cases, among which the deletion of exons 57-79 is a novel mutation that has not been reported before. Sequencing of the breakpoint junctions revealed microhomology of 1bp and 2 bp at two junctions, suggesting that nonhomologous end joining (NHEJ) is the underlying mechanism of these deletion event.
Conclusions This study precisely determined the size of two deletions that missing the 3' end of DMD gene, and helps us to understand the molecular mechanism generating DMD deletion.

CUL4B 在调控间充质干细胞成骨/成脂分化中的作用及其机制研究

于瑞祺 龚瑶琴
山东大学

目的 间充质干细胞是一种多能干细胞，能分化为骨骼和脂肪等多种间质组织。CUL4B 是泛素连接酶复合物的骨架蛋白，本课题组前期研究发现，缺失 *Cul4b* 会导致人类 X 连锁智力低下综合征，患者具有智力低下、身材矮小、短指、肥胖等表型特征，但患者身材矮小的形成机制尚不清楚。我们通过探究 CUL4B 调控间充质干细胞成骨/成脂分化的关键分子和机制，更深层次发掘 *Cul4b* 基因的基本功能，也为间充质干细胞的分化机制提供补充。
方法 我们通过构建间充质干细胞特异性敲除 *Cul4b* 的小鼠模型，分析敲除间充质干细胞 *Cul4b* 基因对骨骼生长发育、骨稳态维持、脂肪发育和成骨/成脂分化平衡的影响。
结果 1. 间充质干细胞特异性敲除 *Cul4b* 使小鼠在成长期骨骼发育变缓。 2. 老龄期骨强度下降且骨髓脂肪细胞含量增加。 3. 特异性敲除 *Cul4b* 的间充质干细胞更易诱导向脂肪细胞分化。
结论 1. CUL4B 促进生长期骨骼发育。 2. CUL4B 防止老龄期骨丢失。 3. CUL4B 促进间充质干细胞向成骨分化，抑制其向成脂分化。

细胞重生促进卵巢癌的转移和血管生成

孙丽丽[1] 刘巧[1] 龚瑶琴[1] 孙龚萍[2]
1.山东大学基础医学院遗传学系
2.山东大学基础基础医学院组织与胚胎学系

目的 卵巢癌复发与转移是病人首要致死原因。近年研究发现，致死剂量的化学物质短暂处理后，一些细胞会在启动凋亡程序激活效应 caspase 分子后存活下来。这一现象被命名为“细胞重生（anastasis）”。本研究旨在确认化疗药物处理后的卵巢癌细胞能否通过细胞重生存活，以及细胞重生是否参与化疗后卵巢癌复发或转移。
方法 1）慢病毒转染方法进行携带效应 caspase 活性报告因子 GC3AI 和示踪系统 CasExpress 卵巢癌细胞株构建。2）活细胞成像仪监测 TRAIL 和紫杉醇处理后的卵巢癌细胞 HEY 和 A2780 是否存在细胞重生。3）CCK8、Transwell、HUVEC 迁移、成管及裸鼠皮下基质胶栓等实验分析重生细胞表型。
结果 1）实时细胞成像发现 TRAIL 和紫杉醇处理后，一部分皱缩并激活了效应 caspase 的 HEY 和 A2780 细胞可以恢复正常形态，即发生细胞重生。2）重生（CasExpress+）、凋亡抵抗（CasExpress-）及对照细胞（Control）没有明显的生长差异，但重生细胞较凋亡抵抗及对照细胞具有更强的迁移能力。3）相较于凋亡抵抗及对照细胞，重生细胞的条件培养基可以明显促进 HUVEC 细胞迁移和体外成管。裸鼠皮下基质胶栓实验也发现含有重生细胞条件培养基的基质胶栓形成的血管更多。
结论 TRAIL 和紫杉醇处理后卵巢癌细胞确实存在细胞重生。重生细胞较凋亡抵抗和对照细胞有更强的迁移能力及促血管生成能力。

T 细胞特异性缺失 CUL4B 阻碍 T 细胞发育

秦丽萍[1] 李培山[1,2] 龚瑶琴[1]
1.山东大学基础医学院
2.苏州大学转化医学院

目的 探究 T 细胞特异性缺失 CUL4B 对于 T 细胞发育和功能的影响
方法 1)、利用 *Lck-cre*$^{+/-}$与 *cul4b*$^{flox/flox}$ 小鼠杂交获得 *Lck-cre*$^{+/-}$*cul4b*$^{f/f}$ 小鼠，即 T 细胞特异性缺失 CUL4B 的小鼠，命名为 CKO 小鼠，同窝 *cul4b*$^{f/f}$ 小鼠作为对照，命名为 WT 小鼠；2）、观察 6-8 周 WT 与 CKO 小鼠胸腺脾脏大小，将胸腺与脾脏制备成单细胞悬液，对细胞进行计数，并利用流式检测胸腺脾脏内 T 细胞亚群的比例；3）、将 WT 与 CKO 小鼠脾脏中 $CD4^+$和 $CD8^+$T 细胞分出，利用 anti-CD3 和 anti-CD28 刺激，随后检测 CD69 升高水平判定其活化能力，用 CFSE 法检测其活化后的增殖能力。
结果 1）、6-8 周 CKO 小鼠胸腺和脾脏均明显小于 WT 小鼠，且胸腺和脾脏中细胞总数目也显著少于 WT 小鼠；2）、CKO 小鼠的胸腺中，DN 亚群细胞比例略有升高，DP 亚群细胞比例与 WT 相当，CD4 SP 与 CD8 SP 亚群细胞比例显著降低，同时，DN 亚群细胞数目维持不变，DP 与 SP 亚群细胞细胞数目明显低于 WT 小鼠；3）、CKO 小鼠脾脏中，$CD4^+$和 $CD8^+$T 细胞比例和数目均显著减少；4）、CKO 小鼠 $CD4^+$和 $CD8^+$T 细胞在 anti-CD3 和 anti-CD28 刺激之后，$CD69^+$细胞显著少于 WT 小鼠，证明其活化能力减弱，同时，其活化后增殖能力较 WT 小鼠也显著降低。
结论 CKO 小鼠胸腺和脾脏 T 细胞显著减少，活化能力减弱，证明 T 细胞特异性缺失 CUL4B 导致其发育受阻，功能受损。

新型复合杂合 PKHD1 突变导致常染色体隐性多囊肾病

张梦杰 吴元明
空军军医大学

目的 探讨 1 例多囊肾家系的致病机制及产前筛查。
方法 提取该多囊肾家系 1 名患者、2 名正常成员的基因组 DNA，和正常成员中的 1 名孕妇羊水 DNA，结合目标序列捕获和高通量测序从多囊肾相关的基因中筛选出候选突变，应用 Sanger 测序和家系共分离分析进行验证，并通过保守性分析、蛋白质结构和功能分析其致病性。之后应用 Sanger 测序对孕妇羊水 DNA 中的致病突变进行筛查。
结果 该家系患者 PKHD1 基因中存在复合杂合突变，其中 1 个突变位点位于 PKHD1 基因的第 58 号外显子 c.9059 T>A（p.L3020Q），另 1 个位于第 32 号外显子 c.4274 T>G（p.L1425R），分别来自于患者的父亲和母亲，且与表型共分离。羊水穿刺检测发现胎儿仅携带第 58 号外显子 c.9059 T>A（p.L3020Q）致病突变。
结论 PKHD1 基因的 2 个突变位点，第 58 号外显子 c.9059 T>A（p.L3020Q）和第 32 号外显子 c.4274 T>G（p.L1425R），为该多囊肾家系的致病突变，该结果进一步扩大了导致 ARPKD 的 PKHD1 基因突变谱，并改善 ARPKD 家庭的遗传咨询和产前筛查。

CIZ1 在细胞凋亡中的作用及调控机制

姚晨[1] 刘巧[1] 孙龚萍[2]
1.山东大学基础医学院医学遗传学系
2.山东大学基础医学院组织与胚胎学系

目的 *Ciz1* 是肌张力障碍的致病基因之一。CIZ1 是核基质蛋白，参与 DNA 复制起始以及细胞周期调控。之前有研究报道老年 *Ciz1* 敲除小鼠表现出运动和认知功能障碍，并且与对照小鼠相比，*Ciz1* 敲除小鼠的脑组织内 DNA 损伤、氧化压力以及细胞凋亡都显著升高。目前 CIZ1 在细胞凋亡中的作用和调控机制尚不清楚。本研究通过构建 *CIZ1* 敲低或过表达细胞系，分析 CIZ1 在细胞凋亡中的作用，并探究其调控机制。
方法 利用慢病毒感染构建 *CIZ1* 敲低和过表达的稳转细胞系；使用 staurosporine 作为凋亡诱导药物；利用 Western Blot 和流式细胞术检测细胞凋亡；利用 Western Blot 检测 CIZ1 蛋白剪切。
结果 1. *CIZ1* 敲低细胞较对照细胞在 staurosporine 处理后凋亡比例明显上调；2. *CIZ1* 过表达细胞较对照细胞 staurosporine 处理后凋亡比例明显上调；3. 凋亡细胞中，CIZ1 蛋白被剪切成两个片段；抑制 caspase 活性可以抑制 CIZ1 的剪切。
结论 1. CIZ1 的表达水平对细胞对于凋亡的敏感性至关重要，过高或过低的 CIZ1 水平都会增强细胞对于凋亡的敏感性；2. CIZ1 在凋亡细胞中发生依赖于 caspase 活性的剪切，提示其可能是 caspase 的底物。

一个毛细血管扩张症家系的致病基因筛查

雷星星 廖世秀
河南省人民医院

目的 遗传性出血性毛细血管扩张症（hereditary hemorrhagic telangiectasia,HHT）是一种以大量、反复鼻出血为主要临床症状的遗传性疾病，本研究旨在对一例 HHT 家系进行致病变异鉴定。
方法 收集到一例疑似 HHT 患者，签署知情同意后，采集外周静脉血样本，提取基因组 DNA。对先证者进行全外显子组测序，对候选变异位点采用 Sanger 测序验证，同时参考正常人群数据库、保守性及生物学预测软件对变异进行致病性分析。

结果 分析全外显子测序数据后，检测到先证者 *ACVRL1* 基因（NM_000020）c.738T>G（p.Tyr246*）无义杂合变异，ExAC 数据库中无该变异的人群携带频率。该基因编码激酶 1 样激活素受体（activin A receptor typeII-like1），是 TGF-β 配体超家族的 I 型细胞表面受体，主要在内皮细胞中表达，在血管的发育中发挥着重要作用。
结论 本研究中明确了该例疑似 HHT 患者的病因，并且基因检测对于症状单一的患者可进行早期筛查明确诊断，便于疾病的早期预防。

父亲吸烟对后代精子 DNA 甲基化及长期代谢综合征的影响

柳云云 余波澜
广州医科大学附属第三医院

背景 虽然父亲吸烟可能导致后代肥胖和代谢综合征，但其潜在机制尚未明确。
方法 在本研究中，我们分析了吸烟正常男性（SN）、非吸烟正常男性（N）和非吸烟弱精男性（OA）的精子 DNA 甲基化谱。利用小鼠模型，我们分析了父亲精子和后代肝脏中 *DLK1* 基因的总甲基化和差异甲基化区域（DMR），定量分析了 *DLK1* 的表达水平。此外，还进行了腹膜内葡萄糖耐量试验（IPGTT），检测了血清代谢物，并分析了 F1 后代的肝脏脂质积累。
结果 SN 组精子 DNA 甲基化水平显著升高（$p<0.05$），N、SN 和 OA 组精子 DNA 甲基化模式不同。重要的是，与 N 组和 OA 组相比，SN 组 *DLK1* 基因（cg11193865）的甲基化水平显著升高（$p<0.001$）。在小鼠模型中，暴露于香烟烟雾提取物（CSE）的组在 10 周龄雄性后代的精子中（$p<0.001$）和 *DLK1* 的 DMR 位点（$p<0.05$）表现出显著较高的 DNA 总甲基化水平，肝脏中 *DLK1* 的表达水平显著增加（$p<0.001$）。此外，F1 后代的 IPGTT 和 LDL 水平发生显著变化（$p<0.001$），肝脏脂肪积累增加（$p<0.05$）。
结论 父亲吸烟导致 F1 代精子 DNA 的总甲基化增加和 *DLK1* 基因 DMR 甲基化修饰的改变可能是遗传的，并可能干扰后代长期的代谢功能。

CUL4B 在糖尿病肾病发生发展中的作用及机制研究

金士琦
山东大学基础医学院

目的 糖尿病作为全球的健康负担，发病率和患病率在全球范围内显著增加。糖尿病肾病是两种类型糖尿病最常见的并发症之一, 病因和潜在分子机制尚未完全阐明。近年来，巨噬细胞在糖尿病肾病中的作用受到越来越多的关注。CUL4B 作为骨架蛋白参与构成真核生物中最大的一类 E3 连接酶家族 Cullin-Ring E3 泛素连接酶复合物，参与调控细胞周期、信号传导、DNA 损伤修复、基因表达、染色质重塑和胚胎发育等过程。CUL4B 在慢性炎症及其相关的肾脏损伤疾病方面的功能几乎完全未知，本研究旨在探究 CUL4B 对巨噬细胞的作用及在糖尿病肾病发生发展的作用。
方法 构建髓系敲除 *Cul4b* 基因小鼠，并利用该鼠和对照鼠建立糖尿病肾病模型，同时结合体外实验研究高糖环境下 CUL4B 对巨噬细胞的作用及在糖尿病肾病发生发展的作用。
结果
CUL4B 蛋白水平在糖尿病肾病患者外周血单核细胞标本中上调
高糖和晚期糖基化产物诱导巨噬细胞 CUL4B 蛋白水平上调
髓系特异性敲除 *Cul4b* 显著减少糖尿病肾病小鼠蛋白尿，减轻系膜基质增生、足细胞损伤以及肾脏纤维化
髓系特异性敲除 *Cul4b* 显著减少糖尿病肾病小鼠肾脏浸润的巨噬细胞
结论 糖尿病小鼠中，高糖可以诱导巨噬细胞内 CUL4B 蛋白上调，进而促进巨噬细胞向肾脏的浸润，加重肾脏的损伤。

CUL4B 在间充质干细胞发挥免疫抑制功能中的作用及其机制

韩宏 于瑞祺 蒋百春 龚瑶琴
山东大学基础医学院医学遗传系

目的 间充质干细胞（MSCs）作为肿瘤微环境的重要组分，在细胞因子的刺激下，能够抑制免疫细胞活性，从而促进肿瘤细胞增殖，发挥免疫抑制功能。CUL4B 作为骨架蛋白参与构成 CRL4B 复合物，通过泛素化多种底物蛋白在各项生命活动中发挥重要作用。本课题旨在探究 MSCs 在条件性敲除 CUL4B 后对肿瘤发生发展的影响及其潜在机制，以求对 MSCs 发挥免疫抑制功能提供一种全新的认识。
方法 通过对条件性基因敲除鼠中 MSCs 的提取和培养，对其各种生物指标进行检测；另一方面，将敲除型 MSCs 与肿瘤细胞进行共培养，探究 CUL4B 敲除后对 MSCs 自身以及对肿瘤细胞的影响，并通过小鼠体内实验进一步验证。
结果和结论 CUL4B 敲除后，与 WT 型 MSCs 相比，敲除型 MSCs 增殖、迁移和干性能力均显著下降，衰老速度明显加快。较 WT 型 MSCs 而言,敲除型 MSCs 条件培养基处理或与肿瘤细胞共培养后，肿瘤细胞各项活性均显著增强；敲除型 MSCs 更能显著促进体内肿瘤发生发展。

细胞重生在结直肠癌耐药中的作用及其机制研究

孙龚萍[2] 龚瑶琴[1] 王墨林[1] 王茹[1]
1.山东大学齐鲁医学院基础医学院医学遗传系
2.山东大学基础医学院组织与胚胎学系

目的 结直肠癌患者对化疗药产生耐药是导致结直肠癌治疗后出现复发转移的重要原因之一。探明结直肠癌化疗耐药机制对提高结直肠癌患者生存率，改善患者预后具有重要意义。细胞重生是细胞在凋亡压力下激活效应 caspase 后存活的现象。本研究旨在明确细胞重生是否参与结直肠癌化疗后的复发与转移。
方法 我们利用 Caspase 活性示踪系统 CasExpress 对经历过 Caspase 活化的细胞进行标记和示踪，再通过流式细胞术分选获得紫杉醇和 5-氟尿嘧啶处理后重生细胞（CasExpress+）和凋亡抵抗细胞（CasExpress-）；通过 MTT、EdU 掺入实验、克隆形成实验和裸鼠皮下荷瘤检测重生细胞和凋亡抵抗细胞的增殖能力和体内成瘤能力；利用 MTT、流式细胞术和克隆形成实验检测重生细胞和凋亡抵抗细胞的对化疗药的敏感性；Transwell 实验检测重生细胞和凋亡抵抗细胞的迁移和侵袭能力；尾静脉注射法检测重生细胞和凋亡抵抗细胞体内转移能力。
结果 结直肠癌细胞在紫杉醇或 5-氟尿嘧啶处理后均有少量细胞发生细胞重生。紫杉醇或 5-氟尿嘧啶处理后重生的结直肠癌细胞的增殖能力、皮下成瘤能力、对化疗耐药性、迁移和侵袭能力以及体内转移能力都显著增强。
结论 本研究表明细胞重生参与结直肠癌紫杉醇和 5-氟尿嘧啶治疗后的复发和转移。

睡眠障碍与孤独症谱系障碍相互作用的基因组学分析

陆逸波 王波
上海儿童医学中心

目的 探讨孤独症谱系障碍(ASD)相关拷贝数变异(CNV)区域中长链非编码 RNA(lncRNA)对神经发育的调控作用，筛选其可能调控的睡眠功能相关编码基因。
方法 运用生物信息学分析方法，根据 SFARI 数据库收录的 17 个 ASD 相关 CNV 位点（截至 2021 年 1 月），结合 lncbook 数据库中最新的人类 lncRNA 注释信息，筛选出映射至上述 ASD 相关 CNV 位点、在脑发育过程中表达的 CNV-lncRNA；选取 EBI ArrayExpress 数据库中的 E-MTAB-6814 数据集（包含了来源于 313 个健康人群组织样本的基因转录组数据），对筛选出的 CNV-

lncRNA 和 19957 个具有基因转录组数据的蛋白编码基因进行加权基因共表达网络分析（WGCNA）；通过文献调研，汇总目前已被报道的睡眠障碍和 ASD 相关编码基因，使用超几何分布检验研究上述基因在 WGCNA 划分的共表达模块中的富集情况。
结果 通过 WGCNA 共划分出 9 个与脑相关（相关系数 r>0.2）的共表达模块,功能富集分析结果表明其与神经功能之间存在关联；超几何分布检验结果表明目前已被报道的 1010 个 ASD 相关编码基因在 brown(p=1.803×10^{-33}), yellow(p=1.343×10^{-15}), magenta(p=0.005)三个共表达模块中显著富集, 这三个模块中与已被报道的 45 个睡眠障碍相关编码基因高度相关(r≥0.8)的编码基因共 578 个。 结论 本研究共筛选出 9 个与脑相关的共表达模块，其中 brown,yellow,magenta 三个模块显著富集了目前已被报到的 ASD 相关编码基因；上述三个共表达模块中共包含 3384 个编码基因和 97 个 lncRNA，其中 578 个编码基因与已被报道的 45 个睡眠障碍相关编码基因高度相关(r≥0.8)，提示上述基因在睡眠障碍与孤独症谱系障碍中具有潜在作用。

利用孕妇血清生物标志物和临床指标预测胎盘植入

陈胜柱 余波澜
广州医科大学附属第三医院

背景 胎盘植入(PAS)是产后出血相关母婴死亡的主要原因，临床迫切需要新的 PAS 预测方法。
目的 本研究的目的是开发利用血清生物标志物和临床指标预测 PAS 的新方法。
方法 在这项研究中，103 个蛋白质从一个大型病例对照研究中分三个阶段进行筛选和验证。使用母体血清生物标记物和临床指标生成 PAS 的预测模型，并在另一独立队列中进行测试。用组织病理学和免疫组织化学(IHC)技术分析生物标记物的表达水平，用 QPCR 检测胎盘中的基因表达。建立二元 Logistic 回归模型，计算曲线下面积(AUC)、敏感度、特异度和 Youden 指数。
结果 PAS 患者血清基质金属蛋白酶-1(*MMP-1*)、表皮生长因子(*EGF*)、血管内皮生长因子-A(*VEGF-A*)水平持续升高，组织型纤溶酶原激活物(*TPA*)水平明显低于正常足月对照组、子痫前期(PE)和前置胎盘(PP)。IHC 和 QPCR 分析证实，在人类胎盘的第三学期中，识别出的生物标记物的表达发生了显着变化。结合血清标志物和临床指标建立的预测模型对 87%的 PAS 病例进行了预测，AUC 为 0.94，对无剖宫产史或高龄妇女的 PAS 预测尤为有效。
结论 目前的预测模型对 PAS 的预测需要较低的专业知识和费用，且具有较高的临床应用价值，为临床产前 PAS 筛查提供了一种可行的方法。

利用循环游离 mRNA 进行妊娠疾病的早期预测

徐秀廷 余波澜
广州医科大学附属第三医院

背景 妊娠相关疾病，如胎盘植入（PAS）、前置胎盘（PP）、子痫前期 (PE)和妊娠糖尿病 (GDM)等，发病机制多与胎盘的病理生理状态相关，严重影响着孕妇和胎儿的健康。妊娠相关疾病的早期预测和早期干预可以有效降低不良妊娠结局的风险。因此，临床上急需一种可以在妊娠早期预测妊娠相关疾病的有效方法。循环 mRNA (cfmRNA)是液体活检的检测对象之一，作为蛋白质表达的载体可以反映所属组织器官的状态和功能变化。大量研究表明，cfmRNA 有可能成为预测妊娠相关疾病的新型生物标志物，用于预测 PE、PP 和 PAS。
目的 分析循环游离 mRNA 预测妊娠相关疾病的可行性。
方法 首先，我们从 121 位孕晚期孕妇（正常对照 34 人、先兆子痫 24 人、前置胎盘 24 人、胎盘植入 25 人及妊娠期糖尿病 33 人）的外周血血浆中提取 cfmRNA，采用双标曲线法运用荧光定量 PCR 检测 cfmRNA 标记物的 CT 值及相对浓度，进行 MOM 值转换后确定一组 15 个基因的 panel（*MMP9*、*EGF*、*PAPPA*、*GAPDH*、*MMP1*、*MMP3*、*PPBP*、*ADAM12*、*IGFBP1*、*PGF*、*FLT1*、*MPO*、*PLAT*、*SERPINE1* 和 *VEGFA*，其中以 *GAPDH* 作为内参）。随后，运用此 panel 对 60 人次的前瞻性队列进行检测，获得 cfmRNA 含量随孕周变化的数据。

结果 病例组与正常对照组相比，PAS 患者血浆中 5 种 cfmRNA(*ADAM12* 、*IGFBP1*、*MMP1*、*PAPPA*、*PGF*)含量上升, *VEGFA* 含量降低；PE 患者血浆中 8 种 cfmRNA（*ADAM12*、*FLT1*、*IGFBP1*、*MMP1*、*MMP3*、*PAPPA*、*PGF* 和 *SERPINE1*）含量上升 *PLAT* 和 *VEGFA* 含量降低；PP 患者血浆中 4 种 cfmRNA（*ADAM12*、*IGFBP1*、*PGF* 和 *SERPINE1*）含量上升，*EGF* 含量降低；GDM 患者血浆 cfmRNA 中 *ADAM12* 和 *SERPINE1* 含量上升，*PLAT 和 VEGFA* 含量降低。
结论 本研究初步证实血循环 cfmRNA 可用于妊娠相关疾病的无创产前筛查和早期预测。

先天性心脏病与孤独症谱系障碍相互作用的基因组学分析

陆逸波 王波
上海儿童医学中心

目的 基于拷贝数变异（CNV）、保守性基因突变等潜在致病因素，探讨先天性心脏病（CHD）与孤独症谱系障碍(ASD)的相互作用机制，筛选可能同时调控心脏和脑发育的长链非编码 RNA(lncRNA)
方法 运用生物信息学分析方法，根据 SFARI 数据库收录的 ASD 病例（截至 2021 年 1 月），CHDGKB 数据库收录的单纯性 CHD 病例（截至 2020 年 5 月）和文献报道，汇总并筛选 ASD 和 CHD 相关的 CNV 位点；结合 lncbook 数据库中最新的人类 lncRNA 注释信息，筛选出映射至上述 CNV 位点、在心和脑的发育过程中表达的 lncRNA(CNV-lncRNA)，并进行心和脑中的差异表达分析；根据 Noncode 数据库记录的 lncRNA 保守性信息，筛选出在大鼠、小鼠中保守，且在心、脑发育过程中有表达的 lncRNA。
结果 共筛选出 17 个 ASD 相关 CNV 位点和 44 个 CHD 相关 CNV 位点，共 7 个交集（1q21.1，7q11.23，8p23.1，16p11.2，16p12.2，22q11.2，22q13.3），包含了 514 个 CNV-lncRNA；共筛选出 1386 个映射至上述 CNV 位点、在心和脑的发育过程中均表达的 lncRNA(CNV-lncRNA)，其中 398 个 CNV-lncRNA 在心、脑中表达有显著差异（经 BH 校正后的 p 值 < 0.05 且 LFC 绝对值大于 1）；保守性分析结果表明 1524 个在鼠中保守的 lncRNA 在心中有表达，2084 个在鼠中保守的 lncRNA 在脑中有表达 结论 本研究共筛选出 7 个与 CHD 和 ASD 共同相关的 CNV 位点，包含了 514 个 CNV-lncRNA；共筛选出 398 个在心、脑中表达有显著差异的 CNV-lncRNA 和 3608 个在鼠中保守的 lncRNA，提示上述基因在心脏发育与神经发育中具有潜在作用。

胰岛 β 细胞特异性 IIB 型 PKA 在细胞增殖信号转导中的作用及其机制研究

刘瑞
复旦大学附属华山医院

胰岛 β 细胞不足是引发糖尿病的主要原因。蛋白激酶 A（PKA）介导胰岛 β 细胞增殖，但是作用机制不清。PKA 由调节亚基（R）和催化亚基（C）组成。根据 R 亚基，PKA 分为 4 个亚型，即 IA、IB、IIA 和 IIB 型。我们检测胰岛中 PKA 的表达谱，发现 IIB 型 PKA 在胰岛 β 细胞中特异的高表达。进一步分析发现，2 型糖尿病患者的胰岛中 IIB 型 PKA 水平高于正常血糖对照。我们在胰岛 β 细胞株中敲除 IIB 型 PKA，细胞的增殖增加，而增加细胞内 IIB 型 PKA 含量，细胞的增殖则减少。在 STZ 诱导糖尿病模型中，IIB 型 PKA 缺失（KO）小鼠的高血糖水平明显下降。对胰岛进行免疫组化分析，发现 KO 小鼠的胰岛 β 细胞容量增加。激活 IIB 型 PKA 抑制细胞周期蛋白 D1 的表达，而敲除 IIB 型 PKA 则增加 D1 的表达。IIB 型 PKA 激活时，细胞停留在 G0/G1 的比例增加。以上结果显示，胰岛 β 细胞表达的 IIB 型 PKA 通过抑制细胞周期，从而抑制细胞增殖，提示 II 型 PKA 可能是治疗糖尿病的新的靶点。

RAD21 调控三阴性乳腺癌细胞对阿霉素敏感性的作用机制研究

李斯
山东大学基础医学院

目的 接受化疗的乳腺癌患者容易产生化疗耐药，然而其中的分子机制尚不明确。 RAD21 是导致乳腺癌的癌症驱动基因之一，本研究探讨 RAD21 参与调控三阴性 乳腺癌细胞对阿霉素化疗敏感性的分子机制。
方法 利用流式细胞术、Western blotting 检测 RAD21 低表达的三阴性乳腺癌细 胞内活性氧水平和 DNA 损伤；利用阿霉素的自发荧光分析敲低 RAD21 对乳腺 癌细胞阿霉素摄入和滞留的影响；CCK-8 实验、RT-qPCR 和双荧光素酶报告基 因实验等分析在三阴性乳腺癌细胞中 RAD21 对阿霉素敏感性、NRF2 通路的影 响。
结果 在三阴性乳腺癌细胞中，随着阿霉素作用浓度的升高和药物作用时间的延 长细胞内 RAD21 蛋白水平显著下降；低表达 RAD21 乳腺癌细胞的存活率较对 照组明显增高，细胞凋亡减少，对阿霉素的敏感性下降；与对照细胞相比，RAD21 低表达减慢了三阴性乳腺癌细胞对阿霉素的摄取，促进了药物外排；敲低 RAD21 导致三阴性乳腺癌细胞内 ROS 水平和 γ-H2AX 增加；RAD21 低表达促进乳腺癌 细胞中 NRF2 蛋白累积，激活 NRF2/ABCC3 信号通路；NRF2 特异性抑制剂 ML-385 可逆转 RAD21 低表达引起的三阴性乳腺癌细胞对阿霉素的外排增加。
结论 低表达 RAD21 通过 ROS 产生和 NRF2/ABCC3 信号通路激活降低了三阴 性乳腺癌细胞对阿霉素的敏感性。

LncRNA 1700020I14Rik 介导 miR-26b 调节小鼠胚胎干细胞定向心肌细胞分化的机制

王涵锐 李丽 彭鲁英
同济大学医学院

目的 探究具有潜在调控小鼠心肌细胞分化能力的非编码 RNA，并阐明其具体的调节机制。
方法 我们基于公共数据库小鼠（GSE47948）的心肌细胞分化数据，利用 MEGENA 方法，分析筛选了表达水平差异显著的 lncRNAs，并通过 qRT-PCR 进行验证,初步确定了目的 lncRNA 为 *1700020i14Rik*。进一步分析发现，该 lncRNA 在心肌细胞分化阶段表达显著上调，通过 Fish 技术观察到其主要分布在细胞质中。随后，我们利用慢病毒构建了 *1700020i14Rik* 稳定过表达的细胞株进行观察分析，发现该 lncRNA 能够在分化早期促进中胚层的分化，并在分化晚期抑制心肌细胞的分化。通过 Starbase 数据库预测分析揭示，*1700020i14Rik* 与 *miR-26b* 具有靶向结合的潜在位点，我们进而通过 RIP 实验检测，证明了两者存在 sponge 作用。此外，*1700020i14Rik* 过表达可导致中胚层时期 STAT3 的磷酸化显著上调，从而促进其从细胞质进入细胞核，作为转录因子调控 *miR-26b* 的靶基因 *Ctdsp1* 的转录。通过 FANTOM（Cage-seq）发现，*Ctdsp1* 与 *miR-26b* 共享一套转录启动子，提示，*1700020i14Rik* 亦可通过调控 *miR-26b* 靶基因 *Ctdsp1* 的表达而间接调控 *miR-26b*。最后我们发现，*1700020i14Rik* 过表达可对 *miR-26b* 下游靶基因 ***Gsk3β*** 进行调控，并介导经典 WNT 信号通路参与心肌细的分化的调节。
结论 LncRNA *1700020I14Rik* 可与 *miR-26b* 发生 sponge 作用，进而调控 *Ctdsp1* 的转录表达，从而协同调控心肌细胞的分化。

GIP 增加脂肪细胞内脂素表达

刘瑞 蒋摇静
复旦大学附属华山医院

目的 检测 GIP 是否调节内脂素的合成,以及对内质网应激状态下脂肪细胞内脏脂肪素表达的调节作用，并探讨其作用机制。
方法 以 3T3-L1 分化成熟脂肪细胞为模型，GIP 干预后，提取总 RNA 定量检测内脂素转录水平，收集培养液酶联免疫法检测内脂素分泌水平；PKA 通路抑制剂 H89 预处理 30 分钟，检测内脂素的转录水平。3T3-L1 分化成熟的脂肪细胞，经 Tg 诱导建立内质网应激模型。内质网应激发生通过测定 sXBP-1 表达水平增加来判断。使用细胞核因子 κB(NF-κB)特异阻断剂 PDTC 预处理 30 min，观察 NF-κB 在 GIP 调节内脏脂肪素表达中的作用。
结果 GIP 呈剂量依赖和时间依赖性提升 3T3-L1 细胞表达内脂素，PKA 通路抑制剂 H89 部分阻断 GLP-1 作用。Tg 诱导后 sXBP-1 表达增加，内脏脂肪素表达下降并呈剂量依赖性；同时给予 GIP 处理后，内脏脂肪素表达增加；PDTC 降低内脏脂肪素基础水平，并未阻断 GIP 作用。
结论 GIP 通过 PKA 途径提升脂肪细胞表达内脂素，GIP 提升内质网应激状态下脂肪细胞内脏脂肪素的表达,进而可能提升胰岛功能和周围组织胰岛素敏感性。

RAD21 促进乳腺癌增殖和转移的作用机制研究

王静
山东大学基础医学院

目的 Cohesin 复合物的核心亚基 RAD21 在乳腺癌中有明显基因扩增和高表达，但其作用机制尚不明确。本研究探讨 RAD21 在乳腺癌增殖、转移中的作用机制。
方法 利用 IHC 检测乳腺癌患者肿瘤组织和癌旁组织中 RAD21 的表达；通过平板克隆形成实验、EdU 掺入实验、迁移、侵袭以及小鼠移植瘤实验分析 RAD21 对乳腺癌细胞增殖、致瘤性及迁移和侵袭能力的影响；通过电镜观察 RAD21 低表达乳腺癌细胞中的自噬小体；利用自噬激活剂和抑制剂作用细胞，并经 Western blotting 及 RT-qPCR 检测细胞自噬标志物的表达水平，分析可能涉及的信号通路。
结果 乳腺癌组织的 IHC 结果提示，RAD21 在癌组织中表达明显高于癌旁组织；与正常的乳腺细胞系 MCF-10A 相比，RAD21 在乳腺癌细胞系中表达较高；敲低 RAD21 能够明显抑制乳腺癌细胞的增殖、侵袭及体内成瘤能力；与对照细胞相比，RAD21 低表达乳腺癌细胞 LC3-II 蛋白水平明显减少，细胞自噬水平增加；自噬抑制剂 BafA1 可部分拯救由 RAD21 低表达引起的细胞迁移和侵袭能力降低；敲低 RAD21 后促进了乳腺癌细胞 YAP 蛋白累积和核定位，增强了 YAP 的转录活性；同时敲低 *RAD21* 与 *YAP* 基因可部分拯救由于 RAD21 低表达所导致的乳腺癌细胞迁移和侵袭能力降低、细胞自噬水平升高。
结论 RAD21 在乳腺癌组织和乳腺癌细胞系中高表达；敲低 RAD21 可降低乳腺癌细胞的增殖、迁移侵袭及体内成瘤能力；RAD21 可能通过调控 YAP-自噬轴促进乳腺癌的增殖和转移。

Rare Copy Number Variation Analysis in Chinese Children of Complete Atrioventricular Canal and Single Ventricle

Xing Zhang
Shanghai Childrens Medical Center Affiliated to Shanghai Jiaotong University School of Medicine

Background Congenital heart disease (CHD) is the most common birth defects. Copy number variations (CNVs) have been proved to be important genetic factors that contribute to CHD. Here, we screened pathogenic CNVs in Chinese children with two rare types of CHD, complete atrioventricular canal (CAVC) and single ventricle (SV) .

Methods We screened CNVs in 262 sporadic CAVC cases and 259 sporadic SV cases respectively, using a customized SNP array. The detected CNVs were annotated and filtered using available databases.
Results Among 262 CAVC patients, we identified 44 rare CNVs in 43 individuals (16.4 %, 43/262), including 2 syndrome-related CNVs (7q11.23 and 8q24.3 deletion). Surprisingly, 88.6% rare CNVs (39/44) were duplications of 21q11.2-21q22.3, which were categorized as trisomy 21 (Down syndrome, DS). In CAVC with DS patients, the female to male ratio was 1.6:1 (24:15), and the rate of pulmonary hypertension (PH) was 41% (16/39). Additionally, 6 rare CNVs were identified in the SV patients (2.3%, 6/259), and none of them was trisomy 21.
Conclusions Our study identified 50 rare CNVs in 262 CAVC and 259 SV patients, representing the largest cohort of these two rare CHD types in Chinese population. The results provided strong correlation between CAVC and DS, which also showed sex difference and higher incidence of PH. The presence of rare CNVs suggests the etiology of complex CHD is incredibly diverse, and CHD candidate genes remain to be discovered.

应用限量 dNTP 竞争性 PCR 结合 HRM 技术 检测染色体 4q35.1 微缺失

张星
上海儿童医学中心

背景 高分辨熔解曲线分析技术（High-resolution Melting Curve Analysis, HRMA/HRM）作为一种新型分子诊断技术，已逐渐应用于基因组拷贝数检测并显现出巨大优势。拷贝数变异与遗传性疾病密切相关，染色体 4q35.1 微缺失是先天性心脏病的致病原因之一。本文旨在应用 HRM 建立一种靶向检测该区域拷贝数变异的方法，从而完成染色体 4q35.1 微缺失的快速诊断。
方法 通过限量三磷酸脱氧核苷酸（dNTP）使参考基因（*GAPDH*）与目标基因（*SORBS2*/*TENM3*）之间形成竞争性二重 PCR，依据扩增子的高分辨熔解曲线分析目标基因的拷贝数目。对经基因芯片验证的 8 例样本进行双盲实验，综合两个目标基因 PCR-HRM 的检测结果，完成 HRM 检测染色体 4q35.1 微缺失方法学的建立和准确性验证。应用该方法筛查 200 例先天性心脏病患儿，比较与基因芯片验证结果的一致性。
结果 通过竞争性二重 PCR 结合 HRM 明确区分目标基因 *SORBS2* 及 *TENM3* 的拷贝数目，完全鉴别双盲实验中 4 例微缺失样本和 4 例正常样本，成功建立 HRM 检测染色体 4q35.1 微缺失的方法，准确性为 100%。筛查 200 例 CHD 样本均为正常人。
结论 本文应用限量 dNTP 竞争性 PCR 结合 HRM 建立了一种能够低成本、高特异性筛查染色体 4q35.1 微缺失的方法，真正实现了闭管操作，满足临床高通量的需求，从而快速高效地完成染色体 4q35.1 微缺失的基因诊断。

老化和 Nrf2 基因敲除对小鼠代谢的影响

杨思
广州医科大学附属第三医院

老化是机体应对外界刺激的能力逐渐下降的过程，成为多疾病易感因素。而机体氧化、ROS 增加是老化的重要过程，*NRF2* 作为氧化和抗氧化平衡的调节因子，可能参与老化过程的调节。因此，本研究用 *NRF2* 敲除（KO）的老化模型小鼠来评估 *Nrf2* 缺失对老化过程的影响。根据周龄、基因型和性别，将小鼠分为 8 组。对 12 或 48 周龄的小鼠称重，并进行 IPGTT 实验。小鼠处死后采集血清，分离肝脏、脂肪组织进行 HE 染色实验。结果显示，*Nrf2* 缺失使老年小鼠增重更明显，血糖波动更大。此外，衰老和 *NRF2* 缺失使雌鼠和雄鼠血清甘油三酯（TG）、胆固醇（TC）、低密度脂蛋白（LDL）和高密度脂蛋白（HDL）水平发生不同程度的变化。与年轻组相比，老年雌性小鼠的雌激素水平下降，雄性小鼠睾酮水平下降，*Nrf2* 缺失使雄鼠的睾酮水平变化更明显。HE 染色结

果则表明，老化使小鼠肝脏的脂质累积和脂肪组织的脂肪细胞面积增加，*Nrf2* 缺失使老年小鼠的脂肪细胞面积增加更显著。以上结果表明，老化可能造成机体糖脂代谢紊乱、性激素水平下降和脂质过氧化，而 *NRF2* 缺失使这些生理现象加重。

ETV4 调控滋养细胞的迁移及侵袭参与子痫前期的发生

揭秋玲 马燕琳
海南医学院第一附属医院

研究背景 子痫前期（preeclampsia, PE）是造成孕产妇和围产儿发病和死亡的主要原因之一。目前 PE 发病机制尚未完全明确，缺乏有效的治疗手段，因此寻找到新的诊断标志物，阐明其发病的分子机制，对 PE 进行早期预测和干预，改善妊娠结局，具有重要的意义。
研究目的 探讨 ETV4 对人滋养细胞功能的调控及其在 PE 中的作用。
研究方法 采用免疫组化、免疫荧光检测 ETV4 在分娩胎盘组织中的表达定位；采用 qPCR、western blotting 及免疫组化比较 ETV4 在 PE 组及对照组胎盘组织中的表达情况；在 HTR-8 细胞中采用 siRNA 沉默 ETV4 或外源性质粒过表达 ETV4 后，采用划痕实验、侵袭实验检测 ETV4 对 HTR-8 细胞迁移和侵袭的影响。
研究结果 ETV4 在分娩胎盘的滋养细胞中有较高表达。qPCR、western blotting 及免疫组化结果均显示，与对照组胎盘组织相比，PE 组胎盘组织中 ETV4 表达水平明显下调（$P<0.05$）。进一步，采用 siRNA 干扰 ETV4 表达后，HTR-8 细胞的迁移及侵袭能力显著被抑制，反之，过表达 ETV4 后，HTR-8 细胞的迁移及侵袭能力显著被提高，提示 ETV4 可调控 HTR-8 细胞的迁移及侵袭能力，进而可能参与 PE 的发生。
结论 ETV4 调控 HTR-8 细胞迁移和侵袭能力，在 PE 的发病机制中具有潜在的作用，具有成为 PE 的新诊断标志物的潜力。

CUL4B 在 KRAS 诱导的肺腺癌发生中的作用和机制

柳晓晨
山东大学基础医学院

目的 探究 CUL4B 在 KRAS 诱导的肺腺癌起始阶段的作用及其机制，旨在为理解肺癌发生机制和发现新的治疗靶点提供理论依据。
方法 构建肺泡 II 型上皮细胞特异性激活 $Kras^{G12D}$ 的小鼠肺癌模型。我们将表达 *SPC-cre*、*LSL-*$Kras^{G12D}$ 及 $Cul4b^{flox/flox}$ 的三种小鼠杂交，得到 *SPC-Cre-*$Kras^{G12D}$ 及 *SPC-Cre-*$Cul4b^{flox/flox}$*-*$Kras^{G12D}$ 两种小鼠肺癌模型，探究 CUL4B 对小鼠肺部成瘤的影响。之后利用免疫组化及流式细胞术分析 *SPC-Cre-*$Cul4b^{flox/flox}$*-*$Kras^{G12D}$ 和 *SPC-Cre-*$Kras^{G12D}$ 两种小鼠肿瘤中免疫细胞的比例。
结果 在 $Kras^{G12D}$ 模型中，肺部特异性敲除 *Cul4b* 的小鼠肺部肿瘤数目显著多于同月龄对照小鼠，且肿瘤体积更大，恶性程度更高。免疫组化和流式结果显示：肿瘤大小相似的 *Cul4b* 敲除小鼠与对照小鼠相比，CD45+细胞浸润显著增多。进一步检测发现，Gr1+细胞浸润显著增多，CD4+和 CD8+ T 细胞以及 B 细胞浸润显著减少，F4/80+和 NK1.1+细胞无显著差异。
结论 CUL4B 可能通过调控体内免疫细胞影响肿瘤微环境进而抑制 KRAS 诱导的肺腺癌发生

Quantification of Human Embryonic ζ-Globin Chains in Southeast Asian Deletion (--SEA) Carriers

Yuhua Ye[1] Guoying Sun[2] Zhe Ren[2] Yidan Liang[1] Hualei Luo[1] Peng Lin[1] Xingmin Wang[1] Wenfang Yu[3] Xianqi Ceng[4] Yajun Chen[4] Qianqian Zhang[1] Jin Huang[1] Ping Zhu[5] Liang Lin[2] Xiangmin Xu[1,6]
1.Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University
2.BGI-Shenzhen, 11 Build, Beishan Industrial Zone, Yantian District, Shenzhen 518083, China
3.Department of Blood Transfusion, Shanghai General Hospital, Shanghai, China
4.Women and Children's Health Hospital of Shaoguan, Shaoguan, Guangdong, China
5.Department of Immunology, Southern Medical University, Guangzhou, China
6.Innovation Center for Diagnostics and Treatment of Thalassemia, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

Human embryonic ζ-globin chain is known to re-activate in the peripheral blood of individuals with Southeast Asian (--^{SEA}) deletional a-thalassemia mutation; however, quantitative dynamic expression of ζ-globin in the carriers of this deletion is yet to be elucidated, which is a fundamental question towards the understanding of how ζ-globin gene is silenced in definitive erythropoiesis. In this study, we set out to purify natural ζ-globin from hemolysate of a Hb Bart's fetus with our already-developed monoclonal antibody. A method for absolute quantification of ζ-globin was then developed by using the purified natural ζ-globin as a protein standard with our previously established sandwich ELISA system. Using this method, we quantified the concentrations of ζ-globin chains in hemolysates of 6079 --^{SEA} carriers (--^{SEA}/αα) and 100 normal individuals (αα/αα). ζ-globin chain was detected in none of the 100 normal individuals while the concentrations of 6021 --^{SEA} carriers ranged from 1.55μg/ml to 1487.78μg/ml. Finally, this ELISA-based quantification was verified by an independent approach of mass spectrum targeting an optimized signal from a peptide fragment of ζ-globin in a second cohort of 141 --^{SEA} carriers, which demonstrates a significant positive correlation between these two approaches (R = 0.681). This study might shed light on the mechanism of programmed ζ-globin gene silencing in human through a follow-up genetic study on those --^{SEA} carriers with extreme ζ-globin levels, and thus providing genetic markers for the precise diagnosis and treatment of α-thalassemia patients with highly diverse clinical severity.

CD146 as a promising therapeutic target for retinal and choroidal neovascularization diseases

Xue Bai Zhenglin Yang Zhenglin Yang
电子科技大学

Blood vessel dysfunction causes several retinal diseases, including diabetic retinopathy, familial exudative vitreoretinopathy, macular degeneration and choroidal neovascularization in pathological myopia. Vascular endothelial growth factor (VEGF)-neutralizing proteins provide benefits in most of those diseases, yet unsolved haemorrhage and frequent intraocular injections still bothered patients. Here, we identified endothelial CD146 as a new target for retinal diseases. CD146 expression was activated in two ocular pathological angiogenesis models, a laser-induced choroid neovascularization model and an oxygen-induced retinopathy model. The absence of CD146 impaired hypoxia-induced cell migration and angiogenesis both in cell lines and animal model. Preventive or therapeutic treatment with anti-CD146 antibody AA98 significantly inhibited hypoxia-induced aberrant retinal angiogenesis in two retinal disease models. Mechanistically, under hypoxia condition, CD146 was involved in the activation of NFkB, Erk and Akt signalling pathways, which are partially independent of VEGF. Given the critical role of abnormal angiogenesis in retinal and choroidal diseases, our results provide novel insights into combinatorial therapy for neovascular fundus diseases.

先天性心脏病相关 lncRNA 高通量功能筛选体系的建立与应用

林玉婉 张星玉 王波 傅启华
上海儿童医学中心

目的 利用 CRISPR 干扰（clustered regularly interspaced short palindromic repeats interference, CRISPRi）技术，在 AC16 细胞系中进行先天性心脏病（congenital heart disease, CHD）相关长非编码 RNA（long non-coding RNA, lncRNA）的筛选，以探究其在 CHD 致病中的作用。
方法 1. 构建 CRISPRi 文库：对法洛氏四联症(Tetralogy of Fallot, TOF)患者心脏组织 RNA-seq 数据进行加权基因共表达网络分析，筛选出心脏转录调控高度相关的共表达模块，在数据库查询挑选心脏特异表达的 lncRNA，根据 lncRNA 的启动子区域序列为每个 lncRNA 设计合成 sgRNA 并构建成慢病毒文库。2. 构建 AC16-dCas9 细胞系模型：利用 lncRNA FGD5-AS1 进行 shRNA 慢病毒感染，以确认 AC16 细胞系能否通过慢病毒感染实现 lncRNA 的敲减；随后通过慢病毒感染建立稳定表达 dCas9 的 AC16 细胞系。3. 建立血管紧张素Ⅱ(Angiotensin Ⅱ, AngⅡ)诱导心肌肥大模型：设置系列梯度以及作用时间，并通过对肥大标志物心房钠尿肽（atrial natriuretic peptide, ANP）和脑钠肽(brain natriuretic peptide, BNP)的转录水平进行 qPCR 检测以确认最佳诱导条件。4. 建立 AC16-dCas9-NF-κB 细胞系模型：利用慢病毒感染构建稳定表达 NF-κB 的细胞系，随后通过 NF-κB 所带的蓝色荧光蛋白进行流式分选得到荧光强度高的单克隆细胞株。5. 建立 AngⅡ诱导肥大并通过药物激活 NF-κB 通路进行报告的体系：通过设置系列梯度以及作用时间来确定 NF-κB 通路激活最佳条件。
结果 1. 筛选出 89 个 lncRNA，为每个 lncRNA 设计 3 个 sgRNA，并包装为慢病毒文库。2. 在 AC16 细胞系中，lncRNA FGD5-AS1 进行 shRNA 慢病毒感染后，其转录受到抑制，转录水平降低到 50%左右，敲减效率可以满足实验需要；对所构建的 AC16-dCas9 细胞系中 dCas9 的表达水平进行检测，qPCR 显示 dCas9 的转录水平提高了约 15 倍，Western blot 显示在 180 kD 有浓集的 dCas9 蛋白条带，证明其可稳定表达 dCas9 蛋白。3. 使用 AngⅡ诱导肥大后对肥大标志物 ANP 和 BNP 的 qPCR 检测结果表明，AngⅡ浓度为 1μM，作用时间为 24h 时转录水平提高较多，为最佳诱导条件。4. 得到了 24 株 NF-κB 荧光强度高的 AC16-dCas9-NF-κB 单克隆细胞株。5. 使用豆蔻酰佛波醇乙酯(phorbol myristate acetate, PMA)激活 NF-κB 通路后，流式分析结果表明，PMA 浓度为 50nM 和 1μM，作用时间为 24h，荧光阳性率较高而且荧光强度高的细胞数量较多，通过 qPCR 对肥大标志物以及 NF-κB 转录水平进行检测，结果表明 50nM PMA 和 1μM AngⅡ联合作用 24h，是诱导肥大并激活 NF-κB 通路的最佳条件。
结论 本研究中，我们建立了基于细胞肥大模型 CRISPRi 的 lncRNA 筛选体系，为后续 lncRNA 的功能验证奠定了基础，为 CHD 相关 lncRNA 的系统研究提供了高通量工具。

宿主 vimentin 对柔嫩艾美耳球虫子孢子入侵的影响

刘展
上海儿童医学中心

目的 由艾美耳属（*Eimeria*）球虫造成的鸡球虫病，给禽养殖业带来了巨大的经济损失。宿主 vimentin 是许多病原体感染过程中的关键蛋白，在前期的磷酸化蛋白质组学研究中我们发现，在柔嫩艾美耳球虫子孢子感染后，宿主 vimentin 的磷酸化水平发生了显著变化。因此，我们对宿主 vimentin 在子孢子入侵宿主细胞中的作用进行了探究。
方法 克隆并表达鸡 vimentin，使用 qPCR、western blotting 和间接免疫荧光检测了子孢子感染后 vimentin 的 mRNA 转录水平、蛋白翻译水平、总磷酸化水平和分布的变化。体外侵袭试验评估了用 vimentin 多克隆抗体处理 DF-1 细胞或用 siRNA 下调 DF-1 细胞中 vimentin 表达后子孢子的侵袭率。
结果 结果显示，vimentin 的转录和翻译水平在子孢子感染后 6~72 h 持续升高，vimentin 的总磷酸化水平也发生了显著变化。在子孢子感染 DF-1 细胞约 24 小时后，vimentin 在的子孢子周围聚

集。用 vimentin 多克隆抗体处理 DF-1 细胞或下调 DF-1 细胞中 vimentin 的表达可显著提高子孢子的侵袭率。
结论 本研究表明宿主 vimentin 在子孢子入侵宿主细胞过程中发挥了抑制作用。本研究结果为阐明球虫与宿主互作关系奠定了基础。

香烟暴露对雄性小鼠生殖系统的影响及富氢水的防护作用

秦丽娜 颜宏利
海军军医大学第一附属医院

目的 吸烟是一个全球性问题，据统计，全球有 36%的男性属于吸烟人群，我国的吸烟人口总数达到 3.2 亿，且仍以每年 2%的比率增长，在中国每年死于烟草相关疾病的人数近 100 万。不孕不育已成为社会公共的健康问题，且睾丸对烟草中的有害物质非常敏感。本研究旨在探讨香烟暴露对雄性小鼠生殖系统的具体损伤效应及富氢水的防护作用。
方法 ICR 雄性小鼠随机分成 3 组，每组 10 只，吸烟组（Cig)每天暴露卷烟烟雾 30min，吸烟富氢水组（Cig+H）每天暴露卷烟烟雾 30min，并每天喂养 3 次富氢水，另设正常对照组（NC）。通过记录体重、摄食量、睾丸重量及体积观察香烟暴露对小鼠一般情况的影响；通过 HE 染色、Tunel 观察睾丸组织损伤及细胞凋亡情况；通过 PCNA 观察睾丸细胞增殖情况；通过 CASA 检测小鼠精子数量、密度及活力。
结果 同正常对照组相比，香烟暴露使小鼠体重下降、吸烟富氢水组及对照组小鼠体重呈逐渐上升趋势；吸烟组小鼠睾丸重量较两组轻，体积也较两组小；吸烟组小鼠睾丸出现生精细胞层数减少、排列紊乱、生精小管直径减小、生精小管内出现空泡及钙化，吸烟富氢水组小鼠睾丸损伤并不明显；Tunel 结果显示吸烟组小鼠睾丸凋亡细胞较吸烟富氢水组和对照组增多；PCNA 结果显示吸烟组小鼠睾丸增值细胞较两组少；CASA 显示吸烟组小鼠精子数量较吸烟富氢水组和对照组少且活力也显著降低。
结论 香烟暴露可对雄性生殖系统造成损伤，富氢水对雄性生殖系统具有一定的防护作用。

从海马神经元兴奋性的角度分析敲除神经系统 Cul4b 对小鼠认知能力的影响

姜威 韩宏 刘玉婷 蒋百春 龚瑶琴
山东大学

2007 年，本课题组和英国研究小组发现 *CUL4B* 突变导致人类智力低下综合征，研究证实 *CUL4B* 突变是 X 连锁智力低下综合征的最常见的三个病因之一。实验室前期研究结果发现神经系统特异性 *Cul4b* 基因敲除小鼠（$Cul4b^{Nestin\text{-}Cre}$ 小鼠）表现出学习和记忆能力缺陷。$Cul4b^{Nestin\text{-}Cre}$ 小鼠多个脑区中 GFAP 阳性细胞增多，并证实 CUL4B 调控 GFAP 阳性细胞的分化是通过 PTGDS 介导的。目前我们对 *CUL4B* 基因突变导致 XLMR 的致病机制仍知之甚少。为了进一步探究 *CUL4B* 在神经系统中的功能以及 *CUL4B* 突变导致人类智力低下综合征的致病机制，我们通过一系列行为学范式、组织学及膜片钳等实验方法，探究了神经系统特异性敲除 *Cul4b* 对中枢神经系统功能的影响。行为学分析显示 $Cul4b^{Nestin\text{-}Cre}$ 小鼠存在空间学习记忆障碍和社交障碍，尼氏染色结果显示 $Cul4b^{Nestin\text{-}Cre}$ 小鼠海马 CA1 区及 CA3 区的神经元数量明显减少；透射电镜分析显示 CA1 区突触间隙明显增宽；膜片钳分析显示缺失 Cul4b 导致小鼠海马 CA1 神经元固有兴奋性明显升高、抑制性基本突触传递减弱、神经元兴奋 / 抑制失衡，提示海马环路兴奋性升高。这些结果对于理解 CUL4B 突变导致智力低下综合征的致病机制具有重要价值。

内质网应激蛋白 IRE1α 在足细胞损伤诱发的糖尿病肾病中的保护机制

谢丽萍 贾伟平 郭凯峰 刘军力
上海交通大学附属第六人民医院

目的 足细胞的损伤与丢失在糖尿病肾病蛋白尿的发生发展中具有举足轻重的作用。大量研究表明，细胞内质网应激与足细胞的功能紊乱及其凋亡密切相关。内质网蛋白激酶 IRE1α 在维持内质网功能的稳态平衡中发挥重要作用。我们的研究发现，高糖可以刺激足细胞中的 IRE1α 发生磷酸化，提示 IRE1α 信号通路在调节足细胞功能方面可能发挥重要的生理学功能。本研究旨在深入了解内质网应激信号通路 IRE1α 如何影响肾脏足细胞的功能，进而为蛋白尿的预防与治疗提供新的分子靶点。
方法 在足细胞中进行高糖等处理，检测在不同的时间点及处理浓度下，内质网应激相关信号分子的转录水平及蛋白水平的变化。在不同糖尿病小鼠模型的肾脏皮质组织中，检测 IRE1α 磷酸化激活水平以及 Xbp1 剪切水平的变化，研究 IRE1α-XBP1 信号通路在糖尿病肾病中的激活与应答变化。在 STZ 诱导的 1 型糖尿病小鼠模型和高脂饮食联合 STZ 诱导的 2 型糖尿病小鼠模型中，利用足细胞特异性敲除 IRE1α 的小鼠，研究 IRE1α 在糖尿病肾病进程中发挥的关键作用。
结果 细胞实验表明，内质网应激蛋白 IRE1α 在足细胞中应答于高糖的刺激。用 STZ 连续注射足细胞特异性敲除 IRE1α 的小鼠（PKO:IRE1α *flox/flox*: podocin-Cre)及对照组小鼠 12 周的结果显示，与对照组小鼠相比，PKO 小鼠出现显著的蛋白尿及肾脏肿大现象，提示足细胞中 IRE1α 的缺失会影响肾小球滤过屏障的正常发挥。PAS 和 Masson 染色显示，PKO 小鼠中出现了更为明显的纤维化与糖原沉积，利用 Fibronetin 免疫染色发现，PKO 小鼠在 STZ 处理后肾小球纤维化显著增多，此外利用 WT-1 免疫染色发现，PKO 小鼠在 STZ 处理后足细胞数目明显减少。
结论 在高糖等应激状态下，IRE1α 信号分子被激活，通过其下游效应分子**(XBP1** 或其他下游效应分子**)**参与足细胞功能的调控，维持肾小球滤过屏障功能的正常发挥，而当 IRE1α 信号通路的保护功能受损时，将诱发严重的足细胞损伤并伴随着糖尿病肾病病程的加剧。

成骨发育不全家系致病基因鉴定及疾病特异性诱导多能干细胞构建

李丹丹 代成甫 罗奇 陈洁萍 汤冬娥 戴勇
深圳市人民医院

背景 成骨不全（OI）是一种以多发性骨折为特征的罕见遗传性疾病。一些 OI 患者还具有生长迟缓、牙齿异常、巩膜蓝变、听力丧失、心血管疾病等临床表现。到目前为止，OI 的表型与基因型之间的关系尚不明确，且没有治愈 OI 的方法。因此，建立一个合适的模拟临床病人特征的疾病模型来理解 OI 的病理生理学十分重要。
方法 采集先证者及其患病儿子和健康女儿的血样，并通过全基因组测序（WGS）进行基因分型。用 7 种转录因子（OCT4、SOX2、NANOG、LIN28、cMYC、KLF4 和 SV40LT）对患者和健康受试者外周血单个核细胞（PBMC）进行重编程，获得疾病特异性 iPSC 细胞系和健康供者 iPSC 细胞系。
结果 先证者及其两名患病后代是 COL1A1 外显子 10，c.725 G>T（核苷酸：NM_000088.3，GRCh37）突变纯合子，预测 p.G242V 替换（蛋白质：NP_000079.1）。成功构建了患者特异性 iPSC 系和健康供体 iPSC 系。iPSC 具有 hESC 样形态、表达多能性标记物以及分化为三个胚层细胞的能力。
结论 在这里，我们报告了一个 OI 家族的表型和 iPSCs 疾病模型。OI 家族的详细基因分型以及从 OI 患者和健康家庭成员中建立 iPSC 将为评估 OI 的病理生理学和开发靶向治疗提供强有力的工具。

CLSTN3 在脂肪组织中的作用及调控代谢的机制研究

白宁宁[1,2] 杨颖[1,2]
1.上海交通大学附属第六人民医院内分泌代谢科
2.上海市糖尿病研究所

目的 脂肪细胞调节代谢途径主要包括脂质合成、脂质分解和产热功能，这些功能受损将导致机体脂肪堆积和肥胖的发生。新基因 CLSTN3β 通过调控脂肪组织产热影响能量代谢，而与其共享两个外显子的 CLSTN3 在脂肪组织中的功能尚不明确。本研究将从不同层面阐明 CLSTN3 在脂肪组织中的作用及调控代谢的机制。
材料与方法 我们利用 Intergrative Genomics Viewer （IGV）观察小鼠和人的皮下脂肪组织 RNA-seq 中 CLSTN3 基因的富集表达情况，并通过 RT-qPCR 和 WB 验证了它在人脂肪组织中的表达和细胞定位；通过全基因组关联研究（GWAS）探讨 CLSTN3 基因的遗传变异位点与临床代谢性状的相关性，并检测其位点变异是否影响其表达；利用 AAV 介导的小鼠皮下脂肪 CLSTN3 过表达模型，观察高脂条件下对整体代谢和脂肪组织功能的影响；探究 CLSTN3 过表达对脂肪分解的影响及可能的机制。
结果 我们通过 IGV 发现小鼠和人皮下脂肪组织 RNA-seq 中 CLSTN3 基因的富集表达模式不同，即小鼠皮下脂肪中 Clstn3 的富集表达极低，而人皮下脂肪中 CLSTN3 的富集表达较稳定。实验证实了人皮下脂肪中的 CLSTN3 主要来自于成熟脂肪细胞部分，且表达定位于细胞膜；GWAS 发现 CLSTN3 遗传变异位点 rs7296261 与多项脂代谢性状如 BMI、体脂及总胆固醇等相关，而且此位点变异增加了人皮下脂肪中 CLSTN3 的表达；动物水平发现高脂条件下，皮下脂肪过表达 CLSTN3 小鼠的皮下脂肪重量增加、脂肪细胞增大及纤维化，糖代谢表现出一定程度上的受损；进一步的离体和体内脂解实验显示过表达 CLSTN3 可以抑制脂解分解；机制研究发现 CLSTN3 可以与淀粉样前体蛋白 APP 结合并且稳定它的表达，从而通过抑制线粒体功能影响脂质分解。
结论 这些结果表明，CLSTN3 通过调节脂解分解进而调控脂肪组织功能和机体能量代谢，这可能成为治疗脂代谢异常及肥胖症的靶点。

Identification of novel variants in the LRP5 gene associated with familial exudative vitreoretinopathy in Chinese families

Rulian Zhao
sichuan provincial people's hospital

Familial exudative vitreoretinopathy (FEVR) is a complex hereditary disorder characterized by incomplete development of the retinal vasculature, particularly common in pediatric groups. NDP, FZD4, LRP5, TSPAN12 and CTNNB1 are involved in the Norrin/β-catenin signaling pathway, which plays significant roles in the retinal angiogenesis.In this study, we identified four novel *LRP5* variants. Overexpression of variant-carrying LRP5 proteins results in down regulation of CTNNB1 and Norrin /β-catenin signaling target genes c-Myc and GLUT1. Our study revealed that four inherited LRP5 variants could cause autosomal dominant FEVR and expanded the variant spectrum of this disease.

mLPIss: predicting mouse lncRNA-protein interactions based on features of sequence and structure

Qin Lin[1,2] Luying Peng[1,2] Li Li[1,2]
1.Key Laboratory of Arrhythmias of Ministry of Education, Tongji University School of Medicine, Shanghai, 200092, China
2.Department of Medical Genetics, Tongji University School of Medicine, Shanghai, 200092, China

Motivation Long non-coding RNAs (lncRNAs) play important roles in multiple biological processes. Identifying lncRNA-protein interactions is key to understanding lncRNA functions in pathological and physiological processes. Although there are many algorithms dedicated to the prediction of lncRNA-protein interactions, however, they mainly focus on cross-species. In fact, lncRNAs are poorly conserved. In addition, mice are one of the most commonly used biological model animals worldwide. There still lacks a robust algorithm specifically for predicting mouse lncRNA-protein interactions.
Results We proposed mLPIss leveraging a more biologically meaningful feature encoding approach for extracting lncRNA and protein features based on sequence and structure. During feature encoding, for lncRNAs, sequence and secondary structure are considered; for proteins, sequence, 3-state secondary structure, solvent accessibility and intrinsically disordered regions are involved. In a five-fold cross-validation training, mLPIss outperformed state-of-the-art algorithms RPISeq, IPMiner and RPITER. Meanwhile, mLPIss achieved accuracy of 97.7% in a further independent test dataset. In addition, considering the case of negative data, we found that many lncRNA-protein interaction prediction algorithms suffer from severe overfitting and bad generalization than mLPIss.
Conclusion Based on feature encoding of biological properties, mLPIss can accurately predict mouse lncRNA-protein interactions and is an effective algorithm with excellent generalization.

27 例 V 型成骨不全症患者基因型与表型相关性研究

周思基[1] 李璐璐[1] 米欢[1] 任秀智[2] 赵秀丽[1]
1.中国医学科学院基础医学研究所
2.天津市武清区人民医院骨科

背景 成骨不全症（osteogenesis imperfecta, OI）是一种常见的单基因骨病，主要临床症状为骨密度低下和反复性骨折等。绝大多数 OI 患者由 *COL1A1* 或 *COL1A2* 的杂合突变所致；V 型 OI 由 *IFITM5* 变异所致，患者有骨间膜钙化和增生性骨痂形成。
目的 对 27 例 V 型 OI 患者进行致病突变鉴定，在明确致病突变的基础上进行基因型和表型相关性分析。
方法 查体和 X 射线照相初步临床分型；采集先证者及其家系成员静脉外周血 3-5ml，酚氯仿法提取基因组 DNA；通过全外显子组测序(WES)或 PCR-Sanger 测序进行致病突变筛查；针对检出的可疑致病变异，利用家系共分离分析、保守性分析及生物信息学分析明确其致病性；在明确致病突变后，统计患者表型，进行基因型和表型相关性分析。
结果 全部 27 例 V 型 OI 患者均为 *IFITM5* 变异 c.-14C>T 的杂合子；27 例 V 型 OI 患者存在显著表型差异，其中 55.6%（n=15）的患者存在蓝巩膜，44.4%（n=12）的患者存在牙本质发育不良，7.4%（n=2）的患者存在听力损失，25.9%（n=7）的患者存在韧带松弛，81.5%（n=22）的患者肘部发生畸形，全部患者上肢出现过肥厚性骨痂。
结论 研究表明 *IFITM5* 变异 c.-14C>T 是中国人 V 型 OI 的突变热点；V 型 OI 存在显著表现度差异，但上肢肥厚性骨痂是该病患者的重要临床指征。鉴定热点致病变异和主要临床指征是实现 V 型 OI 精准诊疗的重要途径。

Melting Curve analysis of Nested Asymmetric PCR for one-step typing of Nondeletional α -thalassemia Mutations

Jiachun Qin Mingli Xu Weilun Huang Yang Li Fangchao Tao Wanjun Zhou
Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University

Objective A rapid DNA-based assay is necessary for clinical diagnosis and population screening in thalassemia prevention.Because of high homology and guanine-cytosine–rich and complex second structure of α-globin genes, it is very difficult to find a simple and feasible method for α-thalassemia genotyping. In this study, a nested asymmetric PCR melting curve analysis method was designed to address these factors and ensure sensitivity and accuracy.
Method A novel one-step melting curve assay with nested asymmetric PCR for genotyping of nondeletional α-thalassemia mutations, including hemoglobin Hb Westmead(*HBA2:c.369C>G*), Hb Quong Sze(*HBA2:c.377T>C*), Hb Constant Spring (*HBA2:c.427T>C*),CD30(*HBA2:c.91-93delGAG*), and CD31(*HBA2:c.95G>A*) in a single closed tube, was established and evaluated.
Result All 5 mutations were accurately detected with 100% agreement in a blind analysis of 255 known genotypes and 1,250 clinical samples.
Conclusion This assay is useful for rapid and reliable genotyping of non-deletional α-thalassemia mutations in clinical practice. In particular, due to its high throughput, sufficient stability, low cost, and simple operation, this strategy may have the potential to be a universal rapid genotyping scheme.

十三个白化病家系的致病突变鉴定

杨玉姣
中国医学科学院基础医学研究所

目的 在 13 个眼皮肤白化病（oculocutaneous albinism, OCA）家系中进行致病基因突变鉴定，并在此基础上为患者家庭提供遗传咨询和产前基因诊断。
方法 收集 13 例临床确诊的无亲缘关系的白化病先证者；根据患者毛发、皮肤和眼睛的临床表现进行疾病分型；在获得知情同意后，采集先证者及其家系成员周静脉外周血 3-5 ml；使用常规酚-氯仿法提取基因组 DNA；通过全外显子测序或候选基因 panel 测序鉴定候选基因变异；针对候选致病变异，通过聚合酶链式反应（PCR）和 Sanger 测序的方法进行突变鉴定；通过患者家系中基因型与表型共分离和变异位点的生物信息学分析、等位基因频率分析等确定变异的致病性。
结果 患者的突变阳性检出率为 100%，共发现 15 个致病变异，其中 2 个为新发现变异(*TYR*: c.650G>C, p.Arg217Pro; *OCA2*: c.516-2A>T)；针对错义突变 *TYR*: c.650G>C(p.Arg217Pro)进行的生物信息学分析、家系共分离分析和蛋白结构预测均提示该变异为致病变异。10 例患者由 *TYR* 基因变异致病，为该基因变异的复合杂合子或纯合子，3 患者为 *OCA2* 基因变异的复合杂合子，所有患者父母均为致病突变携带者。
结论 我们在 13 个 OCA 家系中成功完成致病基因型鉴定，发现 2 种新致病突变，拓展了该病的致病突变谱，为进一步开展精准遗传咨询和产前基因诊断奠定了基础。

Characterization of a new 71.8 KB α0-Thalassemia deletion and summary of a subsequent thalassemia molecular diagnostic.

Mingli Xu Jiachun Qin Weilun Huang Yang Li Fangchao Tao Wanjun Zhou
Department of Medical Genetics,Southern Medical University

Objective Our study aimed to identify a case with a novel α-globin gene deletion, and analyze its influence on the expression of α-globin gene.

Method The proband and his parents' samples were extracted to detect α- and β-globin genes by gap-polymerase chain reaction (Gap-PCR), the reverse dot blot (RDB), Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA). Further, targeted next generation sequencing (NGS) was applied to more precisely located the large deletion, and primers flanking both sides of the juxtaposition were designed to amplify the targets near both ends of the deletion by Gap-PCR and the breakpoints were verified by Sanger sequencing of the amplified products. Additionally, Real-time PCR was conducted to investigate the carrier (the father)'s α-globin mRNA level to analyze the effects of this mutation on gene expression.
Result Hematological phenotypic analysis indicated that the proband was a patient with α-thalassemia, his father was with thalassemia minor and his mother showed no obvious abnormality. A heterozygous deletion in the proband was identified by MLPA and NGS, which had proved to be of paternal origin. Gap-PCR and Sanger sequencing confirmed that the 71,846 bp deletion with 5' breakpoint within coordinates 188,959 and 188,970 and 3' breakpoint between 260805 and 260816 was classified as α^0-thalassemia. RNA analysis on the carrier revealed that the relative expression of HBA was lower than normal control, and almost parallel to α^0-thalassemia carriers.
Conclusion A novel 71.8 kb deletion ($--^{71.8}$) was identified and characterized, which included HBZ (ζ), HBA2 (α_2), and HBA1 (α_1) genes and was causing α^0-thalassemia (α^0-thal).We summarized a practical procedure based on accumulated experience in studies and clinical practice, which can be a guide for molecular screening and clinical diagnosis of thalassemia, especially for identification of undetermined or novel mutations. Also, it indicates that NGS is a useful tool in the location of unknown copy number variations.

低磷性佝偻病突变位点的鉴定及致病性分析

曹一璇[1] 尤祎[1] 王琼[1] 任秀智[2] 李闪[1] 管鑫[1] 李璐璐[1] 夏维波[3] 陈秀敏[1] 杨涛[1] 赵秀丽[1]
1.中国医学科学院基础医学研究所 2.天津市武清区人民医院骨科 3.北京协和医院内分泌科

目的 低磷性佝偻病（Hypophosphatemic rickets，HR）是一类以磷代谢异常及骨骼结构异常为主要特征的单基因病。该病多为 X 连锁遗传，由 *PHEX* 基因突变所致。本研究旨在为 HR 家系提供精准分子诊断。
方法 本研究共收集 9 个中国人 HR 家系，包括 18 名患者；收集患者骨代谢生化和影像学资料，提取患者及家系成员外周血基因组 DNA，通过高通量测序对先证者进行突变筛选，并通过 PCR-Sanger 测序进行家系突变验证；通过候选致病突变的进化保守性分析、VarCards 数据库预测及突变蛋白的空间结构预测等生物信息学手段，评估突变致病性。
结果 所有患者均表现出骨骼变形，牙齿脱落，低血磷和高尿磷的临床症状；在家系 1-8 中，共鉴定出 9 个 *PHEX* 基因突变，包括 4 个新突变（c.1661_1726del、c.980A>G、c.1078A>T 和 c.1017_1051dup）和 5 个已知突变（c.591A>G, c.1735G>A, c.1079+1G>A, c.1965+1G>A, c.1699C>T）；家系 9 为由 *SLC34A3* 新突变引起的低磷性佝偻病伴高尿钙血症，先证者为突变 c.1336G>A 和 c.1364T>C 的复合杂合子；所有错义突变进化上高度保守，并可能对蛋白质空间结构产生影响。
结论 本研究在 9 个 HR 家系中发现 11 个致病突变，包括 4 个 *PHEX* 新突变和 2 个 *SLC34A3* 新突变。该研究进一步拓展了 HR 致病突变谱，为开展患者家系的精准遗传咨询和产前基因诊断奠定了基础。

Induced pluripotent stem cells line derived from a patient with Coffin-Siris syndrome-1 caused by ARID1B variation

Xiaomeng Yang
Qilu Children's Hospital of Shandong University

Purpose Coffin-Siris syndrome is a multiple malformation syndrome characterized by mental retardation associated with coarse facial features, hypertrichosis, sparse scalp hair, and hypoplastic or absent fifth fingernails or toenails. Other more variable features may include poor overall growth, craniofacial abnormalities, spinal anomalies, and congenital heart defects. Mutations in the *ARID1B* gene are the most common cause of Coffin-Siris syndrome. Here we induced a pluripotent stem cells line from a patient with Coffin-Siris syndrome-1 caused by a heterozygous mutation c.1924C>T (p.Q642X).
Methods In this study, PBMCs from the patient with Coffin-Siris syndrome-1 were expanded and reprogrammed with non-integrating episomal vectors containing OCT4, SOX2, KLF4, BCL-XL and c-MYC. Generated iPSC line was picked and purified. To determine the IPS cell line, pluripotent markers TRA-1-60, TRA-1-81, SSEA4, OCT4, NANOG test, Karyotype, EBs formation were demonstrated. The nonsense mutation (c.1924C>T (p.Q642X)) in the *ARID1B* gene was also confirmed by Sanger sequencing.
Reaults Human embryonic stem cell (hESC)-like colonies were collected and expanded successfully and the established hiPSC line presented typical hESC morphology. Immunofluorescence assay demonstrated that the iPSCs expressed typical pluripotency markers TRA-1-81, TRA-1-60, SSEA4, OCT4 and NANOG. Quantitative reverse transcription real time PCR (qRT-PCR) further supported the activation of endogenous pluripotent genes OCT4, SOX2 and NANOG. This cell lines were able to form typical embryoid bodys (EBs) with high expression levels of representative markers of three germ layers, including the ectodermal markers NR2F2, TFAP2A, the endodermal markers GATA4, SOX17 and the mesodermal markers HAND1, RUX1. Furthermore, sanger sequencing conformed the heterozygous mutation (c.1924C>T (p.Q642X)) in the *ARID1B* gene.
Conclusions This study induced an iPSC line with nonsense mutation in *ARID1B*, which leads to Coffin-Siris syndrome-1 (developmental delay, coarse facial features, hypertrichosis, clubbed finger). It represents a useful tool for optimization key factors regulating pathways in Coffin-Siris syndrome-1.

结直肠癌致病相关功能性单核苷酸多态性的初步鉴定

刘照 宋宏丽 苗华雪 任华 秦居亮 钱旻
华东师范大学

目的 个体间遗传差异主要源于单核苷酸多态性（SNP）造成的基因变异，会影响机体对疾病易感性以及药物治疗效果等，因而疾病相关功能性 SNP（fSNP）的研究是实现个性化医疗的关键。GWAS 研究报告了许多与结直肠癌（CRC）风险相关的 SNP，但无法将 fSNP 与偶然位于风险位点的其他特征区分开，因此，有效筛选 CRC 相关的 fSNP，揭示其作用机制具有重要意义和应用前景。
方法 通过构建结直肠癌相关的 SNP 文库并进行 Reel-seq 筛选，经高通量测序、质量控制等，获得与疾病相关的候选 fSNP，进一步功能性验证，揭示 fSNP 及调控网络。
结果 根据 GWAS Catalog 数据库合成 13782 个结直肠癌相关 SNP 库，通过 4 轮筛选，得到 349 个候选 fSNP。选取 SMAD7、ATF1、CDH1 基因座上的 10 个 SNP 进行初步验证，结果显示其中 9 个 SNP 存在与核蛋白结合的差异。鉴于 SMAD7 在 CRC 表达上调，且生存率更低。本文选取 SAMD7 基因上 rs12953717、rs7227023 及 LD （r^2>0.8）SNP（rs34007497、rs58920878、rs8085824）进行竞争性 EMSA 和双荧光素酶报告基因的验证，通过 SDCP-MS 鉴定获得 smad7 基因座上 fSNP 结合的特异性转录因子，并揭示了这些转录因子对 samd7 的调控作用。

结论 通过 Reel-seq 方法可以快速鉴定并筛选获得结直肠癌易感基因的 fSNP、揭示其调控网络，为结直肠癌个性化治疗提供有效的治疗靶点奠定理论基础。

原代细胞培养体系的建立及其在海洋药物研发中的应用

王嘉琦
复旦大学基础医学院

研究目的 为了实现海洋药物的精准研发以及应用，我们利用前期所建立的原代细胞培养体系，构建大规模的具有复杂基因型的原代细胞库，并采用高通量自动化药物筛选系统进行海量的海洋药物筛选，最终筛选出更有效更具个性化的潜在海洋抗癌药物。

研究方法

（1）组织标本来源原代肿瘤细胞的培养

收集癌症患者手术组织及活检标本，利用前期改良的条件性重编程细胞培养技术培养包括膀胱癌、前列腺癌、卵巢癌、肺癌等十多种癌种来源的原代细胞，并统计其培养成功率。

（2）液体标本来源原代肿瘤细胞的培养

收集癌症患者的体液标本，包括胸水、腹水、前列腺液以及尿液等，离心分离其中的肿瘤细胞，采用改良的条件性重编程细胞培养技术进行培养，统计其培养成功率。

（3）原代肿瘤细胞的验证

对所培养的原代细胞进行 HE（苏木精-伊红）和免疫组化染色，确定其组织特异性来源。STR（短串联重复序列）位点鉴定和 WES（全外显子测序）检测确定其是否保有亲本组织的遗传背景。细胞迁移实验和小鼠荷瘤实验确定其是否保有肿瘤细胞特有的迁移性和成瘤性。

（4）高通量海洋药物的筛选

用 Multidrop 高通量分液器将原代细胞铺于 384 孔板中，培养过夜后，采用全自动液体工作站进行细胞加药，药物处理 72 h 后添加 CellTiter-Glo 细胞活力检测试剂，之后用 Enspire 多功能酶标仪进行细胞活力检测，计算各个药物对所测细胞的 50%抑制浓度。

研究结果 作者首先建立了基于饲养层细胞的条件性重编程培养体系，实现了从多种癌症患者的肿瘤组织及液体标本中分离原代细胞，并进行体外长期稳定的培养，成功率可达到 80%以上。采用 HE 染色及免疫组化分析确定所培养的原代肿瘤细胞具有亲本组织的组织特异性（图 1）。STR 鉴定和 WES 分析表明其遗传背景与亲本组织的一致性可达到 80%左右（图 2）；细胞迁移实验和小鼠荷瘤实验分别验证了其具有肿瘤细胞特有的迁移性和成瘤性（图 3）。高通量药物敏感性检测发现不同患者来源的原代细胞对药物的敏感性存在明显差异（图 4）。

研究结论 作者建立了一个改良的原代细胞培养体系，成功从癌症患者的组织标本和液体标本中培养原代肿瘤细胞，并验证了其保有原始亲本组织所特有的分子表型和遗传背景，采用这些原代细胞进行高通量海洋药物的筛选，为海洋药物的开发提供了一个更加精准的体外平台。

一个强直性脊柱炎并发骨软骨瘤家系的致病突变研究

郑颖纯[1] 甘众芷[1] 王健[2] 熊符[1,3]
1.南方医科大学基础医学院医学遗传学教研室
2.南方医科大学南方医院关节与骨病外科
3.广东省单细胞技术与应用重点实验室

目的 强直性脊柱炎是一种主要以脊柱，并累及骶髂关节、外周关节为特征的慢性进展性炎性疾病。骨软骨瘤与 EXT1 和 EXT2 基因突变相关，通常位于干骺端的一侧骨皮质，向骨表面生长。本研究对一个强直性脊柱炎并发骨软骨瘤家系进行临床表型及发病机制研究。

方法 通过全外显子测序及 sanger 测序技术明确致病基因及位点，并通过 HRM 技术分析该突变人群频率。对家系成员进行临床表型分析。通过 QPCR、WB 及亚细胞定位技术对 IL17RC 结构及功能进行研究。

结果 该家系先证者为 38 岁男性，脊柱强直呈驼背畸形伴腰部不适。X 线片显示双侧骶髂关节软骨下骨侵蚀，并骨性关节面下骨质硬化。双侧股骨远端以及双侧腓骨头有瘤性改变。全外显子测序分析发现患者有骨软骨瘤明确致病位点 EXT1 c.1019G>A 和尚未见报道的新致病突变 IL17RC c.1067C>T，在 200 例随机人群中没有发现该突变。体外功能实验发现突变后，IL17RC mRNA 和蛋白表达水平降低，在细胞内定位没有发生明显变化。
结论 首次发现 IL17RC 基因编码区发生 c.1067C>T，产生异常蛋白，导致 IL17RC 蛋白结构及功能异常。我们的研究拓宽了强直性脊柱炎致病基因突变谱，为该疾病致病机制提供新的证据。

三个 McCune-Albright 综合征家系的致病变异鉴定

韩明辰 陈秀敏 米欢 赵秀丽
中国医学科学院基础医学研究所北京协和医学院基础学院医学遗传学系

背景 骨性纤维结构不良（fibrous dysplasia，FD）是一种罕见的先天性疾病，其主要病理特征是骨组织增生和纤维化。McCune-Albright 综合征（McCune Albright syndrome，MAS）为综合征型 FD，患者表现为骨组织结构不良、褐色咖啡斑和内分泌功能异常的三联征，由 *GNAS* 基因变异致病。典型 MAS 主要根据三联征表现来诊断，不典型 FD 和早期发病患者临床诊断困难，需要通过遗传学检测来确诊。
目的 对 3 个 MAS 先证者进行致病变异鉴定，以明确其遗传学病因。
方法 查体和骨骼 X 光检查分析进行临床初诊；在征得患者知情同意的前提下，采集先证者及其家系成员肘静脉外周血 3-5ml，酚-氯仿法提取基因组 DNA；通过先证者全外显子组测序（WES）进行致病变异筛查；针对候选致病变异，通过 PCR-Sanger 测序方法先证者的 *GNAS* 基因第 8 外显子进行突变鉴定，并通过疾病与致病基因型共分离和生物信息学分析确定突变致病性。
结果 测序结果显示家系 1 先证者存在 *GNAS* 基因的杂合错义变异 c.601C>T(p.R201C)；家系 2 和家系 3 先证者均存在 *GNAS* 基因的杂合错义变异 c.602G>A(p.R201H)。两种变异均为已知致病变异。
结论 本研究在 3 个 MAS 家系中均发现了 *GNAS* 基因编码蛋白第 201 位氨基酸的错义变异（R201C 和 R201H），再次证明该氨基酸是 MAS 患者的突变热点，提示建立针对该位点的基因检测方法是诊断该病的有效手段。

Mononuclear phagocyte system blockade using mesenchymal stromal cells-derived extracellular vesicles modified with CD47 on membrane surface for myocardial infarction reperfusion injury treatment

Zilun Wei Junbo Ge
Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, China

Mesenchymal stromal cells (MSC)-derived extracellular vesicle (EVs) with anti-apoptosis and anti-inflammatory properties have received intensive study in the field of myocardial ischemia reperfusion (I/R) injury. However, rapid clearance by mononuclear phagocyte system (MPS) remains a huge barrier for delivery of EV contents into target organs and restricted its wide application, particularly heart. Several efforts had been put into practice. Previous research found that cancer cells have the ability to evade clearance by macrophages through some anti-phagocytic surface proteins called 'don't eat me' signals. Cheng G, et al. developed synthetic nanoparticles decorated with the tumor-derived EVs membrane that evades the immune system clearance and promotes target uptake mainly because of surface protein CD47. Kamerkar S, et al. pushed the research forward using plasmids to overexpress CD47 on the surface of EVs derived from normal fibroblast-like mesenchymal cells. Intraperitoneal injected CD47-EVs suppressed EVs clearance from the circulation and enhanced specificity to cancer cells. This study aims to

explore biodistribution and delivery efficiency of EVs carrying specific membrane protein CD47 and specific anti-apoptotic miRNA inside.
Methods EVs were isolated from MSCs overexpressing CD47 (CD47-EVs) and identified. Fluorescence-labeled EVs were injected through tail vein and tracked by fluorescence imaging. In silico analysis was performed to achieve miRNA profiles in MSCs and heart derived H9c2 cardiomyoblast cell line from hypoxia vs. normoxia condition. Electro CD47-EV was constructed by encapsulating purified CD47-EV with miR-21a via electroporation. The effect of miR21-EVs on pro-apoptotic PTEN was evaluated by dual-luciferase assay, qPCR and WB. Exogenous miR21 distribution, the protein level of PTEN, blood vessel density, anti-apoptotic effect by TUNEL staining, and macrophages and leukocytes infiltration in myocardium were assessed by immunofluorescent staining. Cardiac functional recovery during early stage and recovery period was evaluated by echocardiography.
Results Electro CD47-EVs were preferentially accumulated in the heart with prolonged circulation retention. Exogenous miR-21 efficiently internalized into cardiomyocytes, inhibited apoptosis, alleviated inflammation and improved cardiac function.
Conclusion: Electro CD47-EV efficiently improves biodistribution in heart, shedding new light on the application of two-step EV delivery method (CD47 genetic modification followed by therapeutic content electrotransfection) as a potential therapeutic tool for myocardial I/R injury and may benefit patients in the future.

两个短肋胸廓发育不良家系的遗传学分析

管鑫[1] 赵秀丽[1] 米欢[1] 李闪[1] 朱小辉[2]
1.中国医学科学院基础所
2.北京大学第三医院 妇产科生殖医学中心

目的 短肋胸廓发育不良（Short-rib thoracic dysplasia，SRTD）是一类具有高度遗传异质性的严重危害患儿健康的骨骼系统的单基因病，本研究对两例临床初诊为 SRTD 的引产胎儿进行致病基因变异鉴定，并进行疾病分型。
方法 获取知情同意后，对引产胎儿进行全身体征检查，记录患病胎儿临床表现；采用常规酚-氯仿法从胎儿皮肤组织及其父母外周血中提取基因组 DNA，应用全外显子组测序（Whole exome sequencing, WES）对两例 SRTD 胎儿进行候选致病变异筛选；针对候选致病变异，通过 PCR 扩增和 Sanger 测序验证致病变异，并在患儿家系中进行验证；利用 VarCards 在线致病性预测系统分析变异致病性，进一步结合 Swiss-PdbViewer 蛋白质空间结构分析软件预测致病变异对蛋白三级结构的影响，从而确定候选致病变异的致病性。
结果 在两例 SRTD 胎儿中发现 4 个 *DYNC2H1* 变异。胎儿 1 为错义变异 c.515C>A(p.Pro172Gln)和 c.5983G>A(p.Ala1995Thr)的复合杂合子，胎儿 2 为无义变异 c.5920G>T(p.Gly1974*)和错义变异 c.9908T>C(p.Ile3303Thr)的复合杂合子，患儿父母均为致病变异的携带者。c.9908T>C(p.Ile3303Thr)为本研究新发现致病变异；结合临床表现和致病基因型，两例患儿临床分型属于 SRTD3。
结论 在两例 SRTD 胎儿中均鉴定到了 *DYNC2H1* 基因变异的复合杂合子，提示在人群中进行该基因致病变异携带者的筛查对于该病出生预防具有重要意义。

一例 H1-4 基因变异导致 Rahman 综合征的临床与遗传学分析

杨小萌
山东大学齐鲁儿童医院

目的 Rahman 综合征 (Rahman syndrome，RS)是一种罕见的伴有独特先天性多发畸形的常染色体显性遗传病，其主要特征为轻度到重度的智力残疾、全面发育迟缓、巨头畸形、内眦距过宽、骨骼成熟加速和骨骼发育畸形、新生儿肌张力异常、视力异常。2017 年 Katrina 等人鉴定 H1-4 基因突

变导致 RS，目前只发现了 23 个 H1-4 基因突变。本研究旨在分析一例全面发育迟缓、巨头畸形、特殊面容及先天性心脏病患儿的临床表现与遗传学病因。
方法 对 2020 年 8 月山东大学齐鲁儿童医院儿保所接诊的一例患儿的临床表现进行回顾性分析，并采集患儿及其父母外周血，应用染色体核型分析和全外显子组测序技术进行检测，对突变位点进行患儿及其父母的 Sanger 测序验证和致病性分析。
结果 （1）患儿，男，1 岁 1 月，全面性发育迟缓，先天性心脏病，特殊面容、眼距宽，头围大，1 月不会说话，运动及认知发育落后，先天性心脏病。MRI 脑白质体积小，左脑室略宽，B 超示肝脾大，染色体正常，无家族史。（2）测序发现该患儿 H1-4 基因 c.435dupC (p.T146Hfs*50)杂合变异，为新发突变；致病性分析示 c.435dupC 为未报道的截断突变，根据 ACMG 2015 年指南分析为致病性变异（PVS1+PS2+PS4+PM2）。
结论 该患儿最终诊断为 H1-4 基因突变所致 Rahman 综合征，这是国内第一例 Rahman syndrome 综合征的报道；为临床诊疗和遗传咨询提供了依据

自闭症患者脑组织中的长链非编码 RNA

余文君[1] 陈进发[1] 杨新平[1,2,3]
1.Department of Obstetrics and Gynecology, Nanfang Hospital, Southern Medical University, Guangzhou
2.Key Laboratory of Mental Health of the Ministry of Education, Southern Medical University, Guangzhou
3.Department of Bioinformatics, School of Basic Medical Sciences, Southern Medical University, Guangzhou

目的 自闭症谱系障碍 (ASD) 是最常见的神经精神类疾病之一。但现有的研究主要集中在蛋白质编码基因，对于长链非编码 RNA 的研究比较缺乏。且现有的多个自闭症患者脑组织转录组研究发现，长链非编码 RNA 的表达失调可能参与自闭症的发病。系统研究自闭症中长链非编码 RNA 对脑功能的影响变的尤为重要。
方法 本研究通过收集不同数据来源的自闭症候选基因系统地研究长链非编码 RNA 的层级调控网络参与的自闭症相关分子信号通路。以及长链非编码 RNA 作为支架携带蛋白质复合物到细胞对应位置发挥功能。
结果 研究发现长链非编码 RNA 通过与转录因子，靶基因形成层级调控网络，参与调控免疫和突触形成相关信号通路。长链非编码 RNA 作为支架将蛋白复合物携带到细胞核内，参与转录调控，基因组表观修饰，剪切体形成等功能，部分长链非编码 RNA 能够作为支架携带神经递质蛋白复合物到突触上发挥作用。
结论 长链非编码 RNA 通过 lncRNA-TF-target 层级调控网络调控差异表达基因，并且作为支架协同蛋白复合物在细胞内发挥功能。在自闭症的发生发展中长链非编码 RNA 也发挥重要作用。

Long non-coding RNA XIST exerts tumor suppressive functions in Female hepatocellular Carcinoma by DNA methyl modification via TET2

Zhihui Dai[1] Fu Yang[1] Xinggang Guo[2] Hui Liu[2] Yuefan Wang[1] Haozan Yin[1]
1.Department of Medical Genetics, Second Military Medical University
2.The Third Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital

Objective Sex disparities is a major issue in hepatocellular carcinoma (HCC), with significantly lower incidence in females. In mammals, X-chromosome inactivation (XCI) is triggered by the long non-coding RNA XIST (Lnc-XIST) to equalize gene expression between the females and males. However, it is unclear whether Lnc-XIST involving the gender disparities in HCC. This study aimed to investigate the role of Lnc-XIST.
Methods Quantitative real-time PCR was performed to measure the expression of Lnc-XIST and *TET1*, *TET2* and *TET3* in human HCC samples. Methylation of Lnc-XIST was detected by Sequenom MassARRAY methylation profiling between HCC tissues and adjacent normal liver

tissues, then hMeDIP assay was used to verify the methylation results. Copy number variations of TET2 gene were analyzed using the TaqMan copy number assay. The interaction between TET2/YY1 and Lnc-XIST was detected using chromatin immunoprecipitation (ChIP) aaaay. Co-immunoprecipitation (CoIP) and confocal laser microscopy were used to verify the interaction of TET2 and YY1.

Results We demonstrate that Lnc-XIST is expressed at higher levels in female livers than in male livers and is significantly downregulated in HCC tissues compared with adjacent normal liver tissues. Female patients with lower Lnc-XIST expression predicts poor prognosis. The methylation levels of Lnc-XIST was significantly increased in the Lnc-XIST first exon of female HCC tissues compared with adjacent normal liver tissues. By contrast, no significant change was observed in male HCC patients. *TET2* was downregulated in HCC tissues and the expression level of Lnc-XIST was positively correlated with *TET2* whether in HCC tissues or in adjacent normal liver tissues. Moreover, the copy number of *TET2* was significantly lossed in HCC tissues. In addition, TET2 can interact with YY1 binding to Lnc-XIST promoter.

Conclusions Taken together, our study provides that YY1 and TET2 can interact to form protein complexes binding to the promoter region of Lnc-XIST, regulating the methyl modification level of Lnc-XIST, and then affect the expression of Lnc-XIST. This work offers new insights for sex disparities of HCC incidence and opens up the possibility target for HCC treatment.

DNA Methylation and SNPs of ABCA1 gene promoter affect gene expression and involve in the pathological mechanism of ischemic stroke

Zhihao Li[1] Baixue Zhou[1] Jun Wang[2] Yang Liu[1] Zhaojing Zhang[1] Shangdong Yang[1] Yingying Luan[1] Yuanli Wang[1] Xiaoshuai Bie[1] Yan Xu[1] Jing Jia[1] Dongzhi Yang[1] Aifan Li[3] Ying He[1] Hong Zheng[1]
1.Zhengzhou University 2.Henan Medical College
3.The First People's Hospital of Zhengzhou

Objective ATP binding cassette subfamily A1 (ABCA1) is a key protein in the formation of mature high density lipoprotein (HDL), which plays a crucial role in atherosclerosis. Accumulating evidence has shown that the expression levels of the *ABCA1* gene are upregulated in ischemic stroke (IS) patients. However, the mechanism remains elusive. We hypothesized that DNA methylation and SNPs of *ABCA1* gene promoter affect the expression levels of *ABCA1* gene and involve in the pathological mechanism of IS.

Methods 100 patients with IS and 100 healthy controls were enrolled in the present study. Initially, the mRNA expression levels of *ABCA1* gene were examined by qPCR and the methylation levels was detected by MethyTarget sequencing. Then, rs1800976, rs1800977, rs2246298, rs2437817, rs2740483, rs539621172 in promoter region of *ABCA1* gene were selected for genotyping. Finally, the relationship between the methylation of *ABCA1* gene and gene expression was verified by constructing THP-1 foam cell model.

Results The mRNA expression levels of *ABCA1* gene in the IS group were significantly higher than those in controls (P<0.05). 17 CpG sites in the promoter of *ABCA1* gene were analyzed and the DNA methylation levels of CpG1, CpG7 and CpG15 sites in IS group was significantly lower than control group (P<0.05). Rs2740483, rs1800977 and rs2437817 were significantly correlated with CpG1(P<0.05). Rs1800977 was significantly correlated with CpG3(P<0.05).

Conclusion DNA methylation and rs2740483, rs1800977, rs2437817 of *ABCA1* gene promoter affect the expression levels of *ABCA1* gene, change the clearance rate of intracellular lipids, and participate in the pathogenesis of IS.

CFAP47 可能是原发纤毛运动障碍的一个新致病基因

葛海军 刘雅萍
北京协和医学院

目的 对 3 例原发纤毛运动障碍（PCD）男性患者进行基因突变的检测和验证，并对检测到的基因导致疾病的作用和机制进行初步研究。
方法 收集患者外周血提取基因组 DNA 进行全外显子组测序（WES）。分析 WES 测序结果筛选可疑致病变异，并利用 PCR-Sanger 测序进行验证。应用生物信息学软件预测变异的保守性、致病性。构建体外野生型和突变型表达载体，转染 293T 细胞，实时荧光定量 PCR（qPCR）和蛋白质印迹（WB）比较两者在转录水平和翻译水平上的差异。
结果 本研究报道了 3 例 PCD 男性患者，均有典型的 PCD 临床症状，包括鼻窦炎、支气管扩张、内脏异位和精子形态异常引起的不育。WES 测序检测到 3 例 PCD 患者分别在 X 连锁 *CFAP47* 基因上存在半合子变异 c.4316A>T（p.Asn1439Ile）、c.6953C>T（p.Pro2318Leu）和 c.8657T>c（p.Ile2886Thr），Sanger 测序验证与 WES 结果一致。生物信息学软件预测 1439N、2318P 和 2886I 的氨基酸残基在七种随机脊椎哺乳动物中高度保守，且这些位点变异均为有害变异。qPCR 检测到突变表达载体转染 293T 细胞后 mRNA 表达量减少，对应的 WB 条带明显变弱。
结论 本研究筛查到 3 例 PCD 男性患者携带 X 连锁 *CFAP47* 基因不同位置上的错义突变，体外实验证实这三种变异均可导致蛋白表达量下降。本研究首次报道 *CFAP47* 基因变异可能通过使蛋白质功能丧失而导致，是 PCD 的一个新致病基因。

TET1 通过促进核受体 NR2C2 的 5-hmC 水平维持精原干细胞的自我更新过程

刘晓雯 毛增辉
长沙市妇幼保健院

目的 表观修饰在精子发生过程中发挥重要调控作用。特定位点的 DNA 甲基化动态变化是维持正常精子发生的关键。5-羟甲基胞嘧啶（5hmC）是一种 DNA 表观遗传学特征。TET1（Ten-eleven translocation 1）作为主要的去甲基化酶,编码 5-甲基胞嘧啶双加氧酶，将 5-mC 转化为 5-hmC。TET1 缺陷小鼠精子发生被抑制。然而 TET1 对精原干细胞的调控机制和作用仍不清楚。本研究旨在找到精原干细胞中受 TET1 调控的新基因。
方法 本文主要利用小鼠原代精原干细胞（Spermatogonial stem cells, SSCs）提取和分离技术获得实验材料；Crispr/cas9 基因敲除、慢病毒过表达技术进行基因编辑;体外无限稀释、软琼脂集落形成、Western blot、tunel 等实验检测 SSCs 自我更新、分化和凋亡能力；5-羟甲基化 DNA 免疫沉淀结合实时 PCR 分析（hMeDIP PCR）检测 TET1 对下游基因的调控；功能拯救实验检测 TET1 和其靶基因的功能相关性。
结果 TET1 敲除的 SSCs 自我更新和分化能力显著下降，凋亡水平未发生明显变化， 过表达则结果相反；TET1 敲除的 SSCs 中，核受体 NR2C2 转录起始位点 CpG 岛的 5hmC 水平显著减少；SSCs 中敲除 NR2C2 同样可以抑制 SSCs 的自我更新和分化能力；TET1 过表达可以部分回补 NR2C2 敲除后对 SSCs 自我更新和分化能力的抑制作用。
结论 TET1 通过将核受体 NR2C2 启动子处的 5-mc 转变为 5-hmc，从而促进 NR2C2 的表达水平，最终维持精原干细胞的自我更新并促进分化过程。

Influence of type I collagen α 2-chain protein on proliferation of cystic vestibular schwannoma cells and its relationship with DNA methylation

Jianhui Xu
ENT hospital of Fudan university

Background Cystic Vestibular schwannoma (CVS) and solid Vestibular schwannoma(SVS) are subgroups of vestibular schwannoma(VS). CVS has a worse prognosis than SVS, and its etiology and pathogenesis are still unclear. In the previous study, we found that the expression of type I collagen α 2-chain protein (COL1A2) in CVS was significantly lower than that in SVS by iTRAQ/TMT proteomics.
Objective The objectives of this study were to evaluate the relationship between COL1A2 expression and DNA methylation in CVS and its effect on cell proliferation.
Methods Western blotting, immunohistochemistry and qPCR were used to analyze the expression of COL1A2 in 30 CVS patients and 30 matched SVS patients. Bisulfite sequencing was used to detect the methylation level of COL1A2 promoter in CVS. CCK-8 and Wound healing assay were used to detect the effect of up-regulated COL1A2 on the proliferation of VS cell.
Results Western blotting, immunohistochemistry and qPCR results showed that the expression of COL1A2 in CVS was significantly decreased. The methylation of COL1A2 promoter was negatively correlated with its low expression. Upregulation of COL1A2 inhibits VS cell proliferation.
Conclusion: The hypermethylation of COL1A2 promoter in CVS may be responsible for the down-regulation of COL1A2 expression, and then inhibit cell proliferation.

ARL2 GTPase is crucial for development of photoreceptor outer segments by regulating tubulin biogenesis and microtubule assembly

Haolin Wang Zilong Zhang Yifan Wang Jialiang Yang Houbin Zhang
Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China

ARL2 is a small GTPase belonging to the RAS GTPase superfamily. ARL2 gene mutations in yeast cause aberrant chromosome numbers due to unstable microtubules which are required for chromosome segregation during mitosis. ARL2 can interact with tubulin folding cofactor D (TBCD), a chaperone protein involved in tubulin folding during tubulin biogenesis. Recent evidence showed that ARL2 forms a stable heterotrimer with TBCD and TBCE, another chaperone facilitating tubulin folding. ARL2 also interacts with PDEδ and ARL2BP, mutations of which are associated with photoreceptor degeneration. The role of ARL2 in photoreceptors remains undefined. In the present study, we found that overexpression of wild-type ARL2, or mutant ARL2 with defective GTPase activity, in cultured cells led to disassembly of the microtubule network and inhibition of ciliogenesis. In retina-specific *Arl2* knockout mice, the inner segment microtubule network is disorganized and an outer segment axoneme is not formed due to failure in assembly of α- and β-tubulin dimers. Ablation of *Arl2* resulted in greatly shortened and disorganized photoreceptor outer segments, downregulation of phototransduction proteins and loss of photoreceptor function, leading to rapid retinal degeneration completed by four weeks of age. Taken together, ARL2 is required for ciliogenesis by regulating assembly of tubulin heterodimers in order to maintain microtubule integrity, and plays an essential role in retinal function. These findings provide clues for the underlying mechanisms of human neuronal diseases caused by mutation of *Arl2*-interacting genes, such as *TBCD*, *TBCE*, and *ARL2BP*.

Gene4Denovo: an integrated database and analytic platform for de novo mutations in the human

Guihu Zhao Kuokuo Li Bin Li Zheng Wang Zhenghuan Fang Xiaomeng Wang Yi Zhang Tengfei Luo Qiao Zhou Yijing Wang Qian Chen Lou Xia Beisha Tang Kun Xia Jinchen Li
Xiangya Hospital Central South University

Abstract (Background) De novo mutations (DNMs) contributed to sporadic diseases significantly, particularly in neuropsychiatric disorders. Whole-exome sequencing (WES) and whole-genome sequencing (WGS) provided effective methods for detecting DNMs and prioritizing candidate genes. However, it is still challenging for scientists, clinicians, and biologists to conveniently access and analysis DNMs and candidate genes from scattered publications.
(**Methods)** We collected DNMs from original published literatures with sample size more than 10. We then performed comprehensive analysis of collected DNMs. First, ANNOVAR was used to performed comprehensive annotation of DNMs. Second, the transmitted and de novo association (TADA) model was used to calculate the P-value and false discovery rate (FDR) of each gene with Pfun in each disorder. In present study, two strategies were used to prioritize candidate genes. In the first strategy, we performed TADA to calculate the false discovery rate (FDR) of each gene in each disorder. In the second, we combined DNMs of each gene in all disorders and calculate the FDR. Third, genes with different level of FDR in either of above two strategies were classified by the criterions. In addition, we collected a large amount of meaningful annotations for each DNMs and gene from the public databases. Furthermore, we developed a database called Gene4Denovo (http://www.genemed.tech/gene4denovo/) to catalog, search, browse, and analyze these genetic data.
(**Results)** The Gene4Denovo database totally integrated 583,097 DNMs from 23,983 individuals, across 24 types of phenotypes from 63 publications, include 563,565 DNMs detected by WGS from 13 studies and 19532 DNMs detected by WES from 50 studies. Most of DNMs were collected from 9 phenotypes contain 3,391 unaffected controls (n=174,836), 1,548 individuals with Mix phenotypes (n=107,834) and 7 neuropsychiatric disorders include 6,543 patients with ASD (n=283,075), 4,293 patients with UDD (n=8,362), 2,645 patients with CHD (n=2,990), 1,331 patients with ID (n=1,492), 933 patients with EE (n=1,213), 1,094 patients with SCZ (n=1,069), 812 patients with TD (n=805). We catalogued 29,901 DNMs from disorders in coding region including LoF (n=4,384, 1744 frameshift, 1181 splicing, 1430 stopgain, 29 stoploss), Dmis (n=6,622), Pfun (n=11006), Tmis (n=11,820), Syn (n=6,576), NF (n=499). Given that recurrent DNMs might involved in disorders, among 11796 genes carrying DNMs we found 6670 genes with recurrent DNMs (n=24775) and 2072 recurrent genes with recurrent Pfun DNMs (n=7193). To provide a valuable resources for researchers, we developed a database called Gene4Denovo which features a user-friendly query interface and a set of custom functions that provides a comprehensive overview of DNMs, candidate genes and their annotation information. Gene4Denovo integrated data more than 60 genomic sources to provide comprehensive variant-level and gene-level annotation information and knowledge of DNMs and candidate genes. Both quick and advanced search are provided to access the detailed annotation data of DNMs. In addition, Gene4Denovo provides users interface to freely analysis their genetic data. Furthermore, Gene4Denovo provided end-users without enough bioinformatics skills to analysis their own genetic data, perform comprehensive annotation, and prioritize candidate genes with custom parameters.
(**Conclusions)** In conclusion, Gene4Denovo offer large number of freely available DNMs with uniform curation and annotation across 24 phenotypes. Gene4Denovo provided prioritized candidate gene and comprehensive genetic and clinical knowledge from gene level and variant level. A useful feature of Gene4Denovo is the ability to provide a platform for clinicians, geneticists and biologists to get the meaningful information of the interest variants and avoid searching various websites or annotating DNMs by command line. Gene4Denovo provided real conveniences for the researchers without sufficient bioinformatics skills. We hope this database will brings great convenience to accelerate the interpretation of the pathogenicity and clinical implication of variants for geneticists, biologists and clinicians.

The outgrowth: a significant marker indicating the successful establishment of human embryonic stem cell

Xing Zhao
The First Affiliated Hospital of Hainan Medical University

Objectives The developmental potential of human embryonic stem cells makes them valuable in developmental, pharmacological, and clinical research. However, for wide application of hESCs, the derivation efficiency must be improved. The quality of blastocysts is one of the major effects on derivation efficiency, and the outgrowth is a significant phase from blastocyst to hESC, which predict the outcome of the derivation. Herein, we explore the relationship among the quality of blastocysts, the outgrowth and the hESC, and strive to improve the derivation of hESCs.
Methods 97 blastocysts were included into research, and the hESCs were derived in mTeSR and HFF with mechanical method. Statistic analysis was used to explore the effect of the embryo quality on establishing the hESC, and the time of recutting the outgrowth.
Results 12 hESC lines were derived from the discarded and surplus embryo, two of them couldn't grow beyond passage 2 because of bacterial contamination, and two hESC lines were established successfully without the outgrowth phase, these blastocysts were of good quality. No hESC line was established from poor-quality blastocysts. During the derivation, it would be necessary to recut and reseed the outgrowth when it became equal to or larger than the ICM.
Conclusion High-quality blastocysts could indicate the possibility of the successful derivation, especially those with high-score ICM. Timely isolation of the outgrowth was a valid method to enhance the rate of derivation, it would be another effective approach to attempt to raise the rate of outgrowth.

小鼠上颌突发育轨迹和转录调控网络的探索研究

孙健
上海交通大学医学院附属第九人民医院

目的 利用多种前沿测序手段解析小鼠上颌突组织的早期发育轨迹，初步探索在早期发育过程中起作用的转录调控网络
方法 手术分离胚胎期 10.5、11.5、12.5 天的野生型小鼠的上颌突组织，对其进行 bulk RNA-seq、scRNA-seq 和 ATAC-seq，并对测序结果进行数据分析和比较。
结果 结合 bulk RNA-seq 和单细胞 RNA-seq 检测数据全面描述了小鼠上颌突组织在胚胎期 10.5 天到 12.5 天早期发育期间的转录组动力学，对上颌突组织的间充质细胞不同发育状态的细胞群进行了分类，并绘制了它们的发育轨迹图谱，揭示了上颌突组织在胚胎 11.5 天时发生了向骨软骨生成命运或非骨软骨生成命运的分化分叉，推导了与间充质细胞命运转换相关的核心转录调控因子和基因调控网络，并结合 ATAC-seq 测序数据进一步揭示了在上颌发育过程中与染色质可及性动态变化相关的转录因子。
结论 作者的这项研究为上颌突组织的发育研究提供了丰富的数据资源和重要的见解思路，以实现从宏观层面系统地了解颅颌面形态发生的过程和此过程中可能产生重要作用的转录调控网络，对于理解颅颌面的正常发育和一些先天畸形的病因提供了重要参考。

has-mir-296-5p 通过调控细胞运动相关基因导致精子活力低下的机制研究

麦瀚然 左连东 李苗苗 柯君怡
广州市妇女儿童医疗中心（珠江新城院区）

目的 探索 has-mir-296-5p 在导致低活力精子表型中的调控作用。

方法 1、选择精子总活力<20%的弱精子症病人 10 例以及精子总活力>80%的成年男性 10 例进行 miRNA 测序，对比筛选出在两组人群中有表达差异 miRNA，选择差异表达最显著的 miRNA（即 has-mir-296-5p）并构建该 miRNA 慢病毒载体。
2、用此慢病毒感染正常的 GC2-spg 细胞，得到 has-mir-296-5p 过表达的、敲除以及转染对照组病毒的 GC2-spg 细胞，分别设置为 OE 组、KO 组和 CON 组细胞。
3、将上述三组细胞分别进行 miRNA 实时荧光定量核酸扩增检测，确认病毒感染效果。
4、CON、OE、KO 三组细胞分别进行细胞划痕实验和 Transwell 实验，比较三组细胞的迁移速率。
5、提取三组细胞 RNA 后进行实时荧光定量核酸扩增检测，比较三组细胞中细胞运动相关基因的表达差异。
结果 1、细胞划痕实验中，KO 组细胞向中间空白处迁移的速率明显大于 CON 组和 OE 组细胞，且 OE 组细胞的迁移速率要略小于 CON 组细胞。
2、Transwell 实验中，KO 组细胞穿过小孔的数量要明显多于 CON 组和 OE 组细胞，且 OE 组细胞穿过小孔的数量少于 CON 组细胞。
3、在对 mRNA 的实时荧光定量核酸扩增检测中，KO 组细胞细胞运动相关基因基因表达量明显高于 CON 组和 OE 组细胞，且 OE 组细胞运动相关基因表达量显著低于 CON 组细胞。
结论 has-mir-296-5p 过表达的 GC2-spg 细胞运动能力下降，has-mir-296-5p 下调的 GC2-spg 细胞运动能力增强，说明 miRNA 在调控精子运动能力方面起着一定的作用，但其确切作用靶点基因仍然需要更多实验来验证。另外靶基因的差异表达如何调控细胞运动力仍然需要继续对进行下游通路进行研究。

CUL4B 参与肺癌吉西他滨耐药的机制研究

杨园园
山东大学基础医学院遗传学系

目的 明确 CUL4B 是否参与调控肺癌吉西他滨（GEM）化疗耐药并探明其相关机制。
方法 人肺癌细胞株 A549 和 H1299 细胞中分别转染 CUL4B 敲低质粒及 CUL4B 过表达质粒，建立 CUL4B 敲低和高表达细胞株；通过 MTT、EDU 掺入实验、克隆形成实验等检测并比较 CUL4B 不同表达水平细胞经 GEM 处理后生长、增殖等情况；利用划痕实验检测 GEM 对 CUL4B 不同表达水平细胞迁移能力的影响；Western blotting 检测 CUL4B 不同表达水平细胞中多种耐药相关蛋白的表达情况；芯片检测结合软件分析发现肺癌细胞中可能受 CUL4B 调控并参与耐药蛋白表达调控的候选 miRNA；实时定量 PCR 及 ChIP 等实验明确 CUL4B 下游调参与 GEM 耐药调控的 miRNA 及相关机制。
结果 CUL4B 表达水平与肺癌细胞 GEM 耐药相关；敲低 CUL4B 增强肺癌细胞对 GEM 的敏感性，高表达 CUL4B 可导致肺癌细胞对 GEM 耐药；CUL4B 通过表观遗传抑制 miRNA 进而影响耐药蛋白表达调控肺癌 GEM 耐药。
结论 CUL4B 通过表观遗传学机制参与调控肺癌 GEM 耐药

A genetic variant in IL-6 lowering its expression is protective for critical patients with COVID-19

Yi Yin[1,2] Bo Gong[2] Lulin Huang[2] Yongquan He[2] Wen Xie[3,4] Zhenglin Yang[1,2]
1.Institute of Chengdu Biology, Sichuan Translational Medicine Hospital, Chinese Academy of Sciences, Chengdu, Sichuan, China
2.Human Disease Genes Key Laboratory of Sichuan Province and Institute of Laboratory Medicine, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, Sichuan, China
3.Center for Gene Diagnosis & Department of Laboratory Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China
4.Department of Laboratory Medicine, Wuhan Leishenshan Hospital, Wuhan, Hubei, China

Purpose Critical coronavirus disease 2019 (COVID-19) is associated with high mortality and potential genetic factors have been reported to be involved in the development of critical COVID-19. We performed a genome-wide association study to identify the genetic factors responsible for critical condision with COVID-19.
Methods We identified a genome-wide difference of genetic variant in *IL-6* (A>G) between critical patients with COVID-19 and healthy controls from Chinese population, which was significant association of this variant with COVID-19. And we used elisa kits to measure the level of IL-6 in serum in patients compared with healthy controls. We further detected this variant affect luciferase activity by doul luciferase experiment.
Result We identified a genome-wide significant difference of *IL-6* (p=9.73×10^{-15}, OR=0.41) between 437 critical patients with COVID-19 and 2,551 normal controls in the discovery cohort. When replicated these findings in a set of 195 patients with critical COVID-19 and 470 healthy controls, we detected a significant association of with COVID-19 (p=8.89×10^{-3}, OR=0.67). This variant surpassed the formal threshold for genome-wide significance (combined p=4.64×10^{-16}, OR=0.49). Further analysis found that there was a significantly stronger expression of IL-6 in the serum from patients with critical COVID-19 than in that from patients with asymptomatic COVID-19. An *in vitro* assay showed that the A to G allele changes within IL-6 obviously decreased the luciferase expression activity. When analyzed the effect of this variant on the IL-6 in the serum based on the genotype, we found that the A to G variation decreased the expression of IL-6 especially in male.
Conclusion We identified a genetic variant in *IL-6* that protects against critical condition with COVID-19 though decreasing IL-6 expression in the serum.

先天性心脏病合并内脏异位中 CUX2 基因突变的致病机制研究

冯志宇
复旦大学附属儿科医院

先天性心脏病（先心病）是最常见的先天畸形，是婴幼儿死亡的常见原因之一。研究提示，活产婴儿中先心病患病率为 6‰～10‰。鉴于先心病的致死率较高，影响新生儿的生命质量，有必要对先心病的遗传调控进行探讨及研究。遗传因素和环境因素被认为在先心病的发病中有关键作用，单一因素导致先心病的发生占比较少，约 75%-90%是由这两个因素一起作用所导致。遗传因素主要包括单基因缺陷、多基因缺陷、染色体异常等。环境因素主要指包括物理因素、化学因素和生物因素等。除基因缺陷、染色体异常等导致相关基因的编码区异常外，与心脏发育相关的基因表达异常或者信号通路的异常也可导致先心病的发生。近些年来二代测序技术的迅速发展对先心病的遗传学研究的推动起着极其重要的作用，在对大量先心病核心家系进行高通量测序后，发现了许多致病新基因以及突变位点。
内脏异位是一种内脏器官左右位置随机化的先天性缺陷，可以影响包括脾脏、 肝脏、胃和胆囊等多个器官的 LR 排列，但是影响后果最为严重的是心脏的 LR 结构，这类先心病约占所有先心病 3%左右。先心病与内脏异位高度相关。根据美国国家出生缺陷预防研究收集的 378 例内脏异位合并病例中，有 90.2%患有先心病，其中 82.8%为复杂先心这些发现表明，左右轴发育研究表明，

内脏异位在具有血缘关系的个体重中高发病率和罕见的单基因疾病模式的 存在均表明了内脏异位的发病具有遗传特性，但是内脏异位无论是在表型和基因型上均有异质性使得对此类疾病的基因诊断变得尤为困难。内脏异位主要是散发发病，表明新发错义突变对于内脏异位的发生起着至关重要的作用。随着第二代测序技术（NGS）的迅速发展，对导致先天性发生的遗传致病基因和位点的筛查成为了现实。

同源盒基因是一类转录因子，对于胚胎发育过程中的人体模式起着至关重要的作用，可以指导多细胞动物物种沿头尾轴形成身体结构。一些同源盒基因编码转录因子，另一些形成紧密的相互作用效应参与心脏的发育以及心脏祖细胞的增殖过程。同源盒基因可以调控下游靶标的转录以及表达从而影响细胞和器官的生理功能，因此部分同源盒基因的突变往往都很致命，在出生时或出生后相应的器官包括心脏都会发生明显缺陷。*CUX2* 具有 4 个 DNA 结合域，包括同源盒蛋白结构域。胎儿的心脏和大脑在发育过程中是同步进行的，患有神经系统相关疾病的患儿会有极高风险出现心脏发育异常，*CUX2* 主要在神经发育过程中起着重要作用，例如参与突触、树突分支形成以及脊柱发育等，*CUX2* 的异常表达会导致神经发育障碍如孤独症、精神分裂症以及精神发育迟滞等。除此之外，*CUX2* 还与骨髓增生性肿瘤、甲状腺瘤等癌症相关。

本课题拟观察 *CUX2* 从头错义突变与先心病的发生的关系，以及 *CUX2* 基因缺陷在先心病合并内脏异位发生过程的致病作用和机制。

骨髓间充质干细胞来源的外泌体通过抑制大鼠子宫内膜细胞铁死亡促进子宫内膜损伤修复

肖邦 王芳 朱怡卿 黄金凤 陈美婷 刘梦
海军军医大学

目的 比较研究骨髓间充质干细胞来源的外泌体（BMSCs-Exo）对损伤前后大鼠子宫内膜细胞铁死亡的影响。

方法 采用透射电子显微镜检测 BMSCs-Exo 处理前后大鼠子宫内膜机械损伤模型细胞铁死亡的变化。采用 real-time PCR 和蛋白印迹测定 BMSCs-Exo 处理前后大鼠子宫内膜损伤模型中铁死亡标记分子谷胱甘肽过氧化物酶 4（GPX4）和 4-羟基壬烯酸（4HNE）的表达水平。

结果 机械损伤 48h 后，大鼠子宫内膜组织中细胞线粒体浓缩，线粒体膜增厚，脊减小或消失，线粒体外膜破裂，这提示机械损伤后，子宫内膜组织中的细胞发生铁死亡。铁死亡标记物 GPX4 在损伤子宫内膜组中的表达量显著下调（$P < 0.05$），而 BMSCs-Exo 可以显著上调损伤子宫内膜组织中 GPX4 的表达；机械损伤 48h 后，大鼠子宫内膜组织中 ROS 主要代谢产物 4HNE 的表达显著高于假手术组，BMSCs-Exo 干预可显著地下调大鼠子宫内膜损伤区域中 4HNE 的表达（$P < 0.05$）。

结论 铁死亡可能在损伤后大鼠子宫内膜的病理过程中发挥重要作用，而 BMSCs 来源的外泌体可能通过抑制损伤后大鼠子宫内膜细胞的铁死亡来促进子宫内膜损伤修复。

MTCards: Genetic Landscape of mtDNA in the Chinese Population

Yijing Wang[1,2] Jinchen Li[1,2]
1.Xiangya Hospital, Central South University
2.School of Life Sciences, Central South University

Objective Increasing evidence suggests that mitochondrial dysfunction is implicated in several diseases and aging. However, the genetic landscape of the mitochondrial genome (mtDNA) in the Chinese population has not been fully examined. The aim of this study was to comprehensively characterize the genetic landscape of mtDNA in the Chinese population, from mtDNA variants, haplogroups, and copy number.

Methods We recruited a total of 3,241 unrelated Chinese individuals and performed whole-genome sequencing in all individuals by Illumina HiSeq platform. A well-designed pipeline was used to detect mtDNA variants, including single nucleotide variants (SNVs) and small insertions/deletions (indels). We used the HaploGrep2 software to classify each individual into different mitochondrial haplogroups based on detected mtDNA variants. We calculated mtDNA copy number for each individual by comparing the mean sequencing depth of nuclear DNA and mtDNA.
Results The average sequencing depth of the whole genome was 12-fold, and the average sequencing depth for mtDNA was approximately 1,198-fold, and 98.9% of mtDNA regions were covered at least 500-fold. We identified 3,892 mtDNA variants at a heteroplasmic level of 1% or higher, of which 3,349 (86%) were rare variants. Interestingly, most rare variants were identified in homoplasmic or high heteroplasmic levels. Overall, our results show that each individual carries 37.0 homoplasmies and 4.1 heteroplasmies on average. Notably, 86.5% (n = 2804) individuals had at least one heteroplasmies. Our study observed a distinct purifying selection on mtDNA, which inhibits the accumulation of harmful heteroplasmies at the individual level: (1) the mitochondrial dN/dS ratio was much less than 1; (2) the dN/dS ratio of heteroplasmies was higher than homoplasmies; (3) heteroplasmies had more indel and predicted deleterious variants than homoplasmies. Furthermore, we found that haplogroups M (20.27%) and D (20.15%) had the highest frequencies in the Chinese population, followed by B (18.51%) and F (16.45%). The number of variants per individual differed across haplogroup groups, with a higher number of homoplasmies for the M lineage. Meanwhile, mtDNA copy number was negatively correlated with age but positively correlated with the female sex. Finally, we developed an mtDNA variation database of Chinese populations called MTCards (http://genemed.tech/mtcards/) to facilitate the query of mtDNA variants in this study.
Conclusion This study provides a comprehensive genetic landscape of mtDNA in the Chinese population, which will help us better understand the molecular basis of multiple human diseases caused by mitochondrial dysfunction. We also developed a public research resource of mtDNA variants, MTCards, which is a large-scale dataset, and created a tremendous resource for further identification of pathogenic mtDNA variants in mitochondrial-related diseases in the future.

一个智力发育迟缓家系的 SOX5 致病突变研究

甘众芷
南方医科大学基础医学院医学遗传学教研室

目的 智力发育迟缓是高度异质性疾病,具有复杂的遗传学病因。我们主要对采集的智力发育迟缓家系进行突变基因的功能分析，并揭示其分子机制。
方法 通过对该家系成员进行高精度临床外显 PLUS 检测和分析，检测到 SOX5 基因可能是与该智力发育迟缓家系相关的罕见变异。在生物信息方面，用 SIFT 和 Mutation Tasting 预测 SOX5 蛋白有害性和致病性，并使用 I-TASSER 预测 SOX5 蛋白二级结构和三级结构。在细胞功能方面，构建 SOX5-EGFP 载体，瞬时转染 293T 和 N2A 细胞，然后通过 QPCR、WB、细胞周期流式分析以及亚细胞定位技术对突变的 SOX5 结构及功能进行研究。
结果 该家系临床表型为智力发育落后，生活可自理，做简单工作。全外显子测序分析发现该家系患者 SOX5 基因杂合变异（c.211C>T）。生物信息学分析显示该突变具有有害性和致病性，可以导致 SOX5 蛋白二级结构和三级结构改变，。在体外功能实验中，QPCR 和 WB 显示突变 SOX5 的 mRNA 和蛋白质表达水平增加，WB 和流式发现突变 SOX5 细胞周期阻滞。
结论 该家系 SOX5 基因杂合变异（c.211C>T）可能参与智力发育迟缓发生发展过程，可能通过增加 SOX5 蛋白的水平，阻滞细胞周期，从而影响神经细胞周期的退出，影响神经细胞发育和分化。

EIF2 信号通路在选择性生长受限双胎妊娠中的差异表达

李维 张静
深圳市南山区妇幼保健院

目的 选择性胎儿生长受限双胎妊娠的潜在病理机制尚不清楚，作者前期全转录组测序研究表明其可能与胎盘中的 EIF2 信号通路有关，本研究旨在调查选择性生长受限双胎妊娠和正常生长的同卵双胞胎之间的胎盘 EIF2 信号通路的表达差异。
方法 这是一项单绒毛膜双胎妊娠合并选择性胎儿生长受限的前瞻性研究，样本均为胎盘，包含 15 例选择性胎儿生长受限单绒毛膜双胎妊娠 (疾病组)和 15 例正常生长的双胎妊娠(对照组)。本研究对疾病组和对照组中胎盘中的 EIF2 信号通路的分子 RNA 表达水平采用实时定量聚合酶链反应进行了定量和比较。
结果 EIF2 信号通路中 PI3K、AKT、EIF3、EIF5 和核糖体蛋白的 RNA 表达量在两组样本中出现了显著性差异。双胎中较小胎儿/较大胎儿的比值中位数在疾病组 vs.对照组中分别为: PI3K: 0.42 vs. 0.88; AKT: 0.38 vs. 0.79; EIF3: 1.9 vs. 0.72; EIF5: 0.42 vs. 0.76; 核糖体蛋白： 0.53 vs. 0.82。P 值均<0.05。在选择性生长受限胎盘中，PI3K 和 AKT 下调引起其抑制的下游分子 EIF3 上调，EIF3 上调可促发凋亡。另外，EIF5 和核糖体蛋白的下调可引起蛋白翻译过程广泛受阻。
结论 和正常生长的同卵双胞胎的胎盘比较，EIF2 信号通路在选择性生长受限双胎胎盘中的表达中出现了差异显著，我们的工作揭示了新的胎儿生长受限的病理机制。

PNPLA4 基因在先天性心脏病合并内脏异位发病机制中的作用

高涵
复旦大学附属儿科医院

目的 探究 PNPLA4 基因在先天性心脏病（CHD）合并内脏异位（HTX）发病中的相关机制研究。
方法 收集 2001 年 1 月到 2018 年 12 月在复旦大学附属儿科医院心血管中心住院的散发性先天性心脏病合并内脏异位患儿共计 121 例的临床资料及血液样本，利用高分辨率染色体微阵列分析（CMA）检测并进行生信分析，筛选出复现性拷贝数变异及其包含的致病高度相关基因 PNPLA4。在斑马鱼动物模型利用 mRNA 显微注射及 AC16 心肌细胞模型中利用瞬时过表达技术验证 PNPLA4 的相关致病机制。
结果 在 121 例行 CMA 检查的先天性心脏病合并内脏异位患儿中，发现出室间隔缺损（53 例）和房间隔缺损（58 例）外，内脏异位最常伴发的先天性心脏病为大动脉转位（57 例）、房室间隔缺损缺损（38 例）及右室双出口（37 例）；有 17 例患儿共计携带 18 个有临床意义的拷贝数变异，其中 Xp22.31 重复综合征在两名患儿中重复出现，结合 DECIPHER 数据库中资料，发现 PNPLA4 基因为相关致病基因。在斑马鱼中过表达 pnpla4 基因后发现心脏环化出现异常，同时伴有心包水肿及体轴弯曲。在 AC16 中过表达 PNPLA4 基因后 ATP 含量增多，转录组测序结果提示呼吸链相关过程及纤毛形成过程受影响。进一步分析显示 PNPLA4 可以影响线粒体功能及出及初级纤毛，此外 PNPLA4 也通过干扰 RXRA 功能及 F-actin 形态参与相关致病机制。
结论 PNPLA4 作为新发现的相关性基因，在先天性心脏病合并内脏异位中可能通过线粒体功能及 RXRA 活性引起一定的致病作用。

一罕见 PURA 病例的表型与基因型的相关性研究

郭奕斌[1] 郑诗瑶[1] 黄颖[2] 袁杨杨[3] 杨有朋[1]
1.中山大学医学院医学遗传室
2.中山大学中山医学院医学遗传室 3.中山大学中山医学院生信教研室

目的 揭示一罕见 PURA 综合征病例的分子遗传学发生机制，为今后的产前/植入前基因诊断奠定基础。
方法 在临床初诊的基础上，对先证者及其父母的血样进行全外测序（WES）。经 KING、plink 软件进行亲缘关系鉴定，通过 KGGSeq 对变异信息进行筛选，结合 Phenolyzer、STRING 数据库和文献调研对过滤得到的变异进行分析，确定候选突变，并对核心成员进行测序验证和新突变的致病性鉴定。
结果 (1)通过初筛找到 COL6A3（c.5393G >A/p.R1798H）、DHCR7（c.1168C>T/p.H390Y）、GLB1 （ c.1310A>G/p.N437S ） 、 INPP5E （ c.1381A>G/p.S461G ） 、 KCNT1（ c.3317G>A/p.Rl106Q ）、MLC1（ c.65G>A/p.R22Q ）、PURA（ c.583C>G/p.L195V ）、SCN1A （ c.2378C>T/p.T793M ） 、 SCN3B （ c.328G>A/p.V110I ） 、 TRAK2（c.900+5G>C/splice）等 16 个候选基因及其突变。(2)通过各相关数据库的查询确认，结合遗传模式过滤和变异有害性预测以及表型与基因型的相关分析，同时采用生信软件对该突变部位氨基酸序列的保守性和空间构象进行分析，基本确认 *PURA* 基因的新突变（c.583C>G/p.L195V）为高度相关的致病基因，依 ACMG 标准判为 Likely pathogenic。(3)经实验验证进一步确定 PURA（c.583C>G）突变的致病性，后续深入的鉴定还在进行中。
结论 结合临床诊断、系谱分析、Sanger 测序、新突变的致病性鉴定，基本可以确定先证者所患疾病即为 AD 遗传的 PURA 综合征，*PURA* 基因发生的 c.583C>G 突变是其发病的主要原因之一。

调控 PD-L1 表达的化合物高通量筛选及其作用机制研究

王晓博
复旦大学上海医学院

目的 建立起完备的 PD-L1(Programmed death-ligand 1)表达相关的药物筛选模型，依据现有的高通量筛选平台，试图从化合物库中筛选出有前景的先导化合物。并对其机制做进一步的研究。
方法 首先以一定浓度的化合物处理肿瘤细胞，一段时间后，依据高通量流式筛选系统评估肿瘤细胞表面 PD-L1 的表达量变化，表达量变化较大的视为潜在的肿瘤免疫相关先导化合物。然后利用一些细胞生物学的手段对其作用机制进行深入的研究。最后利用小鼠肿瘤模型评估其抗肿瘤效果及对肿瘤免疫微环境的影响。
结果 从目前实验室已有的化合物库中筛选到了一些具有抗肿瘤效应的先导化合物。我们对其中一个上调 PD-L1 表达比较明显的化合物 C-210 做进一步的研究发现，其上调 PD-L1 的效应是由于激活了 MAPK 信号通路造成的。进一步的，我们发现其在动物体内可以上调 $CD8^+T$ 细胞的数量，并且与 PD-L1 抗体联用展现出了显著的抗肿瘤效果。
结论 组建的高通量流式筛选系统可用于挖掘具有影响肿瘤免疫潜力的先导化合物。

基于基因编辑技术的 DMD 人诱导多能干细胞模型构建

金铭
福建医科大学附属第一医院

目的 运用 Crispr/Cas9 技术，构建假肥大型肌营养不良（DMD）的大片段缺失的人诱导多能干细胞（hiPSCs）模型，用于后续的治疗研究。

方法 使用 deepHF 在线工具，选择 *DMD* 基因 52 号外显子上下游约 800 bp 以内剪切效率最高的 sgRNA，并使用 MIT 特异性分值及 CFD 特异性分值计算工具评估其脱靶效率，选用评分在适用范围内的序列作为 sgRNA。在 293T 细胞上筛选合适的 sg，进行 T7E1 酶切评估切割效率。采用电转质粒的方式，在正常的 iPSCs 中同时导入针对目的区域上下游内含子的 sgRNA+Cas9 质粒，以切除 *DMD* 基因的 52 号外显子，并采用流式分选的方式进行培养单克隆细胞、鉴定。随后，通过 Wnt 信号调节因子和 TGFβ 超家族生长因子处理 hiPSCs 实现心脏分化。将其分化为心肌细胞，在转录本及蛋白质水平证实其符合 52 号外显子缺失表现。
结果 T7E1 分析显示，所选 sgRNA 切割效率最高可达 91%，根据 MIT 及 CFD 特异性评分选择脱靶可能低的 sg 进行后续实验，并选取每条 sg 前 5 位的预测脱靶位点进行 DNA 测序，未发现脱靶情况。流式分选双阳性细胞可达 40.2%。分选所得细胞进行单克隆培养。后续通过 sanger 测序进行基因型鉴定显示成功获得了 52 号外显子切除的 hiPSCs 细胞系。进行染色体核型分析显示未发生染色体倒位、易位、缺失等情况。采用小分子诱导的方式，在第 14 天成功的分化出搏动的心肌细胞，提取其 RNA 测序，证实了该模型表达了 52 号外显子缺失的转录本，提取总蛋白质进行 dystrophin 蛋白凝胶电泳，证实 dystrophin 蛋白缺失。
结论 综上所述，本研究仅以 *dystrophin* 基因的 52 号外显子切除为例，介绍了运用基因编辑工具构建 hiPSCs 模型的方法及流程。这种方法可用于多种疾病的研究，适用于不同类型的基因功能验证。基因编辑构建的 hiPSCs 模型相较于疾病动物模型更贴近人类遗传背景，是在无法获得特定基因突变类型体细胞时的一种有效替代。

Systematic discovery of signaling pathways linking immune activation to schizophrenia

Yue Gao
School of Basic Medical Sciences, Southern medical university

Purpose Immune activation has been shown to play a critical role in the development of schizophrenia, however its underlying mechanism remains unknown. This work is to provide not only valuable resources for the study on molecular mechanisms underlying schizophrenia, but also a systematic strategy for the discovery of molecular pathways of complex mental disorders.
Method The high-quality protein interaction network for schizophrenia (SCZ Network), constructed using our new “neighborhood walk” approach in combination with “random walk with restart” to search across the human interactome network for disease genes and neighborhoods. Furthermore, we induced immune activation at these stages in mice and carried out transcriptome sequencing on immune-activated mouse brains. Integrating the transcriptome data of the immune-activated mouse brains with the SCZ Network to illustrate clear potential molecular pathways and key regulators correlating maternal immune activation during gestation and an increased risk for schizophrenia.
Result The resulting spatiotemporal expression pattern of the immune genes shows that this disease network is sensitive to perturbation by immune activation during both mid- to late gestation and adolescence. We built a “two-hit” mouse model by inducing immune activation twice in mice. The mice with “two hits” showed greater transcription alteration than the mice with the “first hit” or the “second hit” alone, suggesting that the “first hit” may have effects on the brain to make it more sensitive to the “second hit”. We searched for enriched binding motifs in the promoter regions of the differentially expressed genes and found 24 TF-binding motifs corresponding to 26 transcription factors. These transcription factors can be clustered into 6 groups, each regulating a group of pathways. Majority of the downstream pathways identified for each group of TFs overlap with the signaling pathways identified in the SCZ Network, further providing a framework for studying the key regulators of these immune-activated pathways linking to schizophrenia.
Conclusion In summary, our work provides a novel approach to illustrating the molecular mechanism underlying complex psychiatric disorders and a rich resource for novel candidate genes as well as systematically evaluated signaling pathways to study the pathogenesis and therapeutics of schizophrenia.

Identification of PLOD2 as an adverse prognostic biomarker for oral squamous cell carcinoma

Yawei Sun Yanhong Ni
Nanjing Stomatological Hospital，Medical School of Nanjing University

Background Procollagen-lysine, 2-oxoglutarate 5-dioxygenase2 (PLOD2), a key enzyme that catalyzes the hydroxylation of lysine, plays a crucial role in the progression of several solid tumors. However, its spatial expression profile and its prognostic significance in OSCC have not been revealed.
Materials We assessed PLOD2 mRNA level and protein level with several public databases and 6 pairs OSCC patients' tissues. Additionally, PLOD2 spatial expression profile were investigated in 100 OSCC patients by immunohistochemistry and its diagnostic and prognostic value were also evaluated. Lastly, gene set enrichment analysis (GSEA) was also used to investigate the potential functions of PLOD2 in OSCC.
Results PLOD2 mRNA level and protein level was highly expressed in tumor of HNSCC(P<0.001) and OSCC patients (P=0.0223). Histopathologically, PLOD2 was ubiquitous expressed in tumor cells ($PLOD2^{TCs}$) and fibroblast-like cells ($PLOD2^{FLCs}$) of OSCC patients, but absent in tumor infiltrating lymphocytes ($PLOD2^{TILs}$). Patients with highly expressed $PLOD2^{TCs}$ and $PLOD2^{FLCs}$ showed poor differentiation, WPOI and more lymph node metastasis, contributing to higher postoperative metastasis risk and poor survival time. However, only $PLOD2^{FLCs}$ was an independent risk factor for survival outcome in patients with OSCC. Molecularly, GSEA analysis showed highly expressed PLOD2 mainly enriched in epithelial mesenchymal transformation (EMT), TGF-beta signaling and hypoxia pathway which were associated with poor clinical outcomes of OSCC patients with PLOD2 overexpression.
Conclusion PLOD2 is a poor prognostic biomarker for OSCC patients and may affect the metastasis of OSCC through epithelial mesenchymal transformation pathway. These findings might shed novel sights for future research in cancer targeted therapy by targeting PLOD2.

Exploring Distribution and Association between Rare Variants and Phenotypes in Children with Neurodevelopmental Disorders Based on Whole Exome Sequencing

Zhengchang Li Xiaoli Chen
Capital Instituete of Pediatrics

Objective For the shortage of genetic data in Chinese children with neurodevelopmental disorders (NDDs), we seek to create a NDD cohort for case-control comparison from clinical whole-exome sequencing （WES）data. We hope to clarify the distribution of rare variants between NDDs, find the connection between genotypes and phenotypes in NDDs, and mine the potential genes of NDDs.
Methods We performed a WES analysis of 1156 NDDs and 1092 controls of Chinese ancestry. We analyzed the WES data at three levels: variants, genes and pathways. At variants level, we use REVEL score to classify missense variants in three types, B_MIS (<0.3, benign variants), U_MIS (<0.7, unknown effect variants) and D_MIS (>=0.7, deleterious variants). We classify variants as likely gene-disruption variants (LGD) tagged with nonsense, frameshift or splicing. Only allele frequency (AF) lower than 5% were considered and would be classified as rare variants. Of those rare variants, they would be classified as ultra-rare variants (URV) if they merely showed on our data and allele counts (AC) lower than three times. Genes in gene level are enriched by variants and pathways are enriched by genes. We mainly focus on the comparison results of three groups: 1) NDD cases and non-NDD controls; 2) simplex NDDs and complex NDDs; 3) NDD males and NDD females.

Results 1) LGD and D_MIS were significantly enriched in NDDs and the effect size increasing with decreasing of AF. After annotating those URV, we get 108 genes from D_MIS enrichment and 189 genes from LGD. Among those genes, *MYH10* thought as a new candidate pathogenic gene counts three times in cases. Pathway analysis shows that D_MIS genes are enriched in ion channels pathway, while LGD genes are enriched in chromatin remodeling pathway. 2) D_MIS are easy to enrich in Simplex NDD, while LGD are easy to enrich in complex NDD. 3) NDD males carry more ultra-rare variants than females. And sex differential genes are enriched in skeletal and muscle development pathways.
Conclusion We confirmed that children with NDD are prone to enrich for rare variants, especially ultra-rare variants and damaging rare variants, and we proposed MYH10, which is enriched by ultra-rare variants, probably a new pathogenic gene for NDD. We also confirmed that simplex NDD and complex NDD have different genetic bases, and may need to be treated clinically differently. At last, we find a new phenomenon that males carry more deleterious variants than females, which is different from the traditional view of that female protective effect. And we explained the genetic basis of the sex differences between NDDs, which may be derived from the regulation of NDD genes by skeletal and muscle development pathways.

Effect of exercise and diet intervention in NAFLD and NASH via GAB2 methylation

Na Wu[1,3] Fan Yuan[1,3] Siran Yue[2] Fengyan Jiang[2] Decheng Ren[1,3] Liangjie Liu[1,3] Yan Bi[1,3] Zhenming Guo[1,3] Lei Ji[1,3] Ke Han[1,3] Xiao Yang[1,3] Mofan Feng[1,3] Kai Su[1,3] Fengping Yang[1,3] Xi Wu[1,3] Qing Lu[1,3] Xingwang Li[1,3] Ruirui Wang[2] Baocheng Liu[2] Shenglong Le[4] Yi Shi[1,3] Guang He[1,3]
1.Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Shanghai Jiao Tong University, Shanghai, China.
2.Shanghai Innovation Center of Traditional Chinese Medicine Health Service, Shanghai University of Traditional Chinese Medicine, Shanghai, China.
3.Shanghai Key Laboratory of Psychotic Disorders, and Brain Science and Technology Research Center, Shanghai Jiao Tong University, Shanghai, China.
4. Exercise Translational Medicine Center, Shanghai Center for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, China.

Background Nonalcoholic fatty liver disease (NAFLD) is a disorder that extends from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), which is effectively alleviated by lifestyle intervention. Nevertheless, DNA methylation mechanism underling the effect of environmental factors on NAFLD and NASH is still obscure. The aim of this study was to investigate the effect of exercise and diet intervention in NAFLD and NASH via DNA methylation of *GAB2*.
Methods Methylation of genomic DNA in human NAFLD was quantified using Infinium Methylation EPIC BeadChip assay after exercise (Ex), low carbohydrate diet (LCD) and exercise plus low carbohydrate diet (ELCD) intervention. The output Idat files were processed using ChAMP package. False discovery rate on genome-wide analysis of DNA methylation ($q < 0.05$), and cytosine-guanine dinucleotides (CpGs) which are located in promoters were used for subsequent analysis ($|\Delta\beta| \geq 0.1$). K-means clustering was used to cluster differentially methylated genes according to 3D genome information from Human embryonic stem cell. To quantify DNA methylation and mRNA expression of *GRB2* associated binding protein 2 (*GAB2*) in NASH mice after Ex, low fat diet (LFD) and exercise plus low fat diet (ELFD), MassARRAY EpiTYPER and quantitative reverse transcription polymerase chain reaction were used.
Results Both LCD and ELCD intervention on human NAFLD can induce same DNA methylation alterations at critical genes in blood, e.g., *GAB2*, which was also validated in liver and adipose of NASH mice after LFD and ELFD intervention. Moreover, methylation of CpG units (i.e., CpG_10.11.12) inversely correlated with mRNA expression *GAB2* in adipose tissue of NASH mice after ELFD intervention.
Conclusions We highlighted the susceptibility of DNA methylation in *GAB2* to ELFD intervention, through which exercise and diet can protect against the progression of NAFLD and NASH on the genome level, and demonstrated that the DNA methylation variation in blood could mirror

epigenetic signatures in target tissues of important biological function, i.e., liver and adipose tissue.

FTO promotes liver inflammation by reducing IL-17RA mRNA m6A methylation

Yajie Xu Chunmei Ge Zhihui Dai Haozan Yin Yuefan Wang Fu Yang
Naval Medical University

Purpose Liver inflammation is known to promote liver fibrosis and non-alcoholic fatty liver diseases (NAFLD). m6A mRNA methylation has been proved to be involved in liver functions. However, the mechanism of m6A mRNA methylation on liver pathogenesis is still unclear. Our study is to demonstrate that FTO, as an m6A eraser, reduces IL-17RA mRNA m6A methylation to promote liver inflammation.

Methods Clinical samples All frozen clinical samples (normal, para-carcinoma tissues and HCC tissues) were randomly collected from the Eastern Hepatobiliary Surgery Hospital, Naval Medical University.

Animal experiments NAFLD model: 5-week-old C57BL/6 male mice fed with high fat diet (60% fat) for 14 weeks to establish NAFLD model.

Liver fibrosis model: 2-week-old male mice were intraperitoneally injected with 2mg/kg BW DEN. After 2 weeks, mice were intraperitoneally injected with 5ml/kg BW 20% CCl4 twice a week for 14 weeks.

FTO overexpression model: C57BL/6 male mice were intravenously injected with 1×10^{11} vector genome serotype 2/8 adeno-associated virus (AAV), including FTO (AAV-FTO: pAAV-CMV-Fto-3FLAG) or control gene (AAV-NC: pAAV- CMV-MCS-3FLAG).

Groups: In NAFLD model, mice were randomly assigned to 5 groups: control (with normal diet), HFD (high fat diet), HFD+Rhein (high fat diet plus 0.1% Rhein), HFDAAV-NC (AAV-NC mice with high fat diet), HFDAAV-FTO (AAV-FTO mice with high fat diet). In liver fibrosis model, mice were randomly assigned to 4 groups: control (with no treatment), CCl_4 (with CCl_4 treatment), CCl_4AAV-NC (AAV-NC mice with CCl_4 treatment), CCl_4AAV-FTO (AAV-FTO mice with CCl_4 treatment).

Cell culture

HCC-derived Huh-7 cell lines were maintained in DMEM containing 10% fetal bovine serum and 1% penicillin/streptomycin at 37°C, in an atmosphere of 5% CO_2.

Western blot

Total protein was extracted from the frozen clinical tissues, mouse models tissues and cells with RIPA Lysis Buffer. Proteins were resolved by SDS-PAGE and transferred to PVDF membranes. Membranes were incubated with primary antibody overnight at 4℃ and secondary antibody for 2 hours the next day.

MeRIP-Seq

m6A-specific antibody was used to recognize and bind m6A-modified RNA fragments. Recognized m6A-modified RNA fragments were enriched and sequenced with high-throughput sequencing.

Results First, we performed MeRIP-Seq in normal, para-carcinoma and HCC liver tissues samples, showing that m6A methylation levels of genes clearly distinguished among normal tissues, para-carcinoma and HCC liver tissues. KEGG analysis was also performed, showing that pathways of cytokine-cytokine receptor interaction were significantly enriched. Among genes related to cytokine-cytokine receptor interaction, we found that the m6A methylation level of IL17-RA decreased in para-carcinoma tissues, while the protein level of IL17-RA increased. These results suggested that m6A mRNA modifications might be responsible for the abnormal expression of IL17-RA in human livers, contributing to liver inflammation and fibrosis.

In order to reveal the driving forces of changed IL17-RA RNA m6A methylation in the para-carcinoma tissues, we further investigated expressions of m6A methylation writers and erasers by western blot. The results showed that FTO, the m6A methylation eraser, has higher expression in para-carcinoma tissues, while the ALKBH5 protein level showed no significant difference between normal tissues and para-carcinoma tissues. Besides, the expression of m6A methylation writers

were significantly up-regulated in the para-carcinoma tissues. Therefore, FTO upregulation may be the main cause of the decrease of IL17-RA RNA m6A methylation.
We then established Huh-7 cell model of FTO knockdown and overexpression to indicate that FTO plays an important role on downregulating the m6A methylation level of IL17-RA and upregulating the protein level of IL-17RA.
In vivo experiments were also used to demonstrate the pro-inflammatory effect of FTO. In the NAFLD model, HFDAAV-FTO mice showed more severe fat accumulation, ballooning and liver inflammation levels, compared with control, HFD, HFD+Rhein and HFDAAV-NC group. In the liver fibrosis model, CCl_4AAV-FTO mice also showed more extensive collagen deposition and inflammation levels, compared with control, and CCl_4AAV-NC group. FTO overexpression mice in both models also showed higher IL17-RA protein expression levels, confirming that FTO can promote liver inflammation by reducing m6A methylation of IL17-RA.
Conclusion Overall, our study revealed that FTO, the m6A methylation eraser, reduces IL17-RA RNA m6A methylation in Huh-7cells and liver tissues to promote liver inflammation, providing a novel insight of therapeutical strategy focusing on NAFLD and NASH.

WDR62/MCPH2 deficiency result in synaptic dysfunction and ASD-like behaviors in mice, which can be ameliorated by RA repletion

Yiqiang Zhi[2] Dan Xu[1] Yixin Liu[3] Zhiheng Xu[3]
1.Fujian Key Laboratory of Molecular Neurology, Institute of Neuroscience, Fujian Medical University
2.College of Biological Science and Engineering, Institute of Life Sciences, Fuzhou University, Fuzhou
3.State Key Laboratory of Molecular Developmental Biology, CAS Center for Excellence in Brain Science and Intelligence Technology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences

Background Neurodevelopmental disorders (NDDs) show a wide range of overlapping clinical features. Autism spectrum disorder (ASD) is a heterogeneous NDD that sometimes associated with microcephaly and intellectual disability. Genetic analysis indicates the frequent heterozygous mutations of microcephaly-associated genes are likely to be associated with ASD while lack of biological evidence.
Methods We generated *Wdr62*$^{flox/flox}$; ZP3-cre (*Wdr62* KO) mice drive WDR62 deletion in the germ line and *Wdr62*$^{flox/flox}$; Nex-cre (*Wdr62* Nex-cKO) mice make the deletion of WDR62 in early post-mitotic, neurons of the developing forebrain. We investigated and compared the behavioral alterations in these two *Wdr62* KO mice. Morphological and global transcriptome analyses (RNA-seq) analysis was assessed in *Wdr62* KO and littermates mice. Further, all-trans retinoic acid (RA), a derivative of Vitamin A, was applied for therapeutic potential.
Results Our studies indicate *Wdr62* conventional knock out (*Wdr62* KO) lead to reduced brain size with impaired learning and memory but also ASD-related behaviors in mice. Interestingly, aberrant social interaction and repetitive behaviors was also found in *Wdr62* cKO (*Wdr62* flox/flox; Nex-cre) mice in post-mitotic neuron with generally normal brain size and cognitive state. In vivo study indicated *Wdr62* deficiency resulted in markedly decreased synapse densities and maturation. Finally, we showed that *Wdr62* deficiency lead to dysregulation of genes associated with RA signaling and RA oral gavage significantly alleviated ASD like behavior phenotype in WDR62 disrupted mice.
Conclusions Our findings not only provide new sight into the role of WDR62 in brain development but also deepen the understanding of mechanism behind the relationship between microcephaly gene *WDR62* and ASD etiology which will further assists in ASD clinical diagnose and intervention. More importantly, our results indicate RA supplementation is a potential strategy for treating this increasingly prevalent disease.

Spatial maps of hepatocellular carcinoma transcriptomes reveal unexplored characteristics of gene expression

Yuefan Wang[1] Shengxian Yuan[2] Hui Jiang[3] Haozan Yin[1] Zhihui Dai[1] Chunmei Ge[1] Fu Yang[1]
1.Department of Medical Genetics, Naval Medical University
2.Eastern Hepatobiliary Hospital, Naval Medical University
3.Shanghai Changhai Hospital, Naval Medical University

Objectives In recent years, single cell sequencing technology has advanced our understanding the roles of molecular heterogeneity in hepatocellular carcinoma (HCC). However, spatial characteristics of gene expression pattern in HCC have never been documented. Here, we aimed to determine the heterogeneity and similarity of spatial gene expression pattern and explore its influence on HCC prognosis and therapy.
Methods Spatial transcriptomics (ST) sequencing was implemented to three pieces of HCC specimens. Hierarchical clustering and cellular communication analysis were applied to further explore the functional targets. Immunohistochemistry analysis on 293 tumor tissues (EHBH cohort) and 89 tumor tissues (CH cohort) was used to evaluate the relations between patient prognosis and the levels of YTHDF1/2 and CCL15/CD163, respectively. Molecular and cellular assays were conducted to explore the regulating mechanism of YTHDF1 and CCL15 in vitro. Adeno-associated virus applied on subcutaneous tumor and DEN-CCl4 mouse models was for functional study of CCL19 and CCL21 in vivo. The infiltration of lymphocytes was evaluated by flow cytometry and immunofluorescence analysis.
Results All spots of three samples were hierarchically clustered into 18 clusters and then categorized into five sections: Tumor 1, Tumor 2, Tumor boundary region, para-tumor tissue and others. The diverse gene expression pattern of Tumor 1 and Tumor 2 intratumorally indicated the diametrically opposite prognosis. RNA m6A reader YTHDF1 and YTHDF2, which were upregulated and highly correlated in tumor tissue, shared the similar spatial expression pattern and predicted poor prognosis. Furthermore, our data revealed that YTHDF1 could regulate the expression of YTHDF2 by influencing its mRNA stability. Cellular communication analysis and further studies revealed that CCL15 was dominated in tumor tissue and positively correlated with poor prognosis. Further studies found that CCL15 could recruit monocytes and polarize them into M2-like macrophages in vitro and was positively correlated with the infiltration of $CD163^+$ M2-like macrophages in tumor tissue; Whereas CCL19 and CCL21 in close proximity, which were upregulated in tumor boundary region and predicted good prognosis, shared similar gene expression pattern and could recruit $CD3^+$ T cells and $CD20^+$ B cells to inhibit the growth of HCC in vivo. Moreover, joint application of YTHDF1/YTHDF2 or CCL15/CD163 had better predictive values than those used separately.
Conclusions Our studies revealed the features of spatial gene expression pattern in HCC and highlighted its clinical significance of intratumor heterogeneity and similarity, providing novel insights for further developing diagnostic and therapeutic strategies in HCC.

Revised International Staging System (R-ISS) stage-dependent analysis uncovers oncogenes and potential immunotherapeutic targets in multiple myeloma

Jialing Xiao Huan Li Qian Zhang Ping Shuai Liang Wang Yuping Liu Man Yu Yi Shi Yunbin Zhang Bo Gong Ling Zhong
Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, Sichuan, China;

Objective Multiple myeloma (MM), characterized by high intratumour heterogeneity, accounts for ~10% of all haematologic malignancies. Stratified by the Revised International Staging System (R-ISS), little is known about R-ISS-related plasma cell (PC) heterogeneity, gene expression modules in cytotoxic T/NK cells and immunoregulatory ligands and receptors. Herein, we

constructed a single-cell transcriptome atlas of bone marrow in normal and R-ISS-staged MM patients.

Methods Single-cell sequencing (ScRNA-Seq) offers an unprecedented opportunity to study the heterogeneity of plasma cells and immune microenvironments in cancer. This study included 9 MM patients diagnosed as active MM according to International Myeloma Working Group guideline, and two age-matched normal control (transplant donor) . Single-cell RNA-Seq libraries were prepared with Chromium Single cell 3' Reagent v3 Kits according to the manufacturer's protocol. The Cell Ranger software pipeline was used to demultiplex cellular barcodes.

Results Focusing on PCs, we identified and validated a subset of GZMA+ cytotoxic PCs. In addition, a malignant PC population with high proliferation capability (proliferating PCs) was associated with unfavourable prognosis and EBV infection in our collected samples. Ribonucleotide Reductase Regulatory Subunit M2 (RRM2), a specific marker of proliferating PCs, was shown to induce MM cell line proliferation and serve as a detrimental marker in MM. Subsequently, three R-ISS-dependent gene modules in cytotoxic CD8+ T and NKT cells were identified and functionally analysed. Finally, cell-cell communication between neutrophils and proliferating PCs with cytotoxic CD8+ T and NKT cells was investigated, which identified intercellular ligand receptors and potential immunotargets such as SIRPA-CD47 and TIGIT-NECTIN3.

Conclusions Collectively, the results of this study provide an R-ISS-related single-cell MM atlas and reveal the clinical significance of two PC clusters, as well as potential immunotargets in MM progression.

The effect of antibody CD166 on the treatment of mice oral squamous cell carcinomas cells xenograft model and the immunological mechanism

Binbin Yu
Shanghai Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine

To investigate the influence of antibody CD166 on the inhibition of tumor and further investigate the influence on immune cells of tumor and spleen tissues in mice bearing oral squamous cell carcinoma.

Methods The xenograft model was established through subcutaneously injected mouse oral squamous cell carcinomas cells. 10 mice were randomly divided into two groups, one group was used as control and the other was treated with antibody CD166. Hematoxylin-eosin was used to confirm the tissue histopathology of xenograft mice model. Flow cytometry was used to detect the proportion of $CD3^+CD8^+$ T cells, $CD8^+PD\text{-}1^+$ cells and $CD11b^+Gr1^+$ MDSCs cells in the tumor and spleens.

Results After treatment of antibody CD166, the tumor volume and weight in xenograft mice model were significantly reduced. The result of flow cytometry showed that antibody CD166 showed no obvious influence on the proportion of $CD3^+CD8^+$ T cells in the tumor and spleens tissues. In the antibody CD166 treatment group, the proportion of $CD8^+PD\text{-}1^+$ T lymphocyte cells in spleens was significantly lower than that of the control group, 4.5 ± 0.3265% and 8.384 ± 0.6328%, respectively ($p< 0.01$). In the antibody CD166 treatment group, the proportion of $CD8^+PD\text{-}1^+$ T lymphocyte cells in tumor tissues was significantly lower than that of the control group, 4.484 ± 0.4099% and 6.866 ± 0.3735%, respectively ($p< 0.01$).In the antibody CD166 treatment group, the proportion of MDSCs cells in spleens was significantly lower than that of the control group, 3.59 ± 0.2273% and 6.12 ± 0.3546%, respectively ($p< 0.01$). In the antibody CD166 treatment group, the proportion of MDSCs cells in tumor tissues was significantly lower than that of the control group, 2.774 ± 0.4293% 5.046 ± 0.3914%, respectively ($p< 0.01$).

Conclusion Antibody CD166 treatment help reduced the proportion of CD8+PD-1+ and CD11b+Gr1+ MDSCs cells, and produce obvious therapeutic effect on the treatment of mice bearing oral squamous cell carcinoma.

MeCP2 倍增上调雄激素代谢的机制研究

王雨萌[1,2] 吴宇[2] 郑煜芳[1,2] 王红艳[1,3]
1.复旦大学附属妇产科医院
2.复旦大学发育生物学研究所 3.复旦大学附属儿科医院

作为一种表观遗传调控因子，甲基化 CpG 结合蛋白 2(MeCP2)在神经发育过程中起着重要的作用。*MECP2* 基因的拷贝数异常增多可导致男性患有严重的智力障碍和自闭症，即 *MECP2* 倍增体综合征(MDS)。据临床研究报道，MDS 患者会出现伴随高雄激素血症的性早熟，提示 *MECP2* 异常高表达可能导致男性高雄激素血症。然而，MeCP2 是如何参与雄激素代谢过程及调控机制尚不清楚。我们的研究发现 MDS 雄鼠的雄激素水平明显高于野生型雄鼠，且 MeCP2 在负责雄激素合成的睾丸间质细胞中特异性高表达，表明 MeCP2 在调节雄激素合成中发挥重要作用。作用机理上，*MECP2* 倍增导致睾丸中促黄体激素受体 (LHCGR) 的异常上调和芳香化酶的下调。LHCGR 结合促黄体生成素 LH 是睾丸中雄激素合成的第一步，而芳香化酶起到催化雄激素转化为雌激素的作用。因此，MeCP2 是通过增加雄激素合成并下调雄激素向雌激素的转化，从而上调雄激素的水平。此外， 研究结果发现 MeCP2 通过识别 *Lhcgr* 启动子上的 G-四联体并招募转录激活因子 Creb1 以增加 LHCGR 表达。另一方面，MeCP2 也可通过结合 Rorα 基因的 CpG 岛（芳香酶的上游调节因子）下调芳香酶的表达。综上，该研究表明了 *MeCP2* 倍增导致雄性小鼠雄激素增多并对其具体分子机制进行了深入解释。值得注意的是，该研究也证实了 MeCP2 可以识别 G-四联体并发挥调节转录的新功能。

LINC01296 通过调控 Snail 促进头颈鳞状细胞癌的增殖和 EMT 进程

周文凯 曹巍 刘喆麒 林承重 王晓宁 陈万涛
上海交通大学医学院附属第九人民医院

目的 长链非编码 RNA (lncRNAs)在许多类型的肿瘤中被发现，包括头颈鳞状细胞癌(HNSCC)，已有文献报道 double homeobox A pseudogene 9 (DUXAP9)在一些肿瘤发病机制中发挥重要作用。然而，DUXAP9 在头颈鳞状细胞癌（HNSCC）中的表达和功能作用机制仍不清楚。在本研究中，我们旨在确定 DUXAP9 的潜在临床应用，并阐明 DUXAP9 影响头颈鳞状细胞癌(HNSCC)发生发展的机制。
方法 用细胞核/细胞质分离和荧光定位杂交技术评价了 DUXAP9 的亚细胞定位。通过 qRT-PCR，Western Blot 验证 DUXAP9 及 Snail 分子在肿瘤组织中的表达。通过进行 CCK8，平板克隆实验，EdU 实验以及 Transwell 实验等验证 DUXAP9 在头颈鳞癌细胞中发挥的功能。
结果 DUXAP9 在体内外增强 HNSCC 细胞的增殖和转移，并诱导上皮-间充质转化(EMT)。DUXAP9 主要定位于 HNSCC 细胞的细胞核内， DUXAP9 的高表达促进了 EMT 相关基因的转录。
结论 我们的研究发现，DUXAP9 在 HNSCC 组织中的表达明显高于相应的邻近正常组织。DUXAP9 表达升高与淋巴结转移、TNM 分期、总生存率降低相关。此外，体外功能实验表明，DUXAP9 基因的下调抑制了 HNSCC 细胞的增殖、迁移和侵袭性。结果表明 DUXAP9 很可能成为 HNSCC 潜在的治疗靶点。

Application of Autosomal STR Genetic Markers in Half-Sibling Identification

Xiaolian Wu[1] Yunchun Tai[2] Jiayi Zhang[2] Jingwen Yang[1] Qihao Li[1] Luorong Zhang[1]
1.School of Forensic Medicine,Southern Medical University
2.Forensic Medical Centre of the Southern Medical University

Objective To establish the methods for half sibling identification by autosomal short tandem repeat (STR).
Methods Ten thousand pairs of half siblings (HS) and ten thousand pairs of unrelated individuals (UI) were genotyped with 23, 44 and 55 STR loci in computer simulation. Half sib index (HSI) were calculated with ITO method. Introduce the mutational model and compare the HSI before and after mutation. HS and UI discriminant function of lgHSI were established by the fisher discriminant function.
Results The lgHSI data between HS and UI was conform to the normal distribution, which was considered statistically significant (P<0.000). The mutations on HSI of the three systems were statistically different (P < 0.000). In 23 STR loci detection systems, the HSI of HS was1.9Í10^{-3}~1.5Í10^{8}, and the HSI of UI was 3.3Í10^{-6}~844.1; In 40 STR loci detection systems, the HSI of HS was7.9Í10^{-4}~3.8Í10^{10}, and the HSI of UI was 6.4Í10^{-9}~704.3; In 55 STR loci detection systems, the HSI of HS was 6.3Í10^{-4}~1.0Í10^{12}, and the HSI of UI was 3.8Í10^{-11}~236.0. If the HSI thresholds of the three groups were set as "≤1, > 19", the efficiency of the test system was 0.5891 (23), 0. 8415 (40) and 0.9124 (55), and the average misjudgment rates were 0.0041 (23), 0.002 (40) and 0.0011 (55), respectively.
Conclusion More than 40 autosomal STR loci have high application value in the identification of semi-sib relationship**.** In addition, the more loci detected, the higher the efficiency of the system and the lower the risk of misjudgment.

A pathogenic PLXNB3 mutation identified in a patient with congenital heart disease and neuromuscular malformations

Ting Li[1] Wei Sheng[1,2] Guoying Huang[1,2]
1.Cardiovascular Center, Children's Hospital of Fudan University, Shanghai, China
2.Shanghai Key Laboratory of Birth Defects, Shanghai, China

Congenital heart disease (CHD) is one of the most common birth defects. Approximately 7%-50% of patients with CHD can be accompanied by extracardiac malformations, which increases the severe rate and mortality of CHD. It is known that the plexin families play a key role in the development of the heart and the occurrence of neuromuscular diseases. In this study, we performed whole-exome sequencing (WES) on a proband with CHD and neuromuscular malformations and his families, and found a pathogenic mutation in the X-linked PLXNB3 gene (c.A4319T p. E1440V). In addition, we also detected 12 other pathogenic mutations in 1,155 sporadic patients. Further functional analysis showed that this p. E1440V variant will affect the activity of key factors in the Notch signaling pathway, myocardial contraction pathway, and neuromuscular disease pathways. And this mutation promotes cell migration and reduces cell proliferation. These findings suggest that PLXNB3 and the p. E1440V variant may be related to the pathogenesis of congenital heart disease with extracardiac malformations.

Hdac4 deficiency in neural crest cells causes defects in craniofacial bone development

NAYOUNG HA
Shanghai Jiaotong University School of Medicine affiliated Ninth People's Hospital

Objectives

1. To explore the role of *Hdac4* in mice craniofacial bone development.
2. To investigate the mechanism of *Hdac4* knockout induced craniofacial defects in mice.

Methods

1. By constructing *Hdac4*$^{fl/fl}$;*Wnt1-Cre* mice, we observed the phenotype of craniofacial bone using Micro-CT and skeletal staining.
2. MC3T3-E1 cells were transfected with lentivirus to construct *Hdac4* knockdown cell lines, and the knockdown efficiency was confirmed with qPCR. The expressions of *Ki67* was detected by immunofluorescent staining and qPCR. CCK8, EdU staining and cell cycle analysis were performed to assess cell proliferation activity.
3. RNA-seq was performed to detect the effect of *Hdac4* knockdown on gene expression and to identify the genes regulated by *Hdac4*.

Results

Expression of *Hdac4* in developing craniofacial skeleton

At E14.5 and E16.5, Hdac4 protein was strongly expressed in ossification center and osteogenic fronts in frontal bone, maxilla, and mandible, while Hdac4 expression was hardly detected at E12.5**.** *Runx2* expressing domain was in accordance with *Hdac4* expressing domain. These results indicate that *Hdac4* might participate in development of craniofacial skeleton.

Conditional knockout of *Hdac4* in CNCCs leads to impaired craniofacial bone formation in mice

Hdac4$^{fl/fl}$*;Wnt1-Cre* mice exhibited short stature with craniofacial abnormality compared to littermate controls. *Hdac4*$^{fl/fl}$*;Wnt1-Cre* mice showed craniofacial abnormality including deviated maxilla and mandible, and cross bite malocclusion at P21. Next, we analyzed the frontal bone by setting a circular region of interest of diameter of 3mm on the frontal bones of *Hdac4*$^{fl/fl}$*;Wnt1-Cre* and control mice. Frontal bone thickness on coronal section was approximately decreased by 50% in mutant mice. In addition, bone volume and bone mineral density of frontal bones in mutants were also decreased compared to the controls. We evaluated the alveolar bone trabeculae in mandible by analyzing the alveolar between roots of first molar at mandible in *Wnt1-Cre* and *Hdac4*$^{fl/fl}$*;Wnt1-Cre* mice at P21. These results indicate that *Hdac4*$^{fl/fl}$*;Wnt1-Cre*mice exhibit bone dysplasia.

Effect of *Hdac4* on MC3T3-E1 cell proliferation

We established *Hdac4* knockdown MC3T3-E1 cells by lentivirus transfection system. *Ki67* mRNA expression was significantly downregulated in shRNA3 group compared to negative control group (p<0.05). CCK8 assay demonstrated that proliferation rate of shRNA3 group was lower than control group. In addition, flow cytometry analysis showed a significant increase of cell counts in G1 phase (57.4%) and decrease in S phase (23.1%) of cell cycle in shRNA3 groups. EdU staining showed that the ratio of EdU-positive cells in shRNA3 group was significantly lower compared the negative control group (p<0.05). Together, these data indicates that *Hdac4* facilitates cell proliferation in MC3T3-E1 cells.

RNA-seq of Hdac4 knockdown MC3T3-E1 cells

The expression of the genes related to cell proliferation were lower in shRNA3 group. The enrichment analysis for Gene Ontology (GO) terms was conducted for down-regulated genes. GO analysis suggested that *Hdac4* down-regulation suppress cell proliferation through regulation of the biological processes involved in "mitotic nuclear division", "nuclear division", and "chromosome segregation". These data suggest that *Hdac4* down-regulation may suppress cell proliferation via modulating cell cycle in MC3T3-E1 cells.

***Hdac4* knockout in MC3T3-E1 inhibits cell proliferation through regulation of *Hif-1a*/*Vegfa* pathway**

We evaluated the expression of *Hif-1a* and *Vegfa* in *Hdac4* knockdown MC3T3-E1 cells. *Hif-1a* and *Vegfa*expression in *Hdac4* knockdown MC3T3-E1 cells were significantly decreased

compared to the control group. These results suggest that decreased cell proliferation in *Hdac4* knockdown MC3T3-E1 cells attributes to downregulation of *Hif-1a*, which may contributes to craniofacial skeletons deficiencies.

CircINSR 在肝脏中的作用及其机制探讨

郝涛
暨南大学第一附属医院

目的 验证胰岛素受体（Insulin receptor, INSR）形成的 circRNA（circINSR）在肝脏中的表达、功能及相关分子机制。
方法 通过 FISH，PCR 和 qPCR 检测 circINSR 在肝脏中的表达及其丰度。
结果 1.CircINSR 在肝脏中表达。Snager 测序检测"背对背"扩增出来的条带可见序列与已报道接口序列一致。FISH 检测 circINSR 在肝细胞细胞质中表达。
2.肥胖小鼠肝脏中 CircINSR 的表达比正常小鼠肝脏中的表达增多。
结论 INSR 形成的 circRNA 肥胖小鼠中的表达增多。

Caveolin-1 promotes the progression of head and neck squamous cell carcinoma via inhibiting the ferroptosis of tumor cells

Tingwei Lu Ming Yan Zhen Zhang Wantao Chen
Department of Oral and Maxillofacial-Head & Neck Oncology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine; College of Stomatology, Shanghai Jiao Tong University; National Center for Stomatology; National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology

Background Head and neck squamous cell carcinoma (HNSCC) is an aggressive disease worldwide. Much progress has been made in understanding the mechanism and improving the treatment of HNSCC, but only a few studies have focused on ferroptosis, which is a novel mode of cell death.
Methods The expression of caveolin-1 (CAV1) in the HNSCC tumor tissues was measured by immunohistochemistry and qPCR assay. ROS evaluation and intracellular Fe^{2+} content assays were performed to measure the degree of ferroptosis.
Results Our study showed that CAV1 was highly expressed in HNSCC tumors and the high level of CAV1 predicted poor prognosis. Further experiments indicated that CAV1 could inhibit the ferroptosis of tumor cells and promote their proliferation, invasion and migration.
Conclusions The results identified that CAV1 was overexpressed in HNSCC and predicted poor prognosis. CAV1 can inhibit the process of ferroptosis, which further promoted the development of HNSCC. The connection between CAV1 and ferroptosis might be important for designing the diagnostic and combined therapeutic strategies for patients with HNSCC.

N6-Methyladenine DNA modifications in human placental villi of Down syndrome patients

Qiuyan Liao Mei Ye Wenlong Hu Zhipeng Zeng Hui Gao Wanxia Cai Hui Guo Songhui Xu Donge Tang Yong Dai
Shenzhen People's Hospital

DNA N6-methyldeoxyadenosine (6mA) is a novel epigenetic regulator recently identified in a variety of multicellular species. 6mA is the dominant epigenetic modification in higher eukaryotes and 6mA modifications are pronounced in genetic diseases. Herein, we identified characteristics

of the 6mA methylomes in human placental villi from Down syndrome patients and control patients. Our results showed that numbers of 6mA peaks were 87 444, 97 684, 74 751 and 104 307 in DSXIP, NCXIP, DSYIP and NCYIP, respectively. Specific regions modified by 6mA were mainly concentrated in the introns of genes. 6mA, as a normal regulatory modification in cells, was involved in numerous biological activities and performed specific functions, such as ion binding and metal ion binding. We also found that the motif TCTRYCCA, TCCACCYA, TCCATCCR, GKTGGTRA, ATGGTSAT occurs only in human placental villi of Down syndrome pregnancies, the TCTRYCCA motif occurs mostly. And its regulation was confirmed with experiments using in vitro-cultured mouse cells. Overall, our study produced 6mA modification profiles from the human placental villi of Down syndrome patients. 6mA DNA modification may play a crucial role in the human placental villi of Down syndrome patients.

Highly Conserved C-Terminal Region of Indian Hedgehog N-Fragment Contributes to Its Auto-Processing and Multimer Formation

Xiaoqing Wang[1,2]
1.Bio-X-Renji Hospital Research Center, Renji Hospital, School of Medicine, Shanghai Jiao Tong University
2. Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Bio-X Institutes, Shanghai Jiao Tong University,

Hedgehog (HH) is a highly conserved secretory signalling protein family mainly involved in embryonic development, homeostasis, and tumorigenesis. HH is generally synthesised as a precursor, which subsequently undergoes autoproteolytic cleavage to generate an amino-terminal fragment (HH-N), mediating signalling, and a carboxyl-terminal fragment (HH-C), catalysing the autoprocessing reaction. The *N*-terminal region of HH-N is required for HH multimer formation to promote signal transduction, whilst the function of the *C*-terminal region of HH-N remains ambiguous. This study focused on Indian Hedgehog (IHH), a member of the HH family, to explore the functions of the *C*-terminal region of the amino-terminal fragment of IHH (IHH-N) via protein truncation, cell-based assays, and 3D structure prediction. The results reveal that three amino acids, including S195, A196, and A197, were crucial for the multimer formation by inserting the mutual binding of IHH-N proteins. K191, S192, E193, and H194 had an extremely remarkable effect on IHH self-cleavage. A198, K199, and T200 evidently affected the stability of IHH-N. In addition, we also found that ACFD-associated mutation V190A, which is closed to the KSEH in the *C*-terminus of IHH-N, affected the self-cleavage slightly but reduced protein stability obviously, further supporting the significance of the IHH-N *C*-terminus and also implying that V190A mutation may cause disease in part by reducing the IHH-N protein level. This work suggested that the *C*-terminus of IHH-N played an important role in the physiological function of IHH at multiple levels, thus deepening the understanding of HH biochemical properties.

CRISPR/Cas13 RNA 编辑系统的研究进展

陈海珠 王柠 陈万金
福建医科大学附属第一医院

目的 CRISPR/Cas13 系统属第 II 大类第 VI 亚型，是基于细菌适应性免疫系统的 RNA 靶向系统，可保护细菌免受病毒的侵袭。与 CRISPR/Cas9 系统不同，Cas13 特异性靶向切割单链 RNA。根据 Cas13 系统发育可分为 A、B、C、D、X、Y 六个亚型。本文将对 CRISPR/Cas13 RNA 编辑系统的研究进展进行综述。

材料与方法 通过查阅国内外 CRISPR/Cas13 编辑系统研究相关文献，对该系统的特点及研究进展进行总结归纳。

结果 RNA 作为一种生物大分子，参与细胞生命代谢的整个过程，RNA 代谢异常导致多种疾病的发生。靶向 DNA 编辑技术如锌指核酸酶、转录激活因子样效应物核酸酶、CRISPR/Cas9 或 Cas12

技术均较为成熟，且在生物医学、临床医学研究领域广泛应用。由于 DNA 的稳定遗传，DNA 序列编辑具有遗传性和不可回复性，而 RNA 的改变是暂时的，不可遗传且非永久性。CRISPR/Cas13 系统靶向并切割单链 RNA 的特性将使其在 RNA 编辑领域大展身手，主要有以下几个应用：（1）RNA knockdown：Cas13 系统都包含有 HEPN 保守结构域，在 crRNA 的引导下能够切割单链 RNA，但不能切割双链 RNA、单链 DNA 和双链 DNA，因此其具有 RNA 敲低的作用。对于 RNA toxin 疾病，Cas13 系统特异靶向毒性 RNA 的降解是一个潜在干预手段。（2）检测微量核酸：Cas13 在 crRNA 介导下切割 ssRNA 的同时，由于其旁切活性作用，通过设计报告系统可被用于快速检测微量核酸。大型公共卫生危机（新型冠状病毒、埃博拉病毒、寨卡病毒等）出现时，快速、便携的核酸检测手段尤为重要。（3）RNA 水平单碱基编辑：通过对 Cas13 蛋白的 HEPN 结构域引入氨基酸突变使其丧失切割活性但保留 RNA 结合能力（dCas13），偶联 ADAR2 在错配的 crRNA 介导下实现单个碱基的替换；相较于 DNA 的单碱基编辑系统旁观者效应，dCas13-ADAR2 系统介导的 RNA 碱基替换因错配 crRNA 的位点限制，其编辑位点是单一的。
结论 CRISPR/Cas13 系统靶向 RNA 敲低、核酸检测以及 RNA 单碱基编辑对生物医学领域研究及转化应用有实际意义，也为某些疾病的治疗提供了有效且更安全的方法。

基因组中 R-loop 平衡在神经退行性疾病中的研究进展

叶子凌 林翔 王柠 陈万金
福建医科大学附属第一医院

目的 R-loop 是 DNA 与 RNA 杂交形成三维结构，经常被发现于基因组的转录过程。目前在肿瘤以及神经退行性疾病中均有发现 R-loop 的平衡失调，R-loop 的平衡失调会造成 DNA 损伤，转录异常以及基因组的不稳定，导致细胞的死亡。另外，越来越多的研究者发现证实，基因组存在非常规的 R-loop 结构，参与 DNA 修复，基因转录调控以及端粒稳定。本文旨在探讨基因组中 R-loop 平衡在神经退行性疾病中的研究进展。
材料与方法 通过查阅国内外与 R-loop 相关的神经退行性疾病的文献，对其发病机制进行总结归纳。
结果 1.R-loop 与肌萎缩侧索硬化症。肌萎缩性侧索硬化症（ALS）是一种成年起病的神经退行性疾病，其病理特征累及脊髓前角细胞、脑干运动神经核及锥体束的进行性的退行性变性。目前已知的致病基因包括 *C9ORF72*、*Senataxin*、*TDP-43* 及 *FUS2* 均发现存在 R-loop 的平衡失调，有证据表明 R-Loop 的累积可以造成基因组不稳定性从而导致细胞死亡或通过改变启动子的甲基化影响基因表达，但在疾病中特异性 R-loop 累积或消耗的机制尚不明确。2.R-Loop 与脊髓性肌萎缩症。脊髓性肌萎缩症（SMA）是一常染色体隐性遗传的神经退行性疾病，临床上以近端肌无力和肌萎缩为特征。其致病基因位于 5q13 染色体上的运动神经元 1（SMN1）既往研究发现，SMA 小鼠模型中以及在干扰 *SMN* 表达的 SH-SY5Y3 细胞发现 R-LOOP 的累积，导致基因组不稳定。但该作用导致特定运动神经元死亡的机制尚不清楚。3.R-loop 的治疗。如果证实 SMA 和 ALS 中 R-loop 失调造成神经死亡是重要的致病途径，那么 R-loop 形成的调控将变得有意义，因为多种神经退行性疾病可能存在治疗靶作用点。
结论 R-loop 的形成失调在神经退行性疾病病理机制中存在至关重要的作用，也为神经退行性疾病的治疗提供新的思路。

oRG 细胞特异性高表达基因异常影响皮层发育

赵志远 陈万金 王柠
福建医科大学附属第一医院

目的 已有研究通过对 GW16-17 胎儿大脑进行单细胞测序后发现对神经发生至关重要的放射状胶质细胞 outer radial glia (oRG)在皮层发育的关键时期特异性高表达 DAG1、PALLD、KCNK10 等 16

个基因。此外早期研究曾在某些涉及皮层发育异常的神经遗传性疾病中报道过上述基因。本文将以DAG1 为例阐述此类 oRG 特异高表达基因对某些神经遗传性疾病中皮层发育异常表型的贡献。
方法及材料 通过查阅国内外有关 oRG 细胞特异高表达基因与皮层发育异常相关的文献并仔细阅读，对其进行归纳总结。
结果 DAG1 为 oRG 细胞特异高表达基因之一，目前已报道了肌营养不良-抗肌萎缩相关糖蛋白病(MDDG)中最严重的亚型 Walker-Warburg 综合征(WWS)存在 DAG1 缺失突变，患者存在包括Ⅱ型无脑回畸形、桥小脑畸形等脑结构异常。在利用 Cre-loxp 所构建的中枢神经系统特异性 DAG1 敲除小鼠中也观察到包括半球间裂消失、神经元分层紊乱、多微脑回畸形等发育缺陷。免疫荧光结果显示正常神经母细胞迁移所必需的放射状胶质细胞骨架破坏，神经元发生异位。以上证据均提示 DAG1 与 WWS 的无脑回畸形表型密切相关。除 DAG1 外，其它 oRG 特异高表达基因也已报道与神经发生异常以及神经系统疾病相关如 PALLD 缺失突变被证实将导致神经管闭合缺陷; KCNK10 的低甲基化与脑体积减小相关；FAM107A 则被发现在具有自杀倾向的精神分裂症患者额叶皮层中高度富集。
结论 近几年随着单细胞测序技术的兴起已鉴定出与神经发生皮层扩张密切相关的各类神经祖细胞特异高表达基因，而早期研究也报道了其中部分特异高表达基因异常对皮层发育的不利影响。因此针对具有皮层发育异常表型的神经遗传性疾病，关注包括 oRG 在内的一系列神经祖细胞特异高表达基因可能在探索疾病发病机制中具有潜在的价值。

基于 CRISPR 系统的基因编辑技术研究进展

郑基坛 陈万金
福建医科大学附属第一医院

目的 因编辑技术是近年来取得突破性进展的颠覆性技术之一。本综述就基于 CRISPR 系统的基因编辑技术进行回顾和展望。
方法 通过查阅国内外关于 CRISPR-Cas 基因编辑系统的相关文献，对其进行总结归纳。
结果 自 CRISPR 系统被开发用于基因组编辑以来，因其设计简单、效率高等特点，迅速被广泛应用于在生命科学、基础医学、基因治疗等领域。到目前为止，基于 CRISPR 系统，从最初的通过 NHEJ 修复方式介导的基因敲除、与 HDR 介导的精准编辑，到现在广泛应用的单碱基编辑技术，以及新开发的引导基因编辑技术被相继开发应用。每一种基因编辑技术都具有其优势和不足之处，科研人员一直致力于拓宽 CRISPR 的应用范围、提高编辑效率、降低脱靶效率等研究。
结论 本文将对 CRISPR 系统、单碱基编辑技术、引导基因编辑技术的特点及优化等方面进行系统介绍，为科研人员了解、选择及应用基因编辑技术等提供参考。

卵母细胞的自噬及其表观遗传学调控

施陈楠 严正杰 覃莲菊 崔毓桂
南京医科大学第一附属医院（江苏省人民医院）

目的 自噬（autophagy）是一种细胞内的降解途径，正常水平的自噬可以清除细胞内的有害物质和受损细胞器，维持细胞的正常功能。研究证实，卵母细胞的自噬在调节始基卵泡池的建立、卵泡募集和闭锁等卵泡发育过程中发挥重要作用。表观遗传机制可以修饰自噬相关基因，影响其转录和随后的自噬。多囊卵巢综合征（PCOS）、原发性卵巢功能不全（POI）等疾病往往伴随卵泡发育和闭锁功能障碍，导致卵子数量和质量下降，女性生育力减低；自噬及其表观调控可能参与了卵巢衰老、PCOS、POI 的病理生理过程。综述卵母细胞的自噬及其表观遗传调控机制，以及参与卵泡发育和闭锁异常疾病的发生发展，为 PCOS 和 POI 临床治疗提供新思路。
方法 通过检索 pubmed、sinomed 等文献数据库，寻找相关文献。
结果 卵母细胞自噬参与原始卵泡池建立和卵母细胞程序性丢失，参与调节卵巢储备。LSD1 等甲基化调节酶和 SIRT1 等乙酰化调节酶通过调节表观修饰，影响自噬水平。在卵母细胞老化或 POI、

PCOS 等生殖相关疾病，卵母细胞自噬水平异常，导致卵母细胞线粒体功能受损、卵泡过度损耗。但是，卵巢内表观遗传调节的自噬与女性生殖疾病发生发展的关系，仍需进一步研究。
结论 深入研究卵母细胞中自噬的发生和表观遗传调节的相关机制，为卵泡发育障碍相关疾病的临床治疗提供新思路。

单碱基编辑系统在基因治疗中的研究进展

郑基坛 陈万金
福建医科大学附属第一医院

目的 因编辑技术是近年来取得突破性进展的颠覆性技术之一。本综述就基因编辑技术在神经系统疾病基因治疗中的应用进行回顾和展望。
方法 通过查阅国内外基于 CRISPR-Cas 系统的单碱基编辑技术用于神经系统疾病治疗的相关文献，对其进行总结归纳。
结果 基于 CRISPR-Cas 系统的单碱基编辑技术是一种基于人工核酸酶的遗传操作技术,能精确地对 DNA 进行高效改造。CRISPR-Cas 系统广泛存在于细菌中,是一种高效、特异、操作简单易行、可对多种生物的基因组进行遗传改造的工具。目前已有研究人员利用 ABE 单碱基编辑系统,通过编辑 SMN2 基因用于治疗 SMA;也可以直接逆转早衰症 LMNA 基因的异常突变，治疗早衰症；还可以通过编辑 PSK9 基因，降低低密度脂蛋白（LDL）水平等。但单碱基编辑系统也存在着脱靶等安全问题需全面评估。此外，如何将基因编辑工具精确、高效递送到靶器官或者靶细胞，使其更好的发挥作用，也是亟需解决的问题。
结论 基因编辑技术可以广泛应用于神经系统疾病的治疗，具有很好的发展前景，但仍有不少技术问题需要解决。

遗传性痉挛性截瘫 5 型诱导多能干细胞模型构建

赖璐璐 叶子凌 董恩霖 王柠 陈万金 林翔
福建医科大学附属第一医院

目的 遗传性痉挛性截瘫（Hereditary Spastic Paraplegia, HSP）是一组以进行性双下肢痉挛为特征的神经退行性疾病。遗传性痉挛性截瘫 5 型（SPG5）是 HSP 的亚型之一，由 *CYP7B1* 基因突变所致的。常表现为青少年期起病，慢性进展的双下肢肌痉挛和肌无力。我们团队前期对福建地区 52 个常染色体隐性 HSP 家系进行基因突变筛查，共筛查出 18 个 SPG5 家系，发现 SPG5 是最常见的常染色体隐性遗传 HSP 亚型，约占 34.6%（18/52），远高于其他文献报道。且存在 *CYP7B1* 基因突变热点 c.334C>T（p.R112*），进一步的单体型分析结果表明存在奠基者效应。目前暂无有效的治疗手段，因此 SPG5 的致病机制研究尤为重要。诱导多能干细胞（induced Pluripotent Stem Cells, iPSCs）是一类直接由体细胞重编程得来的具有多种分化潜能的干细胞。iPSCs 可以分化为不同细胞类型，且与供体具有相同的遗传背景。本研究旨在通过体细胞重编程技术，通过仙台病毒重编程，获得 SPG5 病人来源的 iPSCs 细胞株，为 SPG5 的致病机制研究提供模型基础。
方法 取得两名 SPG5 病人知情同意后，通过皮肤活检取得皮肤组织。皮肤组织经过培养后得到成纤维细胞。使用 CytoTune-iPS 2.0 Sendai Reprogramming 试剂盒进行重编程。使用免疫荧光技术对重编程得来的 iPSCs 进行胚胎干细胞标志物表达鉴定。
结果 1.两名 SPG5 患者均以行走不稳起病，表现为双下肢肌张力障碍，腱反射增高和病理征阳性。两名患者均携带有 *CYP7B1* 纯合突变 c.334C>T（p.R112*）。2.活检得来皮肤组织经过 3 周左右时间的培养，可以得到成纤维细胞。皮肤成纤维细胞形态呈细长状或梭形。冻存早期代数的成纤维细胞。3.通过仙台病毒感染成纤维细胞，过表达转录因子 KLF4、OCT4、SOX2 和 cMyc，可以得到 SPG5 病人来源的 iPS 细胞株。iPS 克隆呈圆形，细胞排列紧密且边缘规整。4.免疫荧光染

色结果显示，重编程得来的 iPS 细胞株可表达胚胎干细胞相关标志物，包括核蛋白 NANOG、OCT4 和 SOX2，高分子量糖蛋白 TRA-1-60 和膜蛋白 SSEA4。
结论 我们通过体细胞重编程，获得 SPG5 病人来源的 iPS 细胞株，与 SPG5 病人具有相同的遗传背景。后续可将 SPG5 患者得来的 iPS 细胞株分化为皮层运动神经元或构建脑类器官模型，进一步探索 SPG5 的致病机制。

Polymorphisms of OXTR impact subjective well-being: the intermediary role of Attributional style

Lei Ji[1] Changfeng Chen[2] Binyin Hou[1] Decheng Ren[1] Fan Yuan[1] Liangjie Liu[1] Yan Bi[1] Zhengming Guo[1] Fengping Yang[1] Qian Wu[1] Fujun Chen[1] Xingwang Li[1] Chuanxin Liu[2] Zhen Zuo[2] Rong Zhang[3] Zhenghui Yi[1] Yifeng Xu[1] Lin He[1] Yi Shi[1] Tao Yu[1] Guang He[1]
1.Shanghai Jiao Tong University
2.Jining Medical University
3.Shanghai Center for Women and Children's Health

Background Polymorphisms in the oxytocin receptor (*OXTR*) gene have been shown to be related to individual differences in negative emotions, such as depressive symptoms and anxiety. However, it remains unclear the potential roles of *OXTR* polymorphisms in subjective well-being (SWB), which is negatively correlated with depressive symptoms.
Methods We examined hypotheses of associations between SWB, attributional styles, and five polymorphisms of the oxytocin receptor gene (*OXTR* rs53576, rs2254298, rs1042778, rs2268494, and rs2268490) among 627 full-time college freshmen using structural equation modeling.
Results The results indicated that individuals with the *OXTR* rs53576 AA/GA genotype showed higher SWB scores. The AA genotype of *OXTR* rs2254298 referred to high level of SWB and low level of external attributional style. Moreover, external attributional style mediates the association between *OXTR* rs2254298 polymorphism and SWB.
Limitations A far greater number of *OXTR* SNPs will be included to examine their associations with subjective well-being, which would have certainly helped to increase confidence in the replicability of the current findings.
Conclusion Our findings support a role for the genetic variations of oxytocin receptor in the individual differences of subjective well-being. What's more, external attribution style mediates the association between *OXTR* rs2254298 polymorphism and subjective well-being.

C1ORF194 as a new calmodulin, co-combination with GRP75, to mediate Ca2+ transfer from the endoplasmic reticulum to the mitochondria associated with CMT

Fu Xiong[1] Meiyi Li[1] Di Ma[1] Shunchang Sun[2] Cheng Huang[1] Fei He[1] Xiangmin Xu[1]
1.Southern Medical University
2.Shanghai Jiao Tong University School of Medicine

Objective We previously reported that *C1orf194* is one of the pathogenic genes related to Charcot-Marie-Tooth (CMT) disease, which appears to be involved in nervous system development and function with both motor and sensory nerves being affected by loss of function of *C1orf194*. Either gain-of-function or partial loss-of-function mutations in *C1orf194* can specify different causal mechanisms responsible for CMT disease with a wide range of clinical severity. However, the underlying pathogenic mechanism behind these defects is yet to be fully determined.
Methods In this study, we will perform the investigation in vitro and in vivo applying the stable cell line, knock-in and knock-out mice of c1orf194 gene, through protein interaction, calcium ion concentration and channel protein determination, signal pathway analysis and pathological

analysis with axonal degeneration, etc., to investigate the interaction protein with c1orf194 gene, and clarify the regulating target in the involved calcium metabolism signal pathway.
Results Here we demonstrate that C1ORF194 localized to the mitochondria-associated membrane (MAM) *in vitro* and *in vivo*. Moreover, C1ORF194 as a new calmodulin co-combine with glucose-regulated protein 75 (GRP75), to mediate Ca^{2+} transfer from the endoplasmic reticulum to the mitochondria via IP3Rs-Grp75-VDAC complex. *In vitro* studies revealed that the familial CMT-associated I121N mutant of *C1orf194* significantly shortened endoplasmic reticulum (ER)-mitochondria tethering and increased expression of Ca^{2+}-regulatory proteins including Grp75. Simultaneously, the I121N mutant of *C1orf194* increased cytoplasmic calcium concentration but decreased mitochondrial calcium concentration. Similarly, the changes in calcium ion concentration also appeared in Schwann cells of *C1orf194* gene knockin (p.I122N) mice. However, the opposite calcium ion concentration changes and decreased expression of Grp75 appeared in Schwann cells of *C1orf194* knockout mice, which indicated the different pathogenic mechanism on *C1orf194* gene with the either gain-of-function or loss-of-function mechanisms in knock-in and knock-out mice.
Conclusions Altogether, C1ORF194 is a GRP75-coregulator and the mutant C1ORF194 can affect Ca^{2+} shuttling at the MAM with intracellular Ca^{2+} elevation via altered interactions of C1ORF194 with GRP75, thus leading to CMT neuropathy.

子痫前期患者胎盘组织中 lncRNA 的系统研究

刘海华
南方医科大学南方医院

目的 子痫前期（Preeclampsia）是一种妊娠期特有的疾病，主要表现为妊娠 20 周后出现新发高血压和蛋白尿，可伴有器官功能紊乱等症状。目前唯一有效的办法是终止妊娠，胎盘分娩后该病相关的各种症状得到缓解，提示子痫前期是胎盘源性疾病。我们前期系统检测了子痫前期患者胎盘组织的基因表达改变情况，在早发重症患者中约 3000 基因表达发生显著改变。目前的核心问题是：哪些关键调控因子改变了基因水平的表达模式？虽然有报道长链非编码 RNA（long non-coding RNA，lncRNA）能够调控子痫前期基因表达改变，但是缺乏系统研究。
方法 我们收集了 32 个来源正常个体和 9 个来源早发重症子痫前期（early-onset severe preeclampsia）患者的胎盘组织；提取胎盘组织 RNA 并进行转录组测序。随后，我们检测差异表达基因；预测差异表达基因启动子区域显著富集的转录因子（transcription factor，TF）结合位点；通过整合 lncRNA-蛋白互作网络、TF-靶基因调控网络以及 lncRNA-差异表达基因启动子互作网络构建 lncRNA-TF-靶基因层级调控网络。
结果 我们一共得到 3116 个差异表达基因，包括 383 个 lncRNA。我们构建了差异表达 lncRNA（DElncRNA）-蛋白互作网络，该网络中的蛋白质显著富集了 TF。通过预测 DElncRNA 与差异表达基因启动子区域互作的情况，我们发现平均每个 DElncRNA 与 1453 个差异表达基因的启动子区域互作形成三链结构，提示 DElncRNA 可能通过与 TF 互作来调控基因表达。以往研究显示，lncRNA 可以通过与 DNA 相互作用作为 TF-启动子结合的脚手架（Scaffold）以介导或稳定 TF 与启动子的互作。
我们通过 HOMER 预测发现差异表达基因富集了 18 个转录因子结合位点，279 个 DElncRNA 与这些关键 TF 互作。因此，我们整合了 DElncRNA-TF 互作网络、TF-差异表达基因调控网络及 DElncRNA-差异表达基因启动子互作网络，构建 lncRNA-TF-差异表达基因层级调控网络。该层级调控网络包含了大部分差异表达基因（2357，75.64%），提示 lncRNA 在子痫前期胎盘组织广泛影响基因表达。
我们对层级调控网络中的 lncRNA 进行排序，选择表达水平变化大、邻近蛋白编码基因与子痫前期相关以及调控的差异表达基因数目多的 *FLNB-AS1* 进行验证。我们通过 RNA-pulldown 实验联用质谱和 RNA 结合蛋白免疫共沉淀实验，发现 *FLNB-AS1* 与 JUNB（关键 TF 之一）互作。而 JUNB 调控的差异表达基因显著富集 HIF-1 信号通路，我们在 HTR8/SVneo 细胞中过表达 *FLNB-AS1*，发现这些基因表达水平发生显著变化，并且与病人中观察到的表达改变一致。

结论 在本研究中，我们通过整合 lncRNA-蛋白互作网络、TF-靶基因调控网络以及 lncRNA-差异表达基因启动子互作网络，发现 DElncRNA 与 TF 互作在早发重症子痫前期胎盘组织中影响基因表达的改变。*FLNB-AS1* 可能通过调控 HIF-1 信号通路参与子痫前期的发生发展。

A novel heterozygous LMF1 gene mutation (c.1523C>T), compounded with an LPL gene Mutation (c.590G>A), aggravates the clinical symptoms in a case of familial hypertriglyceridemia

Yingchun Zheng[1] Danxia Guo[2] Zhongzhi Gan[1] Hua Zheng[2] Fu Xiong[1]
1.Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University
2.Department of Cardiovascular Medicine, Nanfang Hospital, Southern Medical University

Background Hypertriglyceridemia is an important contributor to atherosclerotic cardiovascular disease (ASCVD) and acute pancreatitis. Familial hypertriglyceridemia is often caused by mutations in genes involved in triglyceride metabolism. Here, we investigated the disease-causing gene mutations in a Chinese family with hypertriglyceridemia and assessed the functional significance in vitro.
Methods Genomic DNA extracted from peripheral blood mononuclear cells was taken from the family members. Whole exome sequencing (WES) and sanger sequencing were performed to identify the pathogenic gene. The function of the mutant LMF1 was studied by bioinformatics, real-time PCR, western blotting, subcellular localization. Cell lysates and media were used to analyze LPL synthesis and secretion.
Results WES identified a missense mutation (c.590G>A) in *LPL* gene, as well as a novel missense mutation (c.1523C>T) *LMF1* gene. A decrease in mRNA and protein expression was observed in 293T cells transfected with plasmids carrying the *LMF1* c.1523C>T mutation. Subcellular localizations showed that both wild-type (WT) and mutant LMF1 proteins were localized at the cell cytoplasm. In the cell medium and cell lysates, these *LMF1* and *LPL* gene mutations both caused a decreased LPL mass, compared to the WT. Moreover, the combination of LMF1 and LPL gene mutations significantly decreased LPL levels compared to their individual effects on the LPL concentrations.
Conclusions The present findings demonstrate that the compound heterozygous c.590G>A mutation in the *LPL* gene and c.1523C>T mutation in the *LMF1* gene are pathogenic, and both reduce the LPL levels. This ultimately contributes to the manifestation of severe hypertriglyceridemia. Our study underscoring the complexity of hypertriglyceridemia and the need for the combination of extensive molecular genetic testing and clinical characterization; in addition, expands the spectrum of *LMF1* mutations. Finally, it help the family members prevent and treat the disease.

SIX1 在非小细胞肺癌中的表达及其细胞功能研究

杨春艳
内江卫生与健康职业学院

目的 SIX1 是一种转录因子，在发育中起主要调节作用，在癌症中经常出现失调。探究沉默 SIX1 基因的表达对人非小细胞肺癌细胞 A549 和 XWLC 增殖、迁移、侵袭、细胞周期和凋亡的影响。
方法 实验分为对照组（siNC）和处理组（siSIX1），非小细胞肺癌 A549 和 XWLC 分别转染 siNC 和 siSIX1，运用 CCK-8（Cell counting kit-8）法和实时细胞分析仪（Real Time Cell Analyzer，RTCA）检测细胞的活性，RTCA 检测细胞的迁移和侵袭能力，流式细胞术检测细胞周期和凋亡，蛋白印迹法（Western blotting）检测细胞相关通路蛋白的水平。

结果 A549 和 XWLC 细胞分别转染 siSIX1 后，与对照组相比，细胞活性明显降低（$P < 0.05$）; 迁移侵袭能力明显降低；实验组细胞周期 G_0/G_1 较对照组显著升高（$P < 0.05$），S 期降低（$P < 0.05$）；细胞凋亡数增加（$P < 0.05$）；通路蛋白 P-ERK，Cyclin-D1，Bcl-2 表达量降低，E-cadherin 表达量升高。
结论 沉默 SIX1 基因抑制非小细胞肺癌 A549 和 XWLC 细胞的增殖，迁移和侵袭能力，阻碍细胞周期向 S 期转换，促进了细胞凋亡并且 SIX1 的表达与预后差有关。说明 SIX1 可能参与了非小细胞肺癌的发生发展。

Whole Exome Sequencing Identifies a Mutation in MYO6 as a Novel Cause of Autosomal Dominate Non-Syndromic Hearing Loss

Yu Zhang Zhaoxin Ma
Shanghai East Hospital

Objectives Autosomal dominate non-syndromic hearing loss (ADNSHL) is characterized by postlingual progressive onset. And MYO6 mutations have been reported to cause congenital severe-to-profound hearing loss. In this article, we report a MYO6 mutation in a Chinese family.
Methods The clinical characteristics of the proband and his relatives were assessed and audiology function examination was performed. Then whole-exome sequencing (WES) was used to screen pathogenic gene candidates by analyzing genomic DNA samples. Sanger sequencing was used to verify the pathogenicity of candidate nonsynonymous variants in ADNSHL genes in family members. We also performed in silico analyses (SIFT, Polyphen2 and MutationTaster) to assess the potential pathogenicity.
Results We identified a novel causative mutation, c.3327delA in *MYO6* (DFNA22), that resulted in a p.V1111Cfs*33 substitution. Co-segregated with the hearing loss phenotype in other family members, this mutation was predicted to be pathogenic by in silicon analyses.
Conclusions In this study, we found a heterozygous missense mutation (*MYO6*: NM_004999: exon32: c.3327delA: p.V1111Cfs*33), which is a candidate deafness mutation in the SD-001 family.

基于单细胞转录组数据比较分析人和小鼠心脏细胞的动态发育过程

商梦悦[1,2] 彭鲁英[1,2] 李丽[1,2]
1.同济大学医学院心律失常教育部重点实验室 2.同济大学医学院医学遗传学系

目的 心脏是胚胎发育中首先形成的器官，其发育过程涉及不同细胞谱系基因的协同作用。小鼠作为主要的动物模型，探究其胚胎心脏发育过程与人类的保守性以及差异能为我们更好地展现物种间不同谱系命运决定等规律，为进一步探讨心脏发育机制提供依据。
方法 本研究对来源于 GEO 数据库的人类和小鼠胚胎心脏不同发育时间点的单细胞转录组数据进行比较分析，以确定人和小鼠心脏细胞的动态发育过程中的保守性和差异。
结果 我们分别在人和小鼠中确定了主要的细胞类型：心肌细胞、心脏成纤维细胞、内皮细胞、心外膜细胞及免疫相关细胞等。我们确定了人类和小鼠心脏各细胞类型在发育过程中共享的以及物种特异的一系列标记基因。同时，我们探究了人类和小鼠在发育中各时期的细胞构成和基因表达差异存在的对应关系。我们构建了主要细胞类型的发育轨迹以确定潜在演化/分化先后关系以及人和小鼠心脏细胞的发育谱系。根据预测的发育轨迹以及随着拟时间发育呈现出的基因表达模式，我们挖掘了与发育阶段相关的基因以找出驱动细胞亚群分化的关键基因。
结论 我们的研究从单细胞水平阐明了人类和小鼠胎儿心脏发育过程中的综合细胞组成和发育途径，揭示物种之间胚胎心脏发育在基因表达模式、异质性和细胞类型的组成方面的相似和差异。

A circular RNA protects the heart from heart failure by competing with a miRNA

Yi Hu[1,2] Luying Peng[1,2] Li Li[1,2]
1.Key Laboratory of Arrhythmias of Ministry of Education, Tongji University School of Medicine, Shanghai, 200092, China
2.Department of Medical Genetics, Tongji University School of Medicine, Shanghai, 200092, China

Aims Circular RNA (circRNA) is a subclass of non-coding RNAs involved in gene regulation in a variety of physiological and pathological processes. Pathological myocardial hypertrophy is a common clinical manifestation in the early stage of heart failure, and the relationship among circRNA, miRNA and mRNA in the heart failure progression remains largely unknown. The present study aimed to explore the ceRNA regulatory mechanism of circRNA in heart failure.
Methods and results In order to reveal functional circRNAs and identify the core circRNA signal pathway in heart failure, a global triple network based on the competitive endogenous RNA (ceRNA) theory using the data from National Center for Biotechnology Information Gene Expression Omnibus and related article was constructed. The network visualization and functional annotation were performed using DAVID and Cytoscape, respectively. It shows that circHFac found in ceRNA Network was down-regulated in the TAC mice and in the cytoplasm of Ang-II-treated neonatal mouse cardiomyocytes. Knocking down the expression of circHFac enhances the cell size and expression of atrial natriuretic peptide and b-myosin heavy chain in neonatal mouse cardiomyocytes. Thus, we screened out the circHFac/miRNA/mRNA axis in the network and verify the relevance to the disease progression. Further, dual-luciferase reporter assay showed that miRNA could interact with CDS region of mRNA gene, and circHFac could block the interactions. The anti AGO2-RNA Immunoprecipitation was used to analyze the interaction between circHFac and miRNA. From the function mechanism, miRNA inhibitor could reverse the hypertrophic effect caused by si-circHFac in mouse cardiomyocytes.
Conclusions This study constructed an ceRNA network related to heart failure to screen out core signaling molecules and demonstrated that circHFac attenuates cardiac hypertrophy via suppressing miRNA leading to enhanced mRNA expression levels.

上皮表达 Six1、Six2 协同调控第一鳃弓极性分化发育

柳稚旭
上海交通大学医学院附属第九人民医院

目的 颌面畸形与第一鳃弓发育异常密切相关。颅神经嵴细胞是第一鳃弓发育的主要参与者，在多组信号分子调控下颅神经嵴细胞定向迁移、分化。已有报道 SIX 家族在调控颅神经嵴细胞前后向分化有重要作用，机制不详。本研究拟通过构建模型小鼠，研究高度同源的 Six1、Six2 在第一鳃弓分化中的作用。
方法 构建 Six1、Six2 不同基因拷贝数缺失小鼠模型，及颅神经嵴细胞特异敲除 Six1 小鼠模型，通过表型观察，明确 Six1、Six2 表型，通过原位杂交探索其下游因子。
结果 SIX 家族同源度最高的 Six1、Six2 在颅颌面发育中具有明确的协同作用，其基因拷贝数的缺失增加，可导致颌面部畸形不断加重。Six1、Six2 不仅表达在第一鳃弓的外胚间充质，其信号分子同时出现在第一鳃弓上下颌突交界区的上皮。条件性敲除小鼠提示，上皮区域表达的 SIX1、SIX2 参与上下颌分化的调控，其表达缺失导致上下颌极性消失、结构混乱。进一步研究提示，转录因子 SIX1、SIX2 可通过抑制 BMP 信号通路、EDN-DLX5/6 信号轴调控了上下颌突极性发育。
结论 Six1、Six2 在 SIX 家族同源度高，协同参与颅颌面的发育过程，通过调控 BMP 信号通路多个因子、EDN-DLX5/6 信号轴参与颅神经嵴细胞在第一鳃弓前后向、背腹向迁移分化。

Suppression of RIP1 activity ameliorates hepatic insulin resistance

yanping wang
Shanghai Jiao Tong University Affiliated Sixth People's Hospital

Objective RIP1-regulated inflammation and necroptosis contributed to several metabolic diseases. This study aims to explore the mechanism how hepatic RIP1 influences insulin resistance.
Methods Primary hepatocytes with Nec-1 treatment or RIP1 expression were exposed to palmitic acid (PA), and then cellular insulin signaling were examined. Phosphorylation sites of RIP1 were detected by LC-MS/MS, and RIP1 variants with mutated phosphorylation sites were overexpressed in hepatocytes to identify the specific residue that influenced the RIP1-mediated insulin resistance.
Results We discovered an aberrant increase in RIP1 activity during the obesity-induced insulin resistance. Inhibition of RIP1 activity with Nec-1 ameliorated PA- or high-fat diet-caused hepatic insulin resistance. With LC-MS/MS analysis and mutagenesis screening, we identified a novel phosphorylation site of RIP1, to be responsible for RIP1-mediated insulin resistance.
Conclusions Our findings highlight the diabetogenic role of RIP1 activity and propose RIP1 as a promising therapeutic target for type 2 diabetes.

DNA 甲基化在阿尔兹海默症中的研究进展

李昕泽
复旦大学上海医学院生物医学研究院

阿尔茨海默病（Alzheimer's disease，AD）是一种神经退行性疾病。AD 发病的分子机制尚不清楚。大量研究表明表观遗传改变对 AD 有重要影响，表观遗传可能是诊治 AD 的重要突破口。目前 AD 表观遗传学研究主要关注 DNA 甲基化、染色质重塑、组蛋白修饰和非编码 RNA 调控等多个方面。本综述聚焦表观遗传 DNA 甲基化分子机制，介绍其在 AD 中的调控机制，并系统回顾了近年来 DNA 甲基化作为一种潜在的生物标志物，及其在 AD 中作用机制的研究。DNA 甲基化在 AD 中具有重要作用，调节 DNA 甲基化可能是干预 AD 的重要方法。

基于第三代测序技术的人类基因组结构变异数据库

江泽航
中山大学中山眼科中心

目的 结构变异(Structural Variations, SVs)是在基因组上大于 50bp 的一系列的基因组重排事件, 主要包括插入(INS)、缺失(DEL)、倒位(INV)、易位(TRA)和重复(DUP)。SV 被证实与诸如肿瘤，精神分裂症等部分人类疾病相关。目前人类 SV 数据库最具代表性的包括 dbVar 和 gnomAD 等以二代测序和 microarray 为主要数据来源的数据库，由于三代测序技术寻找结构变异与二代相比具有更大的优势，为了更全面的研究结构变异与不同群体及表型的关系，我们收集并重分析了 135 例人类三代基因组数据，并将高度整合的 SV 注释在数据库 LRSV 上(http://www.gigagenomics.com/sv_db/index.html)。
方法 我们收集并整理 135 例来自 NCBI 和 EBI 的三代基因组数据，包括 Pacbio Hifi/CCS，Pacbio CLR 以及 ONT 等平台。其中 53%的数据为 Hifi/CCS 数据，样本主要包括欧洲，亚洲(南亚、东亚)，非洲和美洲。我们采用优化过的高度整合的流程对每个样本单独检测 SV，采用 Jasmine 对所有样本的 SV 集进行合并，以 Hifi/CCS 数据为合并的基准，并重新对所有样本进行 genotyping，最后通过注释和过滤得到高度可信的 SV 集。
结果 我们鉴定了总共约 16 万个非冗余 SVs，包括 84641 个 INSs，67255 个 DELs，4201 个 DUPs 和 1447 个 INVs。对所有非冗余 SV 进行 genotyping 和注释后，通过对假阳性位点的进一步过滤，我们注释了总共 77600 个高度可信的位点，这些位点在不同程度上与潜在的致病性及临床

表型相关，我们将这些结果整理在数据库的 Search 界面上。此外，我们还额外注释了 2776 个功能性缺失 SVs (pLoFs)，该结果一并整合在 Search 界面上。除了搜索功能，我们还提供了每个样本 genotyping 后的 vcf 下载地址以及基于 JBrowser2 的可视化界面，方便读者进一步对感兴趣的基因组区域观察。

结论 基于三代测序的人类结构变异数据库为基因组研究提供了更便捷的研究工具，通过高度整合人类基因组和表型数据，我们提供了潜在的 SV 与表型的新的手段。

基于长读长重测序的中国汉族人群全基因组结构变异研究

吴志坤
中山大学中山眼科中心

目的 基因组结构变异（Structure Variantions，SVs）是指基因组上长度超过 50bp 的序列与位置关系变化，SVs 与人类的演化、表型、疾病风险等有关联。利用长读长技术可跨越基因组中复杂和重复区域的优势，绘制中国汉族人群全基因组结构变异图谱，旨在解析由 SVs 引起的群体多样性特征和复杂性遗传变异。

方法 我们对 405 名来自 18 个不同省份，平均年龄为 42 岁且无亲缘关系的中国汉族人外周血进行纳米孔长读长全基因组测序，平均测序深度为 17x，327 人具有 68 种表型和临床指标。我们采用三种工具检测 SVs，并随机选择 10 名汉族人进行 PacBio HiFi 测序，同时挑选 199 个 SVs 设计引物后 PCR，以验证结果的准确性。

结果 我们鉴定了中国汉族人群中 132,312 个非冗余的 SVs，其中 53.3%为首次发现。PacBio HiFi 测序和 PCR 验证结果显示 FDR 为 3.2%。我们注释了 1,929 个功能缺失 SVs，影响 1,681 个基因的编码序列。我们发现了位于 *HBA1/HBA2/HBB* 的罕见缺失与贫血的发生相互关联以及与身高相关的 *GHR* 常见缺失。我们鉴定出可区分中国汉族人群亚群的与免疫相关的 SVs。

结论 挖掘人类所有的基因组变异是基因组学研究的目标，长读长测序提高了发现 SVs 的灵敏度。我们鉴定并分析了中国汉族人群全基因组 SVs 图谱，揭示了 SVs 与表型、疾病和演化的关联，汉族人群队列的重测序也为人类遗传变异研究提供了资源。

Copy number variation analysis reveals novel candidate genes in patients with congenital heart disease and extracardiac malformation

Ping Li Weicheng Chen Wei Sheng Guoying Huang
Children's Hospital of Fudan University

Backgrounds Copy number variations (CNVs) are crucial genetic factors for congenital heart disease (CHD) with extracardiac malformation (ECM). The clinical use of chromosomal microarray(CMA) analysis has been emphasized in these patients to discover candidate CNV. The next logical step in interpreting the mechanisms of this complex disease is to identify disease-causing genes in candidate CNV.

Methods We detected CNV in 103 sporadic CHD patients with ECM by CMA analysis and conducted a set of gene prioritization processes using ToppGene and self-organizing feature map (SOM) analyses.

Results Two gross chromosomal aberrations and sixty CNVs are associated with ECM. The overall diagnostic yield of CMA testing for CHD patients with ECM is 15.53% if considering pathogenic CNV and aneuploidy, and 21.36% if considering pathogenic CNV, likely pathogenic CNV, and aneuploidy as a positive finding. The neurodevelopmental malformations (NDM) is the most frequent comorbidity in ECM, followed by craniofacial defects and urinary system diseases. Using in-depth prioritization processes for NDM-related genes, we identified *NDE1*, *TERT*, and *COL22A1* as candidate genes for CHD and ECM, especially NDM.

Conclusions CMA is valuable in clarifying the genetic mechanisms underlying CHD with ECM, and bioinformatics including ToppGene analysis and SOM clustering may give new insight to identify disease-causing genes in CNV detected by CMA.

利用 SD-OCT 测量大鼠眼部参数

周文慧
中山大学中山眼科中心

目的 谱域光学相干断层成像术（spectral-domain OCT，SD-OCT）是一种对眼球透光组织做断层成像的影像学方法，有分辨高，成像速度快，非接触性的特点，在临床上主要用于眼底检查及记录。以前对于眼轴、晶状体、视网膜厚度的测量主要是通过 A 超及组织学染色来测量，A 超为接触性检查而组织学染色过程会对眼球的形态造成一定的影响，其精度和重复性较低，受到实验过程和手法的影响较大。本研究通过 SD-OCT 测量同基因型同胞同年龄同性别大鼠眼部基本参数，并对其进行统计分析，测试该方法的重复性、精度情况。
方法 选择同基因型、同性别、同胞出生的 6 周、12 周龄、15 周龄鼠各 5 只，使用 Leica Envisu R4310 系统检测其视网膜厚度、前段深度、后段深度、角膜厚度、晶状体厚度、眼轴长度。用与系统配套的软件 Diver 3.4 测量，用 SPSS Statistics 26 进行统计及分析，计算平均值及标准差。
结果 对于所选择的野生型大鼠测量结果为：6 周龄视网膜平均厚度为 0.2194±0.004mm，前段平均深度为 0.669±0.01mm，后段平均深度为 1.302±0.034mm，角膜平均厚度为 0.126±0.014mm，晶状体平均厚度为 3.348±0.053mm；12 周龄视网膜平均厚度为 0.200±0.005mm，前段平均深度为 0.741±0.038mm，后段平均深度为 1.240±0.020mm，角膜平均厚度为 0.128±0.0129mm，晶状体平均厚度为 3.537±0.028mm；15 周龄视网膜平均厚度为 0.200±0.005mm，前段平均深度为 0.755±0.010mm，后段平均深度为 1.241±0.090mm，角膜平均厚度为 0.149±0.014mm，晶状体平均厚度为 3.800±0.053mm 其重复性良好，可精确至 0.001mm。进行组织学切片和 HE 染色后测的眼部参数与略低于 SD-OCT，但变化趋势与其保持一致。
结论 SD-OCT 可以用于大鼠眼部参数的测量，除了视网膜厚度外，眼前后段深度、角膜厚度、晶状体厚度、眼轴等参数，其重复性和精确度都可以满足大鼠的近视、青光眼等疾病模型的表型研究。

角膜营养不良相关基因的变异谱研究

瞿宁 钱卫平
北京大学深圳医院

目的 通过高通量测序研究我国遗传性眼病(IEDs)中角膜营养不良(CDs)的相关基因突变谱，为疑似 CDs 患者的临床前诊断和治疗提供参考。
方法 回顾性研究，招募了一个包括 69 例临床 CD 患者、其他眼疾患者、以及他们的健康家庭成员作为对照的队列。对队列中的所有样本用包含 792 个遗传性眼病相关基因(其中 CD 相关基因 22 个)外显子的芯片进行捕获测序。
结果 在 22 个 CD 相关基因上找到了 2334 个变异，其中 21 个鉴定为致病或疑似致病（含 1 个新发突变），2313 个致病性证据不足。TGFBI 基因以往被报道为疑似致病的 p.D123H、p.M502V、p.P501T 和 p.P501A 在本研究里被重新定义为可能良性。在此基础上，81.16%(n=56/69)的 CD 患者被明确诊断，基因 TGFBI、CHTS6 和 SLC4A11 分别占诊断病例的 91.07%、7.14%和 1.79%。
结论 首次系统地描述了 22 个 CD 相关基因的变异谱，评估了 2334 个变异的频率、致病性，为中国人群的角膜营养不良遗传诊断提供了参考。

Global developmental delay due to a new compound heterozygous mutation of the FRMD4A gene：a case report

Yuhua Pan Fu Xiong
Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University

Background FERM domain-containing protein 4A (FRMD4A) is a scaffolding protein previously proposed to be critical the regulation of cell polarity in neurons and implicated in human intellectual development.
Methods Skull magnetic resonance imaging (MRI) was used to test diffusion-weighted imaging (DWI) of the genu of corpus callosum and splenium of corpus callosum.Blood samples were collected and sent for genetic testing and molecular studies after obtaining informed written consent from the parents.
Results We report a case of a 3-year-old boy with corpus callosum anomaly, macrocephaly, ataxia, and unexplained global developmental delay. Here compound heterozygous missense mutations in the *FRMD4A* gene [c.1830G>A, p.(Met610Ile) and c.2973G>C, p.(Gln991His)] were identified in the proband, and subsequent familial segregation showed that each parent had transmitted a mutation.
Conclusions Our results gave further evidence on the associations of variants in FRMD4A with intellectual development and indicated that for patients with unexplained global developmental delay, the *FRMD4*A gene should be included into the data analysis from whole exome sequencing, which contributes to uncover more patients affected and rich the phenotypic spectrum.

Comprehensive Research on the Distribution of HLA-DRB1 in Chinese Ethnic Groups

Baitong Fan Hao Sun
Institute of Medical Biology, Chinese Academy of Medical Sciences and Peking Union Medical College

HLA-DRB1 plays an important role in the immune system by presenting antigen peptides. However, the allele frequency of HLA-DRB1 exon 2 across China has not yet been comprehensively studied, especially in minority ethnic groups. A total of 3757 people from 49 ethnic groups and branches from 59 locations were sampled. The region of HLA-DRB1 exon 2 from 212 bp to 463 bp in each ethnic group was sequenced by Sanger sequencing and genotyped by SBTengine software. The allele frequency was identified using GenAlex6.5. Nineteen high-frequency alleles with a frequency greater than 0.1 in one or more ethnic groups and 63 low-frequency alleles with a frequency less than 0.1 in each ethnic group were identified. According to our results, the genetic distance of DRB1 is generally large across the different ethnic groups based on language and location. The geographic location and origin of ethnic groups influence the frequency of DRB1 alleles. Alleles with high frequencies that differ greatly between Southern and Northern ethnic groups, such as DRB1*12:02:01 and DBR1*07:01:01, show distinct characteristics related to antigen affinity and the incidence of some diseases. Pathogen spectra may also influence the frequency of DRB1 alleles through natural selection.

KCNH2 mutant rats recapitulate long QT rhythm and embryonic development defects

Luying Peng Zhigang Li Chang Liu Li Li
Tongji University

Objectives:
Kcnh2 gene encodes the Kv11.1 potassium channel which is crucial in conducting the rapid delayed rectifier K+ current in cardiomyocytes. KCNH2 mutations in human leads to long QT syndrome, and also involve in intrauterine fetal loss. Thus, this study focuses on understanding the underlying mechanism.

Materials and Methods:
Kcnh2 mutant rat was generated using the rat embryonic stem cell-based gene-targeting technology. Wild-type and *Kcnh2*+/- rats were then used to check the ECG, structure of the heart and whole cell current. Then *Kcnh2*-/- embryos were used to study the mechanism of embryo lethality.

Results:
Kcnh2+/- rat models successfully showed the arrhythmia of prolonged QTc interval which could be corrected using beta blocker, while the whole cell current of cardiomyocyte in newborn rats displayed normal status. *Kcnh2*-/- rats were found dead usually at embryonic day 11.5 due to heart configuration defect. Apoptosis was also revealed to be trigged in the homozygote embryos, which could attribute to the failure to form a complex of ERG with ITGB1 that was essential to prevent the process via inhibiting FOXO3A.

Conclusions:
We recapitulate the classic pathological LQT phenotype in rats by knocking-out KCNH2, and revealed the basic mechanism of KCNH2 in maintaining embryonic heart development, hereby, providing evidence for understanding the dual role of the classic gene and an in vivo platform for screening potential molecules to interfere arrhythmia.

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An optimized proliferation system of embryonic stem cells for generating the rat model with large fragment modification

Chang Liu Li Li Luying Peng
Tongji University

Objective Rats have long been an ideal model for disease research in the field of biomedicine，but the bottleneck of in vitro culture of rat embryonic stem (ES) cells hindered the wide application as genetic disease models.
Materials and Methods Here, we optimized a special medium which we named 5N-medium for rat embryonic stem cells, which improved the in vitro cells with better morphology and higher pluripotency. We then established a drug selection schedule harboring a prior selection of 12 hours that achieved a higher positive selection ratio.
Results These treatments induced at least 50% increase of homologous recombination efficiency compared with conventional 2i culture condition. Moreover, the ratio of euploid ES clones also increased by 50% with a higher germline transmission rate. Finally, we successfully knocked in a 175kb human Bacterial Artificial Chromosome (BAC) fragment to rat ES genome through recombinase mediated cassette exchange (RMCE).
Conclusion We provide a promising system for generating sophisticated rat models which could be benefit for biomedical researches.

嘌呤能受体 P2Y1 在类风湿性关节炎中的功能和机制研究

张晓雨 秦居亮 赵一晗 任华 钱旻 杜冰
华东师范大学

类风湿性关节炎是一类通过诱导大量免疫细胞浸润造成关节损伤的慢性自身免疫性疾病。然而对于浸润免疫细胞在滑膜组织中的相互作用机制仍有待进一步深入。论文研究发现，滑膜组织中的炎性巨噬细胞通过 ADP/$P2Y_1$ 信号通路加剧中性粒细胞在滑膜组织中的浸润从而加剧类风湿性关节炎的发生。我们的研究发现，在类风湿性关节炎患者以及胶原诱导的关节炎小鼠模型中都出现了显著的胞外 ADP 增加以及受体 $P2Y_1$ 表达升高。更重要的是胞外 ADP 通过诱导巨噬细胞分泌 CXCL2 显著提高关节组织中中性粒细胞的浸润以及类风湿性关节炎的症状。在关节炎小鼠模型中加入 ADP 同样可以显著提高中性粒细胞在关节中的浸润。但是 $P2Y_1$ 受体的敲除以及抑制可以将 ADP 加剧的关节炎症状消除，提示 ADP 是通过 $P2Y_1$ 相关信号通路调节类风湿性关节炎的发生。进一步的分子机制研究发现 ADP 通过诱导巨噬细胞内 $G\alpha q/Ca^{2+}$-NF-κB/NFAT 信号通路促进 CXCL2 的表达或分泌招募更多的中性粒细胞而加剧类风湿性关节炎的发生。综上所述，我们的研究表明在类风湿性关节炎发生的过程中胞外 ADP 通过诱导巨噬细胞内 $P2Y_1$ 相关信号通路加剧了关节损伤的发生，为深入理解类风湿性关节炎发生的分子机制奠定了理论基础。

黄绿青霉素对神经细胞 PC-12 损伤作用的研究

杨菁
宁德师范学院附属宁德市医院

目的 研究黄绿青霉素（Citreoviridin，CIT）诱导神经细胞 PC-12 的损伤作用。

方法 CIT 处理组分为三组，终浓度分别为 2.5 μmol/L、5 μmol/L、10 μmol/L，设 DMSO 为空白对照组。药物处理细胞 24 h 后，观察细胞形态的变化，CCK-8 法测细胞活性，流式细胞仪测 ROS 荧光值；取细胞培养液测 LDH 释放率、NO 含量及 MDA；细胞裂解液检测 GSH 含量及 SOD 活力。

结果 PC-12 与 CIT 共培养后，细胞成团，出现空斑。与对照组比较，CIT 组的细胞活力显著降低（P<0.01），LDH 释放率显著升高（P<0.01）；NO 含量明显下降（P<0.05），呈剂量效应关系；氧化应激相关指标 MDA 含量显著升高（P<0.01）；ROS 含量在低、中、高剂量组中均显著升高（P<0.01，P<0.05）；GSH 含量呈下降趋势，10 μmol/L 组效果显著（P<0.05）；SOD 活力显著升高（P<0.01）。

结论 黄绿青霉素对神经细胞 PC-12 有明显的损伤作用，可能与氧化应激机制有关。

A study of single nucleotide polymorphisms and gene function of NGFR in psychiatric disorders

Binyin Hou
Shanghai Jiao Tong University

Background Psychiatric disorders are a class of complex disorders characterized by brain dysfunction with varying degrees of impairment in cognition, emotion, consciousness and behavior, which has become a serious public health issue. The *NGFR* gene encodes the p75 neurotrophin receptor, which regulates neuronal growth, survival and plasticity, and was reported to be associated with depression, schizophrenia and antidepressant efficacy in human patient and animal studies.

Method Four *NGFR* SNPs were detected based on a study among 1010 schizophrenia patients, 610 patients with major depressive disorders (MDD) and 1034 normal controls respectively. We then knocked down the expression of NGFR protein in the hippocampal dentate gyrus of mouse brain by injection of shRNA lentivirus to further investigate its behavioral effect in mice.

Results We found significant associations of s2072446 and rs11466162 for schizophrenia. *Ngfr* knock down mice showed social behavioral abnormalities, suggesting that it is linked to the etiology of neuropsychiatric disorders.

Conclusion We found significant associations between *NGFR* and schizophrenia and that *Ngfr* may contribute to the social behavior of adult mice in the functional study, which provided meaningful clues to the pathogenesis of psychiatric disorders.

rhEGF 对受损的人子宫内膜间质细胞的修复作用

杨菁
宁德师范学院附属宁德市医院

目的 研究 rhEGF 对受损的人子宫内膜间质细胞（ESCs）的作用，为子宫内膜损伤的临床治疗提供新思路。

方法 选择手术切除的子宫内膜，用 1% Ⅰ型胶原酶消化过滤后，分离纯化 ESCs，用免疫荧光法鉴定细胞。采用不同浓度米非司酮损伤 ESCs，以正常细胞为对照组；设置不同损伤时间，用 MTS 法检测细胞活性，确定最佳的损伤浓度和时间。用不同浓度的 rhEGF 与受损的 ESCs 共培养 24h，检测细胞活性，明确 rhEGF 对受损的 ESCs 是否有修复作用。通过划痕实验，观察 24h 细胞迁移情况，计算愈合比，验证 rhEGF 对受损的 ESCs 迁移能力的影响。

结果 ESCs 分离 24h 即可贴壁，刚开始呈三角形，单个分布，随后生长成为呈现有成纤维细胞形态的梭形细胞，通过鉴定间质细胞的纯度可达 95% 以上。米非司酮对 ESCs 的损伤呈时间-剂量效应，作用时间超过 48h ，ESCs 活性急剧下降（P<0.05），选择 48h 作为最适损伤时间。米非司酮浓度超过 60μmol/L 时，ESCs 活性显著下降（P<0.05），选择 60μmol/L 作为损伤最适浓度。rhEGF 与受损的 ESCs 共培养 24h，高剂量 rhEGF 能够显著提高损伤 ESCs 活性（P<0.05）。划

痕实验中，细胞迁移速度随 rhEGF 剂量增大而提高，100 ng/mL rhEGF 以上的剂量组愈合比具有统计学意义（P<0.05）。
结论 rhEGF 与米非司酮损伤的 ESCs 共培养后，细胞活性和迁移能力能够显著提高，rhEGF 对其具有明显的修复作用。

卵巢功能不全发病及低骨密度的免疫细胞图谱分析

吕波
同济大学

方法 从 POI(卵巢功能不全)患者、LBMD(卵巢功能不全合并低骨密度)患者和 Health 捐赠者中获取 PBMC 样本，通过单细胞测序获取到各个样本的单细胞表达矩阵，使用 R 语言 Seurat 包进行细胞聚类分析并通过标记基因对细胞分群进行注释，通过 metascape 进行 GO_BP 富集分析重要细胞亚群的功能，通过对 T 细胞进行再分群并进一步分析 T 细胞的功能，通过构建转录因子共表达网络分析预测基因的上游调控途径。
结果 单细胞测序获取到大量 Neutrophils 细胞和 T 细胞，以及少量 CD14+ Monocyte、CD16+ Monocyte、platelet、eosinophil、RBC、DC、B、Plasma B 和 NK 细胞，通过差异分析获取到各个细胞亚群中 POI 和 LBMD 组与 Health 组的差异基因交集，富集分析发现中性粒细胞的激活减少，T 细胞介导的氧化应激下降，且 T 细胞介导多种免疫细胞的激活，对 T 细胞亚群进行再分群发现 T 细胞可以分为 CD4+ T 细胞、CD8+ T 细胞、DNT 细胞、NKT 细胞和 NK 细胞，差异分析后进行富集分析并综合拟时序分析，我们发现在 POI 发病过程中，免疫反应和氧化应激降低，而在 POI 并发低骨密度症的过程中，免疫反应和氧化应激升高。转录因子共表达分析确定了 T 细胞相关的 24 个转录因子。分析中性粒细胞发现其激活降低，从而导致免疫反应降低。
结论 POI 发病过程中，免疫反应和氧化应激降低，但在 POI 合并低骨密度的过程中，免疫反应和氧化应激升高。

The Mechanism of Dlic1 Affecting Cerebellar Nerve Development

Lingling Liu[1] Hongyan Wang[2] Wufan Tao[3]
1.School of Life Sciences, Fudan University
2.The Obstetrics & Gynecology Hospital of Fudan University
3.Institute of Developmental Biology and Molecular Medicine, Fudan University

Objective The cerebellum developmental disorder or dysplasia leads to various congenital neurological diseases, such as human congenital ataxia and Joubert syndrome. Our study aims to clarify the mechanism of Dlic1 affecting cerebellar nerve development.
Method The Dlic1-knockout mice was constructed using Cre-LoxP technology. Then the pathological sections of mouse cerebellum were studied. We also measured the Footprints of knockout mice to verify whether their cerebellar function was normal. In addition, qPCR, Western blot and primary nerve cell culture were used to explore the mechanism in our study.
Result We found that the cerebellum of Dlic1 deficient mice were hypoplastic and dysfunctional, and the dendrite length of cerebellum nerve cells became shorter and the branches decreased. Moreover, the protein level of RhoA increased in the cerebellar neurons of Dlic1-deficient mice and its intracellular distribution was abnormal.
Conclusion Dlic1 deficiency results in abnormal development of cerebellar nerve cells may through the inhibition of RhoA retrograde transport and the abnormal accumulation of RhoA protein in cerebellar nerve cells.

Genome recombination-mediated tRNA up-regulation conducts general antibiotic resistance of bacteria at early stage

Gong Zhang
Jinan University

Bacterial antibiotic resistance sets a great challenge to human health. It seems that the bacteria can spontaneously evolve resistance against any antibiotic within short time without the horizontal transfer of heterologous genes and before accumulating drug-resistant mutations. To discover the universal mechanism of spontaneous drug resistance, we subcultured *E. coli* BW25113 with ciprofloxacin at sublethal concentrations under isolation conditions to 45 generations. Genome and transcriptome sequencing were performed on all generations of bacteria, to explore mutations in coding genes and regulation of translation-related gene expression. Nanopore sequencing was performed to obtain long reads to conform the structural variation events. tRNA sequencing and polyacrylamide gel electrophoresis were performed to investigate the tRNA variation during drug-resistance acquisition. Competitive experiment and overexpression experiment were performed to validate whether tRNA upregulation contribute to early stage of AR. Bacteria evolve antibiotic resistance without detectable mutations in protein-coding regions. Translation is up-regulated as a response against antibiotics at early stage. tRNA up-regulation during the subculture provided antibiotic resistance. Genome recombination is enriched near tRNA genes. Suppressing recombination repair system decreases the evolution of intrinsic AR. Overexpression of the detected glycine tRNAs (glyU-glyX-glyY) in sensitive strain increases the antibiotic resistance. With these results, we proposed a multi-stage model of bacterial antibiotic resistance in an isolated scenario: the early stage (recombination tRNA up-regulation translational regulation); the medium stage (up-regulation of efflux pump); the late stage (resistance mutations). These results also indicated that the bacterial DNA recombination system and tRNA could be targeted to retard the bacterial spontaneous drug resistance.

Transcriptomic Analyses of the Adenoma-Carcinoma Sequence Identify Hallmarks Associated With the Onset of Colorectal Cancer

Qin Hong[1,3] Bo Wen[2]
1.Fujian Provincial Hospital
2.School of Basic Medical Sciences, Fudan University
3.Institutes of Biomedical Sciences, Fudan University

Background The concept of the adenoma-carcinoma sequence in colorectal cancer (CRC) is widely accepted. However, the relationship between the characteristics of the transcriptome and the adenoma-carcinoma sequence in CRC remains unclear.
Method The transcriptome profiles of 15 tissue samples from five CRC patients were generated by RNAseq.
Dynamic expression patterns(DEPs) of differentially expressed genes (DEGs) were generated by mFuzz. Weighted correlation network analysis associated DEPs with pathological phenotypes. Gene Ontology(GO) and Kyoto Encyclopedia of Genes and Genomes(KEGG) analyses identified biological function of DEPs and potential partners of hD53. Overall survival analysis screened DEGs in cluster 6, and cell proliferation, colony formation, wound healing, and transwell invasion assays identified that malignant effect of TPD52L1. mass spectrometry was used to identified potential partners of hD53.
Result Six specific dynamic expression patterns of CRC formation were characterized. DEGs in cluster 4 and cluster 6 were highly associated with carcinoma tissues and non-normal tissues. GO and KEGG identified metabolic dysregulation as a consistent finding throughout the transition process, whereas downregulation of the immune response occurred during normal to adenoma

transition, and the upregulation of canonical pathways was associated with adenoma to carcinoma transition. TPD52L1 was screened as a marker of poor prognosis and high expression levels of TPD52L1 promoted malignant behaviors. Most of these 70 potient interacted proteins were slightly up-regulated along with TPD52L1 during the formation of CRC, and among them, expression patterns of 10 DEGs was consistent with TPD52L1 (TPD52L1, DNAJB6, YWHAG, NUP07, NUP93, XPOT, MAD2L1, CTPS1, SLC7A5, and MYO1B).
Conclusion CRC formation was associated with three cancer hallmarks: dysregulation of metabolism, inactivation of the immune response, and activation of canonical cancer pathways. The TPD52L1 gene was identified as a potential marker to track tumor formation in CRC and as an indicator of poor patient prognosis.

DNAH9 在先天性心脏病发生中的功能研究

高云倩 傅启华
上海儿童医学中心

目的 先天性心脏病（CHD）是一类最为常见的出生缺陷，为了实现对 CHD 的早期诊断及防控，鉴定新的 CHD 致病基因并明确其发病机制极为关键。
方法 我们在前期研究中，通过对 250 例法洛氏四联症（TOF）患者样本进行全基因组重测序并结合罕见变异关联分析，鉴定相关基因。
结果 我们前期鉴定出 *DNAH9* 基因与 TOF 显著相关（$p=9.83x10^{-4}$）。*DNAH9* 被证明是运动纤毛动力蛋白臂的组成部分，且被发现在内脏异位的不动纤毛综合征（PCD）患者中存在丧失功能性突变，被认为是导致内脏异位的原因之一。有的内脏异位患者合并大血管转位、左心室发育不良等异常，且纤毛与心脏发育及 CHD 的发生密切相关。因此我们推断，在胚胎发育早期，*DNAH9* 变异可能使胚结内运动纤毛功能受损从而导致心脏早期发育异常。我们利用课题组已有的 *Dnah9* 基因敲除小鼠模型及心肌细胞诱导分化模型，研究在心脏早期分化过程中 DNAH9 功能异常对心脏发育的影响。通过对敲除小鼠模型研究发现敲除小鼠并没有导致胚胎致死，在 2 个月时间通过检测小鼠心脏超声和组织切片染色评估心室功能发现小鼠没有明显异常。
结论 DNAH9 基因可能不是导致先天性心脏病的关键基因，可能协同主效基因发挥其微效作用。

CCL 趋化因子家族成员 CCL17/CCL22 可预测头颈部鳞状细胞癌患者的预后和免疫检查点阻断治疗的效果

刘喆麒[1,2] 周文凯[1,2] 陈万涛[1,2] 曹巍[1,2]
1.上海交通大学医学院附属第九人民医院
2.上海市口腔医学重点实验室

目的 头颈部鳞状细胞癌(HNSCC)被认为是免疫抑制性恶性肿瘤。肿瘤细胞和免疫细胞之间的相互作用对肿瘤的发生进展有着重要的影响。而这种交互作用由趋化因子（Chemokine）调节。目前趋化因子 CCL（CC ligand）家族成员在 HNSCC 中发挥的作用尚未阐明。
方法 本研究中，我们研究了 CCL 家族成员在 HNSCC 预后和免疫检查点阻断治疗反应方面的预测价值。通过共表达分析，筛选出 CCL17、CCL22 为头颈部鳞状细胞癌中关键的 CCL 趋化因子。此外，基于 TIMER 评估了 CCL17/CCL22 表达与癌症免疫浸润之间的相关性，并通过一组 scRNA-seq 数据进行了验证。此外，我们利用 TIDE 数据库评估了 CCL17/CCL22 的表达水平，以预测一组癌症类型对免疫检查点封锁治疗的反应。
结果 CCL17/CCL22 与头颈部鳞状细胞癌患者的总生存率有较高的共表达相关性，且与总生存率有轻微统计学意义(P 值分别为 0.057 和 0.055)。我们的研究结果显示，在 HNSCCs 中，CCL17/CCL22 的高表达与 CD4+ T 细胞浸润水平呈正相关，并且在 CD4+ T 细胞中激活 mTORC1 信号通路。TIDE 进一步分析显示，高表达的 CCL17/CCL22 可能预示着头颈部鳞癌患者对免疫检

查点阻断治疗的良好反应。这些发现为 CCL17/CCL22 在头颈部鳞状细胞癌中的预测作用提供了新的见解。

Genotype–Phenotype Association Analysis Reveals New Potential Pathogenic Mutation Sites for Niemann–Pick Disease

Ruisong Wang Tieliu Shi
Hunan University of Arts and Science

Types A and B of the rare genetic disease Niemann–Pick disease (NPD) are caused by a defect in sphingomyelin phosphodiesterase (ASM) due to *SMPD1* gene mutation. Except for the liver and spleen enlargement and lung disease, the two subtypes have completely different onset time, survival time, ASM activity, and neurological abnormalities. To comprehensively explore the genotype–phenotype association and pathophysiological characteristics of NPD, we searched the literature to collect NPD cases with strict quality control (n = 144). Variations in ASM activity can differentiate NPD type A from type B. More severe mutations, such as deletions and insertions, can cause complete loss of ASM function, leading to type A, whereas relatively mild missense mutations generally lead to type B. Different populations have different prevalence of mutations. The mutation at position 247, the amino acid glycine; p.Arg3AlafsX76 mutation is highly prevalent in the Chinese population, when mutations at p.R608del is common in Mediterranean countries. Seven variants, including c.C1804T:p.R602C, c.G689A:p.R230H, c.C995G:p.P332R, c.G1133A:p.R378H, c.A1280G:p.H427R, c.A958G:p.N320D and c.A1106G:p.Y369C that have been annotated with conflicting clinical significance appear to be pathogenicity, we also annotated more potential pathogenic mutations in smpd1 genes. We systematically explored the genotype-phenotype among different populations, which provides new insights into the genotype-phenotype association, which can help in NPD diagnosis.

基于 FastQTL 或 Matrix eQTL+TreeMap 方法进行顺式表达数量位点分析的优劣比较

韩璐 姜茜
首都儿科研究所

目的 比较目前最先进的两套分析流程：FastQTL 以及 Matrix eQTL+TreeMap，判断分析结果优劣，指导进行肠组织样本顺式表达数量性状位点（*cis*-eQTL）分析的工具选择方案。
方法 对 150 例先天性巨结肠患者狭窄段肠组织样本进行全基因组测序和全转录组测序。分别使用两种先进的分析方法进行 *cis*-eQTL 分析。第一种方法：使用 2016 年发表的 FastQTL 软件并依据作者提供的标准分析流程进行 eQTL 分析。第二种方法：先使用经典工具 R 包 MatrixEQTL 并依据作者提供的标准分析流程进行 eQTL 分析，再使用 2021 年发表的 R 包 TreeMap 进行分析结果优化。比较两种分析方法得到的 *cis*-eQTL 的数量及特征。
结果 我们使用第一种方法得到 934 个顺式作用调控对，除 *ZNRD1* 基因对应 2 个 eSNP 以外，每个 eGene 仅对应 1 个 eSNP。对于第二种方法，MatrixEQTL 运算后得到 9635 个顺式作用调控对，涉及 1220 个 eGene，每个 eGene 对应 1 至 811 个 eSNP。以 *XRRA1* 基因为例，FastQTL 得到 1 个与其对应的 eSNP，为 rs2298746 （chr11_74553834_C_T）。而 MatrixEQTL 共得到 233 个与其对应的 eSNP，经 TreeMap 优化，仅 rs2298746（chr11_74553834_C_T）被认定为 eSNP，其余位点均与 rs2298746 呈连锁不平衡关系。综上，两种方法最终运算结果基本一致，但是第一种方法更加简洁、快速、高效。因此，我们推荐使用 FastQTL 软件进行 *cis*-eQTL 分析。
结论 基于 FastQTL 方法进行顺式表达数量位点分析是更加优化的分析流程。

Survivin 在脂肪组织重构与代谢稳态中的作用及机制

米日阿依·阿里木江 杨颖
上海交通大学附属上海市第六人民医院

目的 Survivin 是凋亡抑制蛋白家族中的一员，本课题组前期研究表明，长期高脂饮食 (HFD)喂养可诱导小鼠脂肪细胞中 Survivin 的表达，以及胰岛素在体外可通过激活 PI3K/mTOR 信号通路上调 Survivin 表达。本研究中通过使用脂肪细胞特异性敲除 Survivin 的 SKO 小鼠进一步研究 Survivin 在脂肪细胞中的作用。
方法 通过将 Survivin$^{loxp/loxp}$ 小鼠与 Adiponectin-Cre$^{+/-}$小鼠杂交获 SKO 小鼠，并在普通饲料 (CD)和 HFD 喂养条件下，观察 SKO 小鼠整体代谢表型。其次，在冷暴露条件下检测小鼠脂肪组织中产热基因及蛋白的表达情况。另外，分离出皮下脂肪组织（SAT）和棕色脂肪组织（BAT）中血管基质细胞（SVF），并将起诱导分化为成熟脂肪细胞，在细胞水平检测 survivin 缺失对成熟脂肪细胞功能的影响。
结果 SKO 小鼠出生后 BAT 重量显著低于对照组（Con）小鼠，并且在 CD 喂养条件下，SKO 小鼠 BAT 中产热蛋白 Ucp1 表达量显著降低，但是 SKO 小鼠体重、摄食量、葡萄糖耐量级胰岛素敏感性等整体代谢表型均未受到影响。在 HFD 喂养 16 周后，SKO 小鼠在体重未发生显著变化的前提下，出现了葡萄糖耐量受损及胰岛素敏感性降低，并且 SKO 小鼠 SAT/BW 和 BAT/BW 比值显著低于 Con 小鼠，并导致更严重的肝脏脂质异位沉积。在冷暴露条件下，SKO 小鼠 BAT 和 SAT 中产热基因和蛋白表达显着低于 Con 小鼠，与此同时 SKO 小鼠 BAT 中线粒体结构出现了异常，并伴有自噬活性激活。同样，Survivin 敲除的米色和棕色脂肪细胞中不仅产热基因和蛋白表达量降低，并且伴有线粒体氧化磷酸化水平的降低，同时自噬活性增加。
结论 我们的研究结果揭示 Survivin 在体内维持正常 BAT 重量和产热功能中发挥重要作用，并且在营养过剩状态下有利于 SAT 的适度扩张及维持整体代谢稳态。在体外，Survivin 可促进脂肪细胞产热和线粒体氧化磷酸化功能，而该作用或许通过抑制自噬活性来实现。

A Case Report: a De novo GBA Gene Mutation in a Patient with Gaucher Disease.

Fei He
Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University

Gaucher disease (GD, ORPHA355) is a rare, autosomal, recessive genetic disease caused by mutations in the GBA1 gene, located on chromosome 1 (1q21). More than 300 GBA mutations have been described in the GBA1 gene. Recently, a de novo GBA Gene Mutation c.1240G>C (p.Val414Leu) was found in a Patient compound c.1342G>C (p.Asp448His). In this study, we report the structural and functional characterization of the novel alleles. It is a pathogenic mutation predicted through polyphen-2 software. Further, the conservative analysis of the mutation showed that both p.Val414Leu and p.Asp448His were highly conserved sites, which explained the pathogenicity of the mutation. The secondary and tertiary structure of the protein were predicted, 11 amino acids after the mutation site changed from the original linear to the helix in the secondary structure of p.Val414Leu. In addition, the pEGFP-N1-GBA WT vector which contains two mutation sites was successfully constructed and 293T cells were transfected. It was found that the two mutation sites did not change the cell location which will not cause abnormal cell positioning. Finally, the detection and analysis of β-galactosidase activity showed that there was a statistical difference in the reduction of enzyme activity caused by the denovo mutation. In summary, the denovo mutation was a pathogenic mutation.

新型血小板和凝血酶抑制剂短肽 (PTIP) 的研制及药效学研究

于锦超[1,2] 于敏[1,2]
1.复旦大学基础医学院生物化学与分子生物学系
2.代谢与分子医学教育部重点实验室

目的 由动静脉血栓引起的心脑血管的疾病已成为人类死亡的首要病因。根据动静脉血栓形成的不同机制，研发既可以抗动脉血栓又可以抗静脉血栓的药物对有效的防栓抗栓、解决心脑血管疾病和提高人均寿命具有重要的意义。
方法 本实验室根据天然水蛭素设计出一种衍生物重组水蛭素 (r-hirudin)，可以抑制血栓的形成，目前已经进入到 I 期临床试验，但是在后期实验中发现其只能通过静脉方式给药，且出血副作用大。因此，以 r-hirudin 结构为依据，通过同源建模以及分子模拟的方法，保留 r- hirudin 的主要的功能性氨基酸残基，通过优化氨基酸序列，在合适的位置插入 RGD 序列，得到了具有抗血小板聚集防动脉血栓和抗凝血酶活性防静脉血栓的新型双功能短肽 (PTIP)。
结果 我们通过摇瓶表达和纯化得到了高浓度的 PTIP，通过大鼠体内外药效学实验证明 PTIP 可以有效提高 APTT、PT、TT 等抗凝指标，且血小板聚集试验证明 PTIP 可有效抑制血小板聚集，可产生与替格瑞洛相似的抗血小板效果。通过出血量和出血时间比较证明 PTIP 引起的出血效果与生理盐水组相当。
结论 通过体内和体外药效学实验证明 PTIP 可以作为既预防动脉血栓又可以预防静脉血栓且出血副作用小的新型药物，将来可以成为临床防栓抗栓的新的选择。

长非编码 RNA linc-Foxa2 对核斑的调控功能及机制研究

王千凤[1] 文波[1,2] 胡士斌[1] 吕品[1] 李瑞敏[1] 刘浙潇[1]
1.复旦大学基础医学院及代谢分子医学教育部重点实验室
2.复旦大学遗传工程国家重点实验室

目的 真核生物细胞核内除了染色质，还存在大量由蛋白质和 RNA 聚集形成的无膜包裹核体（Nuclear bodies）。已知经典的核体包括核仁（Nucleoli），核斑（Nuclear speckles），旁核斑（Paraspeckles），PML 体（PML bodies），核体完整性维持与多种生物学过程密切相关。本研究旨在揭示核斑相关长非编码 RNA linc-Foxa2 对核斑完整性的调控功能以及对小鼠成体代谢的调控作用及作用机制。
方法 本研究基于 in situ RNA-FISH、FRAP、ChIRP-MS、IEM、RNA-seq 等多学科的研究手段，在细胞水平及小鼠体内两个层面研究了 linc-Foxa2 的功能及作用机制。
结果 在小鼠肝细胞系 AML12 中的研究发现：1）linc-Foxa2 是小鼠肝细胞核斑结构的新组分，linc-Foxa2 敲低后核斑核心组成蛋白 SC35/SRSF2、ASF/SRSF1、SRRM2 免疫荧光染色信号变弱且更为分散，SC35/SRSF2 免疫电镜结果显示 linc-Foxa2 敲低后核斑结构被整体破坏，表明 linc-Foxa2 为核斑结构维持所必需；2）linc-Foxa2 敲低后 Poly A+ RNA 的聚集体染色变小，且更靠近核膜分布，提示 mRNA 的转运可能受到影响。小鼠在体功能研究显示：1）linc-Foxa2 CKO 小鼠能够抵抗高脂饮食诱导的肥胖和肝脂肪变性，并提高葡萄糖耐受以及胰岛素敏感性；2）在正常喂养条件下，linc-Foxa2 CKO 小鼠虽然体型与正常对照小鼠相比无明显差异，但其代谢稳态有明显改善，表现为葡萄糖耐受性和胰岛素敏感性提高。机制研究显示：在小鼠肝细胞系 AML12 中 linc-Foxa2 与核斑组成蛋白相互作用调控核斑完整性，在小鼠肝脏组织中 linc-Foxa2 同样对核斑结构完整性具有维持作用；在 linc-Foxa2 CKO 小鼠肝脏组织中，包括脂质合成相关基因在内的 300 多种基因表达量显著下调。
结论 linc-Foxa2 能够维持小鼠肝脏细胞核斑结构完整性，并且对小鼠肝脏代谢平衡具有调控功能。

上皮细胞中敲低 Six1/Six2 影响颅颌面及肾脏发育中的囊泡转运功能

罗淞元 王旭东
上海交通大学附属第九人民医院

目的 探讨 Six1/Six2 对颅颌面及肾脏发育中上皮细胞囊泡转运的影响及作用机制。
方法 构建具有敲低 Six1/Six2 作用的以慢病毒介导的短发夹 RNA(shRNA)，慢病毒感染 293T 细胞系，采用 RT-qPCR 和 Western Blot 验证其敲低效率。采用 RNA-seq 高通量测序检测敲低 Six1/Six2 上皮细胞中差异表达基因，GO 和 KEGG 对差异表达的基因进行富集分析。
结果 高通量测序结果显示，敲低 Six1/Six2 上皮细胞中的差异表达基因 5402 个，这些差异表达基因主要参与囊泡转运和离子通道相关功能，并在颅颌面及肾脏发育中起重要作用。
结论 Six1/Six2 调控上皮细胞囊泡转运并影响颅颌面及肾脏的发育。

直接凝血酶抑制剂对血管生成拟态的作用及机制研究

赵冰[1,2] 于敏[1,2]
1.复旦大学代谢与分子医学教育部重点实验室
2.复旦大学基础医学院生物化学与分子生物学系

目的 肺癌转移复发是临床面临的难题，凝血酶在肿瘤恶化过程中发挥重要作用。血管生成是肿瘤生长转移的关键条件。血管生成拟态 (vasculogenic mimicry，VM) 与患者预后密切相关，但目前抗血管生成药物主要以抑制内皮细胞依赖性血管生成为基础，忽略了 VM 的存在。针对肿瘤转移和 VM 的治疗可能成为肿瘤治疗的新突破。
方法 收集人体肺癌标本，统计凝血酶、PAR-1，VM 与患者预后的关系；利用血管生成拟态形成实验，细胞骨架染色、transwell，细胞划痕等实验观察 DTIP 和 r-hirudin 对肺癌细胞侵袭转移和 VM 的作用；构建小鼠转移模型和皮下移植瘤模型检测 DTIP 和 r-hirudin 在体内对肿瘤发生发展的作用；敲除凝血酶受体 PAR-1，观察肺癌细胞侵袭转移能力变化和凝血酶作用变化；构建 PAR-1 敲除肿瘤模型，观察肿瘤发生发展的变化。
结果 PAR-1 表达与 VM 形成呈现正相关性，PAR-1 表达越高，患者预后越差，越容易形成 VM，有 VM 形成的患者预后也越差；在体外，DTIP 和 r-hirudin 可以通过抑制 NF-κb 信号通路抑制肿瘤侵袭转移，通过抑制 EMT 抑制 VM 形成。在肺癌模型中，DTIP 和 r-hirudin 可以延长小鼠存活时间，抑制 VM 形成和肺癌转移；敲除 PAR-1 后，不论体外还是体内，肺癌细胞侵袭和转移能力均受到抑制。
结论 PAR-1 表达和 VM 形成可作为新的生物预后标志物，高特异性的凝血酶抑制剂 DTIP 和 r-hirudin 可以抑制肺癌细胞侵袭转移，为拓展直接凝血酶抑制剂抗肿瘤的临床应用及联合治疗提供理论依据。

一种可通过皮下注射的新型直接凝血酶抑制剂

赵冰[1,2] 于敏[1,2]
1.复旦大学代谢与分子医学教育部重点实验室
2.复旦大学基础医学院生物化学与分子生物学系

目的 凝血酶是血液凝固中的关键因子。重组水蛭素 (r-hirudin) 是在野生型水蛭素分子的基础上进行改造，具有抗凝活性的多肽。但是 r-Hirudin 是一种蛋白质，只能通过静脉注射给药，临床应用范围有限。以 r-hirudin 序列为基础，保留其 C 末端和 N 末端的功能氨基酸残基，利用分子模拟以及同源建模，设计具有抗凝活性的短肽(Direct Thrombin Inhibitor Peptide, DTIP)，以利于皮下用药。

方法 利用毕赤酵母表达 DTIP；经纯化后获得目的蛋白；凝血酶滴定法测定 DTIP 的抗凝活性；HPLC-MS 测定 DTIP 的纯度、分子量，利用生物膜干涉技术测定凝血酶与 DTIP 的亲和力。在体外实验中，通过血栓弹力试验测定 DTIP 对血栓形成的抑制作用。大鼠皮下注射 DTIP，比较给药前后部分凝血活酶时间 (Activated Partial Thromboplastin Time, aPTT)，凝血酶原时间 (Prothrombin Time，PT)，凝血酶时间 (Thrombin Time, TT) 和凝血时间 (Clotting Time) 的变化。分别构建尾静脉注射肾上腺素和胶原诱导的急性肺栓塞模型和 $FeCl_3$ 损伤诱导的肠系膜微动脉血栓模型，研究 DTIP 预防血栓形成的药效学作用。
结果 DTIP 通过 C 末端与凝血酶 exosites I 结合， N 末端与凝血酶活性中心结合。DTIP 可以抑制人，大鼠和小鼠血浆以及人全血凝固。通过对 SD 大鼠皮下注射 DTIP, 显示 DTIP 可显著延长 aPTT, PT, TT 以及 CT, 且不会引起出血。与口服类直接凝血酶抑制剂达比加群酯相比，DTIP 达峰时间更快，且连续服药 5 天后不会引起出血。在急性肺栓塞模型中，DTIP 显著提高小鼠存活率；在肠系膜微动脉血栓模型中，DTIP 显著抑制了血栓的形成。
结论 DTIP 具有抗凝活性，且可以通过皮下注射预防血栓的形成且有效避免出血的发生，可作为一种潜在的皮下注射直接凝血酶抑制剂进行更加深入的研究。

DNM1L 基因突变临床特征及诱导性多能干细胞模型的建立

梁晨[1,2] 上官少方[2] 陈晓丽[1,2]
1.中国医学科学院北京协和医学院
2.首都儿科研究所

目的 DNM1L 基因编码的 Drp1 蛋白属于 Dynamin 超家族，介导线粒体的分裂，是部分神经元存活的必需物质。DNM1L 基因变异可使线粒体裂变受损、膜电位降低和氧化能力降低，从而导致细胞活性氧水平升高和双链 DNA 断裂。本文总结了目前收集到的 DNM1L 基因突变的患者表型信息，进一步探索该病致病机制，并成功建立 ips 细胞系，后续可进行进一步的致病机制研究及药物筛选。
方法 回顾性总结课题组内截止 2021 年前，基于全外显子测序结果诊断的 10 例携带 DNM1L 基因突变的患儿临床表型，其表型具有异质性，可能与变异位点所处功能域位置相关，临床表型可从仅表现为视神经萎缩到突发性致死性癫痫脑病，截止目前国内仅报道过一次，对其致病机制认识尚不足。经知情同意后，采集患者外周血中的单个核细胞进行分离培养，并基于慢病毒转染的方式使外源基因和载体序列进行整合，诱导产生患者的 iPSCs。
结论 此次报道丰富了该病在中国的疾病谱，截止目前该病在我国仅被报道过一次。招募患者遗传方式均为常染色体显性遗传，致病位点不完全相同，表型差异明显，推测可能是由于致病位点位于不同功能域。目前已完成 iPS 建系，但建系中总会观察到细胞因状态不好发生分化，猜测可能是由于该病影响到线粒体的功能，能量代谢受损不足以维持干细胞特性，会导致细胞重编程后状态极度不稳定，进而导致建系失败。该病目前尚无有效治疗手段，后续可以依靠 iPS 细胞系进行药物筛选，以期为患儿获得更多的救治机会。

凝血酶通过免疫微环境影响肿瘤的进展

王天法[1,2] 赵冰[1,2] 于敏[1,2]
1.复旦大学基础医学院生物化学与分子生物学系
2.代谢与分子医学教育部重点实验室

目的 凝血系统在人体生理和病理过程中起着重要作用，参与止血凝血、组织修复和创伤愈合等过程。免疫系统是机体抵御病原菌侵犯最重要的保卫系统。恶性肿瘤发生、发展与凝血系统异常密切相关，异常的凝血系统促进了肿瘤的免疫逃逸。本课题主要是探究凝血系统中重要的凝血因子—凝血酶，是否会改变肿瘤免疫微环境，进而影响肿瘤的进展，从而以此为靶点，为肿瘤治疗提供更多的思路和方法。

方法 构建小鼠肝癌模型，凝血酶及凝血酶抑制剂给药之后，观察小鼠肿瘤生长情况；之后通过免疫组化以及流式细胞术检测肿瘤的免疫细胞浸润情况，并取肿瘤组织进行 RNA 测序；体外通过 CCK8、transwell 及细胞划痕等实验探究凝血酶对肿瘤细胞增殖、迁移侵袭能力的影响。
结果 实验发现凝血酶在非小细胞肺癌患者肿瘤组织中高表达，且凝血酶的表达的与患者预后密切相关，另外还发现凝血酶在肝癌细胞中异常高表达。DTIP 是我们实验室研发的新型直接凝血酶抑制剂，在小鼠肝癌模型中，DTIP 可以显著抑制肿瘤的生长，延迟小鼠存活时间，检测肿瘤组织中免疫细胞和浸润性 T 细胞的数量，发现免疫细胞都集中在癌旁组织，而 DTIP 则可以促进免疫细胞的浸润；而凝血酶则是显著地促进了肿瘤的生长，加快了荷瘤小鼠的死亡；另外 DTIP 并不会影响裸鼠的肿瘤生长。
结论 凝血酶可以改变肿瘤的免疫微环境，进而影响肿瘤的进展。

6864 例新生儿地中海贫血筛查及基因检测结果分析

许海珠
海南省妇女儿童医学中心

目的了解海口市新生儿地中海贫血基因型的分布情况。
方法 选取 2016 年 1 月-12 月在海口市出生的 6864 例新生儿足跟血标本应用滤纸干血片毛细管电泳技术检测血红蛋白，对初筛阳性者进一步采用聚合酶链反应（PCR）和导流杂交技术进行地中海贫血基因分型的检测。
结果（1）在 6864 例新生儿滤纸干血片中，经毛细管电泳检测，初筛阳性数 604 例，占受检总数的 8.80%(604/6864)，经基因检测确诊 342 例，检出率 4.98%(342/6864)，占初筛阳性数的 56.62%（342/604）。（2）在确诊例数中，α-地中海贫血 282 例，占 82.46%（282/342），其中缺失型 253 例，非缺失型 14 例,缺失型杂合非缺失型 15 例。β-地中海贫血 57 例，占 16.67%（57/342），共检出 9 种基因型，其中 CD41-42/N 占 66.67%（38/57）。α、β-复合型地中海贫血 3 例，占 0.88%（3/342）。
结论 海口市新生儿地贫以 α-地贫为主，其中以--SEA/αα 基因型最常见，应重视地贫防控，推广新生儿期地贫筛查，为本地区地中海贫血出生缺陷防控工作提供参考依据。

海南省 585 例苗族新生儿耳聋基因突变分析

许海珠
海南省妇女儿童医学中心

目的 了解海南省苗族新生儿耳聋基因的携带率和基因突变类型的特点，为苗族新生儿遗传性耳聋的防治提供科学依据。
方法 收集琼中黎族苗族自治县、保亭黎族苗族自治县 2017 年 03 月-2021 年 03 月活产苗族新生儿干血斑样本 585 例，采用高通量测序技术对四种常见遗传性耳聋基因 GJB2、GJB3、 SLC26A4、mtDNA12SrRNA 进行测序。
结果 共检出 211 例携带耳聋基因突变，携带率为 36.07%（211/585），检出 8 例纯合突变，2 例单基因复合杂合突变，23 例双基因复合杂合突变。GJB2 基因携带者 160 例，携带率 27.35%（160/585），SLC26A4 基因携带者 28 例，携带率 4.79%（28/585），未检出 GJB3 和线粒体相关耳聋基因。GJB2 基因中 C.109G>A 位点携带率最高（153 例，26.15%），SLC26A4 基因中携带率最高的是 C.1983C>A 位点（14 例，2.39%）。
结论 海南省苗族新生儿的耳聋基因携带率高于全国其他地区，以 GJB2 和 SLC26A4 基因突变为主，突变位点主要是 C.109G>A 和 C.1983C>A 位点。此研究为海南苗族新生儿遗传性耳聋的的防治提供了有利的科学依据。

CAR-T 靶点 CD22 在食管鳞癌中的表达及意义

刘廷珰[1,3] 戴玺铭[1,3] 许忆恩[2,3] 周奇[1,3] 程科[1,3] 周小玲[1,3] 马长春[2,3] 孙平楠[1,3]
1.汕头大学医学院干细胞研究中心
2.汕头大学医学院肿瘤医院
3.汕头大学医学院广东省感染病与分子免疫病理重点实验室

目的 寻找到食管鳞癌潜在的 CAR-T 免疫治疗新靶点
方法 通过生物信息学分析，从 TCGA 数据库下载了 1 例食管正常组织和 81 例食管鳞癌组织的 RNA-seq 数据，得到了所有基因校正后的表达值并绘制热图。用 qPCR 的方法检测 13 个 CAR-T 靶点基因在食管鳞癌细胞系（KYSE140、EC9706）、食管鳞癌组织及其相对应的癌旁中的表达情况。用免疫荧光的方法检测 CD22 在食管鳞癌细胞系（KYSE140、EC9706）中的表达位点。最后，通过免疫组化的方法检测 87 例食管鳞癌患者（包括 45 例食管鳞癌组织及其相应的例癌旁组织和 42 例食管鳞癌组织）的手术切除标本中 CD22 的表达，并分析了实验结果与临床数据的相关性。
结果 （1）首次验证 CAR-T 靶点 CD22 在食管鳞癌中的表达。（2）CD22 在食管鳞癌细胞系（KYSE140、EC9706）的膜和质中均有表达。（3）CD22 在 87 例食管鳞癌组织标本中的细胞膜表达率达 27.59%。（4）CD22 的表达跟生存率、肿瘤的组织浸润和淋巴结转移不相关。
结论 本研究表明 CD22 是 CAR-T 疗法治疗食管鳞癌的一个潜在新靶点。

PRR12 基因新生突变导致神经发育障碍和小眼症

刘晓莉
首都儿科研究所

PRR12 是一种编码富含脯氨酸的核蛋白的基因，在发育过程中，*PRR12* 主要在胎儿大脑和视觉系统的细胞核内高表达。*PRR12* 突变的患儿的临床表型主要包括小眼畸形、虹膜缺损等眼睛表型以及神经发育障碍相关表型如智力障碍、语言发育迟缓等，目前已有 *PRR12* 突变的病例报道，然而该基因的功能以及该基因突变导致疾病的潜在致病机理尚不清楚。PRR12 是一种 DNA 结合蛋白，在 P1168 和 G1202 处含有保守的 AT-HOOK DNA 结合区域，含有 AT-HOOK 的基因如 *MECP2*、*AHDC1* 等已证实与神经发育相关，为探索 *PRR12* 在大脑和眼睛发育中的作用以及致病机理，本研究建立了患者外周血来源的 iPSCs 细胞系并分化为 NPC、NC，通过做 CO-IP、CHIP-seq、Western-Blot 等实验来探索基因的功能，同时建立了 *PRR12* 敲除鼠模型，以观察 *PRR12* 突变导致的行为学以及眼睛表型的改变，并取小鼠组织做染色、蛋白等实验进一步支持 *PRR12* 的致病机理。目前该研究患者的 iPSCs 细胞系以及敲除鼠模型已建立，细胞正处于分化为 NPC 阶段，后续实验将在 NPC 分化成功后进行。

人巨细胞病毒 HCMV 影响肝祖细胞的体外分化

刘琴[1,3] 钟志乾[1,3] 邓月芷[2] 周奇[1,3] 刘廷珰[1,3] 戴玺铭[1,3] 覃青松[2] 周小玲[1,3] 孙平楠[1,3]
1.汕头大学医学院干细胞研究中心
2.汕头大学医学院人类病毒学实验室
3.汕头大学医学院广东省感染病与分子免疫病理重点实验室

目的 人巨细胞病毒（Human Cytomegalovirus,HCMV）可以导致严重肝炎，但其对肝脏发育的影响不清楚。
方法 将人胚胎干细胞定向诱导分化成为肝祖细胞，采用 HCMV 临床病毒株 TB40/E 体外感染肝祖细胞，通过 Western Blot(WB）、免疫荧光、qPCR、 RNA-Seq 等方法分析对肝祖细胞的影响。
结果 （1）分化获得的肝祖细胞表达 TTR、TBX3、CEBPA 等特异性标记及 HCMV 受体 EGFR，继续分化能够获得胎肝细胞。（2）发现 HCMV 能成功的感染肝祖细胞,表达即刻早期蛋白 IE1、早

期蛋白 PP52 及晚期蛋白 PP28。（3）生信分析显示 HCMV 感染肝祖细胞与 EGFR 信号通路相关。（4）感染后 6 天和正常组相比，HCMV 导致了胎肝中 HNF4A、AFP、ALB 等标记的下调，影响了祖细胞的分化。
结论 应用人胚胎干细胞技术，首次发现 HCMV 影响了肝祖细胞的正常体外分化。

OXA1L 基因变异通过调控氧化磷酸化导致线粒体肌病的机制研究

詹永坤 余永国
上海交通大学医学院附属新华医院

目的 探索 *OXA1L* 基因变异与线粒体肌病的关系及可能的致病机制。
方法 收集携带 *OXA1L* 基因变异的线粒体肌病家系的血液构建永生化淋巴细胞系，通过 qPCR 及 Western blot 检测变异对 OXA1L 表达的影响，并利用 qPCR 及 Blue-Native 凝胶电泳技术检测线粒体呼吸链复合体Ⅰ、Ⅱ、Ⅲ、Ⅳ、Ⅴ相关基因的表达以及组装情况。同时利用 siRNA 在 293T 细胞中干扰 *OXA1L* 的表达，进一步过表达 OXA1L 野生型及突变型的质粒进行挽救实验，观察 *OXA1L* 变异对呼吸链复合体合成及组装的影响。
结果 先证者淋巴细胞中 OXA1L 的表达量在 mRNA 及蛋白水平均显著下降，呼吸链复合体Ⅰ、Ⅲ、Ⅳ、Ⅴ相关基因的表达以及复合体的组装均降低。在干扰 OXA1L 的 293T 细胞中过表达 OXA1L 突变体后 OXA1L 的表达及复合体的组装仍降低。
结论 OXA1L 基因变异可能通过调控呼吸链复合体的合成和组装，影响线粒体氧化磷酸化进而导致线粒体肌病。

Genetic and functional analysis reveals TENM4 contributes to schizophrenia

Xin Yi Minzhe Li Guang He Lin He Yong Ping Daizhan Zhou
Shanghai Jiao Tong University

Aim *TENM4,* encoding a member of the teneurin protein family, is a risk gene shared by many types of mental diseases and is implicated in neuronal plasticity and signaling. However, the role and the mechanisms of *TENM4* in schizophrenia (SCZ) remains unclear.
Methods Target sequencing of *TENM4* in 68 SCZ families was performed. Phenotypic assessment of *Ten-m* function in Drosophila was examined by assessing learning ability, sleep and aggression of flies with aberrant expression of *Ten-m*. RNA sequencing on adult head samples of flies with neuronal overexpression and knockdown of *Ten-m* was performed to find mechanisms.
Results We identified possible pathogenic mutations in the *TENM4* gene through target sequencing of *TENM4* in SCZ families. We further demonstrated that aberrant expression of *Ten-m* leads to lower learning ability, sleep reduction and increased aggressiveness in animal models. RNA sequencing showed that aberrant expression of *Ten-m* was related to stimulus perception and metabolic process, and Gene Ontology (GO) enrichment terms were neurogenesis and ATPase activity.
Conclusion This study provides strong evidence that *TENM4* contributes to for SCZ, and its functional mutations might be responsible for the impaired neural circuits and behaviors observed in SCZ.

ChIP-Seq 技术全基因组范围分析高雄激素调控颗粒细胞的靶基因及通路

仇雪梅
枣庄市妇幼保健院

目的 目前多囊卵巢综合征(polycystic ovary syndrome，PCOS)的发生机制并不十分明确，不少研究表明雄激素过多可能是导致 PCOS 的根本原因之一。但是高雄激素导致 PCOS 的分子机制尚不明确。已有的研究发现了众多 PCOS 中差异表达的基因，但是哪些是高雄激素发挥作用的直接效应基因或 PCOS 发病机制的关键基因以及雄激素通过何种机制调控相关基因的表达目前尚不清楚。雄激素的功能发挥需与雄激素受体（androgen receptor, AR）结合。雄激素受体是一种转录因子，能识别靶因子上专一的 DNA 序列并与之结合，从而调控该基因的转录。本研究目的是全基因组范围内探索高雄激素调控卵巢颗粒细胞的直接效应基因及通路，为高雄激素参与 PCOS 的发病机理提供数据支持。
方法 以人卵巢颗粒细胞系 KGN 为研究对象，高浓度睾酮 (10^{-5} mol/L)处理，应用雄激素受体的抗体进行染色质免疫共沉淀，构建 DNA 文库，进行高通量测序及生物信息学分析。
结果 高浓度睾酮处理后，KGN 细胞中雄激素受体结合的 Peak 区域与对照组明显不同。高雄激素诱导其受体结合的 Peak 为 1823 个，大部分集中在基因间区与内含子上。Peak 关联靶基因富集到细胞凋亡、铁死亡、细胞粘附分子（CAMs）、磷脂酶 D 信号途径、cAMP 信号通路、磷脂酰肌醇信号系统、磷酸肌醇代谢、神经活性配体-受体相互作用 8 个信号通路上，共涉及基因 43 个。对富集通路及相关基因在多囊卵巢综合征中的研究进展进行讨论。
结论 研究揭示了高雄激素诱导的卵巢颗粒细胞发生改变的重要信号通路，研究结果有助于从源头上阐明雄激素参与 PCOS 发病机理的机制，并为 PCOS 的治疗提供潜在的靶点。

Transmembrane protein Ttyh1 maintains the quiescence of neural stem cells through Ca2+/NFATc3 signaling

Minhua Zheng Yuan Cao Xiuli Cao Hua Han
Fourth Military Medical University

Objective The quiescence, activation, and subsequent neurogenesis of neural stem cells (NSCs) play essential roles in the physiological homeostasis and pathological repair of the central nervous system. Previous studies indicate that transmembrane protein Ttyh1 is required for the stemness of NSCs, whereas the exact functions *in vivo* and precise mechanisms are still waiting to be elucidated.
Methods and Results By constructing Ttyh1-promoter driven reporter mice, we determined the specific expression of Ttyh1 in quiescent NSCs and niche astrocytes. Further evaluations on Ttyh1 knockout mice revealed that Ttyh1 ablation leads to activated neurogenesis and enhanced spatial learning and memory in adult mice (6 – 8 weeks). However, Ttyh1 deficiency results in accelerated exhaustion of NSC pool and impaired neurogenesis in aged mice (12 months). By RNA-sequencing, bioinformatics and molecular biological analysis, we found that Ttyh1 is involved in the regulation of calcium signaling in NSCs, and transcription factor NFATc3 is a critical effector in quiescence versus cell cycle entry regulated by Ttyh1.
Conclusion Our research uncovered new endogenous mechanisms that regulate quiescence versus activation of NSCs, therefore provide novel targets for the intervention to activate quiescent NSCs to participate in injury repair during pathology and aging.

使用 LSTM 发现影响细胞发育轨迹的疾病关键基因

张雨 田卫东
复旦大学

目的 单细胞测序技术的发展已经被广泛应用于研究正常或疾病组织的异质性，使人们对组织发育和疾病发生有了更深刻的理解。现在已经有一些工具，比如 Monocle、RNAvelocity、VECTOR 等，可以基于单细胞数据绘制细胞发育的轨迹。在很多疾病中，可能是由于在细胞发育轨迹上某些基因的变化，驱动了疾病的发生。因此，开发一个工具去寻找在疾病中影响细胞发育轨迹的关键基因，对于理解疾病的发生与提供治疗方案至关重要。

方法 本工具先利用发育轨迹推测算法输出的伪时间，把每个单细胞标上时间标签。对于每一个基因，随机在正常组或疾病组选取一部分细胞构建一个发育时间序列，并对这个序列标上正常或疾病的标签，然后我们使用长短时记忆网络（LSTM）对这些序列使用五折交叉验证进行训练和效果评估。对每个基因组成的数据集都能给出一个模型评价分数，分数越高表明该基因在疾病中对发育轨迹的影响越关键。

结果 我们对先天性的肢端发育畸形、心脏发育畸形、脑发育畸形等的单细胞数据使用我们的工具进行分析，找到的关键基因集合和先前的报道一致，并且可以很好地解释畸形发生的原因。

结论 我们的工具使用了深度学习的方法，寻找在疾病中影响细胞发育轨迹的关键基因，对于理解疾病的发生过程具有非常重要的意义。

Novel splicing mutation c.335-1 G>A in the cardiac transcription factor NKX2-5 leads to familial atrial septal defect through PI3K/AKT and SAPK/JNK pathways

Jia Li Limeng Dai Xiaoyin Tan Junwen Wang Xintong Zhu Yuanyin Zhao Yun Bai Hong Guo
Army Medical University

Objective Atrial septal defect (ASD) is one of the most common subtypes of congenital heart disease (CHD), leading pulmonary hypertension, right ventricular dilation, and even malignant arrhythmia and sudden death. In this study we detected the pathogenic genes and mutations in an ASD family to improve the genetic spectrum of ASD, and carried out cellular and molecular research to clarify the pathogenic mechanism of ASD, providing theoretical basis for prenatal screening, early diagnosis and prevention of CHD.

Methods We performed gene detections in 3 patients and 1 normal control in an ASD family by whole exome sequencing (WES), as well as co-segregation verification of all members in the family by Sanger sequencing. Transcriptome sequencing of patient's heart tissue was carried out, and bioinformatics such as gene expression and alternative splicing were analyzed. To study the effects of mutations on gene function and the pathogenesis of ASD, an induced pluripotent stem cell (iPSC) line carrying the candidate mutation from a patient was constructed via reprogramming techniques and then differentiated into cardiomyocytes (iPSC-CMs). In addition, RNA-seq, microRNA, dual-luciferase reporter assay, Immunofluorescence (IF), real-time PCR, Flow Cytometry (FCM) and Western blot (WB) were also used.

Result All family patients carried a novel heterozygous splicing mutation c.335-1 G>A in *NKX2-5*, which is one of the most important transcription factors expressed in the early stage of human heart development, and whose mutations can cause a variety of congenital heart diseases. The mutation results in abnormal splicing of *NKX2-5* mRNA, leading the presence of dysfunctional *NKX2-5* transcripts in the patient's heart tissue, and decreased protein expression of NKX2-5 in the patient's iPSC-CMs, showing haploinsufficiency. Weakened proliferation, along with depressed PI3K/AKT signaling were detected in the patient's iPSC-CMs. Meanwhile, increasing apoptosis and activated SAPK/JNK pathway were also found. Combined with the iPSC-CMs RNA-seq data, we confirmed that NKX2-5 regulates the expression and activation of gene *PYK2* through miR-19a/19b, mediating downstream PI3K/AKT and SAPK/JNK pathways, which affect the proliferation and apoptosis of cardiomyocytes.

Conclusion We identified a new heterozygous splicing mutation c.335-1 G>A in gene *NKX2-5* in an ASD family. This mutation leads to haploinsufficiency of *NKX2-5*, reducing the expression of miR-19a/19b, which not only gives rise to the weakened proliferation of cardiomyocytes, but also contributes to the abnormal expression and activation of gene *PYK2*, inducing cardiomyocyte apoptosis. Our findings may help to deepen the understanding of the role of *NKX2-5* in heart development and explain the pathogenesis of ASD.

子痫前期中的 RNA 编辑失调集中在上皮间质转化和免疫相关途径

杨晶
复旦大学

目的 RNA 编辑（RE,RNA Editing）失调在多种人类疾病中都被发现，例如癌症和神经退行性疾病。胎盘的植入涉及母体对胎盘的同种异体识别，具有一些类似于癌细胞的特征，例如生长、侵袭和免疫耐受。关于胎盘中 RE 的情况研究较少且不够全面透彻，最近有几项研究发现子痫前期(PE,preeclampsia)中 RE 失调。但是不知道 RE 与 PE 有多大的相关程度，且目前识别 RNA 编辑位点（RESs，RNA Editing sites）的方法较为粗糙，需要更为精确的 RESs 识别工具。
方法 我们通过对多个正常样本之间回溯，改进了本实验室之前开发的 SPRINT 算法，开发了新的 RESs 识别工具——SPRINT2.0，并利用该工具识别了来自 PE 和其正常对照胎盘样本多个研究的多套数据，每个样本识别了超过 30 万个差异编辑位点。
结果和结论 我们发现 PE 和对照样本的差异 RNA 编辑位点集中在 EMT 和免疫相关通路。我们利用 EMT 打分算法，根据已有的上皮型和间质型基因集合对 PE 样本和正常对照样本进行了打分，发现 PE 样本更偏上皮型，正常样本则更多地表现为间质型，证实了 EMT 在 PE 中发生变化，可能是由于 RNA 编辑引起的。有研究发现 PE 中 EMT 通路降低，可能会导致滋养细胞侵袭障碍，最终导致 PE 的原因，我们的研究表明这一过程可能和 RNA 编辑有关。

3 例 Turner type of X-linked syndromic mental retardation (MRXST) 患者的临床特点及遗传学分析

余婷
武汉儿童医院

目的 探讨 Turner type of X-linked syndromic mental retardation (MRXST) 患者的临床表现及基因突变的特点，并对相关文献进行复习。
方法 对患儿进行临床和实验室检查，抽取患儿及其父母的外周血，应用高通量测序技术对患儿进行全外显子基因变异检测，并对疑似致病性变异进行患儿及其父母的 Sanger 测序验证及生物信息学分析；复习相关文献，总结该病的特点。
结果 3 例患儿均有全面性发育迟缓，面容异常和小头畸形。其中一例合并染色体异常和线粒体 DNA 突变。3 例患儿均为 HUWE1 基因半合突变，其中 c.5639G>A(p.Arg1880His)为未见报道的新发突变。文献复习发现国外约有 58 例该类疾病报道，国内未见报道。总结临床特点发现患者一般表现为全面性发育迟缓，语言发育落后，面容异常和小头畸形、肌张力减退等。
结论 患者 HUWE1 基因突变是导致其全面发育迟缓和面容异常的病因，我们的研究增加了 HUWE1 基因新的突变位点和病例数，并强调了全外显子组测序在临床遗传学诊断中的重要作用。

Novel CNGA1 gene mutation in a Chinese patient with autosomal recessive retinitis pigmentosa

Fangyuan Zhen[1] Ting Wang[2] Tongdan Zou[2]
1.The First Affiliated Hospital of Zhengzhou University
2. School of Medicine, University of Electronic Science and Technology of China

Abstract
Purpose: *Retinitis pigmentosa* (*RP*) is a complex group of hereditary retinal dystrophy. This study is to detect the disease-causing mutations in a nonconsanguineous Chinese family with nonsyndromic autosomal recessive *RP*.
Methods: A Chinese *RP* family with autosomal recessive inheritance, including a total of nine members with one affected patient and eight unaffected individuals were recruited in this study. Integrated ophthalmic examinations were carried out in all these participants, consisting of visual acuity testing, computerized visual field measurement, tests of dark adaptation and color vision, spectral domain optical coherence tomography, and fundus photography. Genomic DNAs was extracted from peripheral blood. Whole exome sequencing was conducted with the affected individual. Candidate disease-causing mutations were amplified by polymerase chain reaction, and direct Sanger sequencing was performed to verify the mutations in the family and 600 ethnicity matched healthy controls.
Results: The affected individual showed classically clinical symptoms of *RP*, including retinal pigmented epithelium atrophy, night blindness, arteriolar constriction, pale discs, and paravascular bone spicule pigmentation. A novel homozygous mutation, c.265delC (p.L89Ffs*3) in the cyclic nucleotide gated channel subunit alpha 1 (*CNGA1*) gene was identified by Whole Exome Sequencing. The pathogenic mutation was validated by direct Sanger sequencing. This mutation was absent from other unaffected family members and 600 ethnicity matched healthy controls. The mutation was co-segregated with the disease phenotype of autosomal recessive retinitis pigmentosa.
Conclusions: A novel homozygous mutation in p.L89Ffs*3 was detected in a Chinese family with autosomal recessive RP. The homozygous mutation was reported for the first time in the public databases.

Generation and characterization of human TPH2 reporter stem cell lines

Ting Xu Jianfeng Lu Lining Cao Guanhao Wang You Li Wenting Lu Yixuan Ren Xudong Sun Xinpeng Pang
Tongji University

Objective Human pluripotent stem cells（hPSCs） provide a considerable source of diverse cell types for drug screening and disease modeling. Serotonin neurons differentiated from hPSCs in vitro are accessible with the current strategy, which is closely bound up with multiple physiological diseases and respiration syndrome. Nevertheless, the heterogeneous cell population differentiated from hPSCs hinders its further applications. We attempted to generate and characterized a TPH2-EGFP reporter hPSC line to monitor serotonin neurons.
Methods In this study, we engineered the hPSCs by inserting the EGFP gene into the TPH2 locus to report human serotonin neurons, using CRISPR/Cas9. Later on, the pluripotency of the reporter lines was evaluated through cell immunostaining and teratoma formation experiments. The reporter activity was validated by using small molecular compounds to induce lineage differentiation. Electrophysiology was applied to detect the maturation and function of the neurons.
Results The TPH2-EGFP reporter cell lines expressed pluripotent markers and were able to differentiate into three germ layers. Moreover, they could be induced to differentiate into serotonin neurons with EGFP exclusively expressed upon modulating WNT, SHH, FGF signaling. The transgene hPSCs derived serotonin neurons were mature and functional, had normal electrophysiological properties, and expressed specific markers.

Conclusions Our EGFP-TPH2 reporter hPSC lines allow for real-time monitoring of serotoninergic neurons in culture and performing electrophysiology effectively. The reporter cell line will not only facilitate our understanding of the serotonin system in modulating human mood and respiration but also accelerate drug screening.

SYK mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells in cancer

Zhiyang zeng
East China Normal University

Immunotherapy that blocks immune checkpoints has been shown to significantly prolong the survival of subjects in some cancers. However, most patients responded poorly to these therapies due to the complex tumor microenvironment (TME) and high level of immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs). Spleen tyrosine kinase (SYK) regulates multiple cancer pathways ,but its role in MDSCs、TME and cancer immunotherapy remains unknown. Using murine tumor models in WT and SYK^{S544Y} gain of function mice, in vitro systems, adoptive transfer approaches and clinical tumor samples, we uncovered a SYK mediated pathway governing MDSCs function in multiple cancers. Here we found that pSYK is activated in colorectal cancer and correlates with clinicopathologic stage. Activation of SYK significantly promotes MDSCs expansion, their expression of immunosuppressive molecules such as arginase-I and their ability to suppress T cell proliferation. Targeting SYK using inhibitor R406 significantly reduces MDSCs abundance and enhanced T cell activation, thus retards tumor growth. Our data reveal the potential of SYK signaling to govern MDSCs expansion and immunosuppressive function which can be mitigated by treatment with SYK inhibitor R406. Therefore, targeting SYK could help to overcome immune suppression and may enhance the efficacy of cancer immunotherapy.

遗传病面部表型量化

尧甜 田卫东
复旦大学

遗传病种类多，表现复杂，这造成临床上的诊断困难。人类表型本体作为疾病异常的标准知识库，广泛的运用到遗传病的诊断中。许多遗传病具有可识别的面部特征，如唐氏综合征，天使综合征等，这对于遗传病的诊断有非常大的帮助。在近五年来，深度学习较多的应用到疾病的诊断中来，在有些研究中，其诊断正确率达到了临床专家的水平。本文在查阅大量文献的基础上，对遗传病面部表型分析方法进行了评述，在此基础上给出本课题的方案，结合图像处理技术，建立遗传病面部表型分析模型，能够量化面部表型，运用到遗传病的分析中。

Variants in VAX1 provide insights into NSCL/P in western Han Chinese population

yue you Zhonglin Jia
State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & Department of Cleft Lip and Palate, West China Hospital of Stomatology, Sichuan University, Chengdu, China.

Objective Non-syndromic cleft lip with or without palate (NSCL/P) represents congenital structural anomalies of the labiopalatine region. We previously identified association between rs7078160 at *VAX1* and NSCL/P in western Han Chinese population. However, the functional SNP at *VAX1* has not been totally elucidated.

Methods Targeted sequencing was performed , followed by statistical analyses and extensive functional annotation of the candidate SNPs, to identify new promising candidate SNPs.
Results In this study, 29 SNPs in *VAX1* (P＜0.0001) were identified to be associated with NSCL/P in western Han Chinese population, most of which increase the risk of illness through affecting the binding ability of transcriptional factors. In addition, we found subtype-specific genetic associations, 27 SNPs were found specifically associated with NSCLP.
Conclusion In summary, our study provide insight into the pathogenic mechanism of NSCL/P in western Han Chinese population, which opens up new possibilities for further molecular studies on craniofacial development and may contribute to clinical prenatal diagnosis.

PRRT2 基因突变诱导多能干细胞模型的建立及发病机制的研究

梁晨[1,2] 刘芳[1,2] 陈晓丽[1,2]
1.中国医学科学院北京协和医学院
2.首都儿科研究所

目的 深入探讨 PRRT2 基因变异的致病机制，建立疾病的诱导性多能干细胞系，分析相关疾病的临床表型和基因型特点之间的关系。
方法 完成了全外显子测序和 16p11.2 区域深度测序并进行变异分析。采集 PRRT2 基因突变患者的外周血单个核细胞，基于细胞重编程方法诱导产生 PRRT2 基因突变患者的特异性 iPSCs，利用 iPSCs 的多潜能性将其定向诱导成特异性皮层神经元。
结果 基于全外显子测序技术的遗传学诊断结果，我们现招募了四个携带 PRRT2 突变的家系，其中一例为新生突变（c.649delC，p.R217fs*12），三例为常染色体显性遗传突变（c.649dupC，p.R217Pfs*8；c.649dupC，p.R217Pfs*8；c.649delC，p.R217Efs*12）。患者间存在一定的表型差异，对 PRRT2 突变所致疾病发病机制的研究一直在不断发展中，已有的很多研究表明，其最终都是通过 PRRT2 功能缺失致病，而临床表型的不同，可能与基因、环境等多种因素相关。我们建立了 PRRT2 基因变异（c.649delC，p.R217fs*12）的诱导性多能干细胞系，为探索 PRRT2 基因突变的发病机制、药物筛选等提供了良好的细胞模型。

新生儿 G6PD 缺乏症与氨基酸谱的相关性研究

俸诗瀚
广西医科大学第二附属医院

目的 通过对本院新生儿筛查的数据分析，研究新生儿葡萄糖-6-磷酸脱氢酶(G6PD)筛查结果与体内氨基酸水平变化的相关性。
方法 将 1000 例同时进行了 G6PD 筛查和串联质谱筛查的新生儿分为两组进行分析(1 组为 G6PD 缺乏组，2 组为 G6PD 正常组)，比较 938 例 G6PD 正常新生儿与 62 例 G6PD 缺乏新生儿两组队列之间氨基酸浓度水平和比值变化情况。
结果 两组队列中发现，丙氨酸 (Ala)、甘氨酸(Gly)、酪氨酸(Tyr)和 Arg/Phe 差异均有统计学意义(P＜0.05) ；而精氨酸(Arg)、瓜氨酸(Cit)、亮氨酸+异亮氨酸(Leu+Ile)、甲硫氨酸(Met)、鸟氨酸(Orn)、苯丙氨酸(Phe)、脯氨酸(Pro)、缬氨酸(Val)、Val/Phe 比值变化差异无统计学意义(P＞0.05)。
结论 新生儿筛查中可以根据串联质谱中丙氨酸(ALA)、甘氨酸(Gly)、酪氨酸(Tyr)和 Arg/Phe 比值变化情况来协助诊断葡萄糖-6-磷酸脱氢酶缺乏症，同时我们将在下一步的研究中结合 G6PD 基因诊断来进行进一步的分析研究。

SMN2 7 号外显子非蛋白编码区突变引起 SMN2 全长转录本含量增高的研究

洪舜彦 林翔 陈海珠 郑基坛 叶子凌 王柠 陈万金
福建医科大学附属第一医院

目的
SMN2（survival motor neuron1）是脊髓性肌萎缩（spinal muscular atrophy, SMA）基因治疗的重要靶点。使用单碱基编辑器对 SMN2 7 号外显子剪接调控元件进行编辑从而提高全长转录本的比例是一种可行的策略。但对蛋白编码区的基因编辑容易由于旁观者效应（bystander effect）而引起错义突变的发生。本研究拟探索对 7 号外显子内非蛋白编码区进行编辑从而提高全长转录本比例的可行性。
方法 1.设计针对 7 号外显子非编码区的 sgRNA，构建相应的单碱基编辑器（spG-YE1-CBE）质粒，转染 HEK-293T 细胞后流式分选出荧光阳性细胞。抽提 DNA 及 RNA，sanger 测序检测碱基编辑情况，RT-PCR 检测 SMN2 转录本变化情况。2.构建携带相应碱基突变的 SMN2-minigene，转染 293T 细胞后通过 RT-PCR 验证 minigene 的转录本情况。
结果 spG-YE1-CBE 成功对 HEK-293T 细胞 7 号外显子非编码区的 52G、53G 位点实现了 G→A 的突变；RT-PCR 结果表明，相比未经干预的 HEK-293T 细胞，SMN2 来源的全长转录本含量出现了明显的提升。Minigene 验证同样表明，G52A、G53A 可有效提升全长转录本比例。
结论 通过高保真的 spG-YE1-CBE 可以对 SMN2 7 号外显子非蛋白编码区位点 52G、53G 进行编辑，并有效提升全长转录本，这一位点无发生蛋白错义突变的风险，具有较高的安全性。

基于高保真单碱基编辑系统的 SMAΔ7 小鼠受精卵基因编辑研究

洪舜彦 林翔 陈海珠 郑基坛 叶子凌 王柠 陈万金
福建医科大学附属第一医院

目的 脊髓性肌萎缩（spinal muscular atrophy, SMA）是一种以脊髓前角运动神经退行性变为主要特征的疾病，多由 SMN1（survival motor neuron1）缺失引起，SMN2 为其主要修饰基因。通过高保真单碱基编辑器（mini-ABE），可在 HEK-293T、SMA-mES、SMA-iPS 等细胞中实现 7 号外显子中外显子剪接沉默子 B（Exon splicing silencer B）突变，从而提高全长 SMN 转录本含量，挽救相应细胞的表型。本研究拟探讨 mini-ABE 编辑器能否在 SMA-Δ7 小鼠受精卵中进行编辑，阐明该编辑方案用于小鼠胚胎水平治疗的可能性。
方法 对雌性 SMA-Δ7 杂合子小鼠（JAX，005025）进行超数排卵后同品系杂合子雄鼠合笼，隔日处死取受精卵。利用体外转录获取 mini-ABE mRNA 及靶向人源 SMN2 7 号外显子剪接沉默子-B 的 sgRNA，通过显微注射方法注入受精卵内并过夜培养，次日取发育良好的受精卵移植入假孕 ICR 雌鼠体内。待 F0 代小鼠出生后，剪脚趾提取 DNA，通过 PCR 及 Sanger 测序进行基因型鉴定。选择阳性小鼠与 SMA-Δ7 杂合子小鼠交配获得子代 F1，以同样方法进行基因型鉴定。
结果 1.出生的 F0 代小鼠中，部分小鼠测序可见 SMN2 7 号外显子含有 A36G 峰。2. 基因编辑后的 F0 代 SMA-Δ7 杂合子小鼠外观与未编辑的 SMA-Δ7 杂合子小鼠无明显差异，可正常生长并繁殖。3. F1 代 SMA-Δ7 杂合子小鼠中可见 A36G 杂合、A38G 杂合双位点编辑的小鼠。
结论 mini-ABE 可在 SMA-Δ7 小鼠受精卵中实现 SMN2 7 号外显子的编辑，并可观察到旁观者效应（bystander effect）的发生，因此这一编辑位点的安全性有待进一步观察。

他莫昔芬（TMX）诱导面肩肱型肌营养不良小鼠模型的前期研究

王丽莉[1,2,3] 陈龙[1,2,3] 王志强[1,2]
1.福建医科大学附属第一医院
2.福建省神经病学研究所 3.福建医科大学

目的 面肩肱型肌营养不良症(FSHD)是最常见的肌营养不良症之一相对良性， 进展缓慢，约 20%患者最终需要使用轮椅，目前缺乏有效的治疗药物，成为本病亟待解决的关键问题。因此，FSHD 动物模型的研究有助于阐明 FSHD 发病机制， 探寻到潜在治疗靶点。
方法 我们已从美国 Jackson 实验室（The Jackson Laboratory）引进 FLExDUX4- cre 小鼠模型（Stock No.028710），他莫昔芬（TMX）诱导 DUX4 基因高表达。将 14 周龄 TMX 诱导表达后的小鼠作为实验组（n=3），野生型为对照组。实验组连续 注射 LY2090314（GSK3β 抑制剂）3 天，（注射剂量 25mg/kg），对照组连续注 射 3 天同等剂量的 DMSO。通过四肢攀爬试验，检测小鼠肌力的变化，通过称量 体重来评估肌肉含量的改变。组织切片 HE 染色及天狼星染色镜下观察肌肉组织 的病理改变，qPCR 检测 DUX4 基因的表达量。
结果 1. 两组小鼠四肢攀爬实验，比较具有统计学差异（P=0.0078）。 2. 病理 上，经 TMX 75mg/kg/d 连续注射 7d 的实验组，HE 染色可见大小不一的肌纤维， 肌细胞核内移，细胞膜完整性破坏，细胞周围有炎细胞浸润；对照组肌纤维间的 间隙正常，细胞核位于周围，肌纤维，未见炎细胞浸润。 3. 在腹腔注射（IP） TMX 后 16 天后检测 DUX4-fl mRNA 表达水平，对照组 DUX4-fl mRNA 相对表 达量与实验组的 DUX4-fl mRNA 的相对表达量相比具有统计学意义（p =0.0078）； 4. IP 连续注射 LY2090314 （GSK3β 抑制剂）3 天的实验组与注射 DMSO 的对 照组相比，肌肉病理切片 HE 染色镜下可见肌纤维萎缩与肥大并存。嗜碱性肌纤 维：即肌纤维再生；再生肌纤维比周围正常肌纤维小，肌质嗜盐基性；5. 镜下可 见对照组 Dux4-cre 与实验组 Dux4-cre+LY2090314 小鼠，腓肠肌天狼星染色，红 色纤维的含量，明显高于对照组（n=5，p=0.0079）；6. QPCR 显示 DUX4 下游 靶基因 Trim36-mRNA 表达量对照组为 1，实验组为 1.41；成纤维基因 Col1a1- mRNA 表达量对照组为 1，实验组为 0.395（n=3）

Brown adipose transplantation improves polycystic ovary syndrome phenotypes involved metabolomic remodeling

Siliang Xu[1] Liwen Song[2]
1.The first afflicated hospital with nanjing medical university
2.Tongren hosipital shanghai jiao tong university school of medicine

Polycystic ovary syndrome (PCOS) is a common and complex reproductive, endocrine and metabolic disorder in reproductive-age women. Emerging evidences indicated that brown adipose tissue (BAT) improve the reproductive and metabolic phenotypes of PCOS rats. In dehydroepiandrosterone (DHEA)-induced PCOS rat model, we aimed to study the role of metabolites in the process of BAT transplantation. We identified 22 differential metabolites of brown adipose tissues in DHEA+BAT group compared with DHEA+Sham group using LC/MS analysis, which belonged to different metabolic pathways, such as glycerophospholipid metabolism, amino acid metabolism. Compared to the DHEA+Sham group, significant decrease in the levels of glycerophosphoinositols (PI(18:0/22:5(4Z,7Z,10Z,13Z,16Z)), PI(18:0/22:6(4Z,7Z,10Z,13Z, 16Z,19Z)), PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))), sphingolipids (N-Palmitoyl-D-erythro-sphingosine), amino acids (L-Glutamine), and increase in glycerophosphocholines (PC(P-15:0/0:0), Lyso-PAF C-16), peptides (Asp Ile Lys Arg), Glycerophosphoethanolamines (LysoPE(0:0/22:4(7Z,10Z,13Z,16Z))) level were observed in the brown tissues of the DHEA+BAT group. The glycerophospholipids are one of the main lipid components of cell membranes, and the sphingolipids participate in a variety of indispensable metabolic and intracellular signaling processes, which indicated that the altered metabolites might play important roles in the process of treatment of PCOS. Metabolomics analysis has provided new insights for understanding the mechanism and therapeutic effects of BAT transplantation.

LGR4 调控巨噬细胞在急性肝损伤中的功能研究

尹思琪[1] 吴学文[2] 钱颖[1] 钱旻[1] 秦居亮[1] 杜冰[1]
1.华东师范大学
2.上海市奉贤区中心医院

肝脏巨噬细胞包括肝脏组织常驻巨噬细胞（Kupffer cells，KCs）和骨髓来源的巨噬细胞，其在调控肝脏的损伤和修复、炎症反应、肝纤维化以及整个肝脏内稳态过程中发挥着十分重要的作用。我们的研究发现肝脏巨噬细胞表面的 G 蛋白偶联受体 LGR4 在小鼠急性肝损伤模型中表达明显上调，而特异性地敲除巨噬细胞中 *lgr4* 基因可以显著减轻 CCl4 诱导的小鼠急性肝损伤。进一步的研究发现 LGR4 受体的缺失促进了小鼠血清中 TNF-α 和 IFN-γ 等细胞因子的分泌。同时通过体外提取小鼠骨髓来源巨噬细胞和肝脏巨噬细胞，并用 LPS 和 Lgr4 配体 Rspondin1、Rspondin3 刺激后对 TNF-α 等炎症因子进行检测，实验发现激活 LGR4 可以有效抑制 LPS 引起的炎症反应。综述所述，我们的研究发现 LGR4 受体对巨噬细胞介导的炎症反应具有重要调控作用，LGR4 受体的缺失或抑制会促进炎症反应，进一步加剧肝损伤的发生、发展，而有效激活 LGR4 受体可以显著抑制炎症反应，为临床急性肝损伤的治疗提供新的思路和策略。

环状 RNA 在骨髓增生异常综合征中的差异表达及潜在的作用价值研究

吴宛玲
复旦大学附属华山医院

研究背景 circRNA 是一种内源性的环形 RNA 分子，具有重要的生物学功能，是多种肿瘤疾病诊疗的潜在生物标志物。然而目前关于 circRNAs 在骨髓增生异常综合征（MDS）中的作用的研究极少，作用未明。
研究目的 构建 circRNA 在 MDS 中的差异表达谱，并进一步探索异常表达的 circRNA 在 MDS 中的临床价值和功能作用网络。
研究方法 使用 circRNA 芯片分析 MDS 患者和对照组之间 circRNA 的差异表达，构建 circRNA 差异表达谱；接着通过 qRT-PCR 在 100 名 MDS 患者和 20 名对照样本之间进行验证明确差异表达的 circRNA 分子，并进行 ROC 曲线分析和 Kaplan-Meier 生存分析来探究其临床价值；最后，基于生物信息分析技术预测 circRNA 下游的 miRNA 及 miRNA 下游的 mRNA，构建以 circRNA 为中心的 ceRNA 调控网络，同时对 ceRNA 网络下游的基因进行了 GO 和 KEGG 分析，预测 circRNA 在 MDS 中可能参与的信号通路。
研究结果 circRNA 芯片共筛选出了 145 个在 MDS 患者样本中异常上调的和 224 个异常下调的 circRNA，经 qPCR 验证后鉴定出 3 个上调（hsa_circRNA_100352，hsa_circRNA_104056，hsa_circRNA_104634）和 3 个下调（hsa_circRNA_103846，hsa_circRNA_102817，hsa_circRNA_102526）的 circRNA 分子。ROC 曲线分析显示其 AUC 值分别为 0.7266、0.8676、0.7349、0.7091、0.8806 和 0.7472，Kaplan-Meier 生存分析结果提示 hsa_circRNA_100352、hsa_circRNA_104056 和 hsa_circRNA_102817 与总生存率显着相关。以 hsa_circRNA_100352、hsa_circRNA_104056 和 hsa_circRNA_102817 为中心构建 ceRNA 调控网络，GO 和 KEGG 分析提示这 3 个 circRNA 参与了多种重要的肿瘤相关功能和通路的调控。

破解精准医学“不精准”难题-高精度的生命组学质控标准

陈洋[1] 张弓[1] 卢红[1] 金静洁[1] 卢少华[1,2]
1.暨南大学 2.广州医科大学

目的 当今生命组学数据因样品处理方式，测定平台以及分析方法的多样化和不精准，降低了跨平台和跨实验室数据的重复性和可验证性。我们旨在研发出每种生命组学数据质量控制的关键技术和应用示范，建立全流程的生命组学数据质量控制标准方法和自动化工具。
方法 我们使用二代测序和质谱技术对 30 个大肠杆菌和 10 个代次的人肝癌细胞系 MHCC97H 样本进行转录组、翻译组和蛋白质组进行分析，以此评价标准实验流程及分析方法的稳健性。
结果 转录组定量误差为 0.0053%，翻译组定量误差为 0.015%。MHCC97H 每一代次细胞的转录组定量相关性 R^2=0.96 以上，翻译组定量相关性 R^2=0.95 以上，蛋白质组的定量相关性 R^2=0.93 以上。
结论 本课题通过建立一系列生命组学质空标准以及对标准样品 MHCC97H 进行一致性测试，建立了高精度的基因组、转录组和翻译组的测序流程；同时建立蛋白质数据采集全流程的标准操作程序，建立开放式搜索的质控标准，可对各组学的数据质量进行全流程多方位的把控。

神经变性和神经发育障碍——遗传性痉挛性截瘫的“双面性”

苏惠贞
福建医科大学附属第一医院

背景及目的：遗传性痉挛性截瘫（Hereditary spastic paraplegias，HSP）是一组具有高度异质性的单基因遗传病，其特征是双下肢进行性肌痉挛和肌无力。既往尸检病理提示 HSP 患者的皮质脊髓束存在轴索变性。然而，随着越来越多的 SPG 亚型被报道，HSP 被证实是神经发育和神经变性高度重叠的一组临床综合征。现就有关神经发育障碍和神经变性在 HSP 临床表现和发病机制中的作用作一综述。
方法：本文回顾了既往文献报道的 HSP 被克隆的已知致病基因及相应的功能研究，总结神经发育障碍和神经变性在 HSP 患病人群中的临床特征以及发病机制中的影响。
结果：就起病年龄而言，HSP 患病人群覆盖了从新生儿到中老年的所有年龄段。虽然某些遗传亚型的平均发病年龄比其他亚型早，但在同一亚型中，起病年龄也可能存在较大差别；此外，不同亚型的 HSP 患者在病程中，其残疾程度、病情的恶化程度和速度也各不相同。起病年龄和疾病进程的异质性可能反映了神经发育、神经变性以及神经可塑性等多种因素在 HSP 病理机制上的博弈。在临床表现方面，HSP 患者在锥体系受损的同时，既可伴随胼胝体发育不良、小头畸形、骨骼畸形、精神发育迟滞等神经发育缺陷，同时也可出现进行性认知功能下降、帕金森综合征等退行性改变。随着致病基因功能的深入研究和基因型-表型的关联分析，研究者在包括 SPG11 亚型在内的多种复杂型 HSP 的机制研究中寻找到神经发育障碍和神经变性重叠的证据。例如，SPG11 亚型即具有“双面性”，spatacsin 蛋白不同的时空表达将分别引起神经发育和神经变性；SPG81 亚型的 EPT1 基因突变通过影响磷脂代谢导致髓鞘形成异常及神经发育缺陷等。这些致病基因作为研究模型在神经发育表型与神经变性表型之间成功构建了桥梁。此外，基因敲除动物、可诱导性多能干细胞乃至类器官等作为良好的疾病模型，正在为神经发育障碍和神经变性之间的关联性提供更强有力的证据。
结论：神经发育障碍和神经变性在 HSP 的临床症状和病理改变中存在交叉和重叠，但两者在具体的发病机制上存在怎样的区别和联系尚待进一步研究。

The research on biological mechanism and regulation of Chinese medicine prescription Jin Rong granules effective monomers selected by molecular docking in breast cancer

Hongwei Wang
Jinan University

Chinese medicine has the characteristics of low side effects and stable efficacy in the treatment of breast cancer Since the 1980s, the Chinese herbal formula Jin Rong Granules has been used in the clinical treatment of breast enlargement disease. It can effectively eliminate or relieve patients' breast pain and tenderness, reduce the size of lumps and the distribution of lumps, soften lumps and eliminate or relieve the associated concomitant symptoms. We have further discovered the anti-breast cancer therapeutic effect of this prescription in clinical practice, but its molecular mechanism is unknown. This limits its new anti-cancer applications. We obtained the Natural products in the Chinese herbal formula Jin Rong Granules for the treatment of breast cancer through the NP databases (PubChem, UNPD). At the same time, we obtained the target proteins closely related to breast cancer through the investigation of the existing literature. The interaction between monomers and target proteins are calculated by using molecular docking, we screened out monomers that might be effective. Some monomers with low scores were filtered, we selected the 3, 29-o-dibenzoyloxykarounidiol. This monomer is predicted to target Cadherin-1, Histone-lysine N-methyltransferase 2C, Zinc finger protein SNAI2, NAD-dependent protein deacetylase sirtuin-3, mitochondrial protein. In the CCK-8 cell proliferation ability assay, we found that this monomer had a strong inhibitory effect on MDA-MB-231 breast cancer cell line. Also, SKBR3 showed moderate inhibition of the monomer. Although monomer did not significantly inhibit T47D at the beginning, the inhibition of monomer on T47D gradually increased with the increase of treatment time. It showed a time-dependent suppression trend. These results indicate that 29-O-dibenzoyloxyKarounidiol in the Chinese herbal formula Jin Rong granules have an inhibitory effect on breast cancer cells growth by affecting the expression of these proteins.

Comparative study of Ribo-seq and RNC-seq in identification of protein isoforms

Chun Wu
Jinan University

The large-scale identification of protein isoforms produced by gene alternative splicing has always been a hot and difficult research topic. In recent years, Ribo-seq (ribosome profiling sequencing) has been regarded as an indirect method to identify protein isoforms, but its short sequence length brings great challenge to the detection of splice junctions in bioinformatics. We compared the identification effects of Ribo-seq and RNC-seq (full length translating RNA sequencing) on protein isoforms and found that RNC-seq is expected to be a more effective method for identifying protein isoforms.

We compared and analyzed the result of NGS (Next-generation sequencing) data of RNC-seq and Ribo-seq and found that in MHCC97H and HELA cell lines, the rRNA reads ratio of RNC-seq was 15% and 82% lower than that of Ribo-seq, respectively, the unique mapping ratio was 30% and 15% higher than that of Ribo-seq, and the final identified protein isoforms of RNC-seq are 1.5 times and 3 times that of Ribo-seq. This is because there are various kinds of small RNAs in the cell, including degraded RNA fragments with the length of 24~36nt, which are difficult to exclude in the preparation procedures of RPF (ribosome protection fragments). These non-RFP fragments with unrestricted fragment length polymorphism would also appear in the Ribo-seq datasets, resulting in false positives. We further expanded the identification performance of RNC-seq technology on protein isoforms by using nanopore sequencing technology, by which 208 missed protein isoforms outside the Nextprot (PE1-5) database were identified.

In this study, by comparing the results of Ribo-seq and RNC-seq, it is concluded that RNC-seq could improve the accuracy and efficiency of protein isoform identification. Here, we demonstrate a strategy to identify protein isoforms, which can identify a certain number of missing proteins and new protein isoforms by using a cell type–specific protein sequence database supported by RNC-seq information. This study demonstrates the potential of RNC-seq to promote the development of protein isoform identification.

Association between variants around IRF6 and non-syndromic orofacial cleft in Western Han Chinese

Sidi Zhang
State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & Dept. of cleft lip and palate, West China Hospital of Stomatology, Sichuan University

Objectives This study was aimed to investigate association between variants around *IRF6* and subtypes of NSOC, one of the most common craniofacial birth defects, in Western Han Chinese.
Materials and Methods We recruited 380 NSOC case-parent trios, including 126 NSCLO trios, 152 NSCLP trios and 102 NSCPO trios. 22 SNPs were genotyped using SNPscan method; Hardy Weinberg equilibrium test, allelic TDT, sliding window haplotype TDT analysis and parent-of-origin effect were performed using PLINK software. Pairwise LD was computed using the haploview program.
Results In TDT analysis, allele A at rs17015217 (*P*=0.00011, OR=0.61 and 95%CI: 0.47-0.78) and allele T at rs12080691 (*P*=0.00011, OR=0.61 and 95%CI: 0.47-0.78) were identified to be under-transmitted among NSCLO but over-transmitted among NSCPO. Haplotypes including the under-transmitted alleles of the significant SNPs were under-transmitted in NSCL/P, NSCLO, but over-transmitted in NSCPO. In parent-of-origin effect analysis, the two SNPs presented paternal special under-transmission among NSCL/P and NSCLO but over-transmission among NSCPO. No significant difference was found between paternal and maternal transmission.
Conclusion Allele A at rs17015217 and allele T at rs12080691 were newly identified to be associated with NSCLO and NSCPO in Western Han Chinese, with opposite effects on different subtypes: risk for NSCPO but protective for NSCLO.

eNOS 基因多态性与精子发生的相关性分析

崔元戎 管一春
郑州大学第三附属医院

目的 研究 eNOS 基因多态性与精子发生的关系。
方法 采用 case-control 的研究方法，利用荧光定量 PCR 技术，取对照组的正常男性与病例组的原发性少弱精患者血液，对病理组与对照组 eNOS 基因的 Glu298Asp 位点的多态性进行检测及分析，并计算病例组与对照组该基因的基因型及等位基因的分布频率；检测其基因型频率是否符合 Hardy-Weinberg 平衡；对照组与病理组之间差异采用卡方检验。
结果 eNOS 基因 Glu298Asp 位点基因型频率符合 Hardy-Weinberg 平衡；eNOS 基因 Glu298Asp 位点的 T 等位基因可能与弱精症发生的易感性有关。
结论 eNOS 基因多态性与精子发生有相关性。

Inhibition of HIF-2α attenuates AT-II induced cardiomyocyte hypertrophy through a STRIP2-related pathway

Fangyu Liu Qiang Ji
Zhongshan Hospital, Fudan University

Objectives Hypertrophic cardiomyopathy (HCM) has been the leading cause of sudden death in adolescents and athletes. Myocardial ischemia and hypoxia are the key inducing factors for the development of HCM and heart failure. HIF-2α is one of the main regulating factors of hypoxia response. In this study, we would like to investigate the role of HIF-2α in the development of cardiomyocyte hypertrophy and the potential interacting molecules.
Methods Angiotensin II (AT-II) was used to induce rat cardiomyocyte hypertrophy. PT-2385, a selective HIF-2α inhibitor, was used to suppress the molecular function of HIF-2α. Anoxic culture environment was applied to stimulate myocardial hypoxia. The transcription and expression of targeted genes were evaluated by quantitative real-time RT-PCR (qRT-PCR) and Western blotting. Cardiomyocyte hypertrophy was validated by immunofluorescence. Myocardial injury was measured by cardiac biomarker expression levels.
Results Cardiomyocyte hypertrophy was successfully induced after AT-II treatment for 24 or 48 hours. The expression of HIF-2α and STRIP2 increased after AT-II treatment and could be partially reversed by PT-2385. Anoxic condition for four hours before cell collection could aggravate the hypertrophy and promote the expression of HIF-2α and STRIP2. Cardiomyocyte hypertrophy and myocardial injury could be mitigated by the HIF-2α selective inhibitor.
Conclusion Increased HIF-2α expression plays an important role in the development of cardiac hypertrophy. Inhibition of HIF-2α could relieve cardiomyocyte hypertrophy and myocardial injury. STRIP2 expression changed positively related to HIF-2α regulation. The interacting mechanism between them need further investigation.

MAPR 家族成员的结构功能研究现状

白红梅
深圳市龙岗区妇幼保健院

MapR 家族基因在中枢神经系统中大量表达，在神经细胞中具有神经营养作用。4 种 mapR 蛋白 PGRMC1、PGRMC2、neuferricin 和 neudesin 有一个同源的 CyB5 样血红素/类固醇结合域，但与经典的核或膜结合类固醇受体缺乏同源性。MAPRs 还与越来越多的不同蛋白质相互作用，参与了多种细胞功能，包括胆固醇和类固醇的稳态、细胞周期调节、细胞迁移、神经发生、自噬、血红素稳态等。在脂质代谢过程中，PGRMC1 调节胆固醇的合成，而 Neudesin 在脂肪形成中起作用。本文综述了 MapR 家族成员的鉴定、结构和生物活性，并对其生理功能的研究现状进行了综述。

CDK2 activity is required for meiosis I exit in mouse oocytes

Jian Li
Peking University Shenzhen Hospital

Mammalian oocytes are arrested at the diplotene stage of prophase I during fetal or postnatal development. Cyclin-dependent kinases (CDKs) are responsible for the regulation of cell cycle in mammals. During meiotic maturation, it was shown that CDK1 was the sole CDK to drive the resumption of meiosis in mouse oocytes, and CDK2 was dispensable for oocyte meiosis according to the conditional knockout studies. However, taken the compensatory effect between CDKs after gene knockout approach, the physiological function of CDK2 kinase activity in oocyte maturation is still unclear. To address the issue, we applied a specific small-molecule inhibitor to restrain CDK2 kinase activity instantaneously during oocyte meiotic maturation. We found that

transient inhibition of CDK2 activity had no effect on meiotic resumption but significantly prevented the meiosis I exit in mouse oocytes. Then we analyzed the spindle morphology and key checkpoints in mouse oocytes with CDK2 inhibition, we found that CDK2 activity was required for appropriate bi-oriented spindle assembly, transient CDK2 inhibition arrested the oocytes at metaphase I by interrupting anaphase-promoting complex/cyclosome (APC/C)-dependent degradation pathway. In addition, we further observed the spindle assembly checkpoint (SAC) signal was activated in the arrested oocytes. Therefore, our results indicate that CDK2 kinase activity is required for proper spindle bipolar orientation, whose disturbance induces the continuous SAC activation and subsequent inactivation of APC/C-dependent degradation in oocyte meiosis I.

凝血因子 9 信号肽和前肽错义突变导致乙型血友病的分子机制及其潜在临床应对策略

沈国民[1,2,3] 高蒙[2,3] 曹青[2,3] 刘红丽[2,3] 沈滟[2,3] 杨海平[3]
1.河南科技大学 2.河南科技大学基础医学院
3.河南省血栓与止血国际联合实验室

目的 通过研究凝血因子 9 信号肽和前肽错义突变导致乙型血友病的分子机制，为乙型血友病的精准治疗提供指导。
方法 本研究通过构建 FIX-PC 报告基因（N 端为 9 因子的信号肽，前肽和 Gla 结构域，C 端为蛋白 C 的 C 端结构域），通过细胞实验表达报告基因，用 ELISA 方法检测培养基上清中具有 9 因子功能 Gla 结构域的报告基因蛋白和上清中总的报告基因蛋白；用 western blot 方法检测胞内蛋白的表达，成熟加工，以及 r-羧基化；另外，我们在所有突变体中，检测了维生素 K 对功能 Gla 结构域的影响。
结果 通过分析细胞培养基上清中分泌的报告基因蛋白的水平，发现这些突变体大部分减少具有功能的 Gla 结构域蛋白的分泌，这与病人中 9 因子缺陷相一致。进一步分析表明，这些突变存在不同的机制，主要包括影响 9 因子的共翻译易位到内质网上合成（I17N，L20S，L23P 和 L24P），影响信号肽的切割（A26D，C28R/R/W），影响蛋白的表达（V30I），γ-谷氨酰羧化（A37D）和前肽切割（R43W/Q/L，K45N，R46K/T/S）等。通过分析维生素 K 对功能蛋白的分泌，发现具有功能性 Gla 结构域的报告基因蛋白依赖维生素 K 的浓度，这可以很好地解释同一种突变导致不同的出血倾向。
结论 导致 9 因子信号肽和前肽的错义突变存在多种机制导致 9 因子活性下降，此外，我们还发现大部分这类突变通过口服维生素 K 可能减缓病人的出血倾向，这将为乙型血友病的精准治疗提供指导。

肿瘤标志物 MUC1 的靶向降解途径及其临床意义

廖春华、庞智、邓华云、廖晓东、李昇泽、程金科、陈国强、黄雷
上海交通大学医学院

摘要 临床研究发现 MUC1 在 70%的肿瘤中去极化高表达，水平高达正常细胞的 50-100 倍，其异常表达与肿瘤的恶性程度及预后不良密切相关。MUC1 在 90%的乳腺癌中高表达。其中，约 40%是由于 MUC1 基因拷贝数的增加导致的 MUC1 蛋白质水平的升高，另外 60%可能是转录水平以及翻译后修饰的紊乱等所致的蛋白质降解异常等。但 MUC1 蛋白的降解机制却有待阐明。通过质谱分析发现 526 个与 MUC1 互作的蛋白质，对其中参与蛋白降解调控的蛋白质进行分析，最终聚焦 WWP1（WW domain-containing ubiquitin E3 ligase 1）。我们通过基因敲除和过表达等研究策略，证明 WWP1 可降解 MUC1 蛋白。进一步研究发现 WWP1 通过 Clathrin 介导的内体-溶酶体途径调控 MUC1 的降解，激活自噬-溶酶体途径可促进 MUC1 的降解。敲低 WWP1 明显上调 MUC1 的蛋白水平从而促进肿瘤

细胞的恶性特征。此外，利用乳腺癌临床样本进行免疫组织化学（IHC）分析，发现 WWP1 与 MUC1 蛋白存在明显负相关。研究深入解析了 WWP1 调控 MUC1 降解的分子作用机制，即 WWP1 通过 WW1/2 功能域与 MUC1-CQC 基序相互作用并通过 K63 聚泛素化链调控 MUC1-K1231 的泛素化，进而催化 MUC1 的降解。进一步功能研究表明利用蛋白酶体抑制剂硼替佐米（bortezomib, BTZ）可促进 WWP1 降解 MUC1。利用体外细胞功能实验和体内移植瘤模型研究证明，当 WWP1 高表达时，BTZ 可有效降解肿瘤中的 MUC1 并抑制肿瘤的生长。总之，本研究发现了一个可降解质膜上 MUC1 蛋白的新 E3 泛素连接酶 WWP1；阐明了 WWP1 降解 MUC1 的调控机制；找到了激活 WWP1-MUC1 降解信号通路的药物 BTZ，可望为临床 MUC1 阳性肿瘤的早期预防和靶向治疗提供新靶点。（STTT, 2021）

Identification of Novel EYS Mutations by Targeted Sequencing Analysis

戴 超 Lingxi Jiang Yao Wei Weiming Ren Yi Shi
电子科技大学

Purpose Retinitis pigmentosa (RP) is an inherited and progressive degenerative retinal disease. Mutations in the eyes shut homolog (EYS) gene are a frequent cause of autosomal recessive retinitis pigmentosa (arRP). We aimed to identify the causative mutations in the eyes shut homolog (EYS) gene in a cohort of Chinese RP and rod-cone dystrophy families.
Materials and Methods Targeted next-generation sequencing was applied to identify novel mutations in these patients. Candidate variants were evaluated using bioinformatics tools. Mutations were confirmed by Sanger sequencing.
Results We identified eight heterozygous mutations in the EYS gene in the four probands, including a novel frameshift novel insertion mutation, C2439A (p.C813X). This mutation was rare or absent in the Exome Aggregation Consortium (ExAC), 1000 Genomes Project, and Genome Aggregation Database (gnomAD). This mutation had never been reported previously in RP patients and did not present in 1800 control individuals.
Conclusions Expression levels of genetically defective EYS gene transcripts in photoreceptor-directed fibroblasts of EYS-RP patients vary depending on the type of mutation. We identified one novel mutation in the EYS gene, expanding the mutational sclera of EYS in Chinese patients with RP and rod-cone dystrophy.

β-Galactosidase gene codon optimization results in post-transcriptional enhancement of expression

Shuo Tan[1] Yuan Chen[1] Yue Gao[1] Jiaping He[1] Xinbing Guo[1] Simin Zhang[1] Jingzhi Zhang[1,2] Fanyi Zeng[1,2,3]
1.Shanghai Children's Hospital, Shanghai Jiao Tong University, Shanghai Institute of Medical Genetics
2.NHC Key Laboratory of Medical Embryogenesis and Developmental Molecular Biology, Shanghai Key Laboratory of Embryo and Reproduction Engineering
3.Department of Histoembryology, Genetics & Development, Shanghai Jiao Tong University School of Medicine

Objective lacZ encodes for β-galactosidase within the galactose operon of bacterial cells. When used as a reporter gene, bacterial "β-galactosidase" expression is often insufficient for detection in mammalian cells. We intended to optimize the lacZ codon usage according to the most frequently used codons for the seven major proteins in cow's milk, in order to pave a way for the enhancement of transgenic genes expression in eukaryotes.
Results We constructed modified lacZ (named olacZ) according to optional codons used for proteins expressed in cow's milk. The expression of lacZ and olacZ was then compared in HC11 (a murine mammary gland epithelial line), 293T, HeLa, Cos7, and NIH 3T3 cells. While there was no significant difference at the mRNA level between lacZ and olacZ ($P > 0.05$). The quantification of β-galactosidase activity and in situ staining experiments showed a 1.2-fold to 3.3-fold expression improvement when comparing olacZ with lacZ. The levels of β-galactosidase expression at the protein levels from olacZ were approximately 9.2-fold and 2.4-fold respectively for Cos7 and HC11 cells. Furthermore, a 1.9-fold tendency of enhanced expression of olacZ in mammary gland during lactation was observed in transgenic-olacZ mice.
Conclusion This study demonstrates an alternative choice for improving lacZ reporter expression in eukaryotes, especially in the mammary gland of cattle or goats.

Novel mutations in ARR3 in hereditary high myopia: Next-generation sequencing technology and genotype-phenotype correlations

Yao Wei Lingxi Jiang Chao Dai Weiming Ren Yi Shi
电子科技大学

Purpose To identify one novel mutations in Arr3 in a Chinese family with hereditary high myopia(HM) by using next-generation sequencing. The aim of this study is to identify the cause of disease and provide a basis for clinical diagnosis.
Methods A total of 15 patients with Hm from a Chinese family were cured. Ophthalmological evaluations were performed in all patients. All coding regions of Arrr3 were amplified and sequenced directly. Suspected variants were verified by Sanger sequencing. Pathogenicity of the variants were searched through relevant databases and PubMed by following the ACMG guidelines.
Results We found a large Chinese family displaying female-limited early-onset high myopia. Whole exome sequencing of patients identified a novel nonsense mutation (c.682_683insA:p.I228fsX) in the ARR3 gene. We performed basic eye examinations of 15 family members, as well as detailed eye examinations including intraocular pressure, axial length, fundus appearance, optical coherence tomography, visual field examination, and color vision and electrophysiological examination.
Conclusions Our research provides more evidence to support the hypothesis that mutations in ARR3 is a disease-causing gene for hereditary-HM.

七鳃鳗血管紧张素原的抗凝药用价值初步评估

王云杰[1,2] 马晴雯[1,2] 曾凡一[1,2,3]
1.上海交通大学附属儿童医院，上海医学遗传研究所
2.上海市胚胎与生殖工程重点实验室，国家卫健委医学胚胎分子生物学重点实验室
3.上海交通大学基础医学院组织胚胎学与遗传发育学系

目的 抗凝药物的使用对于心脑血管疾病的防治以及外科手术中预防围手术期的血栓形成极为重要。目前面市的抗凝药物自身存在诸多缺陷，现阶段抗凝药物研发的重点和趋势逐渐转向特异作用于凝血级联效应中专一靶点的新型抗凝药物上。我们前期研究发现七鳃鳗血管紧张素原(Lamprey Angiotensinogen, LfAGT) 不仅可以作为七鳃鳗血管紧张素的前体蛋白作用于血压调控、体液水盐平衡等生理过程，而且在肝素作为辅因子时，能够高效特异性地抑制凝血酶 (Thrombin， TH) 的活性，但 LfAGT 抑制 TH 活性的分子机制尚不明确。本研究拟通过对 LfAGT 和人体内关键抗凝血酶 Antithrombin (AT) 关键位点 P3-P3'位 (P3-P2-P1-P1'-P2'-P3') 氨基酸残基对抑制凝血酶活性的作用异同的比较，确定其抑制凝血酶活性的分子机制，初步评估其作为抗凝药物的可能性和深入研究的价值。
材料方法 通过定点突变的方式，将 LfAGT 的 P3-P3'位氨基酸残基以逐一和组合的方式突变为 AT 相应位置的氨基酸残基。通过动物细胞表达上述重组蛋白，将纯化后的重组蛋白 LfAGT 以及其各突变体在体外有和无肝素作为辅因子参与的情况下分别与 TH 进行反应，通过 Western blot 和酶动力学等实验对各突变体在抑制 TH 活性方面的作用进行定性和定量分析，评估 LfAGT 及其各突变体作为抗凝药物进一步进行研究的价值。
结果 在肝素作为辅因子时，LfAGT P2 位脯氨酸突变后，其突变体抑制 TH 活性的速率与野生型相比下降了约 400 倍。相比较而言，P3 位的甲硫氨酸，以及单独的 P2'位的甲硫氨酸和 P3'位的脯氨酸的突变则不会对 LfAGT 抑制 TH 活性作用造成显著影响，但在 P2 位脯氨酸不变和突变后的两个蛋白中，同时突变 P2'和 P3'位的两个氨基酸残基，其抑制 TH 活性的速率相比较于突变前分别降低了约 50 和 20 倍。
结论 LfAGT P2 位的脯氨酸在抑制 TH 活性方面起关键作用，P2'和 P3'位两个位置的氨基酸组合起来对 P2 位的脯氨酸在抑制凝血酶活性方面起到关键的辅助作用。LfAGT P3–P3'中氨基酸残基的这种排列是其参与抗凝血调控的分子基础，该蛋白在作为血管紧张素分子的前体参与到血压调控的同时，不会显著抑制凝血酶的活性，在需要进行抗凝血时，其在肝素存在的情况下作为有效的凝血酶抑制剂而发挥作用，可以同时满足抗凝血和血压调控的双重需求。LfAGT 及其突变体具有作为抗凝血药物进行开发应用的价值。符合目前抗凝药物研究的发展趋势。

Association analysis of SNPs in GRHL3, FAF1 and KCNJ2 with NSCPO sub-phenotypes in Han Chinese

Jialin Sun Zhonglin Jia
West China Hospital of Stomatology, Sichuan University

Objectives Non-syndromic cleft palate only (NSCPO) is a common congenital deformity with complex etiologies. *GRHL3*, *FAF1* and *KCNJ2* have been reported to be involved in the pathogenesis of NSCPO. Up till now, there has been no replication studies based on large Han Chinese. Therefore, this study aimed to investigate associations between *GRHL3, FAF1, KCNJ2* and NSCPO sub-phenotypes patients in Han Chinese.
Material and methods Firstly, we selected 2 SNPs based on previous literatures: *FAF1* (rs3827730) and *GRHL3* (rs41268753). Also, we selected 8 tagSNPs in *GRHL3* (rs557811, rs609352, rs10903078, rs6659209, rs12401714, rs12568599, rs3887581, rs12024148) and 2 tagSNPs in *KCNJ2* (rs75855040 and rs236514). Afterwards, we evaluated these SNPs among 1668 NSCPO patients and 1811 normal controls from Han Chinese. Following data was analyzed by PLINK and Haploview program.
Results Association analysis under additive model showed that allele A at rs12568599 in *GRHL3* gene is significantly associated with NSCPO (*P*=0.0034, OR=1.38 and 95%CI: 1.11-1.72) and its

sub-phenotype incomplete cleft palate (ICP) (*P*=0.0039, OR=1.4 and 95%CI: 1.11-1.75), and it could increase the risk of both NSCPO and ICP.
Conclusions This study firstly found that rs12568599 in *GRHL3* is associated with NSCPO and ICP in Han Chinese, indicating that sub-phenotypes of NSCPO have different etiologies.

氧化应激在甲状腺功能减退导致生殖功能障碍中的作用机制研究

贺文 薛志刚 薛金峰
同济大学

氧化应激（Oxidative Stress OS）是一种由机体活性氧水平和内源性抗氧化能力之间失去平衡所引起的细胞和组织生理与病理反应。由 OS 水平升高参与的最常见的疾病包括甲状腺功能减退症等。甲状腺功能减退是一种由甲状腺激素缺乏引起的常见内分泌系统紊乱疾病，同时伴随严重的生育问题。研究发现，甲状腺在分化和发育过程中受到多种转录因子和复杂基因网络的调控；其中，甲状腺过氧化物酶（TPO）的表达驱动甲状腺滤泡形成与功能分化的最后阶段。因此，本课题利用 CRISPR/Cas 技术构建首例 *Tpo*$^{-/-}$敲除先天性甲减大鼠模型，并通过单细胞转录组测序技术对该突变大鼠睾丸进行分析与体外验证，研究 OS 在甲减导致的生殖功能障碍中具体影响机制。
目的 探究 OS 在 *Tpo*$^{-/-}$先天性甲减大鼠导致雄性不育中的作用机制。
材料与方法 为证明先天性甲减大鼠模型成功构建，我们对 8-10 周 *Tpo*$^{-/-}$大鼠与野生型大鼠进行对比，检测大鼠体重、实质器官重量比和甲状腺的大小；同时，通过 HE 染色观察甲状腺的组织结构以及利用酶联免疫（ELISA）方法测量血清中甲状腺激素 fT3、fT4、促甲状腺激素（TSH）的水平。为明确 *Tpo* 基因突变对大鼠雄性生殖系统的影响，利用 ELISA 测定血清中性激素含量，同时通过 HE 染色观察下丘脑、垂体，以及睾丸组织内部结构发育，并进一步对睾丸组织内 OS 水平进行测定；同时利用单细胞转录组测序技术对睾丸生精细胞进行分析，并在体外分离原代生殖细胞对分析结果进行验证。以期明确 OS 在先天性甲状腺功能减退导致的雄性生殖障碍中的作用机制。
结果 1.*Tpo*$^{-/-}$先天性甲状腺功能减退大鼠模型构建成功。

2. *Tpo*$^{-/-}$大鼠性激素水平降低并伴有雄性不育，且睾丸组织内氧化应激水平升高。

3. 单细胞转录组测序分析并鉴定出 21 个睾丸组织主要细胞 Cluster。其中，支持细胞所占比例在 *Tpo*$^{-/-}$大鼠睾丸中明显增多，同时两组间差异基因表达比较显示与 OS 相关 GO-Term 在支持细胞下调表达基因中高度富集；此外，与精子生成相关 GO-Term 在支持细胞两组差异表达基因中均出现富集。

5. qRT-PCR 鉴定体外分离培养原代支持细胞显示，抗 OS 基因在 *Tpo*$^{-/-}$中表达显著下调；同时参与并维持精原干细胞分化的基因表达明显下调。
结论 甲状腺功能减退引起的睾丸组织支持细胞内 OS 水平的升高抑制了促进精原干细胞分化相关基因表达，进而阻碍了精原干细胞向成熟精子的分化，影响成熟精子的形成与睾丸发育。

SLC44A2 frequency and a new TaqMan Real-time Polymerase Chain Reaction method for HNA-3A / 3B genotyping and using droplet digital PCR to screen for rare HNA-3B blood donors

Yufeng Wang Yuanming Wu
The Fourth Military Medical University

Background CTL2 blood group system, single nucleotide polymorphism in exon 7 of CTL2 gene (*SLC44A2*), the substitution of the base between SNP rs2288904 (c.461G＞A) forms the HNA-3A and HNA-3B antigens. HNA-3 antibodies may be produced when exposed to HNA-3 antigens due to blood transfusion or other factors, and cause transfusion-related acute lung injury (TRALI) and neonatal alloimmune neutropenia (NAIN). In this study, we designed specific primers and probes for allelic polymorphisms and established a sensitive and specific method for HNA-3

genotype screening using TaqMan PCR. Considering of the high sensitivity and accuracy of droplet digital PCR in the identification of rare *SLC44A2*2* allele, we used this technique to find blood donors with rare HNA-3B antigen.
Study design and methods Purified DNA from 208 individuals was collected. TaqMan real-time polymerase chain reaction assays were developed to detect all samples. Results were confirmed by Sanger sequencing. Rare HNA-3B antigens were detected by droplet digital PCR.
Results In 208 northwest Chinese donors, the allele frequency of SLC44A2*1and SLC44A2*2 was 64.9% (59% to 70.8%; 95% confidence intervals, Poisson distribution) and 35.1% (29.2% to 41%) respectively. SLC44A2*2 allele was accurately detected in all pools containing SLC44A2*1:1 sample and in the pool including one SLC44A2*1:2 sample.
Discussion In this study, a new method was established to detect the SLC44A2 alleles and its sensitivity and specificity were verified by Sanger sequencing. Furthermore, rare HNA-3B antigen was successfully detected by droplet digital PCR using the probe we designed.

PAX7 与中国西部汉族人群非综合征型唇腭裂发生相关

杨成位 贾仲林
四川大学华西口腔医学院

目的 PAX7 已被认为是非综合征型唇腭裂发病相关的候选基因，一些已发表的研究已经得出结论认为 PAX7 基因突变与非综合征型唇腭裂发生相关。但 PAX7 基因与中国西部汉族人群非综合征型唇腭裂的发生关系尚不清楚，本研究旨在探讨 PAX7 基因突变在中国西部汉族人群非综合征型唇腭裂中的作用。
材料和方法 在初始筛选研究中，招募了来自四川大学华西口腔医院唇腭裂外科的 159 名非综合征型唇腭裂患者，经外周静脉血采集并提取全基因组 DNA，对 DNA 进行了靶向区域测序，并以 Novogene 内部数据库（http://www.novogene.com/）中 542 名正常个体的全基因组测序数据作为对照，进行关联分析研究。在第二阶段验证实验中，从本课题组先前的 GWAS 中获得了验证样本的基因型数据进行卡方分析。
结果 结果显示 rs12141930 与非综合征型唇裂伴或不伴腭裂（NSCL/P）、非综合征型唇腭裂（NSCLP）和非综合征型单纯唇裂（NSCLO）发病显着相关。Rs192878265 和 rs2236804 与 NSCL/P 和 NSCLP 相关，而其他五个 SNP（rs77336960、rs35836654、rs764289、rs12035204 和 rs2236810）仅与 NSCLP 发病显着相关。此外，在测序过程中，在一个有唇腭裂家族史的家庭中发现了位于 PAX7 上的一个新变体位点 NM_002584.2:c.1106C>T。
结论 本研究发现了 PAX7 上的 8 个 SNP 与中国西部汉族人群的非综合征型唇裂伴或不伴腭裂（NSCL/P）、非综合征型唇腭裂（NSCLP）和非综合征型单纯唇裂（NSCLO）显着相关，并发现了位于 PAX7 基因上的一个新突变位点。PAX7 是中国西部汉族人群非综合征型唇腭裂发生的易感基因。

基于非编码 RNA 编码的新蛋白质作为 EGPA 早期诊断的新生物标志物研究

卢少华 龙飞 彭涛
广州医科大学

目的 嗜酸性肉芽肿性血管炎（EGPA）早期症状与哮喘非常相似，容易被误诊为哮喘。目前尚未有特异性指证 EGPA 早期诊断的分子生物标志物。本研究的目的是从非编码 RNA 编码的新蛋白质中筛查可用于 EGPA 早期诊断以及鉴别诊断 EGPA 患者和哮喘患者的新生物标志物。
方法 首先使用定量蛋白质组学方法从 10 名健康对照、12 名哮喘患者和 23 名 EGPA 患者血清中鉴定差异表达蛋白质，并通过生物信息学方法筛选出由非编码 RNA 编码的新蛋白质作为候选生物标志物；其次，使用靶向定量蛋白质组学方法在 15 名健康对照、21 名哮喘患者和 35 名 EGPA 患者

血清中验证候选标志物；第三，使用 ELISA 实验手段再次验证候选标志物；最后，结合临床价值评估分析，确定可能的新的生物标志物。
结果 我们一共鉴定到 14 个由非编码 RNA 编码的新蛋白质在三组样本中存在表达差异。为筛选差异表达蛋白，我们以 P-value≤0.05 和差异倍数为 1.2 倍为阈值，通过分析，我们发现 EGPA 组和健康组有 10 个差异表达蛋白，其中 5 个表达上调，5 个表达下调，提示这些新的蛋白可能作为 EGPA 早期诊断的生物标志物。此外，EGPA 组与哮喘组有 9 个差异表达蛋白，其中 2 个蛋白表达上调，7 个蛋白表达下调。这个结果提示这些新蛋白可能作为 EGPA 和哮喘鉴别诊断的生物标志物。
结论 综上所述，我们的研究结果首次聚焦于由非编码 RNA 编码的一类"新蛋白质"，目的是筛选和确认特异性指证 EGPA 早期诊断以及鉴别诊断哮喘的生物标志物。此外，以非编码 RNA 编码的新蛋白为聚焦点的研究策略为疾病生物标志物研究和靶向药物研究提供了新的视角。

结直肠癌蛋白丙二酰化的表观遗传学研究

秦娟 张巍 林列文 夏利刚 曾志鹏 蔡晚霞 王威 钟雅芳 王沙燕 汤冬娥 戴勇
深圳市人民医院

目的 探讨蛋白丙二酰化在结直肠癌中的表观遗传学作用。
方法 使用定量蛋白质组学和串联质谱 (LC-MS/MS) 的方法来鉴定结直肠癌组织和癌旁组织之间的差异表达蛋白和差异丙二酰化蛋白。
结果 我们在结直肠癌组织和癌旁组织之间鉴定了它们的差异表达蛋白和差异表达的丙二酰化蛋白。下调的丙二酰化蛋白和丙二酰化位点明显多于上调的蛋白及位点。基于 KEGG 通路的富集分析显示，下调的丙二酰化蛋白在糖异生、氨基酸生物合成和磷酸戊糖通路中显着富集。
结论 差异表达的丙二酰化蛋白可能有助于揭示结直肠癌发病的表观遗传学机制。下调的丙二酰化蛋白可能是结直肠癌的潜在生物标志物。

Gadd45g initiates embryonic stem cell differentiation and inhibits breast cell carcinogenesis

Xinbao Zhang Shoudong Ye
Anhui University

Purpose To identify the genes that direct embryonic stem cells (ESCs) exit from pluripotency and regulate tumor development.
Methods The expression of Gadd45 family members, including Gadd45a, Gadd45b and Gadd45g, were examined by qRT-PCR during mouse ESC differentiation. Next, we regulated Gadd45g expression in mouse ESCs and used high-throughput sequence to screen the downstream mechanism. Finally, the function of Gadd45g was investigated in breast cancer cells.
Results The transcripts of Gadd45 genes were increased upon mouse ESC differentiation. Upregulation of Gadd45 members decreased cell proliferation and induced endodermal and trophectodermal lineages. In contrast, knockdown of Gadd45 genes delayed mouse ESC differentiation. We focused on Gadd45g and mechanism studies revealed that Gadd45g activated FGF/ERK signaling. Therefore, inhibition of FGF/ERK signaling eliminated the differentiation phenotype caused by Gadd45g upregulation. Meanwhile, enforced expression of GADD45G significantly inhibited tumor formation and breast cancer metastasis in mice through limitation of the propagation and invasion of breast cancer cells.
Conclusion Gadd45g is a differentiation and anti-tumor gene. These results will expand our understanding of the regulatory network of ESCs.

基于 16S rDNA 高通量测序分析微生物群落用于皮肤部位溯源的初步探索

梁晓敏
南方医科大学

目的 不同皮肤部位的溯源对于案件现场重建有重要意义，但尚无有效的方法，本研究拟基于微生物标记探索不同皮肤部位溯源的新方法。方法 依据采样标准，采集 10 名男性个体手掌、肚脐、腹股沟和脚掌的皮肤擦拭物，采用 16S rDNA 高通量测序对上述 40 份皮肤样本进行检测，生物信息学方法分析样本微生物群落信息，LEfSe 等统计方法分析各皮肤部位分组的微生物差异。结果 手掌、肚脐、腹股沟和脚掌擦拭物的细菌分别归于 41、40、10 和 21 个属。手掌和肚脐部位的细菌多样性高于腹股沟和脚掌。LEfSe 分析显示 4 个皮肤部位的细菌在属水平上存在显著差异，丰度排名前 5 的细菌分别是：手掌为丙酸菌属（Propionibacterium）、链球菌属（Streptococcus）、罗斯氏菌属（Rothia）、水栖菌属（Enhydrobacter）、微球菌属（Micrococcus），肚脐为丙酸杆菌属（Propionibacterium）、水栖菌属（Enhydrobacter）、短波单胞菌属（Brevundimonas）、嗜冷菌属（Psychrobacter）、伯杰氏菌属（Bergeyella），腹股沟为棒杆菌属（Corynebacterium_1）、皮杆菌属（Dermabaccter）、硝化杆菌属（Bosea）、气单胞菌属（Aeromonas）、代尔夫特菌属（Delftia），脚掌为葡萄菌属（Staphylococcus）、Pseudorhodoferax 属、小梨形菌属（Pirellula）、鞘丝藻属（Leptolyngbya）、热球菌属（Jeotgalicoccus）。基于 Bray－Curtis 距离的 PCoA 结果显示手掌和肚脐的个别样本出现交叉混杂，其他分组样本均能明显区分。结论 手掌、肚脐、腹股沟和脚掌的皮肤优势菌存在显著差异，主成分分析可大致区分四个部位的皮肤样本，但无法很好地区分手掌和肚脐部位，通过加大样本量并结合人工智能模型深入研究，有望实现精细区分。

染色体与 ART 研究进展

张倩[1] 刘春莲[2] 闫慧[1]
1.宁夏医科大学
2.宁夏医科大学总医院

研究目的 筛选因染色体异常行 ART 助孕的不孕症夫妇，分别从染色体嵌合类型、嵌合程度以及染色体多态性对妊娠结局的影响三个方面进行综述。
方法 由第一作者应用计算机检索 PubMed 等多个数据库 2010 至 2020 年收录的相关文献。筛选标题和摘要，查阅全文，最终保留 15 篇文献进行仔细阅读分析。
结果 ①性染色体嵌合患者中与胚胎相关的染色体异常的风险非常低，而常染色体结构异常的嵌合患者发生异常胚胎的风险较高。因此对于性染色体拷贝数异常的嵌合患者不推荐使用 PGT，建议 PGT 用于常染色体结构异常的嵌合患者，尤其是在 16q22 处具有脆弱部位。②嵌合胚胎能发育成健康的整倍体子代，成功率与嵌合程度有关，对于无整倍体胚胎可移植的患者，可以考虑移植嵌合胚胎，优先移植嵌合百分比<40%的胚胎。③inv（9）与胚胎染色体异常风险的增加无关，但 inv（9）有增加其他染色体异常的趋势，且可能影响胚胎种植，导致 RSA 风险增加。④在 IVF 周期中，男性染色体多态性会显著降低累积活产率，增加早期流产率。
结论 染色体异常严重影响辅助生殖技术的妊娠结局，应针对每一位患者制定个体化治疗方案。

A Novel frameshift mutation in FMRI causes Fragile X syndrome

Hui Hu Jiao Liu Xiaofang Lan Penglong Chen
Lishui Maternity and Child Health Care Hospital

Background Fragile X syndrome (FXS) is the most common monogenic genetic disorder of mental retardation and loneliness spectrum disorders. Most FXs are caused by the repeated amplification of a CGG triplet nucleotide sequence at the 5' terminal of FMR1 gene. Although the frameshift mutation of FMRI is rarely reported, it has been shown to be related to FXS. This study describes a newly discovered FMR1 missense mutation in a Chinese family with FXS phenotype.
Methods Use whole-exome sequencing (WES) to screen for pathogenic genes in the FXS family with X-linked incomplete penetrance. The potential variants identified by targeted WES were verified by Sanger sequencing and classified according to the American College of Medical Genetics and Genomics standards and guidelines.
Results A novel hemizygous frameshift variant of FMR1 (c.585_586del) was identified by WES and Sanger sequencing.
Conclusions This study supports the view that the frameshift mutation of FMR1 may cause the FXS phenotype.

FLNA 基因突变导致的耳腭指综合征 家系遗传学分析

胡辉 刘姣 张向东 程晓燕 张智
丽水市妇幼保健院

目的 采用高通量测序技术探讨一个与 FLNA 基因突变相关的 X 连锁遗传的耳腭指综合征家系的遗传学原因。
方法 三维 B 超显示胎儿“小脑发育不良、面部畸形、胸廓发育不良、四肢畸形”。应用全外显子组测序对夫妻双方及胎儿进行致病位点筛查，并对孕妇父母及孕妇弟弟、大女儿通过 Sanger 测序对突变位点进行验证。
结果 全外显子组测序结果显示胎儿 FLNA 基因的 35 号内含子存在一个半合子突变 c.5686+4A>G，孕妇本人为杂合携带者并且为新发突变。先证者临床症状与 FLNA 基因突变相关的 X 连锁显性遗传的耳腭指综合征 2 型（OPD2）疾病表型相符。
结论 FLNA: c.5686+4A>G 突变很可能为该 OPD2 家系患者的遗传学病因，该位点未被报道，新的突变位点丰富了 FLNA 基因突变谱。

丽水市婴幼儿遗传性耳聋流行病学调查

雷永良
丽水市妇幼保健院

目的 通过耳聋基因检测，了解丽水市遗传性耳聋基因突变的发生率以及热点基因突变，探讨在丽水市开展遗传性耳聋基因检测的必要性和意义。
方法 收集 2019 年 5 月-2019 年 12 月在丽水市采集的 11 774 份婴幼儿足跟血血片样本并提取 DNA，应用厦门致善生物科技股份有限公司的遗传性耳聋基因检测试剂盒检测 4 个常见耳聋基因的 15 个突变位点。
结果 11 774 份临床样本中，共检测出耳聋基因异常者 535 例（4.54%），其中携带 *GJB2* 基因突变占 2.67%，携带 *GJB3* 基因突变占 0.25%，携带 *SLC26A4* 基因突变占 1.24%，携带线粒体基因突变占 0.38%。*GJB2* 基因的 c.235delC 杂合突变（2.08%）及 *SLC26A4* 基因的 c.919-2A>G 杂合突变（0.93%）为丽水市的两大热点突变。

结论 遗传性耳聋基因突变在丽水市婴幼儿中具有较高的发生率，且以 *GJB2* 基因突变和 *SLC26A4* 基因突变为主。因此，该地区应将遗传性耳聋检测纳入遗传咨询、产前诊断以及婴幼儿筛查中，从而有效降低耳聋的发生。

7 例遗传性凝血因子 XI 缺陷症患者的基因型与临床表型分析

翁妙珊 林芬
潮州市中心医院

目的 分析 7 例遗传性凝血因子 XI（FXI）缺陷症患者的基因突变类型与临床表型。
方法 采用一期法检测患者 FXI 活性（FXI：C），免疫火箭电泳法检测 FXI 抗原（FXI：Ag）水平，并抽提患者外周血 DNA，PCR 扩增患者 FXI 基因所有的外显子及其侧翼序列，DNA 直接测序进行基因分析。
结果 在 7 例遗传性 FXI 缺陷症患者中共发现 5 种基因突变，包括 3 种无义突变（p.Lys327X、p.Tyr351X、p.Gln263X），1 种移码突变（p.Leu424fsX10）和 1 种剪接位点突变（c.326-1G>A）；除患者 7 为单杂合突变，FXI：C 为 56.7%，FXI：Ag59.2%，其余患者 FXI：C 和 FXI：Ag 均明显降低（<2% 和<1%），基因型为纯合突变或复合杂合突变；患者临床出血表现轻重不一，患者 1、2 均有术后出血不止的表现，而患者 5 则无术后出血表现。
结论 所发现的 5 种基因突变是导致 7 例遗传性 FXI 缺陷症患者的分子发病机制，其中 p.Gln263X 较常见，p.Lys327X 为新发现的 FXI 基因突变类型，而 FXI：C 与患者的临床表型之间无明显相关性。

Functional analysis of ectodysplasin-A mutations and involvement of X-chromosome inactivation

Yuhua Pan[1,2] Fu Xiong[1] Buling Wu[2]
1.Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University
2.Department of Stomatology Southern Medical University,

Objectives The aim of the study was to identify genetic clues for the causes of familial non-syndromic oligodontia and explore the underlying mechanisms involved, while focusing on the role of human dental pulp stem cells (hDPSCs).
Methods The candidate genes sequences were obtained by PCR amplification and Sanger sequencing. Functional analysis was conducted, and the pathogenesis associated with *EDA* mutations in hDPSCs was investigated to explore the impact of the identified mutation on the phenotype. Capillary electrophoresis (CE) was used to detect X chromosome inactivation (XCI) in the blood of female carriers.
Results In this study, we identified an *EDA* mutation in a Chinese family：the missense mutation c.1013C>T (Thr338Met). Transfection of hDPSCs with a mutant EDA lentivirus decreased the expression of EDA and dentin sialophosphoprotein (DSPP) compared with transfection of control EDA lentivirus. Mechanistically, mutant EDA inhibited the activation of the NF-κB pathway. The CE results showed that symptomatic female carriers had a skewed XCI with a preferential inactivation of the X chromosome that carried the normal allele.
Conclusions In summary, we demonstrated that *EDA* mutations result in non-syndromic tooth agenesis in heterozygous females and that, mechanistically, EDA regulates odontogenesis through the NF-κB signalling pathway in hDPSCs.

Susceptible gene variation in severe neonatal hyperbilirubinemia: five case reports

Fen Lin
Central Laboratory, Chaozhou Central Hospital Affiliated to Southern Medical University

Background Neonatal hyperbilirubinemia is a common problem faced by pediatricians. The role of genetic factors in neonatal jaundice has been gradually recognized. This study aimed to identify genetic variants which influence the bilirubin level in five representative cases by next-generation sequencing (NGS).
Case presentation We present five neonates with severe hyperbilirubinemia, they exhibited bilirubin encephalopathy, hypothyroidism, ABO hemolysis, glucose-6-phosphate dehydrogenase (G6PD) deficiency and premature, respectively. A customed 22 genes panel was designed and NGS was carried out in the neonates.Eight variations (G6PD c.G1388A, HBA2 c.C369G, SPTB c.A1729G, ABCC2 c.C3825G, UGT1A1 c.G211A, EB41c.G520A, c.1213-4T>G and c.A1474G) were identified in five patients, which involved in genetic mutations associated with hereditary elliptocytosis, thalassemia, Gilbert syndrome, G6PD deficiency and Dubin-Johnson Syndrome.One of the patients was found with variants combined EPB41 splice site c.1213-4T>G and c.G520A (p.E174K) mutation but no elliptocytewas seen on his blood smear.
Conclusions Pathological factors of severe neonatal hyperbilirubinemia were very complicated, genetic variants may play an important role for an increased risk of neonatal hyperbilirubinemia, and severe jaundice in neonates may be potentially related to the cumulative effect of genetic variants.

PAX6 基因新的杂合移码突变致先天性虹膜缺损合并先天性白内障家系遗传分析

易浩安[1] 顾静[3] 查旭[2] 孔艳波[2] 江伟阳[1] 杨芳[1] 李凡[1] 何永蜀[1]
1.昆明医科大学
2.昆明医科大学第二附属医院
3.云南省残疾人康复中心

目的 研究一个先天性虹膜缺损合并先天性白内障家系的致病基因及遗传方式。
方法 对 2020 年 2 月就诊的一个先天性虹膜缺损合并先天性白内障家系进行临床眼科检查诊断，收集先证者及 5 个亲属全血，提取基因组 DNA。对先证者及丈夫进行全外显子组测序，使用生物信息学分析方法定位可疑致病基因，随后对所有收集样本进行 Sanger 测序验证，确定致病基因及突变位点。
结果 先证者全外显子组测序结果显示 *PAX6* 基因第 8 外显子有 1 个新的杂合移码突变 PAX6:c.415dupA,p.R139fs，该突变在各个物种间高度保守，生物信息学预测突变使蛋白质发生截短并丧失功能。针对此位点的 Sanger 测序结果表明先证者及两名同患此病的子女都携带有该突变，均为杂合子，家系中健康人没有检测到此突变，表明该突变与疾病表型共分离，确定此疾病由 *PAX6* 基因新的移码突变所致。
结论 我们的研究显示 *PAX6* 基因新的杂合移码突变 c.415dupA,p.R139fs 是导致该家系出现先天性虹膜缺损合并先天性白内障的原因。先证者的父母没有发现该突变，也没有该病的临床表型，提示这一新突变为新发突变，遗传方式为常染色体显性遗传。

GFPT1 基因复合杂合突变引起的先天性肌无力综合征

刘思文 姜艳芳
吉林大学第一医院

目的 鉴定 1 例先天性肌无力综合征患者的致病基因并分析突变带来的疾病表型。
方法 对先证者及其父母进行家系全外显子组分析,并用用一代测序进行验证。
结果 发现两种杂合错义突变(c.331C>T;p。Arg111Cys c.1428G > C;p.Lys476Asn)。GFPT1 基因编码谷氨酰胺-果糖-6-磷酸转氨酶 1，在这例常染色体隐性遗传的 CMS 患者中， c.1428 g > C;p.Lys476Asn 是一个以前没有文献报道过的新的突变体，在 ClinVar 数据集和 gnomAD 全球人口数据集中也没有记录过。我们在此报告 1 例患有 CMS 的患者的遗传变异和临床随访。先证者表现为肢体无力，在肢体活动后症状加重。此外，在先证者中，重复性神经刺激可导致肌肉动作电位下降。因此，最初怀疑是重症肌无力，但他从未出现眼睑下垂和视力模糊。先证者的表型与既往关于 CMS 和 TAs 的报道一致。
结论 本研究为 CMS 患者提供了一个新的 GFPT1 基因突变。本研究为 CMS 患者的诊断和治疗提供了重要信息。

基因分析联合免疫印迹 Western blot 技术鉴定 ACADVL 基因新发突变位点的致病性

王彦云
南京市妇幼保健院

目的 探讨基因分析联合免疫印迹（Western blot）技术在极长链酰基辅酶 A 脱氢酶缺乏症（VLCADD）基因新发突变位点致病性鉴定中的临床应用。
方法 收集 2017 年 6 月 1 日至 2020 年 10 月 31 日南京市新筛中心筛查的 290738 例遗传代谢病筛查样本中，通过串联质谱检测疑似极长链酰基辅酶 A 脱氢酶缺乏症的 4 例患儿及家属采集外周血进行基因分析，并用 Western blot 检测外周血中极长链酰基辅酶 A 脱氢酶表达量变化。
结果 4 例患儿通过基因分析被诊断为 VLCADD，共检测到 8 个突变位点（2 个疑似致病变异，5 个临床意义不明，1 个位点为首次报道）。4 个家系共计 12 个外周血样本通过 Western blot 均能检测到极长链酰基辅酶 A 脱氢酶蛋白的表达，但患儿的目标蛋白表达量均明显低于其父母。家系 1 的外周血样本保存时间较另外 3 个家系长，极长链酰基辅酶 A 脱氢酶蛋白在家系 1 的亲属检测中明显低于另外 3 个家系。对比与家系 1 外周血保存时间基本一致的非 VLCADD 家系 5 中，内参 ACTIN 蛋白表达量也出现明显下降。
结论 疑似 VLCADD 患儿的 ACADVL 基因检测的位点为临床意义不明时，建议使用新鲜的外周血样本，通过 Western blot 完善极长链酰基辅酶 A 脱氢酶蛋白检测，该结果与基因检测结果可互为补充。

10q22.3q23.3 微缺失综合征合并高甲硫氨酸血症 1 例并文献复习

王彦云
南京市妇幼保健院

目的 探讨 10q22.3q23.3 微缺失综合征合并高甲硫氨酸血症的临床特征。
方法 回顾分析 1 例 10q22.3q23.3 微缺失综合征合并高甲硫氨酸血症患儿的临床资料。
结果 患儿男性，特殊面容，额突出，鼻根低，眼距宽，内眦赘皮，鼻头轻度上翘，人中浅，耳位低，余未见特殊异常。患儿于出生后 72 小时行串联质谱检测，蛋氨酸（MET）306.02 μmol/L ,召

回复查 MET 升至 695.37 μmol/L。家系验证分析显示，患儿父亲为 10q22.3q23.2 微缺失综合征，其缺失性 CNV 为自发突变（de novo），患儿母亲携带 *MAT1A* 基因 c.74_75delTG（p.Val25GlyfsX7）杂合变异。患儿最终确诊基因型为 10q22.3q23.2 deletion/c.74_75delTG（p.Val25GlyfsX7），为 10q22.3q23.3 微缺失综合征合并高甲硫氨酸血症。确诊后，患儿给予低蛋氨酸饮食联合康复训练，但患儿家属依从性差，MET 控制在 700 μmol/L 左右，肝功能无异常，大运动发育无异常，语言发育迟缓。

结论 报道首例 10q22.3q23.3 微缺失综合征合并高甲硫氨酸血症；10q22.3q23.3 微缺失综合征外显不全，预后差异较大；MET 超过 600 μmol/L 需尽早予以低蛋氨酸饮食治疗。

Loss-of-Function Variants Within LMOD1 Actin-binding Site 2 Cause Pediatric Intestinal Pseudo-obstruction by Impairing Protein Stability and Actin Nucleation

Keqiang Liu Lina Lu Shanshan Chen Beilin Gu Hui Cai Ying Wang Wei Cai
Division of Pediatric Gastroenterology and Nutrition, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine

Pediatric intestinal pseudo-obstruction (PIPO) is a severe gastrointestinal motility disorder occurring in infants and children caused by defected contractility of visceral smooth muscle. Several genes have been associated with visceral myopathy in the last decade, which in turn greatly promoted our understanding of the diseases. However, the overall genetic basis of visceral myopathy has not been well‐characterized. A homozygous nonsense mutation in LMOD1 was recently identified in a patient with megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS). Here we described a male infant with primary PIPO presenting abdominal distention, recurrent diarrhea, intestinal malrotation and severe malnutrition, but no signs of megacystis and microcolon, harboring two compound heterozygous missense variants both affecting highly conserved amino acid residues within the actin-binding site 2 (ABS2) domain of LMOD1 (NM_012134.2:c.1106C>T, p.T369M; c.1262G>A, p.R421H). Over-expression analysis revealed significantly reduced protein amounts of both mutant LMOD1 proteins, especially for p.T369M, which was reversed by addition of proteosome inhibitor MG-132, indicating damaged stability of mutant proteins, at least partially, through proteasome-mediated degradation. Molecular modeling and actin polymerization assay showed that variant p.R421H weakened ABS2-actin intermolecular interaction, thereby resulting in decreased nucleation activity of purified ABS2 and ABS2-C proteins. In conclusion, this study reports the second patient carrying biallelic loss-of-function variants in LMOD1, further supporting LMOD1 as a pathogenic gene underlying MMIHS/PIPO, strengthens the critical role of ABS2 in LMOD1-mediated actin nucleation, and additionally reveals an unrecognized role of ABS2 in protein stability.

罕见 HBA2:c.2T>C 突变血红蛋白 H 病案例家系分析

罗世强[1] 陈杏园[2] 唐宁[1] 黄钧[1] 陈丽竹[1] 钟青燕[1] 王秋华[1] 严提珍[1]
1.柳州市妇幼保健院
2.广西区人民医院

目的 对 1 例罕见 *HBA2*:c.2T>C 突变复合东南亚型缺失共遗传的血红蛋白 H 病的病例及其家系成员进行致病基因分析，了解 *HBA2*:c.2T>C 突变与表型的关系。

方法 采集家系成员外周血进行血细胞分析及毛细管电泳血红蛋白分析，同时采用缺口 PCR（Gap-PCR）、反向点杂交法（RDB）检测 α-globin 基因缺失和重复，采用 Sanger 测序法对 HBA1(α1-globin)和 HBA2(α2-globin)基因序列分析。

结果 先证者检测出 α-地贫--^{SEA}/αα 东南亚型缺失型和 *HBA2* 基因起始密码子 *HBA2*:c.2T>C（p.Met1Thr）突变，在先征者母亲中检测出 *HBA2*:c.2T>C（p.Met1Thr）杂合子突变，父亲检测出--^{SEA}/αα 东南亚型缺失型。
结论 *HBA2*:c.2T>C（p.Met1Thr）杂合子突变可表现为表现为静止型 α-地贫，小细胞低色素性贫血，与东南亚型 α 地中海贫血共同遗传可表现为中间型 α-地贫，报道 *HBA2*:c.2T>C 突变复合东南亚型缺失共遗传对 α-globin 基因表达和对临床表型的影响数据，这有助于指导临床诊断、人群筛查和遗传咨询。

耳聋甲发育不全相关综合征的基因型表型研究进展

高雪[1,2] 戴朴[2] 袁永一[2]
1.火箭军特色医学中心 2.中国人民解放军总医院

目的：耳聋甲发育不全相关综合征包含 DDOD 综合征，DOORS 综合征以及 ZLS 综合征，以上三个综合征临床表现相似，致病基因有重叠，为临床精准诊断带来巨大挑战。
方法：基于本课题组多年来针对 DDOD 综合征系统研究，对目前国际上报道的耳聋甲发育不全相关综合征进行临床表型及基因型的总结，对涉及的信号通路进行整理。
结果：DDOD 综合征主要临床表现为耳聋、甲发育不全，致病基因为 ATP6V1B2；DOORS 综合征主要临床表现为耳聋、甲发育不全、骨发育不全、智力障碍及癫痫，致病基因包括 ATP6V1B2，TBC1D24；ZLS 综合征主要临床表现为牙龈肿大，特征性面部改变，指骨或指甲发育不全，智力障碍等，致病基因包括 KCNH1,KCNN3。耳聋甲发育不全相关综合征临床表型异质性高，相同突变可能引起不同表型。
结论：耳聋甲发育不全相关综合征多为罕见病，尽管关于以上疾病的认识需要积累更多病例、更长时间的随访以及深入的功能研究，但基于已有研究发现的归纳对于更好理解这些综合征的致病机制、确定研究方向有重要意义。遗传学检测对于表型重叠的综合征诊断是推荐的，然而，对于此类疾病的诊断是以临床症状为主还是以基因检测结果为主仍存在争议。本研究以期为该类疾病的诊断及鉴别诊断提供思路及思考。

不良环境因素致新发遗传疾病 1 例报道

张倩[1] 闫慧[1] 刘春莲[2]
1.宁夏医科大学
2.宁夏医科大学总医院

早在 1997 年美国国立健康科学研究所（NIEHS）率先提出了环境基因组计划，其目的是研究具遗传多态性的不同个体多环境致病因素的易感性差异，绝大多数人类疾病是遗传易感性和环境因子相互作用的结果。遗传疾病不仅与基因和表观遗传学有关，环境因素与遗传疾病之间也有密切的关系。现对我中心筛选出的环境-遗传学案例进行汇报：
一、临床资料及方法：
1.病史概述
患者沙某，男，7 月，主因“胎儿 B 超提示心脏横纹肌瘤 7 月余”就诊我院生殖医学中心遗传咨询门诊。入院前已完善头颅 MRI、胃十二指肠及腹部彩超、泌尿系 B 超均未见明显异常。心电图提示：窦性心动过速。心脏彩超：心包脏壁层分离，其中左室后壁下见 2-3mm 液性暗区，右室腔内侧壁基底段见大小约 7*5mm 高回声团附着，左心腔未见明显异常。诊断：右心室腔异常回声附着、心包积液（微量）。否认家族遗传病史，父母工作环境系高压。
2. 检测方法
抽取其外周血 2ml，使用靶向捕获技术+高通量测序方法对人类基因组中约 2 万个基因的外显子区域以及上下游 20bp 进行检测。
二、检测结果

本次送检样本中检出 1 个与受检者提供的临床资料信息相关的可能致病性变异：TSC2 基因（NM-000548.4）外显子 40 中出现杂合的错义突变，即 c.5138G>A，导致蛋白编码在 1713 位精氨酸有组氨酸取代，该变异在 ClinVar、HGMD 数据库中均报道为致病性。基因相关疾病：结节性硬化症 2 型（AD）。

三、讨论：

环境表观遗传学在调节表型形成或疾病病因方面具有重要作用。传统遗传研究是把重点放在 DNA 分子上，即 DNA 分子将遗传物质从父母传递给子代。而现在有大量研究表明环境因素可以通过改变遗传物质从而影响后代的表型。还可以通过配子表观遗传诱导亲本的改变并影响后代的表型。根据此次检测结果及家系 Sanger 验证结果，受检者携带的 TSC2 基因 c.5138G>A 杂合变异在此家系中为新发变异，再发风险低，但不排除患儿父母之一为生殖腺嵌合可能。*TSC2* 相关疾病为结节性硬化症 2 型，其是一种常染色遗传多系统疾病，源于外胚层的发育异常所致。而患儿表型高度符合结节性硬化症。仔细询问病史，否认家族遗传病史，患儿父母工作环境为高压环境，推测患儿变异可能与父母工作环境有关。并且有研究表明特定暴露与种系 DNA 突变之间存在关系。当环境因素永久性地改变生殖系表观基因组时，这些环境改变的表型和疾病的表观遗传学跨代遗传就可能发生。因此建议患儿父母再次准备受孕前，常规给予优生优育指导，建议夫妇双方脱离工作环境半年以上，并在孕前严密产前监测，确保生育健康宝宝。

一例新生儿期起病的先天性全身型脂肪营养不良综合征患儿临床及遗传学分析

聂云亚 陈晓红
武汉儿童医院

摘要：目的：探讨 1 例先天性全身型脂肪营养不良综合征 2 型患儿的临床及基因变异特点。方法：收集患儿的临床资料，采集患儿及其父母的外周血样，应用二代测序技术对患儿进行全外显子组分析，用 Sangcr 测序验证候选变异及其来源。结果：患儿，女，23 天，主要表现为高血糖、高甘油三酯、高胰岛素血症，腹部 CT 提示肝肿大并脂肪肝，2 月龄后出现皮下脂肪消失、四肢多毛。全外显子组测序发现患儿 BSCL2 基因存在母源 c.565(exon5)G>T 及父源 c.793(exon7)G>T 复合杂合变异，二者均可能导致蛋白功能丧失，确诊为先天性全身型脂肪营养不良综合征 2 型。给予苯扎贝特、二甲双胍、葡醛内酯片等治疗后皮下脂肪有所恢复、多毛好转，血糖、血脂、胰岛素维持正常水平。结论：新生儿期疑似糖尿病的患儿，部分由先天性全身型脂肪营养不良综合征引起，全外显子组检测有助于及早明确诊断和治疗干预。

SLC4A1 基因携带增加生酮饮食治疗的高尿钙症风险 1 例

沈雁文[1] 王媛[2] 孟岩[1] 邹丽萍[1]
1.解放军总医院第一临床医学中心
2.郑州儿童医院小儿神经内科

摘要：目的 报道 1 例一例无肾脏异常及酸中毒临床表现但存在生理指标异常，且在进入生酮饮食后迅速出现高钙尿症及血尿的婴儿痉挛患者，强调利用二代全外显子数据对非疾病相关携带基因进行二次或多次重分析并指导临床治疗的意义和重要性。结果 患儿，男，G1P1，足月剖宫产出生，生后喂养及发育可，5-6 月龄出现婴儿痉挛，予托吡酯及维生素 B6 口服治疗，发作控制至 1 周岁再次出现发作，调整抗癫痫药物治疗无好转，查全外显子三人家系基因检查未发现与临床表型高度相关基因变异，1 岁 7 个月开始生酮饮食治疗，抽搐发作明显缓解，但生酮饮食治疗 7 天患儿出现尿隐血阳性，半个月后开始出现尿红细胞逐渐增多，予托吡酯减量并调整生酮饮食比例，患儿尿红细胞仍较高，生酮饮食治疗 2 个月发作再次增多，尿红细胞无改善，尿 pH 值波动 7.0-7.5，尿钙肌酐比明显升高，泌尿系彩超未见明显异常，血气分析 pH7.355，SBE3.6，β 微球蛋白正常高值，尿红细胞畸形率正常，血钠偏低，血氯偏高，血钾波动较大，均正常范围内。方法 对患儿全外显

子数据针对碳酸酐酶相关基因及其可能存在相互作用的基因等进行二次非表型相关致病基因的重新分析，发现患儿存在 CA4 c.800A>G p.K267R（父源）及 SLC4A1 c.2561C>T p.P854L（母源）变异杂合携带。进一步对患儿及其父母尿 pH 值、血 pH 及电解质等进行回顾及连续检测，发现其母尿 pH7.5，其父尿 pH7.0，核对其家庭日常饮食，无饮食偏好，饮水量正常，考虑母源 SLC4A1 可能是患儿难以耐受生酮饮食治疗的原因，予补充枸橼酸钾口服治疗，无好转，半年后停生酮饮食。结论：非病因直接相关的影响功能的携带基因可能影响个体对特殊饮食、环境等因素下的耐受性，充分利用二代全外显子数据进行二次或多次重分析可优化治疗并节省反复检测的费用及时间。

MTHFR is not a possible risk factor for febrile seizures

Yanwen Shen[1] Xiuxia Wang[2] Huacheng Zheng[3] Youfeng Zhou[4] Li-Ping Zou[1]
1.Department of Pediatrics, Chinese PLA General Hospital
2.Department of Pediatrics, the Second Affiliated Hospital of Hebei Medical University
3. Department of Pediatric Neurology, Children's Hospital of Hebei Province, affiliated to Hebei Medical University
4.Department of Pediatrics, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University

Abstract
aims To clarify whether rare monoallelic variations of *mthfr* contribute to febrile seizures as a mild phenotype.
Method A total of 850 febrile seizure patients with febrile seizures were recruited from 2018.12-2019.7.31 national wide. *mthfr* variations in these 850 febrile seizures patients were reanalyzed.
Result Two patients with biallelic *mthfr* variations and another 39 monoallelic *mthfr* carriers were found carrying 19 rare variations (4 unreported). Among those with positive family history for febrile seizures, only 50% were found inherited the rare variations from the affected parents. The frequency of *mthfr* variations (2.0%) among febrile seizures' population was even lower than that in 1000 unrelated health control (4.4%). There was more c.677(rs1801133) CT types among febrile seizures while more TT type among health controls.
Interpretations The thermolability of MTHFR didn't make it a possible contributor for febrile seizures.

Sirolimus in Tuberous Sclerosis Complex prior to epilepsy: evidence from a registery-based real world study

Yanwen Shen[1] Yangyang Wang[1] Mengna Zhang[1] Yong Xu[1] Qian Lu[1] Wen He[1] Huimin Chen[1] Liying Liu[1] Lingyu Pang[1] Qiuhong Wang[1] Shuo Dun[1] Yufeng Li[2] Jing Gao[1] Fang Han[1] Li-Ping Zou[1]
1.Department of Pediatrics, Chinese PLA General Hospital
2.Department of Pediatrics, Shandong Linyi People's Hospital

Objective To evaluate if sirolimus in tuberous sclerosis complex patients prior to epilepsy relieve the later burden of new-onset seizures.
Methods A real world matched case-control trial was nested in another cohort study. For early sirolimus group, children (<1year old) who were diagnosed as tuberous sclerosis complex and had no seizures but taking sirolimus for other symptoms were eligible. For the late sirolimus group, age and genotype were used as the first-place stratifying criteria for 1:4 frequency matching, other symptoms of baseline condition were also assessed between the two group. None preventative drug should be introduced before seizures or before 2 years old in those without seizures in late sirolimus group. Subjects were enrolled from 2015 to 2018 and followed up until June 2020. The main outcome was the change of characteristic of seizures and the final condition of seizures.
Results A total of 42 patients were included in the early sirolimus group, and 168 were matched in the late sirolimus group. Early sirolimus significantly reduced seizure-onset especially for infants < 6month old. The mean onset-age was significantly delayed by sirolimus (11.34±7.93month *vs.* 6.94±6.03month, P < 0.001). The subtypes of seizures benefit most was

infantile spasm (5/42, 11.90% *vs* 73/168, 43.45%, P < 0.001) which might be eliminated or alleviated. Adding sirolimus prior seizures performed better than adding after seizures in reducing refractory seizures (10/42, 23.81% *vs* 70/147, 47.62%, P = 0.004). Seizures related to tuberous sclerosis complex might be none fever-related.
Interpretations: Early sirolimus intervention in tuberous sclerosis complex can prevent some seizures, especially infantile spasm. Early sirolimus modified the disease, delayed seizure-onset and relieved the severity.

Erythrocytosis and metabolic crisis caused by functional anemia in severe α-thalassemia: A case with homozygous --SEA/--SEA deletion

Yanwen Shen Xin Fang Jian Li Yanhui Chen
Fujian medical university affiliated union hospital

Abstract:
Deletion of all four αlpha-globin genes is known to cause very severe consequences. Little is known about the full face of the disease since most of the fetuses will undergo abortion or will die very soon after birth and only very few will survive. Here we reported a case of severe α-thalassemia who showed severe respiratory failure without cyanosis or edema, and unexplained metabolic crisis which presented as dysfunction of mitochondria. And the molecular test revealed homozygous Southeast Asian alpha-thalassemia ($--^{SEA}$) deletion. The difference between the arterial blood gas (ABG) oxygen saturation reading (SaO_2) and pulse oximetry (SpO_2) may reflect a very high oxygen affinity of abnormal hemoglobin which closely combine with oxygen and hard to release it. Erythrocytosis and the metabolic crisis secondary to lacking oxygen in tissue maybe another reason which directly cause the death of severe thalassemia besides hemolytic crisis.

糖原累积症 Ib 型的临床特点分析

姜静婧 马明圣 邱正庆
中国医学科学院北京协和医院

目的:分析糖原累积症 Ib 型的临床特点。
方法：回顾分析 2010-2020 年收治的 30 例糖原累积症 Ib 型患儿的临床资料。
结果：30 例糖原累积症 Ib 型患儿中男 17 例，女 13 例；出现症状平均年龄为（9±3. 9) 月，就诊平均年龄为（2.6±1. 1) 岁。其中 24 例（8%)以肝脏肿大起病,，18 例（60%) 出现反复感染，10 例（33%) 出现口腔和肠道黏膜溃疡、5 例（16.6%) 出现炎症性肠病样表现，5 例（16.6%) 存在关节炎，22 例（73%) 存在身材矮小，17 例（56.6%) 存在生长发育迟滞，29 例（96%) 存在高脂血症，26 例（86.6%)存在粒细胞减少。
结论：糖原累积症 Ib 型临床表现复杂，除代谢异常外，还注意该病免疫系统异常。

儿童早老症一例

陈晓倩
武汉儿童医院

目的：对武汉儿童医院遗传代谢内分泌科诊断一例早老症患儿的临床资料进行回顾性分析。
方法：13 岁 3 月，女性患儿，发现生长发育迟缓 10 余年。查体：体重 16Kg（＜-3SD），身长 116.2cm（＜-3SD），面容异常，头型异常，毛发及眉毛稀少，全身皮下脂肪菲薄，全身皮肤见点片状褐色色素沉着，耳位低，鼻子扁缩，牙齿部分脱落，小下颌，胸廓异常，呼吸平稳，心律齐，

心音尚有力，可闻及 II/6 级收缩期杂音，腹壁韧，肝脏入盆，质地韧，脾脏肋下未触及。双手指间关节不能伸直，指甲/趾甲角化不良。
结果：入院辅助检查：尿常规：葡萄糖 2+，尿蛋白 2+。生化：ALT 63U/L，AST 106 U/L。TC 6.91mmol/L，HDL 0.40mmol/L，TG 13.82mmol/L，LDL 0.46mmol/L。FBG 7.41mmol/L，空腹胰岛素 121.59μIU/ml。糖耐量 2 小时血糖 12.8mmol/L，2 小时胰岛素 127.17μIU/ml。血常规、肾功能、心肌酶、甲状腺、肾上腺功能、IGF-1 无异常。彩超：左心增大、左室收缩功能减低。二尖瓣增厚、毛糙伴重度关闭不全。二尖瓣前向血流速度增快。冠状动脉及颈内动脉、股动脉均血管壁光滑通畅，未见血管病变。肝大；脂肪肝。肝脏硬度较正常稍偏高。脾脏未见明显异常。右肾盂稍充盈。双肾实质回声、结构正常。X 片：颅板及板障变薄，可见较多缝间骨，下颌骨较小，体部变短；蝶鞍部可见条状高密度影（钙化多考虑）。双侧锁骨纤细，较短。双侧锁骨发育不良。双侧肱骨及尺桡骨纤细，髓腔窄，双侧肱骨干骺端膨大。胸腰段椎体曲度稍变直，肋骨纤细，心影明显增大。双手诸指远节指骨较细短，末节指骨远端变细，爪粗隆不明显。指间关节处软组织增厚。基因检测结果示 LMNA 杂合突变 c.1824C>T，导致氨基酸改变 p.G608G，为新生突变，为已报道致病突变。
结论：早老症临床特征主要有生长发育迟缓、皮肤牙齿异常、心血管疾病、骨与软骨异常及内分泌系统异常等。检测 LMNA 基因有助于明确诊断。

儿童颅咽管瘤术后出现肝肺综合征 1 例并文献复习

杜婷婷
武汉儿童医院

目的 探讨儿童颅咽管瘤术后下丘脑及垂体功能障碍出现肝肺综合征（hepatopulmonary syndrome，HPS）的临床特点，并初步探讨发病机制。**方法** 对 2020 年 9 月华中科技大学同济医学院附属武汉儿童医院收治的 1 例颅咽管瘤术后下丘脑及垂体功能障碍出现 HPS 的临床资料及诊治经过进行总结分析，并进行相关文献复习。以“hypopituitarism” “hepatopulmonary syndrome”、“craniopharyngioma” “hepatopulmonary syndrome”以及“垂体功能减退”“肝肺综合征”、“颅咽管瘤”“肝肺综合征”为检索词，分别检索 Pubmed、CNKI 和万方数据库。**结果** 本例为 12 岁 10 月女性患儿，7 岁时诊断 “颅咽管瘤“，行手术治疗，术后出现下丘脑综合征和垂体前叶功能低下，未正规评估和治疗。术后 1 年出现“非酒精性脂肪肝”，未治疗。本次入院前 1 年出现反复呼吸困难伴胸闷，口唇及指端紫绀，后诊断为 HPS。共检索到垂体功能减退合并 HPS6 篇文献，6 例病例，年龄 15 岁～35 岁，男性 4 例，女性 2 例。其中国外文献 5 篇，国内文献 1 篇，国内报道病例合并乙肝，作者分析患者为乙肝后肝硬化，等待肝移植。1 例予垂体激素（包括左甲状腺素钠、氢化可的松及基因重组人生长激素）替代治疗后肝功能正常，无氧情况下可正常活动。2 例行肝移植后均再次出现“脂肪肝”，其中 1 例后予垂体激素替代治疗后肝功能和脂肪肝改善。1 例予垂体激素替代治疗后低氧血症改善不明显，等待肝移植。1 例在诊断 HPS6 个月后进展为门静脉性肺动脉高压，予肺血管扩张剂治疗。本例在给予“二甲双胍、优甲乐、氢化可的松及 rhGH”治疗后，胸闷及呼吸困难等临床症状明显改善，但低氧血症仍明显，等待肝移植。**结论** 国内首次报道了 1 例儿童颅咽管瘤术后下丘脑及垂体功能障碍出现 HPS。HPS 在儿童相对少见，下丘脑功能障碍导致的下丘脑肥胖及垂体功能低下是 HPS 发生的罕见病因。早期予有效垂体激素替代治疗可能改善肝肺综合征的病理和临床症状，但若到严重肝硬化阶段，垂体激素替代治疗可能难以逆转病情。

DMRT1 新发突变致 46XY 性反转合并卵巢无性细胞瘤一例报道及基因分析

李亚坤 杨禄红 姚辉
武汉儿童医院

摘要：目的：分析一例由于 DMRT1 突变所致 46，XY 性发育异常患儿的临床特征及基因，提高临床医生对 46XY 性发育异常的认识。方法：收集一例 46，XY 性反转合并卵巢无性细胞瘤患儿的临床特征，进行内分泌相关功能评估，完善染色体核型分析及基因检测，进行预防性的性腺切除手术并进行性腺病理学检查。结果：患儿为幼女外阴，腹盆 CT 提示盆腔占位，大小 11.5cm*6.8cm*6.8cm，多来源于右侧卵巢。右侧卵巢肿物病理提示卵巢无性细胞瘤，外周血染色体核型 46，XY，SRY 基因阳性，医学外显子检测提示 DMRT1 基因新发突变 c.904-905insC(p.Q302Pfs*10)，父母在此位点均未发生突变。明确致病基因并进行性腺功能评估后，行预防性的左侧性腺切除手术，左侧卵巢病理为纤维组织，其内可见腺样结构，灶性钙化，形态上类似卵巢结构。结论：DMRT1 基因是性别分化的重要基因，其突变可能引起 46XY 患儿出现性发育异常。

囊性纤维化家系临床特征及 CFTR 基因变异分析

罗娟
武汉儿童医院

目的 对 1 例囊性纤维化患儿的临床特征及基因变异进行分析，明确其可能的致病原因，为临床诊断提供理论依据。**方法** 收集患儿及父母的临床资料，同时采集他们的外周血样，应用全外显子组测序技术对患儿进行基因检测，经生物信息学分析后采用 Sanger 测序进行验证。**结果** 基因检测结果显示患儿的 CFTR 基因存在 c.57G>A(chr7-117144310p.W19*) 、 c.2909G>A(chr7-117246728p.G970D)两处杂合变异，家系验证结果显示此双杂合变异分别来自其父母，其哥存在相同的双杂合突变位点，其爷爷 c.2909G>A 位点存在杂合突变，其奶奶此两位点均未突变。根据美国医学遗传学与基因组学学会遗传变异分类标准与指南，c.57G>A(chr7-117144310p.W19*)、c.2909G>A(chr7-117246728p.G970D)变异评级为致病性变异。**结论** CFTR 基因 c.57G>A(chr7-117144310p.W19*)、c.2909G>A(chr7-117246728p.G970D)变异为该例患儿的致病原因，基因检测有助于囊性纤维化诊断，为产前诊断提供了依据。

EEF1A2 基因突变导致全面发育迟滞 1 例

胡曼
华中科技大学同济医学院附属武汉儿童医院（武汉市妇幼保健院）

目的 对一例因发育迟滞就诊的患儿进行临床及及基因分析，明确其诊断和遗传学病因。**方法** 对一例因全面发育迟滞就诊的患儿进行临床及实验室检查，并抽取患儿及父母外周静脉血，采用新一代目标区域捕获高通量测序技术对患儿进行临床外显子的检测，对可疑变异位点进行 Sanger 测序验证。**结果** 患儿临床主要表现为严重全面发育迟滞、小头畸形、肌张力障碍。基因检测发现患儿 EEF1A2 基因第 6 号外显子发生一处突变：c.796C>T,p.R266W,为新发突变，且为已报道致病突变，确诊为常染色体显性智力低下 38 型。**结论** 发育迟滞为儿童较多见的疾病，其病因繁杂，病因诊断困难，基因检测有助于明确诊断。

婴儿 4-羟基丁酸尿症 1 例

翁小芃 陈晓红 聂云亚 丰利芳 杨禄红 胡曼 李亚坤 姚辉
武汉儿童医院

目的：提高临床医生对 4-羟基丁酸尿症的认识和诊断能力。**方法**：对 1 例 4-羟基丁酸尿症患儿作临床分析：患儿，男，4 月 2 天，因“反复咳喘 20 余天” 入院。入院治疗后肺炎好转，但有精神差、姿势异常、不自主运动、烦吵、偶有尖叫等表现，头 MRI 示双侧额颞叶及脑外侧裂增宽，追问病史，患儿入院前 1 月即出现不自主运动、阵发性姿势异常，表现为头后仰及肢体扭转，呈进行性加重。查体：身长 64cm，体重 8kg，头围 44cm，面容无异常，神清，精神反应一般，竖头不稳，双眼不能追物，有短暂凝视，双肺闻及少许湿罗音，心脏听诊未闻及异常。腹软，肝肋下 2.0cm，质软，脾肋下未及。双上肢内旋，四肢不自主运动，姿势异常及不自主运动时四肢肌张力增高，平静时肌张力偏低。腱反射减弱。实验室检查：血常规、肝肾功能、电解质、心肌酶、血气、血脂、血糖、血氨、乳酸基本正常；脑电图：异常婴儿脑电图：背景双侧枕区优势节律不突出，家长指认不自主运动及姿势异常“严重发作”同期可见广泛性慢波活动间断阵发，患儿肢体轻度抖动时不伴相关异常。视觉诱发电位正常。颅脑 MRI：额颞部脑外间隙宽大。血氨基肉碱谱示：游离肉碱稍下降（C0：16μmol/L），酰基肉碱正常；尿有机酸示 4-羟基丁酸升高（36.89mmol/mol 肌酐，参考值为 0），3-羟基戊二酸升高（50.78mmol/mol 肌酐，参考值为 0），戊二酸正常。考虑 4-羟基丁酸尿症可能，但戊二酸血症Ⅰ型不能排除。给予戊二酸血症专用奶粉加米粉喂养，病情严重不能进食期间给予鼻饲；静脉输注葡萄糖补充热卡，左卡尼汀促有机酸排泄及抗感染对症支持治疗。住院 12 天后病情好转后出院，出院时能自行进食，无明显烦吵及尖叫，仍有不自主运动及姿势异常。出院后送检代谢病基因包检测，结果显示：患儿 ALDH5A1 基因存在复合杂合突变（c.685C>A，c.1445C>G），分别来自父母。确诊为 4-羟基丁酸尿症。**结果**：给予普通婴儿奶粉喂养，添加辅食，口服左卡尼汀促有机酸排泄，肌张力异常及不自主运动无明显改善，出院 2 月后在睡眠中夭折。**结论**：4-羟基丁酸尿症是由于琥珀酸半醛脱氢酶（SSADH）缺陷所致的一种罕见的先天遗传性代谢病，为常染色体隐性遗传病，其致病基因 ALDH5A1 位于 6p22。尿 4-羟基丁酸增高是其生化特征，为重要诊断依据之一，因该病发病率极低，目前尚无流行病学资料，且 4-羟基丁酸升高幅度不大，易被忽略。基因突变检测可进一步确诊。目前，4-羟基丁酸尿症患者尚无成功治愈的案例，治疗方法通常以对症处理为主。家长若生下一胎，需要进行遗传咨询。

The importance of genetic screening in the wife of CBAVD patients with gene variation

Lingyan Zheng Zhongkun Liang Wenjun Wang Ping Yuan
Sun Yat-sen Memorial Hospital, Sun Yat-sen University

Background: Azoospermia is the leading cause of male infertility. Congenital bilateral absence of the vas deferens (CBAVD) is an important cause of obstructive azoospermia and male infertility. *CFTR* gene is the main disease-causing gene of CBAVD. To explore the genetic pathogenesis of CBAVD patient and assess the disease risk of the offspring，mutation screening in couple is very important.

Methods:

In present study, we collected three CBAVD patients and their spouses. We performed Sanger sequencing of the *CFTR* gene in the couples, and further bioinformatics analysis to identify pathogenesis of novel variant. Then, couples at risk for a child affected by CF should be informed about the reproductive consequences, which may include the decision to refrain from having own children.

Results:

We identified two heterozygous variants of *CFTR* gene every one of three couples except a CBAVD patient. In couple A, these are compound heterozygous variant c.1210-12T[5] and c.419C>G(P140R) in husband, compound heterozygous variant c.1666A>G(I556V) and

c.3205G>A(G1069R) in wife. In couple B, these are compound heterozygous variant c.1210-12T[5] and c.1657C>T(R553*) in husband, two heterozygous variants c.1666A>G(I556V) and c.1680-1G>A in one allele in wife. In couple C, these are a heterozygous variant c.4056G>C(Q1352H) in husband, two heterozygous variants c.1666A>G(I556V) and c.2684G>A(S895N) in wife ignorant of the cis or trans allele. The variants c.1210-12T[5], c.1666A>G,c.3205G>A , c.1657C>T,c.1680-1G>A, c.4056G>C and c.2684G>A were known disease-causing variants. The variant 419C>G was a novel variant and predicted to be deleterious by PolyPhen-2 and Mutation Taster. Clustal W showed that the location of p.140 was highly conserved .The p.Pro140 was located in the transmembrane domain. When proline is replaced by arginine at this position, it was predicted that the hydrophobicity and stability of CFTR protein were changed. The couple B, a successful double pregnancy was achieved in the first cycle of TESA(Testicular Sperm Aspiration）treatment. We only found a heterozygous variant c.1210-12T[5] in both boy and girl child postnatal. The husband ofcouple C only found one variant in *CFTR* gene but he were diagnosed CBAVD by clinical evidence. According to the classes of *CFTR* variants，we predicted the risk of CF ,CBAVD and CFTR-realative disease at their offspring.

Conclusion:

In our study, we found three couples had variants of *CFTR* both in husbands and wives. The husbands were clinically diagnosed as CBAVD with *CFTR* variants . The wives were no specific clinical phenotype. It maked us alert the offspring risk of the CBAVD patients in the future. On the basis of the variant，We hope to help CBAVD couples make a good eugenic decision in their genetic counseling.

X-连锁迟发性脊椎骨骺发育不良家系 TRAPPC2 基因新突变的功能鉴定

娄桂予 廖世秀
河南省人民医院

【摘要】 目的 X 连锁迟发性脊椎骨骺发育不良（X-linked spondyloepiphyseal dysplasia tarda，SEDL，MIM #313400）是一种 X 连锁隐性遗传性骨骼疾病。其特征是椎体和 / 或长骨骨骺结构缺陷，导致不成比例的身材矮小和关节过早退化。TRAPPC2 （trafficking protein particle complex subunit 2，TRAPPC2）是 SEDL 的唯一的致病基因。本研究报告一个 SEDL 家系患者 TRAPPC2 基因的无义突变，并对该变异进行了初步的功能研究。方法 该家系包括四代，共有 3 位男性患者，分别为先证者外祖父及其表弟。先证者 28 岁，6 岁后出现身高落后，现身高 148CM，臂展 152CM，影像学资料显示：桶状胸，躯干短小，胸腰椎椎体普遍变扁，椎体前部上缘凹陷，而中后部隆起，有典型“驼峰”样改变，髋关节呈现退行性骨关节病改变。根据家庭中患者的临床表现和放射学检查结果，将该家系诊断为 SEDL。提取家系所有成员的外周血 DNA；对先证者进行全外显子测序；提取家系成员外周血淋巴细胞总 RNA，RT-PCR 扩增外显子 3、4 区域，qPCR 检测 TRAPPC2 编码蛋白 sedlin 的转录水平。结果 全外显子测序发现 TRAPP2 基因 c.91A>T 无义突变，2 个健在的男性患者该位点有突变，其母亲为杂合携带者。HGMD （The human Gene Mutation Database）、ClinVar （http://www.nicbi.nlm.nih.gov/clinvar）数据库无该变异致病性的报道；查阅文献表明该变异为新的无义突变。鉴于该无义突变位于第三外显子近 3’端，为证明该位点变异是否影响了转录本的剪接，我们对先证者，其患病的表弟，其基因型正常的其儿子的进行了扩增，RT-PCR 结果显示转录本无异常剪接。qPCR 结果表明患者 TRAPPC2 转录水平显著降低（P<0.01）。我们推测该变异导致 sedlin 蛋白截短，引发了无义介导的 mRNA 的降解。结论 本研究在 SEDL 患者中发现了 TRAPPC2 基因的 c．91A>T 新突变，将 TRAPPC2 基因的突变数量由 60 个扩增至 61 个；为携带者检测、遗传咨询和产前诊断提供实验依据；有助于进一步阐明 sedlin 蛋白在正常骨生长中的作用机制。

CYP2C19 基因在福州地区人群的多态性研究及方法学比较

赖力
福建省立医院

目的：研究福州地区人群 CYP2C19 基因分布的多态性和氯吡格雷代谢相关性，比较不同方法在 CYP2C19 基因检测方面的差异。
方法：对 2021 年 3 月至 6 月于福建省立医院采集的 328 例福州地区人群的全血样本提取基因组 DNA，采用实时荧光定量 PCR 法与荧光 PCR 毛细管电泳检测法两种方法进行 CYP2C19 基因检测，检测结果进行一致性比较，并采用 Excel 软件计算 CYP2C19 的等位基因与基因型频率。
结果：采用上述两种方法在福州地区人群中共检出 CYP2C19*1、CYP2C19*2、CYP2C19*3、CYP2C19*17 等四种等位基因，等位基因频率分别为 58.18%、37.65%、3.24%和 0.93%；共检出 CYP2C19*1/*1 、 CYP2C19*1/*2 、 CYP2C19*1/*3 、 CYP2C19*1/*17 、 CYP2C19*2/*2 、 CYP2C19*2/*3、CYP2C19*2/*17、CYP2C19*3/*17 等 8 种基因型，基因型频率分别为 34.26%、43.52%、3.09%、1.23%、14.20%、0.31%、0.31%，未发现 CYP2C19*3/*3 基因型，两种方法比较检测结果一致。根据《指南》确定受检者氯吡格雷代谢类型，福州地区人群氯吡格雷强代谢型、中间代谢型与弱代谢型的比例分别为 34.26%、47.84%、17.91%，其中弱代谢型比例与国内已报道汉族人群无显著性差异，与日本人群无显著性差异。
结论：在福州地区人群中 CYP2C19*1 基因频率最高；CYP2C19*17 基因频率最低，荧光定量 PCR 法与荧光 PCR 毛细管电泳法在 CYP2C19 基因检测中具有良好一致性，可应用于临床 CYP2C19 基因检测。含有 CYP2C19*2 的基因型是构成福州地区人群氯吡格雷弱代谢的主要类型。福州地区人群中氯吡格雷中间代谢型比例最高，对临床氯吡格雷用药有指导意义。

Molecular characterization of hemoglobinopathies and thalassemias in Northern Guangdong Province, China

Zhanzhong Ma
粤北人民医院

Purpose: To detect the molecular characterization of hemoglobinopathies and thalassemias in Northern Guangdong Province of China.
Methods: We recruited 10,285 subjects screened for thalassemia, and investigated the hemoglobin (Hb) components by complete blood cell counts, electrophoresis, and DNA sequencing. Furthermore, suspected thalassemia was identified by Gap-PCR, PCR-based reverse dot blot, and DNA sequencing.
Results: Among all subjects screened, the overall prevalence of hemoglobinopathies and thalassemias were 0.46% (47/10285) and 19.37% (1992/10285) in Northern Guangdong Province. We found that Hb Q-Thailand is the most common, and other types of hemoglobinopathies are followed by Hb E, Hb New York, Hb G-Chinese, Hb G-Coushatta, Hb J-Bangkok, Hb J-Broussais, Hb Ottawa and Hb G-Taipei. We identified 1340 cases (13.03%) of α-thalassemia, mainly includes $--^{SEA}$ deletion (71.64%), $-\alpha^{3.7}$ deletion (12.01%), $-\alpha^{4.2}$ deletion (4.78%). And identified 652 cases (6.34%) of β-thalassemia, the most prevalent being CD 41/42(-TTCT) (35.89%), IVS-II-654 (C>T) (33.44%), CD 17 (A>T) (10.28%) and -28(A>G) (9.66%). In addition, we found a rare case with -80 (T>A) of β-thalassemia. The results of this study found a high prevalence of hemoglobinopathies and thalassemias in Northern Guangdong Province, China. There were some differences molecular characterizations of thalassemia in different areas of China.
Conclusion: Our results enriched the related information of hemoglobinopathies and thalassemias in the region, which provided valuable references for the prevention and control of thalassemia.

FBN1 微缺失致马凡综合征病例报道

李颖 石磊
哈尔滨医科大学

目的 对一例马凡综合征（Marfan Syndrome, MFS, OMIM 154700）患者行高通量测序分析以寻找致病突变，并探讨突变致病的分子机制。
方法 收集 MFS 患者的临床资料，包括基本体征、眼科检查、影像检查和家族史资料；采集患者及其正常双亲的外周血，提取基因组 DNA，应用芯片捕获高通量测序对所有基因外显子行突变筛查；应用 SIFT 和 PolyPhen-2 预测可疑变异的致病性，并行 ACMG 评级。
结果 患者表现为骨骼细长、关节突出、晶状体脱位、心脏结缔组织异常等 MFS 典型症状，有家族遗传史；根据"修订版 Ghent 标准"诊断为 MFS。该患者的原纤维蛋白-1 基因（*Fibrillin-1*, *FBN1*）存在第 21 号外显子上的新的杂合微缺失【NM_000138.5, c.2432_2433 GC>TT, p.(Cys811Phe)】，该突变的群体频率极低。SIFT 和 PolyPhen-2 软件预测该微缺失对蛋白质的结构和功能有害，ACMG 评级为 Pathogenic（致病）。
结论 *FBN1* 的 c.2432_2433 GC>TT 微缺失为该患者的致病突变，此结果丰富了 *FBN1* 的基因突变谱，为临床诊疗提供了新的分子依据。

SPATA5 突变致癫痫，耳聋和神经发育迟缓综合征病例报道

马晴[1] 黄佳[2] 石磊[1]
1.哈尔滨医科大学
2.河南省人民医院医学遗传研究所

目的 鉴定一例癫痫，耳聋和神经发育迟缓综合征（Epilepsy, Hearing Loss, and Mental Retardation Syndrome, EHLMRS, OMIM 616577）患者的致病突变，丰富临床对 EHLMRS 的认识，提高 EHLMRS 的诊断率，为临床遗传咨询提供依据。
方法 收集家系成员的生长发育史、家族史，以及智力、行为、影像学检查等临床材料；采集先证者及其表型正常双亲的外周血并提取基因组 DNA，采用全外显子组测序（Whole Exome Sequencing, WES）和拷贝数变异测序（Copy Number Variation Sequencing, CNV-seq）联合的策略筛查可疑致病突变；结合生信分析，根据 ACMG 指南对突变位点进行致病等级评定。
结果 患者临床表现为智力低下、语言发育迟缓、逻辑思维能力差、交流障碍和脑积水，诊断为 EHLMRS。高通量测序结果显示先证者的精子发生相关蛋白 5 基因（*Spermatogenesis associated 5*, *SPATA5*）存在双等位基因上的复合杂合错义突变【NM_145207.3, c.580C>T, p.(Arg194Ter); c.1729C>T, p.(Arg577Trp)】；突变等位基因分别来自表型正常的双亲，先证者的姐姐均未携带，符合常染色体隐性遗传模式。c.580C>T 和 c.1729C>T 双变异的人群频率极低，SIFT 和 PolyPhen-2 预测其对基因功能有害，ACMG 评级均为"可能致病"。
结论 *SPATA5* 的复合杂合错义突变（c.580C>T; c.1729C>T）是该 EHLMRS 患者的致病原因。此结果扩展了 *SPATA5* 的突变谱，为临床诊疗提供了新的分子依据。

广西柳州地区 Hb E 及 Hb A2 窗口中洗脱的其他异常血红蛋白的分子及血液学特征分析

陈丽竹 罗世强 钟青燕 王秋华 黄钧 钟鑫 覃柳群 王敬仁 蔡鹏飞 崖娇练 许泽辉 严提珍
柳州市妇幼保健院

目的 研究广西柳州地区 Hb E 分布情况，分析 Hb E 及其他异常血红蛋白和不同类型地中海贫血的复合杂合状态的分子及血液学特征，为本地区地中海贫血防治工作提供参考。

方法 在 2012 年至 2018 年到柳州市妇幼保健院进行婚检、产检、体检的受检者中，采用高效液相色谱法(High Performance Liquid Chromatography ， HPLC)评估在 Hb A2 窗口中洗脱的异常血红蛋白，采用 Gap-PCR 及反向点杂交技术(reverrsedot blot,RDB)检测中国人群常见的 α-地中海贫血基因及 β-地中海贫血基因，对于筛查结果阳性且未检出常见类型地贫基因的病例，运用 Sanger 测序法及多重连接探针扩增技术(multiplex ligation-dependent probe amplification ,MLPA)进行检测。
结果 共检出 Hb A2 升高的样本 400 例，检出 Hb E 的 391 例样本中，Hb E 杂合子 303 例，Hb E 复合 β-地中海贫血 23 例, Hb E 复合 α-地中海贫血 65 例。通过筛选 Hb A2 异常升高的病例，发现 4 例 Hb G-Coushatta，发现 5 例 Sanger 测序法未检出致病变异，通过 MLPA 检出 HBB 基因的 1 号外显子、启动子区、上游区域及 HBD 3 号外显子区域重复的罕见病例。
结论 广西柳州地区是地中海贫血的高发区，地中海贫血的类型复杂多样，其分子及血液学特征也各不相同。单纯 Hb E 杂合子的血液学特征大部分表现为临界；Hb E 复合 β-地中海贫血病例出现严重贫血及 Hb F 异常增高(Hb F>30)，而此基因型同时复合 α-地中海贫血时 Hb F 增高程度较小(Hb F>15)。随着检测技术不断升级，检出的罕见类型病例也越来越多，检测技术互相协同可以减少漏诊、误诊的情况；与此同时，部分罕见病例对个体临床表现及血液学表型的影响也有待进一步研究探索。本研究旨在进一步降低柳州地区出生缺陷，为地贫人群进行遗传咨询、产前诊断，有针对性的制定地中海贫血防治计划提供数据基础。

PDE4D 基因突变导致肢端发育不全 2 型一例并文献复习

徐艺文
中国医学科学院北京协和医院

目的 分析一例肢端发育不全 2 型患儿的临床特点及基因变异，提高对该疾病的认识。
方法 对患儿进行病史采集、查体、基因检测，分析临床特点及基因变异。
结果 3.5 岁女孩，主因“发现下肢畸形 1 年余”来院。生后即存在运动及语言发育迟缓，4 个月会抬头，1 岁会独坐和腹爬，2.5 岁可独走，目前可小跑，会说简单 2-3 个字，能完成简单指令。无抽搐。查体：身长 87cm（<P3=92cm），指间距 81cm，头围 48.5cm，体重 15.7kg（P50-P75）。步态异常，头发棕红，面容特殊（前额大，饱满，鼻梁低平，鼻尖发育明显差，鼻翼发育稍差，上唇鱼唇样，双耳轻度招风，耳廓简单），双手明显异常（短宽，远端指骨发育明显短，三叉样），双肘轻度屈曲，双腕、双肩（-），双膝内翻，膝间距 5-6cm。考虑先天性骨骼发育不良。基因检测示患儿携带 *PDE4D* 基因 c.919A>G（p.K307E）杂合变异。
结论 PDE4D 基因 c.919A>G（p.K307E）变异与常染色体显性遗传的肢端发育不全 2 型伴或不伴激素抵抗的发生相关。该病罕见，临床表现为骨骼发育不良，特征是短指畸形，面部发育不良和脊椎狭窄，多伴有智力障碍，部分患者伴激素抵抗。该病在国内外鲜有报道，已报道的 PDE4D 基因变异位点有 c.1813T>C（p.Tyr605His）（杂合）、Y677D（杂合）、c.569C>T（p.Ser190Phe）（杂合）等。本例的 PDE4D 基因 c.919A>G（p.K307E）变异位点在国内外为首次报道。

一例新生儿发病的肾小管酸中毒家系及基因分析

李弢 陆军 罗劲松 李濛 王婕
武汉大学人民医院

目的 探讨原发性肾小管酸中毒的临床表现及家系、基因突变分析。
方法 回顾性总结分析 1 例 2017 年 11 月武汉大学人民医院收治的新生儿期发病的肾小管酸中毒患儿的临床资料、家庭成员表型及 Panel 基因检测结果。
结果 1.患儿，女，出生后 21 天因不能纠正的低钾血症、代谢性酸中毒，确诊为新生儿肾小管酸中毒，家长放弃进一步诊治。患儿于 10 月龄复诊，生长发育明显落后，肾脏超声示髓质海绵肾改变， 腕片示 2-3 个月骨龄，血清 HCO3 15.4mmol/L、BE-8、K 3.26 mmol/L、Na 136.00 mmol/L、阴离子间隙正常；尿液 PH 8。开始枸橼酸钠钾口服液治疗。期间不规律复诊及服药。

2021-05-21（3 岁 6 月）血气分析：pH 7.44， PCO_2 20mmHg，HCO3 13.6mmol/L，BE -8.3mmol/L， Na 143mmol/L，K 4.1mmol/L，Cl 116mmol/L；尿常规:比重 1.010，PH 7.50，白细胞酶 微量，白细胞 22.55 个/μL, 结晶 40.09 个/μL； 尿液：α1-微球蛋白 47.70mg/L,β2-微球蛋白 21.90mg/L；超声示双侧肾脏髓质海绵肾改变，双肾结石，右肾积水；骨龄片：2.7 岁；生长发育评估：身高 95cm（中下），体重 12kg（下等），BMI 13.3（中下），心智发育（正常）。2.家系发病情况：患儿胞姐生长发育落后，代偿性代谢性酸中毒，肾脏钙质沉着；患儿父亲反复肾脏小结石；母亲健康；奶奶患肾结石；外婆高血压、糖尿病、尿毒症。3.基因检测：家长迟至患儿 3 岁 6 月同意行基因检测，结果提示患儿 ATP6VOA4 基因（c.844C＞T、p.Q282X）纯合突变，其父、母、姐均为该位点杂合变异，此位点为新发现位点。

结论 新生儿期发病的肾小管酸中毒罕见，肾小管酸中毒与髓质海绵肾并存在儿童亦罕见，发现不明原因的低钾性代谢性酸中毒，需考虑遗传性肾小管酸中毒可能。ATP6VOA4 基因（c.844C＞T、p.Q282X）纯合突变与原发性远端肾小管酸中毒、髓质海绵肾发病有关。早期治疗及基因检测有助于患儿及家系成员早期诊断，并能改善预后。

GLDC 基因异常导致非酮性高甘氨酸血症患者的临床与遗传学分析

徐云云 李弢 罗劲松
武汉大学人民医院

目的 探讨 GLDC 基因变异所致的非酮性高甘氨酸血症（Nonketotic hyperglycinemia，NKH）患儿的临床表现及基因变异特点。

方法 总结患者的临床资料，应用全外显子测序技术（WES）对患儿进行基因变异分析，Sanger 测序法对可能的变异位点进行验证；利用荧光定量 PCR 对基因拷贝数及表达水平进行定量分析。

结果 1. 患者全外显子测序分析：患者 1 的 GLDC 基因存在 c.307A>T 以及 c.568G>T 复合杂合突变，其中 c.307A>T 使 GLDC 基因编码的蛋白第 103 位氨基酸由精氨酸突变为终止密码子，突变未见报道，根据 ACMG 指南，该位点为致病性改变。c.568G>T 为错义突变，导致 190 位氨基酸由天冬氨酸突变为酪氨酸，文献及数据库未收录，根据 ACMG 指南，该位点为可能致病性改变。利用 Sanger 测序验证后发现两个突变分别遗传自患者父母。患者哥哥携带 c.568G>T 杂合突变，见图 1。患者 2 发现 GLDC 基因存在 c.997delT 纯合突变，突变导致编码蛋白提前终止。患者母亲该位点为杂合突变，患者父亲该位点未见异常。进一步分析全外显子数据以及利用 qPCR 验证发现患者及其父亲均存在 GLDC 基因外显子 6-16 杂合缺失，见图 2。**2. GLDC 基因表达水平分析**患者及对照的新鲜外周血提取 RNA 后进行荧光定量 PCR 分析，结果显示：相对于同龄对照，患者 1 的 GLDC 患者的表达水平低于对照组，但不存在统计学差异（P>0.05）；患者 2 GLDC 基因表达水平显著低于正常对照儿童（P=0.011），见图 3。

结论 GLDC 基因变异是导致非酮性高甘氨酸血症的常见原因，该类疾病主要临床表现为癫痫发作等神经系统异常；本研究增加了 GLDC 基因的突变谱。

OFD1 基因突变致 Joubert 综合征一例临床表现与遗传学分析

贺歆瑶
成都市妇女儿童中心医院

目的 分析 OFD1 基因突变致 Joubert 综合征的临床与遗传学特点。

方法 收集 2021 年 3 月成都市妇女儿童中心医院内分泌科 1 例疑诊 Joubert 综合征患儿相关病历资料，并完善患儿及父母的分子遗传学测序。

结果 患儿男，7 月龄，因“发育迟缓、肥胖”就诊，生后至今有 2 次“肺炎、吼喘”病史，头颅 MRI 示“磨牙征”，小脑半球间见“中线裂”表现，第四脑室可疑“蝙蝠翼”状，基因检测示 OFD1 基因存在杂合

点突变（c.2626C>T/p.Q876X），来源于母亲，既往未见相关报道，该突变可致 OFD1 蛋白第 876 位谷氨酰胺转变为终止密码子。
结论 该例患儿临床表现为全面发育迟缓、肌张力减低，同时合并典型头颅 MRI 表现，基因检测提示 OFD1 存在无义突变，可明确诊断为的 Joubert 综合征 10 型。

两例 POLR3B 基因突变导致低髓鞘化脑白质营养不良伴性腺功能减退突变位点分析及功能验证

杨帆[1,2,3] 沈英[1,2] 杨燕婷[1,2] 刘洪倩[1,2]
1.四川大学华西第二医院医学遗传科/产前诊断中心
2.四川大学出生缺陷与相关妇儿疾病教育部重点实验室
3.洛阳市妇幼保健院医学遗传与产前诊断科

目的 探讨两例 POLR3B 基因突变相关的常染色体隐性遗传低髓鞘化脑白质营养不良伴性腺功能减退患者（兄妹）的临床表型、基因突变特点及其功能验证。
方法 对四川大学华西医院内分泌科收治的 1 例来自非近亲结婚家庭的男性先证者进行详细的体格检查及辅助检查，对该家系成员进行全外显子测序，应用生物信息学软件对突变位点进行致病性分析。构建 POLR3B 过表达野生型和突变型质粒载体，使用 293T 细胞转染后进行 qPCR 及 Western Blot 检测表达量。
结果 先证者自幼运动发育迟缓，走路不稳伴肌张力障碍，双侧乳房发育伴男性性腺发育不良等。头颅 MRI 平扫可见小脑体积缩小、脑回变细，小脑周围脑沟及脑池明显扩大；小脑萎缩。胞妹有类似症状。全外显子测序发现该先证者及其胞妹 POLR3B 基因存在可疑致病的复合杂合突变 c.1615G>T；c.165_167del，父母分别为携带者，父母均无相关症状，符合家系共分离。qPCR 及 Western Blot 检测 POLR3B 过表达突变型载体的 mRNA 及蛋白质表达量较野生型载体降低，且有统计学意义。
结论 POLR3B 基因突变导致低髓鞘化脑白质营养不良伴性腺功能减退临床表型，但不同个体表型严重程度存在一定差异。本例患者 POLR3B c.165_167del 突变位点无相关病例报道，为新发变异，扩大了该病的遗传突变谱。通过遗传学分析及相关功能验证为患者家庭提供了准确的遗传咨询和诊断意见。

一例 NSD1 基因新发突变导致中枢性巨人症综合征 1 型临床表型及突变位点分析

杨帆[1,2,3] 刘洪倩[2,3] 宁昊丰[1] 王亚男[1]
1.洛阳市妇幼保健院医学遗传与产前诊断科
2.四川大学华西第二医院医学遗传科/产前诊断中心
3.四川大学出生缺陷与相关妇儿疾病教育部重点实验室

目的 探讨一例 NSD1 基因相关的常染色体显性遗传中枢性巨人症综合征 1 型患者的临床特点及突变位点分析。
方法 对一例中枢性巨人症综合征 1 型患者进行详细的体格检查及辅助检查，采用全外显子测序技术对先证者进行基因检测，同时对该家系成员进行一代测序位点验证，应用生物信息学软件对突变位点进行致病性分析。
结果 先证者出生后 4 月诊断为右侧肾上腺神经母细胞瘤（未分化型），行外科手术治疗。2 岁 9 月龄表现出认知，智力发育落后，语言能力差；前额突出，眼距稍宽，体格及生长发育大于同龄儿童。头颅 MRI 平扫可见双侧额颞部蛛网膜下腔显示稍宽，双侧侧脑室稍宽，胼胝体压部稍薄，枕大池稍宽。全外显子测序发现该患者 NSD1 基因存在一处杂合突变 c.6013_6014insA p.R2005fs*，ACMG 致病性分级为致病（PVS+PS2+PM2）。对其父母及胞姐行该变异位点一代验证均为野生型，因此该患者为新发突变。

结论 NSD1 基因突变导致中枢性巨人症综合征 1 型，通过遗传学分析为患者家庭提供了准确的遗传咨询和诊断意见。本例患者 NSD1 c.6013_6014insA p.R2005fs*无相关病例报道，该位点突变为新发变异。该临床病例扩大了中枢性巨人症综合征 1 型的遗传突变谱及表型谱，为相似患者提供了临床参考。

FBN1 错义突变致马凡综合征病例报道

张祎[1] 石磊[1] 谭建强[2]
1.哈尔滨医科大学 2.柳州市妇幼保健院医学遗传科

目的 分析一例马凡综合征（Marfan Syndrome, MFS, OMIM 154700）家系临床特征，明确该家系的致病突变并探讨其分子机制。
方法 收集家系成员的临床资料，包括家族史、基础体征、眼科检查和实验室检测结果，并采集成员外周血行高通量测序分析，筛选和验证可疑致病位点，应用生信软件和 ACMG 标准评价致病性。
结果 家系患者均表现为四肢纤细，足关节突出，双眼晶状体脱位伴视力损伤。外显子及 Sanger 测序发现患者的 *FBN1* 存在错义突变【NM_000138.5, c.1463G>A, p.(Cys488Tyr)】，而正常家系成员不携带该突变，且该突变尚无文献及数据库报道。MutationTaster、SIFT 和 PolyPhen-2 软件预测该错义突变对蛋白质结构和功能有害，ACMG 评级为可能致病。
结论 *FBN1* 的 c.1463G>A 错义突变为该家系的致病突变，此结果丰富了马凡综合征的遗传突变谱，为遗传咨询，临床诊疗，以及早期管理提供了新的分子依据。

Identification of Clusterin as a serum biomarker candidate contributed to the lung fibroblasts activation in chronic obstructive pulmonary disease

Qiang Zhang
Shengjing Hospital of China Medical University

Background Fibrosis in peripheral airways contributes to airflow limitation in chronic obstructive pulmonary disease (COPD). Nevertheless, key critical proteins still remain poorly understood. Thus, we intended to identify potential differentially expressed proteins (DEPs) between smokers with or without COPD patients, and explore the effects of one of the biomarker candidates on lung fibroblasts, together with the possible mechanism(s).
Methods DEPs were analyzed by the isobaric tags for relative and absolute quantitation (iTRAQ)-based proteomic analysis. The mRNA and/or protein expression of Clusterin was confirmed in COPD patients and 12% cigarette smoke extract (CSE)-treated human bronchial epithelial (HBE) cells at indicated times. In addition, COPD *in vitro* model was established by administration of 8% CSE to normal human lung fibroblasts (NHLFs) at indicated times. Thereafter, the effects of CSE and/or silencing of Clusterin on proliferation, inflammatory response, differentiation and collagen matrix deposition in lung fibroblasts were analyzed.
Results A total of 144 DEPs were acquired between COPD patients and smoker samples. Clusterin was identified as a biomarker candidate by proteomics. Moreover, we found that Clusterin was significantly increased in Global Initiative for Obstructive Lung Disease (GOLD) II ($P < 0.0001$), III ($P < 0.0001$) and IV ($P < 0.0001$) patients and correlated with forced expiratory volume in 1 s (FEV1, R = -0.7705, $P < 0.0001$), residual volume (RV, R = 0.6281, $P < 0.0001$), RV/total lung capacity (TLC, R = 0.5454, $P < 0.0001$), computerized tomography (CT) emphysema (R = 0.7878, $P < 0.0001$). Besides, Clusterin was also significantly increased in CSE-treated cells at indicated times (all $P < 0.0001$). CSE statistically inhibited human lung fibroblasts proliferation, promoted inflammatory response, differentiation, and collagen matrix

deposition and induced cell apoptosis, however, the above effects were partly reversed by silencing of Clusterin.
Conclusion Our results suggest that Clusterin might play significant roles in airway fibrosis of COPD by regulation of lung fibroblast function.

196 例人类染色体新核型报告及遗传学分析

李琳
临沂市人民医院

目的 通过对临沂及周边地区 12899 例有不良孕产史、不孕不育、性别发育障碍、原发及继发性闭经、智力障碍、先天畸形等遗传咨询患者进行染色体核型分析，探讨临沂及周边地区染色体异常核型的种类及与疾病之间的关系，为患者的诊断、治疗和遗传咨询提供依据。
方法 取患者外周血进行淋巴细胞培养，按常规方法制备染色体，应用 G、C 显带、FISH、微阵列、高通量测序等技术进行染色体核型分析及验证。异常核型根据人类细胞遗传学国际命名体制（ISCN）命名。
结果 在 16478 例患者中检出异常染色体核型（不包括多态变异）1923 例，检出率为 11.67%，明显高于正常人群。经中南大学医学遗传学国家重点实验室专家鉴定，有 196 例核型为国内、外首次报道的染色体异常核型。包括男性 88 例，女性 108 例；年龄最小的 4 天，最大 68 岁。异常核型类型有：染色体平衡易位 162 例，臂间倒位 7 例，臂内倒位 4 例，插入易位 3 例，3 条染色体复杂易位 2 例，其他非平衡性染色体核型 18 例。
结论 染色体异常是引起不孕不育、自然流产及死胎、生育异常儿、原发及继发性闭经、智力低下、性别发育障碍、先天畸形等的重要原因，对有相关临床症状的患者进行染色体检查非常必要。

Citrullinemia type I is associated with two novel mutants, c.649_651del and c.1048C>T, in ASS1: a case report and literature review

Liu Jing
Hunan Provincial Maternal and Child Health Care Hospital

Background Citrullinemia type I (CTLN1) is a rare autosomal recessive disorder of the urea cycle caused by a deficiency in the argininosuccinate synthetase (ASS1) enzyme due to mutations in the *ASS1* gene. Only a few Chinese patients with CTLN1 have been reported, and *ASS1* gene mutations have been identified sporadically in China.
Case presentation A Chinese family with one member affected with mild CTLN1 was enrolled. Clinical presentation, initial citrulline and ammonia levels, and molecular genetic analysis were retrospectively evaluated. Newborn screening (NBS) showed remarkably increased concentrations of citrulline with elevated ratios of citrulline/arginine and citrulline/phenylalanine. The urinary organic acid profile was slightly abnormal. Targeted exome sequencing was performed on the probands, and Sanger sequencing was used to validate the detected mutations. We also reviewed the genetic and clinical characteristics of CTLN1 in Chinese patients that have been published to date. Two novel compound heterozygous variants c.1048C>T and c.649_651del in the *ASS1* gene was identified in the proband, and it was predicted to be likely pathological and uncertain. To date, only 11 Chinese patients with CTLN1 have been reported, with a total of 17 *ASS1* mutations identified and no high frequency or hot spot mutations found; the mutation spectrum of Chinese patients with CTLN1 was heterogeneous.
Conclusions We described a severe Chinese CTLN1 case with two novel variants, c.649_651del and c.1048C>T in *ASS1*, and reviewed previous genotypes and phenotypes in Chinese patients with CTLN1. Thus, our findings contribute to understanding the molecular genetic background and clinical phenotype of CTLN1 in Chinese population.

南充地区早期自然流产病因及流产组织染色体异常分析

宋琪玲
川北医学院附属医院

目的 回访早期自然流产夫妇调查流产相关因素，通过绒毛细胞培养及绒毛染色体核型分析探讨早期自然流产病因及流产胚胎染色体异常检出情况。
方法 选取本院 304 例早期自然流产患者临床资料，均行盆腔 B 超、引产胚胎染色体检查，并成功电话回访 103 对早期自然流产夫妇调查流产相关因素，分析早期自然流产患者病因及染色体异常情况。
结果 在 103 对早孕期流产夫妇中从居住地、文化程度、工作环境、生活习惯、女性因素、男性因素、辅助生殖七个方面进行了流产原因的统计分析，其中 84.5%的夫妇生活在城镇，86.4%夫妇文化程度在高中以上，具有吸烟、喝酒、熬夜的夫妇占比合计 55.3%。染色体培养情况共收集 307 例绒毛组织， 2 例存在污染，1 例因绒毛坏死变性，细胞生长不佳导致培养失败，304 例培养成功，培养成功率为 98. 21%。304 例早期自然流产患者中，143 例次染色体异常占比 47.04%。包括三体 97 例，单体 12 例，多倍体 30 例，结构异常 4 例，4 例结构异常有 3 例是遗传于夫妻一方，1 例为新发。在流产次数大于等于 3 次的女性发生染色体异常的百分比（57.69%）高于流产 1-2 次女性（18.18%），且 $p<0.05$，具有统计学意义。年龄低于 35 岁女性染色体异常率（44.98%）低于年龄大于等于 35 岁女性染色体异常率（62.85%），且 $p<0.05$，具有统计学意义。
结论 染色体异常尤其是染色体非整倍体改变是早孕期自然流产的重要原因。良好的生活习惯及避免有毒有害物质接触，有利于优生优育。流产次数的增加，发生染色体异常的风险会有所增加。母亲高龄是引起胚胎染色体异常的高危因素。对发生早期自然流产的女性行绒毛染色体检查十分必要，有利于找到流产原因，指导遗传咨询。

不明原因 ID 家系遗传学检测策略分析

邬玲仟[1,2] 陈新[1,2]
1.中南大学生命科学学院医学遗传学研究中心
2.医学遗传学湖南省重点实验室

目的 对 46 例不明原因智力障碍（ID）家系同时进行 CNVs 和 SNVs/InDels 检测，探究其遗传学病因，比较 CNVs 和 SNVs/InDels 的分层检测策略和同时检测策略，探讨不明原因 ID 患者最优分子遗传学检测流程。
方法 本研究收集了 46 个不明原因 ID 家系 54 例患者的 DNA 样本，所有患者已排除染色体非整倍体和脆性 X 综合征。先证者行 CNV-seq 检测，同时对核心家系进行 trio-WES 检测，若家系中有多个患者则同时对其他患者行 WES 检测，对发现的候选变异结合数据库和相关文献进行致病性分析。分析 CNVs 和 SNVs/InDels 同时检测策略的诊断率，并对分层检测策略进行假设分析。
结果 CNVs 和 SNVs/InDels 同时检测策略总诊断率为 57%（31/54）。13 例患者通过 CNV-seq 检出 9 个致病性及 5 个可能致病性 CNVs，诊断率为 24%（13/54）；trio-WES 检测为 17 个家系筛选出 8 个致病性变异和 9 个可能致病性变异，诊断率为 35%（19/54），其中 13 个为未报道过的新变异。有 3 个家系获得了两个不同的分子诊断。假设分析结果表明，CNV-seq 优先和 WES 优先的分层检测策略均检测周期较长，且具有 97%的敏感性和 3%的漏诊率。
结论 CNVs 和 SNVs/InDels 同时检测策略可避免具有多个分子诊断家系的漏诊，且能够缩短检测周期，为家系再生育的遗传咨询节省时间；对于有多个遗传学病因的患者，分层检测策略可能漏诊；本研究为 26 个 ID 家系明确了遗传学病因。

Hyperhaemolysis in a pregnant woman with a homozygous β0-thalassemia mutation and two genetic modifiers

Jiwu Lou[1] Manna Sun[3] Meixiang Lai[2] Ying Zhao[1] Yanhui Liu[1]
1.Prenatal Diagnostic Center, Dongguan Maternal and Children Healthy Hospital
2.Department of Obstetrics & Gynecolog, Dongguan Liaobu Hospital
3.Department of Obstetrics & Gynecolog, Dongguan Maternal and Children Hospital

Introduction Patients with a homozygous β^0-thalassemia mutation usually have a transfusion-dependent β-thalassemia major phenotype. However, some β-thalassemia patients present with a relatively mild and even normal phenotype and always have a high level of Hb F induced by genetic modifiers.
Methods In this study, we identified a homozygous β^0-thalassemia mutation (*HBB*: c.126_129delCTTT) in a 36-year-old pregnant woman. She had not presented any clinical symptoms of β-thalassemia since birth. To investigate her unexpected mild phenotype, known genetic modifiers that ameliorate the severity of β-thalassemia were analyzed. Besides, we described the haematological changes during pregnancy.
Results Two genetic modifiers (a heterozygous *KLF1*: c.519_525dup mutation and two homozygous *HBS1L-MYB* locus SNP variants, rs7776054 and rs9399137) were identified. However, she showed a gradually decreased level of Hb during pregnancy, and serious transfusion complication of hyperhaemolysis was induced and complicated the pregnancy.
Conclusion This report is in accordance with previous findings that genetic modifiers can ameliorate the clinical severity of β-thalassemia, even without obvious clinical symptoms in a prolonged steady state. However, the steady state can be disrupted during pregnancy. In addition, raising awareness of hyperhaemolysis among clinicians treating patients with thalassemia is necessary.

Genetic and Phenotypic Characteristics of Congenital Hypothyroidism in a Chinese Cohort

Wei Long Fang Guo Yuqi Yang Ying Wang Bin Yu
Changzhou Maternal and Child Health Care Hospital

Background The molecular etiology and genotype-phenotype correlation of congenital hypothyroidism (CH) remain unclear.
Methods We performed genetic analysis in 42 newborns with CH using whole-exome sequencing. Patients were divided into single gene group and multi-gene group according to the number of affected gene, or divided into monoallelic group, biallelic group and oligogenic group according to the pattern of detected variants. Clinical characteristics were compared between groups.
Results Thyroid dysgenesis (TD) was observed in 10 patients and goiter in 5 patients, whereas 27 patients had normal-sized gland-in-situ (GIS). We identified 56 variants in 5 genes in 29 patients. Genes with the most frequent variants were *DUOX2* (69.6 %), followed by *TSHR* (12.5 %), *DUOXA2* (10.7 %), and *TPO* (5.4 %). Variants in the genes causing dyshormonogenesis (DH) were more common than those in genes causing TD (87.5 % versus 12.5 %). Among the patients with detected variants, 26 (89.7%) patients harboring a single gene variant (single gene group), including 21 patients harboring biallelic variants (biallelic group) and 5 patients harboring monoallelic variant (monoallelic group). Three (10.3%) patients harbored variants in 2 or 3 genes (multi-gene group or oligogenic group). Compared with the single gene group, the L-T4 dose at 1 year of age was higher in the oligogenic group (P = 0.018). In addition, the doses at 1 year of age and current in the oligogenic group were higher than those in the biallelic group (P-values were 0.012 and 0.022, respectively) in the comparison between subgroups. A controllable reduction in the L-T4 dose was observed in 53.8 % of the patients in the single gene group, however, no patients were observed in the multi-gene group .

Conclusions Patients with normal-sized GIS accounted for the majority of our cohort. Genetic defects in genes causing DH were more common than those in genes causing TD, with biallelic variants in *DUOX2* being dominant. DH might be the leading pathophysiology of CH in Chinese individuals. Relatively high doses of L-T4 were administered in patients with oligogenic variants. Hence, oligogenic variants might affect the severity of CH.

一例 GM1 神经节苷脂沉积症合并 DMD 家系的遗传学病因分析

黄超 李红 王挺
苏州市立医院

目的 明确一个单唾液酸四己糖神经节苷脂（GM1）神经节苷脂沉积症合并杜氏肌营养不良症（DMD）家系的遗传学病因并进行产前诊断。
方法 联合运用全外显子组测序技术、Sanger 测序技术、染色体微阵列分析技术、染色体核型分析技术、MLPA 技术对该家系先证者及其父母和第二胎胎儿进行基因检测分析。
结果 联合基因检测结果提示家系先证者 *GLB1* 基因存在 c.446C>T（p.S149F）和 c.1214C>T（p.T405I）复合杂合突变，其中 c.446C>T（p.S149F）是已知致病突变，c.1214C>T（p.T405I）为新发突变，但意义尚不明确。两个错义突变分别来自于先证者父亲 c.1214C>T（p.T405I）和母亲 c.446C>T（p.S149F），第二胎胎儿未见 *GLB1* 基因突变，但通过染色体微阵列分析技术检测发现存在 *DMD* 基因外显子 49 缺失，并通过 MLPA 技术验证确认。
结论 单一的遗传学检测应用已难以满足临床遗传咨询的需求，联合应用多种遗传学检测技术手段有助于提高出生缺陷遗传学病因的检出率，对出生缺陷的二、三级预防有着重要的应用价值，也为新时代临床遗传学诊疗方案的改革提供了新的思路。

NeoSeq: A New Method of Genomic Sequencing for Newborn Screening

Bin Yu
Changzhou Maternal and Child Health Care Hospital affiliated to Nanjing Medical University

Objective Recently, genomic sequencing, including whole genome sequencing (WGS), exome sequencing (ES) or gene panel sequencing, has shown potential utility in newborn screening (NBS). It may become another technological innovation, after tandem mass spectrometry (TMS). Although some studies fully demonstrated the advantages and prospects of nGS in new-born screening, there are still many limitations. Here, we started a new project named “NeoSeq”, which is based on the multiplex PCR amplicon sequencing assay (MTA-Seq). We explored the clinical application of NeoSeq in NBS and hope to provide an effective method for new-born genomic screening.
Methods Based on the results obtained from traditional NBS by TMS, three cohorts were recruited into the present study: 36 true positive cases (TPC), 60 false-positive cases (FPC), and 100 negative cases. The dried blood spots of the infants were analyzed with NeoSeq, which is based on multiplex PCR amplicon sequencing. The NeoSeq panel contained 2,500 variations of 135 pathogenic genes, which correspond to 75 types of newborn common genetic diseases. The criteria for diseases and genes to be included in the NeoSeq panel was drawn from the literature and characteristics of common pathogenic genes in the Chinese population.
Results Both NeoSeq and TMS-NGS screening were performed on 196 infants in three cohorts. Overall, the agreement between the results of the two NBS projects was 55.6% (20/36). NeoSeq screening identified 20 of 36 TPC infants with disease-related genes. In addition, five infants (3.1%) with disease-risk variants were found in the FPC and NC cohorts. Both of the methods detected the same genes for the IEM disease. Unexpectedly, eight children with positive IEM results were not identified by NeoSeq. Among sixty infants with TMS false-positive results, NeoSeq was deemed to represent abnormal positive results in three cases. Additionally, NeoSeq analysis identified 42 out of 160 participants (26.3%) as being carriers of a disease in FPC and

NC cohorts. Meanwhile, there was a significant difference in the length of time from testing to diagnosis, between the two methods. With TMS-NGS screening, the participants were able to get results in 20~153 days (median 43 days), although medical interventions were provided in time according to other examinations. In contrast, NeoSeq usually provided results within 7~10 days of testing.

Conclusions NeoSeq is an effective method of genomic sequencing for newborn screening. It can detect most inborn errors of metabolism, reduce the rate of false positive results, shorten the reporting cycles, and reduce the screening cost.

Molecular Genetic Screening of Neonatal Intensive Care Units Using Targeted Next-Generation Sequencing: Hyperbilirubinemia as an example

Yuqi Yang Yu Wang Wei Long Lingna Zhou Bin Yu Huaiyan Wang
Changzhou Maternal and Child Health Care Hospital affiliated to Nanjing Medical University

Objective To explored the clinical application of newborn genomic screening of neonatal hyperbilirubinemia，and hope to provide an effective method for NICU infants.

Methods 96 hyperbilirubinemia newborns were enrolled in this study. Dried blood spots (DBSs) were collected after 72 hours of birth, and were carried out the tandem mass spectrometry (TMS) screening and Angel Care genomic screening (GS, based on Targeted next generation sequencing) at the same time.

Results No infant were identified with inborn errors of metabolism (IEM) by TMS, while 6 infants (6.25%, 6/96) were suspected to have a genetic disorder by Angel Care, including 2 cases of Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD), and 1 case of Maple Syrup Urine Disease Type 1B (MSUD1B), Autosomal Recessive Deafness 1A (DFNB1A), Leber Hereditary Optic Neuropathy (LHON), Thyroid dyshormonogenesis 6 (TDH6) each. In addition, 44 infants (45.8%) were detected having at least one variant which confers a carrier status for a recessive childhood-onset disorder. 33 (55.0%) out of 60 variants reported for carrier status are pathogenic (P), 24 (40.0%) are likely pathogenic (LP), and 3 variants are variant of uncertain significance (VUS). Top six common genes of carrier status were *GJB2*, *DUOX2*, *PRODH*, *ATP7B*, *SLC12A3*, *SLC26A4*. Two newborns showed abnormalities in eliminary screening o TMS, but were confirmed as false positive after recall. Their results of Angel Care didn't found abnormality.

Conclusions Neonatal hyperbilirubinemia is closely related to genetic variation. "Angel Care" is an effective method of genomic sequencing for newborn screening.

1 例以双下肢乏力为主要症状的青春期儿童戊二酸血症 II 型的病例报道

钟燕兰 曾华松
广州市妇女儿童医疗中心

戊二酸血症Ⅱ型又称多种酰基辅酶 A 脱氢酶缺乏症，是一种以低酮或非酮症性低血糖症和代谢性酸中毒为临床特征的遗传代谢病，为常染色体隐性遗传病。临床表现轻重不一，如能早期发现、合理治疗，部分患儿预后较好。本文报道以双下肢乏力为主要症状的青春期儿童戊二酸血症 II 型的病例。

病例报道 患儿，女，13 岁，主诉"双下肢乏力近 2 年"，曾在外院住院，考虑免疫性肌炎可能，仅予以瑞安吉口服治疗后，患儿双下肢乏力症状有好转，但后又反复且较前有加重，故于 2020-11-10 入住我院风湿免疫科。入院后查肌酸激酶、乳酸升高，炎症指标无明显异常，大腿 MRI 示皮肌炎改变可能。故为明确诊断进一步行肌活检，结果示：符合脂质沉积病理改变。考虑与典型的皮肌炎病理改变不符，需考虑是否存在代谢异常，行尿液 GCMS 及血酰基肉碱分析均示：符合戊二酸

血症Ⅱ型。也完善了戊二酸血症Ⅱ型 ETFDH 基因分析，示：发现复合杂合突变，分别源自父母。综上所述，该病例戊二酸血症Ⅱ型诊断明确。治疗上予以大剂量维生素 B2、辅酶 Q10、左卡尼丁口服，患儿双下肢乏力较前好转。

讨论 戊二酸血症Ⅱ型分为 3 种类型，即新生儿期发病伴先天畸形、新生儿期发病不伴先天畸形，以及轻症和/或迟发型。本病例为迟发性戊二酸血症Ⅱ型。迟发性戊二酸血症Ⅱ型临床表现多变。病人可在生后数周出现间歇发作性呕吐、低血糖症和酸中毒，或在儿童期无任何症状，成人期出现发作性呕吐、低血糖、肝大和近端肌病。其它表现可有进行性脂质沉积性肌病、肉碱缺乏或进行性锥体外系运动障碍等。本案例患者为青春期儿童，以双侧下肢乏力为主要症状，且伴有 CK 升高，大腿 MRI 示皮肌炎改变可能，肌活检提示脂质沉积病理改变，临床上容易误诊为免疫性肌炎，因此在临床对于不典型肌炎诊断时需要考虑为戊二酸血症等代谢性疾病可能，需要进一步鉴别。

TRNT1 突变致 SIFD 临床特征及基因分析

陈香元 曾华松
广州市妇女儿童医疗中心

目的 分析一家非血缘关系的姐弟两人 TRNT1 突变致铁粒幼细胞贫血、B 细胞免疫缺陷、周期性发热和发育迟缓（SIFD）的临床特征及基因表型，为临床医生对 SIFD 的认识提供参考。

方法 收集广州市妇女儿童医疗中心免疫风湿科确诊的 2 例姐弟 SIFD 患儿的临床资料，抽取患儿及其父母外周血进行全基因组测序分析。

结果 先证者，女，14 岁，自生后 9 月起出现反复发热、炎症标志物升高。2 岁左右出现双眼白内障并失明，伴有右膝关肿痛伴发屈曲畸形。发育迟缓，生长停滞，至今不会说话，不能行走，无月经来潮。先证者同胞弟弟，男，7 岁，生后 3 月左右体检发现低免疫球蛋白血症，B 细胞计数正常。4 月起出现腹泻，8 个月左右因发热、支气管肺炎、腹泻住院，此后易反复发热、腹泻。生后 19 个月时出现双膝关节炎，2 岁出现双眼白钠障，复查免疫球蛋白 A 低于正常，B 淋巴细胞计数正常，自 27 月起不定期输注免疫球蛋白，关节肿痛渐有好转，发热次数减少。发育迟缓，生长停滞，能说简单的 3～7 字的短句，发音欠清晰，能理解并执行父母的命令。能独走，稳定性欠佳。患儿及其父母外周血进行全基因组测序发现 TNRT1 双等位基因复合杂合突变，c.1056+1G>A/c.1246A>G(p.K416E)。

结论 TRNT1 基因突变致 SIFD 为常染色体隐性遗传性疾病，其临床表现多样，进行基因检测明确 TRNT1 基因致病突变是临床诊断的依据。临床医生提高对该病的认识，早期诊断及干预处理可提高生活质量。

1 例 X 连锁淋巴增殖综合征临床特征和诊断

黄怡玲 曾华松
广州市妇女儿童医疗中心

患儿，男，14 岁，从 5 岁起出现周期性发热、皮疹，表现为反复高热，伴畏寒、寒战，全身肌肉酸痛及乏力，全身皮疹，伴瘙痒。无四肢关节疼痛，无咳嗽，无腹痛、腹胀，精神倦，大小便正常。发病期多次查外周血白细胞总数减少，EBV 壳抗原 CA-IgM 阳性，铁蛋白明显升高，肝功能异常。嗜血细胞综合征突变基因报告：未检测到致病基因突变点。2011 及 2015 年先后在本院诊断传染性单核细胞增多症？幼年特发性关节炎（全身型）？巨噬细胞活化综合征？予甲泼尼龙、环孢素治疗，体温可降至正常，后甲泼尼龙、环孢素逐渐减停。此次因反复发热、皮疹 1 月余入院。既往有慢性肛裂、混合痔、食管溃疡病史，对淡水鱼、鸡蛋、青霉素严重过敏，多次注射疫苗后有过敏反应，母亲有自然流产病史 1 次，外祖母及母亲均容易过敏。

实验室检查：血常规 白细胞 2.3×10^9/L, 血红蛋白 99g/L, 血小板 127×10^9/L, 中性粒细胞 21%。ESR、CRP 正常。铁蛋白 3212.10ng/mL。免疫球蛋白、淋巴细胞计数未见异常。自身抗体阴性。骨髓涂片示反应性骨髓象。代谢生化 1：丙氨酸氨基转移酶 258U/L, r-谷氨酰转移酶 254U/L,, 甘油

三酯 1.91mmol/L, 高密度胆固 1.88mmol/L。EBV 壳抗原 CA-IgG 阳性, EBV 核抗原 NA-IgG 阳性, EB 病毒 IgG 抗体高亲合力 阳性(+)。肝炎全套、CMV、呼吸道病原体 gM 检测均阴性。超声：肝、脾大。胆囊、胰未见明显异常。普通心电图：窦性心律大致正常心电图。X 光照片：胸部未见明确异常。

基因分析：该样本分析到 XIAP 基因有 1 个半合子突变基因：XIAP 染色体位置 ：chrX-123022478- 12302248 转录本外显子： NM_0011 67;exon3 核苷酸氨基酸 ： c.888_892 del (p.K299L fs*8 ）致病性分析 ：Pathogenic ，遗传方式 ：XLR，疾病表型：X 连锁淋巴增殖综合征 2 型 。变异来源：患儿母亲。

一例 22q11.2 微缺失综合征患儿的遗传学分析

王海芹 何红琴
山西省运城市妇幼保健院

目的 探讨 1 例发育迟缓患儿的遗传学病因。

方法 首先采集患儿外周血并提取 DNA,然后通过低深度全基因组测序技术（copy number variation sequencing, CNV-seq）对患儿的基因组进行分析。

结果 患儿的 CNV-seq 结果为 22q11.21 存在约 2.58Mb 杂合缺失（22q11.21（18880001-21460000）x1，hg19），该缺失片段完全覆盖 Decipher 数据库收录的 22q11 缺失综合征(Velocardiofacial / DiGeorge syndrome)的区域，综合分析认为 22q11.2 微缺失综合征是导致患儿发育迟缓的主要原因。

结论 22q11.2 微缺失综合征是是一种多系统疾病，表型几乎涉及机体各个部分，即使在同一家系的患者中也具有表型异质性，儿童中该病的发病率约为 1/3000。通过使用 CNV-seq 基因检测技术能提高 22q11.2 微缺失综合征患儿的确诊率,为早期临床干预提供依据。

先天性手足裂 III 型基因型及表型变异

张秀泉[1] 王建[2] 熊符[2] 吕伟标[3] 杨少民[4]
1.南方医科大学顺德医院妇产科
2.南方医科大学基础医学院医学遗传教研室
3.南方医科大学顺德医院检验科
4.南方医科大学顺德医院放射科

先天性手/足裂畸形（Splited hand-foot malformation, SHFM）严重影响患者手的精细运动和心理健康。SHFMⅢ型病因乃染色体 10q24.31-32 区域重复，该位点的 10q24.31 基因重复拷贝的基因片段与表型发病有关。目的：我们鉴定了一个 SHFMⅢ型家族遗传病基因，并分析了患者的遗传和表型变异。方法：阵列 CGH 检测发现该家族患者中存在一个重复的 678kb 的 10q24.31 片段。然而，单倍型频率分析发现母系单体在兄弟间遗传不同。结果：先证者的母系遗传单倍体检测结果(165-251- 289-219-102)显示与其弟弟的母系遗传单倍体结果(165-251-289-219-107)有一个基因位点差异。然而，在表型表现上，先证者有典型的 SHFM，表现为末端肢体中轴严重畸形，发育不良，第二和第三指/趾发育不良，手足正中分裂。与先证者的表型相比，其弟弟的畸形较小，只有第三右中趾发育不良和第一和第二右趾融合。结论：10q24.31 的重复不仅引起典型的 SHFM，而且其基因单倍型差异可能与表型的临床表现有关。由此提出一个问题，那就是 102 位点是不是胚胎发育过程中形成典型 SHFM 的关键，还是环境因素在胎儿早期发育过程中起着关键作用，值得进一步研究。

Two novel mutations in TCIRG1 induced infantile malignant osteopetrosis: a case report

Ping Wu
Guangzhou Women and Children's Medical Center

Background Infantile malignant osteopetrosis (IMO) is a rare autosomal recessive disease characterized by a higher bone density in bone marrow caused by the dysfunction of bone resorption. Clinically, IMO can be diagnosed with medical examination, bone mineral density test and whole genome sequencing.
Case presentation We present the case of a 4-month-old male infant with abnormal skull development, hypocalcemia and premature closure of the cranial sutures. Due to the hyper bone density showed by his radiographic examination, which are characteristic patterns of IMO, we speculate that he may be an IMO patient. In order to confirm this diagnosis, a high-precision whole exome sequencing of the infant and his parents is performed. The analysis of high-precision whole exome sequencing results lead to the identification of two novel heterozygous mutations c.504-1G>C (a splicing site mutation) and c.1371delC (p.G458Afs*70, a frameshift mutation) in gene TCIRG1 derived from his parents. Therefore, we suppose that there is a close association between these two mutations and the onset of IMO.
Conclusions To date, these two novel mutations in gene TCIRG1 have not been reported in the reference gene database of Chinese population. These variants have likewise not been reported outside of China in the Genome Aggregation Database (gnomAD). Our case suggests that the whole exome sequencing to detect these two mutations will improve the identification and early diagnosis of IMO, specifically the identification of homozygous individuals with TCIRG1 gene mutation. We propose that these mutations in gene TCIRG1 could be a novel therapeutic target for the IMO in the future.

雄激素不敏感综合征患者细胞分子遗传学研究与临床分析

张建林[1] 张俊荣[1] 姚金含[2] 徐琳婕[2] 苏敏[1] 张玉泉[1] 肖明兵[1]
1.南通大学附属医院
2.南通大学

目的 分析 1 例原发性闭经患者的遗传学病因。
方法 收集患者的临床资料，采集外周血行 G 显带染色体核型分析、单核苷酸多态微阵列芯片（single nucleotide polymorphisms array, SNP array）分析后，使用目标区域捕获及二代测序（next generation sequencing, NGS）技术对与性发育及分化异常相关的致病基因进行检测，Sanger 测序对患者及其母亲 AR 基因进行验证。
结果 患者染色体核型为 46, XY，SNP array 未发现微缺失微重复。二代测序结果为雄激素受体（androgen receptor, AR）基因 c.1832dup（p.N611Kfs*12）半合子变异，为移码突变。Sanger 测序验证患者 AR 基因突变源于其表型正常的杂合变异携带者母亲。
结论 患者 AR 基因突变与雄激素不敏感综合征（androgen insensitivity syndrome, AIS）相关，结合其临床体征、性激素及影像学检查，考虑完全型雄激素不敏感综合征（complete AIS，CAIS）是该患者青春期原发性闭经的原因。

ACE 和 MTHFR 基因多态性与柳州地区妊娠高血压综合征发病的相关性研究

张美瑜 严提珍
柳州市妇幼保健院

目的 探讨孕产妇外周血 *ACE* 和 *MTHFR* 的基因多态性与妊娠高血压综合征（PIH）发病的相关性，以了解相关基因多态性在本地区人群遗传的分布情况，为妊娠女性预防 PIH 的发生发展提供理论依据。
方法 选取 2018 年 05 月到 2019 年 09 月在本院分娩的符合 PIH 诊断标准的孕妇 200 例作为疾病组，并按年龄相差<3 岁为配比条件，以 1：1 配对的方式选取本院非 PIH 孕妇 200 名作为对照组。采用多色探针熔解曲线分析技术反应体系（MMCA）检测 *ACE* 和 *MTHFR* 的基因多态性，统计基因多态性频率分布情况，比较两组别中相关基因多态性的异常情况与 PIH 的相关性，评估孕妇 PIH 的发生风险。
结果 *ACE I/D* 基因型频率（疾病组/对照组）：DD 型 10.28%/10.73%，ID 型 40.19%/45.50%，Ⅱ型 49.53%/43.78%，疾病组和对照组基因型频率比较无显著性差异（*P*>0.05）；*MTHFR 667C>T* 基因型频率（疾病组/对照组）：CC 型 54.20%/57.51%，CT 型 40.19%/35.62%，TT 型 5.61%/6.87%，两组基因型频率比较无显著性差异（*P*>0.05）。两组间妊娠期高血压风险级别分布差异无统计学意义。
结论 *ACE I/D* 和 *MTHFR 667C>T* 基因多态性在柳州地区妊娠期高血压孕妇人群及妊娠非高血压孕妇人群间分布无显著性差异，可能不是妊娠高血压疾病的危险因素，与妊娠高血压疾病的发病无明显相关性，但也可能是回顾性研究的局限性导致的研究偏差。

口腔黏膜细胞染色体检查在 Turner 综合征遗传效应中的应用价值

张美瑜 韦小妮 陆碧玉 韦朔峰 徐玉婵 罗世强 严提珍
柳州市妇幼保健院

目的 探讨口腔黏膜细胞染色体联合外周血染色体检查在 Turner 综合征遗传效应中的应用价值。
方法 采集患者的肘静脉血进行外周血淋巴细胞染色体核型检查，利用 G 显带技术对染色体核型进行分析；同时采集外周血及口腔黏膜细胞提取 DNA 后进行 MLPA 检测。
结果 外周血 G 显带染色体核型分析结果为 45,X[95]/47,XXX[4]/46,XX[1]，45,X 嵌合比例为 95%；而 MLPA 结果显示外周血为 X 杂合缺失，而口腔黏膜细胞未检测出异常。MLPA 提示了两组织间核型结果不一致的结果。
结论 同一个个体不同组织间染色体核型不一定完全一致，外周血淋巴细胞核型分析是诊断 Turner 综合征的金标准，联合口腔黏膜细胞染色体检查可作为评估患者整体染色体构成的有效工具，为临床提供有效的诊疗依据。

基于高通量测序方法对 123 例女性进行妇科肿瘤易感基因遗传学分析

徐盈
西京医院

【摘要】目的：评估高通量测序方法在鉴定妇科肿瘤患者致病性变异的临床应用价值。**方法：**应用 Ion PGM Hi-Q 高通量测序方法对 123 例不同适应症的女性（67 个肿瘤患者、16 个有癌症家族史的女性和 40 个健康体检者）进行妇科肿瘤相关的易感基因的胚系变异检测，并通过 Sanger 测序

法对可疑致病性突变进行验证。**结果**：受试者筛查的平均年龄为 52.3±10.1 岁，范围 26~75 岁。在 123 例筛查人群中共检测出阳性样本 24 例，阳性率为 19.5%。其中在妇科肿瘤患者样本中鉴定出 14 种不同胚系突变 BRCA1c.4801A>Tp.Lys1601Ter，BRCA1c.5251C>Tp.Arg1751Ter，BRCA1c.2110_2111delAAp.Asn704fs，RAD51Cc.1026+1G>C，MUTYHc.1037C>Tp.Ser62Leu, BRCA1c.2572C>Tp.Gln858Ter，BARD1c.1075_1095delTTGCCTGAATGTTCTTCACCA，STK11c.1062C>Gp.Phe354Leu，BRCA1c.5586delTp.ser1862fs，BRCA1c.2694insAp.Lys898fs，BRIP1c.2440C>Tp.Arg814Cys，MLH1c.1151T>Ap.Val384Asp，BRCA1c.3895C>Tp.Gln1299Ter，TP53c.797G>Ap.Gly266Glu。在具有肿瘤家族史女性样本中鉴定出 2 种可能致病性突变 *BRCA1*c.2694insAp.Lys898fs 和 *BRCA1*c.3288_3289delTT。而在查体女性外周血样本中检测到 3 种临床意义不明确或可能致病性突变 *MLH1*c.1151T>Ap.Val384Asp，*RAD51D*c.184C>Tp.Gln62Ter 和 *MSH6*insTTGAp.-1356L。**结论**：该研究扩大了妇科肿瘤风险相关基因突变谱，提示基于 NGS 的多基因检测方法可以有效筛查妇科遗传性肿瘤相关的致病突变，从而预测特定肿瘤的风险，开展针对性的健康管理。

EYA1 基因新杂合突变导致鳃耳综合征

王际平[1] 吴红敏[1] 周慧群[1] 陈正侬[1] 时海波[1,2] 殷善开[1,2]
1.上海交通大学附属第六人民医院耳鼻咽喉头颈外科
2.上海市睡眠呼吸障碍疾病重点实验室

目的：鳃裂-耳综合征（Branchio-Oto syndrome，BO）是一种常染色体显性遗传的综合征型耳聋，主要表现为双侧鳃裂瘘管或囊肿、感觉神经性和（或）传导性听力丧失、耳前凹以及外耳、中耳或内耳的结构缺陷。本研究对一散发病例进行研究分析，以期揭示耳聋患者的遗传性致病因素。
方法：先症者 23 岁，出生时有鳃裂瘘，10 岁时进行过相关手术治疗，12 岁左右发现有听力异常，左侧耳听力下降。对先证者进行全面的体格、听力学及影像学的检查。提取其核心家庭成员外周血有核细胞基因组 DNA，进行全外显子测序及相关生物信息学分析。对先症者一家及 200 名听力正常人群的候选突变位点进行 Sanger 测序验证。
结果：听力学检测证实患者左耳为中重度混合性聋，影像学显示患侧有听骨链异常；全外显子测序和遗传分析显示家系先证者携带 EYA1;NM_000503.4:c.1577T>G(p.Ile526Ser)突变。依据 ACMG 指南，该变异被判断为意义未明变异（PM1+PM2+PP3）。Sanger 测序验证该突变仅存在于先症者，父母无携带，提示该突变为新发突变；一代测序验证显示 200 名听力正常人均不携带该突变。
结论：本研究提示 EYA1(1577T>G)杂合突变可能是先症者 BO 的遗传病因，据此为先症者提供了婚育相关的遗传咨询建议。该位点的发现丰富了 EYA1 基因突变导致的 BO 突变谱。

一例四氢生物蝶呤缺乏性高苯丙氨酸血症 A 型患儿的临床特点及基因分析

崔晓玉[1,2] 刘洋[1] 周伟玮[1,2] 聂艳艳[1] 刘晓军[1] 张芳[1] 舒剑波[3,4]
1.天津市儿童医院（天津大学儿童医院）新生儿内科
2.天津医科大学研究生院
3.天津市儿科研究所
4.天津市儿童出生缺陷防治重点实验室

目的 本研究旨在对 1 例四氢生物蝶呤缺乏性高苯丙氨酸血症 A 型患儿的临床特点及基因分析进行分析，提高对本病的认识。
方法 回顾分析天津市儿童医院新生儿内科 1 例四氢生物蝶呤缺乏性高苯丙氨酸血症 A 型患儿的临床特点、遗传学检测、家系 sanger 验证信息及实验室检测资料。

结果 患儿 1 月时因“精神弱、吃奶差”就诊，主要表现为睡眠及吃奶时间延长，吃奶量减少，吸吮无力。血苯丙氨酸 25.37mg/dl；氨基酸分析示苯丙氨酸 377.3umol/L；尿筛示高苯丙胺酸血症可疑；血筛示 Phe，Cit/Arg，Phe/Tyr，Tyr/Leu 增高，Asp，Pro，数种氨基酸比值降低。换用婴儿苯丙酮尿症患儿配方奶喂养后患儿精神反应及吃奶较前好转。遗传学检测示患儿 *PTS* 基因存在第 5 外显子 c.286G>A (p.Asp96Asn)杂合变异和第 6 外显子 c.317C>T (p.Thr106Met)杂合变异。Sanger 测序结果显示第 5 外显子 c.286G>A 遗传自父亲；第 6 外显子 c.317C>T 遗传自母亲。经过生物信息学软件预测，c.286G>A 变异为致病变异；c.317C>T 为可疑致病变异。

结论 新生儿期出现持续性精神弱、吃奶差的患儿，应警惕高苯丙氨酸血症等遗传代谢性疾病的可能，苯丙酮尿症配方奶喂养有助于病情的缓解。遗传学检测有助于此类患儿的早期诊断和治疗，以及病情评估及遗传咨询。

1 例新生儿复杂染色体畸变报告

孙超[1] 刘洋[1] 崔晓玉[1,2] 周伟玮[1,2] 张芳[1] 舒剑波[3,4]
1.天津市儿童医院（天津大学儿童医院）新生儿内科
2.天津医科大学研究生院
3.天津市儿科研究所
4.天津市儿童出生缺陷防治重点实验室

目的 染色体畸变是导致新生儿致死致残的重要原因之一，本文报告 1 例复杂染色体畸变患儿，以提高对此类疾病的认识。

方法 回顾分析天津市儿童医院新生儿内科 1 例复杂染色体畸变患儿的临床特点及遗传学检测资料。

结果 患儿出生后 9 小时因“呼吸困难 9 小时”就诊，主要表现为小于胎龄儿，呼吸衰竭，右侧第 3 足趾与第 4 足趾部分重叠及左侧隐睾。肺 CT 及三维重建提示存在右主支气管及其分支纤细，超声心动提示存在肺动脉瓣狭窄。遗传学检测示染色体核型为 46，XY；5 号染色体 p15.33p15.2(140413-14769310)X3 存在 14628.897kb 的片段重复，以及 18 号染色体 q21.31q23(55711883-78005241)X1 存在 22293.358kb 的片段缺失，其中 18 号染色体的缺失突变可引起 18q 缺失综合征。

结论 对于多发畸形的新生儿应及时完善遗传学检测。18 号染色体 q21.31q23 覆盖多个关键致病区域，可能是导致患儿异常表型的主要原因。

Chromed CpG 在慢性淋巴细胞增生性疾病的骨髓染色体核型分析中的应用效果分析

谢节 任远亮
合肥金域医学检验实验室有限公司

目的 探讨使用骨髓细胞培养添加剂（Chromed CpG）添加到骨髓细胞培养基中，做骨髓染色体培养的技术方法，分析可行性。方法 使用本室 2020 年 3 月到 2021 年 7 月的 120 例慢淋及慢性 B 淋巴细胞增生性疾病的样本，使用两种不用的培养方法，对其培养制片后的效果进行统计分析。结果 对照组不添加 CpG,培养成功率为 8.3%，阴性结果占 6.7%，阳性结果占 1.7%，实验组添加 CpG,培养成功率为 89.2%，其中阴性结果占 65.8%，阳性结果占 23.3%，差异具有统计学意义（P<0.05）。结论 通过本实验研究发现用 Chromed CpG 能够刺激成熟的 B 淋巴细胞，提高骨髓染色体的培养成功率，提高异常检出率。

45,XX,psu idic(7)(p22.3)一例

李琳
临沂市人民医院

患者，女，23 岁。结婚 2 年，妊娠 3 次均于 40 天左右自然流产。月经规律。体检：妇科检查正常，优生四项检查及内分泌检查无异常。夫妻非近亲结婚，孕期无患病及服药史，无有毒有害物质及放射线接触史。细胞遗传学检查：常规外周血淋巴细胞培养、染色体制备、G 显带分析，计数 30 个分裂相，镜下分析 5 个，患者核型为 45，XX，psu dic(7)(qter→p22.3::p22.3→qter)，见图 1；患者丈夫表型、染色体核型正常。
家系调查：父母结婚 25 年，母亲月经规律，生育 3 女，无异常妊娠生育史。患者 2 个妹妹未婚。父母染色体核型正常。
讨论 具有两个着丝粒的染色体称为双着丝粒染色体（dicentric chromosome,dic），由于双着丝粒染色体在细胞分裂的后期可形成染色体桥，故它是一种非稳定性的结构畸变，一般不能在人体中保存。在人类中已记载的仅有以下两种：①两个着丝粒极为靠近的衍生染色体，如 dic（Y）、dic（X）、dic（13；14）（p11;p11）等。②在两个或多个着丝粒中仅一个有功能的假双或假三着丝粒染色体（pseudodicentric chromosome,psudic; pseudotricentric chromosome,psutri），由于这种染色体可能是由于两个染色体的断裂和不对称性交换或端端相接形成，故又名末端重排（terminal rearrangement,ter rea），如 45，XX, ter rea(12;14)(12qter→cen→12p13::14p13→14qter)，即这种细胞有 45 条染色体，一个第 12 号染色体和一个第 14 号染色体发生了末端重排，14 号染色体的着丝粒失活，仅 12 号染色体的着丝粒具有活性。本例 45，XX，psu dic(7)(qter→p22.3::p22.3→qter)由两个 7 号染色体的短臂末端相接形成。可以推测，仅有一个 7 号染色体着丝粒有活性。该核型形成机制不明。

一例 Prader-Willi 综合征患儿的遗传学分析

王海芹[1] 夏艳洁[2]
1.山西省运城市妇幼保健院
2.郑州大学第一附属医院

【摘要】 目的 采用基因检测技术协助一例 Prader-Willi 综合征可疑患儿明确诊断。 **方法** 首先采集患儿外周血并提取 DNA,然后采用甲基化特异性多重连接依赖性探针扩增技术（MS-MLPA）检测患儿 Prader-Willi 综合征基因组印记区域 15q11～q13 的父源性片段和母源片段的缺失/重复情况。 **结果** 患儿 Prader-Willi 综合征基因组印记区域 15q11～q13 存在父源/母源片段缺失。结合患儿的临床表现，推测其为 15q11～q13 印记区域父源性缺失导致的 Prader-Willi 综合征患者的可能性大。 **结论** Prader-Willi 综合征是一种涉及多器官组织的遗传综合征，大部分（70%）是由于父源染色体 15q11～q13 区间微缺失，约 25%由于该染色体区间的母源单亲二倍体。通过使用 MS-MLPA 基因检测技术能提高 Prader-Willi 综合征可疑患儿的确诊率,为早期临床干预提供依据。

A case report of primary infertility with BPES syndrome with FOXL2 gene mutation and PADI6 gene mutation

Zhao Zhang[1] Hongbo Wu[1] Yueyuan Jiang[2] Shisheng Lin[2] Yuling Shi[2]
1.The Maternal and Child Health Hospital of Qinzhou
2.GuangXi Medical University

The human forkhead boxl2 (FOXL2) gene is closely related to female ovarian function. Mutations in the FOXL2 gene often lead to BPES syndrome[1] BPES is divided into POF (BPES type I) and non-POF (BPES type II). Studies have shown that multiple FOXL2 gene loci are related to this syndrome. Patients with BPES I syndrome usually need assisted reproductive technology to

obtain successful pregnancy. However, this case report shows that when the FOXL2 gene is combined with PADI6 gene mutation, patients may have egg maturation disorder in addition to premature ovarian failure. As a result, the patient cannot obtain embryos during art, which eventually leads to the patient's inability to obtain pregnancy.
This report further confirmed the relationship between FOXL2 gene mutation and BPES type I and showed that patients with FOXL2 gene mutation combined with a PADI6 gene mutation might be complicated with egg maturation disorder and POF. Therefore, the purpose of this paper is to provide more basis and help for clinical diagnosis

甲基丙二酸血症表观遗传学检测

王朝[1,2,3] 王洪[1] 李东[1] 舒剑波[1,2,3]
1.天津市儿童医院（天津大学儿童医院）
2.天津市儿科研究所
3.天津市儿童出生缺陷防治重点实验室

目的

甲基丙二酸血症（Methylmalonic Acidemia, MMA）是一类由甲基丙二酰辅酶-A 缺陷或钴胺素代谢障碍引起的罕见的遗传性代谢病，主要以常染色体隐性方式遗传，根据是否合并同型半胱氨酸血症和致病基因可分为多种不同亚型。目前发现部分患儿基因致病模式并非双等位基因突变，表观遗传学改变发挥着同等重要的作用，本研究旨在探讨表观遗传学检测在 MMA 中的意义。

方法

对 MMA 患儿进行全面的体格和实验室检查，检测血清维生素 B_{12} 浓度以排除继发性 MMA。以质谱法对患儿血液和尿液中的代谢产物进行筛查。结合 Sanger 测序法和高通量测序技术以经典遗传模式对 MMA 家系进行基因分析。以 Sanger 测序法对基因检测结果为阴性的合并型 MMA 患儿的 *PRDX1* 基因编码区和内含子外显子交界区进行突变检测。以甲基化特异性的 PCR（Methylation-specific PCR，MSP）和亚硫酸氢盐测序法（Bisulfite sequencing PCR，BSP）对 *MMACHC* 基因启动子和第一外显子区（CpG 岛）行甲基化检测。

结果

共 55 例临床确诊的 MMA 患儿进行了基因检测，在其中 52 例患儿中检测出复合杂合突变或纯合突变，这些突变均为明确的致病性突变。在 1 例合并型 MMA 患儿 *MMACHC* 基因中只检测到一个杂合致病突变 c.658_660delAAG（p.Lys220del），在另外 2 例合并型 MMA 患儿中未检测到可解释的致病突变。通过 Sanger 测序未在上述 3 例 MMA 患儿的 *PRDX1* 基因编码区及剪接位点区域发现可疑的致病性突变。MSP 和 BSP 结果显示上述 3 例患儿 *MMACHC* 基因启动子 5'端 CpG 岛呈非甲基化状态。

结论

表观遗传学检测可以作为遗传病致病基因检测经典分析模式的补充，*PRDX1* 基因变异所致 *MMACHC* 基因表观遗传学改变可以解释个别未找到完整双等位基因突变的 MMA 病例，但是仍然有部分病例未在基因组层面找到原因，相关检测技术和致病机制有待进一步探索。

Identification of a homozygous synonymous variant in the PLOD1 gene in a Chinese neonatal family with the Ehlers-Danlos syndrome

xiaodan Yan Yang Liu Jianbo Shu Yanyan Nie Ying Zhang Ping Wang Weiwei Zhou Xiaoyu Cui
Tianjin Children's Hospital

Background:The kyphotic type of Ehlers-Danlos syndrome (EDS ⅥA; OMIM225400) is a rare autosomal recessive genetic disease caused by variants in the PLOD1 gene. This research was to verified the disease-causing gene in a Chinese neonatal family with the Ehlers-Danlos syndrome.
Methods: We recruited a Han Chinese neonatal family with kyphotic Ehlers-Danlos syndrome, including three members in this research and the proband was without kyphoscoliosis. Whole exome sequencing was conducted by the proband and Sanger sequencing was performed on all family members to confirm the variants. The variants site was predicted affecting splicing by NetGene2 Server. We further conducted reverse transcription PCR and quantitative real-time PCR on all family members to verify that the synonymous variant affected splicing function.
Results: A homozygous synonymous variant, c.1095C > T (p.Gly365=) in the PLOD1 gene was found and verified in the family with kyphotic Ehlers-Danlos syndrome. This variant resulting in premature termination codon of exon 10 affect the expression of the four bases GCGC. The expression level of qPCR in the proband was impaired, indicating that the variant affected mRNA splicing and protein function.
Conclusion: Our research verified a homozygous synonymous variant in a Chinese neonatal family, which contributed to a better understanding of the molecular pathogenesis of PLOD1.

一个 Pendred 综合征家系 SLC26A4 基因的突变分析

周伟玮 刘洋 闫晓丹 舒剑波
天津市儿童医院

目的 本研究旨在对 1 例 Pendred 综合征患儿进行致病基因的遗传学分析，提高对本病的认识。
方法 回顾分析了天津市儿童医院 1 例听力障碍新生儿，*SLC26A4* 基因突变导致的 Pendred 综合征的遗传学检测、家系 sanger 验证信息。
结果 遗传学检测示先证者 *SLC26A4* 基因存在第 8 号外显子 c.919-2A>G 纯合变异，为已报道的致病变异。Sanger 测序结果显示突变遗传自父亲及母亲。经过软件预测，证实 c.919-2A>G 为剪接位点突变。
结论 *SLC26A4* 基因突变引起的 PDS，c.919-2A>G 剪接位点突变是本例患者的致病原因。全外显子组测序技术对遗传综合征性耳聋的诊断具有很大优势，对患者的遗传咨询和产前诊断具有重要意义。

一例 Turner 综合征患者的临床及遗传学分析

赖怡
四川大学华西第二医院

目的 探讨 1 例一例 Turner 综合征患者的遗传学病因，并分析两种检测方法检测复杂性结构异常合并数量异常核型的效果。
方法 应用常规染色体 G 显带核型分析和染色体微阵列分析（chromosome microarray analysis,CMA）两种方法对患者进行检测。

结果 患者的核型分析结果为 46,X,der(X)(qter→q13::p22→qter)[35]/45,X[15]，CMA 结果为缺失 arr[GRCh38]Xp22.33p22.2 （ 251888-13032423 ） ×1 （ 12.781Mb ） 和 缺 失 （ 嵌 合 型 ） arr[GRCh38]Xp22.2q13.1（13032423-68787736）×1.5（55.755Mb）。
结论 对于复杂的染色体结构异常合并数量异常时，可结合常规染色体 G 显带核型分析和 CMA 两种方法一起分析，必要时加做荧光原位杂交（fluorescence *in situ* hybridization,FISH）以明确嵌合比例。

一例复合杂合胱氨酸尿症家系临床表现及基因突变研究

王子秋[1,2] 王朝晖[1]
1.上海交通大学医学院附属瑞金医院 2.上海交通大学医学院

目的 通过分析 1 例胱氨酸尿症家系，探讨胱氨酸尿症的临床特征、诊治要点及致病基因突变。
方法 搜集分析 1 例胱氨酸尿症家系病例资料，提取先证者及家系成员外周血 DNA 样本，利用目标序列捕获高通量测序技术筛查突变基因，并结合文献探讨胱氨酸尿症的诊疗进展。
结果 该家系先证者为 28 岁男性，首诊于 15 岁，主要临床表现为复发性泌尿道结石合并轻度蛋白尿，结石成分测定为 L-胱氨酸。其母亲主要表现为轻度蛋白尿，父亲无肾脏受累症状。测序结果示先证者存在 SLC3A1 基因复合杂合突变（NM_000341:exon3:c.703delG:p.D235Ifs*21）及（NM_000341:exon8:c.1366C>T:p.R456C）。经过软件预测评分（包括 PolyPhen2、SIFT、REVEL）、保守性分析、家系相关成员 Sanger 测序验证，据 ACMG 指南评分后，两突变均判定为疑似致病性变异。家系验证证明上述 3 号外显子突变来源为先证者母亲，为新突变，其致病性证据为 PVS+PM2；8 号外显子突变来源为父亲，致病性证据为 PS1+PM2+PP3+BS2。
结论 胱氨酸尿症是一种常染色体隐性遗传病，其临床表现主要为复发性泌尿道结石。在该家系中，先证者临床表现符合胱氨酸尿症，且存在分别源自父母的 2 种 SLC3A1 致病突变，可诊断为复合杂合胱氨酸尿症。从本例病例中可以发现，对起病年龄小的复发性泌尿道结石患者应高度怀疑遗传代谢性疾病，基因检测是诊断胱氨酸尿症的重要手段。

1 例睑裂狭小-内眦赘皮-上睑下垂综合征（BPES）全外显子检测漏诊病例分析

张美姿
天津市第一中心医院

目的 一例不孕不育女性（33 岁），临床表现为卵巢储备功能低下（AMH 分别为 0.3 和 0.06ng/ml）、卵巢功能不全（FSH35.86mIU/ml）并伴有双眼上睑下垂、双眼先天性小睑裂（已进行了修复手术），临床初步诊断 BPESⅠ型，寻找该疾病的遗传因素。
方法 根据 BPES 患者遗传情况，涉及细胞遗传学的染色体重排（涉及 3q23 处的臂内缺失和易位）和 FOXL2 的基因变异，其中 FOXL2 基因变异主要包括微小变异（122/199,61.3%）和大片段变异（70/199，35.2%），因此对该患者序贯地进行了染色体核型分析、CNV-seq 和全外显子检测。
结果 染色体核型、CNV-seq 和全外显子检测均未见异常，进一步针对 FOXL2 基因进行基因全长 PCR 和 sanger 测序，结果表明 FOXL2 基因 NM_023067.3: c.843_859dupGGCCGCACCCCCGCCTC(p.Pro287Argfs*75)发生移码变异，经 ACGM 评分判定为致病性，父母验证提示为新发变异，该位点杂合变异也有致病患儿的文献报道。针对全外显子该区域的数据再分析发现，该区域 GC 含量高，检测 20×仅有 1 个 read，数据分析时被过滤掉了，因此漏诊。
结论 临床高度怀疑存在某个基因的问题时，需要再次进行全外数据分析，了解该基因 reads 覆盖是否均一，尤其针对高 GC 区域，避免致病变异的漏诊发生。

染色体微阵列技术诊断 18 例 Phelan-McDermid 综合征

李琳 潘虹 吴海荣 王松涛 裴珮 郑雪飞
北京大学第一医院

目的 用微阵列比较基因组杂交技术（array CGH）诊断 18 例以运动、智力及语言发育落后为主要表现的患儿为 Phelan-McDermid 综合征（PHMDS)，并对 6 例患儿母亲进行了产前诊断。
方法 取北京大学第一医院 2015 年 1 月至今收治的 18 例患儿和其中 3 对父母外周血，以及 6 例患儿母亲的羊水，提取基因组 DNA；用 array CGH 检测分析基因组拷贝数变异。
结果 array CGH 检测显示 18 例患儿存在染色体 22q13.3 缺失，大小 0.896~7.914Mb，均包含关键基因 *SHANK3*；3 对父母染色体不存在该变异，患儿 22q13.3 缺失为新生变异；6 例患儿母亲羊水标本的染色体均不存在 22q13.3 缺失变异。
结论 对于运动智力发育落后、语言发育障碍的患儿进行 array CGH 检测是诊断 Phelan-McDermid 综合征的有效且特异的方法，对有不良产史的母亲可进行针对性的产前诊断。

Trans-eQTLs of the CYP3A5 associated with tacrolimus trough blood concentration in Chinese renal transplant patients

Huijie Lu[1] Haixia Jiang[2] Siyao Yang[1] Chuanjiang Li[3] Chengcheng Li[1] Ruifan Shao[1] Yinuan Cai[1] Pai Zhang[1] Daoyi Wang[1] Xiaojie Bao[1] Hailan Wang[1] Huana Qi[1] Liang Li[1]
1.Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University
2.Department of Clinical Laboratory, Nanfang Hospital, Southern Medical University
3.Department of Hepatobiliary Surgery, Nanfang Hospital, Southern Medical University

This study aimed to systematically investigate trans-eQTLs of *CYP3A4* and *CYP3A5* affecting tacrolimus trough blood concentrations in Chinese renal transplant patients. We used Plink v1.90 to perform data quality control and linear regression analysis on GTEx v8 data. SNPs with *p*-value < 0.05 were selected and the GTEx eQTL Calculator was used to further prioritize the eQTLs of *CYP3A4* and *CYP3A5* in the liver and small intestine. The eQTLs with a *p*-value < 1×10^{-5} and MAF≥0.01 in the CHB population were selected as candidate eQTLs. The genotyping of candidate eQTLs was performed using high-resolution melting (HRM) assays. This study included 845 Chinese renal transplant patients who received tacrolimus as an immunosuppressive agent. Association between 32 candidate eQTLs and log-transformed tacrolimus concentration/dose ratio (log (C_0/D)) in this cohort was conducted using the SNPassoc package of R software. In the end, a total of 75,632 liver eQTLs of *CYP3A4*, 69,558 liver eQTLs of *CYP3A5*, 48,596 small intestine eQTLs of *CYP3A4* and 28,616 small intestine eQTLs of *CYP3A5* were obtained using the GTEx v8 eQTL Calculator. Of the 32 candidate eQTLs, rs75727207 was significantly associated with tacrolimus log(C_0/D) using a codominant (*p*=0.0186) and a recessive (*p*=0.0064) genetic model. Compared with other currently study, we discovered a substantial number of novel eQTLs of *CYP3A4* and *CYP3A5* in liver and small intestine, also found that rs75727207 may affect tacrolimus trough blood concentrations in Chinese renal transplant patients.

17 例 RCAD 综合征产前诊断病例遗传学病因研究

彭莹 席惠 庞佳伦 刘静 杨舒亭 胡建成 王华
湖南省妇幼保健院

目的 遗传性多囊肾（Polycystic Kidney Disease，PKD）是一种广泛累及双侧肾脏的遗传性疾病，产前超声主要表现为胎儿肾脏体积增大，皮髓质分界不清，肾实质回声弥漫性增强或强光点。在活产儿中发病率约为 1/20000，可以分为常染色体显性遗传 PKD 和常染色体隐性遗传 PKD，其病因复杂。本研究通过染色体微阵列技术鉴定了 17 例双肾实质回声强及多囊肾胎儿的致病原因，为家系成员提供遗传咨询及再生育指导。
方法 收集 17 例双肾实质回声强及多囊肾胎儿羊水或脐血样本，应用染色体 G 显带核型分析、单核苷酸多态性微阵列技术进行检查，并采集其中 5 对父母外周血样本进行来源分析。
结果 核型分析均未见异常，单核苷酸多态性微阵列检测结果示：17 例胎儿样本均存在 17q12 杂合性缺失，缺失片段大小约 1.4~1.6Mb，生信分析为致病性拷贝数变异。经父母芯片对照，2 例来自母源，1 例来自于父源，2 例为新发变异。
结论 通过分析胎儿的超声表型与基因型关系，明确 17 例胎儿系 17q12 杂合性缺失导致的 RCAD 综合征（renal cysts and dia—betes syndrome），扩宽了该疾病在胎儿期的超声表型，同时为进一步研究疾病的发生机制奠定了基础。

cffDNA 检测在常染色体非整倍体限制性胎盘嵌合中的临床应用

马娜
湖南省妇幼保健院

目的 探讨 cffDNA 检测技术对 13-三体/18-三体/21-三体（T13/T18/T21）以外的常染色体非整倍体的检测效能及其产前诊断检测策略。
方法 收集 2019 年 3 月至 2021 年 3 月在湖南省妇幼保健院医学遗传科就诊的 cffDNA 检测提示 T13/T18/T21 以外高风险孕妇的病例资料，分析胎儿羊水常规 G 显带核型分析和单核苷酸多态性微阵列芯片（single nucleotide polymorphism-based arrays,SNP-array）以及胎盘或皮肤低深度全基因组高通量测序技术（low-coverage massively parallel copy number variation sequencing,CNV-seq）结果。
结果 （1）3/5 例 cffDNA 检测 16-三体高风险病例产前诊断提示存在 16 号染色体大片段杂合度缺失，5/5 例胎儿存在宫内发育迟缓/胎死宫内，胎盘 CNV-seq 检测提示胎盘为嵌合型 16-三体。（2）2 例 cffDNA 检测 9-三体高风险病例羊水核型分析提示 42%和 50% 9-三体嵌合，SNP-array 检测提示 9 号染色体大片段杂合度缺失但未见拷贝数变异，脐血核型分析未见异常；胎盘 CNV-seq 检测提示胎盘为嵌合型 9-三体。
结论 NIPT 对 T13/T18/T21 以外的 16-三体具有一定检测效能；NIPT 提示 T13/T18/T21 以外高风险结果行产前诊断核型分析同时，建议结合 SNP-array 排除低比例嵌合和杂合度丢失并警惕胎盘限制性嵌合所带来的不良妊娠结局。

IFT-A 复合体相关基因突变导致儿童肾消耗病的表型-基因型研究

方晔[1,2,3] 向天超[1,2,3] 汤小山[1,2,3] 饶佳[1,3,4]
1.复旦大学附属儿科医院
2.上海市肾脏发育和儿童肾脏病研究中心
3.上海市出生缺陷防治重点实验室
4.复旦大学脑科学研究院医学神经生物学国家重点实验室

目的 常染色体隐性遗传肾消耗病（Nephronophthisis, NPHP）是引起儿童和青少年终末期肾脏疾病（ESRD）的常见病因之一。NPHP 是由纤毛这一亚细胞器结构功能缺陷造成的，约有 15％的患

者合并其他肾外表型（如眼睛，肝脏，骨骼和中枢神经系统）。本研究聚焦纤毛结构中物质运输相关蛋白复合体 IFT-A 的相关基因，旨在发现 NPHP 患儿中新致病突变，验证功能缺陷表型。
方法 运用家系全外显子基因测序（trio-WES），在 NPHP 患儿队列中筛选 IFT-A 复合体相关基因致病突变。在人肾小管上皮细胞（HK2）中进行致病突变点的功能验证，阐明 IFT-A 复合体基因突变参与 NPHP 发生的分子机制。
结果 本研究中经 trio-WES 筛选出来自 7 个家系的 7 位 NPHP 先证者，分别携带了 IFT-A 复合体中 *IFT122*，*IFT140*，*IFT144* (*WDR19*) 及 *IFTAP*(*C11ORF74)*四个基因的双等位基因突变。通过系列生物信息学整合分析，对突变位点的种系间保守性，人群中突变频率及 SHIFT/CADD 等计算机预测软件分析其致病性。筛选确认共计 12 个突变位点，包括 2 个纯合突变位点，均为首次报道突变位点，其中 *IFTAP* 为新发现的致病基因。临床表型包括蛋白尿，肾功能损害及肾脏囊性改变；肾外表型包括眼底视网膜色素变性，听力下降，脊柱侧凸，精神运动发育迟滞及颌下横纹肌肉瘤。在 HK2 细胞体外生物学 Rescue/nonrescue 实验，分别构建 IFT-A 复合体 *IFT122*，*IFT140*，*IFT144* 及 *IFTAP* 基因敲低的缺陷模型，通过免疫荧光检测发现相较于对照组细胞，敲低细胞模型中初级纤毛的长度均有明显缩短，扫描电镜结果发现初级纤毛形态也存在差异（P<0.05）。利用稳定表达 IFTAP 的 HK2 细胞系，免疫荧光结果表明 IFTAP 在细胞中定位在初级纤毛上，并且稳定表达 *IFTAP* 两个突变点的 HK2 细胞的纤毛长度短于稳定表达 *IFTAP* 全长的细胞（P<0.05）。此外，我们在 *IFT122* 功能缺陷细胞中观察到了 BBS9 定位异常，在 *IFTAP* 功能缺陷细胞中发现 IFT140 定位异常。
结论 本研究报告了 NPHP 患儿中发现 IFT-A 复合体相关的 4 个致病基因以及 12 个新的致病突变及对应的纤毛功能缺陷表型。基于 WES 筛选 IFT-A 复合体相关基因突变，加速 NPHP 的精准诊断及分型，深入 IFT-A 复合体功能研究有助于致病机理解析。

LAGE3 基因参与 Galloway-Mowat 综合征的机制研究

施画[1,2,3] 饶佳[1,3,4]
1.复旦大学附属儿科医院
2.上海市肾脏发育和儿童肾脏病研究中心
3.上海市出生缺陷防治重点实验室
4.复旦大学脑科学研究院医学神经生物学国家重点实验室

目的 Galloway–Mowat 综合征(GAMOS) (MIM 251300)是一种罕见的累及肾脏、神经系统的疾病，特点为先天性肾病综合征、小头畸形、脑发育异常和生长发育迟缓等，还可伴有癫痫、特殊面容、寿命缩短等临床表现。已报道 GAMOS 患儿中发现 KEOPS 复合体中 *LAGE3*，*OSGEP*，*TP53RK* 或 *TPRKB* 突变。本研究从中国儿童遗传性肾脏病数据库中筛选先天性肾病合并神经系统发育异常的家系，聚焦 *LAGE3* 基因变异导致 GAMOS 综合征，解析 *LAGE3* 基因致病分子机制。
方法 基于 *LAGE3* 基因变异家系临床表现及基因诊断，以秀丽隐杆线虫为工具，观察寿命表型；光镜/DAPI 染色观察生殖腺发育及受精卵发育情况；应用内质网应激/线粒体通路报告品系 *Hsp-4*::GFP/*Hsp-6*::GFP 线虫，探究 *LAGE3* 对内质网应激通路及线粒体功能的影响等，从而探索 *LAGE3* 遗传因素对 GAMOS 综合征的影响及分子机制。
结果 收集 2 例 *LAGE3* 基因变异肾病综合征患者家系信息。#1 先证者男，4 岁，因非肾病范围蛋白尿就诊，肾脏组织病理提示局灶节段性肾小球硬化（FSGS）。先证者同时合并精神运动发育迟缓，其家系中多名男性患者罹患肾脏疾病幼年期辞世。患儿基因变异位点: g.153707066C>T，变异来自母亲。家系 WES 检测及遗传共分离证实家系中多名女性携带 *LAGE3* 基因变异，对 1#患儿及其直系亲属进行端粒长度检测，患儿及其哥哥未发现端粒长度异常，其父母端粒长度均低于正常值。#2 先证者男，8 岁，临床表型为激素耐药型肾病综合征，肾脏组织病理提示 FSGS。患儿基因变异位点：c.193C>A:p.Leu65Ile，变异来自母亲。
基于 KEOPS 复合体参与端粒酶调控的生理功能，进一步在线虫中验证 *LAGE3* RNAi 秀丽隐杆线虫的寿命表型。*LAGE3* 敲低线虫平均寿命为 15.887±0.441 天，低于对照组平均寿命（18.351±0.481 天，p<0.05），*LAGE3* 组线虫最大寿命 23 天，低于对照组（27 天），即 *LAGE3* 组线虫出现寿命缩短的表型；基于 KEOPS 复合体参与线粒体损伤及内质网应激的前期研

究，在线虫中探索线粒体及内质网功能改变，*LAGE3* 敲低的线粒体功能报告品系 *Hsp-6*::GFP 线虫平均荧光强度低于对照组（29.2 AU vs 33.4 AU, *p*=0.01），提示 *LAGE3* RNAi 线虫线粒体通路可能受到抑制；*LAGE3* 敲低的内质网应激报告品系 *Hsp-4*::GFP 线虫平均荧光强度与对照组相比无统计学差异，不支持 *LAGE3* RNAi 线虫内质网应激通路激活的猜想。生殖腺 DAPI 染色提示 *LAGE3* 敲低线虫的生殖腺发育、卵母细胞减数分裂无异常，光镜观察发现 *LAGE3* 组出现虫卵体积较对照组增大、排列密集重叠，提示其异常可能在受精卵发育阶段出现。

结论 *LAGE3* 基因变异可由 X 连锁隐性遗传导致 GAMOS 男性患者儿童期发病，临床突出特点为激素耐药型肾病综合征，FSGS, 伴或不伴神经系统发育缺陷。*LAGE3* 基因缺陷可能通影响线粒体功能、受精卵发育等途径参与发病。

Phenotypic spectrum and genetics of PAX2-related disorder in the Chinese cohort

Yaqi Li[1,2,3] Xue Yang[1,2,3] Ye Fang[1,2,3] Hua Shi[1,2,3] Tianchao Xiang[1,2,3] Jiaojiao Liu[1,2,3] Jialu Liu[1,2,3] Xiaoshan Tang[1,2,3] Xiaoyan Fang[1,2,3] Jing Chen[1,2,3] Yihui Zhai[1,2,3] Qian Shen[1,2,3] Yunli Bi[1] Yanyan Qian[1] Bingbing Wu[1] Huijun Wang[1] Wenhao Zhou[1] Duan Ma[3,5] Haitao Bai[6] Jianhua Mao[7] Lizhi Chen[8] Xiaowen Wang[9] Xiaojie Gao[10] Ruifeng Zhang[11] Jieqiu Zhuang[12] Aihua Zhang[13] Jia Rao[1,3,4]

1.Children's Hospital of Fudan University
2.Shanghai Kidney Development and Pediatric Kidney Disease Research Center
3.Shanghai Key Lab of Birth Defect
4.State Key Laboratory of Medical Neurobiology, Institutes of Brain Science and School of Basic Medical Science, Fudan University
5.Key Laboratory of Metabolism and Molecular Medicine, Ministry of Education, Department of Biochemistry and Molecular Biology, Institutes of Biomedical Sciences, School of Basic Medical Sciences, Fudan University
6.The First Affiliated Hospital of Xiamen University
7.The Children Hospital of Zhejiang University School of Medicine
8.The First Affiliated Hospital of Sun Yat-sen University
9.Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science & Technology
10.Shenzhen Children's Hospital
11.Xuzhou Children‘s Hospital
12.The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University
13.Children's Hospital of Nanjing Medical University

Objective Pathogenic variants of *PAX2* cause autosomal-dominant *PAX2*-related disorder, which includes variable phenotypes ranging from renal coloboma syndrome (RCS), congenital anomalies of the kidney and urinary tract (CAKUT) to nephrosis. Phenotypic variability makes it difficult to define the phenotypic spectrum associated to genotype.

Methods We performed clinical phenotyping in patients enrolled in the China national multicenter registry who were diagnosed with pathogenic variant in *PAX2* and reviewed all the published cases with *PAX2*-related disorder. We conducted a phenotype-based cluster analysis by variant type and molecular modeling of the structural impact of missense variants.

Results Twenty different *PAX2* pathogenic variants were identified in 32 individuals (27 families) with diagnosis of RCS (9), CAKUT (11) and nephrosis (12) from the Chinese cohort. Individuals with abnormal kidney structure (RCS or CAKUT group) tended to have a likely/presumed gene disruptive (LGD) variants (*Fisher test*, p<0.05). A system review of 234 reported cases to date indicated a clear association of RCS to heterozygous loss-of-function *PAX2* variants (LGD variants). Furthermore, we identified a subset of *PAX2* missense variants in DNA-binding domain predicted to affect the protein structure or protein-DNA interaction that associated with the phenotype of RCS.

Conclusion Defining the phenotypic spectrum combined with genotype in *PAX2*-related disorder allow us to predict the pathogenic variants associated with renal and ophthalmological development. It highlighted the approach of structure-based analysis can be applied into diagnostic strategy aiding precise and timely diagnosis.

9 个杜氏肌营养不良家系临床特征和基因变异分析

王宁[1,2,3] 王鑫慧[1,2,3] 王萍[1,2,3] 王学韬[1,2,3] 舒剑波[1,2,3] 蔡春泉[1,2,3] 李东[1,4]
1.天津市儿童医院（天津大学儿童医院）
2.天津市儿科研究所
3.天津市儿童出生缺陷防治重点实验室
4.天津市儿童医院神经内科

目的 杜氏肌营养不良症 (Duchenne muscular dystrophy, DMD) 是由编码抗肌萎缩蛋白(dystrophy)基因突变所致的 X-连锁隐性遗传病，主要表现为进行性对称性骨骼肌无力和萎缩。本研究中对 9 个杜氏肌营养不良（DMD）患儿的家系临床资料进行分析并探讨其病因及分子遗传学机制。
方法 收集 9 个 DMD 患儿的临床资料，提取外周血 DNA 进行全外显子测序，明确 9 个 DMD 家系相关基因的变异情况，随后通过 Sanger 测序或 MLPA 检测对其进行验证。
结果 9 个 DMD 患儿年龄为 22 月-8 岁，以 1-4 岁为主，其中有两例女性。基因检测发现 *DMD* 基因的 9 种变异，包括 8-27 号外显子重复、46-48 号外显子半合子缺失、46-49 号外显子缺失、c.31+1G>C、c.4284G>T p.(Lys1428Asn)、49-52 号外显子缺失、51 号外显子杂合缺失、18 号外显子半合子缺失和 49-50 号外显子半合子缺失变异。其中，c.31+1G>C 为未在 DMD 中报道过的一个导致剪接位点改变的新变异，c.4284G>T p.(Lys1428Asn)为一个新的错义变异。Sanger 测序和 MLPA 检测验证与全外显子测序结果一致。
结论 丰富了 DMD 疾病的基因突变谱，为基因诊断和遗传咨询提供了依据。

一例肌营养不良患儿的 TTN 基因变异分析

王宁[1,2,3] 王萍[1,2,3] 王学韬[1,2,3] 舒剑波[1,2,3] 蔡春泉[1,2,3] 李东[1,4] 张玉琴[1,4]
1.天津市儿童医院（天津大学儿童医院）
2.天津市儿科研究所
3.天津市儿童出生缺陷防治重点实验室
4.天津市儿童医院神经内科

目的 肌营养不良（muscular dystrophy，MD）是一类原发性进行性骨骼肌疾病，引起细胞膜功能紊乱，肌源纤维断裂，肌肉坏死，临床上主要表现为不同程度和分布的进行性加重的骨骼肌萎缩和无力，也可累及心肌，部分肌营养不良症会导致运动受损甚至瘫痪。本研究中对 1 个临床拟诊肌营养不良的患儿及父母进行基因变异分析，明确其致病原因，为遗传咨询及产前诊断提供依据。
方法 应用全外显子测序方法对患儿相关致病基因进行初步筛查,再通过直接测序对患儿及父母可疑致病基因进行验证，寻找可能的致病突变位点，采用 SIFT 及 PolyPhen-2 生物信息学软件对变异位点进行致病性预测。
结果 全外显子及 Sanger 测序结果显示患儿 TTN 基因第 266 外显子 c.59170A>G（p.Lys19724Glu）和第 54 外显子 c.12967G>A（p.Val4323Ile）复合杂合变异，父亲携带 c.59170A>G 杂合变异，母亲携带 c.12967G>A 杂合变异。c.59170A>G 变异导致 TTN 基因编码的第 19724 位赖氨酸被谷氨酸替代，生物信息学软件预测其有致病可能性，c.12967G>A 变异导致第 4323 位缬氨酸被异亮氨酸替代，生物信息学软件预测其致病可能性较小，该变异都尚未见文献报道，患儿的复合杂合变异分别来自父母。
结论 TTN 基因第 266 外显子 c.59170A>G p.(Lys19724Glu)和第 54 外显子 c.12967G>A p.(Val4323Ile)变异可能是患儿的致病原因，新变异的发现丰富了 TTN 基因变异谱。

Understanding the new mechanisms of Down syndrome using transcriptomic and proteomic analysis

Xi Wang Donge Tang
The First Affiliated Hospital (Shenzhen People's Hospital), Southern University of Science and Technology

Background Down syndrome (DS) is the most common birth defect of human aneuploidy with no effective remedy.
Methods On account of mass spectrometry depend on data-independent acquisition (DIA) strategies, in combination with transcriptome data, we aimed to explore the molecular mechanisms of DS.
Results: After quantifying the changes of protein levels in the umbilical cord blood between DS fetuses and healthy control fetuses, we got a total of 313 differentially expressed proteins (DEPs) between DS fetuses and healthy fetuses. Especially, a panel of proteins has been shown to be closely related to oxidative phosphorylation, notably ubiquinone oxidoreductase subunit A6 (NDUFA6).
Conclusions These proteins may play an important role in the occurrence and development of Down syndrome, help us to explain the molecular mechanism of DS, and provide a theoretical basis for targeted therapy.

MAN2B2 复合杂合变异导致先天性糖基化障碍一例

田畦 舒荔 彭莹 席惠 王华 毛翛
湖南省妇幼保健院

MAN2B2 基因致病变异引起的先天性糖基化障碍 (CDG) 是一种极为罕见的代谢疾病。迄今为止，文献史仅报道了 1 例 MAN2N2-CDG，其临床结果包括联合免疫缺陷、面部畸形、凝血病、严重生长迟缓伴发育障碍。我们在一家系中收集相应临床信息，并采取全外显子组测序 (WES) 和 Sanger 测序验证的方式对家系成员突变情况进行检测。通过 MALDI-TOF 质谱仪测量分析血清中的 N-聚糖。我们在该先天性糖基化障碍患儿中检出 MAN2B2 复合杂合变异。虽然我们的先证者有一些 MAN2B2-CDG 的临床特征，例如发育迟缓或智力障碍，但他表现出与报道的一些不同的临床表现。但我们的患者没有表现出严重的免疫缺陷，但有上腭裂、枕骨突出、尿道下裂。MAN2B2-CDG 诊断生物标志物是通过质谱分析发现血清 N-聚糖上核心岩藻糖基化的缺失。该研究为第二例 MAN2B2-CDG 病例，我们患者具有发育迟缓和多种新特征，包括常规免疫系统、上腭裂和尿道下裂。我们的研究有助于扩展这种疾病的分子和临床知识，并强调基因检测和 MALDI-TOF MS 分析在 N-糖基化疾病中的有用性。

SEMA6B 基因移码变异导致全面发育迟缓和热性癫痫

舒荔[1,2] 田畦[1,2] 鄢慧明[1,2] 彭莹[1,2] 席惠[1,2] 毛翛[1,2] 王华[1,2]
1.湖南省妇幼保健院
2.国家卫健委出生缺陷研究与预防重点实验室

背景 Hamanaka 等人于 2020 年首次发现的 *SEMA6B*（MIM 60873）为一种进行性肌阵挛性癫痫（PME）的致病基因。他们在 5 个无血缘关系的 *SEMA6B* 致病突变携带者中发现 *SEMA6B* 基因的 4 个致病变异，这些变异均位于该基因的最后一个外显子。这些携带 *SEMA6B* 基因新发截短变异的患儿以进行性认知功能下降（发病年龄小于 2 岁）、肌阵挛癫痫（发病年龄 1 岁 5 月到 6 岁）。这些位点均位于基因的最后一个外显子，可以逃避无义介导的 mRNA 降解（NMD 机制），可能以显性负效应或者功能获得性机制致病。
目的和方法 在我们的研究中，我们通过全外显子组测序在一个全面发育迟缓的患儿中发现一个新发框移变异 (chr19:4544346-4544346; NM_032108.3: c.1934delG: p.G645fs)，并且通过 Sanger

测序进行了父母验证。和已报道的临床表现不同的是，我们的患儿表现为全面发育迟缓和热性癫痫。患儿足月出生，孕期无异常。六月时出现症状仅能短暂地抬起头，但不能翻身、不能追物。出现全面强直阵挛发作，表现为眼球上翻、四肢强直抖动。发作 2 分钟自然缓解，发作时体温为 40.5℃。血常规、C 反应蛋白、降钙素原、血培养、脑脊液检查均未提示感染。磁共振正常。磁共振提示夜间中央顶区、中线区散发低波幅棘慢波。2 岁时患儿可以爬和扶坐，因为热性癫痫再次入院，临床表现为全面强直阵挛癫痫，体温为 39℃。

结果和结论 本研究首次报道 *SEMA6B* 基因相关全面发育迟缓和热性癫痫，该临床表现扩大了 *SEMA6B* 基因的表型谱。

Mosaic isodicentric Y chromosome harboring intact AZF region in a cryptozoospermic male with normal hormone levels

Shengyu Xie Yuan Yang
Department of Medical Genetics, State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University,

Objective To report the cytogenetic and molecular genetic analysis of chimerism karyotype in an infertile Chinese male who was diagnosed with idiopathic cryptozoospermia caused by pseudo dicentric Y chromosomes.
Methods AZF-STSs analysis. Cytogenetic and molecular genetic analyses, including chromosomal G-banding, copy number variant detection and fluorescence in situ hybridization, were conducted to characterize the patient's genetic defect.
Results The results showed that the male carried a mosaic isodicentric Y chromosome, designated 45,X[5]/46,X,ish psu idic(Y)(q11.23)(SRY++, DYZ3++)[25]. Endocrine tests showed that the patient's hormone levels were normal. AZF-STSs analysis excluded complete deletion of AZFa, AZFb or AZFc.
Conclusions This is a very rare case, characterized by a fusion of two Y chromosomes at the proximal end of the Yq telomere with normal hormone levels and intact AZF region, which may provide evidence for the hypothesis that idic(Y) primarily contributes to severe spermatogenic failure via disturbed meiosis, caused by a structural aberration of the Y chromosome. Therefore,molecular analyses(like CNV-seq and FISH)should be applied to male with severe oligozoospermia or cryptozoospermia who try to conceive with the help of assisted reproductive technique to prevent their child from congenital abnormalities in case their abnormal Y chromosome might pass to next generation.

一例先天性类脂质性肾上腺皮质增生伴癫痫的病例报道

张新杰 雷梅芳 舒剑波 李东
天津市儿童医院

目的 探讨先天性类脂质性肾上腺皮质增生症（congenital lipoid adrenal hyperplasia，CLAH）患儿的临床表征及分子遗传机制。
方法 选择就诊于天津市儿童医院的一例 CLAH 患儿为研究对象。回顾性的分析其临床病历资料，并对其行全外显子测序分析。
结果 一般资料：患儿女 9 岁，孕足月剖宫产系 G4P2，智力运动发育正常，否认家族抽搐、智力低下、遗传代谢病家族史。临床表现：出生后 9 天因"发现皮肤黄染 9 天，阵发性青紫 3 天"于我院新生儿科住院治疗。住院期间查体发现肤色深，以口唇、外阴部、双手掌指关节伸面、膝关节尤为明显，结合血生化指标及影像学检查诊断为肾上腺皮质增生症，予以口服激素治疗。于 2020 年（患儿 9 岁）开始出现头晕、头痛及抽搐发作等症状，表现形式主要为局灶泛化全身强直阵挛发作、复杂左局灶发作、左局灶泛化全身发作，持续数分钟后自行缓解，伴或不伴发热。给予奥卡西平和左

乙拉西坦规律治疗。抽搐发作情况控制可。实验室检查结果：血浆 17α-羟孕酮水平正常，血促肾上腺皮质激素>1250pg/ml，血钠低、血钾高。肾上腺 CT 提示肾上腺皮质增生。头核磁示双侧脑室旁白质区点线样稍长 T1 长 T2 信号影。视频脑电图示异常儿童脑电图，背景活动慢化，双侧额极、额、枕、前颞区尖形慢波、慢波发放，确诊为癫痫。颅脑 MRA 检查未见异常。高通量测序结果：全外显子检测未见癫痫相关基因变异，但提示 CLAH 相关 STAR 基因上 c.772C>T(p.Gln258*)的纯合突变，其母亲为该位点的杂合突变，父亲未提供标本验证。该变异为无义突变，其所编码的蛋白质第 258 位氨基酸由 Gln 变为终止密码子，在 dbSNP147 数据库有收录，可认为是致病性变异。

结论 CLAH 为先天性肾上腺皮质增生症中的罕见类型，本研究补充了我国该类患者的病例资料。对患儿及其家属的基因检测有助于 CLAH 的诊断，在丰富了基因突变谱的同时，研究基因型与表型的相关性可为临床的诊断鉴别提供帮助。

一例胎儿合并 EEC 综合征及泌尿系统发育异常的产前诊断

吴怡 王彦林 苏敏 赵欣荣 杲丽 华人意 孙金铃 祝菁
上海交通大学医学院附属国际和平妇幼保健院

背景 EEC（Ectrodactyly-Ectodermal Dysplasia-Cleft Syndrome）综合征是一种非常罕见的单基因病，其经典临床表型为手足裂，外胚层发育不良，唇腭裂。其他伴随症状还包括泌尿系统发育异常，神经系统发育迟缓，听力障碍等。该病绝大多数是由于 TP63 基因致病性变异导致。

病例报道及结果 G2P0，高龄孕妇，36 岁，孕 11W 前来我院进行 NT 检测，超声提示 NT1.6mm，但膀胱直径 12mm。建议介入性产前诊断，但孕妇拒绝。孕 15W，无创 NIPT 提示结果低风险。孕 21W 畸形筛查提示胎儿双侧唇裂，右侧多囊肾，左肾积水。羊水穿刺及产前全外显子测序提示 TP63 基因出现新发致病变异(c.1027C>T R304W) 。确诊为 EEC 综合征。

结论 由于 EEC 病例中最常见的临床表型外胚层发育不良在产前超声中无法检测，故给临床诊断造成一定难度。通过文献学习，我们发现 EEC 综合征的产前病例中最常见的超声表型是唇腭裂（64.3%），其次为泌尿系统发育异常，包括多囊肾，肾积水，输尿管扩张等（57.1%）。故在产前诊断临床工作中，当出现唇腭裂合并泌尿系统结构异常时，应考虑 EEC 综合征可能。产前 trio 全外显子测序是诊断 EEC 综合征的有效方法。

Gene mutations and mitochondrial DNA levels were decreased in breast cancer

Tong Zhang[1,2] Fengxiang Wei[1,2] Guoqiang Zhao[1,2] Yanan Liu[1,2]
1.Longgang District Maternity&Child Healthcare Hospital of Shenzhen City
2.Jiamusi University

The prevalence and death rate of breast cancer are the first among all the female cancers in the world, and there is a clear familial genetic tendency. About 70-85% of BRCA1/BRCA2 gene mutation carriers are prone to structural or functional abnormalities that lead to a high risk of breast cancer. At present, one of the common causes of breast cancer is mitochondrial dysfunction due to reduced mitochondrial DNA content. On the one hand, HER2, RAS, EGFR, ERBB2 and other oncogenes are used to directly regulate mitochondria by transferring to the organelles. On the other hand, activating multiple specific signaling pathways can also control the amount of mitochondrial DNA, thus maintaining the normal morphology and function of cells. Breast cancer patients have different subtypes, molecular characteristics and clinical manifestations. Targeted therapy based on its characteristics can provide a better therapeutic advantage to determine the target of various individual therapies. The relationship between the decreased mitochondrial DNA content and the survival time, disease-related fatigue and

chemotherapy-related cognitive impairment can also be analyzed to assist the formulation of targeted chemotherapy guidance and use. In conclusion, mitochondrial DNA content may be a new target for early diagnosis and treatment of breast cancer. The common decrease of mitochondrial DNA content and potential expression of mitochondrial DNA, as well as the decrease of mitochondrial DNA expression and content in non-tumor tissues are helpful for the identification and detection of the formation and metastasis of breast cancer. To provide new directions for disease prevention and early diagnosis and treatment of breast cancer patients in the approximately 5-10% of high-risk population with a family history of breast cancer.

罕见 X 连锁鱼鳞病伴发杜氏进行性肌营养不良患者家系的遗传学分析

张庆华 张钏 郝胜菊 惠玲 冯暄 陈雪 王兴 郑雷 刘芙蓉 周秉博
甘肃省妇幼保健院

目的 对 1 例疑似 X 连锁鱼鳞病（X-linked ichthyosis，XLI）合并杜氏进行性肌营养不良(Duchenne muscular dystrophy,DMD)的男性患儿及其家系成员进行遗传学分析，明确其致病原因。
方法 采集先证者及其父母外周血提取 DNA，对先证者进行全外显子组测序(whole exome sequencing, WES)，通过多重连接探针扩增杂交技术(multiplex ligation-dependent probe amplification， MLPA）运用探针 P160 及 P034/035 探针分别检测患儿的 *STS* 与 *DMD* 基因。
结果 先证者检测到 STS 基因半合子缺失及 DMD 基因 48-54 外显子区域半合子缺失。患儿 STS 基因半合子缺失来源于母亲，患儿 DMD 基因 48-54 外显子缺失为自发突变，其母亲未检测到该杂合突变。患儿考虑为双基因突变致 XLI 合并 DMD 的患者，两种疾病均为 X 连锁隐性遗传，符合孟德尔遗传规律。
结论 先证者共患 XLI 与 DMD，截至目前，该先证者为首例报道的共患 XLI 与 DMD 的患者。

Clinical study of compound Sophora flavescens injection combined with ET in the treatment of breast cancer

Yao Xu[1,2] Fengxiang Wei[1,2]
1.Longgang District Maternal and Child Health Care Hospital of Shenzhen City, Guangdong Province
2.Jiamusi University

Objective To study the clinical effect of compound Matrine injection combined with ET in the treatment of breast cancer.
Methods A total of 72 cases were included and diagnosed with breast cancer. They were admitted to our hospital from March 2019 to October 2020. The control group was treated with ET regimen, and the observation group was treated with compound matrine injection combined with ET regimen. The clinical efficacy of the two groups was compared.
Results The disease control rate and clinical remission rate of the observation group were higher than that of the control group, and the immune factor level of the observation group was better than that of the control group, the difference was significant ($P < 0.05$).
Conclusion Compound Matrine injection combined with ET in the treatment of breast cancer has not only ideal curative effect, but also can improve the immune function of the body, which can be popularized and applied.

Simultaneous identification of both MFSD8 and RDH12 pathogenic variants in a Chinese family affected with Retinitis Pigmentosa

Yihui Wang[1] Yanling Teng[1] Desheng Liang[1,2] Zhuo Li[1] Lingqian Wu[1,2]
1.Center for Medical Genetics & Hunan Key Laboratory of Medical Genetics, School of Life Sciences, Central South University
2.Hunan Jiahui Genetics Hospital

Retinitis Pigmentosa (RP) is characterized by tremendous genetic and phenotypic heterogeneity. Here, we investigate pathogeny of RP family further in order to provide evidence for the genetic and reproductive counseling of families. While the pregnant woman of 8^{+3} weeks presented with RP, her first-born with retinitis pigmentosa, epilepsy and cerebellar atrophy. The research identified a compound heterozygous mutation (c.998+3_998+6del/deletion) in the *MFSD8* gene of the first-born, explains the cause of proband's disease which cannot explain the mother's. Then a homozygous mutation c.343+1G>A in *RDH12* of the mother was found. RT-PCR is employed to find that there is a skipping of exon 10 in *MFSD8* and a 15-nucleotide retention of intron5 in *RDH12*. The coexistence of two independent RP caused by distinct genes in one pedigree is demonstrated. Based on the diagnosis, a prenatal diagnosis performed on the fetus found that the fetus *MFSD8* is affected by the same mutation as the proband. The research underscoring the complexity of RP and the need for the combination of extensive molecular genetic testing and clinical characterization, in addition, expands the spectrum of *MFSD8* mutations. Finally, it is expected that the family members would be prevented from reproducing children of the similar disease.

Identification of a novel ANK1 mutation in Hereditary spherocytosis co-existing with BWS

Qinghua Zhang[1] Chuan Zhang[1] Yupei Wang[1] Shengju Hao[1] Jingyun Shi[2] Xuan Feng[1] Lei Zheng[1] Xing Wang[1] Xue Chen[1] Bingbo Zhou[1] Furong Liu[1] Fangping Zhao[2] Xuetao Li[3] Liaoyuan Deng[3] Jun Hou[3] Zhaoyan Meng[4]
1.Medical Genetics Center, Gansu Provincial Maternity and Child-care Hospital
2.Department of Neonatal Intensive Care Unit, Gansu Provincial Maternity and Child-care Hospital
3.The Laboratory of Computational Medicine and Systems Biology, School of Medicine, South China University of Technology
4.Department of Obstetrics, Gansu Provincial Maternity and Child-care Hospital,

Beckwith-Wiedemann syndrome (BWS) is an inherited disorder affecting 1 in 10,500 to 13,700 newborns worldwide. The disease is caused in vast majority patients by a molecular defect in the imprinted chromosome 11p15.5. Hereditary spherocytosis (HS) is a form of hemolytic anemia associated with a variety of mutations leading to congenital red blood cell (RBC) membrane defects. The prevalence of HS varies by geographic regions around the world, ranging from 1.2 in 100,000 in Asia to 1 in 2000 in Northern Europe. Herein, we report for the first time a rare case diagnosed with co-existing BWS and HS. Based on the classical presentations, including macroglossia, hepatosplenomegaly and macrosomia, the patient was first suspected with BWS. MS-MLPA confirmed the BWS diagnosis by hypomethylation of maternal 11p15.5 (KCNQ1OT1), but no copy number variations in chromosome 11 was detected by CNV-seq. Nevertheless, to scrutinize molecular causes of other symptoms of the patient, including anemia, hyperbilirubinemia, and jaundice, a whole exome sequencing (WES) was performed. We identified a novel and de novo mutation in *ANK1* gene (c.520delC). This frameshift mutation of *ANK1* gene results in a truncated protein without important functional domains and impaired membrane stability and structure of the resultant red blood cells, leading to a definitive diagnosis of HS. The present case demonstrated that multiple genetic and epigenetic aberrations might coexist in the complex genetic diseases. For such kind of complicated cases, the different types of molecular tests, such as WES and MS-MLPA should be utilized in combination to reveal

independent causal molecular events. The identifications from this study added new insights into the understanding of molecular mechanisms underlying the co-existing HS and BWS.

一例进行性肌营养不良患者 DMD 基因新变异的鉴定

张晗[1,2] 张学[2] 徐英春[1]
1.中国医学科学院北京协和医院，检验科
2.中国医学科学院基础医学研究所，医学分子生物学国家重点实验室

目的 对一例进行性肌营养不良患者进行致病基因变异鉴定。
方法 收集患者及家庭成员临床资料，签署知情同意书并采集外周血，从患者及家庭成员外周血中提取基因组 DNA 并进行全外显子组测序，对进行性肌营养不良的已知致病基因和相关基因进行筛查。筛查出可疑致病变异，采用 PCR 扩增相关序列，对候选变异位点进行 Sanger 测序验证及基因型-表型共分离分析。
结果 患者携带 *DMD* 基因第 2 外显子处 c.C92T（p.A31V）新变异，该变异属于错义变异，呈 X-连锁隐性遗传，遗传自母亲，在家系中呈基因型-表型共分离，并且尚未见文献报道。
结论 *DMD* 基因 c.C92T（p.A31V）处变异可能导致该患者患进行性肌营养不良。

α-珠蛋白基因簇大片段缺失与重复导致地中海贫血的两例中国家系分析

朱迪娜 徐琳琳 张燕霞 梁观霞 魏小凤 商璇
南方医科大学基础医学院医学遗传学教研室

目的 地中海贫血是我国南方常见的一种遗传性血红蛋白疾病，由珠蛋白基因缺陷导致 α-珠蛋白链和 β-珠蛋白链不平衡引起，α-珠蛋白基因簇的拷贝数变异是该病的原因之一，本研究对两个来自中国南方的地中海贫血家系进行了表型分析和基因鉴定。
方法 采集家系成员的外周血，进行血常规和血红蛋白电泳。提取 RNA，采用定量 RT-PCR 检测 α/β mRNA 比值。提取 DNA，在地中海贫血常规筛查的基础上，采用 MLPA、WGS、PCR 和 Sanger 测序等方法确定 CNV 类型及其重复和缺失范围。
结果 在家系 A 中发现了一个新的 159 kb 重复($\alpha\alpha\alpha^{159}$)，先证者由于合并遗传了 $\alpha\alpha\alpha^{159}/\alpha\alpha$ 和 $\beta^{CD41\text{-}42}/\beta$ 突变导致严重的中间型 β 地中海贫血。在家系 B 中发现了一个新的 259 kb 缺失($--^{259}$)，先证者基因型为$--^{259}/--^{SEA}$，导致了巴氏胎儿水肿综合征。
结论 本研究首次报道了两个的 α-珠蛋白簇的新重排，确定了其分子结构，并描述了 CNV 携带者的临床表型特征。这两种新 CNV 的成功鉴定和表征拓展了地中海贫血突变谱系，为地中海贫血相关 CNV 的鉴定和结构分析提供了例子。

两例着色性干皮病家系 ERCC5 复合杂合突变的研究

施亚君[1] 吴宝玉[3] 李敏[2] 孙淼[1]
1.江苏省苏州大学附属第一医院
2.江苏省苏州大学附属独墅湖医院
3.江苏省徐州市儿童医院

目的 对两例着色性干皮病（XP）患儿进行全外显子测序筛选致病基因，探讨该病可能的发病分子机制。
方法 收集家系临床资料，绘制家系谱，采集家系成员血样，提取基因组 DNA，送全外显子测序，确定致病基因，再用 Sanger 测序法进行双向验证。

结果 例 1 为 5 月龄女孩，3 月前于日晒后出现面部红肿、脱屑、干燥，红肿消退后出现白、褐色斑点并累及全面部；例 2 为 15 岁女孩，四肢、面部散在黑色斑点、丘疹，伴逐渐加重 13 年，斑点及丘疹组织病理示：基底细胞癌和原位鳞癌。均呈常染色体隐性遗传，全外显子及 PCR-Sanger 测序发现例 1 ERCC5(NM_000123)基因存在复合杂合突变，即父源性的 c.205C＞T(p.R69*)和母源性的 c.204delT 突变；例 2 ERCC5 基因也存在复合杂合突变，即父源性的 c.109C＞T(p.Q37*)和母源性的 c.410_411dupTT(p.R138Ffs*33)突变；其中 c.204delT 为新突变。
结论 本研究发现的 ERCC5 基因复合杂合突变是 G 型着色性干皮病的致病原因,早期临床特点结合基因检测有助于着色性干皮病患者的准确诊断及分型。

一例 16p11.2 微缺失综合征伴发 Rett 综合征患儿的临床特征及分子遗传学分析

蔺朋武 石静云 郝胜菊 张庆华 冯暄 陈雪
甘肃省妇幼保健院

摘要 对 l 例 16p11.2 微缺失综合征（Chromosome 16p11.2 deletion syndrome）伴发 Rett 综合征（Rett syndrome，RTT）的先证者及其家系成员进行全外显子测序（Whole exome sequencing，WES）分析，探讨其可能的分子生物学致病原因。
方法 抽提先证者及其家系成员的外周血基因组 DNA，采用高通量测序方法结合 Sanger 法测序验证对其全外显子进行基因检测。
结果 WES 提示先证者在 chr16:29556331-30199917 区域缺失 0.643Mb，该区域包含该综合征的关键基因 *ALDOA*、*CORO1A*、*KIFF22*、*PRRT2* 和 *TBX*6 等，为致病性变异，患儿父亲在相同区域也存在缺失，患儿母未检出拷贝数异常；此外，该样本分析到 *MECP2* 基因有 1 个半合子无义突变：763 号核苷酸由胞嘧啶 C 变为胸腺嘧啶 T（c.763C>T），导致氨基酸发生无义突变（p.R255X）。经家系分析，先证者父亲该位点无变异，其母该位点存在杂合变异。
结论 先证者同时存在微缺失和点突变，导致其同患 2 种不同的遗传性综合征，提示遗传病患者中可能同时存在 2 种或以上的疾病表型，在诊断中需加以重视。

染色体易位携带者的胚胎基因组拷贝数变异分析

李哲涛
柳州市妇幼保健院

目的 探讨染色体易位对胚胎染色体组成的影响，分析平衡易位携带者胚胎染色体减数分裂的分离特点。
方法 通过二代测序平台分析 PGT 周期中染色体易位携带者胚胎拷贝数变异情况，比较不同携带者性别、不同易位及染色体类型及不同断裂点位置下胚胎染色体的非整倍体情况及分离特点。
结果 相互易位携带者胚胎染色体异常率（80.4%）明显高于罗氏易位携带者（64.4%），差异有统计学意义（c^2=25.527，P＜0.000），在相互易位和罗氏易位携带者中，女方携带者胚胎染色体异常比率分别为 85.5%和 83.5%，均高于男方携带者（76.5%和 57.1%），且差异有统计学意义（P＜0.05）。在胚胎异常染色体来源的分析中，相互易位携带者胚胎产生亲缘易位异常染色体比例（34.0%）明显高于罗氏易位携带者（16.9%），差异有统计学意义（c^2=44.947，P＜0.000），而罗氏易位携带者比相互易位更容易产生新发异常染色体胚胎（51.4% VS 24.1%，c^2=42.682，P＜0.000）。在相互易位和罗氏易位中，男方易位携带者胚胎新发异常染色体比例（32.6%和 59.8%）均明显高于女方携带者（17.0%和 37.9%）。女方易位携带者更易发生 2:2 邻近-2 和 3:1 分离，相互易位携带者中，是否有近端着丝粒染色体参与，以及断裂点是否位于染色体末端，胚胎的异常率均无显著差异，但有近端着丝粒染色体参与的携带者，其胚胎发生 3:1 分离的几率要高于非近端着丝粒参与组。

结论 胚胎染色体的组成与易位类型及携带者性别相关，近端着丝粒染色体和断裂点位置与配子分离方式相关，但不影响胚胎整倍体的比例。

一个 MECP2 重复综合征家系的临床特征及基因突变分析

王俊霞 高健 楚伟 王方娜 霍平
河北省人民医院

目的 现国内外报道的 MECP2 重复综合征（MDS）多为个案报道，家系报道的病例很少。本文将该家系的临床特征和基因突变特点进行总结，以提高临床医生对 MECP2 重复综征合征的认识。
方法 报道一家系 5 例男性患者临床表型和基因检测结果，并结合相关文献进行分析。
结果 先证者于新生儿期发现患儿四肢肌张力低，进食慢，运动发育落后，不能正常抬头、翻身，5 岁才能独立行走，但不稳易摔倒，走路呈前倾姿势，双手不能伸展，智力低下，无语言交流能力，9 岁时出现癫痫症状，口服药物治愈，10 岁前易发生呼吸道感染。AffymetrixytoScan HD SNP-Array 芯片检测结果显示先证者及其两个姨表兄弟、两个舅老爷在 X 染色体 Xq28 区段均存在重复，该基因突变与 X 染色体连锁显性遗传的 Rett 综合征(Rett syndrome)等疾病相关。AffymetrixytoScan HD SNP-Array 芯片检测结果显示先证者的母亲等六人在 X 染色体 Xq28 区段存在重复，证实先证者及其他患者 X 染色体 Xq28 区段存的重复均为遗传自母亲。
结论 该家系 MECP2 重复综合征患者为 MECP2 基因重复致病，根据遗传学诊断结果可以对其家系后代进行遗传咨询和产前诊断。

De novo nonsense variant in ASXL3 in a Chinese girl causing Bainbridge–Ropers Syndrome: a case report and review of literature

Qin Wang
Shenzhen Maternity and Child Healthcare Hospital

Background Bainbridge-Ropers syndrome (BRPS, OMIM #615485) was first identified in 2013 by Bainbridge et al. and is a neurodevelopment disorder characterized by failure to thrive, facial dysmorphism, and severe developmental delay. BRPS is caused by heterozygous loss-of function (LOF) variants in the additional sex combs-like 3 (ASXL3) gene which are mostly located in two mutational cluster regions (MCR). Due to the limited specific recognizable features and overlapping symptoms with Bohring–Opitz syndrome, clinical diagnosis of BRPS is challenging.
Case presentation In this study, a 2-year-8-month-old Chinese girl was referred for genetic evaluation of severe developmental delay. Reduced fetal movement was found during antenatal period and bilateral varus deformity of feet was observed at birth. Whole exome sequencing and Sanger sequencing were used to detect and confirm the variant. A novel nonsense variant c.1063G>T (p.E355X) in the *ASXL3* gene (NM_030632.3) was identified in the proband and the clinical symptoms were compatible with BRPS. The parents were physical and genetic normal and prenatal diagnosis was requested for her pregnant mother with a negative Sanger sequencing result.
Conclusion The study revealed a *de novo* LOF variant in the *ASXL3* gene and expanded the mutation spectrum for this clinical condition. By performing a literature review, we analyzed the clinical phenotype with limited fetal features and summarized genetic results of all BPRSs reported so far. More cases study may help to elucidate the function of *ASXL3* gene that may be critical to understand the genetic etiology of this syndrome and assist in accurate genetic counselling, informed decision making and prenatal diagnosis.

一个 X 连锁 α-地中海贫血/精神发育迟滞综合征家系的 ATRX 基因突变分析

吴少敏
东莞市人民医院

目的 针对一个 X 连锁 α-地中海贫血/精神发育迟滞综合征（ATR-X 综合征）家系进行致病基因突变分析，为该家系的临床精准诊断和遗传咨询提供依据。
方法 收集患者临床资料，通过全外显子组测序寻找基因变异并通过 Sanger 测序进行验证；提取先证者及其母亲、健康对照者外周血淋巴细胞 RNA，逆转录后进行荧光定量 PCR 检测 ATRX mRNA 水平。使用 Mutation Tasting 对突变位点的致病性进行预测，LUMC Mutalyzer3 对氨基酸序列改变进行预测，I-TASSER 预测 ATR-X 蛋白变异后的结构。
结果 先证者临床表现为严重智力障碍、体格发育迟缓，特殊面容、癫痫、双侧隐睾等多发先天异常。全外显子组测序发现 ATRX 基因第 3、4 外显子剪接供点插入突变（NM_000489: c.189+1dupG），该突变还未见报道。Sanger 测序验证突变遗传自携带杂合突变的母亲，父亲未携带该突变。在线软件预测，变异所在剪接区核苷酸高度保守，有害性预测结果显示为有害。实时荧光定量 PCR 产物 Sanger 测序提示先证者 cDNA 第 189 位与第 190 位碱基之间插入碱基 G，导致发生剪切异常，导致蛋白翻译提前终止形成一个截短蛋白。mRNA 水平验证表明，该变异可导致 ATRX 基因转录产物下降（$P<0.05$）。
结论 该家系中发现了一个 ATRX 基因新的突变，功能研究显示该突变是导致该家系呈现 ATR-X 综合征的致病原因。本研究拓展了 ATRX 基因的突变谱，并为该家系的临床确诊和遗传咨询提供了依据。

5 号染色体短臂缺失综合征的产生机制与诊断方法

李婷婷 赵彦艳
中国医科大学附属盛京医院

目的 综合分析已收集患者的临床表现，探讨形成机制，总结诊断经验。
方法 收集 12 例 5p-患者，回顾性研究患者或产前胎儿的异常临床症状，揭示共同的临床表征，结合 CNV 和核型结果以及患者家系遗传背景，分析 5 号染色体短臂缺失的产生机制。
结果 1.临床表现： 4 例患儿表现为发育迟缓，特殊面容，猫叫哭声，听阈增高，以及腰骶隐裂，脑室增宽，胼胝体发育不良等。8 例产前胎儿的临床表现为唐筛高危或 NIPT 异常，发育迟缓，室间隔缺损，单脐动脉，足畸形（内翻或外翻），侧脑室增宽等。3. 患者家系信息：8 例有家系信息，其中 5 例父母核型或 CNV 结果正常（其中有 2 例曾引产过 5p-的异常胎儿），1 例父亲为平衡易位携带者，2 例遗传自母亲。4. 缺失产生机制：1）遗传自亲代：缺失的 5 号染色体来源于父母（亲代）平衡易位后的染色体或者原本就异常的染色体。2）断裂热点：从上述病例分析可知 5p31, 5p14, 5p13 是 5 号染色体短臂上容易发生断裂的热点，发生断裂的原因可能与该区域内的碱基序列和负责有丝分裂以及减数分裂的粘着蛋白复合物有关。5. 临床诊断的经验：当患者出现发育迟缓，胼胝体发育不良，腰骶隐裂，室间隔缺损，以及特征性猫叫样哭声，需要考虑 5 号染色体短臂缺失综合征的可能，进行核型分析和 CNV 检测，完善家系信息采集和其他相关遗传检测以明确诊断。
结论 5 号染色体短臂缺失综合征是一类常见的染色体病，其发生机制与亲代遗传和断裂热点有关。对于产前胎儿，超声异常和 NIPT 是有效的筛查手段，对于出生后的患儿其特殊的临床表现也可以提示。临床上需要将核型分析和高通量测序相结合进行诊断，同时需完善家系遗传信息，用于指导下一次受孕。有遗传背景或多次孕育异常胎儿的夫妇建议进行植入前诊断，其他夫妇再次怀孕后建议完善产前诊断，以减少异常胎儿的出生。

Pathogenicity of circRNAs in high myopia cataract

Shiyu Ma[1,3] Bowen Zhang[1] Jing Ma[1,3] Jin Zhang[1] Duan Ma[1,2] Yi Lu[3]
1.Fudan University
2.Children's Hospital of Fudan University
3.Eye & ENT hospital of Fudan University

Background and Objects High-myopic cataract (HMC) refers to the cataract accompanying high myopia with an axis more than 26mm. It is characterized by earlier onset and rapid progress and mainly affects the lens nuclear. More and more evidences show that circRNAs are involved in many regulatory processes in a variety of eye diseases.
Methods and Results We collected lens epithelium samples from 24 HMC patients and 24 age-related cataract(ARC) patients. Every eight lens epithelium samples were pooled together as a biological repeat to obtain enough RNA to be for whole transcriptome sequencing. After in-depth bioinformatics analysis, a competing endogenous RNA regulation network (ceRNA) can be established by predicting the combination between circRNAs and miRNAs and its downstream mRNA. The differentially expressed mRNAs were enriched by GO function and KEGG analysis. Besides, ORFINDER software was used to predict the ability of circRNAs to encode peptides. Compared with the ARC group, 6070 differentially expressed circRNAs (Fold change > 2, p-value < 0.05) were identified in the HMC group, including 3823 upregulated and 2247 downregulated circRNAs. Through bioinformatics analysis and literature review, we selected an upregulated circRNA in HMC: circ-AFF1 for the further study.
Conclusions Circ-AFF1 may affect the expression of downstream molecules related to HMC development through miRNA sponge pathway and coded peptides.

Diagnosis of Shashi-Pena Syndrome Caused by Chromosome Rearrangement via Nanopore Sequencing

ya wang Jianxin Tan Yan Wang An Liu Fengchang Qiao Mingtao Huang Cuiping Zhang Jing Zhou Ping Hu Zhengfeng Xu
Nanjing Maternity and Child Health Care Hospital

Objective To uncover the neogenesis of a delayed psychomotor development, variable intellectual disability proband in a family, of whom chromosome microarray (CMA) and whole exome sequencing (WES) do not provide credible results.
Methods In this study, clinical testing methods such as MRI of the brain, echocardiography, X-rays examination of the wrist, CMA, WES, karyotyping and other traditional clinical examination were conducted. Long read sequencing Oxford nanopore technology (ONT) and RNA-seq analysis were performed on peripheral blood mononuclear cells. Genes with a fold-change ≥ 1.5 (in either direction) and t test P ≤ 0.05 were identified as differentially expressed.
Results Clinical examinations showed that the proband's features was similar to a rare autosomal dominant neurodevelopmental syndrome, Shashi-Pena syndrome (MIM #617190), and the grandmother passed the t(2;11)(p23; q23) on to the proband through her son. Long read sequencing found 102 balanced translocations (TRA) and 145 inversions at an average of 15×, which affected introns and exons of 247 genes. Combined with the results of RNA-seq of the family, 22 candidate genes were finally identified, among which the average mRNA expression of ASXL2 decreased in the patients.
Conclusions We identified a complex chromosome rearrangement affecting ASXL2 as a pathogenic mechanism of Shashi-Pena syndrome in a Chinese family. The founding of the case suggested that nanopore sequencing was suitable for pathogenic analysis of complex rearrangement, and might blaze the trail in the diagnosis of genetic diseases.

A capillary electrophoresis-based mutation hotspot genotyping method for rapid, reliable, and single-tube analysis of the phenylalanine hydroxylase gene in the Chinese Han population

Binbin Shao An Liu Jingjing Zhang Yan Wang Fengchang Qiao Cuiping Zhang Yuqing Zhu Yingchun Lin Ping Hu Jianxin Tan Zhengfeng Xu
Nanjing Maternity and Child Health Care Hospital

Abstract Hyperphenylalaninemia (HPA) is a common autosomal recessive disorder of phenylalanine metabolism, mainly caused by the deficiency of phenylalanine hydroxylase gene (PAH). A simple, fast, accurate assay to achieve early diagnosis for children with HPA is required. In the present study, we established a SNaPshot-based assay that allows the simultaneous genotyping of 89 hotspot mutations in the *PAH* gene. First, 18 Chinese HPA patients were analyzed by next generation sequencing (NGS) and SNaPshot in parallel. Then, the SNaPshot assay was performed to analyze the mutational spectrum of the *PAH* in 4276 individuals of childbearing age in Eastern China. A total of 36 variants in the *PAH* gene were successfully identified by NGS, while the SNaPshot assay identified 34 PAH variants in these patients. Thus, the SNaPshot assay achieved the sensitivity and specificity of 91.6% and 100.0%, respectively. Furthermore, the carrier rate was approximately 1 in 58 (1.73%) in 4276 individuals, and c.728G>A was the most common variant. In summary, SNaPshot can accurately and rapidly detect *PAH* gene mutations at a comparable performance and lower cost as compared with NGS. Our results suggest that SNaPshot may serve as a promising approach for a routine genetic test in clinical practice.

一例因 WDR34 基因突变所导致的短肋胸椎发育不良 11 型中国患者

刘刚 马定远 胡平 蒋涛 许争峰
南京市妇幼保健院

目的 伴或不伴多指畸形的短肋胸椎发育不良（Short-rib thoracic dysplasia，简称 SRTD）是一组常染色体隐性遗传性骨骼纤毛病，其特征是胸廓狭窄、肋骨短、管状骨缩短、髋臼顶呈“三叉戟”外观。 SRTD 包括 Ellis-van Creveld 综合征（EVC）、先前称为 Jeune 综合征或窒息性胸部营养不良（ATD）、短肋多指综合征（SRPS）和 Mainzer-Saldino 综合征（MZSDS）。多指畸形是可变存在的表型并在各种类型 SRTD 中存在表型重叠，这不同于其内脏畸形和干骺端外观。非骨骼受累可包括唇唇腭裂以及主要器官的异常，如大脑、眼睛、心脏、肾脏、肝脏、胰腺、肠道和生殖器。某些形式的 SRTD 在新生儿期是致命的，归因于胸腔严重受限所致的呼吸功能不全；而其他形式的 SRTD 可与生命相容。当前已发现可导致 SRTD 的基因约有 22 个，包括 *SRTD1*、*IFT80*、*DYNC2H1* 、*TTC21B* 、*WDR19* 、*NEK1* 、*WDR35* 、*WDR60* 、*IFT140* 、*IFT172* 、*WDR34* 、*EVC*、*EVC2* 等。我们描述了一名 17 周+的 B 超提示四肢短小骨骼异常的胎儿患者在 WDR34 基因上被检出复合杂合突变而被诊断为短肋胸椎发育不良 11 型。
方法 针对该患者及其父母的相关基因，使用 WES 测序技术和 real time PCR 技术等进行分子研究。
结果 在这一名患者中鉴定出 *WDR34* 基因（NM_052844.3）存在复合杂合型突变：c.544C>T（p.Arg182Trp）/ exon1~2 deletion，且分别遗传自患儿的父母。
结论 新的大片段缺失突变 exon1~2 deletion 可导致 *WDR34* 基因不能正常履行正常的功能。同时，对于 SRTD 患者进行 WES 测序可能较好地做出基因水平的诊断结果。

DAX-1(NR0B1)基因突变致先天性肾上腺发育不全的产前诊断家系研究及致病机制探讨

李璃 刘刚 马定远 王亚 刘安 周静 季修庆 许争峰
南京市妇幼保健院

目的 分析探讨 DAX-1(NR0B1)基因突变所致的先天性肾上腺发育不全（Adrenal hypoplasia congenital, AHC）患者家系、发病机制及产前诊断临床咨询。
方法 对 3 例先天性肾上腺皮质功能不全患者及家系取外周血并提取 DNA，对 DAX-1 基因外显子测序分析。
结果 患儿 1：DAX-1 基因第 1 外显子 c. 676delG 半合子突变，为移码突变，导致氨基酸 p.Ala226LeufsX38 突变；患儿 2：DAX-1 基因第 1 外显子 c. 572_573ins、c. 509_572dup 突变；患者 3：DAX-1 基因第 1 外显子存在的 c.409G>T 半合子变异，可导致氨基酸序列发生 p.Glu137X 改变。前 2 例基因位点突变目前尚未见国内外文献报道。
结论 虽然 DAX-1 基因突变所致的 AHC 全球发病率仅为 1/(70000～600000)[1]，但 DXA-1 基因位点突变是儿童 AHC 常见分子病因。历史研究表明基因突变类型与临床表型间并无相关性。早期诊断其分子病因对患儿的用药选择及监测患儿青春期发育成长均具有十分重要的临床意义。

15q11.2-13.1 微重复四倍体综合征一例

王涛
河南省人民医院

患儿，男，8 岁，因“运动智力发育落后 7 年”来我科就诊。病史描述：该患者 2011 年足月顺产，体重 3.65kg，出生时无明显产伤，8 月龄时体检发现不能独坐，至 1 岁时仍不能独坐，且动作协调能力差，外院就诊曾诊断为“中枢神经发育迟缓”，随后进行康复治疗，效果欠佳。查体：发育尚可；四肢肌张力低，跑跳等动作可正常进行，但低于同龄儿；智力明显低于正常人，沟通能力差。自述脑部磁共振检查未见明显异常。无家族史。
细胞遗传学检查：取患儿及其父母外周血进行淋巴细胞培养，常规方法制备染色体，G-显带。采用德国 leica cytovision 软件分析制备良好的中期分裂相 30 个。染色体核型按《人类细胞基因组学国际命名体系》(ISCN2016)描述。父母染色体核型未见异常。患儿染色体核型为 47, XY, +idic(15)(q13.1)，Array CGH 结果为 arr[GRCh37]15q11.2q13.1(22770421_29062448)x4。
讨论 15q11.2-13.1 微重复四倍体综合征为极为罕见的染色体异常，多为散发，绝大部分是由于母源性的 15q11.2-13.1 等臂双着丝粒额外染色体-包含两个 15q11.2-13.1 额外拷贝引起。15q11.2-13.1 拷贝数增加可导致严重的神经系统疾病，主要临床特征：中至重度的发育迟缓或智力低下、肌张力低下、孤独症样行为、难治性癫痫、语音落后或缺失和其他异常体征等。15q11.2-13.1 微重复四倍体综合征的发病机制可能与该区域众多重要基因的过度表达有关，如母源性 UBE3A 基因过度表达损害神经认知发育，导致孤独症；GABAA 亚族基因和癫痫有关等。进行及时有效地遗传咨询和临床干预有着重要意义，当母亲再次妊娠时，及时做产前诊断可避免染色体异常患儿的出生。

单核苷酸多态性-微阵列技术在 Silver-Russel 综合征遗传学诊断中的应用

周冉
南京市妇幼保健院

目的 探讨核苷酸多态性-微阵列（SNP-array）技术在 Silver-Russel 综合征中的诊断价值与局限性。

方法 3 月龄患儿“生长发育迟缓”，采集患儿及父母外周血淋巴细胞，提取外周血 gDNA 行 SNP-array 全基因组分析，UPD-tool 软件行 UPD 来源分析，MS-MLPA 对结果进行验证以明确诊断。
结 果 患儿外周血淋巴细胞核苷酸多态性-微阵列结果为 arr[hg19] 7q11.23q34(73280201_138336608) hmz，考虑 7 号染色体单亲二倍体（UPD）可能；家系 SNP-array 联合 UPD-tool 分析提示：患儿的 7 号染色体为母源单亲二倍体，其中 7p22.3q11.23 为母源单亲异二体，7q11.23q34 为母源单亲同二体，7q34q36.3 为母源单亲异二体；MS-MLPA 进一步明确 7 号母源单亲二倍体；综上所述，明确患儿 Silver-Russel 综合征的诊断。
讨论 Silver-Russel 综合征中大约 10%是由母源性 7 号染色体单亲二体导致，家系 SNP-array 连锁分析在 Silver-Russel 综合征诊断中具有一定的价值。

Two factors affecting the successful rate of a second noninvasive prenatal screening after an initial no call result: experience from single tertiary center in China

Dong Liang Ying Lin Ping Hu Hang Li Chunyu Luo Zhengfeng Xu
Nanjing Maternity and Child Health Care Hospital

Objective One inevitable shortcoming of noninvasive prenatal screening (NIPS) is the ‘no call’ result, mainly caused by insufficient fetal fraction. Our objective is to investigate the factors associated with a successful second NIPS in these cases, and to seek an optimal management for women with initial no call results.
Method We retrospectively analyzed NIPS cases with initial no call results due to insufficient fetal fraction from 2017 to 2019 in our center. We collected maternal and pregnancy information of these cases, and made comparison between cases yielding a successful second NIPS result and cases receiving no call results for a second time.
Results Among the 33684 NIPS cases, 137 cases with a no call result underwent a retest. When comparing the 87 (63.50%) cases with a successful retest to the other 50 (36.50%) cases, both initial fetal fraction and maternal BMI had significant difference, while other factors showed no substantial differences. In addition, with an initial fetal fraction lower than 2.00%, the successful rate of a retest was very limited.
Conclusion We identified two major factors, including initial fetal fraction and maternal BMI, associating a successful retest in our cohort, suggesting a specialized management for this subset of cases, which would be instructional for the counseling for these women.

A novel UBE2A mutation in a Chinese family with X-linked mental retardation

Qinxin Zhang Fengchang Qiao Ping Hu Zhengfeng Xu
Nanjing Maternity and Child Health care Hospital

Background Nascimento form of syndromic X-linked mental retardation (MRXSN), also known as UBE2A deficiency syndrome, is an intellectual disability syndrome characterized by moderate to severe intellectual disability, dysmorphic facial features, speech impairment, hypoplastic genitalia and dyskinesia. The syndrome is caused by mutations of the *UBE2A* gene, or larger deletions of Xq24 encompassing *UBE2A*.
Methods We report the case of a 7-year-old male with MRXSN, who showed severe mental retardation, prominent dysmorphic features, impaired speech and urogenital malformations. Trio-whole exome sequencing (WES) was performed to identify the disease-causing mutations in this patient.
Results A novel deletion CNV with a size of 111.70 kb encompassing exons 4 to 6 of the *UBE2A* gene, *NKRF* gene and *SEPTIN6* gene (seq[GRCh37] del(X)(q24q24)chrX:g.118715433_118827132del) was identified in patient. The clinically

unaffected mothers were confirmed to be heterozygous carriers of the deletion. The deletion CNV was confirmed by qPCR.
Conclusions The present study identified a novel deletion CNV encompassing *UBE2A* and adjacent genes. Our findings expand the mutational spectrum of the *UBE2A* gene, also confirm the interest of combining WES with CNV analysis to provide a molecular diagnosis to patients with rare mendelian disorders.

血性羊水染色体制备技术的改进

黄宁 刘艳秋 杨必成 黄淑晖 周吉会 黄婷婷 胡燕玲
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

目的 研究一种培养成功率高，适宜推广的血性羊水染色体制备方法。
方法 选取 93 例严重血性羊水，抽取成功肉眼判定为血性羊水后即刻加入肝素抗凝，3000rpm，离心 10min，每份标本同时采用两种方法进行对比分析，实验组方案为吸取血细胞表层白膜层接种，对照组方案为传统方法吸取所有沉淀细胞接种。
结果 实验组 93 例全部培养成功，平均收获时间 9.16 天，平均有效分裂相数 42.35 个。对照组 93 例培养失败 3 例，平均收获时间 10.87 天，平均有效分裂相数 29.74 个，统计学处理采取配对 t 检验，两组收获时间 P<0.01，有效分裂相数 P<0.01，具有显著性差异。
结论 改进的血性羊水制备技术中选取羊水细胞白膜层接种，明显提高了羊水培养成功率，缩短了细胞培养时间，增加了有效分裂相数，操作简便，适宜推广应用。

新西兰大白兔耳廓软骨发育的形态学及生物力学特性

陈丽丽[1,3] 傅窈窈[3] 何爱娟[3] 马竞[1,3] 马端[1,2] 张天宇[3]
1.复旦大学
2.复旦大学附属儿科医院
3.复旦大学附属眼耳鼻喉科医院

背景 先天性耳廓畸形是较常见的一类颅面部出生缺陷，主要包括耳廓结构畸形和耳廓形态畸形。其中耳廓形态畸形发病率为 25%~55%，虽然不存在软骨及皮肤的发育不全，但患儿在学龄前时期，可能会因为异常耳廓引发相关社会心理问题。耳郭形态畸形仅 30％可自行恢复正常，大部分仍需外界干预。过去矫形手术是治疗耳廓形态异常的常规方法，存在感染、血肿、二次修复手术等风险。耳模矫正技术作为一种无创治疗方法，可对新生儿的畸形耳廓进行力学矫正，从而避免手术风险和相关心理伤害。该方法治疗耳郭形态畸形最佳时机为患儿出生后 6 周内，之后随着年龄增长效果越来越差。因为耳模矫正效果与软骨的可塑性和延展性相关，有研究显示新生儿体内含有大量产妇雌激素，可增加耳廓软骨的延展性和可塑性；之后雌激素浓度逐渐降低，在出生后 6 周时恢复到正常水平，软骨的可塑性和延展性也随之降低。软骨这些生物力学特性在很大程度上取决于软细胞外基质的主要成分，包括胶原纤维、 弹力纤维、糖胺聚糖、水等。
材料与方法 为了探索不同发育时期软骨的细胞外基质特点及生物力学性能，明确耳模矫正疗效的相关因素，我们采用具有较大耳廓并且与人亲缘性接近的新西兰大白兔作为实验动物模型。设置 5 个日龄组（0 天、5 天、15 天、60 天、6 月），分别代表人类刚出生、耳模矫正最佳治疗时间 6 周、耳模矫正时间窗 3 月、1 岁、成年。因为耳模矫正本质是通过外力作用改变耳廓形态，我们就通过胶布折叠不同日龄兔耳廓软骨，分别在折叠后 1 天、5 天和 10 天，拆除胶布后拍照计算耳廓折角。耳廓出现成角形变代表耳模矫正动物模型构建成功。对软骨进行组织学染色（HE 染色、番红 O 染色、Masson 染色和 II 型胶原免疫组化染色），观察不同日龄细胞外基质成分的差异。检测软骨含水量和 DNA 含量分析软骨生化特性。使用纳米压痕仪分析软骨生物力学情况。
结果 拆除胶布后，每个组别均可观察到耳廓即刻成角。拆除后连续观察 5 天，日龄越小所形成的耳廓夹角更小，成角形变更持久。组织学染色显示，软骨细胞的密度随日龄增大而减少，细胞外基

质所占面积、细胞外糖胺聚糖含量和 II 型胶原含量随日龄增大而增加。生化结果表明小日龄软骨含水量和 DNA 含量更高（P<0.05）。软骨的杨氏模量和表观粘度也随着日龄的增加显著升高。
结论 在这个研究中，我们成功构建了耳模矫正新西兰大白兔动物模型，可用于耳模矫正方案的优化及治疗相关因素的研究。本研究验证了小日龄软骨具有更好的可塑性和延展性，在外力作用下更能产生持久形变。这种良好的可塑性主要由于幼稚软骨细胞外基质水分含量较高，糖胺聚糖和 II 型胶原含量较低，导致其弹性模量和表观粘度较小，对力学刺激更敏感。

CMA 结合核型分析在两例染色体平衡易位携带者产前诊断中的应用

饶慧华 邹永毅 周吉会 黄淑晖 杨必成 刘艳秋
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

目的 应用染色体微阵列（chromosome microarray analysis，CMA）技术对两例胎儿核型分析疑似不平衡易位者进一步进行拷贝数变异（copy number variations，CNVs）检测，探讨 CMA 在产前诊断中的应用价值。
方法 应用 G 显带染色体核型分析两例超声结构异常的胎儿及其父母的染色体核型，应用 CMA 技术检测胎儿 CNVs。
结果 病例 1 因超声显示胎儿心脏发育异常，双肾体积稍小，单脐动脉，左心室强光点来我院行产前诊断，胎儿初步核型结果为 47,XN,+add(X)(?::p22.3→qter),CMA 结果为 5 号染色体 q22.3q35.3 重复 67.41Mb，X 染色体 p22.3q28 重复 146.47Mb，进一步检测妻子染色体核型为 46,X,t(X;5)(p22.3;q22)，丈夫染色体正常，胎儿核型结果最终更正为 47,XX,+der(X)t(X;5)(p22.3;q22)；病例 2 因胎儿双肾体积稍小来我院行产前诊断，胎儿初步核型结果为 46,XN,add(9)(?::p23→qter)，CMA 结果为 6 号染色体 p25.3p22.3 重复 18.55Mb，9 号染色体 p24.3p23 缺失 10.85Mb，进一步检测妻子染色体核型为 46,XX,t(6;9)(p22;p23)，丈夫染色体正常,胎儿核型结果最终更正为 46,XN,der(9)t(6;9)(p22;p23)。
结论 对染色体核型分析不够明确的结构重排，进一步行染色体微阵列分析有助于明确异常片段来源，特别是对染色体平衡易位携带者产前诊断具有重要的临床应用价值。

Meckel-Gruber 综合征 TMEM231 基因变异检测及功能研究

杨书雅[1] 侯巧芳[2]
1.河南大学人民医院
2.河南省人民医院

目的 通过基因检测明确一个 4 次妊娠均出现胎儿枕后脑膨出家系的病因，并对致病变异进行功能分析。
方法 应用全外显子组测序（Whole-exome sequencing，WES）技术对一例疑诊为 Meckel-Gruber 综合征（Meckel-Gruber Syndrome, MKS）的引产胎儿组织及其父母样本进行 WES 检测，生物信息学分析可能的致病基因及变异位点；RT-PCR、qPCR 及 TA 克隆测序，分析变异对基因转录的可能影响，免疫荧光技术探究 *TMEM231* 基因变异对纤毛结构的影响。
结果 引产胎儿组织 WES 提示 *TMEM231* 基因 c.583-1G>C 和 c.583-2_588delinsTCCTCCC 剪接位点复合杂合变异，变异分别来自于父亲、母亲；该变异数据库均尚未见报道，依据 ACMG 评分标准，属于致病性变异(PVS1+PM2+PM3+PP4)。TA 克隆测序证实 c.583-1G>C、c. 583-2_588delinsTCCTCCC 两个剪接位点变异均导致外显子 5 跳跃（c.583_664del）的缺失移码，在第 195 位氨基酸处引起移码并于第 199 位氨基酸提前形成终止密码子，导致蛋白截短，qPCR 证实在肾脏、心脏及肝脏 *TMEM231* 基因 mRNA 表达显著降低，推测可能触发无义介导的 mRNA 降解（Nonsense-mediated mRNA decay，NMD）。*TMEM231* 基因变异导致纤毛显著减少。

结论 本研究在中国人群中首次报道了由于 *TMEM231* 基因两个新发复合杂合变异导致的 MKS 家系，为该家系的遗传咨询和产前基因诊断提供了依据，拓展了 *TMEM231* 基因变异图谱，并为 MKS 的临床诊断提供了参考。

应用扩展性携带者筛查对一个 PRF1 基因突变携带家系进行基因分析及产前诊断

张雯 袁慧珍 陈佳 阳彦 谢康 黄淑晖 杨必成 邹永毅 刘艳秋
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

目的 应用染色体微阵列（chromosome microarray analysis，CMA）技术对两例胎儿核型分析疑似不平衡易位者进一步进行拷贝数变异（copy number variations，CNVs）检测，探讨 CMA 在产前诊断中的应用价值。
方法 应用 G 显带染色体核型分析两例超声结构异常的胎儿及其父母的染色体核型，应用 CMA 技术检测胎儿 CNVs。
目的：针对表型未见异常的备孕或孕早期夫妇进行单基因遗传病的扩展性携带者筛查，指导产前诊断和遗传咨询。**方法**：利用目标区域捕获-高通量测序技术对一对表型未见异常夫妇行单基因遗传病扩展性携带者筛查，筛查结果为同型致病性变异携带者，妊娠后于孕中期行羊膜腔穿刺抽取羊水，利用 PCR 结合 Sanger 测序对胎儿进行相关基因突变位检测。
结果：单基因遗传病扩展性携带者筛查结果显示该夫妇携带家族性噬血细胞性淋巴组织细胞增多症 2 型相关的 *PRF1* 基因变异，妻子携带 c.503G>A (p.Ser168Asn)杂合变异，丈夫携带 c.65delC (p.Pro22Argfs*29)杂合变异；产前诊断结果显示胎儿 *PRF1* 基因存在 c.65delC 及 c.503G>A 复合杂合变异。
结论：单基因遗传病扩展性携带者筛查可以帮助夫妇在孕前及孕早期了解隐性单基因遗传病的携带状态，指导产前诊断及遗传咨询，避免单基因遗传病患儿出生，提高出生人口素质。

先天性非综合征小耳畸形中长链非编码 RNA 综合调控网络的生物信息学分析

马竞[1,3] 陈施余[1] 李辰龙[3] 陈鑫[1,3] 卢鑫雨[3] 吴培瑄[1] 马端[1,2] 张天宇[3]
1.复旦大学
2.复旦大学附属儿科医院
3.复旦大学附属眼耳鼻喉科医院

背景和目的 先天性非综合征小耳畸形（congenital non-syndromic microtia, CNSM）是由于遗传、表观遗传和环境因素的相互作用导致的外耳和中耳发育畸形，常表现为耳廓畸形，外耳道闭锁和（或）中耳畸形，并伴有不同程度的听力损害。长链非编码 RNA(long non-coding RNA, lncRNA)是近年来表观遗传学的研究热点，尽管已有研究提示 lncRNA 可能参与了 CNSM 的发病，但其具体作用和发病机制尚不清楚。
材料与方法 为了进一步探讨关键 lncRNA 在 CNSM 中的作用，我们收集了 10 例三度单侧 CNSM 患者的残耳软骨组织和 5 例正常对照（中耳炎患者）的耳软骨组织，提取 RNA，利用芯片分析两组间 lncRNA 的差异表达谱。经过深度生信分析，对差异表达的 lncRNA，使用 miRcode、miRDB、miRTarBase 和 TargetScan 数据库预测靶向 microRNA，关联分析 microRNA 下游的 mRNA，进而构建了内源竞争 RNA（competing endogenous RNA，ceRNA）调控网络。此外，我们对 ceRNA 网络中的 mRNA 进行 KEGG 和 GO 功能富集分析。
结果 与正常对照组相比，在 CNSM 组中鉴定出 4660 个差异表达的 lncRNA，包括 2047 个上调的 lncRNA 以及 2613 个下调的 lncRNA。构建的 ceRNA 网络包含 lncRNA，mRNA 和 microRNA。GO 和 KEGG 分析显示在 ceRNA 网络中的 mRNA 显著富集了“感觉器官发育”，“细胞间连接”等功

能。据此，我们筛选出了六个可能与软骨发育相关的 lncRNA，其中有三个 lncRNA（TUG1, HOTAIRM1, ZFAS1）在 CNSM 中表达上调， 三个 lncRNA（CYTOR, HCP5, GACAT3）表达下调。 这六个 lncRNA 的关联 mRNA 是 *MYH9* 和 *WNT9B*，均报道与小耳畸形相关。
结论 LncRNA 在 CNSM 耳软骨组织中存在差异表达，我们筛选出来的六个 lncRNA 可能通过 ceRNA 途径影响下游的 *MYH9* 和 *WNT9B* 靶分子表达，从而参与 CNSM 的发病。

一例遗传性球形红细胞增多症家系的致病基因鉴定与遗传学研究

徐琳琳 魏小凤 梁观霞 朱迪娜 张燕霞 商璇
南方医科大学基础医学院医学遗传学教研室

目的 遗传性球形红细胞增多症（Hereditary Spherocytosis,HS）是一种以球形红细胞增多为特征的遗传性红细胞膜疾病，其临床表现具有明显的异质性。在中国人群中，ANK1 基因缺陷是导致 HS 的主要原因。本研究收录了一例中度贫血的患儿，为明确其病因进行分子鉴定。
方法 收集先证者及其父母的外周血，进行血涂片形态观察和膜蛋白电泳分析。提取外周血中的 DNA 进行全基因组测序，寻找突变位点。扩增 cDNA 并测序发现其剪接的机制。
结果 在先证者及其父亲的外周血涂片中可以观察到球形的红细胞，电泳结果显示锚蛋白含量的降低。测序结果表明先证者为 ANK1 剪接突变 c.4391-2A>C 的携带者，且该突变遗传自其父亲。突变将产生延长的转录产物，导致翻译提前终止，产生截短的蛋白质。
讨论 本研究明确了一个球形红细胞增多症家系的致病基因，首次报道了一种新的 ANK1 剪接突变 c.4391-2A>C，并明确了致病性及其剪接的机制。这对完善 HS 的突变谱，开展产前诊断和遗传咨询都具有重要的意义。

Progress in the genetics of cerebral palsy

Tong Zhang[1,2] Fengxiang Wei[1,2] Guoqiang Zhao[1,2] Yanan Liu[1,2]
1.Longgang District Maternity&Child Healthcare Hospital of Shenzhen City
2.Jiamusi University

Cerebral palsy, is a non-progressive disorder that occurs in the developing fetus or infant's brain. It's a group of permanent motor and postural developmental disorders that result in limited movement. Risk factors for patients with cerebral palsy mainly occur in four aspects: preconception, prenatal, perinatal period, and infant and neonatal periods. The incidence of cerebral palsy was up to 2 – 3 per 1,000 live-born children. In particular, genetic factors before birth are closely related to their susceptibility. Congenital malformations can occur when the number or structure of chromosomes, gene mutations, or congenital metabolic defects occur, which manifests as abnormal neonatal ontogeny. Currently, the occurrence of cerebral palsy has been associated with multiple susceptibility genes such as APB1, APS1, SAPS2, SBF1. The ZNF804B, MGC26647, STEAP1 genes on 7q21.13 related to maternal inheritance, the DAAM1 gene on 14q23.1 with uncertain inheritance, and the microduplications of TUBGCP5 and CYFIP1 genes on 15q11.2 have all been confirmed to cause cerebral palsy. Abnormalities in the genes of cerebral palsy symptoms such as SPG, ATL1, GCDH, and NPHP1 have also been shown to cause clinical manifestations such as movement disorders, intellectual disabilities, posture disorders, speech disorders and behavioral disorders in patients with cerebral palsy. Therefore, according to the definition of cerebral palsy and various classification systems are of great significance to further understanding the complex causal pathway leading to cerebral palsy. It is also helpful for early disease prevention, determine targeted diagnosis and treatment programs, and prognostic rehabilitation, and then design preventive measures to reduce the incidence of patients with cerebral paralysis.

KLF1 复合杂合突变引起儿童溶血性贫血：一例报告和文献综述

徐琳琳 朱迪娜 张燕霞 梁观霞 魏小凤 商璇
南方医科大学基础医学院医学遗传学教研室

目的 贫血是世界儿童最常见的疾病之一，因基因突变导致的遗传性溶血性贫血（hereditary hemolytic anemia，HHA）仅依靠临床表型难以诊断。在中国南方等地贫高发区，具有 HHA 表型的儿童通常被诊断为 β 地中海贫血。然而，HHA 也可能由其他基因缺陷引起。这里我们收录了一名被初诊为地中海贫血的患儿，但初步的分子检测并未显示有任何珠蛋白基因突变。
方法 对患儿及其父母进行临床表型分析和基因测序，并回顾相关的文献报道。
结果 依据该患儿的表型资料，判断该患儿为重度的 HHA 患者。经 Sanger 测序发现 KLF1 基因上有两种突变，分别为错义突变 c.892G>C（p.Ala298Pro）和移码突变 c.525_526insCGGCGCC（p.Gly176Argfs*179）。 此外，通过对该病例和文献的回顾，总结了 KLF1 的突变谱并明确了基因型-表型相关性。
讨论 本研究纠正了一例 HHA 患儿的误诊并明确了病因，这对患者的治疗以及预防其家庭中另一个孩子的分娩非常重要。此外，本研究为更好的区分 β 地贫的 HHA 患者与 KLF1 突变的 HHA 患者提供了帮助。

Mutation analysis of patients with 6-pyruvoyltetrahydropterin synthase deficiency

Qing Lu Feng Wang Xiaolan Xu Huizhen Yuan Yongyi Zou Shuhui Huang Bicheng Yang Yanqiu Liu
Medical Genetic Center; Jiangxi Provincial Key Laboratory of Birth Defect for Prevention and Control,Jiangxi Maternal and Child health Hospital

Objective To characterize the gene variation spectrum of patients with 6-pyruvoyltetrahydropterin synthase deficiency (PTPSD) in Jiangxi Province, in order to provide the theoretical foundations for early diagnosis, treatment, genenetic consultion and prenatal diagnosis of BH4D.
Methods The *PTS* gene was examined by means of polymerase chain reaction (PCR) and DNA sequencing analyses in 48 PTPSD families.
Results 92 variants were detected among the 96 alleles，which included 14 types of variants, with the detection rates being 95.8％. Common variants included P87S(47.8%), IVS1-291A>G(18.4%), N52S(8.6%), D96N(6.5%) and L127F(5.4%). All variants were mainly located in exons 5(52, 56.5％), 2(8, 8.6％)，6(7, 7.6％) and intron 1(17, 18.4％). In addition, IVS2-36A＞G was novel.
Conclusions *PTS* gene variants identified in Jiangxi mainly distributed in exons 5, 2, 6 and intron 1, in which the most common variant was P87S, followed by IVS1-291A>G. One novel variant was detected.

葡萄胎分子遗传病因探究及分类

王丽娟[1] 郭辉[1] 宋雅琴[1] 高慧[1] 马迪[1] 聂锐[1] 王沙燕[1] 胡芷洋[2] 周俊[2] 刘锦[3]
1.深圳市人民医院（暨南大学第二临床医学院，南方科技大学第一附属医院）法医物证室 广东深圳 518020
2.深圳市人民医院（暨南大学第二临床医学院，南方科技大学第一附属医院）产科 广东深圳 518020
3.深圳市人民医院（暨南大学第二临床医学院，南方科技大学第一附属医院）计划生育科 广东深圳 518020

目的 葡萄胎（Hydatidiform Mole, HM）是一种胚胎发生过程中绒毛滋养层细胞过度增殖形成的疾病，根据组织病理学，可分为完全性葡萄胎（Complete Hydatidiform Mole, CHM）和部分性葡萄胎（Partial Hydatidiform Mole, PHM）。CHM 大部分由父源性单亲二倍体（Uniparental Disomy, UPD）所致，而父源和母源基因表达失衡则会导致 PHM，二者继发妊娠滋养细胞肿瘤的风险不

同，需及时区分。本研究联合应用多种分子遗传技术，对超声提示疑似葡萄胎的绒毛样本进行分子遗传学病因探究及分类。
检测对象：2 例流产绒毛，孕早期超声均提示宫腔内回声紊乱，存在无回声蜂窝状团块；1 例早产新生儿，孕期多次超声提示蜂窝状胎盘与胎儿共存，采集羊水穿刺样本以及分娩后胎盘组织，胎盘组织分别留取形态正常和异常（水泡状、红色结节状）的不同部位，并采集胎儿父母外周血样本。
检测方法 收集样本提取 DNA 后，多重连接探针扩增（Multiplex Ligation-Dependent Probe Mmplification, MLPA）P095 试剂盒和 PowerPlex 21 短串联重复序列（Short Tandem Repeat, STR）分型试剂盒进行染色体倍性和亲缘关系分析；荧光原位杂交（Fluorescence In Situ Hybridization, FISH）对存在嵌合现象的样本验证分析。
结果 2 例流产绒毛 MLPA 检测未见异常，STR 分型提示存在父源性 UPD（46,XX），分类为 CHM。早产胎儿羊水 MLPA 及 STR 分型均未见异常（46,XY）。分娩后胎盘组织中形态正常胎盘 MLPA 及 STR 结果与羊水一致。水泡状和红色结节状胎盘 MLPA 结果均存在 X 与 Y 染色体信号不平衡，提示有性染色体异常嵌合；STR 分型结果可见各基因座最高信号峰均为父源，提示存在父源性 UPD（46,XX）嵌合，并且两种方法均提示红色结节状胎盘组织的父源性 UPD（46,XX）比例较高；FISH 确证该葡萄胎为 46,XY 与 46,XX 嵌合，综合判断胎盘同时存在完全性葡萄胎与出生胎儿正常胎盘组分，妊娠过程中可能发生了二者的融合现象。
结论 联合利用多种分子遗传学方法可快速准确阐明葡萄胎分子遗传学病因，为葡萄胎分类、以及孕妇继发妊娠滋养细胞肿瘤风险的及时评估、遗传咨询提供证据支持。

鳃-耳-肾谱系疾病的临床与遗传学进展

杨润[1,3] 朱雅颖[3] 马竞[1,3] 马端[1,2] 张天宇[3]
1.复旦大学
2.复旦大学附属儿科医院
3.复旦大学附属眼耳鼻喉科医院

摘要 鳃-耳-肾谱系疾病（Branchio-oto-renal spectrum disorder，BORSD）是一种由于胚胎发育时期基因突变，导致鳃器、耳及肾脏发育异常的单基因遗传病，包括鳃-耳-肾综合征（Branchio-oto-renal syndrome，BOR syndrome，BOR）和鳃-耳综合征（Branchio-oto Syndrome，BO syndrome，BOS）两大类。BORSD 是导致先天性鳃裂畸形、耳聋、耳畸形及肾脏畸形的重要疾病之一，发病率为 1/40, 000。BORSD 临床表型的异质性为确诊带来困难，而基因诊断技术在临床应用为该病提供了确诊手段。自从 1997 年、2004 年和 2007 年，眼缺乏同源物 1（Eyes Absent Homolog 1, *EYA1*）、SIX 同源框 1（SIX Homeobox 1, *SIX1*）和 SIX 同源框 5（SIX Homeobox 5, *SIX5*）先后被确定为该疾病的主要致病基因以来，已有多种动物及细胞模型被用于探究这一疾病背后潜在的分子机制。随着基因组测序技术的进展，针对其遗传学的研究也在不断深入。本文综述了从 1975 年至今国内外发表的 BORSD 相关文献，首先梳理了该病的发现史及命名史，强调了 BOS 与 BOR 在遗传背景、临床表现等各方面的异同及将二者通称为同一谱系疾病的原因。其次，详述了 BORSD 在鳃裂、耳、肾及其他各器官的临床表现，并纳入了对罕见表型的报道。在其遗传学病因和发病机制方面，不仅总结了 3 个已知致病基因相关研究及所致的临床表型的差异，还首次综述了 5 个候选致病基因：SHANK 相关 RH 结构域作用物（SHANK Associated RH Domain Interactor，*SHARPIN*）、成纤维细胞生长因子 3（Fibroblast Growth Factor 3，*FGF3*）、同源框 A 基因簇（Homeobox A Cluster，*HOXA* Cluster）、Spalt 样转录因子 1（Spalt like transcription factor 1，*SALL1*）、苯胺素肌动蛋白结合蛋白（Anillin Actin Binding Protein，*ANLN*）的潜在致病机制。最后，概述了 BORSD 在诊断、治疗、预防，特别是耳部疾病表现及治疗效果等方面近三年内的进展。本综述旨在提高对这一多见于耳鼻咽喉头颈外科的遗传病的认识。

Integrated Proteomics and Transcriptomics Analyses of Nonsyndromic Microtia

Xin Chen[1,3] Chenlong Li[3] Xinyu Lu[3] Peixuan Wu[1] Jing Ma[1,3] Duan Ma[1,2] Tianyu Zhang[3]
1.Fudan University
2.Children's Hospital of Fudan University
3.ENT institute, Eye & ENT Hospital, Fudan University

Background Nonsyndromic microtia (NSM) is a congenital malformation of the outer and middle ear caused by genetic and environmental factors. At present, the underlying causes and pathogenesis are still unclear. Although a few unambiguous predisposing genes have emerged, they are far from enough to explain the disease. In addition to gene sequence variation, the occurrence and development of NSM may be accompanied by abnormal gene expression. In the present study we sought to analyze the protein and gene expression profiles in auricle cartilage between normal controls and patients to identify molecular mechanism associated with NSM.
Methods and Results We collected auricular cartilage samples from ten patients with third-degree NSM and five normal controls. RNA was extracted and the differential expression profile of mRNAs between the two groups was analyzed by microarray. A total of 5,681 differential expression genes (DEGs) (2,691 up-regulated and 2,990 down-regulated) were identified and based on KEGG enrichment analysis, a considerable proportion of significantly down-regulated DEGs were annotated to MAPK signaling pathway. We performed WGCNA on DEGs and predicted the transcription factors and their target genes of hub genes in each module by HOCOMOCO motif and hTFtarget databases. The magenta module has been proved to be most closely related to NSM, and the hub genes in this module were also mainly enriched in MAPK signaling pathway. At the same time, proteins were extracted and analyzed by TMT-based quantitative proteomics technology. A total of 314 differential expression proteins (DEPs) (94 up-regulated and 210 down-regulated) were identified and 85 genes overlapped at the intersection in both the transcriptomics and proteomics data. Based on KEGG enrichment analysis, down-regulated genes at both protein and mRNA levels mainly enriched in ECM−receptor interaction, focal adhesion and PI3K−Akt signaling pathways. The expression levels of *HSPG2* (a hub gene in magenta module) and *COMP* were significantly down-regulated at both mRNA and protein levels, and verified it by PRM. Through PPI analysis, there may be interaction between HSPG2 and COMP. COMP is an abundant cartilage ECM protein, which plays a role in the formation of mesenchymal chondrogenesis by promoting the organization and assembly of the main components of cartilage ECM. HSPG2 plays a vital role in the formation of cardiovascular, neural and cartilage tissues. HSPG2 deficiency significantly can significantly inhibit the calcium signaling, ECM-receptor interaction and focal adhesion pathways.
Conclusions The results of transcriptomics and proteomics analyses suggested that the ECM−receptor interaction, focal adhesion and PI3K−Akt signaling pathway are closely related to NSM. HSPG2 and COMP, which were significantly down-regulated at mRNA and protein levels, are likely to participate in the pathogenesis of NSM by inhibiting ECM-receptor interaction and focal adhesion pathway.

Expression profiles of exosomal microRNAs derived from cerebrospinal fluid in patients with congenital hydrocephalus determined by microRNA sequencing

Shiyu Chen[1] Jing Ma[1,3] Nan Jiang[1] Jin Zhang[1] Duan Ma[1,2]
1.Fudan University
2.Children's Hospital of Fudan University
3.Eye & ENT Hospital, Fudan University

Background and Objects Congenital hydrocephalus is one of the most common birth defects worldwide. Exosomal microRNAs (miRNA) in body fluids have been implicated in many diseases.

However, their involvement in cerebrospinal fluid from congenital hydrocephalus is not well understood. This study aimed to investigate the role of dysregulated exosomal miRNAs in congenital hydrocephalus.
Methods and Results We collected cerebrospinal fluid samples from 15 congenital hydrocephalus groups and 21 normal control groups. We used miRNA sequencing to generate exosomal miRNA expression profiles in three pairs samples. We identified 31 differentially expressed exosomal miRNA in congenital hydrocephalus and predicted their target mRNAs. Three microRNAs(hsa-miR-130b-3p, hsa-miR-501-5p, hsa-miR-2113) were selected according to their fold changes and the function of their target mRNAs, and only hsa-miR-130b-3p and hsa-miR-501-5p were confirmed their expression levels in all samples. Moreover, upregulated hsa-miR-130b-3p might mediate the downregulation of the phosphatase and tensin homolog gene, which has been associated with hydrocephalus, via binding to its 3′ untranslated region by dual-luciferase reporter assay.
Conclusions This study implicates that abnormal expressed exosomal miRNAs in cerebrospinal fluid may be correlated with in the pathogenesis of congenital hydrocephalus pathogenesis.

儿童获得性脱髓鞘综合症（ADS）与血清维生素 D 代谢相关基因的研究

崔亚琼[1,2] 支秀芳[1,2] 舒剑波[1,2] 蔡春泉[1,2] 李东[1,3]
1.天津市儿童医院
2.天津市儿科研究所，天津市儿童出生缺陷防治重点实验室
3.神经内科

目的 探讨维生素Ｄ代谢相关基因单核苷酸多态性（SNP）与 ADS 发生的相关性。
方法 收集儿童脱髓鞘患者和健康对照的外周血样本，提取 DNA，选取 5 个维生素 D 代谢相关基因的 5 个 SNP 位点进行研究，即 *NADSYN1* 基因 rs12785878 位点、*CYP2R1* 基因 rs12794714 位点、*GC* 基因 rs7041 位点、*VDR* 基因 rs1544410 位点以及 *CYP24A1* 基因 rs17216707 位点。通过 PCR 扩增相关 DNA 片段，通过 Sanger 测序、高分辨溶解曲线进行基因分型，分析病例组及对照组的 SNP 位点基因型及等位基因分布有无统计学差异，筛选出维生素 D 代谢相关基因的 5 个 SNP 位点中与 ADS 相关的危险因素。
结果 1、共收集 55 名儿童 ADS 患者和 56 名健康对照的外周血样本。选取的 5 个维生素 D 代谢相关基因的 SNP 位点中，*NADSYN1* 基因 rs12785878 位点存在 GG、GT、TT 三种基因型和 G、T 两种等位基因；*CYP2R1* 基因 rs12794714 位点存在 CC、CT、TT 三种基因型和 C、T 两种等位基因；*GC* 基因 rs7041 位点存在 TT、TG、GG 三种基因型和 T、G 两种等位基因；*VDR* 基因 rs1544410 位点存在 GG、GA 两种基因型和 G、A 两种等位基因，未发现 AA 型；*CYP24A1* 基因 rs17216707 位点存在 TT、TC 两种基因型和 T、C 两种等位基因，未发现 CC 型。 2、*NADSYN1* 基因 rs12785878 位点、*CYP2R1* 基因 rs12794714 位点和 *GC* 基因 rs7041 位点的基因型和等位基因在病例组和对照组的频率具有统计学差异（$P<0.05$）。 3、*NADSYN1* 基因 rs12785878 位点中 G 等位基因，*CYP2R1* 基因 rs12794714 位点中 C 等位基因，*GC* 基因 rs7041 位点中 T 等位基因在 ADS 中的频率高于健康对照组，提示可能是 ADS 发生的危险因素。*VDR* 基因 rs1544410 位点、*CYP24A1* 基因 rs17216707 位点基因型和等位基因在各组分布均无统计学差异。

结论 本课题选取的 5 个维生素 D 代谢相关基因的 SNP 位点中 *NADSYN1* 基因 rs12785878 位点中 G 等位基因，*GC* 基因 rs7041 位点中 T 等位基因和 *CYP2R1* 基因 rs12794714 位点中 C 等位基因可能为儿童 ADS 发生的危险因素。

A novel CREBBP inframe deletion variant in a Chinese girl with atypical Rubinstein-Taybi syndrome phenotypes

Haiming Yuan
Dongguan Maternal and Child Health Care Hospital

Loss-of-function variants in CREBBP or EP300 result in Rubinstein–Taybi syndrome (RSTS). The previously reported cluster of variants in the last part of exon 30 and the beginning of exon 31 of CREBBP, overlapping with the ZNF2 (zinc finger, ZZ-type; residues 1701 to 1744) and ZNF3 (zinc finger, TAZ-type; residues 1764 to 1853) domains, is associated with atypical RSTS. The main features include developmental delay, short stature, microcephaly, distinctive facial features, autistic behavior, feeding
difficulties, recurrent upper airway infections, and hearing impairment. Here, we report a 2-year-7-month-old Chinese girl presenting mild cognitive impairments, developmental delay, short stature, recurrent upper airway infections, and facial dysmorphism that resembled the phenotypes of previously reported atypical RSTS patients. The characteristic facial and limb dysmorphism for RSTS was absent in our patient. In addition, our patient exhibited novel phenotypes including attention deficit hyperactivity disorder (ADHD), sleep problem, and abnormal walking posture. Whole-exome sequencing (WES) identified a novel de novo in-frame deletion variant in the beginning of exon 30 of CREBBP (NM_004380:c.4897_4899delTTC, p.Phe1633del) in the HAT domain where no pathogenic variants have been previously reported to be responsible for atypical RSTS. Our case allows us to more accurately define the borders of the CREBBP coding sequence resulting in atypical RSTS, which are extended to the beginning of exon 30 (residue 1633) at the 5′ end of CREBBP in the HAT domain, and reveals novel phenotypes observed in our atypical Chinese RSTS patient.

Microdeletion and microduplication of 1p36.11p35.3 involving AHDC1 contribute to neurodevelopmental disorder

Haiming Yuan
Dongguan Maternal and Child Health Care Hospital

Xia-Gibbs syndrome is a rare genetic condition characterized by intellectual disability, growth retardation, delayed psychomotor development with absent or poor expressive language, distinctive facial features, hypotonia, laryngomalacia and obstructive sleep apnea. At present, Xia-Gibbs syndrome has been reported to be mainly caused by truncating mutations in AHDC1 gene located on chromosome 1p36.11. However, the evidence supporting AHDC1 deletion as a cause of this syndrome is still limited. Here we report an 8-year-old boy carrying a de novo 575 Kb microdeletion at 1p36.11 including AHDC1 gene. The boy is characterized by intellectual disability, developmental delay, short stature, expressive language delay, facial dysmorphism, obstructive sleep apnea and multiple congenital anomalies, which are mostly consistent with the characteristics of Xia-Gibbs syndrome. Therefore, we provide further supporting evidence that AHDC1 deletion causes Xia-Gibbs syndrome through a haploinsufficiency mechanism. Currently, clinical consequences of AHDC1 gene duplication has never been reported. Here, we identify a de novo 480Kb duplication at 1p36.11p35.3 spanning the entire AHDC1 gene in a 2-year-8-month boy, who displays similar clinical features with that of Xia-Gibbs syndrome, in particular, expressive language delay, hypotonia, laryngomalacia and obstructive sleep apnea, as well as mirrored phenotypes such as overgrowth and advanced bone age. WES test excludes to the degree possible other known genetic causes. This case suggests that AHDC1 gene duplication may be clinical significance.

Analysis of the application progress of MammaPrint 70 gene spectrum in detecting breast cancer

Guoqiang Zhao[1,2] Fengxiang Wei[1,2] Tong Zhang[1,2]
1.Longgang District Maternal and child Health Care Hospital
2.Jiamusi University

Breast cancer is a highly heterogeneous disease that can only be considered curable if it is diagnosed early and treated effectively. Until the beginning of this century, oncologists relied on classical clinical and pathological variables to aid chemotherapy decisions, but remained highly unsatisfied, especially for patients with low-risk non-negative disease, for whom a combination of all variables often led to so-called gray areas and a high risk of overtreatment. Prior to the start of the MindAct trial, there was no formal literature search for consideration of chemotherapy use, but a high degree of unmet clinical need became apparent and documented in the early 2000s, suggesting that many patients with early-stage breast cancer were overtreated with chemotherapy. The American Society of Clinical Oncology (ASCO) has approved two multi-gene markers, the 21 gene relapse score (Oncotype DX, USA) and the 70 gene predictive marker (MammaPrint, Agendia, Amsterdam, Netherlands), which have shown level 1 clinical utility, The prognosis of patients receiving adjuvant endocrine therapy without chemotherapy can be identified. This paper presents a unified review of the development of mammaPrint gene detection system and the prospective clinical trial MindAct, hoping to increase the understanding of it.

一例单纯 17q25.3 拷贝数重复导致全面性发育迟缓和多发性先天异常

王清明
东莞市妇幼保健院

目的 探讨单纯 17q25.3 拷贝数重复的临床特征，遗传方式及基因型与表型的关系。
方法 应用全外显子测序(Whole exome sequencing, WES)、染色体微阵列(Chromosomal microarray analysis, CMA)、染色体核型分析、荧光原位杂交(Fluorescence in situ hybridization，FISH)技术联合对先证者及其家系成员进行分析。
结果 先证者为一名 4 岁多发性先天异常男性患儿，WES 和 CMA 鉴定在 17q25.3→qter 发生 5.7Mb 拷贝数重复，为患儿致病原因。FISH 检测证实该拷贝数重复是遗传自携带该片段平衡易位的母亲，其外祖母也为该片段平衡易位携带者，且生育三个健康子女，无不良妊娠史，舅舅为该片段平衡易位携带者，而小姨完全正常。
结论 结合以往报道，本文丰富了单纯 17q25.3 拷贝数重复的临床表型谱为全面性发育迟缓，矮小，智力障碍，脑发育不良，小头，特殊面容，肌张力低下，注意力缺陷多动障碍(attention deficit hyperactivity disorder, ADHD)，共济失调，骨骼和心血管异常等，也为该拷贝数重复的遗传咨询提供了指导，并初步探讨了 *P4HB*、*ACTG1*、*BAIAP2* 及 *TBCD* 基因为 17q25.3 拷贝数重复候选基因。

Xp11.22 Duplications in Four Unrelated Chinese Families: Delineating the Genotype-phenotype Relationship for HSD17B10 and FGD1

Qingming Wang
Dongguan Maternal and Child Health Care Hospital

Background Xp11.22 duplications have been reported to contribute to nonsyndromic intellectual disability (ID). The HUWE1 gene has been identified in all male Xp11.22 duplication patients and is associated with nonsyndromic ID. Currently, few Xp11.22 duplication cases have been reported in the Chinese population, with limited knowledge regarding the role of other genes in this interval.
Case presentation We investigated four unrelated Chinese male Xp11.22 duplication patients, performed a comprehensive clinical evaluation for the patients and discussed the role of other genes in this interval. All patients presented with similar clinical features, including ID, speech impairments and motor delay, which were mostly consistent with those of the Xp11.22 duplication described previously. We searched and compared all cases and noted that one of the probands (Family 1) and DECIPHER case 263,219, who carried small overlapping duplications at Xp11.22 that only covered the entire HSD17B10 gene, also suffered from ID, suggesting the important role of HSD17B10 in this interval. Furthermore, three patients (two probands in Families 3 and 4 and DECIPHER case 249, 490) had strikingly similar hypogonadism phenotypes, including micropenis, small testes and cryptorchidism, which have not been previously described in Xp11.22 duplication patients. Interestingly, the FGD1 gene was duplicated only in these three patients. Sufficient evidence has suggested that haploinsufficiency of the FGD1 gene causes Aarskog-Scott syndrome, which is characterized by hypogonadism and other abnormalities. Given that, we are the first group to propose that FGD1 may be a potential dosage-sensitive gene responsible for the hypogonadism observed in our patients.
Conclusion We reported novel genotypes and phenotypes in Chinese male Xp11.22 duplication patients, and the HSD17B10 and FGD1 genes may be involved.

FGFR3 gene mutation plus GRB10 gene duplication in a patient with achondroplasia plus growth delay with prenatal onset

Haiming Yuan
Dongguan Maternal and Child Health Care Hospital

Background Achondroplasia is a well-defined and common bone dysplasia. Genotype- and phenotype-level correlations have been found between the clinical symptoms of achondroplasia and achondroplasia-specific FGFR3 mutations.
Result A 2-year-old boy with clinical features consistent with achondroplasia and Silver-Russell syndrome-like symptoms was found to carry a mutation in the fibroblast growth factor receptor-3 (FGFR3) gene at c.1138G > A (p.Gly380Arg) and a de novo 574 kb duplication at chromosome 7p12.1 that involved the entire growth-factor
receptor bound protein 10 (GRB10) gene. Using quantitative real-time PCR analysis, GRB10 was over-expressed, and, using enzyme-linked immunosorbent assays for IGF1 and IGF-binding protein-3 (IGFBP3), we found that IGF1 and IGFBP3 were low-expressed in this patient.
Conclusions We demonstrate that a combination of uncommon, rare and exceptional molecular defects related to the molecular bases of particular birth defects can be analyzed and diagnosed to potentially explain the observed variability in the combination of molecular defects.

Progress in the application of 21-gene detection for breast cancer

Guoqiang Zhao[1,2] Fengxiang Wei[1,2] Tong Zhang[1,2] Cong Wang[2]
1.Longgang District Maternal and child Health Care Hospital
2.Jiamusi University

Breast cancer is the most frequently diagnosed cancer among women in the United States and around the world , and also constitutes the main cause of cancer death among women worldwide, which seriously affects the physical and mental health of the majority of women. At the same time, breast cancer is a kind of special and heterogeneous malignant tumor, and the diagnosis and treatment measures and effects for different types of patients are also different. Nevertheless, cancer diagnosis and treatment decisions still rely to a large extent on classical histopathological and immunohistochemical techniques. Therefore, more quantitative diagnostic methods and reasonable individualized treatment are needed. The available gene-21 test evaluates distant recurrence and provides prognostic information independent of clinicopathologic features in patients with early-stage breast cancer who are hormone receptor positive, human epidermal growth factor receptor 2(HER2) negative, and lymph node (ALN) negative. In order to increase the understanding of the clinical application and research progress of gene 21 detection technology in breast cancer, a unified review is made now.

Two novel KCNA1 variants identified in two unrelated Chinese families affected by episodic ataxia type 1 and neurodevelopmental disorders

Qingming Wang
Dongguan Maternal and Child Health Care Hospital

Background Pathogenic KCNA1 variants have been linked to episodic ataxia type 1 (EA1), a rare neurological syndrome characterized by continuous myokymia and attacks of generalized ataxia that can be triggered by fever, abrupt movements, emotional stress and fatigue. Currently, over 40 KCNA1 variants have been identified in individuals with EA1.
Methods A male patient displayed partial seizures in addition to EA1 symptoms, often triggered by fever. A sibling presented with typical EA1 symptoms, seizures and learning difficulties. In addition, the older brother displayed cognitive impairment, developmental delay and slurred speech, which were absent in his younger sister. Whole exome sequencing (WES) was performed for the patients.

Results A novel de novo missense variant in KCNA1 (p.Ala261Thr) was identified in the male patient, which is located in a base of the 3rd transmembrane domain (S3). The other novel KCNA1 variant (p.Gly376Ser) was identified in the sibling and was inherited from an unaffected father with low-level mosaicism. The variant was located in the S5-S6 extracellular linker of the voltage sensor domain of the Kv channel. Next, we systematically reviewed the available clinical phenotypes of individuals with EA1 and observed that individuals with KCNA1 variants at the C-terminus were more likely to suffer from seizures and neurodevelopmental disorders than those with variants at the N-terminus.
Conclusion Our study expands the mutation spectrum of KCNA1 and improves our understanding of the genotype-phenotype correlations of KCNA1. Definitive genetic diagnosis is beneficial for the genetic counseling and clinical management of individuals with EA1.

外显子测序技术用于 Joubert 综合征 2 型胎儿的产前诊断

乔凤昌 许争峰
南京市妇幼保健院

目的 为连续两次脑部异常，怀疑为 Joubert 综合征胎儿进行产前诊断，并为该家系提供遗传咨询和生育指导。
方法 收集胎儿孕期超声等资料，提取胎儿羊水及父母外周血 DNA，采用外显子测序技术（exome sequencing, ES）检测患儿的变异位点，根据美国医学遗传学与基因组学学会（ACMG）原则寻找胎儿的致病原因，并利用 Sanger 测序技术对家系及另外一例胎儿的位点进行验证。
结果 外显子测序技术检测结果发现两例胎儿 *TMEM216* 基因发生复合杂合突变，分别遗传自父亲的错义突变 c.217C＞T (p.R73C)和母亲的三碱基插入突变 c.357_359dup (p.I119.dup)，两个位点均判定为可疑致病；Sanger 测序验证结果与外显子测序结果一致。胎儿为 Joubert 综合征 2 型患者。胎儿父母最终决定终止妊娠。
结论 利用外显子测序技术可为 Joubert 综合征 2 型患者进行诊断，在临床决策、遗传咨询及再次妊娠计划中发挥重要作用。

胚胎植入前遗传学诊断应用于 COL2A1 突变致软骨异常型骨关节炎家庭的临床研究

孟露露 王艳 乔凤昌 马定远 胡平 许争峰
南京市妇幼保健院

目的 研究携带 COL2A1 致病基因突变的家庭中，胚胎植入前遗传学诊断(PGT-M)技术在帮助实现孕育正常后代、阻断软骨异常型骨关节炎垂直传递中的效果。
方法 采用单细胞全基因组扩增技术(MALBAC)、高通量测序技术及 SNP 分型技术，对 1 组夫妻中患病女方及患病女儿均携带 COL2A1 基因已知致病突变的家庭进行胚胎植入前遗传学诊断，挑选健康胚胎进行移植，在早孕期行绒毛穿刺产前诊断基因型，新生儿出生后进行体格检查。
结果 本组家庭经 PGT-M 成功受孕，并生育体格检查正常的新生儿。
结论 对于明确致病基因的家庭,PGT-M 技术能够阻断致病基因的垂直传播，还可以避免选择非整倍体胚胎而导致的流产问题，帮助生育健康胎儿。

Recurrent fetal malformation caused by RPGRIP1L novel compound heterozygous variants with Meckel syndrome in a Chinese family

Ping Zhang[1] Bingbing Wu[1] Yaqiong Wang[1] Yunyun Ren[2] Gang Li[1] Caixia Lei[2] Huijun Wang[1]
1.Center for Molecular Medicine, Pediatrics Research Institute, Children's Hospital of Fudan University
2.Obstetrics and Gynecology Hospital of Fudan University

Meckel syndrome (MKS) is a rare fetal lethal ciliopathy caused by variants in genes encoding proteins that are structural or functional components of the cilia. The *RPGRIP1L* gene is one causative for MKS. Homozygous or compound heterozygous variants in *RPGRIP1L* cause either MKS5 or Joubert syndrome 7, which is determined by the nature of variants. Although 48 variants in *RPGRIP1L* have been reported as pathogenic in the Human Gene Mutation Database (HGMD). However, only 5 MKS5 cases have been reported with harboring 4 different variants currently. In addition, variants in *RPGRIP1L* leading to MKS have not previously been reported in Chinese. This study describes a Chinese family with recurrent history of fetal malformation, that was suspected of having MKS. Trio whole-exome sequencing revealed two novel compound heterozygous variants in *RPGRIP1L* (c.427C>T, p.Gln143Ter and c.1351-11A>G) in the proband.

cDNA studies of the splicing variant demonstrated a reading frame shift with a subsequent premature stop codon (p.Glu451Serfs*6). In summary, this study reports the first case of MKS5 in Chinese population and identifies two novel variants in *RPGRIP1L*, which expands the mutation spectrum of *RPGRIP1L.*

环状 RNA 在先天性非综合征小耳畸形中的致病性研究

马竞[1,3] 吴培瑄[1] 李辰龙[3] 陈鑫[1,3] 卢鑫雨[3] 马端[1,2] 张天宇[3]
1.复旦大学
2.复旦大学附属儿科医院
3.复旦大学附属眼耳鼻喉科医院

背景 先天性非综合征小耳畸形（congenital non-syndromic microtia, CNSM）是由于遗传、表观遗传和环境因素的相互作用导致的外中耳发育不良，临床表现严重程度可从轻微的耳廓形态畸形到无耳，可伴发传导性耳聋。环状 RNA（circular RNA, circRNA）是一类具有稳定闭合环状结构的内源性 RNA 分子，序列高度保守，在哺乳动物中大量并稳定存在，可作为微小 RNA（microRNA, miRNA）的海绵吸附体调节 mRNA 表达，在人类疾病发生发展中发挥重要作用，部分 circRNA 具有编码微肽的能力，是近年来表观遗传学的研究热点。尽管已有研究分析了小耳畸形 circRNA 表达谱，提示 circRNA 可能参与了小耳畸形的发病，但其具体作用和发病机制尚不清楚。
材料和方法 为了进一步探讨关键 circRNA 在 CNSM 中的作用，我们收集了 10 例三度单侧 CNSM 患者的残耳软骨组织和 5 例正常对照（中耳炎患者）的耳软骨组织，提取 RNA，利用芯片分析两组间 circRNA 的差异表达谱。经过深度生信分析，对差异表达的 circRNA，使用 miRcode、miRDB、miRTarBase 和 TargetScan 数据库预测靶向 microRNA，关联分析 microRNA 下游的 mRNA，进而构建了内源竞争 RNA（competing endogenous RNA，ceRNA）调控网络，并对 ceRNA 网络中的 mRNA 进行 GO 功能富集分析。此外，我们使用 ORFinder 软件预测 circRNA 编码微肽的能力。据此，挑选与软骨相关的上调的两个 circRNA，构建了真核过表达质粒，在人软骨细胞系 C28i2 中利用 CCK8 及 EDU 方法检测 circRNA 对细胞增殖的影响。
结果 与正常对照组相比，在 CNSM 组中鉴定出 340 个差异表达的 circRNA（倍数值大于 2，p-value 小于 0.05），包括 152 个上调的 circRNA 以及 188 个下调的 circRNA。通过生信分析和查阅文献，我们筛选出了两个在 CNSM 中表达上调的 circRNA：circ-SPARC 和 circ-COL1A2 进一步研究。Circ-COL1A2 预测可与 has-miR-665 结合，该 miRNA 与软骨发育相关； 体外实验中，过表达 circ-COL1A2 促进 C28i2 细胞增殖。Circ-SPARC 中存在跨环开放阅读框，体外实验也被证明具有翻译微肽的能力，且过表达 circ-SPARC 也明显抑制 C28i2 细胞增殖。
结论 CircRNA 在 CNSM 耳软骨组织中存在差异表达，我们筛选出来的 circ-COL1A2 可能通过 miRNA 海绵吸附作用途径影响下游分子表达，circ-SPARC 可能通过编码的微肽，抑制软骨细胞增殖，从而参与 CNSM 的发病。

NEMO-associated mutations in three female patients with incontinentia pigmenti

Ning Jia
Shanghai Dermatology Hospital，Tongji University of Medicine

Incontinentia pigmenti (IP; Online Mendelian Inheritance in Man catalog #308300) is a rare chromsome X dominant disorder characterized by typical staged cutaneous lesions. Mutation in the gene named nuclear factor κB essential modulator (*NEMO*) (or named *IKBKG,*the inhibitor of κ polypeptide gene enchancer in B cells, kinase γ) has been known as primary pathogenic factor of IP. To distinguish mutations in *NEMO* in sporadic three Chinese patients with IP, peripheral blood had been obtained from patients, from which genomic DNA was separated. Meanwhile, Sanger sequencing of the whole exons of *NEMO* gene was performed to identify the mutations. Two novel nonsense mutations, c.970C>T in exon 6 and c.451C>T in exon 3, were found

in *NEMO* gene in two Chinese young girls, respectively. Moreover, c.1167dupC, a recurrent heterozygous frameshift mutation, occured in *NEMO* in a Chinese 11-year-old female patient. This study extended the mutation spectrum of *NEMO* and provided possible evidence for IP analysis of causes.

一例由 DENND5A 基因突变引起的罕见发育性癫痫性脑病

易丹英 王锦 秦胜芳 席娜 汪雪雁
四川省妇幼保健院

目的 发育性及癫痫性脑病(Developmental and epileptic encephalopathy, DEE) 是一组临床和遗传均有极大异质性的神经系统疾病，与遗传和环境因素有关，在 OMIM 数据库中已有 96 个基因与 98 种不同的亚型。通过全外显子测序技术，我们对一例先证者具有“婴儿痉挛”，“发育迟缓”，“智力低下”，“肌张力亢进”，“小脑发育不良”，“侧脑室扩张”，“视力异常”，“小头畸形”，“拇指内收”等临床表型的家系进行遗传诊断，为该家系再生育产前诊断提供遗传学依据。
方法 临床症状及家族史收集：除先证者存在上述神经发育异常，异常面容，拇指内收等临床症状外，其父母还曾于 2019 年引产一男胎，其双侧脑室扩张，小脑、视神经、胼胝体疑似发育不良，脑穿通畸形及神经元移行异常待除外。通过家系全外显子组高通量测序（trio-WES）进行基因诊断。
结果 家系 WES 检测发现患儿 DENND5A 基因复合杂合突变，NM_015213.4:exon7:c.1559_1571del (p.Phe520Serfs*66)和 exon6:c.1265dup (p.Glu423*)，分别遗传自父母。两个变异位点按照 ACMG 指南评估为致病性基因变异（PVS1+PM3+PM2_Supporting+PP4）。
结论 先证者临床表型结合家系基因检测结果，符合常染色体隐性遗传发育性癫痫性脑病（DEE49 型，MIM 617281） 诊断，DENND5A c.1559_1571del 和 c.1265dup 复合杂合突变可能是先证者患病的分子基础。

一个症状类似 SMA 的脑桥小脑发育不全家系的遗传学病因分析

霍晓东 廖世秀
河南省人民医院

目的 探讨一疑似脊髓性肌萎缩症家系的致病原因，为遗传咨询提供依据。
方法 抽取患者及患者父母外周血标本，采用全外显子测序分析技术对家系样本进行 Trio 分析，根据表型筛选致病基因，采用 Sanger 测序法对候选基因变异进行验证。
结果 患者女性，姐弟 5 人，本人及 3 妹、4 妹自小学起出现手指麻木后逐渐出现双下肢对称性肌肉萎缩，进行性累及呼吸肌。3 妹 4 妹均已去世。全外显子测序结果发现患者携带 *VRK1* 基因（NM_003384）c.721C>T（p.Arg241Cys）错义杂合变异，遗传自患者母亲；*VRK1* 基因（NM_003384）c.1124G>A（p.Trp375*）无义杂合变异，遗传自患者父亲。
结论 *VRK1* 基因变异所致的“脑桥小脑发育不全 1A 型”是一组严重的神经退行性疾病，影响脑干和小脑的生长和功能，导致发育不良或不发育。症状类似婴儿脊髓性肌萎缩，其他临床特征还包括肌张力减退、先天性挛缩和出生后呼吸功能不全。WES 结果提示患者携带 *VRK1* 基因复合杂合变异：遗传自患者父亲的 c.1124G>A（p.Trp375*）无义杂合变异和遗传自患者母亲的 c.721C>T（p.Arg241Cys）错义杂合变异。本研究结果为肌萎缩患者的病因扩展了思路，为鉴别诊断肌萎缩疾病提供了临床参考。

Genetic analysis of children with unexplained developmental delay and/or intellectual disability by whole exome sequencing

Jingjing Xiang Yang Ding Fei Yang Ang Gao Wei Zhang Hui Tang Jun Mao Quanze He Qin Zhang Ting Wang
the Affiliated Suzhou Hospital of Nanjing Medical University

Background Whole exome sequencing (WES) has been recommended as a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders (NDDs). We aimed to identify the genetic causes of 17 children with developmental delay (DD) and/or intellectual disability (ID).
Methods WES and exome-based CNV analysis were performed for 17 patients with unexplained DD/ID.
Results SNV/Indel analysis and exome-based CNV calling yielded an overall diagnostic rate of 58.8% (10/17), of which diagnostic SNV/Indel accounted for 41.2% (7/17) and diagnostic CNV accounted for 17.6% (3/17).
Conclusions Our findings expand the known mutation spectrum of genes related to DD/ID, and indicate that exome-based CNV analysis could improve the diagnostic yield of patients with DD/ID.

12 例琥珀酸半醛脱氢酶缺陷症患儿的临床及基因变异分析

徐晓薇[1,2,3] 闫单单[1,2,3] 范文轩[1,4] 王萍[1,2,3] 李东[1,4] 舒剑波[1,2,3]
1.天津市儿童医院（天津大学儿童医院） 2.天津市儿科研究所
3.天津市儿童出生缺陷防治重点实验室
4.天津市儿童医院神经内科

目的 琥珀酸半醛脱氢酶缺陷症（SSADHD）是一种罕见的常染色体隐性遗传 γ-氨基丁酸(GABA)代谢缺陷，国内报道病例较少。本研究对不同 SSADHD 患儿的临床特征和基因变异特点进行分析，以讨论临床表型与基因型间的关联。
方法 回顾性分析天津市儿童医院 2012 年 6 月至 2020 年 12 月共 12 例临床确诊为 SSADHD 患儿的临床资料及实验室检查结果，完成对所有患者家系的 *ALDH5A1* 基因 10 个外显子和侧翼内含子区域的突变分析。
结果 12 例患儿临床症状以抽搐、精神运动发育落后为主，尿液有机酸分析均显示 γ-羟基丁酸升高。基因变异分析显示 *ADLH5A1* 基因共检出 12 种变异，其中 c.1568C>T 变异检出频率最高，达 50%。
结论 SSADHD 患者临床表型复杂，分子遗传检测在 SSADHD 患者确诊中具有重要性；相同基因型患者也可产生轻重不一的临床症状，需要对变异行进一步功能试验研究。

3 例丙二酸合并甲基丙二酸血症的临床特点及基因分析

王萍[1,2,3] 于晓莉[1,4] 郑洁[1,2,3] 张春花[5] 舒剑波[1,2,3]
1.天津市儿童医院（天津大学儿童医院） 2.天津市儿科研究所
3.天津市儿童出生缺陷防治重点实验室 4.天津市儿童医院神经内科
5.MILS International 株式会社，日本

目的 丙二酸合并甲基丙二酸血症（CMAMMA）是一种罕见的由 *ACSF3* 基因纯合或复合杂合变异引起的遗传代谢性疾病。该疾病的临床表型具有高度异质性，涉及从无症状到严重的神经系统异常等。国内尚未见 CMAMMA 的病例报告。本研究旨在分析基因型和表型的相关性，初步探讨 CMAMMA 的疾病病因和分子遗传学机制。

方法 本研究收集了三例在接受其他治疗时意外诊断为 CMAMMA 的患儿。详细记录患儿的临床表型，通过综合遗传代谢病尿筛查和全外显子组测序结果进行多维度分析，疑似变异通过 Sanger 测序进行验证。
结果 3 例患儿的临床表现差异较大，主诉分别为贫血、黄疸和尿检异常，其临床症状主要由感染等原因引起，均没有表现出经典的甲基丙二酸血症的特异性表型，但尿液有机酸分析显示所有患儿的丙二酸和甲基丙二酸均存在反复升高。全外显子组测序发现 3 例患儿均存在 *ACSF3* 基因的变异，且均遗传自父母。病例 1 携带复合杂合变异 c.689G>A (p.Trp230*)/c.1456G>A (p.Ala486Thr)。病例 2 携带 c.473C>T (p.Pro158Leu)/c.1456G>A (p.Ala486Thr)的复合杂合变异。病例 3 携带纯合变异 c.1447A>G (p.Lys483Glu)。Sanger 测序结果与全外显子组测序结果一致。在后续的随访中，患儿没有表现出精神运动迟缓的迹象，生长发育均达到其所在年龄的里程碑。
结论 本研究首次报道了 3 例国内 CMAMMA 病例，报告了 4 个 *ACSF3* 基因变异位点，包括 3 个错义变异和 1 个无义变异，其中 c.1447A>G (p.Lys483Glu)是未见文献报道的新变异。我们的研究强烈提示在儿科患者中 CMAMMA 可能是一个不影响个体生长发育的良性状态，但当存在感染等其他诱因时，可能会出现严重的临床表型，后续长期的随访数据有助于验证此观点。本研究首次系统阐述了国内 CMAMMA 的病例特征，丰富了 *ACSF3* 基因的变异谱，为基因诊断和遗传咨询提供了依据，为病因学研究奠定了基础。

TUBGCP6 突变在先天性非综合征小耳畸形中的致病性研究

陈颖[1,3] 张博文[1] 李辰龙[3] 马竞[1,3] 马端[1,2] 张天宇[3]
1.复旦大学 2.复旦大学附属儿科医院
3.复旦大学附属眼耳鼻喉科医院

背景 先天性非综合征小耳畸形（congenital non-syndromic microtia，CNSM）是一种外耳和中耳软骨发育异常的第二大颌面部先天性畸形，其临床表型的严重程度可以从轻微的耳廓形态异常到整个耳的结构缺失。CNSM 是由遗传和环境因素共同作用导致的复杂性疾病，遗传因素在其中发挥了重要作用。目前研究尽管发现了其少数几个较明确的易感基因，但远不足以解释非综合征型小耳畸形，而且很多遗传变异的和疾病的关系没有得到验证，分子机制也不明确。
材料与方法 为了深入研究 CNSM 的遗传学病因，我们收集了 47 个 CNSM 家系的全血样本，抽提 DNA，对其进行全外显子测序。利用 ExAC 数据库（包含 60706 名不同种族个体的全外显子测序数据）作为正常对照参考。经过严格的质控以及深度生物信息学分析后，对筛选出来的新的候选易感基因微管蛋白，γ 复合体关联蛋白 6（ tubulin, gamma complex associated protein 6，*TUBGCP6*）基因的变异进行 Sanger 测序验证。采用 SIFT、Polyphen2 和 MutationTaster 数据库预测突变位点的致病性，利用 UCSC 数据库进行物种保守性分析。体外，利用免疫荧光检测 TUBGCP6 在人类软骨细胞系 C28/12 的细胞定位；构建 TUBGCP6 的 siRNA 慢病毒质粒； 在下调 TUBGCP6 的 C28/12 细胞中利用 CCK8 法检测细胞增殖能力的变化，运用免疫荧光在有丝分裂周期中观察纺锤体形态的变化。
结果 我们在 5 个 CNSM 家系中发现 *TUBGCP6* 基因分别存在 5 个突变，包括 4 个错义突变和 1 个非移码插入突变，而且在不同物种间高度保守和具有较高的致病性。TUBGCP6 通过 γ 微管蛋白复合体结合蛋白定位于微管组织中心，参与微管的晶核起始，中心粒复制以及有丝分裂纺锤体的组装。C28-i2 细胞定位分析显示 TUBGCP6 在细胞质和细胞核均存在，但以细胞核为主。在 C28-i2 细胞中下调 *TUBGCP6* 表达，会抑制细胞增殖并出现多极纺锤体的现象。
结论 我们首次发现 5 个 CNSM 家系中存在 *TUBGCP6* 突变， *TUBGCP6* 的下调可能通过影响纺锤体组装抑制软骨细胞增殖，从而参与 CNSM 的发病。

Downregulation of lncRNA SNHG3 inhibited cell proliferation, migration and Chondrogenic differentiation

Shiyu Chen[1] Jing Ma[1,3] Duan Ma[1,2]
1.Fudan University
2.Children's Hospital of Fudan University
3.ENT Institute, Eye & ENT Hospital, Fudan University

Background and Objects Non-syndromic cleft lip and palate (NSCLP) is one of the most common congenital malformation with multifactorial etiology. Although long non-coding RNAs (lncRNAs) have been implicated in the development of lip and palate, their roles in NSCLP is not fully elucidated. This study aimed to investigate how dysregulated lncRNAs contribute to NSCLP.
Methods and Results We collected lip tissue samples from 38 congenital cleft lip and palate groups and 15 normal control groups. The relative expression levels of lncRNAs was measured by quantitative real-time polymerase chain reaction (qRT-PCR) technology. Cell Counting Kit(CCK-8), transwell assay were carried out to explore cell proliferation and migration capacity. Furthermore, chondrogenic differentiation assay was carried out to measure the ability of chondrogenic differentiation in human umbilical cord mesenchymal stem cells (HUC-MSCs).
Using lncRNA sequencing, bioinformatics analysis and clinical tissue sample detecting, we identified lncRNA SNHG3 was significantly downregulated in NSCLP. In vitro, downregulation of SNHG3 inhibited cell proliferation and migration in human oral keratinocytes and HUC-MSCs, and also repressed chondrogenic differentiation of HUC-MSCs.
Conclusions This study implicates that downregulation of SNHG3 in NSCLP may be correlated with in the pathogenesis of NSCLP through inhibiting cell proliferation, migration and chondrogenic differentiation.

多发性家族性毛发上皮瘤家系 CYLD 基因大片段缺失的突变研究

许洁[1] 白云[2]
1.温州市中西医结合医院
2.上海皮肤病医院

目的 检测一例多发性家族性毛发上皮瘤（multiple familial trichoepithelioma，MFT）家系基因的遗传变异。
方法 抽取先证者及其 11 名家系成员的外周血，提取基因组 DNA，通过定制化的外显子捕获测序，对先证者该疾病常见致病基因 *CYLD* 的所有外显子进行检测；同时采用荧光定量 PCR（qPCR），在家系其他成员中验证 *CYLD* 基因的大片段缺失。
结果 外显子捕获测序显示先证者 *CYLD* 基因存在大片段缺失（chr16:50,826,498-50,835,697）；qPCR 结果显示先证者和所有发病的家系成员均存在该大片段缺失；同时我们还发现尚未发病的先证者的 2 名子女也携带有该缺失，提示将来可能发病。
结论 本研究首次在我国发现 MFT 家系中 *CYLD* 基因存在大片段缺失变异，提示部分基因拷贝数的变异对该病的发病也有影响，建议在今后的分子诊断中增加基因拷贝数的筛查。

1 例新发 9p 部分三体综合征产前诊断病例报道

周世豪 杨梦月 王卫红 李红玉 胡兰萍 贺骏
长沙市妇幼保健院

目的 产前诊断明确一例 B 超正常的 9 p 部分三体综合征胎儿。
方法 对孕妇进行 NIPT 检测，并在 B 超引导下行羊膜腔穿刺术抽取羊水进行核型及染色体微阵列检测。

结果 NIPT 结果提示 dup(9p24.2-p11.2，43.12Mb) 。羊水细胞核型 G 显带分析结果：47,XN,+ del (9)(q11)。CMA 结果：9 号染色体 9p24.3p13.1 区域 38.56Mb 重复，为致病性拷贝数变异。
结论 因"NIPT 结果异常"产前诊断 1 例 9p 部分三体综合征。NIPT 能有效的在胎儿出生前筛查出染色体病及基因组病，从而有效的预防缺陷儿的出生。

Single Cell Transcriptomics Reveals Pathogenic Dysregulation of Previously Unrecognized Chondral Stem/Progenitor Cells in Children with Microtia

Jing Ma[1] Tianyu Zhang[3] Duan Ma[1,2]
1.Fudan University
2.Children's Hospital of Fudan University
3.ENT institute, Eye & ENT Hospital, Fudan University

Background and Objects As one of most common birth defects worldwide, microtia results from auricular cartilage dysplasia and is accompanied by several unfortunate physical and psychological consequences for children. However, existing treatments have adverse outcomes and its pathogenesis is poorly understood. Since characterization of cell type composition and function in auricular cartilage can increase our understanding of microtia, we used single-cell RNA sequencing (scRNA-seq) to conduct the first comprehensive investigation of the single-cell transcriptomic landscape in human auricular cartilage.
Methods and Results Auricular cartilage tissues were collected from three microtia children and six normal controls (NC) for scRNA-seq. The atlas of 47,969 single-cell transcriptomes was obtained for further analysis. The location of stem/progenitor cells in human auricular cartilage was validated by immunofluorescence staining using the markers discovered in scRNA-seq. The expression differences of key transcription factors in specific type of cell between microtia and NC were verified by immunohistochemical analysis.
Comprehensive bioinformatic analysis identified seven cartilage-related cell subtypes belonging to the chondral and stromal lineages. The age-associated changes in gene expression were found to be shared across all subtypes in the chondral lineage of NC. Additionally, the previously unrecognized chondral stem/progenitor cells (CSPCs) were revealed to be mainly located in the chondrium, which could have the potential for directed chondrogenic differentiation. It was also showed that dysregulation of the transcription factors SOX8 and EGR1 in CSPCs of microtia impaired cartilage development and enhanced oxidative stress response, respectively, suggesting the pathogenic role of CSPCs in microtia.
Conclusions These findings shed light on the potential mechanisms of microtia pathogenesis and offer novel avenues for the development of treatment strategies.

河南郑州市汉族 HLA-DQB1 基因多态性的群体调查

郭谦楠
河南省人民医院

目的 从基因水平分析河南郑州市汉族人群 HLA-DQB1 等位基因型和频率，并了解其多态性分布状况。
方法 通过聚合酶链式反应－序列特异性引物（PCR-SSP）方法对 1000 名郑州籍汉族健康人群进行 DQB1 等位基因分型。
结果 共检出 5 种 DQB1 等位基因型，频率最高的等位基因型为 DQB1*03（39.10%），频率最低的等位基因型为 DQB1*04（5.70%）。与上海、深圳、昆明和大连四城市比较，DQB1*03 和 06 基因型均为该五个城市的优势基因型，但郑州汉族人群的 DQB1*03 基因型频率显著低于上海、深圳、昆明和大连四城市（P<0.05）；郑州汉族人群 DQB1 各等位基因型频率分布顺序与上海汉族

人群一致，但是上海的 DQB1*05 基因型频率显著低于郑州（P<0.05）；深圳、昆明和大连三城市的 DQB1*02 基因型频率均显著低于郑州（P<0.05）。
结论 郑州汉族人群的 DQB1 基因型频率与上海、深圳和昆明存在相似性但也存在显著差异性，表明 HLA-DQB1 的各等位基因型分布不仅存在地域相似性也存在显著的地域差异性; 显著的 HLA-DQB1*03 低频率基因型为郑州汉族人群的特点。

孤立性黄斑发育不良及眼球震颤疾病的临床及基因研究

蒋奕 黎仕强 肖学珊 孙文敏 张清炯
中山大学中山眼科中心

目的 先天性黄斑发育不良是一组缺乏黄斑中心凹且假定中心凹区域视网膜神经感觉层相对保留的独立性或者合并其他眼科或者全身病变的疾病。本文主要探讨孤立性黄斑发育不良相关遗传机制
方法 对本研究收集 33 个孤立性黄斑发育不良及眼球震颤家系行全外显子测序及靶向外显子测序检测相关基因突变。通过生物信息学分析，家系共分离实验，基因型-表型分析对三个基因 (*PAX6*, *AHR*, *SLC38A8*)上的基因突变分析筛选出致病变异。
结果 在本研究收集的 23 个孤立性黄斑发育不良家系中发现相关致病变异，其中 *PAX6* 相关家系有 18 家，同时 *SLC38A8* 相关有 5 家，且在本研究中未发现 *AHR* 相关致病变异。对于部分家系随访发现，*PAX6* 相关孤立性黄斑发育不良家系中的患者虹膜虽然完整但存在细微纹理上的改变。与孤立性黄斑发育不良相关 *PAX6* 基因上致病变异，其中错义变异占 94%，截短变异占 6%。*PAX6* 相关错义变异主要位于配对盒序列的 C 端。
结论 进一步证实 *PAX6* 和 *SLC38A8* 为孤立性黄斑发育不良的主要致病基因。孤立性黄斑发育不良相关 *PAX6* 基因上致病变异主要为在配对盒序列 C 端的错义变异，提示该结构上错义变异与孤立性黄斑发育不良而非先天性无虹膜存在特殊联系。对于携带孤立性黄斑发育不良相关 *PAX6* 基因突变的患者，虹膜虽然完整，但是有细微虹膜纹理改变。对于眼球震颤及孤立性黄斑发育不良就诊的患者，此类临床特征可以作为 PAX6 相关孤立性黄斑发育不良诊疗线索。

一例 DEPDC5 基因变异所致局灶性癫痫的基因诊断分析

顾春钰[1] 卢晓卫[2] 蒲林洁[1] 支秀芳[1] 舒剑波[3] 李东[2] 蔡春泉[3,4]
1.天津医科大学研究生院
2.天津市儿童医院神经内科
3.天津市儿童医院（天津大学儿童医院）天津市儿科研究所，天津市儿童出生缺陷防治重点实验室
4. 天津市儿童医院神经外科

目的 家族性局灶性癫痫伴可变灶（familial focal epilepsy with variable foci, FFEVF）是一种少见的常染色体显性遗传性癫痫，
以临床表现复杂、家族中不同成员发作部位起源不同、发作严重程度不同为主要特征。临床上仅凭表现、影像学、脑电图等检查难以将 FFEVF 与其他家族性局灶性癫痫相鉴别，本文探讨 1 个家系中局灶性癫痫患者的临床诊断及遗传学病因。
方法 签署知情同意书后，采集患者及父母外周静脉血，提取基因组 DNA。应用全外显子测序技术对先证者进行致病变异筛查，使用 Sanger 测序法对先证者及其家系成员进行验证。
结果 全外显子测序结果显示先证者 *DEPDC5* 基因存在第 22 号外显子 c.1696delC (p.Gln566fs) 杂合缺失变异，是新变异。该变异遗传自父亲，父亲为健康携带者。
结论 *DEPDC5* 基因第 22 号外显子 c.1696delC (p.Gln566fs) 变异为本例患者发病的遗传学病因，结合患者临床表现、脑电图等检查结果，考虑诊断为 FFEVF。该变异丰富了 *DEPDC5* 致病基因变异谱，为 FFEVF 临床诊断提供依据，同时对遗传咨询有重要提示作用。

基于大数据和公共数据库比对揭示 PRPF 系列基因的致病变异特点和临床特征

王俊文 肖学珊 黎仕强 孙文敏 王攀峰 张清炯
中山大学中山眼科中心

目的 前 RNA 剪接（PRPF）系列基因的变异是导致常染色体显性视网膜色素变性 (ADRP) 的常见原因之一。本研究旨在探讨和总结五个 PRPF 基因中致病变异的特征和临床表现。
方法 PRPF 系列基因的变异收集于 7092 个参与者的外显子组测序数据，其中包括 1019 名 RP 患者。根据 ACMG/AMP 指南和临床表型筛选致病变异。通过对内部数据库、gnomAD 数据库和文献回顾的比对来探讨和归纳基因型-表型特征。
结果 在本研究中共有 29 个杂合致病变异在 33 个 RP 家系中被鉴定出来，其中包括 17 个新发变异。在我们的数据库中，PRPF 系列基因的变异能解释约 3.2%的 RP 家系。不同基因的致病变异类型不同，部分以截短变异为主，部分以错义变异为主。致病变异在部分基因的特定区域有富集。对于部分变异致病性的评估需要谨慎对待，部分基因中之前报道的致病变异经过我们的系统分析发现其可能不致病。PRPF 系列基因相关的 ADRP 似乎有特殊的表现，例如骨细胞样色素沉着从中周部开始向远周边视网膜蔓延而血管拱环内不明显，比其他 ADRP 更容易出现黄斑受累。
结论 基于表型和大数据的系统比对分析有助于阐明这些基因中致病变异的特征。我们的研究结果总结了致病变异的特点并归纳了 PRPF 系列基因相关的 ADRP 的临床表现，同时还提示对于部分变异致病性的评估需要谨慎对待。

基于中国患者队列研究 PROM1 基因 p.Arg373Cys 变异的特征：黄斑变性加上周边视网膜骨细胞样色素沉着

王濛苇 王攀峰 黎仕强 欧阳嘉敏 贾小云 肖学珊 杨军兴 李雪晴 孙文敏 张清炯
中山大学中山眼科中心

目的 据报道，*PROM1* 基因 p.Argr373Cys 变异可导致显性 Stargardt 病、锥杆细胞营养不良，偶尔还可导致视网膜色素变性。本研究旨在评估中国患者中与该变异相关的常见表型。
方法 本研究中所有 *PROM1* 的变异是从实验室内部外显子组数据中收集的。通过选择潜在致病突变，进行验证，然后经过 Sanger 测序和共分离分析进行确认。同时对眼部表型和眼科检查进行了总结。
结果 *PROM1* 基因中的 c.1117C>T (p.Argr373Cys)变异在不相关家系中发现。在来自这几个家系的 p.Arg373Cys 变异患者中，有 60%的患者进行了全面的扫描激光眼底检查，结果显示不同程度的黄斑营养不良，同时伴有视网膜周围典型的骨细胞样色素沉积。在黄斑和周围视网膜病变区域之间有一个相对保留的区域。其余 40%患者未接受扫描激光眼底检查。30%接受视网膜电流图检查的患者显示视锥和视杆细胞功能的异常。
结论 虽然以往 p.Arg373Cys 变异被认为主要表型是 Stargardt 病，但是在我们的研究中，所有进行全域眼底检查的患者均表现为黄斑营养不良加上类似于视网膜色素变性的周围性视网膜病变。与 p.Arg373Cys 变异相关的不同表型实际上可能反映了同一疾病的不同阶段:早期主要呈现的是中央视锥细胞受累的表型，随着变性的发展，外周区域也出现变性。评估全域的眼底情况，特别是更多携带有此变异患者的外周区域将进一步证实我们的发现。

SLC5A2 基因连接跨膜域突变致儿童家族性肾性糖尿的表型研究

匡新宇 孙蕾 黄文彦
上海交通大学附属儿童医院

目的 家族性肾性糖尿是一种持续尿糖、血糖浓度正常且无肾小管功能障碍的罕见遗传性疾病。SLC5A2 基因突变所致钠/葡萄糖共转运体（SGLT2）功能异常导致近段肾小管重吸收葡萄糖显著降低是发病的主要原因。现已发现近百种 SLC5A2 基因突变，尚无明确热点突变，且大都为成人报道，该基因在儿童中的突变方式和临床表型仍不清楚。因次，本研究拟分析我中心 7 例家族性肾性尿糖患儿的基因型与表型，明确该疾病在儿童中的临床特点。
方法 回顾性分析上海市儿童医院肾脏风湿免疫科 2014.6 至 2021.6 在我中心确诊家族性肾性糖尿的 7 例患儿的临床特征（包括性别、年龄、起病时间、尿糖及血糖水平和家族史等一般特征）；所有患儿及其家系成员均抽取外周血 2ml 行全外显子测序明确突变基因和突变类型；本研究实验数据采用 SPSS 21.0 软件进行分析，所有定量资料均以均数±标准差的形式来表示，两组之间的定量资料采用两独立样本 t 检验的方法进行，两组之间的定性资料采用卡方检验的方法进行比较，检验水准=0.05，P<0.05 具有统计学意义。
结果 7 例患儿中 5 例男性，2 例女性，起病年龄从 10 个月到 7 岁，平均 4.35±2.56 岁，生长发育正常，均为体检时发现尿糖阳性，2+ ～ 4+，24h 尿糖 0.33 ～ 7.51g/1.73m^2，平均 2.27±2.64g/1.73m^2，属于轻度糖尿。同时检测患儿空腹血糖、餐后 2h 血糖、C 肽、胰岛素、糖化血红蛋白、肝肾功能、电解质、24h 尿蛋白、尿电解质、血气分析、泌尿系统超声等均未见明显异常。全外显子测序后发现 7 例患儿均发现有 SLC5A2 基因突变，其中 1 例合并有 SLC2A2 基因突变。5 例患儿存在复合杂合突变，2 例为杂合突变。7 例患儿共发现 8 个 SLC5A2 基因突变位点，其中有 5 个新发突变，均为致病性突变。除 3 个剪切突变外，5 个错义突变突变均位于该基因连接跨膜域结构。与成人报道热点突变不同，仅有 2 例患儿发现 SLC5A2 基因热点突变位点 c.886-31_886-10del22 剪切变异，但有 3 例患儿存在 c.C1540T 复合杂合突变，24h 尿糖平均 1.39±0.73g/1.73m^2，低于 7 例患儿的平均尿糖水平，提示该错义突变致病性可能较轻。家系分析发现虽然突变基因和位点均来自于父母，但无家长有尿糖或糖尿病表现，提示单纯杂合突变外显率低，复合杂合突变是致病的主要突变方式。
结论 儿童家族性肾性糖尿临床表现较轻，主要为 SLC5A2 基因复合杂合突变所致，c.C1540T 可能为儿童热点突变位点。

首次报道五十年后，第二例罕见的雪花玻璃体视网膜变性在东亚人群中再次出现

郑羽茜 张清炯
中山大学中山眼科中心

目的 雪花玻璃体视网膜变性 (SVD) 于 1974 年被首次报道，直到 2008 年发现了 KCNJ13 中的突变位点。但是，详细的真实世界临床数据仍然有限。本病例旨在不同人群中验证 KCNJ13 基因突变会导致雪花玻璃体视网膜变性，并描述患者的临床表现。
方法 招募了具有各种眼部疾病的先证者及其家庭成员，并提取基因组 DNA 进行外显子组测序。通过选择潜在 KCNJ13 致病突变，进行验证，然后经过 Sanger 测序和共分离分析进行确认，对眼部表型和眼科检查进行了总结。
结果 KCNJ13 的五个杂合变体在五个不相关的家系中被鉴定出来。 5 五例患者中，一例患者全眼底检查显示广泛的白带状压迹、雪花样变性、视网膜血管鞘和色素团块，而这曾被定义为 SVD 的不同分期。而在两名患者中也观察到黄斑变性。
结论 KCNJ13 p.R162W 突变可导致另一种种族背景下的 SVD，并报道了 4 个引起了 SVD 的新突变位点。

RPGR 变异的基因型-表型分析

杨军兴[1] 周琳[1,2] 欧阳嘉敏[1] 肖学珊[1] 孙文敏[1] 黎仕强[1] 张清炯[1]
1.中山大学中山眼科中心
2.四川大学华西医院眼科

目的 *RPGR* 是 X 连锁视网膜色素变性(RP)最常见的病因，女性携带者也常受累。本研究的目的是基于我们实验室的数据和先前的研究，探讨 *RPGR* 的变异频谱和相关表型。
方法 通过外显子组测序，从具有不同眼遗传病的数据库中选取 *RPGR* 的变异。先证者及其家人接受了全面的眼科检查。通过在 PubMed、Web of Science 和 Google Scholar 上搜索并收集以前的发表数据。对 *RPGR* 基因型、表型及其相关性进行系统分析。
结果 系统地分析来自我们实验室、文献和 gnomAD 的变异表明，*RPGR* 的大多数致病变异是截短变异，致病的错义变异和框内变异富集在 RCC1 结构域。男性和女性携带者之间存在显著的表型差异，女性携带者的屈光不正更严重，但最佳矫正视力(BCVA)好于男性。随着年龄的增加，男性患者的 BCVA 显著降低。位于外显子 1-14 变异的男性比位于 ORF15 变异的男性 BCVA 更好。对于女性携带者，BCVA 也随年龄的增加而显著降低，但携带外显子 1-14 变异的女性与 ORF15 变异的女性相比，BCVA 无明显差别。
结论 *RPGR* 的大多数致病性变异是截短变异。位于 RCC1 结构域外的错义和框内变异可能是良性的，对于这些变异的致病性标准应该更加谨慎考虑。男性和女性携带者的 BCVA 和屈光不正有差异。随着年龄增长和变异位于 ORF15，男性患者有着更差的 BCVA。这些结果对了解 *RPGR* 的基因型和表型具有重要意义。

Norrie 样改变相关基因的表型特征分析

杨军兴 肖学珊 黎仕强 贾小云 王攀峰 孙文敏 张清炯
中山大学中山眼科中心

目的 研究 Norrie 样改变相关基因变异的眼部表型特征。
方法 通过外显子组测序，收集携带 Norrie 样改变相关基因的患者。收集眼底照相、荧光血管造影、眼部超声和光学相干断层扫描成像等临床资料并对其进行总结分析。
结果 对携带有 Norrie 样改变相关基因变异的患者评估分析发现，共有 31 个患者表现为 Norrie 样改变，其中由 *NDP* 变异导致的 Norrie 样改变 16 例，另外 15 例由常染色体遗传基因导致。
结论 Norrie 样改变除了由 *NDP* 变异导致，还可由常染色体遗传基因导致。在我们的队列研究中，由 *NDP* 导致的 Norrie 病和由常染色体遗传基因导致的 Norrie 样改变频率相当。认识到 Norrie 样改变相关基因的眼部表型特征会增进我们对这一灾难性疾病的理解和更好地评估预后及可能的结果。

无脉络膜症的临床表型及基因突变分析

易姝彤
中山大学中山眼科中心

目的 无脉络膜症是一种由 *CHM* 基因的变异所导致的遗传性眼病。本研究旨在分析中国人无脉络膜症不同阶段的眼底特征。
方法 在对大量全外显子组及靶向外显子组测序数据进行多重生物信息学分析后，筛选具有 *CHM* 致病变异的家系并系统地分析了其临床表型。
结果 筛选出来的 *CHM* 致病变异都是截断变异，并且都位于倒数第二个外显子中最后 55 个核苷酸的上游。在男性患者中，60%有着典型晚期眼底改变，包括脉络膜硬化、视网膜脉络膜萎缩、色素沉着以及保留的多边形黄斑部分，40%有着与视网膜色素变性相似的早期眼底改变；光学相干断层扫描扫描分别有 100%、55.6% 和 27.8%有视网膜脉络膜萎缩、视网膜囊样改变和视网膜外层管状

改变；视网膜电流图中视杆和视锥细胞反应均无波形；最佳矫正视力范围从手动到 1.0（65.5%≥0.5），并可以保持相对稳定直至 40 岁。在三位女性携带者中，有两位视力正常且眼底可观察到玻璃疣样斑点，另一名眼底则表现为典型男性患者晚期改变。

结论 与浅肤色人种相比，中国无脉络膜症患者早期眼底与视网膜色素变性的相似程度更高。保留多边形黄斑部分、临床基因检测、扫描激光眼底和女性携带者眼底检查是识别无脉络膜症的重要方法。识别基因型-表型特征可能有助于预防和干预无脉络膜症。

一例甲状旁腺功能减退-感音神经性耳聋-肾发育不良(HDR)综合征患者的基因分析

王学韬[1,2,3] 舒剑波[1,2,3] 顾春钰[1] 蒲林洁[1] 蔡春泉[1,2,3]
1.天津市儿童医院（天津大学儿童医院）
2.天津市儿科研究所
3.天津市儿童出生缺陷防治重点实验室

目的 探讨 1 例 chr10p14 杂合缺失导致甲状旁腺功能减退-感音神经性耳聋-肾发育不良(HDR)综合征临床及分子遗传学特征。

方法 分析 1 例甲状旁腺功能减退-感音神经性耳聋-肾发育不良(HDR)综合征患儿的临床资料，利用全外显子测序(whole exome sequencing，WES)技术对先证者及其家系成员基因变异进行筛查，同时基于 WES 进行拷贝数变异分析(copy number variation sequencing,CNV-seq)。利用荧光定量 PCR（fluorescence quantitative polymerase chain reaction，qPCR）对发现大片段杂合缺失进行验证，并明确异常变异来源。

结果 该家系中，双胎之小 WES 结果发现一段大片段杂合缺失[hg19]chr10p14(7657935-11805939)X1，大小约 4.148Mb，家系中其他成员并未发现明确的致病变异。利用 qPCR 对该家系进行验证，结果为 10 号染色体 GATA3 基因第 1 外显子和 ECHDC3 第 5 外显子引物扩增区存在缺失，考虑系 chr10p14 大小约 4.148Mb 片段杂合性缺失所致。

结论 该患儿头围小（-2SD），听力筛查未过，发育商评估均处于轻至中度发育迟缓，肾脏彩超及甲状旁腺素检测未见异常,基因检测发现患儿存在 chr10p14(7657935-11805939)存在约 4.148Mb 大片段杂合缺失，其家系其他成员均未见异常。本例患儿 chr10p14 杂合缺失少有文献报道，其缺失片段所涵盖 GATA3,ECHDC3，USP6NL,TAF3,KIN,ATP5C1,ITIH2 等功能基因。GATA3 编码属于 GATA 转录因子家族锌指蛋白，这种蛋白质参与脊椎动物甲状旁腺、听觉系统，以及肾脏的胚胎发育。文献中研究表明 GATA3 基因突变与 HDR 综合征明显相关。感觉神经性耳聋是 HDR 综合征最常见的临床特点，常在出生时出现双侧听力下降，也可是双耳轻重不等的损害。甲状旁腺功能减退症也是 HDR 综合征常见的临床表现，发生在超过 90%的患者。此外，GATA3 的缺失已被证明影响前庭听觉传出神经元的分化，这解释了与 GATA3 基因突变相关的神经性听力损失。该患儿 GATA3 杂合缺失，从而造成了单倍剂量不足，不足以维持正常的生理功能，导致其出现感觉神经性耳聋。在先前的报道中，均为 GATA3 基因点突变造成的，且患者通常为三联征，在文献报道指仅有一例患者只发生感觉神经性耳聋，与本患儿表型一致。

中国人群 X 连锁视网膜劈裂临床特征与基因相关分析

肖赛男
中山大学中山眼科中心

目的 本研究主要是对中国 X 连锁视网膜疾病患者观察，探讨中国人群 X 连锁视网膜劈裂基因突变特点及规律、临床表型特征以及基因型-表型相关性。

方法 通过外显子测序技术筛选 X 连锁视网膜劈裂基因突变，根据 ACMG 分析致病性。收集家系的临床资料进行分析，归纳中国人群 X 连锁视网膜劈裂基因突变的特征表型。

结果 本研究人群中，87.5%的患者存在黄斑劈裂，10.7%存在黄斑萎缩，0.9%黄斑正常伴随周边劈裂，0.9%的患者存在非典型的黄斑病变。黄斑萎缩组的年龄大于黄斑劈裂组（P<0.05）的同时，视力基本一致（P>0.05）。存在周边视网膜劈裂的情况下，视力显著低于周边正常亚组（P<0.05）。热点突变组内，视网膜脱离、玻璃体积血的发生率显著高于非热点突变组（P<0.05）。

结论 在中国人群中，携带 X 连锁视网膜劈裂致病突变的男性患者都存在典型的黄斑和/或周边部劈裂改变；黄斑萎缩年龄显著高于黄斑劈裂，视力保持相对稳定；视网膜脱离、玻璃积血的发生率在热点突变内显著高于非热点突变组。

一例 RELN 基因杂合变异致家族性颞叶癫痫的病例报道

支秀芳[1] 顾春钰[1] 蒲林洁[1] 闫单单[2] 蔡春泉[2,3] 李东[4]
1.天津医科大学研究生院
2.天津市儿童医院（天津大学儿童医院），天津市儿科研究所，天津市儿童出生缺陷防治重点实验室
3.天津市儿童医院神经外科
4.天津市儿童医院神经内科

目的 探讨 1 例由 *RELN* 基因杂合变异导致的常染色体显性遗传的家族性颞叶癫痫（Familial temporal lobe epilepsy，FTLE）患儿的临床特征、影像学特征、基因突变特点、诊断、治疗及预后。

方法 收集患儿临床资料，获取患儿及其父母外周血标本进行家系全外显子测序，并进行 Sanger 测序进一步验证。

结果 患儿女，8 岁，临床表现为间断抽搐 2 年余，清醒及睡眠时均有发作，主要为 2 种表现形式，1 种为睡眠中突然醒来，双眼向右或同左凝视，频繁眨眼，呼之不应，牙关紧闭，四肢强直微抖，面色发绀，持级数分钟至 1 小时缓解；另一种表现为清醒状态下，突然出现双侧嘴角频繁抖动，嘴角向右侧歪斜，伴流涎，意识模糊，左上肢屈曲微抖，其余肢体及面色无改变。近半月病情较前加重，发作较前频繁。外院核磁癫痫定位协定序列示：双侧顶叶、左侧额叶皮层下白质、左侧基底节区异常信号，考虑脱髓鞘或髓鞘化不良可能。外院视频脑电图提示左侧 Rolandic 区为主广泛性棘慢波、多棘慢波发放，监测到 1 次癫痫持续状态。患儿智力正常，父母均体健，患儿父亲的外祖母可疑抽搐病史（具体不详），患儿舅老爷抽搐史（具体不详）。全外显子测序结果显示患儿及其父亲均携带 *RELN* 基因 NM_005045.3 ：c.2T>G p.(Met1？)杂合变异，该变异导致起始密码子发生改变，影响蛋白质翻译的起始，从而影响蛋白质的正常功能，为致病性变异。可能由于不完全外显的原因，患儿父亲无相关临床表现。患儿给予丙戊酸钠、托吡酯、拉莫三嗪口服抗癫痫治疗，启动生酮饮食，予营养神经等对症治疗，住院后体温正常，未再抽搐。随访

结论 *RELN* 基因的 NM_005045.3 ：c.2T>G p.(Met1？)变异为患儿的致病性变异，导致常染色体显性遗传的 FTLE，临床较罕见。

一例 RPS6KA3 基因 5-7 号外显子大片段缺失所致的 Coffin-Lowry 综合征的基因诊断分析

蒲林洁[1] 顾春钰[1] 支秀芳[1] 舒剑波[2] 蔡春泉[2,3] 李东[4]
1.天津医科大学研究生院
2.天津市儿童医院（天津大学儿童医院）天津市儿科研究所 天津市儿童出生缺陷防治重点实验室
3.天津市儿童医院神经外科
4.天津市儿童医院神经内科

目的 探讨 1 例 *RPS6KA3* 基因大片段缺失导致 Coffin-Lowry 综合征（Coffin-Lowry syndrome，CLS）患儿临床及分子遗传学特征。

方法 利用全外显子测序(whole exome sequencing，WES)技术结合拷贝数变异分析对先证者进行基因变异筛查，使用半定量 PCR 对先证者及其家系成员进行验证。
结果 全外显子测序结果显示先证者 chrXp22.12(20211595-20213273)区域存在大片段半合子缺失，包括 *RPS6KA3* 基因第 5-7 号外显子的半合子缺失，该缺失遗传自母亲，既往未见文献报道，多个数据库未见收录。
结论 *RPS6KA3* 基因 5-7 号外显子半合子缺失为本病的致病原因。本病例丰富了 *RPS6KA3* 基因的突变谱，进一步证实了该基因高新突变率的特征。CLS 确诊主要依靠患儿的临床表现，结合基因检测手段进一步确诊。临床上对于精神运动发育迟缓的患儿应考虑本病的可能，尽早进行基因筛查以明确诊断。

两例 Wolf-Hirschhorn 综合征的产前超声表现与遗传学诊断分析

李素萍 金玉霞 阮家瑜 周赤燕 刘晓丹 唐萍
嘉兴市妇幼保健院

目的 应用多种遗传学检测技术，研究 2 例 Wolf-Hirschhorn 综合征（Wolf-Hirschhorn Syndrome, WHS）家系，分析 WHS 患儿产前超声特征及患儿产后的临床特点，为家系遗传咨询和再生育指导提供依据。
方法 采用单核苷酸多态性微阵列（single nucleotide polymorphism array，SNP-array）技术，对 1 例 WHS 患儿和 1 例超声异常的胎儿进行诊断，并结合染色体核型分析和荧光原位杂交(fluorescence in situ hybridization, FISH)技术对其家系进行验证分析。
结果 病例 1 患儿经高分辨染色体核型及 FISH 验证核型为 46,XY，del(4)(p16.1),父母不存在平衡易位。病例 2 胎儿 SNP-array 检测提示胎儿染色体 4p16.3p16.1 区存在 8Mb 的杂合性缺失，同时，在 5 号染色体 5q35.3 区段存在 1.7Mb 的重复。
结论 胎儿单脐动脉和肾发育异常为 WHS 超声表型之一，胎儿这些超声软指标应行产前诊断。SNP-array、 FISH 技术是染色体核型分析的良好补充，多种技术结合应用可以为产前诊断提供重要的遗传学依据。

ALA-PDT successfully treated multiple cSCC in situ and AK in a patient with Epidermodysplasia Verruciformis

Zijun Zhao
Shanghai Skin Disease Hospital

5-aminolaevulinic acid photodynamic therapy (ALA-PDT) has emerged as a non-invasive treatment modality for premalignant and malignant skin lesions. It has the advantage of better tolerance and providing better cosmetic outcomes than conventional treatment methods. Herein, we report a patient who suffered from multiple cutaneous squamous cell carcinoma (cSCC) in situ and actinic keratosis (AK) scattered in the body's sun-exposed areas, which had led him to undergo multiple surgical resections since the age of 16. Next-generation sequencing-based on a targeted gene capture panel revealed compound heterozygous mutations c.G559A and c.G1389A in the TMC8 gene. Combined with the typical clinical manifestations and mutation analysis, the patient was diagnosed with Epidermodysplasia verruciformis (EV). Due to the multiple AK and cSCC in situ lesions,ALA-PDT was applied. After 8 courses of ALA-PDT all lesions were successfully cleared without causing any scarring. Therefore, the use of ALA-PDT treatment may constitute a very promising and effective therapeutic modality for multiple cSCC in situ and AK secondary to EV.

1 例 Schimke 免疫性骨发育不良 SMARCAL1 基因的突变分析

张海燕 刘毅 张洪霞 盖中涛
山东大学齐鲁儿童医院

目的 Schimke 免疫性骨发育不良（Schimke immuno-osseous dysplasia, SIOD）是一种多系统受累且进行性加重的常染色体隐性遗传病，发病率为 1:3,000,000-1:1,000,000，以脊柱骨骺发育不良、特殊面容、身材矮小、肾病、T 细胞缺乏为主要临床特征，SMARCAL1 基因突变是该病的致病原因。本研究旨在利用新一代测序技术明确 1 例 SIOD 患儿的遗传学病因。
方法 对一例疑似 SIOD 患儿进行临床检查和遗传学分析，采集患儿及家系的外周血提取 DNA。应用高通量测序技术进行外显子捕获，对突变位点进行 Sanger 测序验证，并对新突变进行致病性分析。
结果 （1）患儿，女，4 岁 5 月，生长缓慢，智力发育正常，高频听力异常。实验室检查尿蛋白（+++）， 24h 定量 2261.12mg，白蛋白 24.3g/L，胆固醇 5.5mmol/L，肾功能正常，TSH 偏高。（2）患儿携带 SMARCAL1 基因的复合杂合突变，共有 2 个突变位点（c.1334+1G>A (splicing);c.971dupC (p.A325Sfs*34)）。（3）经 Sanger 验证 c.1334+1G>A (splicing)来自于母亲，为剪接突变，该突变未在 ExAC 等正常人数据库中检出，文献数据库已有该位点的病例报道，为致病突变，故此突变为报道过的致病突变。c.971dupC (p.A325Sfs*34)来自于父亲，为移码突变，该突变未在 ExAC 等正常人数据库中检出，为未经报道的新突变，最小等位基因频率为 0，故此突变为致病突变。
结论 *SMARCAL1* 基因突变可能是该例 Schimke 免疫性骨发育不良的遗传学病因，新发现突变扩展了 *SMARCAL1* 基因的突变谱。

延胡索酸酶缺乏症 1 例并文献复习

杨明
北部战区总医院

延胡索酸酶缺乏症是一种罕见的遗传代谢病，发病率仅 4 亿分之一，1986 年度首次报道尿延胡索酸排泄量增加、低钾、小头畸形、嗜睡症的病例，至今报道 42 例，中国尚未见报道。现汇报我们发现的中国汉族延胡索酸酶缺乏症患儿一例，并综合相关文献加深对该病的认识。该患儿生后 19 小时即出现呼吸困难及明显酸中毒，喂养困难，经完善基因学检查明确诊断为延胡索酸酶缺乏症，后患儿持续反复抽搐及酸中毒，表现典型。

一例 XYY 综合征合并 3-甲基戊烯二酸尿症 I 型患儿的遗传学分析

张鑫丽 应羽燚 沈国松 潘黎明
湖州市妇幼保健院

目的 报道一例 XYY 综合征合并 3-甲基戊烯二酸尿症 I 型（3-methylglutaconic aciduria Type I, MCGA I）的患儿，并分析其遗传学病因。
方法 首先应用染色体微阵列分析（chromosomal microarray analysis，CMA）对患儿进行初步检测后，采用二代测序法检测遗传代谢性疾病相关基因外显子变异，并通过 sanger 法测序验证，最后对可疑的基因变异位点进行生物信息学预测。
结果 CMA 提示患儿染色体核型为 47，XYY，二代测序发现患儿 *AUH* 基因存在复合杂合变异 c.677G>A（p.R226H）和 c.373C>T（p.R125W），父母均为变异携带者，该两处变异国内未见报道。

结论 患儿患有 47，XYY 综合征，并且，由于 *AUH* 基因的复合杂合变异，引起 3-甲基戊烯二酸尿症 I 型。

FMR1 基因 CGG 重复序列与育龄期卵巢功能减退患者的相关性研究

黎彩敏[1] 杨芳[2]
1.南方医科大学第一临床医学院
2.南方医科大学珠江医院胎儿医学与产前诊断科

目的 FMR1 基因 CGG 重复序列的异常扩增会导致脆性 X 相关疾病，严重损害女性的卵巢功能。因此，探讨育龄期卵巢功能减退（DOR）患者与 FMR1 基因 CGG 重复序列的关系，有助于女性生殖系统疾病的早期发现与管理。
方法 DOR 入组标准为：年龄<40 岁，抗苗勒管激素（AMH）<1.1 ng/ml 和（或）10 IU/L<基础促卵泡激素（FSH）<25 IU/L，入组前 6 个月无妊娠或哺乳史，入组前 3 个月无激素药物使用史，无卵巢手术史。记录入组参与者的年龄、血清性激素等血清生化指标，采用三引物荧光 PCR 结合毛细管电泳分析技术检测 FMR1 基因的 CGG 重复数，并把女性 2 个 FMR1 基因 CGG 重复数较小的等位基因定义为“Allele 1”，较大的定义为“Allele 2”，对 DOR 组与对照组的 CGG 重复数、性激素以及血脂水平进行差异分析。
结果 本研究共招募了 121 名 DOR 患者和 430 名健康女性，其 AMH 水平（0.7±0.3 vs 3.6±2.5 ng/ml）、基础 FSH 水平（8.0±4.0 vs 5.2±1.3 IU/l）、年龄和睾酮水平之间的差异均有统计学意义（P＜0.001）；而雌二醇、孕酮、黄体生成素、泌乳素、FMR1 基因 Allele1 和 Allele 2 的 CGG 重复数之间的差异均无统计学意义（P＞0.05）。两组的 FMR1 CGG 重复数总体分布相似，最常见的 CGG 重复数均为 29 和 30。在两组的 Allele 2 中均发现了 CGG 重复数为 29-31 处的主要峰和 36-37 处的第 2 个峰（次要峰）。根据 CGG 重复数分为 7 个连续的分组（分别为：＜25，25-29，30-34，35-39，40-44，45-54，55-200）和 4 个连续的分组（分别为：＜25，25-34，35-44 和＞44），DOR 组与对照组的 Allele 1 分布、Allele 2 分布、黄体生成素、泌乳素、血脂四项之间的差异均未发现统计学意义（P＞0.05）。
结论 FMR1 基因前突变在 DOR 患者和正常女性中的发生率均较低，FMR1 基因的 CGG 重复序列动态突变并不是 DOR 人群的重要致病突变。次要峰的存在可能与不同种族之间的不同结果相关。睾酮可能在保护卵巢功能方面有积极的作用。

一例 β 脲基丙酸酶缺陷症合并线粒体病病例报道

支秀芳[1] 雷梅芳[2,3] 舒剑波[3,4,5] 郑洁[1] 张莹[1] 蔡春泉[3,4,5,6] 张玉琴[2,3]
1.天津医科大学研究生院
2.天津市儿童医院神经内科
3. 天津市儿童医院（天津大学儿童 医院）
4.天津市儿科研究所
5.天津市儿童出生缺陷防治重点实验室
6.天津市儿童医院神经外科

目的 报道一例 β 脲基丙酸酶缺陷症合并线粒体病患儿的临床表现、诊断、临床治疗经过及预后随访情况。
方法 收集 1 例于 2018 年 8 月就诊于天津市儿童医院神经内科患儿的临床资料。
结果 患儿，男，8 岁，因生长发育落后 2 年首次就诊于天津市儿童医院。1 个月后，因头晕、呕吐、间断出现癫痫发作再次入院。血清乳酸水平为 7.04mmol/L。基于气相色谱-质谱（GC-MS）的尿液代谢组学分析显示 β-脲基丙酸酶缺乏。全外显子测序结果显示患儿携带 *UPB1* 基因 c.977G>A（p.R326Q）纯合变异。Sanger 测序显示患儿父母分别携带 c.977G>A 杂合变异，诊断 β 脲基丙

酸酶缺陷症。患儿既往实验室检查提示反复严重代谢性酸中毒、高乳酸血症、脑脊液乳酸高，与 β-脲基丙酸酶缺乏的典型特征不一致。进一步行线粒体 DNA 遗传分析，结果表明，患儿 *MT-TL1* 基因变异 m.3243A>G，异质性水平为 65%，母亲为 17.8%，母亲无相关临床表现。7 个月后，患儿因发作性视力障碍 3 天，头痛、精神弱 4 小时再次入院，头 CT 示右侧枕部小片状低密度影，左侧基底节稍高信号影，头 MRI 示于 T2WI 及 FLAIR 序列见右侧顶枕叶皮层及皮层下区高信号影，最终，患儿确诊为 β-脲基丙酸酶缺乏合并线粒体脑肌病伴高乳酸血症及卒中样发作(Mitochondrial encephalopathy-lactic acidosis-stroke like episode, MELAS)。随后接受鸡尾酒疗法和托吡酯抗癫痫治疗。两个月后血清乳酸下降。随访 4 个月，癫痫无复发。

结论 据我们所知，这可能是首例 β-尿苷丙酸酶缺乏症合并 MELAS 的病例报道。全外显子测序不能涵盖所有基因变异相关疾病，需要依据临床实际情况选择合适的基因检测手段来辅助诊断疾病。

高分辨率熔解曲线技术检测患者 ABO 基因 SNP 位点方法的建立及评价

盛文超[1,2] 支秀芳[1,2] 郑洁[1,2] 蒲林洁[1,2] 顾春钰[1,2] 郭德统[1,2] 舒剑波[1,3,4] 蔡春泉[1,3,4,5]
1.天津儿童医院
2.天津医科大学研究生院
3.天津市儿童出生缺陷防治重点实验室
4.天津市儿科研究所
5.天津市儿童医院神经外科

目的 建立高分辨率熔解曲线（HRM）分析技术 alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase（*ABO*）基因 rs657152 位点单核苷酸多态性（SNP）的方法并进行评价。

方法 通过 PCR 反应扩增 30 例样品包含 *ABO* 基因 rs657152 位点在内约 242bp 片段，测序获得 *ABO* 基因 rs657152 位点 3 种不同基因型，将该 3 种基因型作为对照，设计高分辨溶解曲线引物，并建立 HRM 技术检测 *ABO* 基因 rs657152 位点基因型方法。利用 50 份待测 DNA 样品进行 HRM 方法检测相应的 *ABO* 基因 rs657152 位点的基因型，同时通过普通 PCR 反应扩增该 50 例样品，并进行测序从而获得相应的基因型，以对 HRM 方法准确性、重复性及稳定性进行评价。

结果 建立的 *ABO* 基因 HRM 分析方法扩增反应正常，T/T,T/G,G/G 3 种基因型区分明显，扩增产物 Melt 曲线良好，未发现非特异性产物；与基因序列测定结果对比显示准确性良好。

结论 建立的 *ABO* 基因 rs657152 位点 HRM 检测方法准确性高、重复性及稳定性良好，为下一步临床分析 *ABO* 基因 SNP 提供一定的技术支持。

高分辨率熔解曲线技术检测患者 LZTFL1 基因 SNP 位点方法的建立及评价

郑洁[1,2] 支秀芳[1,2] 盛文超[1,2] 顾春钰[1,2] 蒲林洁[1,2] 郭德统[1,2] 舒剑波[1,3,4] 蔡春泉[1,3,4,5]
1.天津市儿童医院（天津大学儿童医院）
2.天津医科大学研究生院
3.天津市儿科研究所
4.天津市儿童出生缺陷防治重点实验室
5.天津市儿童医院神经外科

目的 建立高分辨率熔解曲线（HRM）分析技术 leucine zipper transcription factor like 1（*LZTFL1*）基因 rs11385942 位点单核苷酸多态性（SNP）的方法并进行评价。

方法 通过 PCR 反应扩增 30 例样品包含 *LZTFL1* 基因 rs11385942 位点在内约 278bp 片段，测序获得 *LZTFL1* 基因 rs11385942 位点 2 种不同基因型，将该 2 种基因型作为对照，设计高分辨溶解曲线引物，并建立 HRM 技术检测 *LZTFL1* 基因 rs11385942 位点基因型方法。利用 50 份待测

DNA 样品进行 HRM 方法检测相应的 *LZTFL1* 基因 rs11385942 位点的基因型，同时通过普通 PCR 反应扩增该 50 例样品，并进行测序从而获得相应的基因型，以对 HRM 方法准确性、重复性及稳定性进行评价。
结果 建立的 *LZTFL1* 基因 HRM 分析方法扩增反应正常，A/A,dupA/A 2 种基因型区分明显，扩增产物 Melt 曲线良好，未发现非特异性产物；与基因序列测定结果对比显示准确性良好。
结论 建立的 *LZTFL1* 基因 rs11385942 位点 HRM 检测方法准确性高、重复性及稳定性良好，为下一步临床分析 *LZTFL1* 基因 SNP 提供一定的技术支持。

1 例先天性中枢性甲状腺功能减退症的临床和基因分析

黄新文 黄新文
浙江大学医学院附属儿童医院

探讨 1 例先天性中枢性甲状腺功能减退症的临床、生化及遗传学特点。
方法 对患儿的临床表现、甲状腺功能及治疗随访等进行分析，应用二代测序技术遗传学检测并对变异位点进行生物信息学软件评估。
结果 患儿在新生儿期存在中枢性甲状腺功能减退、黄疸延迟消退、贫血和体格生长落后，不伴其他垂体激素缺乏，左甲状腺素替代治疗 2 年后体格指标好转，认知、运动功能无异常；包含目的基因的高通量测序显示患儿携带母源性的 X 连锁 IGSF1 基因 c.1918G>T（p.G661W）半合子错义突变，数据库提示非多态性，生物信息学软件分析该位点变异导致蛋白糖基化不稳定，中度危害，已有同一位置 c.1981G>A 半合子致病的报道。
结论 国内首次报道 1 例 X 连锁 IGSF1 突变导致的罕见男性先天性中枢性甲状腺功能减退症，基因检测有助于该病的诊断、治疗及家系的遗传咨询。

递送及储存条件对新生儿干血斑标本中氨基酸和肉碱浓度的影响

黄新文
浙江大学医学院附属儿童医院

目的 探讨不同递送和储存条件对新生儿干血斑标本中氨基酸和肉碱浓度的影响，为提高串联质谱筛查新生儿遗传代谢病的准确性及可靠性提供依据。
方法 根据不同递送和储存条件将 1 254 616 名在浙江省新生儿疾病筛查中心进行遗传代谢病筛查新生儿的干血斑标本分为 3 组:室温递送储存(室温组，n =338 467) 、冷链递送+低温储存(冷链+低温组,n= 480 021)、冷链递送+低温低湿储存(冷链+低温低湿组,n=436 128)。应用串联质谱技术检测干血斑标本中氨基酸和肉碱浓度，SPSS 24.0 软件进行数据分析，分析递送和储存过程中温度和湿度对氨基酸和肉碱浓度稳定性的影响。
结果 三组样本氨基酸和肉碱浓度均呈偏态分布，氨基酸和肉碱浓度组间差异均有统计学意义(均 P＜0.01)。酪氨酸浓度中位数冷链+低温组与冷链+低温低湿组相近，室温组较冷链+低温组和冷链+低温低湿组分别降低 18%和 16%; 室温组的蛋氨酸浓度中位数与冷链+低温组相近，分别较冷链+低温低湿组降低 15%和 11%；3 组精氨酸浓度中位数均有差异，室温组和冷链+低温组分别较冷链+低温低湿组降低 12%和 25%。室温组的游离肉碱浓度中位数与冷链+低温组相近，较冷链+低温低湿组增高 12%。冷链+低温组的乙酰肉碱、丙酰肉碱、丙二酰肉碱+3-羟基丁酰肉碱、戊二酰肉碱+3-羟基己酰肉碱、十六碳酰肉碱等浓度中位数与冷链+低温低湿组相近，室温组较冷链+低温组和冷链+低温低湿组降低 21%～64%。其他氨基酸和酰基肉碱浓度组间差异较小。除瓜氨酸、甲基丙二酰肉碱+3-羟基异戊酰肉碱、戊酰基肉碱外，室温组其他氨基酸和肉碱浓度月中位数变异系数均高于冷链+低温组和冷链+低温低湿组。
结论 使用冷链递送和低温低湿储存可以有效延缓干血斑标本中部分氨基酸和肉碱的降解速度，提高串联质谱检测结果的准确性和可靠性，从而保证新生儿遗传代谢病筛查质量。

全自动荧光免疫分析仪在新生儿 G6PD 缺乏症筛查中的应用

黄新文
浙江大学医学院附属儿童医院

目的 验证全自动荧光免疫分析仪（genetic screening processor, GSP）检测新生儿葡萄糖-6-磷酸脱氢酶缺乏症（Glucose-6-phosphate dehydrogenase deficiency,G6PD 缺乏症）的性能，并分析其在 G6PD 缺乏症筛查中的应用。
方法 对 GSP 检测 G6PD 的准确度、精密度和稳定性进行评价。采用 GSP 和 1420 荧光免疫分析仪同步检测新生儿筛查与确诊样本，对检测值进行比较。检测 195 万新生儿筛查样本，分析两仪器的检测效能，结合百分位数法评价 GSP 筛查 G6PD 缺乏症的切值。
结果 GSP 检测卫生部室间质控品的检测值与靶值的相对偏移均在±5%内；试剂盒质控品批内精密度为 4.34%-4.91%，批间精密度为 0.85%-2.12%，总精密度为 5.44%-5.72%；不同实验批次低、高质控平均 CV 均在 10%以内。与 1420 同步检测筛查和确诊样本，检测值一致性较好（*Kappa*=0.937），相关性显著（*r*=0.740）。GSP 检测 G6PD 敏感度、特异性高达 100%和 99.83%，假阳性率下降，阳性预测值上升至 73.59%。根据人群 99.1%百分位制定切值，男性为 26.1U/dL，女性为 29.1U/dL。
结论 GSP 检测性能良好，自动化程度高，通量大，筛查效率高，一定程度减少女性杂合子的漏筛，可用于临床新生儿 G6PD 缺乏症的大规模筛查。

串联质谱检测阴性的 1 例甲基丙二酸合并同型半胱氨酸血症 cblX 型患儿临床及遗传学分析

黄新文
浙江大学医学院附属儿童医院

目的 探讨 1 例甲基丙二酸合并同型半胱氨酸血症 cblX 型的临床表型及遗传学特点。
方法 对先证者行超高效液相色谱-串联质谱和全外显子组检测，对先证者父母及姐姐行 Sanger 验证。
结果 全外显子组测序及 Sanger 验证显示先证者为 *HCFC1* 基因 c.202C>G(Q68E)半合子变异，遗传自其母亲，父亲和姐姐均未携带该变异。患儿 2 月龄开始出现癫痫性痉挛发作和局灶性发作，发作频率逐渐增加，多种抗癫痫药物治疗效果不佳，于 4 月龄死亡。新生儿筛查和急性发作期串联质谱检测丙酰肉碱、丙酰肉碱/乙酰肉碱、丙酰肉碱/游离肉碱均未见明显异常，超高效液相色谱-串联质谱检测血甲基丙二酸和同型半胱氨酸均增高，才确诊为甲基丙二酸合并同型半胱氨酸血症 cblX 型。
结论 甲基丙二酸合并同型半胱氨酸血症 cblX 型串联质谱检测可能存在阴性，结合血液/尿液甲基丙二酸的检测更有利于疾病诊断。

Region 4 Stork 系统在串联质谱新生儿极长链酰基辅酶 A 脱氢酶缺乏症筛查中的应用

黄新文
浙江大学医学院附属儿童医院

目的 探讨国际协作的新生儿筛查数据平台 Region 4 Stork（R4S）系统联合切值法分析应用于新生儿极长链酰基辅酶 A 脱氢酶缺乏症（VLCADD）串联质谱筛查的可行性。
方法 回顾性分析 2013 年 10 月至 2018 年 7 月浙江省新生儿疾病筛查中心 2 040 072 名新生儿应用串联质谱技术筛查的数据，使用 R4S 系统对其中依据传统切值法判别疑似 VLCADD 阳性的 910

例样本原始数据进一步分析，以临床诊断及 ACADL 基因检测结果为依据，统计比较两者的筛查效率。

结果 切值法判读的疑似 VLCADD 阳性 910 例数据经 R4S 系统进一步分析后，阳性判读减至 238 例（含 9 例确诊阳性），确诊患儿 ACADL 基因测序共发现 16 种不同变异。假阳性率由 0.44‰（901/2 040 072）降至 0.11‰（229/2 040 072），阳性预测值由 0.99%（9/910）增至 3.78%（9/238），筛查特异度由 99.96%（2 039 162/2 040 063）增至 99.99%（2 039 834/2 040 063）。切值法单独应用与联合 R4S 系统分析两者阳性率有统计学差异（χ^2=393.5，*P*<0.05）。

结论 R4S 系统联合切值法应用于串联质谱 VLCADD 新生儿筛查可显著提高筛查性能，降低假阳性率，具有一定的临床应用价值。

多种酰基辅酶 A 脱氢酶缺乏症新生儿筛查及临床分析

黄新文
浙江大学医学院附属儿童医院

目的 了解新生儿多种酰基辅酶 A 脱氢酶缺乏症（MADD）的患病率、临床特征及基因变异特点。

方法 采用串联质谱技术对 2009 年 1 月至 2020 年 12 月浙江省新生儿疾病筛查中心 3896789 名新生儿进行遗传代谢病筛查，结合尿有机酸分析及 ETF 或 ETFDH 基因检测确诊。确诊患儿进行饮食和生活管理，补充左卡尼汀、核黄素、辅酶 Q 治疗，长期进行随访观察并评估患儿的生长和智能发育情况。

结果 确诊 MADD14 例，2 例 II 型，其余均为迟发型，患病率为 1/278342。14 例患儿中 2 例死亡，4 例因感染诱发出现以低血糖为主要表现的急性代谢失调，1 例出现肌张力减低，其余患儿随访发育良好（随访时间 2~45 个月）。患儿初筛血 C4-C18:1 不同程度地增高。13 例患儿进行基因检测，1 例 ETFA 基因复合杂合变异，1 例 ETFA 基因纯合变异，1 例 ETFB 基因复合杂合变异，8 例为 ETFDH 基因复合杂合变异，1 例为 ETFDH 基因纯合变异，1 例只检测出一个 ETFDH 基因位点。c.250G> A 为本研究中热点变异，

结论 MADD 临床表现高度异质，新生儿期发病较为严重，迟发型常无明显临床症状，最常见基因变异为 c.250G> A，C4 增高与疾病严重程度有关。

MT-TL1 基因 m.3243 位点变异引起的 DMDF 且伴小脑萎缩患者的临床报道

刘思文 姜艳芳
吉林大学第一医院

目的 探讨一例具有糖尿病、耳聋、小脑萎缩症状患者的临床表型及其线粒体基因变异情况。

方法 结合患者的临床症状及辅助检查结果，分别对其及家系成员外周血的线粒体基因进行测序。

结果 患者具有临床表现为血糖升高，双耳感音神经性聋，头颅 MRI 显示枕大池增宽，双侧小脑半球脑沟增宽加深，患者母亲及有耳聋及糖尿病的症状，外公外婆糖尿病。测序结果显示，患者外周血线粒体 MT-TL1 基因存在 m.3243A>G 异质突变，突变比例为 50.27%，患者母亲该位点突变频率为 15.62%，患者外公及外婆该位点突变频率无变异。

结论 *MT-TL1* m.3243A>G 变异引起的 DMDF 综合征患者，除具有糖尿病、耳聋的症状外，还有小脑萎缩的表型（MELAS 综合征的表型之一），表明线粒体变异引起的疾病不仅在同一疾病当中异质性明显，还可同时表现出不同病种间的症状。

一例罕见 Y 染色体重排致性发育异常患者的遗传学分析

夏俊珂 孔祥东
郑州大学第一附属医院

目的 对一例罕见 Y 染色体重排致性发育异常患者进行遗传学分析，明确病因。
方法 收集患者临床资料，联合应用染色体 G 显带核型分析、荧光原位杂交（fluorescence in situhybrid ization,FISH）、*SRY* 基因检测、低深度全基因组测序拷贝数变异分析技术（low-coverage massively parallel copy number variation sequencing, CNV-seq）、全外显子测序（whole exome sequencing, WES）、全基因组测序（whole genome sequencing, WGS）对患者进行遗传学检测。
结果 患者 14 岁，社会性别为女性，因“身材矮小，第二性征发育不良”就诊。外周血染色体核型为 46,XY，携带 *SRY* 基因。WES 未检测到相关基因致病性变异，提示 Yp11.32q12 处存在重复。CNV-seq 结果为 47,XYY，外周血 FISH 结果示患者为双着丝粒 Y 染色体嵌合体携带者，WGS 发现 Yp11.32q11.223 存在大小为 23.66 Mb 的重复，同时 Yq11.223q11.23 存在约 5.16 Mb 的缺失，断裂点位于 chrY:23656267。综合分析，患者的染色体核型应为 46,X,psu idic(Y)(q11.223)/46,X,del(Y)(q11.223)嵌合体。
结论 单一的遗传学检测方法有技术局限性，联合多种遗传学检测明确了患者的遗传学病因，为患者的临床诊疗提供了依据。

吉林地区遗传性乳腺癌/卵巢癌基因变异分析

何佳雪 胡欣彤 陈立国 姜艳芳
吉林大学第一医院

目的 探讨吉林地区遗传性乳腺癌/卵巢癌相关基因变异情况及其基因变异特征。
方法 回顾性分析吉林地区乳腺癌/卵巢癌相关基因变异情况。以外周血为样本，采用目标区域捕获结合二代高通量测序技术，检测乳腺癌/卵巢癌相关的 26 个基因基因外显子及其邻近±20bp 内含子区变异（包括点突变，20bp 以内的缺失插入突变）并进行分析。
结果 191 例受检者中，确诊患者占比 92%，其余 8%为有遗传史的高危人群。确诊患者中，有家族史患者占 62%。所有受检者中，已知致病突变检出率为 17.8%（34/191），疑似致病突变检出率为 10.47%（20/191），意义未明突变检出率为 32.46%（62/191），阴性（未检出与疾病有关的胚系变异）占 39.27%（75/191）。检出的已知致病突变主要位于 BRCA1、BRCA2、MSH6、MSH2、ATM、TP53、RAD51C、RAD50、PALB2 等基因上，其中 BRCA1 突变占 51.52%（17/33），BRCA2 突变占 27.27%（9/33）。在致病性的 BRCA 变异中，检出 BRCA1 基因罕见大片段缺失 1 例。。
结论 吉林地区遗传性乳腺癌/卵巢癌患者基因变异以 BRCA1 为主，其次是 BRCA2。

CD46 基因突变相关非典型溶血尿毒综合征 1 例病例报告

简珊 陈兆煜 董耀华 李卓 宋红梅 魏珉
北京协和医院

背景 补体介导的非典型溶血尿毒综合征(atypical hemolytic uremic syndrome, aHUS)是一种相对罕见的疾病，欧洲儿童的估计患病率为 7/100 万，可导致微血管病性溶血性贫血、血小板减少和急性肾损伤等。CD46，曾称为膜辅蛋白（ MCP) 基因突变可导致 aHUS。本文探讨 CD46 基因突变导致的 aHUS 患者的临床特点和基因特点。
方法 回顾性分析 2019 年 6 月我院收治的 1 例 CD46 基因突变导致的 aHUS 患者的临床资料和基因检测结果，并文献复习。

结果 女性患儿，12 岁。生后 5 个月起间歇性腹泻，3 岁起间歇性水肿。 5 岁时出现面色苍白、水肿、少尿、高血压，实验室检测 HBG 61g/L、PLT75×10^9/L、ALB 17g/L、ALT 96U/L、AST 78U/L、Cr119.4umol/L，C3 0.63g/L↓；C4、ANA 和 ENA 正常；尿中红细胞 34.4/ul；24hUP 0.98g。当地诊断为 HUS，对症治疗后好转。之后多次反复腹痛、腹泻、水肿、少尿，Bp 波动在 125-134/80-90mmHg，HGB 61-104g/L，PLT44-543×10^9/L，Alb 20.5- 27.5g/L；24hUP 0.27-0.14g，当地对症治疗后可好转。9 岁时因病情反复发作，蛋白尿持续存在，当地医院肾活检，考虑为膜性增生性肾小球肾炎，经泼尼松治疗后，尿蛋白转为阴性，但腹痛和腹泻持续存在。11 岁时水肿、腹痛、腹泻症状加重，就诊我院，行胶囊内镜检查发现小肠淋巴管扩张；淋巴成像显示淋巴管发育不良和蛋白质丢失性胃肠病，予中链甘油三酯（MCT）饮食，并于世纪坛医院行胸导管探查松解术，之后腹痛、蛋白尿等症状曾全部缓解。12 岁时病情再次反复，实验室检查：ALB 20g/L，Cr111μmol/L，C3 0.680g/L↓； C4、ANA、ENA、ANCA 正常；24hUP 0.38g；尿液 BLD 80 细胞/μL。我院再次肾活检，免疫荧光为“满堂亮”表现，考虑膜性增生性肾小球肾炎。基因检测发现 CD46 的复合杂合突变（c.1054del，c.375T>G），分别来自父母。予 MCT 饮食、激素及 ACEI 等 治疗后，病情可控制，但易反复。

结论 CD46 缺乏相关性 aHUS 多发病于儿童期早期、多数患者肾脏结局良好、但容易频繁复发。原发性淋巴管发育不良是会导致淋巴系统功能异常，并可导致淋巴水肿或腹泻。如两者同时存在，患儿回频繁发作 aHUS，影响肾脏结局。当低白蛋白血症和蛋白尿不平行时，应考虑肾脏以外的因素导致的低白蛋白血症。

涉及 1 号、9 号和 18 号染色体复杂重排伴无精症一例

傅文婷 王柏贤 周冰燚 黄嘉敏 李佩佩
广东省生殖科学研究所（广东省生殖医院）

患者 男，汉族，25 岁，身高 172 cm，体重 63 kg，结婚 3 年其妻未孕，夫妻非近亲婚配，否认遗传病家族史，患者的表型和智力发育均正常，无不良嗜好，否认药物和化学毒物及放射线接触史。查体：患者第二性征、外生殖器发育良好。实验室检查：精液常规分析和睾丸活检均提示无精，性激素水平除泌乳素升高（为 473.38 mU/L，正常参考范围：86~324 mU/L），其余指标都在正常范围内。家系调查：先证者父母及姐姐、妹妹表型及智力均正常。其母在怀孕早期有农药接触史。患者有二姐一妹，均已婚育，且无不良孕产史。细胞学检查：患者核型为 46,XY,der(1)inv(1)(p13q25)t(1;9;18)(p13;p22;q21)，染色体微阵列比较基因组杂交技术未检测到有临床意义的基因拷贝数缺失、重复。AZF 检测提示 AZFa、AZFb、AZFc、AZFd 均未见缺失。

讨论 平衡型染色体重排(BCA)是一种常见的染色体结构变异，其发生率在 1/500 到 1/625 之间。相互易位、倒位和插入，是 BCA 最常见的几种类型，平衡型染色体重排因没有染色体片段增加或减少，相对应的基因仅有位置的变化，数目无异常，故携带者本身通常无比较明显的表型异常，智力、外貌及发育情况正常，但却存在生育问题，在人类健康中发挥着重要作用，与智力障碍、癌症和不孕等疾病密切相关。近年来，通过对染色体平衡型重排断裂点的分析，已找到了很多单基因病致病基因、癌基因和无精子症相关基因等。本例患者表现为无精症，AZF 检测提示未见缺失，aCGH 检测结果未发现明显异常，患者的无精症也可能与断裂位点所涉及的碱基序列影响了相关基因的表达有关。本例患者涉及 1 号、9 号和 18 号染色体的平衡复杂重排，而且 1 号染色体同时存在倒位和易位，非常罕见。其无精症可能与染色体异常有关。

SNRNP200 基因的致病变异频谱分析和相关表型

黎仕强 江红梅 肖学珊 贾小云 张清炯
中山大学中山眼科中心

目的 *SNRNP200* 基因突变是显性遗传性视网膜色素变性的常见原因之一，本研究目的是基于课题组大样本量的外显子组测序数据，分析 *SNRNP200* 基因的致病变异和相关表型特点。

方法 从课题组已有的外显子组测序数据中选择 *SNRNP200* 基因的变异，通过生物信息学方法，包括人群频率、在线预测、功能结构域位置等，评估变异的致病性，对携带致病变异的病人，分析和总结其临床表现的特点。
结果 通过生物信息学对课题组的大样本量外显子组测序数据分析显示，*SNRNP200* 基因的可能致病变异均为错义变异，且富集在功能结构域区域。该基因截短变异可能良性。携带致病变异的病例的临床特点有：夜盲起病，中周部视网膜可见骨细胞样色素沉着，视网膜电流图显示视锥细胞和视杆细胞的反应振幅均重度降低。
结论 生物信息学分析为评估 *SNRNP200* 基因变异的致病性评估提供证据，本研究扩展了对 *SNRNP200* 基因致病变异以及表型特征的认识，有助于对携带该基因变异患者的临床诊疗。

一例 DNMT3A 基因杂合缺失导致的 Tatton-Brown-Rahman 综合征的遗传学分析

余秀蓉 [1,2] 王志红 [1,2]
1.厦门大学附属东方医院（第九〇〇医院）
2.联勤保障部队第九〇〇医院

目的 对一个临床表现为说话和语言发育延迟、智力障碍、运动发育延迟、脑发育不全、全面性发育迟缓、身材高大的先证者及其家系进行遗传学分析。
方法 收集先证者表型，分别采集先证者及其父母（表型正常）的外周血，通过 Trio-WES+Trio-CNVseq 寻找可疑的致病变异，然后对发现的可疑致病变异进行致病性分析。
结果 Trio-WES 结果显示先证者 *DNMT3A* 基因 EXON:2-23 杂合缺失，其父母亲均为野生型。Trio-CNVseq 结果显示先证者染色体核型 46,XY，染色体微缺失/微重复检测结果 seq[GRCH37]del(2)(p24.1p23.3)(chr2:23608318-25907862)位置存在约 2.30Mb 的可能致病性的杂合缺失，该区域包含 *DNMT3A* 基因，其父母亲均为野生型。*DNMT3A* 基因变异导致的 Tatton-Brown-Rahman 综合征临床表现为身材高大、巨头畸形、圆脸、睑裂狭小、视神经发育不全、智力障碍、癫痫发作、全身性低张力、脐疝、房间隔缺损、脊柱侧弯、小脑扁桃体下疝畸形 I 型、脑软化、小睑裂等。经查阅 HGMD、OMIM 和 Clinvar 数据库，先证者的杂合缺失为未报道过的新发（denovo）变异。根据 ACMG 遗传变异分类标准与指南，该变异符合 PVS1+PS2+PM2，可以判断为致病性变异。此外，先证者突变符合 Tatton-Brown-Rahman 综合征常染色体显性遗传（AD）疾病发病机制，先证者及其家系成员符合表型及基因型的共分离。
结论 根据生物学致病性分析、遗传模式以及临床表型基因型比对，提示先证者 *DNMT3A* 基因变异的危害性与其表型存在相关性，即先证者 *DNMT3A* 基因杂合缺失导致 Tatton-Brown-Rahman 综合征可能性大。*DNMT3A* 基因新发致病性变异的检出为该家系的遗传咨询和分子诊断提供了可靠依据，丰富了该基因的突变谱。

1 例全身网状色素异常症患者的分子诊断

余秀蓉 [1,2] 王志红 [1,2]
1.厦门大学附属东方医院（第九〇〇医院）
2.联勤保障部队第九〇〇医院

目的 对一例临床表现为全身网状色素异常，伴有复发性中耳炎和支气管扩张症的男性患者进行分子诊断。
方法 取患者腹部皮肤切除标本行 HE、刚果红染色及免疫组化检测。分别采集患者及其父母（表型正常）的 EDTA 抗凝外周血各 2 ml，通过家系三人全外显子组测序（Trio-WES）寻找可疑的致病变异，并用 Sanger 测序验证可疑致病变异，并进行致病性分析。
结果 腹部皮肤切除标本 HE 染色：淀粉样变；刚果红：+++；免疫组化：Kappa +，Lambda +。Trio-WES 及 Sanger 测序检出先证者 *POLA1* 基因 c.1375-354(IVS13)A>G 半合子变异，父亲为野

生型，母亲携带杂合变异。该变异已有文献报道，功能研究表明该变异有害。生物学致病性分析：根据 ACMG 遗传变异分类标准与指南，该变异符合 PS3+PM2，判断为可疑致病性变异。此外，该变异先证者为半合子，符合 X 染色体隐性遗传（XR）疾病发病机制，先证者及其家系成员符合表型及基因型的共分离。*POLA1* 基因变异导致的 X-连锁网状色素异常症主要表现为：反复肺炎，角化过度，腹股沟疝，角膜瘢痕形成，视力丧失，畏光，少汗，结肠炎，胃肠道复发性感染，广泛性网状褐色色素沉着，角膜基质混浊，淀粉样变性等。以上结果提示先证者 *POLA1* 基因变异与先证者的临床表型相关。

结论 综合分析患者的临床表型、皮肤病理以及 Trio-WES 检测结果，该男性患者为 *POLA1* 基因 c.1375-354A>G 半合子变异导致的 X-连锁网状色素异常症。

ASXL1 基因变异致 Bohring Opitz 综合征一例

张在卉[1,2] 王志红[1,2]
1.厦门大学附属东方医院（第九〇〇医院）
2.联勤保障部队第九〇〇医院

目的 分析 1 例 Bohring-Opitz 综合征（Bohring-Opitz Syndrome，BOS）患儿的临床特征及 *ASXL1* 基因突变情况，明确其遗传学病因。

方法 收集患儿的临床资料，采集患儿及父母的外周血，提取基因组 DNA 行核心家系全外显子组测序（whole exon sequencing, WES)、拷贝数变异（copy number variation, CNV）分析及 Sanger 测序验证。针对检出的致病变异，对该家系行羊水产前诊断。

结果 先证者，女，8 岁，临床主要表现为全面性发育迟缓、重度智力障碍、小头畸形、额头鲜红斑痣，毛发浓密、肘和膝关节挛缩、宫内发育迟缓。家系全外显子组测序提示先证者 *ASXL1* 基因 c.4243C>T 杂合突变，导致提前引入终止密码子（p.R1415Xfs*127）。Sanger 测序确证先证者存在 c.4243C>T 杂合变异，其父母均为 c.4243C 野生型。根据美国医学遗传学与基因组学学会遗传变异分类标准与指南，*ASXL1* 基因 c.4243C>T 变异为致病性变异（PVS1+PS2+PM2+PP3）。羊水产前诊断提示胎儿不携带该致病变异，随访至新生儿 1 周岁，一切正常。

结论 *ASXL1* 基因 c.4243C>T（p.R1415Xfs*127）突变很可能是该家系先证者的致病原因。基因检测结果可以为家系遗传咨询及产前诊断提供可靠依据。

3 个多囊肾病家系的胚胎植入前遗传学诊断

张在卉[1,2] 王志红[1,2]
1.厦门大学附属东方医院（第九〇〇医院）
2.联勤保障部队第九〇〇医院

目的 探讨携带多囊肾病（polycystic kidney disease，PKD）致病基因突变的家系中，胚胎植入前遗传学诊断（preimplantation genetic diagnosis，PGD）技术在帮助实现孕育正常后代、阻断 PKD 致病基因垂直传递中的可行性及效果。

方法 选择 3 个已明确分子诊断并要求 PGD 助孕的 3 个 PKD 家系，ADPKD 家系 1： *PKD2* 基因 IVS10+2T>C 杂合突变；ADPKD 家系 2： *PKD2* 基因 c.602delG 杂合突变；ARPKD 家系 3： *PKHD1* 基因 c. [889T>A];[11314C>T]复合杂合突变），采用囊胚滋养外胚层细胞活检、单细胞全基因组扩增（whole genome amplification，WGA）及 NGS（Next-generation sequencing）平台，运用联合诊断单基因病和染色体病非整倍体高通量测序与连锁分析（mutated allele revealed by sequencing with aneuploidy and linkage analyses，MARSALA）策略进行胚胎植入前遗传学诊断，挑选健康胚胎进行移植，在孕中期行羊水穿刺产前诊断，新生儿出生后进行跟踪随访。

结果 3 个家系 4 个 PGD 周期共检测 15 枚囊胚，每个家系均获可移植胚胎，其中包括正常基因型的整倍体胚胎 6 枚，表型正常的 ARPKD 携带者基因型的整倍体胚胎 2 枚。家系 1 先后移植 3 枚胚

胎但未受孕，家系 2,3 移植正常胚胎后成功受孕，羊水产前诊断结果与 PGD 结果一致，且已生育健康后代，生后随访一切正常。

结论 对于明确致病基因突变的 PKD 家庭，基于 MARSALA 策略的 PGD 技术能够阻断致病基因的垂直传播，帮助生育健康胎儿。

6 例 Wiskott-Aldrich 综合征致病基因突变分析及产前诊断

徐若琛[1] 贾竟[1] 杨尚栋[1] 孔祥东[2] 贺颖[1] 郑红[1]
1.郑州大学
2.郑州大学第一附属医院

目的 Wiskott-Aldrich 综合征（WAS）是一种罕见的 X-连锁隐性遗传性疾病，主要表现为血小板异常伴出血、湿疹、免疫缺陷等。本研究通过对 Wiskott-Aldrich 综合征患者家系发病的遗传学机制分析，提高对此病产前筛查和产前诊断的新认识。

方法 收集 6 个 WAS 家系成员的病史信息、临床资料。采集样本包括外周血、羊水及绒毛。应用基因测序以及生物信息技术，对 6 个家系中 6 名胎儿及其母亲，3 例先证者的 *WAS* 基因的外显子区及侧翼序列进行突变分析，确定突变位点并进行产前诊断。

结果 6 个家系中，筛查对象均为胎儿（4 例绒毛，2 例羊水），其中 3 个家系有先证者。先证者均表现出一定程度的血小板异常、湿疹等临床症状。基因测序结果显示 5 名胎儿的 *WAS* 基因均携带错义突变（c.273G>A，c.91G>A，c.134C>T，c.399G>T，c.223G>A），其中 c.273G>A 为首次报道。1 个家系中的先证者及母亲携带 c.946dupC 移码突变，但胎儿基因检测正常。对突变基因进行致病性分析，显示上述 6 种突变基因均可具有致病性。

结论 *WAS* 基因 c.273G>A 错义突变为首次报道的突变，应用 NGS 明确 WAS 患者病因，定制产前诊断是对有家族史的 WAS 家庭避免再次生育患儿的有效手段。

3 例圆形精子症的鉴定及基因诊断

李清琴[1] 唐珍珍[1,2] 王宇林[1,2] 叶宇[1,2] 兰风华[1,2] 张朵[1,2]
1.联勤保障部队第九〇〇医院
2.福建医科大学

目的 圆头精子症是一种罕见的男性原发性不育症，占男性不育症比例＜0.1%,表现为产生无顶体的圆头精子。目前为止 DPY19L2 突变是圆头精子症主要的致病原因，本研究建立 DPY19L2 基因突变的诊断策略，对三例圆头精子患者 DPY19L2 基因的突变情况进行报道和探讨。

方法 对圆头精子症患者进行精子浓度，活力，存活率，巴式染色，顶体抗原 CD46 免疫荧光检测同时采用 PCR 扩增，二代测序，Sanger 测序技术对圆头精子症患者进行 DPY19L2 基因检测。

结果 巴式染色，顶体抗原 CD46 免疫荧光检测显示三例患者均为 I 型圆头精子症患者。PCR 扩增，二代测序，Sanger 测序技术证明三例患者均发生 DPY19L2 纯合缺失，两例为 DPY19L2 新发缺失分别为 2-22 外显子纯和缺失，14-15 外显子纯和缺失，一例为 BP2 位点断裂引起的非等位基因重组缺失，2-22 外显子纯合缺失患者行 ICSI 成功生育一名健康婴儿。

结论 新发的 DPY19L2 纯合缺失会导致圆头精子症的发生，对圆头精子症的致病机制研究具有重要的补充意义，已建立的 DPY19L2 基因诊断策略对圆头精子症患者的临床检测诊断具有一定的参考依据，ICSI 治疗可使 DPY19L2 纯合缺失的圆头精子患者成功受精并生育后代。

SMN1 基因的 c.683T>A 及 c.844C>T 突变可触发无义介导的 mRNA 降解

张梦雅 林炎鸿 何韵杰 颜俊 兰风华 曾健
联勤保障部队第九〇〇医院

目的 通过设计 *SMN1* 小基因，构建野生型及三种无义突变型表达质粒，在转录水平分析其 mRNA 表达量的变化，探究 NMD 在 SMA 中的作用机制。
方法 首先，在 NCBI 上查找 *SMN1* 基因组序列，选择 HGMD 数据库中记载的位于 *SMN1* 基因第 1、5、7 外显子的无义突变点（分别对应 c.43C>T、c.683T>A 、c.844C>T），设计包含三种拟突变点的 *SMN1* 小基因。其次，将其与表达载体 pcDNA3.1(-)/myc-His A 连接，构建野生型表达质粒 PcMV-Mini-SMN-WT；利用突变试剂盒及突变引物得到三种无义突变型表达质粒（E1，E5，E7）。最后，将四种质粒转染 HeLa 细胞，通过 qRT-PCR 分析质粒正常转录本的表达水平；并通过翻译抑制剂放线菌酮的处理，观察药物处理前后 mRNA 表达量的变化，从而明确 NMD 在 SMA 中的作用。
结果 实验数据显示野生型表达质粒发生正确剪接；qRT-PCR 结果显示其中两种突变型质粒（E5，E7）的正常转录本表达水平与野生型相比明显下降；而 E1 突变体与野生型质粒的 mRNA 表达量无明显差异。此外，在放线菌酮处理后，E5 和 E7 突变型质粒的 mRNA 表达量明显升高。而野生型及 E1 质粒的 mRNA 表达量无明显变化。
结论 本研究通过构建 *SMN1* 小基因体外模型及 NMD 体外实验发现无义突变 c.683T>A 及 c.844C>T 发生了 NMD，而无义突变 c.43C>T 未触发 NMD，提示其发生了 NMD 逃逸。这为 NMD 在 SMA 发病机制中的作用提供了线索。

ODF1 基因多态性与断头精子发生的关系

梅晓妍 陈国勇 董荔红 张慧 谢鹏 黄吴键 张朵
联勤保障部队第九〇〇医院

目的 探讨 ODF1 基因变异与人类断头精子发生的关系。
方法 收集断头精子（acephalic spermatozoa syndrome, ASS）患者精液和血液标本，提取精子中的 RNA，通过 RT-PCR 的方法扩增 ODF1 cDNA，Sanger 测序对扩增产物进行检测。提取血细胞 DNA，针对 ODF1 cDNA 中发现的变异位点设计扩增 ODF1 DNA 相应位点的引物，PCR 扩增后，Sanger 测序对 DNA 扩增产物进行检测，100 名已生育男性的精子 DNA 作为对照。Western blot 和免疫组化检测 ODF1 蛋白在精子中的表达和分布。*SUN5* 基因是目前已知的 ASS 的主要致病基因，构建 *ODF1* 与 *SUN5* 基因的重组真核表达载体，转染 HEK293T 细胞后，免疫共沉淀实验检测 ODF1 与 SUN5 之间的相互作用。
结果 14 例 ASS 患者中，3 例携带 *ODF1* 基因一处 27bp 纯合缺失（c.760T_787Gdel，p.Asn219_Cys227del），6 例患者为该位点杂合子携带者，14 例 ASS 患者的变异频率为 0.43。其中纯合子占 21%。100 例对照中，该位点的变异频率为 0.321，其中纯合子仅占 2%。生物信息学分析发现该缺失为一基因多态性（rs568456031），在千人数据库中的变异频率为 0.313。在人类疾病数据库中，未对该多态性做注释。
结论 *ODF1* 基因多态性（rs568456031）在 ASS 患者中的纯合子携带率远远高于已生育对照组，提示该多态性可能对 ASS 患者发病起某种程度辅助作用，是 ASS 发病的修饰基因。

一例小眼畸形患儿的遗传学诊断

吴东 高越 张梦汀 张倩 王凤阳 廖世秀
河南省人民医院

目的 对一例小眼畸形患儿进行遗传学诊断，明确病因。
方法 采用微阵列比较基因组杂交和全外显子组测序对患儿及其父母进行遗传学检测。
结果 患儿及其健康父亲检出在 8 号染色体短臂存在 8.1Mb 缺失，该缺失为可能致病性拷贝数变异，该区域未发现与小眼畸形发育相关基因，未检出患儿其它遗传学变异。
结论 小眼畸形与遗传、环境等多种因素相关，本例患儿虽检出可能致病性拷贝数变异，但未发现其与小眼畸形相关，本例患儿未能明确小眼畸形发生原因。

一例新发 DNAH1 基因移码突变分析

张慧 黄吴键 陈国勇 梅晓妍 兰风华 张朵
联勤保障部队第九〇〇医院

目的 对 2 例临床表现为严重弱精子症、精子鞭毛形态多发异常（Multiple Morphological Abnormalities of the Flagella，MMAF）的原发性不育患者进行致病基因分析，探讨 *DNAH1* 基因新的突变位点在精子尾部多发畸形发生中的致病作用。
方法 抽取两名患者的外周血进行全外显子组测序，由于该两名患者为兄弟，父母为表亲关系，发现可疑致病位点后，在该家系内部及 100 名健康个体中针对该突变位点进行 PCR 扩增、Sanger 测序进行验证分析，利用 Mutation Taster 等软件对突变位点进行蛋白功能危害性分析。
结果 全外显子组测序结果发现该 2 名患者存在同一个纯合突变，为轴丝动力蛋白重链 1(在该家系内部及 50 名健康个体中针对该突变位点进行 PCR 扩增、Sanger 测序进行验证分析，利用 Mutation Taster 等软件对突变位点进行蛋白功能危害性分析。*Dynein Axonemal Heavy Chain1，DNAH1)*第 31 号外显子上的移码突变：c. 5093delA（p.Lys1698Argfs*9），其父母、奶奶都被确定为该突变的杂合子携带者，在 100 名健康个体中未检测到上述突变。该突变位点查阅相关文献及突变数据库，未见报道。运用 Mutation Taster 对其进行预测，该突变可能造成终止密码子提前，翻译提前终止，产生截短蛋白，或其所转录的 mRNA 被无义密码子介导的 mRNA 降解机制（NMD）所降解，从而无法发挥正常功能而最终致病性。
结论 MMAF 是一种由遗传因素导致的精子严重畸形症，临床表现为男性不育，本研究通过全外显子组测序发现一个 *DNAH1* 基因新发可疑致病突变位点，有待后续功能分析进一步验证其致病性。

Pathogenesis of acephalic spermatozoa syndrome caused by SUN5 Variant

Duo Zhang Wujian Huang Lihong Dong Ying Tang Hui Zhang Guoyong Chen Qingqin Li Xiaoyan Mei Zhihong Wang Fenghua Lan
900 Hospital of the Joint Logistics Team

Background Variants of Sad1 and UNC84 domain containing 5 (*SUN5*) is the main genetic cause of acephalic spermatozoa syndrome (ASS), however, its pathogenesis remains unclear.
Objective To identify the pathogenesis of *SUN5* in ASS.
Methods Whole-exome sequencing was performed on 10 ASS patients. The expression of SUN5, ODF1 and Nesprin3 was detected in normal and ASS sperm by immunohistochemistry and Western blot. Interactions between SUN5 and ODF1, SUN5 and Nesprin3, and ODF1 and Nesprin3 were detected in transfected HEK293T cells by co-immunoprecipitation.
Results Two homozygous variants c.381delA[p.V128Sfs7*] and c.675C>A[p.Y225X] and one compound variant c.88 C>T[p.R30X] and c.381[p.V128Sfs7*] in *SUN5* were identified in 4 ASS patients. c.381delA was pathogenic proved by previous reports. c.675C>A and c.88 C>T were

two novel variants first identified in our study. These two variants led to a premature termination codon (PTC), which resulted in loss of SUN5 and might be pathogenic too. The *SUN5* mRNA and protein hardly be detected in ASS with *SUN5* nonsense mutation. The immunofluorescence analysis showed that distribution of ODF1 and Nesprin3 changed in sperm of ASS with *SUN5* variants. The co-immunoprecipitation analysis indicated that SUN5 and ODF1, SUN5 and Nesprin3, and ODF1 and Nesprin3 interacted with each other in transfected HEK293T cells.
Conclusion Proteins SUN5, Nesprin3, and ODF1 might form a “triplet” structure through interactions at the head-tail junction of sperm. When SUN5 lost caused by gene variants, the “triplet” structure disappears and then the head-tail junction becomes fragile, leading to the occurrence of ASS.

父源杂合、母源 CNV 缺失 GLDC 基因纯合变异甘氨酸脑病 1 例

陆光双 杨武
安徽医科大学附属六安医院（六安市人民医院）

目的 分享 1 例父源杂合、母源 CNV 片段缺失 GLDC 基因纯合变异甘氨酸脑病诊治过程和基因特点，加深对甘氨酸脑病认识。
方法 回顾分析我院 2021 年 1 月确诊的 1 例 GLDC 基因新发突变致婴儿早发型癫痫性脑病临床资料，并复习相关文献。
结果 1）患儿 4 月 13 天男童，3 月龄左右开始出现抽搐，2 天内抽搐 6 次入院，抽搐表现为局灶运动性发作、肌阵挛发作及痉挛发作，生化、脑脊液、头颅 MRI、心脏彩超、血尿串联质谱等无明显异常；视频脑电图示高度失律、清醒期 3 次孤立痉挛发作；全外显子组基因测序示 GLDC 基因 c.1129G>C(p.Ala377Pro)杂合，父亲携带；CNV 检测示 chr9p24.1(6602099-6606679)X1 4.6Kb 缺失（包含 GLDC5-8 号外显子）；母亲指定区段 qPCR 验证结果示 GLDC 基因 5-8 号外显子杂合缺失。2）入院后予丙戊酸钠、维生素 B6、降颅压等治疗，并予激素、丙球冲击治疗，基因结果出来后先后加用右美沙芬、托吡酯、氯硝西泮等，目前随访半年，8 月龄仍不能抬头，每天仍有抽搐发作，1 月前开始予生酮饮食，发作次数减少。
结论 GLDC 基因变异可导致甘氨酸脑病，表现为难治性癫痫、肌张力低下、发育迟缓等，是早发型癫痫性脑病重要病因，苯甲酸盐、右美沙芬及生酮饮食等可能有效。

Identification of a Novel NF1 Variant in one Chinese Family

Weili Shi Bingtao Hao Shixiu Liao
Henan Provincial People's Hospital

Aim Neurofibromatosis type 1 (NF1; OMIM 162200) is an autosomal dominant disease which is caused by variants in the *NF1* gene. This disease is characterized by the presence of multisystem tumors throughout the skin, bones, and nervous system. In order to identify the genetic cause of the disease, genetic testing was performed.
Methods In this study, we customized a targeted gene panel of *NF1*/*NF2* for the clinically suspected as NF1 patients. Sanger sequencing was further performed to verify the variants. This study was carried out in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the participating individual.
Results A novel variants *NF1* (NM_001042492.2): c.2600delT (p.Met867Argfs*11) was identified in the thirteen years old girl. This girl who was found a thoracic mediastinal tumor this time had been performed a surgeon to remove a Nerve sheath tumor in her brain three years ago. This variant co-segregated with the disorder in the pedigree, and it is absent in the gnomAD database. It is classified as a pathogenic variant according to ACMG guideline (PVS1, PM2, PP4)
Conclusion This *NF1* variant broadens the *NF1* variants spectrum. And it is helpful in genetic counseling, even in gene therapies for NF1.

A novel intronic mutation in AIFM1 associates with fatal encephalomyopathy and mitochondrial disease in infant

Xiaomei Lu Qi Peng Keze Ma Chunbao Rao
Dongguan Children's Hospital

AIM To investigate the genetic causes in a patient with fatal encephalomyopathy and mitochondrial disease.
Methods We performed whole exome sequencing (WES) for the infant with mitochondrial encephalopathy and his healthy parents (trio) in a Chinese family in order to detect genetic variants. Bioinformatics analysis was carried out to predict the function of mutant genes. Skin fibroblast cultures were obtained using explants from skin punch biopsies from patient to study the function of intronic variant.
Results WES data analysis, confirmed by Sanger sequencing analysis, identified a novel intronic variant (c.1164+5G>A) in intron 11 of the AIFM1 gene (NM_004208.4) in the proband and his mother. This mutation also exists in his brother who died due to similar symptoms. Analysis of RNA transcripts from fibroblasts of the proband confirmed the deleterious impact of the intronic variant on splicing, causing exon 11 skipping in mature mRNA.
Conclusions This is the first report of a pathogenic variant at intron in AIFM1 gene, which enlarges the mutation spectrum of AIFM1 and points out the necessity of intronic sequence analysis and the importance for integrative functional studies in the interpretation of sequence variants.

Targeted sequencing on 1p22 among non-syndromic orofacial clefts from Han Chinese population

Mujia Li Zhonglin Jia
State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases, Dept. of cleft lip and palate, West China Hospital of Stomatology, Sichuan University

Objective Rs560426 at 1p22 was proved to be associated with NSCL/P (Non-syndromic cleft lip with or without palate) among several populations, including Han Chinese population. Here, we conduct a deep sequencing around rs560426 to locate more susceptibility variants in this region.
Subjects and Methods 2293 NSCL/P cases, 886 NSCPO (Non-syndromic cleft palate only) cases, and 3235 normal controls were recruited in this study. After sequencing, association analysis and burden analysis were performed. RNA sequencing and RT-qPCR were conducted for functional analysis of candidate variant.
Results Association analysis indicated that rs77179923 was specifically associated with NSCLP (P=4.73E-04 ， OR=1.84, 95%CI: 1.31-2.58). Moreover, de novo harmful rare variant NM_004815.3, NP_004806.3; c.1652G>C, p.R551T in *ARHGAP29* was also associated with NSCLP, and it resulted in a decreased expression level of *ARHGAP29*, which in turn affected NSCL/P related biological processes, however, no overt cleft palate (CP) phenotype was observed.
Conclusions rs77179923 and rare variant NM_004815.3, NP_004806.3; c.1652G>C, p.R551T at 1p22 were both associated with NSCLP among Han Chinese population. However, this missense variation contributes to no overt CP phenotype due to dosage insufficient or compensation from other genes. Furthermore, this study indicated genetic heterogeneity among NSCLO, NSCPO and NSCLP.

RNA-binding protein RBMS3 promotes the osteogenic differentiation of C3H10T1/2 and C2C12 cells via repression of Tmem64 mRNA

Yuexin Xu[1] Jing Ma[2] Guohua Xu[3] Duan Ma[1]
1.Fudan University
2.ENT institute, Eye & ENT Hospital, Fudan University
3.Changzheng Hospital, Second Military Medical University

Background and Objects Osteoporosis is a common form of systemic bone disease that is costly to treat and is primarily diagnosed on the basis of bone mineral density. The purpose of this study was to explore the role of RNA binding motif single stranded interacting protein 3 (RBMS3) in osteoporosis.
Methods and Results Quantitative real-time PCR and western blot assay were conducted to corroborate the RBMS3 expression in osteoporotic bone tissues from osteoporotic patients and ovariectomy (OVX) -induced osteoporotic mice. Cell line C3H10T1/2 and C2C12 were transfected with lentivirus to repress Rbms3 expression or overexpress Rbms3 and vector controls. The CCK8 assay and the EdU assay were adopted to examine the effect of Rbms3 on cell proliferation abilities of osteoblast cells. The transwell migration assay and the wound-healing assay were also carried out to detect the effects of RBMS3 on migration of osteoblast cells. Alkaline phosphatase activity assay, alizarin red staining, and quantitativereal-time PCR and western blot assay of osteogenic marker genes were applied to evaluate the activity of osteogenic differentiation. RNA immunoprecipitation sequencing (RIP-seq) assay coupled to RNA immunoprecipitation (RIP) assay, together with dual luciferase reporter assay were employed to screen cellular mRNAs bound by Rbms3 and validate the binding of Rbms3 and Tmem64 mRNA. Direct joint administration of rAAV9-Rbms3-OE was performed to assess bone loss in osteoporotic mice.
RBMS3 expreesion was downregulated in bone tissues from the osteoporotic patients' and OVX-induced osteoporotic mice' compared with normal control groups. Rbms3 depletion resulted in diminished osteogenesis and cell migration, and induced cell proliferation abilities in C3H10T1/2 and C2C12 cell lines. Ectopic Rbms3 expression also contributed to enhanced osteogenesis and cell migration, and reduced cell proliferation abilities in C3H10T1/2 and C2C12 cell lines. Furthermore, Rbms3 promoted the decay of Tmem64 mRNA via a 3′UTR AU-rich element (ARE). Also Rbms3-induced osteogenesis of C3H10T1/2 and C2C12 cell lines could be reversed by forced Tmem64 expression. In vivo, direct joint administration of rAAV9-Rbms3-OE in OVX-induced osteoporotic mice abrogated bone loss and improved bone mechanical properties.
Conclusions Together, our findings uncover important roles of RBMS3 in osteogenesis and osteoporosis through regulation of Tmem64 mRNA, and provide new clues for future therapeutic strategies of osteoporosis.

HOXB6 的下调在非综合征先天性小耳畸形中的致病性研究

杨润[1,3] 李辰龙[3] 陈鑫[1,3] 卢鑫雨[3] 吴培瑄[1] 马竞[3] 马端[1,2] 张天宇[3]
1.复旦大学
2.复旦大学附属儿科医院
3.复旦大学附属眼耳鼻喉科医院

背景 作为最常见的颌面部出生缺陷之一，先天性小耳畸形（Congenital Microtia，CM）是由于胚胎来源的第一、第二鳃弓以及神经嵴细胞（Neural crest cell，NCC）的发育异常所导致的先天性外中耳软骨发育畸形。CM 的全球发病率约为 0.8~17.4/10 000，我国发病率为 3.06/10 000，且呈逐年上升趋势。 CM 的临床表现严重程度可从轻微的耳廓形态畸形到无耳。其中 90%严重的 CM 都伴发传导性耳聋。CM 可以单独发生, 即非综合征型，也可以作为综合征序列征状的重要表现之一。综合征型 CM 往往都是单基因疾病，而且致病基因绝大多数已知。而非综合征型 CM 是环境和遗传因素相互作用所致的复杂性疾病，遗传因素在其中发挥了重要作用。尽管目前已有研究提示部

分基因的序列变异或者表达异常可能参与了非综合征型 CM 的发生发展，但其病因及致病机制仍不明确。

材料与方法 为探究编码基因表达异常在非综合征型 CM 中的作用，我们收集了 10 例三度单侧非综合征型 CM 患者残耳软骨组织和 5 例正常对照（中耳炎患者）耳软骨组织，提取 RNA 进行转录组芯片分析。经过深度生信分析，对挑选出来的候选基因转录水平在 30 对扩大临床样本中进行 qPCR 验证。构建候选基因的过表达真核质粒以及 siRNA 慢病毒质粒，在人软骨细胞系 C28/I2 中上调和下调该基因, 体外观察与软骨发育不良相关的表型。在斑马鱼模型中利用 Crispant 方法敲低该基因，体内观察 NCC 以及与人类中耳软骨同源结构下颌骨的发育情况。

结果 我们挑选出转录因子同源盒基因 B（*HOXB6*），先前报道 *Hoxb6* 全敲小鼠有第一肋骨缺失表型，但未有研究显示其与 CM 有关。芯片分析结果显示其转录水平在非综合征型 CM 患者耳软骨中下调，扩大临床样本也验证了这一变化趋势（p=0.0188）。体外实验显示 *HOXB6* 在 C28/I2 中具有较高的表达丰度，下调 *HOXB6* 后抑制 C28/I2 增殖、促进其凋亡。体内实验显示斑马鱼中 *HOXB6* 的两个同源基因 *hoxb6a*、*hoxb6b* 高表达于胚胎咽弓发育的关键时期（12-48hpf）。分别敲低 *hoxb6a*、*hoxb6b* 后，斑马鱼下颌骨间充质中的 NCC 数量均显著减少，下颌骨均发育异常。

胰岛素基因突变致永久性新生儿糖尿病一例

沈凌花 杨海花 付东霞 杨威 陈永兴 卫海燕
郑州大学附属儿童医院 河南省儿童医院 郑州儿童医院

目的 报道一例胰岛素基因内含子区突变致永久性新生儿糖尿病（PNDM）的临床和遗传学特点。

方法 对郑州大学附属儿童医院 2019 年 12 月诊断的一例 PNDM 患儿的临床特征、实验室资料进行分析；运用二代测序技术对先证者基因测序，对发现的突变运用 Sanger 测序技术验证突变父母来源。

结果 先证者检测到胰岛素基因（NM_000207.2）一个内含子区杂合变异 c.188-31G>A，患儿父母未检出该突变。c.188-31G>A 突变导致内含子 3′端插入 29 个核苷酸的异位拼接位点，导致转录翻译成异常蛋白质产物导致 PNDM，国内 PNDM 患者中目前尚未见该突变报道。

结论 中国人群存在胰岛素基因 c.188-31G>A 突变导致的 PNDM，口服格列苯脲无效，需要胰岛素治疗。临床上可疑 PNDM 患者应早期行胰岛素基因检测。

先天性高胰岛素血症 40 例临床特征和遗传学分析

沈凌花 付东霞 张英娴 李杨世玉 杨威 陈永兴 卫海燕
郑州大学附属儿童医院 河南省儿童医院 郑州儿童医院

目的 对 40 例先天性高胰岛素血症(CHI)患儿的临床特征及致病基因携带情况进行总结及分析。

方法 收集郑州大学附属儿童医院 2015 年 4 月至 2021 年 4 月收治的 40 例 CHI 患儿临床资料，并应用高通量测序技术检测 CHI 相关致病基因，利用 Sanger 测序对患儿变异位点进行验证，并对父母样本该位点进行分析，确定突变来源。

结果 40 例（男 17 例，女 23 例）患儿，平均出生体重 3 646g，12.5%（10/40）系巨大儿，67.5%（27/40）生后 3 月内起病，85%（34/40） 出现抽搐。50%（20/40）携带 CHI 已知致病基因。12 例(30％)患儿携带 ABCC8 基因突变：携带复合杂合突变者 1 例 ，携带 ABCC8 母系遗传突变者 2 例，携带 ABCC8 父系遗传突变者 6 例，携带 ABCC8 新生突变者 3 例，5 例应用二氮嗪进行治疗有效，7 例二氮嗪无效者其中 5 例奥曲肽治疗有效，2 例行胰腺切除术，1 例术后血糖正常，1 例术后仍应用奥曲肽治疗。 3 例(7.5%)患儿携带 GLUD1 基因突变：应用二氮嗪进行治疗，均有效。2 例(5%)患儿携带 INSR 基因突变：1 例奥曲肽治疗有效，1 例二氮嗪治疗无效，行胰腺切除术。1 例(2.5%)患儿携带 GCK 基因突变，突变来源未知，对二氮嗪治疗无效，行胰腺切除术。1 例(2.5%)患儿携带 HADH 基因纯合突变，突变来自父母，对二氮嗪治疗有效。1 例(2.5%)患

儿携带 SLC16A1 基因突变，为父系遗传，对二氮嗪治疗有效。发现 ABCC8 基因 3 个新的错义突变位点（Exon37:c.4451G>A；Exon33:c.4078G>C；Exon9:c.1433C>A）。
结论 ABCC8 基因突变和 GLUD1 基因突变是 CHI 的主要致病基因，INSR、GCK、HADH 和 SLC16A1 基因突变所致 CHI 为罕见类型，不同基因突变类型对药物治疗反应不同，二氮嗪或奥曲肽仍为首选治疗方案。发现 ABCC8 基因 3 个新的突变位点，丰富了基因突变谱。

DNA Methylation Profile of Lip Tissue from Congenital Non-syndromic Cleft Lip and Palate Patients by Whole Genome Bisulfite Sequencing

Bowen Zhang[1] Jing Ma[1,3] Duan Ma[1,2]
1.Fudan University
2.Children's Hospital of Fudan University
3.ENT institute, Eye & ENT Hospital, Fudan University

Backgrounds Congenital non-syndromic cleft lip and palate (NSCLP) is one of the most common malformations worldwide. DNA methylation has been implicated in many diseases. However, its involvement in lip tissue from NSCLP is not well understood. This study aimed to investigate the role of dysregulated DNA methylation in NSCLP.
Methods and Results DNA methylation profile was determined in 8 injured and 5 self normal lip tissue samples from children with NSCLP by Whole Genome Bisulfite Sequencing (WGBS). By differential methylation region (DMR) analysis with stringent bonferroni multiple testing correction, a total of 2711 DMRs, corresponding to 1231 genes were identified. Given the important role of promoter methylation in regulating gene expression, the promoter DMR-related genes were concerned. The enriched biological processes and pathways analysis suggested some of them were related with NSCLP.
299 genes with methylation difference in promoter regions were selected out. There into, the very known NSCLP susceptibility gene, GLI Family Zinc Finger 2 (*GLI2*) with unknown role of its DNA methylation in NSCLP was selected. The promoter hypomethylation and higher mRNA expression level of *GLI2* were observed in injured lip tissues by another extended samples verification. Moreover, dual luciferase reporter assay indicated that promoter hypermethylation of *GLI2* inhibited its transcription.
Conclusions Overall, this study implicated that abnormal DNA methylation in lip tissue may be correlated with the pathogenesis of congenital NSCLP.

湖州地区不育男性 Y 染色体微缺失情况对妊娠结局影响的研究

丁忠英 邵生声
湖州市妇幼保健院

目的 本研究主要是了解湖州地区不育男性患者（非阻塞性无精症或严重少精症）Y 染色体微缺失频率分布及其对妊娠结局的影响。
方法 2016 年 1 月至 2020 年 6 月期间于本院就诊的不育男性进行回顾性队列研究，采集 744 名不育男性患者精液分析、激素水平、Y 染色体微缺失（AZF 缺失）、阴囊探查、睾丸活检和精子提取等检测数据。
结果 744 例患者 AZF 缺失率为 7.8%，将精子浓度阈值降低到 50 万/毫升，敏感性依旧 100%，特异性提高到 35%，并显著节约成本。在 43 例 AZFc 患者中，7 例经 TESE 后获得睾丸成熟精子(16.3%)，经 ICSI 治疗后，临床妊娠率和胚胎着床率只有 25.6%和 2.3%，与 AZF 未缺失不育患者比较，差异有统计学意义。

结论 本研究了解了中国湖州地区不育男性患者 AZF 缺失情况，且发现低精子浓度（50 万/毫升）可以在不影响灵敏度情况下提高不育男性 AZF 基因检测的特异性，从而提高不育患者受精成功率。

唇腭裂相关基因 IRF6 新突变位点 c.C748T 的确定及其分子机制的初探

李娜[1] 谢雨琪[1] 崔人婕[1] 胡颖熹[1] 张进[1] 马端[1,2]
1.复旦大学
2.复旦大学附属儿科医院

背景 干扰素调节因子-6(IRF6)基因是唇腭裂（CL/P）候选基因之一,研究表明其突变可导致 Van der Woude 综合征(VWS)以及胭窝翼状胬肉综合征(PPS), 也参与 NSCL/P 的发病,目前认为单纯性唇裂或腭裂发生的 12%的遗传因素可归因于 IRF6 基因的变异。IRF6 在口腔及颌面部发育中起到重要作用,但其作用的分子机制，以及 IRF6 突变蛋白的病理机制均有待阐明。
材料方法与结果 本研究在一中国汉族家系中，首次鉴定出 IRF6 c.C748T(p.R250X)新突变位点，在人口腔角质细胞分别上调野生型 IRF6 和 IRF6 c.C748T(p.R250X)突变表达基因，通过 RNA-seq 对比分析了 c.C748T 突变基因对口腔角质细胞基因表达的影响。
与野生型 IRF6 基因相比，c.C748T 突变基因表达细胞中，TGFβ 表达及其通路相关蛋白表达降低，另外 TGFβ 相关非编码 RNA TGFB2-AS 的表达也显著降低。还发现 c.C748T 突变基因表达细胞中，凋亡相关蛋白 CASP14 的表达显著升高。
结论 已有研究表明，TGFβ 通路在腭板发育过程具有重要的功能，抑制其活性可直接抑制腭板融合，而上皮细胞凋亡在腭板融合中亦发挥重要作用，本研究提示 TGFβ 通路以及 CASP14 是唇腭裂突变致病基因 IRF6 重要的下游基因。

高通量连接探针扩增技术联合染色体微阵列分析技术在早期自然流产遗传学诊断中的应用

王艳
南京市妇幼保健院

目的 探讨高通量连接探针扩增（High-throughput ligation-dependent probe amplification, HLPA）联合染色体微阵列分析（Chromosomal microarray analysis, CMA）技术在早期自然流产遗传学诊断中的应用价值。
方法 收集 2020 年 2 月至 2021 年 2 月在南京市妇幼保健院就诊的早期自然流产病例 722 例，分离流产绒毛样本并提取基因组 DNA，采用荧光定量 PCR（QF-PCR）技术排除严重母体污染样本后，对无/轻度母体污染绒毛样本进行 HLPA 检测，HLPA 检测阴性的样本进一步行 CMA 检测。
结果 排除 10 例严重母体污染样本后，共计纳入 712 例流产绒毛病例，QF-PCR/HLPA 联合 CMA 技术对早期自然流产病例总体染色体异常检出率为 60.8%（433/712），其中偶发性流产为 62.6%（269/430），复发性流产为 58.2%（164/282）。
结论 QF-PCR/HLPA 联合 CMA 技术具有快速、准确、便宜等优势，有望在早期自然流产遗传学诊断中得以推广。

在汉族 PKU 患者 PAH 基因中筛选和鉴定一个新的缺失变异

杨帆 [1,2,3]
1.遵义医科大学附属医院
2.上海交通大学 Bio-X 研究院
3.广州医科大学附属第三医院

目的 苯丙酮尿症（Phenylketonuria，PKU）是常见的单基因遗传病。前期，我们对山东省临沂地区的 PKU 和高苯丙氨酸血症（Hyperphenylalaninemia，HPA）患者开展了全面的遗传诊断，以提供遗传咨询，辅助患者治疗和优生优育。
方法 利用一代测序对 111 例 PKU 或 HPA 患者及其父母的 *PAH* (Phenylalanine hydroxylase)基因全外显子序列进行检测与分析。
结果 在一例 PKU 患者（血液 Phe 浓度为 1502 mmol/L）中同时鉴定了一个全新的 8 bp 缺失变异 *PAH*: c.1034_1041del (p.G346fs)和致病变异 c.728G>A (p.R243Q)，二者形成复合杂合变异。溯源结果显示该缺失变异遗传自母亲，而错义变异遗传至父亲。该缺失变异致使 PAH 蛋白质翻译阅读框移码，并产生一个使翻译提前终止的密码子。qRT-PCR 和免疫印迹实验结果显示，相比于野生型 *PAH*，纯合变异 c.1034_1041del 使 *PAH* mRNA 的表达水平降低约 70%，且使 PAH 蛋白质表达量显著降低约 90%，且蛋白分子量减小。酶活性检测结果显示，纯合变异 c.1034_1041del 使 PAH 酶活性几乎完全丧失。此外，我们在一例 HPA 患儿（确诊的 Phe 浓度为 283 mmol/L）中发现了复合杂合变异：错义变异 *PAH*: c.301G>A (p.D101N)和缺失变异 c.208_210del (p.S70del)，qRT-PCR 和酶活性检测结果显示，纯合变异 c.301G>A 使 *PAH* mRNA 表达量降低约 40%，且使 PAH 酶活性降低约 10%。
结论 遗传学、分子生物学和临床证据表明，新发的缺失变异 c.1034_1041del (p.G346fs)具有明确的致病性，而 c.301G>A (p.D101N)是很可能具有轻度致病性的变异。

Cytogenetic and molecular analysis of distal 4q duplication with distinctive phenotype in Chinese population

Jianlong Zhuang Yuying Jiang
Quanzhou women's and children's hospital

Aims Little information is available on the partial trisomy 4q; the genotype-phenotype correlation is poorly understood. Herein, two families with partial distal 4q duplication were described in Chinese population.
Methods Two pedigrees with 4q duplication were enrolled in this study. Karyotyping and single-nucleotide polymorphism (SNP) array detection were performed for prenatal diagnosis. FISH analysis was performed to further verify the copy number variants.
Results In this study, two families with partial trisomy 4q were identified. The fetus in pedigree 1 exhibited multiple ultrasound anomaly including inter uterine growth restriction and atrioventricular septal defect, had a duplication of 4q28.3-qter associate with 6p25.2-p25.3 deletion, which resulted from a balanced translocation in his father t(4;6)(q28.3;p25.2). The fetus in pedigree 2 had a distal 4q28.3-qter duplication associated with monosomy of Xp21.3-p22.3, the karyotype was described as 46,XX,der(X)t(X;4)(p21.3;q28.3), which originally inherited from the pregnant woman who exhibited clinical phenotype limited to short stature.
Conclusions In this study, partial trisomy 4q associate with monosomy 6p or Xp deletion were first identified in Chinese population. Moreover, our finding further strengthens that normal phenotype in 4q duplication may due to the spreading of X inactivation to the autosomal in derivation of chromosome X.

全基因组测序揭示深部内含子突变在神经发育障碍相关疾病中的作用

史蒙蒙[1,2,3,4] 董梓瑞[4] 陈兢思[2,3,5] 庄淑贞[6] 蔡光伟[4] 陈敦金[1,2,3] 曹也[4,6]
1.广州医科大学附属第三医院 妇产科
2.广州市妇产科研究所
3.广东省产科重大疾病重点实验室
4.香港中文大学妇产科学系
5.广州医科大学附属第三医院 产前诊断科
6.香港中文大学儿科学系

目的 神经发育障碍(NDDs)是一类具有高度临床和遗传异质性的疾病。目前临床常规的遗传学检测技术无法通过单一的平台全面检测各类遗传变异。因此，仍有大量患者无法明确诊断。本研究基于全基因组测序(WGS)全面检测不同遗传变异（包括单核苷酸变异[SNVs/InDels]，拷贝数变异[CNVs]和染色体重排[SVs]）的能力，探究 NDDs 患者的遗传病因学。
方法 自 2018 年至 2020 年我们从香港中文大学遗传门诊招募了 22 个患有 NDDs 且常规遗传学检测（染色体核型、芯片或全外显子组测序）未明确诊断的核心家系。对其行 WGS (深度>30X)，基于自主研发的分析流程，全面分析 SNVs/InDels，CNVs 和 SVs。体外 minigene 实验用于相关突变的致病性验证。
结果 我们在 10 例（47.6%）患儿中发现与临床表现高度相关的突变，其中 3 个突变位于深部内含子区域 (超出内含子-外显子交界区 20bp)。体外 minigene 实验对其中一个位于 5q32 的深部内含子突变验证，发现该突变在内含子区域产生新的剪切供体，与经典的剪切位点发生竞争，最终产生异常剪切体，引发无意义介导衰变。
结论 本研究发现与 NDDs 相关的遗传突变可涉及编码及非编码区。WGS 可以全面检测不同基因组变异，是诊断这类疾病理想的技术手段。然而在分析 WGS 的数据过程中将会产生大量的临床意义不明的变异，适当采取功能学验证将有助于数据的分析。

遗传性易栓症合并妊娠一例

赵璐 贺晓菊
南昌大学第二附属医院

遗传性易栓症是指静脉血栓形成的遗传倾向。其最常见的病因是凝血因子Ⅴ Leiden（FVL）突变和凝血酶原基因突变（PGM），蛋白 S 缺乏、蛋白 C 缺乏和抗凝血酶（AT）缺陷占据了其余病例中的绝大部分。亚甲基四氢叶酸还原酶（MTHFR）（C677T，1298C）的纯合突变是血浆同型半胱氨酸水平轻度升高的也是一种相对常见的病因。本例患者遗传性易栓症合并妊娠，其因蛋白 S 基因突变引起易栓症。

OFD1 基因突变导致口面指综合征一家系报道

程青青
河北省人民医院

目的 对一位拟诊为口面指综合征 I 型（OFD1）的患者进行遗传学诊断，并进行家系验证，探讨基因型与临床表型之间的关系，提供遗传咨询意见。
方法 收集患者及近亲的临床资料和外周血样本，对患者行全外显子组基因检测（whole exome sequencing, WES）,并针对发现的基因突变位点进行家系验证及分析。
结果 WES 结果提示患者 OFD1 基因（NM 003611.2）存在 c.224A＞G（p.Asn75Ser）杂合突变，家系验证提示患者的妹妹及母亲存在相同的杂合突变，但三者的临床表型差异较大。患者表现

为先天性口面指畸形：面部不对称、鼻根和眼距较宽、口腔系带增生、口腔内牙齿发育不良伴部分缺如、错位牙、分叶舌、舌错构瘤（婴儿期已行手术治疗）、小下颌等，左手小指呈弯曲状，右手小指与无名指并指，智力发育和语言表达能力低于常人；患者母亲表现为上唇正中裂，牙齿及舌头症状与患者类似；而患者妹妹仅表现为轻度舌异常。

结论 口面指综合征 I 型的临床表现差异性较大，未发现基因型与表型有明显相关性，轻症患者易漏诊。

生成延长 β-珠蛋白肽链的 HBB:c.313delA 的表型及分子特征研究

林宛颖
南方医科大学基础医学院

目的 β-地中海贫血具有丰富的突变谱，同时在修饰基因的作用下，其表型具有高度异质性。我们注意到先前报道的一个发生在第二外显子末端的移码突变 HBB:c.313delA 被归类为为 β^0-地贫，而其它相邻位置或生成相似延长珠蛋白肽链的变异却表现为显性遗传。本研究通过扩大家系分析及体内外分子实验对该突变进行基因型及表型的关联分析研究。

方法 扩大家系分析并进行系统的临床表型信息收集，利用 NGS 和 Sanger 测序完成基因检测分析。利用体外转染的 293T 细胞和先证者外周血 $CD235^+$细胞，在转录、翻译及蛋白层面上研究变异对 *HBB* 基因功能产生的影响。对比研究变异 β-珠蛋白链的氨基酸序列及蛋白质三维结构，分析变异蛋白的结构及功能改变。

结果 先证者是 HBB:c.126_129delCTTT 和 HBB:c.313delA 的重型地贫患者，而存在该变异的家庭成员均存在小细胞低色素贫血。HBB:c.313delA 是移码突变，移码后终止密码子向后移动 10 位，生成的 β-肽链延长了 10 个氨基酸。

结论 在本研究中，通过综合系统的临床表型数据、系列的体内外分子实验及蛋白结构预测分析共同阐明 HBB:c.313delA 的基因型与表型的关系。最后我们总结该突变的临床表型与突变 mRNA 的合成、突变蛋白的降解和包涵体的出现有关。

甲状腺肿大、月经稀发——甲状腺激素抵抗综合征

曾芳芳
上海市华山医院

目的 通过全外显子基因测序，鉴别 TSH 瘤和甲状腺激素抵抗综合征。

方法 一例 26 岁女性患者，因“甲状腺肿大 12 年，月经稀发 2 年”发现甲状腺功能异常。甲状腺功能呈现 FT_3、FT_4 升高伴 TSH 轻度升高，外院曾考虑甲亢行放射性碘治疗。治疗后多个医疗机构多次复查甲状腺功能，均呈现 FT_3、FT_4 升高伴 TSH 轻度升高，而促甲状腺素受体抗体阴性。奥曲肽抑制试验 TSH 抑制率 70%。垂体增强 MRI 提示垂体约 1cm 占位。TSH 瘤与甲状腺激素抵抗综合征鉴别困难。完善家属甲状腺功能检测，父亲及弟弟呈现类似表现，目前甲状腺功能正常。临床考虑甲状腺激素抵抗综合征可能大。与患者及家属充分沟通后，完善全外显子基因检测。

结果 患方知情同意后，提取其外周血 DNA，进行全外显-单项的检测和分析，发现 THRB 基因杂合变异 c.1312C>T(p.R438C)。明确诊断甲状腺抵抗综合征。

结论 临床上，对促甲状腺激素不适当分泌综合征患者，临床拟诊甲状腺激素抵抗综合征患者，建议行全外显子基因检测，助力临床诊疗。

一例 PEX13 复合杂合突变导致的 Zellweger 综合征谱系障碍

李悦 刘毅 李晓莺 盖中涛
山东大学齐鲁儿童医院

目的 PEX13 编码过氧化物酶体膜上的整合蛋白，调节过氧化物酶体基质蛋白的转入，其突变导致的过氧化物酶体生物合成障碍（PBD）与 Zellweger 综合征谱系障碍(ZSS)密切相关。作为一种罕见的常染色体隐性遗传病，ZSS 在北美的出生流行率约为 1/50000，在日本约为 1/500000。本文报道了一例临床症状较典型的患儿，并对其进行遗传学分析以明确病因。
方法 对患儿进行临床和实验室检查，利用高通量外显子捕获测序技术对患儿样本进行检测，就与临床表型高度相关的突变位点进行了生信分析，并对该家系样本进行 Sanger 测序验证。
结果 该男性患儿眼距宽、鼻梁低平，左侧隐睾，四肢肌张力低下，偶有不自主抖动，颅缝开裂，有颅内出血及轻度脑积水，右侧枕、颞区有似痫性放电，生化检查提示肝功损害。测序发现患儿 PEX13 基因存在复合杂合突变：c.350_353dupGATT(p.F118Lfs*7)与 c.980C>T(p.P327L)，经 Sanger 测序验证其分别来自于母亲及父亲。经查数据库发现，移码突变 p.F118Lfs*7 及错义突变 p.P327L 均未在 ExAC 等正常人数据库中检出，SIFT 及 PolyPhen-2 预测突变 p.P327L 为有害。利用同源建模平台 SWISS-MODEL 分别模拟了两种突变后的蛋白结构，并借助 mCSM 平台预测了蛋白稳定性变化。
结论 该患儿为 PEX13 基因复合杂合突变导致的 Zellweger 综合征，其携带的两种突变均未见报道，该病例拓展了中国人群的 ZSS 突变谱，对产前诊断及遗传咨询具有指导意义。

De novo HBB frameshift mutation in a patient with dominant β-thalassemia major

Xiaoman Zhou
Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University

Background β-Thalassemia is an autosomal recessive disease with diverse clinical phenotypes. Although the underlying disease-causing mutations in *HBB* gene encoding hemoglobin subunit β have been extensively characterized, identification of other currently unknown mutations is still required.
Methods We investigated a 3-year-old Chinese boy with severe anemia with no known *HBB* mutations. We used next-generation sequencing to identify underlying disease-causing mutations and verified the results by Sanger sequencing. We also confirmed the identities of the proband's parents and conducted chimerism analysis to determine the origin of the mutation. *In vitro* validation was carried out to assess the effect of this novel mutation.
Results We identified a *de novo* heterozygous frameshift mutation (HBB:c.399delA) at codon 133 at exon 3 of *HBB* in a child with β-thalassemia major. Based on structural prediction and subsequent *in vitro* functional validation, we demonstrated that this novel mutation would lead to an elongated stop codon, thus producing an elongated β-globin chain with 10 additional amino acids at the COOH terminus. Furthermore, the HBB:c.399delA mutation remarkably reduced *HBB* gene expression.
Conclusion We identified a novel form of dominant β-thalassemia caused by a *de novo* frameshift mutation (HBB:c.399delA) in a β-thalassemia major child. This mutation led to dominant β-thalassemia without detectably abnormal hemoglobin.

反复乏力伴低钾血症——Gitelman 综合征

刘文娟 张烁 杨叶虹 龚伟 何敏 张朝云 叶红英
复旦大学附属华山医院

目的 临床表现为不明原因低钾血症、代谢性碱中毒且血压正常或偏低的患者，通过全外显子基因测序，协助诊断 Gitelman 综合征
方法 三例青中年男性患者，均表现为无明显诱因下出现反复发作性低钾血症，既往均无高血压病史，且均无家族中其他成员出现类似表现。双侧肾上腺影像学未提示明显占位性病变，激素水平无明显异常。电解质结果示低血钾、低血氯、低血镁，尿氯化物排泄增加、尿钙排泄减少，同时伴血碳酸氢根升高。临床考虑 Gitelman 综合征诊断可能性大。与患者及家属充分沟通后，完善全外显子基因检测。
结果 患方知情同意后，提取其外周血 DNA，进行全外显-单项的检测和分析，3 例患者分别发现 SLC12A3 基因纯合变异 c.911C>T (p.T304M)、SLC12A3 基因纯合变异 c.1084G>A (p.G362S)、SLC12A3 基因杂合变异 c.676G>A (p.A226T)和 c.2786T>C (p.L929P)。结合既往文献和病例报道，明确诊断 Gitelman 综合征。
结论 经典的 Gitelman 综合征患者远端小管噻嗪类敏感性 NCC 的编码基因（SLC12A3）发生了突变，产生类似于持续性噻嗪类利尿剂的作用。由于该类患者肾小管缺陷无法得到矫正，故可通过使用非甾体类抗炎药、血管紧张素抑制剂、口服补充钾镁等方法控制患者低钾症状的发作。因此，临床实践中，对疑诊 Gitelman 综合征的患者，建议行全外显子基因检测，助力临床诊疗。

SHARPIN Promotes Melanoma Progression via Rap1 Signaling Pathway

Liang Yanhua
Shenzhen Hospital of Southern Medical University

SHARPIN, as a tumor-associated gene, is involved in the metastatic process of many kinds of tumors. Herein, we studied the function of SHARPIN in melanoma metastasis and the relevant molecular mechanisms. We found that SHARPIN expression was increased in melanoma tissues and activated the process of proliferation, migration and invasion *in vitro* and *in vivo*, resulting in a poor prognosis of the disease. Functional analysis demonstrated that SHARPIN promoted melanoma migration and invasion by regulating Rap1 and its downstream pathways, including p38 and JNK/c-Jun. Rap1 activator (8-pCPT-2'-O-Me-cAMP) and inhibitor (ESI-09 and farnesylthiosalicylic acid-amide) treatment could partially rescue invasion and migration of tumor cells. Additionally, SHARPIN expression in cell lines and public datasets also indicated that factors other than BRAF and N-RAS contribute to SHARPIN activation. In conclusion, our broad-in-depth work suggested that SHARPIN promoted melanoma development via p38 and JNK/c-Jun pathways through upregulating Rap1 expression.

经济版一家三口的全基因组测序技术诊断危重症新生儿遗传病

肖非凡 吴冰冰 卢宇蓝 董欣然 程国强 彭小敏 杨琳 王慧君 周文浩
复旦大学附属儿科医院

目的 探讨经济版一家三口的全基因组测序技术（optimized trio genome sequencing, OTGS）在危重症新生儿疾病中的应用价值。
方法 纳入 2019 年 8 月至 2019 年 9 月在复旦大学附属儿科医院使用 OTGS 的 15 例患儿。OTGS 患儿样本的测序深度为 4×～50×，患儿父母样本的测序深度为 8×～10×。结合父母的测序数据、患儿的临床特征，分析患儿基因检测结果及转归和结局。

结果 15 例患儿中男 9 例，女 6 例；早产儿 8 例，足月儿 7 例；剖宫产 9 例，顺产 6 例。主要入院原因为呼吸异常 7 例，反应差 2 例，喂养困难 2 例，发热、低体温、早产、抽搐各 1 例。OTGS 平均检测周期为 94 小时。结果显示，4 例患儿获得基因诊断，诊断阳性率为 26.67%（4/15）。检测出的 4 例阳性致病基因分别为 *PTPN11*、*CHD7*、*COL11A1* 和 *PHOX2B*。在基因诊断阳性的患儿中， 3 例患儿基因检测结果可解释病因，但因病情较重，父母最终放弃治疗，自动出院后死亡; 1 例患儿于送检样本当日死亡，基因检测结果可解释病因。

结论 OTGS 技术具有快速高效但又相对经济的特点，可为临床怀疑为遗传病的危重症新生儿提供全面的、快速的、高性价比的遗传检测技术，节约遗传检测的时间窗，为临床处置危重症病例提供遗传依据。

Neonatal metabolic acidosis in the neonatal intensive care unit: what are the genetic causes on ?

Haiyan Ma[1] Feifan Xiao[2] Yulan Lu[2] Xinran Dong[2] Bingbing Wu[2] Wenhao Zhou[2] Huijun Wang[2]
1.Zhuhai Women and Children's Hospital
2.Children's Hospital of Fudan University

Background Neonatal metabolic acidosis (NMA) is a common problem, particularly in critically ill patients in neonatal intensive care units (NICUs). Complex etiologies and atypical clinical signs make diagnosis difficult; thus, it is crucial to investigate the underlying causes of NMA rapidly and provide disorder-specific therapies. Our study aims to provide an overview of the genetic causes of NMA in patients from NICUs.
Methods We performed next-generation sequencing (NGS) on neonates with NMA from January 2016 to December 2019. Clinical features, genetic diagnoses, and their effects on clinical interventions were collected for analysis.
Results In the 354 enrolled patients, 131 (37%) received genetic diagnoses, with 95 (72.5%) autosomal recessively inherited diseases noted. Two hundred and fifteen variants spanning 57 genes were classified as pathogenic (P) or likely pathogenic (LP) in 131 patients. The leading cause was metabolic disorders due to 35 genes found in 89 patients (68%). The other 42 NMA patients (32%) with 22 genes had malformations, renal, neuromuscular, and immune-hematological disorders. Seven genes (MMUT, MMACHC, CHD7, NPHS1, OTC, IVD, and PHOX2B) were noted in more than four patients, accounting for 48.9% (64/131) of the identified pathogenic/likely pathogenic variants. NMA was corrected in 64.9% (85/131) diagnosed patients.
Conclusions In conclusion, 37% of neonates with metabolic acidosis had genetic disorders. NGS should be considered when investigating the etiology of NMA in NICUs. Based on early molecular diagnoses, valuable treatment options can be provided for some genetic diseases and achieve better outcomes.

De novo Frame-shift mutation of CTNNB1 identified by Whole-exome sequencing in a patient with Familial Exudative Vitreoretinopathy

Yunqi He
Sichuan Provincial Key Laboratory for Human Disease Gene Study, Center for Medical Genetics, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China

Purpose To extend the Familial Exudative Vitreoretinopathy (FEVR) related mutational spectrum and to characterize the pathological defects in the *de novo* frame-shift mutation in *CTNNB1* from the FEVR patient.
Methods This work evaluated a patient with FEVR by detailed clinical ophthalmic examinations. Whole-exome sequencing data analysis, Sanger sequencing validation, and segregation analysis were used to identify FEVR-related mutations. Dual-luciferase reporter assay, Western blotting,

and coimmunoprecipitation (co-IP) were used to characterize the functional change of the affected protein. A quantitative real-time PCR assay was performed to investigate the Norrin/β-Catenin downstream protein expression levels with β-Catenin depletion in human retinal endothelial cells (ECs).
Results We identified one *de novo* frame-shift heterozygous variant in *CTNNB1*: c.307 delT (p.Leu103*). β-Catenin activation in the TOPflash reporter of the mutant protein was remarkably reduced compared with that of the wild-type protein. The frame-shift mutation destabilizes the protein and caused truncation. The truncation endows mutation in *CTNNB1* in HEK 293T with decreased AXIN2 expression and with reduced cell adhesion ability. The deletion of *CTNNB1* in human retinal endothelial cells downregulates Norrin/β-Catenin signalling in mRNA level.
Conclusion We report one *de novo CTNNB1* mutations causing FEVR. Importantly, this mutation encoded loss-of-function truncated β-Catenin, leading to the inhibited Norrin/β-Catenin signalling and reduced cell adhesion ability. These findings reinforced the current Norrin/β-Catenin paradigm of FEVR pathogenesis and enlarged the FEVR-causative *CTNNB1* mutation spectrum.

人源化 GBA 基因 F213I 突变戈谢氏病小鼠模型的建立和分析

郭珈妮[1] 李娜[1] 崔人婕[1] 胡颖熹[1] 葛润生[1] 姜楠[1] 张进[1] 马端[1,2]
1.复旦大学
2.复旦大学附属儿科医院

目的 戈谢氏病是由于葡萄糖脑苷酶（GCase）缺陷引起的溶酶体贮积病。目前已报道的发生在编码 β-葡萄糖脑苷酶（GBA）的基因上的、可引起戈谢氏病的突变有三百余种，其中我国人群最常见的依次为 L444P、F213I。为获取符合我国流行病学且可用于基因修饰治疗 GD 小鼠模型，我们构建了引入 F213I 突变的 Gba 基因部分人源化小鼠。
方法 我们在体外将小鼠 Gba 的 6-8 外显子换成了人的 5-7 外显子，构建出部分人源化的 cDNA。另一组在人源化基础上引入 F213I 突变。将上述两种 cDNA 连同鼠野生型 Gba 的 cDNA 过表达载体转入 GBA 缺陷的人 293A 细胞中，于体外表达 GCase 并测定酶活性。之后我们采用 ES 细胞打靶的方式，对 Gba 基因进行部分人源化并引入 F213I 突变，通过突变杂合子代小鼠交配获得突变纯合小鼠，进行表型观察、组织切片染色和 GCase 酶活性测定。
结果 体外测定显示部分人源化的 GCase 酶活性和野生型无明显差异，引入 F213I 的一组 GCase 活性明显下降。突变纯合小鼠在出生后 24 小时内死亡，其表皮角质层嗜碱性，与野生型的嗜酸性角质层有明显差异。突变纯合小鼠的大脑、肝脏、表皮 GCase 酶活性均显著降低。
结论 Gba 部分人源化对小鼠 GCase 活性影响不明显；F213I 突变可导致突变小鼠大脑、肝脏及表皮酶活显著降低，小鼠最终死于表皮屏障受损。

EXT1 基因一无义突变导致遗传性多发性骨软骨瘤的遗传学研究

施宏彪[1] 刘奇迹[1] 刘琦[2] 宋立军[2] 李曦[1] 孙文杰[1] 李江夏[1]
1.山东大学基础医学院医学遗传学系，实验畸形学教育部重点实验室
2.山东大学齐鲁医院风湿科

目的 寻找一常染色体显性遗传性多发性骨软骨瘤（hereditary multiple exostoses，HME）家系的致病基因，确诊该疾病并且为该家系成员的遗传咨询和产前诊断提供帮助。
方法 采集该家系各成员外周静脉血样本，提取基因组 DNA，对先证者进行全外显子组测序，之后根据测序结果，对全体成员进行 Sanger 测序。
结果 遗传性多发性骨软骨瘤是一种罕见的遗传性疾病，表现为多发性软骨覆盖的骨突出，多发生在长骨干骺端，也可发生在长骨骨干。此外，扁骨、脊椎和肋骨也可能受到影响，但通常不会影响到颅骨。患者通常表现出腿部、手部和前臂畸形。儿童早期发病，男性比女性更严重，病变继续生长直至骨骺板闭合。

本课题组收集了一遗传性多发性骨软骨瘤家系。该家系共有 3 代，共 12 名成员，为典型的常染色体显性遗传。临床初步诊断为遗传性多发性骨软骨瘤。对先证者进行全外显子组测序，结果发现患者中 *EXT1* 基因存在 c.1091G>A（p.W364X）无义突变，Sanger 测序证实该突变在家系中与表型共分离，根据 ACMG 评价，此变异为可能致病。

结论 该家系根据临床表现初步诊断为遗传性多发性骨软骨瘤，遗传学分析发现该家系由 *EXT1* 基因 c.1091G>A（p.W364X）无义突变导致，该变异尚未见报道，为一新的致病变异。本研究结果丰富了 *EXT1* 基因突变谱，可用于家系成员的症状前诊断，对该家系成员的未来生育给予遗传指导。

Advances in the genetics of congenital ptosis

Peixuan Wu[1] Jing Ma[1,3] Tianyu Zhang[3] Duan Ma[1,2]
1.Fudan University 2. Children's Hospital of Fudan University
3.ENT institute, Eye & ENT Hospital, Fudan University

Congenital ptosis is a common ophthalmologic condition, characterized by the drooping of the upper eyelid. It presents at birth or by 1 year of age, either in isolation or as a part of many different systemic disorders. The estimated prevalence of ptosis varies between 0.79 and 1.99 per 10,000 people in different populations, and it is more common in males. The underlying causes of congenital ptosis are thought to be myogenic and neurogenic, related to the development of muscles and nerves. Although most cases are sporadic, there are familial transmission characteristics, including autosomal dominant, recessive mode and X-linkage inheritance patterns. Moreover, some forms have been reported that are due to chromosomal aberrations and mutations and deletions in mitochondrial DNA. Genes associated with simple congenital ptosis are ZFHX4 and COL25A1. The clinical aspects of various syndromes involving congenital ptosis are partly related to single gene mutations. However, the pathogenesis of congenital ptosis is not fully understood. At present, surgical correction is still a commonly used treatment. In this article, we discuss the anatomy and histopathology of congenital ptosis. We focus on the genetic aspects of congenital ptosis and associated syndromes.

Identification of a double mosaic aneuploidy screening by NIPT with karyotype of 47,XY+21/47,XXY/46,XY

Ting Wang Li Guo Liai Pan Qianyi Du Chanhui Cai Hanbiao Chen Laiping Zheng Yinhuan Zhong Fangmei Xu
Guangdong Women and Children Hospital

Background Double mosaic aneuploidy is a rare condition with only a few case reported to date.
Methods The conventional G-banding and fluorescence in-situ hybridization were performed to verify a fetus screening by NIPT with high risk of double aneuploidy.
Results The amniocentesis revealed a mosaic karyotype of mos 47,XXY[4]/47,XY,+21[5]/46,XY[24].In-situ culture of amniocytes was employed to detect the mosaic condition of the fetus.Among the 33 colonies of two independent culture,four colonies had a karyotype of 47,XXY and five colonies had a karyotype of 47,XY,+21,while the rest colonies had normal karyotype. Quantitative fluorescent polymerase chain reaction(QF-PCR) analysis indicated that the fetus was sex chromosome aneupoidy, which may be mosaicism of XY/XXY.Interphase FISH on uncultured amniocytes revealed that the fetus was a double mosaic aneuploidy which included three different cell lines.A total of 100 amniotic interphase cells were counted by using the DXZ1/DYZ3/D18Z1 mixed centromeric probes, in which 48 cells(48/100) had 2 signals on X chromosome and 1 signal on Y chromosome.FISH analysis with BCR and D21S259/D21S341/ D21S342 mixed probes showed trisomy 21 in 10/100 cells(10%).
Conclusion The combination of multiple molecular cytogenetic detection is helpful in the validation of fetuses with two chromosome aneuploidy screening by NIPT.

ATL1 基因错义突变导致一遗传性痉挛性截瘫家系的分子遗传学研究

杨景辰[1] 刘奇迹[1] 巩振华[2] 李曦[1] 孙文杰[1] 李江夏[1]
1.山东大学基础医学院医学遗传学系，实验畸形学教育部重点实验室
2.山东省淄博市桓台县妇幼保健院医学遗传科

目的 寻找一常染色体显性遗传的遗传性痉挛性截瘫（HSP）家系的致病基因，确诊该疾病，为该家系成员的遗传咨询和产前诊断提供基础。
方法 采集该家系各成员外周静脉血样本，提取基因组 DNA，对先证者进行全外显子组测序。
结果 遗传性痉挛性截瘫（HSP）是一组以缓慢进行性加重的双下肢肌张力增高、无力为主要特点的神经系统单基因遗传病，具有高度的临床和遗传异质性。HSP 的遗传方式有常染色体显性，常染色体隐性，X 连锁和线粒体遗传。目前发现其患病率受地域和诊断水平等影响，平均患病率为十万分之一到万分之一。由于 HSP 患病率低，临床病例少见，故对该疾病治疗的相关研究较少。HSP 虽一般不会影响病人的生存，但由于其进行性加重的特点，会严重影响病人的劳动能力和生活自理能力，且目前尚无有效的治愈方法。
本课题组收集了一 HSP 家系。该家系共有 4 代，为典型的常染色体显性遗传。临床初步诊断为遗传性痉挛性截瘫 3A 型。外显子组测序结果发现患者中 *ATL1* 基因存在 c.1024C>T（p.P342S）错义突变，Sanger 测序证实该突变在家系中与表型共分离，ACMG 致病性分类为 Pathogenic。
结论 该家系根据临床表现初步诊断为遗传性痉挛性截瘫 3A 型。遗传学分析发现该家系由 *ATL1* 基因 c.1024C>T（p.P342S）错义突变导致。本研究结果从分子水平上明确了疾病的诊断，同时为家系成员的症状前诊断及产前诊断提供了遗传学依据。

MVD 基因一错义突变导致汗孔角化症

施宏彪[1] 刘奇迹[1] 蔡大幸[2] 李曦[1] 孙文杰[1] 李江夏[1]
1.山东大学基础医学院医学遗传学系，实验畸形学教育部重点实验室
2.山东大学齐鲁医院皮肤科

目的 明确一常染色体显性遗传的汗孔角化症家系的致病基因，为该家系成员的遗传咨询提供帮助。
方法 采集该家系各成员外周静脉血样本，提取基因组 DNA，对患者进行全外显子组测序。
结果 汗孔角化症是一种罕见的皮肤遗传病，其特征是有一个或多个环形空斑，周围的角质边界散布离心。这种病变通常在青少年时期开始发展并在 30 到 40 岁达到几乎完全的外显。*MVD* 基因突变可以造成多种汗孔角化症，被称作弥漫性浅表性光敏性汗孔角化症、非光化传播表面汗孔角化症、太阳面部汗孔角化病、线性汗孔角化症以及角化过度型汗孔角化症。弥漫性浅表性光敏性汗孔角化症是最常见的一种，其特征为主要位于皮肤暴露于阳光下的皮肤区域的多个小的，环状的，无组织的，角化的病变，比如脸部，颈部以及四肢末端。
本课题组收集了一汗孔角化症家系，为典型的常染色体显性遗传。临床初步诊断为多形性汗孔角化症 7 型。外显子组测序结果发现患者中 *MVD* 基因存在 c.746T>C（p.F249S）错义突变，Sanger 测序证实该突变在家系中与表型共分离。
结论 该家系根据临床表现初步诊断为多形性汗孔角化症 7 型。遗传学分析发现该家系由 *MVD* 基因 c.746T>C（p.F249S）错义突变导致，该致病变异为已知变异，已被 OMIM 收据库收录，但在中国人群中为首次报道。

Discrepancy of karyotype and CMA/NGS in a PGD patient with cryptical complex chromosomal rearrangement

Ting Wang Li Guo Yinhuan Zhong Xianzheng Li Hanbiao Chen Jian Lu Weiwei Huang Chuangqi Chen
Guangdong Women and Children Hospital

Introductions Complex chromosome rearrangement (CCR) is a structural rearrangement involving more than two breakpoints.CCR carriers are at high risk for phenotypic abnormalities or reproductive failure, such as chromosomal abnormalities in fetuses and infertility.In this study, we presented a carriers with chromosome (3,18) balanced translocation,whose fetus had duplications in chromosome 3 and deletions in chromosome 10 demonstrated by chromosomal microarray analysis (CMA).By revealing the cryptical translocation, we aimed to provide CCR carriers with more accurate risk assessment of abnormal pregnancy and better assisted reproduction with CMA and next generation sequencing(NGS).
Results By using the high resolution of GTG-banding technology,a cryptical translocation in chromosome 10 was found and the karyotype of the carrier was revised as 46,XY,t(3;10;18)(p26.3;q26.1;q21.1).In the cycle of preimplantation genetic diagnosis (PGD),21 oocytes were retrieved,and 15 were fertilized.At last 7 embryos were biospied and sent to diagnosis by next generation sequencing(NGS).Unfortunately, none of the NGS results from the 7 biopsy embryos were normal.Combining previous literature and our results, we assessed the odds of a balanced embryo in a CCR carrier to be about 9.3%(28/302).The transferable embryo rate was approximately 71.4%(20/28) and healthy live born delivery rate was 55%(11/20).
Conclusions NGS and CMA featured high automation, relatively low cost, high throughput, and high repeatability, which made them commonly used during prenatal diagnosis and PGD.The multiple technology combination can provide more accurate diagnosis and better fertility services for CCR patients.
Key words:Complex chromosome rearrangement; preimplantation genetic diagnosis;next generation sequencing;chromosome microarray analysis

A novel missense variant c.71G>T (p.Gly24Val) of the CRYBA4 gene contributes to autosomal‐dominant congenital cataract in a Chinese family

Xinyue Zhang Yunqiang Liu
West China Hospital, West China Medical School, Sichuan University

Background Congenital cataracts are highly heterogeneous in phenotype and genotype. Understanding the genetic etiology of congenital cataracts is essential for defining clinical diagnoses, performing early treatment, and guiding genetic counseling.
Objective To investigated the potential genetic defects in a five-generation Chinese family with autosomal dominant congenital cataract (ADCC).
Methods Whole exome sequencing was performed to search the variants in the candidate genes associated with congenital cataract. Sanger sequencing was used to validate the variants and examine their co-segregation in the patients and their relatives. The potential effect of the variants was analyzed using several bioinformatic methods, and further examined through Western blotting and co-immunoprecipitation.
Results A missense variant c. 71 G>T (p. Gly24Val) in the *CRYBA4* gene, a known ADCC candidate gene, was identified to be heterozygously present in the patients, and co-segregate with cataract in the family. The mutation were absent in all of the searched databases, including our in-house exome sequences of 10,000 Chinese. The alignments of the amino acid sequences of CRYBA4 in a variety of species revealed that the amino acid residue Gly24 was evolutionarily highly conserved, and the *in silico* analysis predicted that the missense mutation of Gly24Val was damaging for the protein structure and function of CRYBA4. Then, the *in vitro* expression analysis

further revealed that the Gly24Val mutation in CRYBA4 inhibited its binding with CRYBB1. The impaired interaction of β-crystallin proteins may affect their water-solubility and contribute to the formation of precipitates in lens fiber cells.
Conclusion We identified a novel missense variant in the *CRYBA4* gene as a pathogenic mutation of ADCC in a Chinese family. Our finding expanded the *CRYBA4* variation spectrum associated with congenital cataracts.

一个 FBN2 基因新剪接位点变异致先天性挛缩蜘蛛指畸形的遗传学分析

谭晓兰 刘运强
四川大学华西医院

目的 对 1 例疑似先天性挛缩蜘蛛指畸形或马凡综合征患者进行变异筛查，探讨其可能的分子遗传学发病机制，为临床诊断提供依据。
方法 应用全外显子测序技术筛查基因变异。候选致病基因剪接位点变异经 Sanger 测序验证后，经 RT-PCR、TA 克隆测序确定新转录本序列。
结果 患者 *FBN2* 基因存在 c.533-1G>C 杂合变异，未见报道。mRNA 测序显示该变异导致 *FBN2* 基因原剪接受位消失的同时，激活 c.533-71 处潜在剪接受位位点，由此产生的新转录本中插入了 70bp 序列。推测新转录本编码多肽在氨基酸 179 处由缬氨酸（Val）变成丝氨酸（Ser），并移码 26 位后终止（p.Val179Serfs26*）。根据美国医学遗传学与基因组学学会指南，*FBN2* 基因 c.533-1G>C 变异判定为致病性变异（PVS1+PM2+PP3）。
结论 *FBN2* 基因 c.533-1G>C 变异引起新转录本发生功能丧失性变异，可导致先天性挛缩蜘蛛指畸形。

全外显子测序鉴定一例新生儿先天性肾病综合征的基因突变

任凌雁 黄盛文
贵州省人民医院

目的 对于一名先天性肾病综合征的男孩及其父母，应用全外显子测序技术检测，并利用 Sanger 测序进行验证，筛查先天性肾病综合征的致病基因，为该家庭提供遗传咨询。
方法 先证者，男，1 月 12 天。腹泻 1 月+，浮肿 20+天入我院。临床表现有：蛋白尿、低蛋白血症、支气管肺炎和水肿。签署书面知情同意后，采集父母、先证者的外周血并提取 DNA，进行全外显子测序及 Sanger 测序。
结果 先证者 19 号染色体上 NPHS1 基因的 8 号外显子存在一个杂合突变位点：c.928G>A (p.D310A)，此位点的变异来源于父亲。此外 20 号外显子存在发生一个三碱基重复：c.1864_1866dupACC (p.T622dup)，此位点的变异来源于母亲。根据美国医学遗传学与基因组学学会（ACMG）指南，这两个变异初步判定为疑似致病性变异。c.928G>A 的变异 SIFT、PolyPhen_2、REVEL 的预测结果为疑似有害，OMIM 数据库检索与肾病综合征 1 型有关。c.1864_1866dupACC 的变异 SIFT、PolyPhen_2、REVEL 的预测结果为未知。
结论 经全外显子和 Sanger 测序，确诊先证者为先天性肾病综合征，致病突变为 NPHS1 基因，变异位点为 c.928G>A (p.D310A)，c.1864_1866dupACC (p.T622dup)的复合杂合突变，变异来源分别于父亲、母亲。测序结果可为患者及家属遗传咨询提供依据。

UBTF 基因突变所致儿童发病性神经退行性变伴脑萎缩一例病例报告

吴非霏[1,2] 付小惠[2] 张会婷[2] 崔东[1] 胡宇慧[1] 廖建湘[1] 陈淑丽[1]
1.深圳市儿童医院
2.中国医科大学

目的 报道国内首例 UBTF 基因突变所致儿童发病性神经退行性变伴脑萎缩病例，并探讨其发病特点、临床表现等。
方法 回顾性分析一例 UBTF 基因突变所致儿童发病性神经退行性变伴脑萎缩患儿的临床资料，并对既往文献报道进行复习。
结果 本文中患儿系国内首例 UBTF 基因突变所致儿童发病性神经退行性变伴脑萎缩病例，主要表现为精神运动发育落后，基因结果提示 UBTF 基因突变，致病位点为 c.628G> A，该位点为第 628 号核苷酸上鸟嘌呤替换为腺嘌呤，使谷氨酸替换为赖氨酸，导致 rDNA 表达增加，造成神经系统损害。该位点为国外已报道的致病突变，国内未见该基因致病的报道。
结论 UBTF 基因突变所致儿童发病性神经退行性变伴脑萎缩为一种罕见的单基因遗传病，主要表现为 2.5 岁后出现的精神运动发育倒退、言语及认知障碍等。典型的临床表现及影像学特征对该病有重要的诊断意义，确诊需要依靠基因检测。目前尚无特异治疗方法。本例为国内首例 UBTF 基因致病病例相关报道。

RPS6KA3 基因外显子 1 的 Taqman 探针荧光定量 PCR 检测方法的建立

秦胜芳 王锦 尹雁 邓凤秋 叶梦玲 张卓 陈希敏 席娜 严梦珈 易丹英 赵一桐 汪雪雁
四川省妇幼保健院四川省产前诊断中心

目的 因发育迟缓和特殊面容就诊的一例 6 月龄男性患儿，外周血标本全外显子测序结合 CNVSEQ 分析发现 chrX:20257168-20299113 约 41kb 大小的缺失，包含 RPS6KA3 基因外显子 1（Exon1），为致病性基因拷贝数变异。其临床症状符合 Coffin-Lowry 综合征[MIM: 303600]。患儿母亲为该缺失的携带者。患儿母亲再次妊娠 22 周前来我院进行该基因缺失的产前诊断。由于该缺失片段较小、结构复杂、GC 含量高，我们拟建立 Taqman 探针荧光定量 PCR 的实验方法进行拷贝数定量，并进一步产前诊断。
方法 PrimerExpress 软件设计引物与探针，FAM 荧光标记 Taqman 探针。采用 AB 3500Dx Analyzer 进行 Sanger 测序，Sequencing Analysis 5.2 软件分析测序结果验证引物的特异性。采用 ABI 7500 Real Time PCR System 进行荧光定量 PCR 检测，基因组 DNA 以 1:4、1:16、1:64、1:256 的浓度梯度建立标准曲线，测试荧光定量 PCR 的扩增效率；以 RNASEP 基因作为内参。CopyCaller2.1 软件定量分析 RPS6KA3 基因 Exon1 的拷贝数。以上实验均采用 3 次重复检测。
结果 Sanger 测序结果与目的基因序列一致；荧光定量 PCR 扩增效率为 98%，扩增曲线 R2 为 0.999，建立了良好的标准曲线。正常女性和男性的 RPS6KA3 基因 Exon1 的拷贝数分别为 2 和 1，男性患儿、患儿母亲和患儿母亲胎儿的拷贝数分别为 0、1 和 2，提示患儿为该片段的半合缺失，母亲为携带者，本次妊娠胎儿未检测到该片段拷贝数缺失。
结论 我们建立了 RPS6KA3 基因 Exon1 的 Taqman 探针荧光定量 PCR 检测方法，其特异性、扩增效率和重复性均很好，能准确、快速定量检测 RPS6KA3 基因 Exon1 的拷贝数，填补了常规方法不能准确检测该片段的空缺。严格控制好质量，能满足临床检测的需求。

无创提示常染色体单体的临床效果分析

代鹏 孔祥东
郑州大学第一附属医院

目的 探讨 NIPT 检出 21、18 和 13-三体外的常染色体单体的发生率、产前诊断和妊娠结局，为 NIPT 提示常染色体单体高风险孕妇的妊娠管理提供临床指导。
方法 回顾性分析 2016 年 1 月至 2020 年 12 月在我中心接受 NIPT 的 69,608 例孕妇的临床检测数据，筛选和总结常染色体单体高风险孕妇的产前诊断以及妊娠结局。
结果 共检出 101 例常染色体单体高风险孕妇，阳性检出率为 0.15%。2-22 号染色体均有不同频率的检出，最常见的是 21-单体（30.6%、31/101）和 16-单体（6.9%、7/101），其次是 13-单体和（5.9%、6/101）和 18-单体（5.9%、6/101），而 1-单体没有被检出。75 例常染色体单体高风险孕妇行侵入性产前诊断，确诊 6 例，阳性预测值为 8.0（6/75）。4 例产前诊断与 NIPT 结果的不一致。产前诊断确诊的 10 例胎儿染色体异常包括 8 例染色体缺失、1 例染色体重复和 1 例染色体微缺失/微重复。成功随访 99 例，随访率为 98%（99/101）。101 例常染色体单体高风险孕妇的妊娠结局包括：93 例胎儿出生，4 例孕妇直接终止妊娠，1 例因染色体异常选择终止妊娠，1 例因超声异常选择终止妊娠，2 例失访。
结论 在临床实践中，NIPT 额外发现的常染色体单体并不少见，但大多数孕妇具有良好的妊娠结局。因此，临床上检出常染色体单体高风险的孕妇应进行遗传咨询，妊娠期间进行连续的超声检查，监测胎儿的发育生长情况，而不是直接终止妊娠。若发现结构畸形或软指标异常，行侵入性产前诊断，避免缺陷儿的出生。

Prenatal diagnosis and pregnancy outcome of rare autosomal trisomies by non-invasive prenatal testing

Peng Dai Xiangdong Kong
The First Affiliated Hospital of Zhengzhou University

Objective Exploring the incidence, prenatal diagnosis and pregnancy outcome of rare autosomal trisomies (RATs) detected by NIPT, to provide clinical guidance for pregnancy management of pregnant women with high risk of RATs.
Methods We performed a retrospective study and reviewed data from 69,608 pregnancies undergoing NIPT at our center from January 2016 to December 2020, screened and summarized the prenatal diagnosis and pregnancy outcome of pregnant women at high risk of RATs.
Results 161 pregnant women with high risk of RATs were detected, with a positive screening rate of 0.23%. Each chromosome had a different frequency of detection, the most common RAT was trisomy 7 (17.4%, 28/161), followed by trisomy 20 (12.4%, 20/161), and the lowest detection rate was trisomy 17 (0.6%, 1/161). 98 pregnant women with high risk of RATs underwent invasive prenatal diagnosis, 5 cases were diagnosed, and the positive predictive value was 5.26% (5/98). The prenatal diagnosis of 7 cases were inconsistent with the results of NIPT. The 12 cases of fetal chromosomal abnormalities confirmed by prenatal diagnosis included 2 cases of mosaic chromosome number abnormalities and 10 cases of chromosomal microdeletion/microduplication. 153 cases were successfully followed up, with a follow-up rate of 95% (153/161). The pregnancy outcomes of 161 pregnant women with high-risk of RATs included: 139 fetuses were born, 9 pregnant women terminated their pregnancy directly, 3 pregnant women selected to termination of pregnancy due to chromosomal abnormalities, 1 case was spontaneous abortion, 1 case was embryo stopped developing, and 8 cases were lost to follow-up.
Conclusion The fetus with high risk of RATs, detected by NIPT, may be related to the adverse pregnancy outcomes, but 90.8% (139/153) of positive cases have normal pregnancy outcomes. Clinically, pregnant women with high risk of RATs should undergo invasive prenatal diagnosis or continuous ultrasound during pregnancy to monitor the development and growth of the fetus,

rather than directly termination of pregnancy. Genetic counseling should pay attention to uniparental disomy caused by rare chromosome copy variations.

HPRT1 基因突变临床表型 及其功能研究

郭妙
上海市儿童医院

摘要： 背景：Lesch-Nyhan 病(LND)是一种罕见的由于低黄嘌呤-鸟嘌呤磷酸核糖转移酶(HGprt)缺陷导致的 x 连锁遗传的嘌呤代谢神经遗传疾病，该病又名自毁容貌综合征，由于嘌呤代谢异常引起一系列表现，其典型的临床表现为高尿酸血症、生长发育迟缓、智力低下、身材矮小、舞蹈状手足徐动、攻击行为、强迫性自残。**方法：**我们在一个家系中发现了一个点突变 c.151C>T（p.Arg51*），我们分析了一个家系中患儿的临床特征，并获得患儿父母及其兄弟姐妹的血用于二代测序，同时，我们也进行了 HPRT1 基因表达量的分析比较和蛋白质的三维结构预测，并分析了该基因缺陷所引起的临床表现。**结果：**该突变导致转录在第 51 位精氨酸处终止，导致产生截短的蛋白质；HPRT1 基因在患者体内的相对表达量明显低于患儿其余家人和 10 例随机对照。**结论：**该突变导致蛋白翻译的提前终止，形成一个截断的 HPRT 蛋白，丢失了重要位点，导致该蛋白的功能受到影响，从而产生相应的临床表现。

一例多种酰基辅酶 A 脱氢酶缺乏症家庭的携带者诊断性检测与遗传咨询

宁昊丰 王亚男
洛阳市妇幼保健院

目的 对一例曾育有多种酰基辅酶 A 脱氢酶缺乏症患儿的家庭进行携带者诊断性检测，明确可能的遗传学病因。
方法 询问家族史：G3P3A1。G1，7 月龄时因注射疫苗诱发发热、烦躁，后不明原因死亡。G2，2 岁半时无诱因发热、抽搐，后治疗无效死亡，血串联质谱检测提示多种中长链酰基肉碱增高，高度符合多种酰基辅酶 A 脱氢酶缺乏症。G3，11 月龄，生长发育良好，未见异常。利用医学外显子组测序技术同时对夫妻二人进行检测，并根据候选变异类型用 Sanger 测序或 qPCR 进行验证，判断变异致病性，评估 G3 发病风险，对夫妻二人进行遗传咨询与再生育指导。
结果 丈夫 *ETFDH* 基因(NM_004453.4)存在 c.251C>T 杂合变异，妻子存在 exon6-13del 杂合变异，二者均判定为可能致病。*ETFDH* 是多种酰基辅酶 A 脱氢酶缺乏症的致病基因。推测 G2 的遗传学病因可能是遗传了来自夫妻双方的 *ETFDH* 基因复合杂合变异。G3 验证结果为野生型，不患病。该家庭再次生育时，后代患病风险为 25%。可选择自然妊娠并进行产前诊断；或选择第三代试管婴儿，用 PGT-M 技术阻断单基因病。
结论 结合家族史与病史，利用医学外显子组测序技术对于无先证者样本留存的家庭中夫妻双方同时进行携带者诊断性检测，是一种经济、高效的筛查策略，有助于帮助此类家庭提供科学的遗传咨询与再生育指导。

一例全面性生长发育落后患儿 EEF1A2 基因变异分析

王亚男
洛阳市妇幼保健院

目的 对一例全面生长发育落后的患儿进行全外显子组基因测序分析，明确其遗传学病因。

方法 收集表型：患儿，2 岁 4 月，自幼发育落后，步态不稳，四肢肌力偏低，语言量少。父母既往体健，无相关家族史。提取患儿外周血 DNA，进行全外显子组测序分析，对检测到的可疑位点用 Sanger 测序进行验证，同时进行父母比对，根据基于 ACMG/AMP 和 ClinGen 框架的遗传变异解读规则判断变异致病性。
结果 该患儿 *EEF1A2* 基因（NM_001958.5）存在 c.44A>G（p.His15Arg）杂合错义变异，父母均为野生型，该变异判定为“可能致病”（PM1+PM6+PM2_supporting+PP3+PP4）。*EEF1A2* 基因与常染色体显性复杂神经发育障碍相关，患儿表型与之相符。NM_001958.5:c.44A>G 先前未被报道或被数据库收录，为新发现变异。
结论 *EEF1A2* 基因 c.44A>G 变异可能是该患儿的遗传学致病原因，本研究报道的变异类型丰富了 *EEF1A2* 基因的变异谱。

散发垂体生长激素腺瘤患者 AIP 基因突变及相关临床特征研究

何敏
复旦大学附属华山医院

目的 观察中国散发性垂体生长激素瘤患者芳羟基受体相互作用蛋白（arly hydrocarbon receptor-interactin protein，AIP）基因突变发生率及其与临床特征的关系。
方法 对 176 例散发垂体生长激素腺瘤患者的外周血 DNA 进行 AIP 基因测序，分析 AIP 突变的发生率，比较 AIP 突变患者与野生型患者临床特征的差异。
结果 6.25%（11/176）的患者存在 AIP 突变，其中 30 岁以下 8.08%（8/99），30 岁以上 3.9%（3/77）。共检出 10 个突变位点，均首次报道于中国汉族患者。R304X、R81X 是既往国外已报告的致病位点；G83G、G21G、T48T 是 dbSNP 收录的单核苷酸多态性位点；C254R 经软件分析与编码蛋白功能破坏有关；K103fs、Q228fs 根据 ACMG 指南评级为可能致病。与非突变组相比，AIP 突变组显示更高的随机 GH、IGF-1、肿瘤体积、海绵窦侵袭的趋势，IGF-1 指数则显示低于非突变组的趋势；突变组显示更高的 SSAs 耐药率、更高的稀疏颗粒型比例和更低的 SSTR2 表达趋势。但上述结果均未见显著统计学差异。
结论 AIP 突变在中国汉族散发性垂体 GH 腺瘤患者中具有较高的发生率，尤其是 30 岁以下的年轻患者。AIP 突变位点多样。AIP 突变患者具有 GH 水平更高、肿瘤更大更易侵袭的倾向，且更倾向于发生 SSAs 抵抗。

OPN1LW 外显子 2-5 缺失致红绿色盲的病例报告

赖光锐 何蓉 崔灿
中国医科大学附属盛京医院

目的 红绿色盲是一种常见的 X 连锁隐性遗传病，由 *OPN1LW* 或 *OPN1MW*（opsin 1, long or middle wave sensitive）基因突变引起。为明确一红绿色盲患者家系的可能致病原因，提供合理的遗传咨询及生育指导。
方法 收集一红绿色盲患者家系外周血样本，对家系成员中的两名红绿色盲患者和一名女性携带者进行全外显子组测序；并通过聚合酶链反应(PCR)对 *OPN1LW* 的基因座控制区（LCR）和 *OPN1LW* 外显子 2、4 和 5 进行扩增分析。
结果 全外显子组测序提示该家系两名男性红绿色盲患者 *OPN1LW* 第 2–5 外显子缺失，一名女性携带者 *OPN1LW* 第 2–5 外显子杂合缺失，并利用 PCR 验证了上述结果；此外，该家系的 LCR 未见异常。
结论 首次发现 *OPN1LW* 第 2–5 外显子缺失是导致该家系红绿色盲的原因，并针对该家系做遗传咨询及生育指导。

一例新发 PKD1 基因剪切变异导致 ADPKD 家系的鉴定

白洁
河南省人民医院

目的 利用基因组学及分子生物学实验鉴定 ADPKD 家系致病变异
方法 全外显子测序、MLPA 以及 Long-PCR 结合 NGS 捕获测序方法 ACMG 检测先证者多囊肾相关基因 PKD1、PKD2 变异情况，根据 ACMG 遗传变异分类标准进行测序数据注释分析；对发现的变异位点在家系中进行 sanger 测序分析，所得结果与 PKD1 基因标准序 列 GRCh37/hg19 NM_001009944 进行比对, 从而验证高通量测序结果。体外构建包含变异位点在内相邻基因序列进行 Minigene 实验分析该变异对 PKD1 基因转录的影响。
结果 先证者血标本行全外显子测序，PKD1、 PKD2 基因 MLPA 以及靶向捕获及高通量测序, 结果为先证者 PKD1 基因存在 c.1723-23A>G 杂合突变，查阅相关数据库未见该位点变异报道。一代测序验证显示该位点在该家系中出现家系共分离。Minigene 体外实验显示该位点变异可引起 PKD1 基因 9 号外显子转录缺失。经软件预测 9 号外显子缺失可产生提前终止密码子，PKD1 产生截短功能改变。
结论 基因测序分析以及 Minigene 实验显示该变异位点是导致该家系发生多囊肾的潜在致病位点。尚需采取适宜策略进行患者体内该位点对 PKD1 基因转录影响的验证。

先天性心脏病胎儿羊水的遗传学诊断

崔灿 赖光锐 赵彦艳
中国医科大学附属盛京医院

目的 先天性心脏病（简称先心病）是最常见的出生缺陷，研究表明环境因素和遗传因素共同作用导致先心病的发生。为明确先心病的可能的致病遗传因素，我们对孕有先心病胎儿的羊水进行核型分型和 CNV-seq。
方法 收集我院 2019 年~2021 年孕中期（22-26^{+3} 周）超声筛查检出胎儿先心病异常 44 例羊水（40 例单纯室间隔缺损、1 例室间隔缺损合并房间隔缺损、3 例法洛四联症），行 G 显带染色体核型分析和高通量测序 CNV-seq 后统计分析。
结果 2 例（2/44,4.5%）羊水染色体核型异常结果（1 例 18 三体；1 例染色体不平衡易位，CNV-seq 提示 4p16.3-p14 约 39 Mb 致病性重复），其余 42 例(42/44,95.5%)染色体核型正常者，在 42 例染色体核型正常者，CNV-seq 未见明显异常。
结论 先心病胎儿染色体或基因组异常比例并不高，提示其他因素（如单基因病、代谢、环境等）可能在其发病机制中具有重要作用，需要更大样本量、更深入的研究其机制。

A retrospective study of nine patients with progressive pseudorheumatoid dysplasia: to explore early diagnosis and further treatment

Jian Wang Lei Yin Youying Mao Yunfang Zhou Yongnian Shen Wei Zhou Yanliang Jin Hua Huang
Shanghai Children's Medical Center

Objectives Most patients with progressive pseudorheumatoid dysplasia (PPRD) are initially misdiagnosed because of disease rarity and lack of awareness by most clinicians. The purpose of this study was to provide further early diagnostic options and potential treatment to patients with PPRD.
Methods A retrospective study was performed by collecting and orgnizing clinical manifestations, radiographic features, laboratory tests results, genetic test outcomes, treatment and follow-up

records of the patients with PPRD. Time to diagnosis, phenotype and genotype correlation were analyzed.
Results 9 PPRD children with causative *CCN6* mutation were included. There were 3 pairs of siblings and one patient had parental consanguinity. Five patients were misdiagnosed as juvenile idiopathic arthritis (JIA). The interval from onset of symptoms to obtaining the diagnosis for 8 of the patients varied from 3.6 years to 20 years. The onset of symptoms included enlarged and stiff interphalangeal joints of the fingers, gait disturbance or joint pain. Laboratory tests revealed normal range of inflammatory parameters. Radiographic findings included different degree of abnormal vertebral bodies and epiphyseal enlargement of the interphalangeal joints. After the treatment of calcitriol in 5 patients with low level of 25-hydroxyvitamin D3 for 1.25 years to 1.75 years, two of them kept stable, while 3 of them improved gradually.
Conclusions Combining the patient's family history, clinical features, normal inflammatory markers, and the characteristic radiographic findings, the clinical diagnosis of PPRD for the patients could be obtained at very early stage of the disease. The patients with PPRD having c.624dupA variant in *CCN6* may have delayed onset. Underlying vitamin D deficiency should be sought and corrected in patients with PPRD.

全外显子测序鉴定一例近亲家系成骨不全症基因突变

黄盛文
贵州人民医院

目的 对于一名未知原因反复骨折的男孩，应用全外显子测序技术检测，并对其父母进行 Sanger 测序验证，筛查骨折的致病基因，为该家庭提供遗传咨询。
方法 先证者，男，16 周岁。出生至今反复骨折，怀疑为软骨病。临床表现有：从小常在轻的外伤或没有明显病因的情况下发生骨折，蓝色巩膜、骨骼畸形、牙齿发育不良，智力和内分泌功能正常。父母近亲结婚，母亲精神分裂症，其父母为表兄妹。签署书面知情同意后，采集父母和先证者的外周血并提取 DNA，进行全外显子测序和 Sanger 测序。**结果** 先证者 17 号染色体上 COLIA1 基因的 c.3G>A 发生突变：COLIA1：NM_00088.3:exon1:c.3G>A:p.M11，父母均未发生突变。经 OMIM 数据库查询，成骨不全综合征疾病特征与本案例表型相符，主要表现为：复发性骨折、蓝巩膜、耳硬化症、骨质减少等。根据 ACMG 指南，该变异初步判定为可能致病突变位点（PM2+PM6+PVS1_Moderate+PP4）：该变异在多个人群频率数据库中没有发现；该变异为未经双亲亲缘关系验证的新发变异；该变异为起始密码子变异，与下游预测新的起始密码子之间存在已知致病变异；且对应疾病与本案例表型相符。该变异在 Clin Var 数据库中评定为 P。SIFT、PolyPhen_2、REVEL 的预测结果均为未知。
结论 经全外显子和 Sanger 测序，确诊先证者为成骨不全综合症，致病突 COLIA1 基因，c.3G>A:p.M11 变异，先证者父母均未发生突变。测序结果可为患者及家属遗传咨询提供依据。

PSMD12 基因变异致 1 例 STISS 综合征临床特征及基因变异分析

徐磊 [1,2]
1.上海儿童医学中心
2.江西省儿童医院

目的 分析 *PSMD12* 基因变异导致 STISS 综合征的临床和遗传学特点。
方法 对在上海儿童医学中心诊断的 1 例 STISS 患者的临床资料及基因检测结果进行总结分析，并以“Stankiewicz-Isidor syndrome”，“STISS 综合征”，“*PSMD12*”为关键词，检索 PubMed、在线人类孟德尔遗传数据库(OMIM)、中国知网数据库(CNKI)和万方数据库，对 STISS 综合征进行文献复习。

结果 先证者，男性，3 岁 11 月，患者严重矮小，轻度智力运动发育落后，室间隔缺损，房间隔缺损，动脉导管未闭，多指畸形，双肾偏小，*PSMD12* 基因杂合无义变异（c.601C＞T，p.Arg201*），父母未携带，为“致病性 pathogenic”变异，结合目前文献报道的 13 例单核苷酸变异患者，约 64%为 c.367C＞T（p.Arg123*）变异位于 4 号外显子，92.9%为无义变异。
结论 *PSMD12* 基因变异导致 STISS 综合征在国内为首次报道，由于 *PSMD12* 基因变异临床异质性大，是否引起严重身材矮小有待于进一步探究，生长激素治疗对其有效性和安全性仍亟待于观察。

男性先天性肾上腺增生症（21-羟化酶缺陷）两例

向博妮
复旦大学附属华山医院

先天性肾上腺皮质增生症（congenital adrenal hyperplasia, CAH）是一大类由于肾上腺皮质类激素合成通路中不同催化酶基因突变所引起的常染色体隐性遗传病，其中 21-羟化酶缺陷（21-hydroxylase deficiency, 21-OHD）是 CAH 最常见的类型，占所有 CAH 的 90%~95%。21-OHD 是由编码 21-羟化酶的 CYP21A2 基因突变引起。根据基因突变的程度及临床表现的不同，21-OHD 分为经典型和非经典型，前者又包括失盐型和单纯男性化型。单纯男性化型及非经典型在男性患者中的表现常隐匿或不典型，因此常被漏诊或误诊。本研究报道了 2 例 21-OHD 男性患者病例：患者 1 为青年男性，因体检发现双侧肾上腺占位，双侧术后病理提示左肾上腺髓性脂肪瘤、右肾上腺皮脂腺瘤，术后 10 年随访期间患者无明显皮质功能亢进或减退的症状与体征，复查血皮质醇>13ug/dl 但 ACTH 明显升高，小剂量地塞米松抑制试验提示可被抑制，CT 监测肾上腺提示双侧肾上腺结节样增生且病灶有逐年增大趋势，完善肾上腺激素质谱检测，显示血 17-羟孕酮升高，同时伴有 17 羟孕烯醇酮、雄烯二酮水平升高，全血送检先天性肾上腺皮质相关基因突变检查，发现 CYP21A2 基因双杂合变异：c.293-13C>G 与 c.1070G>A(p.R357Q)，明确诊断后予地塞米松片 0.375mg 每天口服治疗，治疗半年，复查 17-羟孕酮水平降至正常范围，ACTH 水平亦明显下降。病例 2 为青年男性，因继发不孕就诊，查血 FSH、LH 水平偏低，睾酮水平正常范围内，精液检查提示无精症，睾丸 B 超未见明显异常，行 HCG 兴奋试验及 GnRH 兴奋试验均不能兴奋，患者血皮质醇水平不低，ACTH 偏高，肾上腺 CT 提示左侧肾上腺内侧支占位，双侧肾上腺体部结节状增粗，行肾上腺激素质谱检测，显示 17-OHP 水平升高，同时有雄烯二酮、17 羟基孕烯醇酮、孕烯醇酮水平升高，送检先天性肾上腺皮质相关基因突变检查，发现 CYP21A2 基因纯合变异 c.518T>A(p.I173N)。明确诊断后予地塞米松片 0.375mg 每天口服，治疗 2 月后患者妻子顺利怀孕。这两例案例充分体现了从临床医学到遗传学、再由遗传学反哺临床决策的过程，为男性 21-OHD 的诊治提供了宝贵经验。

发育障碍患儿 15q24 微缺失的遗传特征和临床表型

张媛媛
中国医科大学附属盛京医院

目的 染色体 15q24 微缺失是一种罕见的遗传变异，其临床特征为动作、语言发育迟缓，特殊面容，眼、耳、手指、泌尿生殖系统畸形，有时伴有自闭症谱系障碍（Autism Spectrum Disorders, ASD）。本研究旨在探讨发育障碍患儿 15q24 微缺失的患病率，遗传特征和临床表型。
方法 利用多重连接依赖探针扩增（MLPA）probe mix P245 结合毛细管电泳对 7077 例发育障碍患儿进行筛查；对筛出的 15q24 微缺失患儿进一步利用 MLPA probe mix P371 进行验证，并确定变异范围。
结果 15q24 微缺失在发育障碍患儿中的患病率约为 1/1425。共有 5 例患儿存在不同程度的 15q24 微缺失。其中，2 例患儿携带的缺失覆盖了文献报道的 1.1 Mb 典型区域；另有 2 例患儿携带 0.57 Mb 微小缺失，位于低拷贝重复（LCR）15 B-C 区域，患儿有明显的发育迟缓和轻度的 ASD，表

明该区域是与 15q24 微缺失表型相关的关键区域；还有 1 例患儿携带 0.11 Mb 纯合缺失，同样位于 LCR 15 B-C 区域，表现为免疫低下、喉鸣和严重下肢肿胀。
结论 本研究揭示了发育障碍患儿 15q24 微缺失的遗传特征和临床表型，为儿科医生临床诊疗提供一定依据。

儿童 I 型神经纤维瘤患者的基因诊断和随访研究

姚如恩 王剑
上海交通大学医学院附属上海儿童医学中心

目的 通过对疑似 I 型神经纤维瘤患儿进行基因诊断和疾病进展分析及随访研究，探索研究携带 NF1 基因突变患儿的基因型表型联系。
方法 回顾性选取 2016 年 9 月至 2018 年 1 月在上海儿童医学中心疑似 I 型神经纤维瘤诊断的患儿共 32 例，男 17 例，女 15 例，年龄 2 个月至 5 岁，进行相应的遗传学检测明确基因突变，并对阳性患儿进行 3 年以上长期的随访和病情跟踪，对疾病的进展以及基因型表型关联性进行分析。
结果 27 例患儿检测到明确致病性的 NF1 基因突变，包含 3 例未曾报道过的致病性突变；这 27 例患儿中仅 3 名患儿突变遗传自明确诊断且有表型的父母，其余均为新发突变。大部分患者随访期间无明显表型变化（14/27），部分患者（7/27）在随访期间发现矮小、肺动脉狭窄和发育迟缓等，其中矮小与肺动脉狭窄分别可能与 NF1 基因错义突变和严重截断变异存在关联性。
结论 无家族史的 I 型神经纤维瘤患儿其早期诊断更加依赖于基因检测。低龄患儿早期随访应根据突变的类型和位置进行相应的调整，错义突变患儿应增加心血管异常的早期随访，造成严重截断变异的患儿应关注身高发育情况。

利用全外显子测序识别下颌面骨发育不全综合征患者一例

陈颖 李辰龙 马竞 单晶 张天宇
复旦大学附属眼耳鼻喉科医院

目的 多个基因参与先天性外中耳畸形综合征的发病。本研究利用全外显子测序对一例合并颅面畸形、先天性外中耳畸形患者进行致病基因检测，探究其发病病因。
方法 签署知情同意后对该患者采集临床资料和外周血。利用全外显子测序进行基因组 DNA 测序，通过生物信息学分析方法识别可能致病的突变位点，并进一步进行 Sanger 测序验证，预测突变所致蛋白改变。
结果 该患者全身发育在正常范围，无智力低下，双侧外耳 II°畸形，外耳位置低垂，下颌骨发育短小，牙列不齐的症状明显；全外显子测序结果分析并进行 Sanger 测序验证后，鉴定该患者携带 EFTUD2 上的杂合突变 NM_004247.3：c.216insT，预测该框移突变导致产生提前出现的终止密码子，基因编码蛋白截短。该突变为首次报道，所致突变可致下颌面骨发育不全综合征，Guion-Almeida 型（Mandibulofacial dysostosis, Guion-Almeida type，MFDGA），为国内首例报道 MFDGA 患者。
结论 本研究利用全外显子测序检出该先天性外中耳畸形综合征患者携带 EFTUD2 基因插入突变 c.216insT，导致其蛋白编码提前终止，造成单倍剂量不足而致病。

一个重型血友病家系的基因诊断

祁娜
河南省人民医院

目的 通过对一个重型甲型血友病患者家系的临床分析和基因检测，为患者母亲再次怀孕进行产前诊断提供遗传学依据。

方法 针对在本科室就诊的一个甲型血友病患者家系，全面收集患者及其父母的临床和实验室资料，提取家系成员的外周血基因组 DNA，首先经高通量分子测序寻找 *F8* 基因的可疑变异位点，设计引物行 PCR 扩增并进行一代测序验证, 若未发现 *F8* 基因存在可疑变异，对样本进行倒位实验，即采用 LD-PCR 技术原理进行扩增，扩增产物通过琼脂糖电泳法进行分析。
结果 未发现该血友病患者 *F8* 基因存在可疑变异。通过倒位实验发现患者存在 *F8* 基因内含子 22 倒位，其母为 *F8* 基因内含子 22 倒位携带者，父亲未检测到存在 *F8* 基因内含子 22 倒位。
结论 该患者母亲为重型甲型血友病携带者，建议再次怀孕时做相应的产前筛查及诊断。

Identification of SOFT syndrome caused by a pathogenic homozygous splicing variant of POC1A: a case report

Guoqiang Li Guoying Chang Chen Wang Tingting Yu Niu Li Xiaodong Huang Xiumin Wang Jian Wang Jiwen Wang Ruen Yao
Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Objective SOFT syndrome is a rare primordial dwarfism condition characterized by short stature, onychodysplasia, facial dysmorphism and hypotrichosis, and mutations in *POC1A* gene are related with SOFT syndrome.To our knowledge, this is the first report of a SOFT syndrome patient diagnosed with a homozygous splicing variant, which could help to extend our understanding of the genotypic and phenotypic information of the disease.
Methods The proband was a seven-year-old boy with main complaint of short stature and facial dysmorphism. We observed clinical characteristics of the patient, did laboratory examinations and surveyed his family members. Whole-exome sequencing (WES) was carried out to detect disease-causing mutations and transcriptional experiments were performed to evaluate the splicing effects of the variant.
Results The patient presented symmetrical short stature and facial features, including prominent forehead, inverted triangular face, epicanthal fold, small teeth and enlarged ears. Moreover, mild acanthosis nigricans occurred in his neck and axillary fossa. Laboratory tests displayed mild insulin resistance. A homozygous splicing variant (c.981+1G>A) in the patient which was inherited from his heterozygous parents was identified and confirmed by Sanger sequencing. Further transcriptional experiments of the splicing variant revealed aberrant percentage of exon 9 skipping transcripts.
Conclusion This is the firstly reported case of a SOFT syndrome patient with a novel homozygous splicing variant and detailed delineation of the aberrant transcript in proband and carrier of the variant in Chinese. Our study enriched mutational spectrum of *POC1A* which could help in further genetic diagnosis and counselling of SOFT syndrome patients.

儿童 steel syndrome 一例

张红蕾[1,2] 袁永一[1] 吴捷[1] 戴朴[1]
1.中国人民解放军总医院
2.空军特色医学中心

Steel syndrome（钢铁综合征）(OMIM：615155)是一种非常罕见的常染色体隐性遗传性疾病，目前已知 *COL27A1* 为其致病基因。该病主要临床表现为：特征性面容，包括突出的前额、宽扁的鼻梁，双耳中重度非进行性感音神经性聋，身材矮小、双侧髋关节脱位、双侧马蹄外翻足、脊柱侧弯等。国外于 1993 年首次报道，国内尚无报道。本文报道 1 例具有先天性双耳中重度感音神经性聋听力表型的 Steel syndrome 患儿，其基因检测结果显示 *COL27A1* 基因 c.118C>T（p. Gln40Ter）/c. 3988G>C (p. Gly1330Arg)复合杂合变异，这两个变异均为该基因新发现的变异。

1 例原发性厚皮性骨膜增生症 SLCO2A1 基因突变鉴定

秦利涛 廖世秀
河南省人民医院

目的 原发性厚皮性骨膜增生症（Primary hypertrophic osteoarthropathy，PHO）（OMIM：167100）是一种罕见的常染色体隐性遗传疾病，其主要临床表现为杵状指、进行性皮肤增厚和骨膜增生。HPGD 和 SLCO2A1 是 PHO 的主要致病基因，虽然该病为隐性遗传，但有报道指出杂合亦可致病，导致的症状较轻。本报道旨在通过全外显子测序（Whole exon sequencing， WES）技术鉴定 1 例 PHO 家系的致病基因。
方法 收集先证者临床资料，提取基因组 DNA，利用 WES 技术对先证者进行测序，Sanger 测序验证 WES 结果并进行家系验证，生物信息学对突变基因功能预测。
结果 WES 发现先证者携带 SLCO2A1 基因 c.1929 C > G (p.I643M)和 c.232G>T (p.E78*)两个突变；根据 ACMG 突变分类指南，c.232G>T (p.E78*)为致病性突变（Pathogenic），c.1929 C > G (p.I643M)为功能未知突变（Uncertain significance）。Sanger 验证发现，同为患者的先证者哥哥携带以上两个突变，且两个突变分别遗传自母亲和父亲。保守性分析发现 c.1929 C > G (p.I643M)在不同物种中高度保守。
结论 通过 WES 发现 SLCO2A1 基因新的致病性突变，有助于患者明确病因，有利于后期的产前诊断及遗传咨询。

全外显子测序诊断一例罕见 Melnick-Needles 综合征

黄盛文
贵州省人民医院

目的 对于一名不明原因骨骼发育异常、身材矮小的青年女性患者及其父母应用全外显子测序筛查致病基因，为该家系提供遗传咨询依据。
方法 患者，女，21 岁。1 岁时开始出现胸廓发育异常，呈鸡胸和漏斗胸。8 岁时出现脊柱后凸，双眼突出，生长发育迟缓，身材矮小，无智力障碍。近 5 年反复出现心悸、胸闷、咳嗽、咳痰，呼吸困难。家族中无类似患者。查体：身高 130cm，体重 25kg。特殊面容，双眼突出，眼距增宽，上唇较厚，下巴短小。脊柱后突，胸廓畸形，手脚指细长，末端粗大。CT 检查提示：鸡胸合并漏斗胸，双肺灌注异常。DR 检查提示：颈椎生理曲度变直，脊柱胸段后突。心脏彩超检查提示：右房、右室增大。采集先证者及其父母外周血样本，提取基因组 DNA，采用家系全外显子组测序（Trio-WES）筛查先证者致病基因及突变位点，并用 Sanger 测序进行验证。
结果 WES 发现先证者位于 X 染色体上的 *FLNA* 基因有一杂合变异位点：NM_001110556.2: c.3562G>A（p.A1188T），父母均为野生型。该变异在神州基因组数据库、人类外显子数据库(ExAC)、参考人群千人基因组 (1000G)和人群基因组突变频率数据库(gnomAD)中没有发现。该变异在 ClinVar 数据库中评定为 P，在 HGMD 数据库中评定为 DM。根据 ACMG 指南，提示 *FLNA* 基因的 c.3562G>A 突变为一个致病突变位点，与 X 连锁显性遗传疾病 Melnick-Needles 综合征相关，证据包括 PS2、PM2、PS4、PP2 和 PP3。国内未见该致病位点报道。
结论 经 Trio-WES 和 Sanger 测序，确诊一例罕见 Melnick-Needles 综合征，致病 *FLNA* 突变 c.3562G>A 在国内为首次报道，检测结果为患者及家属遗传咨询提供了依据。

24 小时极速全基因组测序在一例危重症新生儿临床诊疗中的应用

张萍 张蓉 张澜 卢宇蓝 李刚 倪琦 王慧君 周文浩 吴冰冰
复旦大学附属儿科医院

目的 分析 24 小时极速全基因组测序（whole genome sequencing, WGS）技术在危重症新生儿临床诊疗中的应用价值。
方法 回顾性分析 2021 年 6 月复旦大学附属儿科医院应用 24 小时极速 WGS 明确分子诊断的一例危重症新生儿的临床表现、基因检测流程、基因变异特点及治疗策略等资料。
结果 患儿男，因“35+2 周早产，全身水肿 5 小时”入新生儿重症监护病房。患儿出生后表现为全身水肿，窒息，体重和头围均增大（＞P97），低血糖（0.8-1.1mmol/L），心脏发育异常，心功能不全和呼吸衰竭等。24 小时极速 WGS 流程在患儿入院第 4 天被启动，次日全部完成，共用时 23.5 小时。患儿检测到 *HRAS* 基因上一个新发杂合致病变异（c.35G>A，p.Gly12Asp），结合临床表现，诊断为 Costello 综合征。明确分子诊断后，组织多学科专家会诊并与家长沟通后及时调整临床治疗策略为姑息支持方案。
结论 24 小时极速 WGS 流程为临床危重症新生儿提供了一个快速、高效的遗传病因诊断手段，为临床医生针对病因进行个体化干预治疗提供了依据。

发育性癫痫性脑病 75 型一家系的临床特征和遗传学分析

路曼 [1] 廖世秀 [2]
1.郑州大学人民医院
2.河南省人民医院医学遗传研究所

目的 对一个发育性癫痫性脑病 75 型（developmental and epileptic encephalopathy 75, DEE75）家系的临床特征和基因变异进行分析。
方法 分析先证者及家系成员的临床特征及资料，对先证者及其父母进行全外显子组测序，对鉴定的可疑致病变异在先证者及核心家系成员中采用 Sanger 测序法进行验证。
结果 该家系三个患儿均存在小头畸形、发育迟缓、智力障碍等表型，其中先证者哥哥（已夭折）有癫痫表现；检测到先证者及其弟弟均存在 *PARS2* 基因 c.283G>A（p.Val95Ile）、c.664A>G（p.Thr222Ala）及 c.1059A>C（p.Glu353Asp）变异；c.283G>A 来源于表型正常的母亲；c.664A>G 及 c.1059A>C 来源于表型正常的父亲。
结论 *PARS2* 基因 c.283G>A 及 c.664A>G 复合杂合错义变异可能是该家系三个患儿罹患发育性癫痫性脑病 75 型的遗传学病因，本研究丰富了 *PARS2* 基因的变异谱。

Comprehensive review the roles of autoantibodies in diseases

Gongjun Tan
zhuhai weman and children'hospital

Antibodies are an essential immune component mediating both clearance and control of infections. autoantibodies, which recognize the host’s own molecules and tissues, play a crucial role in the pathology of autoimmune disorders. Autoantibodies are most commonly associated with autoimmune diseases, but a large body of evidence indicates that they are also present in numerous other diseases. Surprisingly, with the increase of autoantibody research methods and the change of research technology, the incidence and prevalence of autoantibodies in the disease is large and underestimated. Increasing number of autoantibodies being reported suggests that currently "idiopathic" diseases may someday be explained by neutralizing or

agonizing autoantibodies. In this review, we comprehensive overview of autoantibodies in human diseases, the production mechanism of autoantibodies, the method of identification of autoantibodies as well as the application potential of autoantibodies.

Application of complement 1q for the identification of immune complex antigens in breast cancer

Gongjun Tan
zhuhai weman and children's hospital

Immune complexes (ICs) are the direct and stable products of immunological recognition by humoral immunity, comprehensive identification and profiling of antigens in immune complexes (ICs) in plasma or serum is useful for developing early diagnostic biomarkers and specific therapy for breast cancer. “immune complexes analysis” has been used for the identification and profiling of antigens in ICs. However, protein A&G purification of ICs is nonselective because the binding antibodies and the unbinding antibodies cannot be distinguished by protein A&G. To selectively purified ICs with enhanced sensitivity, in this study, complement 1q (C1q) was used to replace protein A&G to separated ICs from serum of breast cancer and health controls. Result showed that C1q capture Method provided the high selective and sensitive detection of IC-antigens compared to protein A&G, without interference by the unbinding antibodies and proteins non-specifically bound to the microplates. These data suggest that C1q capture ICs separation technique is a good general pretreatment technique for the identification of antigens incorporated in ICs.

SLC6A8 基因变异致脑肌酸缺乏综合征 I 型家系的遗传学分析

宋雅倩
河南大学人民医院

目的 探讨 SLC6A8 基因变异所致的脑肌酸缺乏综合征（cerebral creatine deficiency syndrome，CCDS）I 型家系的临床表现及遗传学的特点。
方法 分析患儿临床特征，应用全外显子组测序技术(whole exome sequencing，WES)对患儿及其父母进行全外显子水平变异分析，Sanger 测序法对可能的变异位点进行验证，并复习文献总结该类疾病的特点。结果:患儿临床表现为发育落后，智力低下，理解能力差，走路不稳。四肢肌力及肌张力均未见明显异常，动作不灵活。高通量测序发现该患儿 SLC6A8 基因存在 c.1631C>T 半合子变异，患儿母亲 SLC6A8 基因存在 c.1631C>T 杂合变异，父亲 SLC6A8 基因存在 c.1631 位点野生型。结论:本研究发现 SLC6A8 基因一个未见报道的变异，丰富了该基因的变异谱。

Emerging Molecular Markers for Developing Disease Biomarker Panels in Lupus

Gongjun Tan
zhuhai weman and children's hospital

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease which affects various organs and tissues, posing significant challenges in clinical diagnosis and treatment. It is known that elevated autoantibody production and hyper-proliferation and activation of autoreactive T cells and B cells are major hallmarks of this devastating disease, however, the etiology of SLE is highly complex, contributed by environmental factors, stochastic factors and genetic susceptibility. The current criteria for diagnosis of SLE are mainly based on the combination of clinical manifestations and traditional laboratory tests. However, these tests are suboptimal in sensitivity

and specificity and are not able to inform disease cause or guide physicians in decision-making for medication. Therefore, there is an urgent need to develop a more accurate and robust biomarker of SLE for effective clinical management and drug development for lupus patients. It is fortunate that the emerging Omics has empowered the discovery and identification of potential novel biomarkers of SLE, especially markers from blood, urine, cerebral spinal fluids (CSF) and other body fluids. In this review, we summarize the sensitivity, specificity and performance of detection of these novel disease markers and discuss the potentials of these markers for the development of biomarker panel based diagnostics or disease monitoring system in SLE.

1 例先天性糖基化病 Ib 型 MPI 基因的突变分析

王斌 刘毅 张海燕 律玉强 杨露 盖中涛
山东大学齐鲁儿童医院

目的 先天性糖基化病是（congenial disorders of glycosylation，CDG）是一组罕见的常染色体隐性遗传代谢性疾病，临床表现各异。主要由低聚糖在蛋白质和其他糖缀合物上的组装、转移或加工受阻而致病。CDG-Ib 型又称“肝肠型-CDG”，*MPI* 基因缺陷引起，主要累及肝脏和胃肠道等脏器。本研究旨在利用新一代测序技术明确 1 例 CDG-Ib 型患儿的遗传学病因。
方法 对一例疑似 CDG-Ib 型患儿进行临床检查和遗传学分析，应用高通量测序技术进行外显子捕获，利用预测软件 REVEL 对蛋白功能进行预测，采用 ClinVar 数据库对突变位点进行致病性分析。
结果 (1)患儿，女，5 月 24 天，腹胀，腹泻，体重不增，腹水，肝功能异常，低蛋白血症，贫血。（2）患儿携带 *MPI* 基因的复合杂合突变，共有两个突变位点（c.1193T>C；c.376_384dupCCGCAGCAC）。（3）经 Sanger 验证 c.1193T>C 来自于父亲，为错义突变，在正常人群数据库中为低频变异，文献数据库已有该位点隐性遗传的病例报道，根据 ACMG 指南，该变异初步判定为疑似致病性变异；c.376_384dupCCGCAGCAC 来自于母亲，为整码突变，在正常人群数据库中为低频变异，文献数据库未有该位点的相关性报道，该变异初步判定为疑似致病性变异。
结论 *MPI* 基因突变可能是该例先天性糖基化病 Ib 型的遗传学病因，新发现的突变拓展了突变谱。

中国糖原累积病 VI 型患者诊治及随访的回顾性研究

罗小梅 段颖 房迪 孙昱 肖冰 张惠文 韩连书 梁黎黎 龚珠文 顾学范 余永国 邱文娟
上海交通大学医学院附属新华医院

目的 糖原累积病(GSD)是一组由于先天性酶缺陷造成的糖原分解、糖酵解、葡萄糖释放和糖原合成的遗传代谢疾病，包括 0、Ia、Ib、II、IIb、III、IV、V、VI、VII、IXa-d 和 XI 型，其中 0、Ia、Ib、VI、IXa-c 和 XI 型以肝脏病变为主，III 和 IV 型可导致肝脏和肌肉病变。GSD VI 型是由 *PYGL* 基因变异引起的肝糖原分解障碍疾病，目前文献仅报道了约 50 例患者，大众对该疾病的临床和遗传特征的认知存在局限性。为了探究 GSD VI 患者的临床特征、分子诊断和长期随访结果，本团队对 2000 年-2021 年于上海新华医院儿内分泌遗传科就诊的 GSD VI 病人进行了回顾性研究。
方法 GSD VI 型患儿经确诊后使用生玉米淀粉治疗，对 56 名患儿治疗前和末次随访时的身高、血糖、转氨酶、血脂、乳酸、尿酸进行了评估，其中身高数值转化为通过遗传身高校正的 Ht SDS，尿酸数值根据不同年龄阶段不同性别的参考值转化为 UA SDS。应用的分子诊断方法随着技术革新而发展改进，包括：Sanger 测序、靶基因测序、外显子组测序、对外显子组测序数据分析片段缺失重复、以及荧光 gap PCR 验证大片段缺失。
结果 入组患者治疗前的主要临床表现包括肝脏肿大、身材矮小、肝转氨酶升高、高甘油三酯血症、空腹低血糖和高尿酸血症。经生玉米淀粉治疗后，患者身高和生化指标得到了明显改善，然而大多数患者到青少年时期再次发生了高尿酸血症。分子诊断为 54 例患者检测出 *PYGL* 双等位基因变异，2 例患者检测出 *PYGL* 单等位基因变异，其中有 43 个新变异。本研究发现了西南和华南地

区 GSD VI 型患者的两个热点变异：c.1621-258_2178-23del 和 c.2467C>T (p.Q823*)。c.1621-258_2178-23del 是一个 3.6 kb 的缺失，容易被常规的分子诊断策略遗漏，该变异可导致 RNA 两种异常剪接，分别是框外缺失 r.1621_2177del 和框内缺失 r.1621_2265del。
结论 本研究首次提出青春期后的 GSD VI 患者可能会再次发生高尿酸血症，建议对 GSD VI 型患者长期监测尿酸。本研究拓宽了 *PYGL* 基因的变异谱，发现了中国西南和华南地区患者的两个热点变异。

基于真实临床数据对自动化变异判读工具的评估与优化

周莹 刘慧丽 罗小梅 许汀 孙昱 顾学范 余永国 范燕洁
上海交通大学医学院附属新华医院

目的 全外显子测序（WES）广泛应用于分子诊断领域，然而其常检出成千上万个候选变异，疾病诊断需要进行变异的筛选、优化和判读，从候选变异中找到可解释疾病表型的变异。这是一个繁琐、耗时耗力的过程，且不同人容易产生不同解读结果，不利于 WES 在临床上的规范和高效应用。因此许多自动化变异评级工具应运而生，其中 Exomiser 和 Xrare 在报道中认为有较高准确率。然而这些工具通常只基于人工合成数据集、特定类型的疾病数据或是小规模病例进行评估。在实际临床工作中，表型记录通常异质性大、不完整、不准确，自动判读工具是否有足够鲁棒性尚不得而知。故本研究选择 Exomiser 和 Xrare，采用上海交通大学医学院附属新华医院临床遗传中心 1614 例连续的 WES 样本，从总体性能、不同类型疾病偏好性和输入表型质量等方面评估这两个自动化解读工具的性能，并利用熵权重总和模型（entropy-WSM）优化两工具判读结果。
方法 选取 2019-2020 年上海交大临床遗传中心 1614 例连续的 WES 样本，包含不同科室送检的代谢病、皮肤病、智力落后、矮小等各类疾病，整理人工判读结果作为评估标准。根据 HPO 对入组样本临床信息进行标准化，输入 Exomiser 和 Xrare 判读工具分别进行判读。计算提取入组样本 HPO 的信息量（IC）值作为输入表型质量描述指标。统计人工判读所报告位点（诊断性变异）分别在 Exomiser 和 Xrare 结果中的排序(rank)，计算总体、不同类型疾病以及不同 IC 统计量 Rank 值累积分布（CDF），从不同方面评估两工具性能。用 entropy-WSM 对两工具结果整合，计算合并分数（EXCS）评估整合后结果，并同第三方公司分析结果进行比较。
结果 Exomiser 和 Xrare 自动解读出的候选变异中，诊断性变异位于前 30 的比例分别为 92.7%和 91%，体现了自动化变异解读工具较高的准确率。但在不同类型疾病中 Exomiser 和 Xrare 的表现各有优劣，其中 Exomiser 在代谢异常疾病中明显优于 Xrare，而 Xare 在脑结构异常疾病明显优于 Exomiser。HPO 词条的信息量对两工具也有影响，特别是极端宽泛表型的输入，Xrare 的解读将受到较大的影响。通过 entropy-WSM 对两工具结果整合计算 EXCS，可将诊断性变异位于前 30 名的比例提高至 95.7%，并降低病种间偏好性和极端宽泛表型输入对判读结果影响。进一步我们将 EXCS 结果同第三方公司判读的结果进行比较，第三方公司的最终解读结果包含 86.67%的诊断性变异，而 EXCS 排序前 10 的变异可覆盖 87.33%的诊断性变异。
结论 Exomiser 和 Xrare 在真实数据集下均表现出了良好的性能，但两工具在不同疾病间具有不同偏好且受极端宽泛输入表型影响不一。利用 entropy-WSM 对 Exomiser 和 Xrare 结果进行合并能降低不同病种间偏好和极端宽泛输入表型的影响，缩小变异解读范围，提高疾病诊断效率。

MOCS3 复合杂合变异导致钼辅离子缺乏症一例

田畦 王华
湖南省妇幼保健院

钼辅离子缺乏会导致钼依赖性酶失活并导致严重的神经系统症状和后遗症。现已知钼辅离子缺陷是由 *MOCS1*、*MOCS2* 和 *GPHN* 基因的致病变异引起，其典型临床特征是新生儿发作的顽固性癫痫发作、喂养困难、发育落后甚至死亡。基础研究提示，*MOCS3* 可能通过影响钼辅离子生物合成影响神经元受体并导致神经元死亡而参与神经发育疾病的发病机制。目前尚无报道指出 *MOCS3* 引起

的典型钼辅离子缺乏临床病例。在本研究中，我们确认一由 *MOCS3* 基因复合杂合变异的典型钼辅离子缺乏病例。该患儿表现出典型且严重的神经系统症状，包括癫痫发作、肌张力亢进、喂养困难和严重发育迟缓。核磁共振显示双侧大脑囊性软化，皮质坏死和硬膜下积液。由于钼辅因子缺乏症临床与严重缺血缺氧性脑病有较高相似度，易被临床医师忽略遗传学病因，分子遗传检测不及时，导致患儿家庭再生育时存在较高的疾病再发风险。虽然钼辅因子缺乏症的脑损伤进展速度明显比缺血缺氧性脑病快，但临床极易误诊为严重缺血缺氧性脑病，因为分娩此类患儿的产妇产程常存在异常，加上患儿大脑 MRI 呈现的多发囊性软化灶，临床表现与缺血缺氧性脑病十分相似，该患儿父母数年夭折的第一胎，被诊断为严重缺血缺氧性脑病，实际上有较大可能亦是由于 MOCS3 基因突变而导致的钼辅因子缺乏症，但却因忽略了遗传基因检测和遗传咨询被诊断为缺血缺氧脑病，导致该家庭二胎再次出生类似疾病胎儿。该病例为第一个由 *MOCS3* 引起的钼辅离子缺乏症的报道。该研究可能有助于钼辅离子缺乏缺陷的产前诊断和遗传咨询

Proteomic Analysis of Atrial Appendages Revealed the Pathophysiological Changes of Atrial Fibrillation

Cuimei Zhao[1] Luying Peng[2]
1.Department of Cardiology, Tongji Hospital
2.Tongji University School of Medicine

Atrial fibrillation (AF), known as the most common arrhythmia in the developed world, affects 1.5-2.0% of the population. Numerous basic studies have been carried out to identify the roles of electric and structural remodeling in the pathophysiological changes of AF, but more explorations are required to further understand the mechanisms of AF development. Proteomics enables researchers to identify protein alterations responsible for the pathological developing progresses of diseases. Compared to the genome, the proteome is closely related to the disease phenotype and can better manifest the progression of diseases. In this study, AF patients proteomically analyzed to identify possible mechanisms. Totally 20 patients undergoing cardiac surgery (10 with paroxysmal AF and 10 with persistent AF) and 10 healthy subjects were recruited. The differentially expressed proteins identified here included AKR1A1, LYZ, H2AFY, DDAH1, FGA,FGB, LAMB1, SMC1, MYL2, MYBPC3, MYL5, MYH10, HNRNPU, DKK3, COPS7A, YWHAQ, and PAICS. These proteins were mainly involved in the development of structural remodeling. The differently expressed proteins may provide a new perspective for the pathological process of AF, and may enable useful targets for drug interference. Nevertheless, more research in terms of multi-omics is required to investigate possible implicated molecular pathways of AF development.

A novel heterozygous variant of MSL3 in a Chinese female with Basilicata-Akhtar syndrome: a case report and literature review

wei su[1,2]
1.Shanghai Children's Medical Center
2.Shenzhen Children's Hospital

Background Basilicata-Akhtar syndrome is a rare developmental disorders characterized by global developmental delay, progressive gait disturbance, and recognizable facial dysmorphism. *MSL3* pathogenic variations have been confirmed as the molecular basis of the syndrome, which encodes protein responsible for bulk histone H4 lysine 16 acetylation (H4K16ac).
Case presentation Whole-exome sequencing was applied to detect likely pathogenic variants in a patient with clinical symptoms of global developmental delay, attention deficit, poor logical thinking ability and characteristic dysmorphic. Genetic study revealed a nonsense mutation (c.570C > G) and RT-PCR revealed prematurely termination of amino acid translation, leading to

truncated polypeptide chains in the MRG domain. The patient has the clinical phenotype of the patient is different from that of the existing cases.
Conclusions This is the first report of diagnosed Basilicata-Akhtar syndrome patient with Chinese origin, and the unique clinical features will help extend our understanding of the genetic and phenotypic spectra of X-linked MSL3-related disorders. Accumulating clinical information of rare syndrome patient offers help in expanding phenotype spectrum of disease and may help improve the recognition efficiency of patients among different races.

THRA 基因变异致甲状腺激素抵抗综合征临床随访及文献复习

余月 [1,2]
1.上海儿童医学中心
2.安徽医科大学第二附属医院

目的 探讨 THRA 基因导致的甲状腺激素抵抗综合征的遗传学病因、临床表现及治疗。
方法 回顾分析 1 例患儿的临床及基因检测资料,并对其进行临床随访及治疗。
结果 患儿，16.5 岁，男，甲状腺功能减退症伴身材矮小。全外显子提示 *THRA* 基因存在错义变异 c.802G＞A，p.Asp268Asn（杂合），据 ACMG 指南评估为可能致病性突变，可引起“甲状腺激素抵抗综合征”。患儿经左甲状腺素钠片（L-T4）替代及生长激素（GH）联合治疗 2 年余，生长速率约 8.7cm/年。现患儿身高、体重均在正常范围，甲状腺功能、IGF-1 等相关指标无异常。
结论 甲状腺激素抵抗综合征属遗传性罕见病，主要致病基因为 *THRA*，主要临床症状为甲状腺功能减低、身材矮小、骨骼发育异常、心动过缓、贫血、便秘等，L-T4 联合 GH 治疗有效。

Neoseq 在新生儿脂肪酸氧化代谢类疾病筛查中的应用

杨宇奇 郭方 龙伟 韩小亚 虞斌
常州市妇幼保健院

目的 基于多重 PCR 扩增子测序（MTA-Seq）的 Neoseq 是一种新的分子筛查技术。本研究旨在探讨 Neoseq 筛查模式在新生儿脂肪酸氧化代谢类疾病（FAOD）筛查与诊断中的应用价值。
方法 采用回顾性病例对照研究方法，以本地区出生的 163500 例活产新生儿作为研究对象，分别采用两种模式进行 FAOD 筛查与诊断：（1）传统模式。所有新生儿足跟采血进行串联质谱（TMS）筛查，初筛阳性召回复查，并进行 NGS panel 检测及其他鉴别诊断。（2）Neoseq 模式。传统模式所有确诊病例，以及初筛阳性、筛查阴性样本中随机抽样，进行 Neoseq 检测分析。比较分析两种模式对于 FAOD 的检出率、假阳性率、额外发现、报告周期等参数。
结果 （1）FAOD 发病情况。基于传统模式共筛查诊断 18 例 FAOD 确诊病例，本地区发病率为 1/9083。TMS 初筛阳性率为 0.55%，筛查阳性率为 0.04%，阳性预测值为 2.0%，阳性召回样本中 98%为假阳性。（2）Neoseq 筛查效果：① 18 例确诊病例中 16 例检测到致病基因突变，比对两种方法突变位点符合率为 88.9%。2 例确诊病例 Neoseq 未检出，包括 1 例 β 酮硫解酶缺乏（BKTD）检出一个致病性突变位点，1 例中链酰基辅酶 A 脱氢酶缺乏症（MCAD）未检出致病性突变。② 57 例 TMS 初筛假阳性样本中，Neoseq 均未发现致病基因突变。③ 100 例 TMS 初筛阴性样本中，Neoseq 额外检出 1 例 *DUOX2* 杂合突变，1 例 *MTTL1* 半合子突变。④传统筛查模式筛查与诊断周期为 28 天~104 天（中位数 43.5 天），TMS-Neoseq 模式报告周期为 10 天~15 天（中位数 12.0 天）。
结论 作为新的新生儿疾病分子筛查技术，Neoseq 可以作为新生儿脂肪酸氧化代谢病串联质谱筛查的重要补充，不仅能及时有效地明确诊断，而且能明显降低初筛假阳性。

基于二代测序的新生儿耳聋基因筛查

胡旭昀 郭若兰 齐展 郭琦 李巍 倪鑫 郝婵娟
首都医科大学附属北京儿童医院

听力丧失是儿童最常见的出生缺陷之一，大约 50%的病例可归因于遗传因素的影响。传统的新生儿听力筛查包括生后及 42 天体检时接受的耳声发射检查和自动听性脑干反应测试。一些地区还包括对高频的热点突变进行耳聋基因芯片检查。作为新生儿基因筛查项目（NESTS）的一部分，我们在前期 15406 例新生儿队列研究中鉴定到 220 例携带一个或两个包含在耳聋基因芯片检测范围内的高频致病变异的新生儿。通过 Sanger 测序证实，我们发现在 9 例新生儿中，耳聋基因芯片未能检测到致病性突变，导致 4.1%的假阴性率。此外另有 2 例为假阳性结果，假阳性率为 0.054%，表明二代测序在检测 13 个热点突变方面有更好的表现。除热点突变外，我们还发现了 *GJB2*、*SLC26A4* 和 *GJB3* 中的其他 50 种致病性/可能致病性变异，并且等位基因频率与先前的研究相当。在后续的临床可行性评估中，我们对 9426 名新生儿的 105 个耳聋相关致病基因进行二代测序，其中初筛阳性（显性遗传致病基因上检出至少 1 个致病性/可能致病性变异；阴性遗传致病基因上检出至少 2 个变异，其中至少 1 个变异为致病性/可能致病性变异）的新生儿 389 名（4.1%）。在所有 9426 新生儿中有 9235 名完成了常规新生儿听力筛查，其中 8834 名完成了热点突变耳聋芯片检查。我们对 8834 名新生儿进行了电话随访，随访率为 85.3%（7535/8834）。研究表明二代测序在新生儿耳聋基因筛查方面有更好的表现。

外显子组测序在 PICU 单基因疾病诊断中的临床应用

郭若兰 刘颖超 胡旭昀 郭俊 齐展 李巍 钱素云 郝婵娟
首都医科大学附属北京儿童医院

背景 外显子组测序（ES）在新生儿/儿童危重症疑似遗传病诊断中的应用逐渐受到关注。然而，该技术在我国儿科重症监护病房（PICU）的应用仍然缺乏相关数据。本研究旨在调查北京儿童医院 PICU 的单基因疾病谱以及 ES 的诊断率和临床实用性。
方法 2017 年 7 月至 2020 年 2 月，对在北京儿童医院 PICU 的 169 名疑似单基因疾病的危重患儿进行 WES 检查。分析临床特征、人类表型术语（HPO）和临床影响评估。
结果 入选儿童的年龄中位数为 10.5 个月（1 个月至 14.8 岁）。进行 ES 检测后，共有 43 名患者（25%）被诊断为单基因疾病。最常见的疾病类别为代谢性疾病（33%）、神经肌肉疾病（19%）和多发性畸形（14%）。患有“代谢/内稳态障碍”、“生长迟缓”或“眼部异常”的患儿诊断率高于没有这些特征的患儿。此外，在患儿中观察到更多表型特征时，诊断率也会增加。ES 的结果对 30 例患者（70%）的治疗产生了影响：（1）治疗策略的改变（n=11），（2）疾病监测的启动（n=18），（3）其他系统评估（n=3），（4）家庭干预（n=2），以及（5）康复和转向姑息治疗（n=12）。
结论 ES 可作为 PICU 有遗传病倾向患儿的有效诊断工具，对疑似单基因疾病患者的治疗有重要影响。

Whole-exome sequencing enables rapid diagnosis and prenatal diagnosis of inherited skin disorders

Hong Guo Kexin Zhang Xintong Zhu Jia Li Na Luo Yun Bai
Army Medical University

Objective Around 80% of genodermatoses are monogenic skin diseases. The genetic and clinical heterogeneity brings great challenges for diagnosis in dermatology. The whole exome sequencing (WES) not only expedites the discovery of the genetic basis of more inherited diseases, but also contributes to genetic counselling and prenatal diagnosis.

Methods In this study, 25 patients with genodermatoses were recruited. Based on the initial clinical and pathological diagnosis, SNVs were identified by WES. The pathogenicity of the CNVs and SNVs were evaluated according to ACMG guidelines. Variants were confirmed by Sanger Sequencing.
Results Totally 25 cases were collected in the study, including 5 Neurofibromas, 4 Epidermolysis bullosa, 4 Tuberous sclerosis complex, 3 Albinism, 2 Ichthyosis vulgaris, 2 Keratosis follicularis and 5 other cases. Night novel variants (c.5546G>C and c.1457delC in *NF1*, c.6110G>T in *COL7A1*, c.2127delG in *TSC1*, c.1445C>A and c.1265G>A in *TYR*, Xp22.31 deletion in *STS*, c.908C>T in *ATP2A2*, c.1371insC in *IKBKG*) and nine known ones were found in the corresponding pathogenic genes by WES In 16 cases. Prenatal diagnosis was applied in 6 pregnant women by amniocentesis.
Conclusions Our findings highlight the value of WES in determining the molecular diagnosis and in genetic counseling. We also discovered the distribution of genodermatoses in this region, which provided a novel clinical dataset for dermatologists.

性染色体型性发育异常的遗传学分析及临床意义

李翠
西安交通大学第一附属医院

目的 探讨不同类型性染色体型性发育异常（disorders of sex development, DSDs）患者的遗传学改变及临床意义。
方法 356 例性染色体型 DSD 患者进行 G 显带染色体分析，对其中 18 例 45,X/46,XY 嵌合体者进行 Y 染色体微缺失检测。
结果 356 例染色体型 DSD 患者中，克氏综合征 210 例，Turner 综合征 124 例，47,XYY 综合征 8 例，47,XXX 综合征 8 例，45,X/46,XY 男性 3 例，Y 染色体结构异常 3 例。18 例 45,X/46,XY 患者中，3 例存在微缺失，其中 AZFc 位点缺失 2 例，AZFa+b+c 位点缺失 1 例。
结论 染色体型 DSD 以克氏综合征最常见，其次为 Turner 综合征。对 45,X/46,XY 男性患者进行 Y 染色体微缺失检测，有助于明确病因和选择更优的辅助生殖技术方案，实现优生优育。

一个 TOR1A 基因变异导致的张力失调家系的基因诊断及产前诊断

杨科
河南省人民医院

目的 对 1 个张力失调家系的临床特征及基因变异进行分析，明确其遗传病因。
方法 对家系中患儿进行全外显子测序，就发现的可疑致病变异使用 Sanger 测序法对患儿及其父母进行检测，明确先证者病因后，进一步对家系中的胎儿进行产前诊断。
结果 测序结果显示先证者 TOR1A 基因（NM_000113）存在 c.765C>A（p.S255R）杂合变异，变异来源于其父亲。同时对 100 名正常人 DNA 进行 TOR1A 基因（NM_000113）c.765C>A 变异筛查均未发现相同变异。经验证，胎儿为 TOR1A 基因（NM_000113）c.765 位点为野生型,预测胎儿不会出现张力失调。
结论 TOR1A 基因（NM_000113）存在 c.765C>A（p.S255R）杂合变异可能是该家系罹患张力失调的遗传病因。

一例极早发型炎症性肠病临床及 IL10RA 基因新变异位点分析

董睿
济南市儿童医院

目的 炎症性肠病（IBD）是一类慢性、复杂的胃肠道疾病，包括溃疡性结肠炎、克罗恩病和未定型结肠炎。极早发型炎症性肠病单独定义了年龄小于 5 岁或 6 岁的 IBD 患者，其临床症状更重，对多数常规治疗不敏感。我们对一例婴儿期出现肛周病变、腹泻及多处肠穿孔的患儿进行临床和遗传学分析，以明确诊断并积极治疗。
方法 对患儿进行临床和实验室检查，采用全外显子组测序技术对其进行基因突变分析，并对家系成员进行疑似致病性突变的 Sanger 测序，明确基因诊断。
结果 患儿，男，4 个月，因“肛周脓肿、肛瘘、腹胀、腹泻 2 月”来诊。专科查体：截石位，于肛周 1 点、5 点处距离肛门缘分别 2cm、0.5cm 可见两处针孔样瘘口，肛周红肿明显，直肠粘膜外翻、糜烂，6 点钟方向可见一瘘口，周围红肿并有分泌物。患儿基因测序提示 *IL10RA* 基因 c.301C>T 和 c.188+1G>A 复合杂合突变（其中 c.188+1G>A 突变未见报道），诊断 *IL10RA* 相关极早发型炎症性肠病，给予抗感染、补液、静脉营养等治疗，症状无减轻，后患儿出现横结肠、升结肠多处穿孔，随行“结肠切除、回肠造瘘术”，术后患儿腹胀、肛周病变逐渐减轻、缓解。
结论 患儿确诊为 IL10RA 相关极早发型炎症性肠病。新发现的 c.188+1G>A 变异扩大了 *IL10RA* 基因的突变谱。

22q11.2 微缺失综合征缺失区域 microRNA 与表型的分析

田园
沈阳市妇婴医院

目的 对 10 例通过产前诊断确诊为 22q11.2 微缺失综合征的胎儿进行表型分析，探讨 22q11.2 区域 microRNA 与临床表型可能存在的关系。
方法对产前超声提示有先天畸形的胎儿进行染色体核型分析、基于高通量测序的拷贝数变异（CNV-seq）检测，结合相关生物信息学数据库对诊断为 22q11.2 微缺失综合征胎儿的缺失区域的 microRNA 进行分析，探讨 22q11.2 微缺失综合征的胎儿的遗传学病因。
结果 胎儿羊水细胞染色体核型均未见异常。CNV-seq 分析表明检测出的 10 例胎儿均存在 22q11.2 区域约 2.5 Mb 左右的缺失，为经典缺失型。该区域覆盖了 TBX1、HIRA 及 COMT 等 22q11.2 微缺失综合征的关键基因，同时包含 4 个明确的 microRNA 基因。
结论 经典缺失型 22q11.2 微缺失是导致胎儿临床表型的主要分子病因，其中 microRNA 的缺失可能是临床表型谱广且变异程度大的关键原因。

一个肢带型肌营养不良症 1F 家系的 TNPO3 基因新变异与临床表型分析

高敏 张开慧 律玉强 马健 王东 盖中涛 刘毅
山东大学齐鲁儿童医院

目的 肢带型肌营养不良症(Limb-girdle muscular dystrophies,LGMD)是一组具有遗传和临床异质性的疾病，主要表现为近端肌无力，患病率为 1.63～5.00/10 万。LGMD 可分为 LGMD1(呈常染色体显性遗传)和 LGMD2(呈常染色体显性遗传)， LGMD1 约占 LGMD 的 10%，其中 LGMD1F 亚型仅数例报道，国内尚未有报道。本文报道了国内首例 LGMD1F 患儿。
方法 对患儿进行临床和实验室检查，并抽取患儿及其父母的外周静脉血，应用二代目标区域捕获测序技术对患儿进行遗传病疾病相关基因的检测，对可疑突变位点进行保守性及致病性预测，并进行患儿及其父母亲的 Sanger 测序验证。

结果 男，4 月 11 天，以“发育迟缓”就诊。现不能竖头，不追视，不追听，查体：四肢肌力低，俯卧不抬头，扶站双足不支撑，双下肢活动少。基因检测示患儿 *TNPO3* 基因存在 c.1432C>T，为新发现的突变，母亲携带。该突变为无义突变，造成蛋白翻译的提前终止，用 SWISS-MODEL 软件构建野生型和突变型运输蛋白 3 蛋白的三维结构图，结果提示突变蛋白部分结构缺失，且已有结构构象改变，生物学软件预测具有致病性。
结论 *TNPO3* 基因的 c.1432C>T 变异引起肢带型肌营养不良症 1F，可能是患儿的遗传学病因。这是国内首例该病的病例报道，该病例的发现丰富了 *TNPO3* 基因的突变数据库。

高通量测序确诊 Hermansky-Pudlak 综合征 5 型（HPS-5）患儿一例及文献综述

王东 黄静 律玉强 高敏 马健 宛雅 盖中涛 刘毅
山东大学齐鲁儿童医院

目的 Hermansky-Pudlak 综合征（HPS）是一组常染色体隐性遗传疾病，该病具有明显的遗传异质性，当前 OMIM 数据库共描述了 11 种 HPS 亚型，各亚型之间在临床表现上存在一定差异，以眼皮肤白化病（oculocutaneous albinism，OCA）症状，出血倾向和组织内蜡样脂质聚积为 HPS 的主要特征。本研究旨在对 1 例临床表现为低色素、眼部白化病及眼球震颤的患儿进行高通量测序分析，以明确其临床诊断。
方法 患儿为 1 岁 5 月女孩，临床表现为自幼眼球震颤，眼底检查发现视网膜大部分色素脱失，为进一步明确诊断，抽取患儿及其父母外周血，应用高通量测序技术对患儿进行测序分析，对可疑致病突变位点进行患儿及其父母的 Sanger 测序验证。同时对目前文献报道的所有 Hermansky-Pudlak 综合征 5 型（HPS-5）案例进行综述，总结该病的临床和基因突变特征。
结果 测序结果示患儿 *HPS5* 基因存在复合杂合突变：c.1562_1563del 和 c.1404C>A，经 Sanger 测序验证分别遗传自患儿的父亲和母亲。根据 ACMG 指南，患儿携带的两个变异均判定为致病性变异。本研究中患儿的临床表现符合 HPS5 的主要临床表现。
结论 该患儿最终被确诊为 *HPS5* 基因突变所致的 Hermansky-Pudlak 综合征 5 型（HPS-5），高通量测序分析为明确诊断该类疾病提供了重要工具。本文综述了目前报道的所有 HPS-5 案例，使临床医生能够对该疾病有更全面、深入的了解。

A novel truncating variant in BCL11B associated with craniosynostosis and global developmental delay

Xuemei Zhao Huijun Wang Bingbing Wu Chenbin Dong Huiyao Chen Ping Zhang Yanyan Qian Xiaomin Peng Xinran Dong Yaqiong Wang Gang Li
Children's Hospital of Fudan University

Background Craniosynostosis is the premature fusion of cranial sutures and is the most clinically important developmental disorder of the skull vault. Craniosynostosis is a high risk of genetic syndrome and one quarter of the patients can be identified with genetic diagnoses. However, there is, only one paper, published in 2019, that notes a patient who has craniosynostosis and with normal global development.
Method The patient and his parent were performed whole exome sequencing and the pathogenicity of variants were analyzed by bioinformatic and genetic analyses. Sanger sequencing and follow-up clinical interviews were performed when possible. The 3-D protein structure of BCL11B was produced and analyzed using the new published neural network AlphaFold. Brain MRI showed multiple brain structural abnormalities and the brain CT with 3D reconstructions showed the multi-craniosynostosis.
Result We report a Chinese patient, a 25-months-old boy. He had midfacial hypoplasia, a small mouth, a thin upper lip, arched eyebrows and a long philtrum. A novel frameshift mutation c.2346_2361del in *BCL11B* gene (NM_138576.4) was identified by whole exome sequencing as

a *de novo* truncating variant in the family. Brain MRI showed multiple brain structural abnormalities, and brain CT with 3D reconstructions showed multi-craniosynostosis. This patient exhibited pneumonia and cerical lymph node enlargement, the percentage of eosinophil and IgE values were significantly increased.
Conclusion Our study expanded the variants of *BCL11B* gene which help to conduct etiological assessment of craniosynostosis and genetic counseling.

Spexin levels are Associated with Painful Diabetic Peripheral Neuropathy

Rui Liu
Huashan Hospital affiliated to Fudan University

Background Spexin is a peptide hormone with multiple functions in regulating energy metabolism and glucose homeostasis. Spexin levels were decreased in diabetes patients. Painful diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes. Recent experimental studies in mice have shown that Spexin has an antinociceptive effect, but there are no relevant reports in clinical studies. This study aimed to evaluate Spexin levels in people with painful DPN and assess the correlation between serum Spexin levels and painful DPN.
Methods This is a cross-sectional study including 20 diabetes patients without DPN (non-DPN), 24 patients with painless DPN, and 16 patients with painful DPN. Questionnaires and laboratory surveys were conducted to collect demographic and clinical data. The existence and severity of DPN were assessed using neurological symptom score, neurological examination, and electromyography. Serum Spexin was measured by ELISA.
Results Painless DPN patients had similar Spexin level with non-DPN diabetes patients, while painful DPN patients had a significant lower level of Spexin than non-DPN diabetes patients ($p<0.001$) and painless DPN patients ($p=0.035$). Furthermore, the prevalence rate of painful DPN was higher in individuals with lower levels of Spexin compared with those with higher levels of Spexin. Spexin levels were negatively correlated with neuropathic pain score. Binary logistic regression analysis showed that the odds ratios for painful DPN were significantly elevated along with decreasing Spexin levels after adjusting for age, sex, BMI, diabetes duration, HbA1c, 2hPBG, hypertension and smoking or drinking status. Serum Spexin levels have a sensitivity of 84.1% and a specificity of 56.2% for predicting painful DPN.
Conclusions Decreased serum Spexin levels were strongly associated with painful DPN, suggesting a possible role of this peptide in pain-related pathogenesis.

预测法布雷病男性患者肾脏受累进展的新风险评分

欧阳彦 潘晓霞 任红 谢静远 王伟铭 李晓 林力 俞夏莲 陈楠
上海交通大学医学院附属瑞金医院肾内科

背景 法布雷病作为一种多脏器系统受累的 X 连锁遗传溶酶体贮积症，肾脏是主要受累靶器官之一。本研究目的为临床医生构建评分工具，来精确预测患者肾脏预后，以尽早给予酶替代治疗干预。
方法 选取 2011 年 11 月-2019 年 11 月，上海瑞金医院肾脏科的法布雷患者作为研究对象。入组标准为：已确诊法布雷病的男性患者；估算肾小球滤过率（eGFR）≥15ml/min/1.73m^2；已检测血浆 lysoGb3；签署知情同意书；有随访肌酐；未接受过酶替代治疗。随访期间，主要肾脏结局定义为 eGFR 较基线降低≥50%或终末期肾脏病（ESRD） 的复合终点。通过 Cox 风险回归分析建立风险模型，并通过 bootstrap 重采样分析进行验证。应用 ROC 曲线来检验风险评分的表现。分析软件为 R 语言（version 3.5.3）。
结果 本研究最终纳入 70 例男性法布雷病患者。入组患者的中位年龄 31.8 岁。中位基线血浆 lysoGb3 水平、eGFR-EPI 和蛋白尿分别为 61.8(0.2-381) ng/ml、89.7±43.0 ml/min/1.73 m^2

和 1.03(0.01-26.4)g/24 h。中位随访时间为 32.8 个月，期间 25 例患者进展至 ESRD，30 例患者发生复合终点事件。通过 Cox 回归分析，最佳风险模型包括血浆 lysoGb3, eGFR 和蛋白尿 。 相比于单个临床指标，该风险评分在预测肾脏终点方面的表现更为出色。
结论 我们的研究表明，确诊时 eGFR 较低且蛋白尿较重、底物水平更高的法布雷病患者出现肾脏不良结局的风险较高。基于这三个变量的风险评分为临床医生提供与风险分层的有效工具。

X 连锁 α-地中海贫血精神发育迟滞综合征一家系临床及 ATRX 基因新变异分析

董睿
济南市儿童医院

目的 X 连锁 α-地中海贫血精神发育迟滞综合征（X-linked alpha thalassemia mental retardation syndrome, ATR-X syndrome）是一种由 ATRX 基因突变引起的 X 连锁隐性遗传病，与发育迟缓、α-地中海贫血、生殖器异常、骨骼畸形等多种临床表现有关，部分患者可完全没有 α-地中海贫血的迹象。该病十分罕见，目前全球约有 200 例患者，国内尚未见报道。这里我们通过对 1 例发育迟缓、特殊面容且有阳性家族史的患儿家系进行临床和遗传学分析，为临床诊断提供依据。
方法 对先证者进行家族史调查、临床和遗传学分析，采集先证者及其父母、2 个兄长血液提取基因组 DNA，采用全外显子组测序对先证者进行基因变异测序分析，并对疑似致病性变异进行 Sanger 测序验证和家系分析。
结果 患儿，男，5 个月，因“竖头不稳、不会翻身”来诊。查体：特殊面容（眉毛外侧稀疏，内眦赘皮，鼻梁低平，鼻小三角形上翘，上唇薄形似帐篷，下唇厚外翻，门牙间隙宽），发育迟缓，小阴茎；实验室检查：血红蛋白 118g/L；头颅 MRI：部分脑外腔隙较宽；基因测序显示患儿及同症兄长 X 染色体 ATRX 基因存在 c.5275C>A（p.His1759Asn）杂合变异，来自母亲，父亲及健康兄长未携带。该变异未见报道。
结论 患儿及同症兄长确诊为十分罕见的 X 连锁 α-地中海贫血精神发育迟滞综合征。新发现的变异扩大了 ATRX 基因的突变谱。

一个口-面-指综合征 1 型家系的 OFD1 基因分析及产前诊断

曹培暄 朱湘玉 顾雷雷 李洁
南京鼓楼医院

目的 对 1 个口-面-指综合征 1 型（oral-facial-digital syndrome type 1，OFD1）家系进行致病基因分析，明确其致病变异，为家系的遗传咨询和产前诊断提供依据。
方法 应用全外显子测序技术对先证者进行基因变异筛查，发现 *OFD1* 基因可疑变异位点后，用 Sanger 测序技术对该家系成员和 100 名正常对照进行验证，确定该家系的致病位点。使用 X 染色体失活分析判断两条 X 染色体的活性比例，并对家系中孕 20 周胎儿抽取羊水标本进行产前诊断。
结果 先证者及家系中所有患者均携带 *OFD1* 基因 c.1189_1192delAATC（p.Q398Lfs*2）杂合变异，而家系中正常成员和 100 名正常对照均未检测到此变异。孕妇及其妹妹存在 X 染色体非随机失活，家系中其余女性患者均为 X 染色体随机失活。产前诊断结果为胎儿携带 *OFD1* 基因 c.1189_1192delAATC（p.Q398Lfs*2）杂合变异。
结论 *OFD1* 基因 c.1189_1192delAATC（p.Q398Lfs*2）杂合变异是该家系的致病原因，新变异的检出丰富了 *OFD1* 基因变异谱，但家系内表型差异性的原因仍需要更深入的研究证实。

三个瓜氨酸血症 I 型家系的临床及 ASS1 基因变异分析

董睿
济南市儿童医院

目的 瓜氨酸血症 I 型（Citrullinemia Type I，CTLN1）是一种罕见的常染色体隐性遗传病，是由 ASS1 基因突变导致其编码的精氨琥珀酸合成酶（argininosuccinate synthetase, ASS）缺陷，从而引起一系列临床症状的代谢性疾病。国外报道发病率约为 1/57000，我国目前仅有少数 CTLN1 患者的病例报道[1]。在本次研究中，我们对 3 个瓜氨酸血症 I 型（Citrullinemia Type I，CTLN1）家系进行基因测序分析，总结中国 CTLN1 的临床和遗传学特征。
方法 对 3 个先证者及其家系进行家族史调查、临床和实验室检查，并采集 3 个家系先证者及父母外周血提取 DNA，应用二代测序技术进行全外显子组测序，并对疑似致病性突变进行 Sanger 测序验证和家系分析。
结果 先证者 1 和 2 均为男性新生儿，表现为嗜睡，四肢肌张力增强；头颅 MRI 提示脑内多发异常信号；血液检查：总胆红素、间接胆红素升高，血氨与瓜氨酸明显升高。先证者 3 为 3 个月大男婴，因“瓜氨酸水平升高”就诊，现无明显症状，肌力、肌张力正常，患儿生长发育正常。曾因“新生儿高胆红素血症”就诊，1 月大时黄疸消退。3 例先证者 *ASS1* 基因分别检测到 c.207_209delGGA 和 c.1168G>A、c.349G>A 和 c.364-1G>A、c.970G>A 和 c.470G>A 复合杂合突变，其中 c.207_209delGGA、c.364-1G>A 未见报道。患儿父母均为变异携带者。
结论 新发现的 c.207_209delGGA、c.364-1G>A 变异扩大了 *ASS1* 基因的突变谱。中国 CTLN1 患者表型具有明显异质性。

AHDC1 基因致病变异致 Xia-Gibbs 综合征 3 例病例报告并文献复习

陈宾 王慧君
复旦大学附属儿科医院

目的 报告 3 例 *AHDC1* 基因致病变异致 Xia-Gibbs 综合征病例，总结临床特征及基因突变的特点。
方法 回顾性分析 3 例由 *AHDC1* 基因突变导致 Xia-Gibbs 综合征患儿的临床资料和家系全外显子测序(WES)结果；系统检索文献，对 *AHDC1* 基因突变导致 Xia-Gibbs 综合征的临床特征及基因变异特点进行文献复习。
结果 3 例患儿均有发育迟缓、肌张力低下和特殊面容表型。WES 检测到患儿均有 *AHDC1* 基因的新发杂合致病变异。病例 1 为热点突变 c.2373_2374delTG(p.C791Wfs*57)；病例 2 为 c.2062C>T(p.R688X)；病例 3 在染色体 1p36.11-1p35.3 区域有 2004.675kb 的片段缺失(*AHDC1* 是主效基因)。本研究病例合并文献检索到的 18 篇英文文献和 4 篇中文文献，共有 55 例病例，包括 42 个致病变异被纳入分析。49 例点突变中，除 1 例为杂合外，其余均为截短突变，最常见的热点突变位点为 c.2373_2374delTG (12.7%，7/55)；最常见的临床表型为发育迟缓(100%)、面部畸形(93.62%)、肌张力障碍(89.58%)和头颅 MRI 异常(81.25%)。
结论 本研究检测到 3 个 *AHDC1* 基因致病变异，c.2373_2374delTG 是 *AHDC1* 基因的热点致病位点。Xia-Gibbs 综合征的表型谱宽，临床确诊依赖分子诊断，早期基因诊断可为临床及时干预和遗传咨询提供依据。

一个矮妖精综合征小家系的遗传学研究

谭娟
连云港市妇幼保健院

目的 对 1 例异常面容伴发育迟缓的 26 月龄矮妖精综合征患儿及其父母进行遗传学检测，探讨其致病机理并分析致病基因与临床表型之间的关系。
方法 整理总结患儿的临床特征，采集患儿及父母双亲的外周血进行染色体微阵列（CMA）及全外显子组测序(WES)进行遗传学分析，并利用 Sanger 测序及荧光定量 PCR(QF-PCR)验证 WES 的检测结果。
结果 WES 结果提示患儿 19p13.2 区域存在父源性 INSR 基因片段缺失，大小为 2,364bp，同时存在 INSR 基因 18 号外显子存在母源性的杂合突变位点 c.3355C>T(p.R1119W)，造成复合杂合突变。
结论 患儿 INSR 基因同时存在点突变与微缺失形成复合杂合突变，可导致矮妖精貌综合征的发生。

一例 SLC9A7 基因变异引起 X 连锁智力发育障碍 108 型患儿的临床和遗传学分析

杨亚楠
山东大学齐鲁儿童医院

目的 智力发育障碍 (MR)是一种复杂且高度异质的疾病，在一般人群中的发病率为 2%，其中 13%–15%的 MR 是由 X 染色体上的基因突变引起的。现对一例临床表现为智力发育障碍患儿进行临床和遗传学分析。
方法 对患儿进行临床检查和遗传学分析检查。抽取患儿及其父母的外周血，应用二代测序技术，进行分子遗传学检测分析，对可疑突变位点进行 Sanger 测序验证和致病性分析。
结果 患儿，男，10 月 7 天，不会坐、爬，阴茎短小，双侧阴囊可触及睾丸。发育迟滞，营养良好，神志清，精神、反应一般。其头颅 MRI 检查提示脑发育不良或代谢性脑病。测序结果显示患儿 X 染色体上的 SLC9A7 基因有 1 个突变 c.1030G>C（splicing），家系验证分析显示该突变遗传自母亲，为半合子突变，该变异导致氨基酸发生剪接突变，使得编码蛋白无法正确翻译，功能丧失，最终导致 X 连锁智力发育障碍 108 型的发生。根据 ACMG 指南，将 c.1030G>C 判定为疑似致病性变异（PVS1+PM2）。该变异为未报道过的新变异。
结论 我们应用二代测序技术检测到 SLC9A7 基因 c.1030G>C（splicing）半合子变异，可能是导致患儿 X 连锁智力发育障碍 108 型发生的遗传学病因；新突变的发现扩展了 SLC9A7 的突变谱并为患者的遗传咨询提供了理论依据。

胎儿颈部水囊瘤、骨骼畸形家系的遗传学分析

杨舒亭
湖南省妇幼保健院

目的 对一例三次超声提示胎儿颈部水囊瘤、骨骼畸形病例进行遗传学诊断，探讨其发病机制，为遗传咨询及指导生育提供依据。
方法 应用全外显子测序技术及 Sanger 测序验证对该家系进行遗传学诊断。
结果 CNV-Seq 未发现致病性拷贝数变异，全外显子测序证实胎儿为 *SLC26A2* 基因 c.1020_1022del:p.V341del 纯合变异，分别来自其父亲和母亲，ACMG 评级为致病性变异，该基因变异与多种骨骼系统疾病相关。

结论 全外显子测序技术在产前超声异常胎儿尤其是多次妊娠超声提示相同畸形病例的诊断中具有重要的临床应用价值，且可为遗传咨询及指导生育提供依据。

Johanson-Blizzard 综合征一家系临床与遗传学分析

张开慧
山东大学齐鲁儿童医院

目的 对一例特殊面容、全面发育落后伴有腹泻、低蛋白血症、低纤维蛋白血症的患儿进行临床和遗传学分析，明确其病因。
方法 采集患儿及其家系成员的病史，应用实验室检查、彩超和新一代测序技术对该家系进行临床和遗传学分析。
结果 先证者，2 岁，男孩，G1P1，患者临床表现为腹泻、腹腔积液、水肿、发育迟缓、营养不良、特殊面容和牙齿损坏，曾在 4 月大罹患婴儿肝炎综合征、抽搐，9 月大时因贫血、低钾血症、骨骼发育不良疑似糖原累积病住院治疗。先入院后实验室检查提示为低蛋白血症、低纤维蛋白血症。二代测序发现该患儿 UBR1 基因(NM_174916.3)存在复合杂合突变 c.3167C>G（p.S1056X）和 c.1911+14C>G（splicing），分别遗传自父亲和母亲，c.3167C>G 为新突变，c.1911+14C>G 为已报道致病突变，两个突变一个为截断突变，一个预测可以引起剪切改变。根据 ACMG 标准，c.3167C>G 预测为致病突变，c.1911+14C>G 预测为疑似致病性突变。目前 HGMD 数据库收录了 UBR1 致病突变 64 个，包括错义突变、截断突变和剪切突变等。
结论 结合临床症状和基因检测结果得出该患儿为 UBR1 基因突变引起的 Johanson-Blizzard 综合征（JBS；OMIM: 243800），为常染色体隐性遗传病，中国人群中已有三例 JBS 患者的报道。二代测序技术为分析该类疾病提供了强有力的诊断工具。

西安市 246 例非综合征型耳聋患者遗传性耳聋基因突变位点分析及遗传咨询

贺芳 王翔
西安交通大学第一附属医院

目的 调查西安市 246 例耳聋患者常见耳聋相关基因 GJB2、SLC26A4、线粒体 12SrRNA 和 GJB3，突变位点分布情况，为寻求适合该地区人群的遗传咨询模式做数据支持。
方法 通过微阵列芯片法，对西安地区 246 例非综合征型耳聋患者，进行四个常见遗传性耳聋基因 9 个热点筛查，在后续遗传咨询中，进一步实施了家系调查，并针对性的进行 GJB2、SLC26A4 基因全外显子序列分析。
结果 246 例耳聋患者中，基因突变检出率 34.55%（85/246），其中，GJB2 基因突变率 17.48%(43/246)，SLC26A4 基因突变率 14.23%(35/246)，7 例线粒体 DNA 12SrRN A1555A>G 均质突变，占比 2.85%（7/246））。另外，家系调查结果显示 GJB2、SLC26A4 基因突变携带率 48.72%（19/39）。最后， GJB2 和 SLC26A4 基因全外显子序列分析，在 GJB2 基因上发现了额外的突变位点 c.605ins46，c.79G>A，c.341A>G，c.257C>G，c.109G>A。
结论 西安市 246 例耳聋患者基因筛查应以 GJB2、SLC26A4 基因突变为主，另外，不可忽视全面家系调查及适时联合 GJB2、SLC26A4 基因全外显子序列分析在后续诊断、治疗、生活及婚育指导等个性化遗传咨询上的重要作用。

Genetic and clinical analysis to identify a novel site mutation of the PRKAR1A gene in a Chinese family with Carney complex with fibroepithelial polyp of the external auditory canal

Wei Wan Huadong Wu Hongqun Jiang Yuanping Xiong
The First Affiliated Hospital of Nanchang University

Background Carney complex (CNC) is an extremely rare multiple neoplasia syndrome with autosomal dominant inheritance which due to PRKAR1A mutation.CNC is characterized by spotty skin pigmentation, myxoma, and endocrine overactivity. The phenotype of hereditary fibroepithelial polyp of the external auditory canal has not been reported in this syndrome, and no direct correlation has been established between disease-causing mutations and phenotype.
Methods Clinical data of proband and their family members were collected, including 4 patients and 50 healthy normal controls. Their peripheral blood samples were tested for the whole exome.
Results The sequencing analysis indicated that in the proband, the PRKAR1A gene had C. 824_825delAG(NM_002734.3:c.824_825delAG), which led to an amino acid changes. The proband's younger brother and mother also had this mutation, while family members with normal phenotypes did not.
Conclusion Analysis of this family suggests that the c.824_825delAG mutation in the PRKAR1A gene leads to a new ear phenotype in this autosomal dominant multiple tumor syndrome, and has important implications for further studies of the clinical phenotype and pathogenesis of Carney complex.

一例 XI 凝血因子缺乏的报道

黄蕾 刘春莲 闫慧 张倩
宁夏医科大学总医院

XI 凝血因子缺乏症（Factor XI deficiency）是一种常染色体出血性疾病，呈常染色体隐性遗传或常染色体显性遗传。主要临床表现为血浆中 XI 凝血因子水平降低（低于 15 IU/dL），创伤或手术后出血倾向，根据 F11 抗原与活性的一致性或不一致性，该病可分为较常见的交叉反应阴性（CRM-）和较罕见的交叉反应阳性（CRM+）两类，个体间临床表现存在差异性。F11 基因编码 XI 凝血因子，以酶原的形式存在于血浆中，是一种独特的血浆凝固酶，该基因致病性突变可导致 XI 凝血因子缺乏症。

遗传性肾性尿崩症的临床分析并文献复习

何杨文
广西医科大学第一附属医院

目的 通过分析遗传性肾性尿崩症患者的临床特征并进行相关文献复习，总结本病的诊断、治疗、随访经验，累积治疗管理经验。
方法 1、收集入组患者及其家庭成员的相关资料，并对同意基因检测者进行基因检测。2、监测患者身高、体重、尿量、饮水量、电解质、尿常规等指标评价药物治疗效果及副作用。3、收集遗传性肾性尿崩症的相关文献。4、统计学分析。
结果 1、入组 HNDI 患者共 8 例，均为男性，首诊原因包括（单独/合并出现）：反复发热 7 例，生长发育迟缓 5 例，多饮、多尿 4 例，反复电解质紊乱 2 例；首次诊断包括：发热待查 3 例，肾性尿崩症 2 例，营养性疾病 2 例，反复电解质紊乱 1 例；首诊时中位数年龄 24.5 个月、中位数身高 74.5cm、中位数体重 7.65kg，中位数尿量 2625ml/天，中位数饮水量为 3025ml/天，治疗前均存在

不同程度的生长发育落后情况，5 例身高、体重均低于正常同龄儿的-2SD。 2、7 例患者行基因检测，1 例未能明确突变类型，3 例为 AQP2 基因突变，3 例为 AVPR2 基因突变。 3、8 例患者治疗后临床症状均有改善，身高、体重标准差较前改善，BMI 较治疗前增长。 4、8 例患者接受治疗期间观察无皮疹、体液潴留等副作用。5、回顾分析 2000-2021 年临床资料较完整的 86 篇国内外文献：5.1 共计 464 例 HNDI 患者，其中男性 402 例，女性 62 例。423 例提供基因检测结果，AVPR2 基因突变 363 例，AQP2 基因突变 60 例。464 例患者首次诊断时平均年龄为 24.4 个月，其中 324 例患者身高、330 例患者体重低于正常同龄儿童的-2SD；5.2 149 例患者提供首诊原因，主要包括（单独/合并出现）：多饮及多尿 140 例、生长发育迟缓 72 例、反复发热 36 例、反复呕吐及恶心 35 例、非尿路感染 33 例、反复电解质紊乱 20 例；149 例患者提供首次诊断：肾性尿崩症 112 例，中枢性尿崩症 12 例，感染性疾病 11 例，消化系统疾病 8 例，营养性疾病 4 例，其他疾病 2 例；5.3 53 例患者提供治疗效果相关信息，治疗前 32 例患者身高、37 例体重低于正常同龄儿童的-2SD；治疗后 20 例身高、18 例体重低于正常同龄儿童的-2SD。

结论 1、HNDI 发病率低、且以男性患者为主，首诊原因繁多、容易误诊及漏诊，对于该类患者、尤其男性患者，特别是婴幼儿期以反复发热、呕吐及生长发育迟缓等起病的，均应考虑本病的可能。2、HNDI 起病年龄小、常生后即出现临床症状，对加压素治疗无效等均是重要的鉴别点，基因检测可明确诊断。3、HNDI 患者均存在不同程度的生长发育落后，尽早进行干预治疗可改善临床症状及生长发育情况。

KRIT1 基因 p.L436fs 突变导致脑海绵状血管瘤一家系报告

曹春艳
河南科技大学第一附属医院

目的 通过对脑海绵状血管瘤的一家系研究，了解家族性海绵状血管瘤的临床表现及致病基因突变位点。

方法 收集 2019 年 10 月入住河南科技大学第一附属医院神经内科的脑海绵状血管瘤的一家系，根据临床表现、头颅磁共振成像（MRI）平扫+弥散加权成像+磁敏感加权成像表现和 Zabramski 分型标准，诊断为脑海绵状血管瘤 1 型，对其进行临床资料的收集及基因测序。

结果 58 岁女性的先证者及其家系成员头颅 MRI 可见多发海绵状血管瘤，通过基因检查确定此家系为家族性脑海绵状畸形 1 型，与根据头颅 MRI 的表现的 Zabramski 分型结果一致，家族性脑海绵状畸形 1 型致病基因突变位点为 KRIT1 基因 p.L436fs，目前尚无家族性脑海绵状血管瘤 1 型的该基因突变位点的完整报告。

结论 本研究发现了此家系中脑海绵状畸形 1 型，KRIT1 基因突变位点为 p.L436fs，让我们对家族性海绵状血管瘤的临床表现及致病基因突变位点有更全面的了解。

A novel mutation in MYH6 coiled-coil domain in a large Chinese Han family with familial inherited atrial septal defect

Shufang Huang Ping Li
Guangdong Provincial People's Hospital

Secundum atrial septal defect (ASD II, OMIM: 603642) is the second common congenital heart defect (CHD) in China. However, the genetic etiology of familial ASD II remains elusive. Using whole-exome sequencing (WES) and Sanger sequencing, we identified a novel myosin heavy chain 6 (*MYH6*) gene insertion variation, NM_002471 c.5470_5471insGGGAGC (p.L1824delinsREL), in a four generation Chinese Han family with ASD II. The variant p.L1824delinsREL co-segregated with the disease in this family with autosomal dominant inheritance. The insertion variant in the coiled-coil domain of the MYH6 protein is highly conserved across species and homologous myosin proteins. In transfected myoblast C2C12 cell

lines, the *MYH6* p.L1824delinsREL variant significantly impaired myofibril formation and increased apoptosis but did not significantly reduce cell viability. Furthermore, molecular simulations revealed that the p.L1824delinsREL variant impaired the myosin α-helix, increasing the stability of the coiled-coil myosin dimer, suggesting that the p.L1824delinsREL variant has an effect on the coiled-coil domain self-aggregation. These findings indicate that this mutation plays a crucial role in the pathogenesis of ASD II. Collectively, our findings expand the spectrum of *MYH6* variations associated with familial ASD II and may provide a pathogenicity of genetic variant for the Chinese family in genetic counseling and prenatal diagnosis.

胚系 BRCA 1/2 基因变异与乳腺癌和卵巢癌临床特征研究

黄斐 陈馨宁 郁俐 姜惠琴 史庭燕 沈敏娜 潘柏申 王蓓丽 郭玮
复旦大学附属中山医院

目的 分析乳腺癌和卵巢癌胚系 *BRCA* 1/2 基因变异，研究乳腺癌胚系 *BRCA* 1/2 基因变异与临床特征的关系。
方法 回顾 2019 年 6 月至 2021 年 4 月于复旦大学附属中山医院就诊的 319 例乳腺癌和卵巢癌患者。采用二代测序检测胚系 *BRCA* 1/2 基因变异。收集 94 例乳腺癌患者的发病年龄、组织学分级、淋巴结状态以及 ER、PR 和 HER-2 表达等信息。采用卡方检验和 Fisher 精确检验分析胚系 *BRCA* 1/2 基因变异与乳腺癌临床特征的关系。
结果 乳腺癌和卵巢癌患者胚系 *BRCA* 1/2 基因变异率为 12.3%和 20.8%。乳腺癌患者变异检出率显著高于公共数据库报道（*P*=0.023），而卵巢癌患者中携带胚系 *BRCA* 1 基因变异远多于 *BRCA* 2 基因（*P*=0.012）。96.4%的变异发生于外显子，3.6%发生于内含子的剪接区。移码变异、无义变异、错义变异和大片段重排占 45.5%、34.5%、9.1%和 5.5%，其中 5 例为未报道的新变异位点。胚系 *BRCA* 1/2 基因变异与乳腺癌发病年龄（*P*=0.000），双侧乳腺癌（*P*=0.001）和三阴型乳腺癌（*P*=0.025）有关。在 ER 和 PR 阳性的乳腺癌患者中，携带胚系 *BRCA* 2 基因变异显著多于 *BRCA* 1 基因（*P*=0.041 和 *P*=0.026）。
结论 胚系 *BRCA* 1/2 基因变异在乳腺癌和卵巢癌中的分布存在差异。本研究积累了乳腺癌和卵巢癌相关的胚系 *BRCA* 1/2 基因变异的数据，为个体化精准治疗提供理论参考。

Identificaiton of Novel TSPAN12 Variants in Autosomal Dominant Familial Exudative Vitreoretinopathy

Shujin Li
Sichuan Provincial People's Hospital

Background Familial exudative vitreoretinopathy (FEVR), a group of rare inherited retinal vascular disorders, is the major cause of vision loss in juveniles. At present, the diagnosis of FEVR remains difficult due to its clinical and genetic heterogeneities.
Aims To identify the causative genetic variants in two unrelated FEVR-affected families: one Indian family and one Chinese Han family.
Materials and Methods: Five affected patients from two families were recruited for this study. Whole-exome sequencing was applied to the probands, and Sanger sequencing was performed for validation. Stringent whole-exome sequencing data analyses were performed to evaluate all of the identified pathogenic variants.
Results Two novel variants in the TSPAN12 gene, namely, one missense variant c.437 T>G (p.Leu146Arg) and one nonsense variant c.477 C>A (p.Cys159*), were identified. Both variants co-segregated with the disease in the investigated FEVR-affected families. Additionally, both variants inactivated the ability of TSPAN12 to enhance Norrin/β-catenin signaling.
Conclusion This study expands the mutational spectrum of TSPAN12 for FEVR.

GPCards: 人类遗传疾病的基因型-表型数据综合分析平台

李滨
中南大学湘雅医院

基因型-表型相关性的研究是人类遗传疾病精准分子分型、个体化用药的基础。如何快速、便捷地获取各种遗传变异与临床表型之间的相关性，对于临床医生和科研人员来说是一个巨大的挑战。为了解决这一难题，我们在 PubMed 上手动搜索了所有基因组学相关的研究，并从 1,710 份出版物中收集了 16,102 名患者携带的 1,160 个基因的 7,849 个遗传变异以及对应的临床表型信息。基于这些基因组学和表型信息，我们研发了一个在线分析数据库 GPCards (http://genemed.tech/gpcards/)。该数据库不仅能够提供了基因和疾病表型之间的相关性，还涵盖了各种临床表型的患病率以及这些临床表型与碱基变异之间的相关性。与此同时，我们整合了 62 个已知的基因水平和碱基变异水平基因组数据来源，包括功能预测、不同人群的等位基因频率和疾病相关信息。此外，GPCards 能够实现自动分析用户上传的基因测序数据，并全面注释，然后将所有的基因按照其功能变异进行优先排序。在此过程中，用户具有充分的自主性，可并使用自定义参数识别基因型-表型相关性。总之，GPCards 将加速人类遗传疾病中基因型-表型相关性的分析、亚型分类，并对候选基因优先排序。

一例罕见新报道变异 Chediak-Higashi 综合征及基因型-表型分析

王聪慧 孔祥东
郑州大学第一附属医院

目的 Chediak-Higashi 综合征（Chediak-Higashi syndrome， CHS）是一种罕见常染色体隐性遗传综合征型白化病，有致死风险。*LYST* 基因变异是 CHS 致病原因。本研究通过对一例新报道变异 CHS 家系结合基因变异数据库进行统计分析，探讨 CHS 基因变异和临床症状的关系。
方法 综合分析先证者病史、临床表现和辅助检查结果，通过全外显子组测序分析先证者基因变异，并经 Sanger 测序进行家系验证。通过基因变异数据库统计分析 CHS 基因变异和临床症状的关系。
结果 患儿表现为部分皮肤白化合并色素异常沉着、反复感染、轻度贫血及易淤伤等，基因检测结果显示先证者为 *LYST* 基因 c.2437C>T（p.Arg813*）和 c.6077dupA（p.Tyr2026fs）复合杂合变异所致 CHS 患者，父母分别为上述变异携带者，该变异均为新报道变异。CHS 基因型-表型分析，*LYST* 基因变异以功能缺失（loss of function, LOF）变异类型为主（79.9%），HEAT repeats 结构域为 CHS 严重临床表型高发区域（81.6%）。
结论 本研究结果丰富了 CHS 相关 *LYST* 基因变异谱，并进一步探讨 CHS 基因型和表型关系，为临床诊断、产前诊断和预后评估提供依据，为研究 LYST 在囊泡运输过程中的分子机制提供线索。

伴镶边空泡的远端型肌病两个家系临床及遗传特点分析

杨康 王志强 陈万金 王柠
福建医科大学附属第一医院

目的：GNE 肌病是 GNE 基因突变引起的一种罕见的常染色体隐性遗传疾病，多于 20-40 岁起病，病程进展缓慢，首发症状多为步态异常，下肢远端肌群受累明显，但股四头肌相对不受累。骨骼肌病理改变可见镶边空泡。我们报道两个 GNE 肌病的家系，分析该病的临床、病理和遗传特点。
方法：收集经基因确诊的两家系患者的临床资料，绘制家系图，对先证者行肌肉组织病理检查，并进行多种组织化学、酶学染色。根据家系的临床特点，应用 sanger 测序、全外显子测序技术技术检测基因的突变情况。

结果：共收集 2 个家系，家系 1 共有 3 例患者，家系 2 共有 2 例患者，均表现为渐进性四肢无力，远端为主，伴有四肢肌肉萎缩，不伴感觉异常。父母均非近亲结婚，家中亲属有类似症状。先证者的肌电图均提示肌源性损害，肌酸激酶轻度增高或正常。肌肉活检标本提示肌源性损害，MGT 可见镶边空泡。家系 1 中先证者基因外显子测序存在 GNE 基因复合杂合突变（c.1313dupT, p.S439Kfs*6; c.1618C>T, p.H540Y），家系 2 中先证者存在（c.1399C>T, p.Q467*; c.1618C>T, p.H540Y）。对家系 1 先证者的亲属包括母亲、兄弟姐妹、孙子、孙女等进行验证，发现患者均携带先证者的两个突变，无症状患者携带一个位点。
结论：隐性遗传模式的远端型肌病同时骨骼肌病理伴有镶边空泡的患者，需要高度怀疑 GNE 肌病。

一例线粒体 HMG 辅酶 A 合成酶缺乏症患儿的临床及基因变异分析

律玉强 盖中涛
山东大学齐鲁儿童医院

目的 线粒体 HMG 辅酶 A 合成酶缺乏症（HMG-CoA synthase deficiency，HMCSD），属常染色体隐性遗传病，由 *HMGCS2* 基因突变引起，是一类由调节酮体生成的酶缺陷而导致的遗传性代谢紊乱症。常由禁食或者其它疾病诱发，主要临床症状表现为呕吐、嗜睡、低酮体性低血糖，伴有肝肿大、代谢性酸中毒和脑病，若无及时治疗，将导致昏迷甚至猝死，本研究对 1 例临床表现为呼吸急促、代谢性酸中毒和肝大的患儿进行临床和遗传学分析。
方法 对患儿进行临床和实验室检查，提取患儿及其父母基因组 DNA，应用高通量测序技术进行测序分析，并对疑似致病性突变进行患儿及其父母的 Sanger 测序验证及生物信息学分析。
结果 患儿精神反应差、呼吸急促、顽固性代谢性酸中毒、肝大、电解质紊乱以及中度贫血。对患儿进行高通量测序发现患儿 *HMGCS2* 基因存在 c.1201C>A (p.E401X)和 c.559+1C>A (splicing)复合杂合突变，Sanger 测序结果显示两突变分别遗传自父母。根据 ACMG 2015 年指南对 c.1201C>A 和 c.559+1C>A 突变进行致病性分析显示两突变均为致病性突变。
结论 本研究中我们对临床表现为呼吸急促、代谢性酸中毒和肝大的患儿进行高通量测序及相关基因突变分析，发现患儿 *HMGCS2* 基因存在 c.1201C>A 和 c.559+1C>A 复合杂合突变，提示患儿为 HMCSD。HMCSD 极其罕见，世界范围内报告不足 30 例，本研究发现的一例 HMCSD，丰富了 *HMGCS2* 基因突变谱和临床表型谱。

TBX5-AS1 在心手综合征中调控上肢与心脏的发育的机制研究

方晴 项盈 安莹 刘展 傅启华
上海儿童医学中心

目的 结合本院 200 例心手综合征患者研究 LncRNA TBX5-AS1 在心手综合征中调控心脏和上肢发育的机制研究。
实验部分：
（1）应用 rt-qPCR 与 Western Blot 技术，在 U2OS、BMSCs、细胞中检测 TBX5-AS1 基因敲剪后对 TBX5 的 rna 与蛋白表达的影响，结果表明敲减该基因后，TBX5 的 mRNA 与蛋白表达均下降。
（2）应用流式细胞分析仪技术，检测 TBX5-AS1 基因敲剪后对细胞增值与凋亡的影响，结果表明在 BMSCs 与 iPS 细胞系敲减 TBX5-AS1 基因后，细胞系的增殖能力分别下调了约 30%与 28.5%，同时促进了细胞的凋亡。在 BMSCs 细胞系中敲剪 TBX5-AS1 后通过影响细胞外基质中透明质酸的表达影响了骨骼发育。iPS 细胞中敲剪 TBX5-AS1 后通过影响细胞心肌细胞分化过程从而影响心脏的发育。

（3）收集 BMSCs、iPS 细胞分化前后时期样本进行转录组测序，评估 TBX5-AS1 在成骨分化与心肌分化相关通路的作用。
结论 TBX5-AS1 在调控心脏与骨骼发育过程中发挥重要作用，通过影响细胞外基质中透明质酸的表达影响了前肢骨骼发育异常，同时该基因通过影响心肌细胞分化过程造成心脏发育异常。

两例 CTCF 基因突变所致精神发育迟滞 21 型的临床特征和遗传学分析

律玉强 盖中涛
山东大学齐鲁儿童医院

目的 精神发育迟滞 21 型（ Autosomal dominant mental retardation 21, MRD21）是一种常染色体显性遗传病，其致病基因为 *CTCF*（CCCTC-binding factor）基因，主要临床症状表现为发育迟缓、智力低下、喂养困难、发育不良以及适应行为障碍等。本研究对两例临床表现为发育迟缓、智力低下的患儿进行临床和遗传学分析。
方法 完善临床和实验室检查，对患儿进行外周血染色体 G 显带核型分析，提取患儿及其父母基因组 DNA，应用高通量测序技术进行测序分析，并对疑似致病性突变进行患儿及其父母的 Sanger 测序验证及生物信息学分析。
结果 两例患儿均有不同程度的发育迟缓和智力低下。染色体核型分析结果均为 46,XX，高通量测序结果显示先证者 1 *CTCF* 基因存在 c.489delG (p.Q165Rfs*14)移码变异，父母未检测到该变异。先证者 2 *CTCF* 基因存在 c.1157_1158delAT (p.Y386Cfs*22)移码变异，父母未检测到该变异。两个变异均为未见报道的新变异。根据 ACMG 指南对 c.489delG 和 c.1157_1158delAT 突变进行致病性分析显示两突变均为致病性突变。
结论 本研究中我们对临床表现为发育迟缓和智力低下的两例患儿进行染色体核型分析及高通量测序分析，发现两例患儿 *CTCF* 基因分别存在 c.489delG 和 c.1157_1158delAT 杂合突变，提示两例患儿为 MRD21，为家系的遗传咨询和产前诊断提供了依据。目前，MRD21 有 50 例报道，中国人群报道极少，仅 4 例，本研究发现的两例 MRD21，丰富了 *CTCF* 基因突变谱和临床表型谱。

一例 DYSF 基因复合杂合变异所致 2B 型肢带型肌营养不良

杨康 林锋 陈万金 王柠
福建医科大学附属第一医院

目的 报道一例 DYSF 基因新的复合杂合突变导致 2B 型肢带型肌营养不良的患者临床表现和基因改变的特点。
方法 对一例患者及其家系成员进行临床资料收集、肌肉活检、肌肉组织免疫组织化学染色和电生理分析，根据该家系的临床特点，应用 sanger 测序、全外显子测序技术检测基因的突变情况。
结果 先证者主要临床表现为双下肢近端无力，表现为上下楼梯困难、蹲立困难，无肌肉萎缩，无肉跳，无言语含糊、吞咽困难等。否认家族史。查体：神清，精神可，颈屈肌力正常，颅神经检测未见异常。四肢肌张力正常，双下肢近端肌力 IV 级，余肌力未见异常，四肢腱反射减退，病理征阴性，指鼻试验正常，深浅感觉未见异常。肌电图示肌源性损害，肌酸激酶 9255U/L。肌肉活检标本免疫组织化学：肌纤维肌膜 dysferlin 表达缺失。患者基因外显子测序存在 DYSF 基因两个突变（c.712A>T，p.K238*和 c.4200delC，p.I1401Sfs*47）。对患者的双亲进行验证，发现患者父亲携带 DYSF 基因 c.712A>T，母亲携带 c.4200delC。
结论 本研究发现 2B 型肢带型肌营养不良的 DYSF 新的复合杂合突变，增加了人群 DYSF 基因突变的多样性。

全外显子测序鉴定一例白化病基因突变

黄盛文
贵州人民医院

目的 对一名具有白化表现、精液检查无精子的男性应用全外显子组高通量测序技术，并进行 Sanger 测序验证，筛查该男子的致病基因，为该家庭提供遗传咨询。
方法 先证者，男，40 岁。临床表现及怀疑疾病：白化病，无精症。精液检查无精子，左侧附睾囊性结节，外周血核型分析结果：46,XY，性激素正常。先证者本人及姐姐患白化病，父母近亲婚配。签署知情同意书后，采集先证者外周血并提取 DNA，使用全外显子组高通量测序检测技术，利用变异位点检测系统和变异位点注释解读系统对数据进行分析。
结果 先证者 11 号染色体上 TYR 基因的 2 号外显子发生移码突变：c.929dup（p.R311Kfs*7）。根据美国医学遗传学与基因组学学会(ACMG)指南及 ClinGen 序列变异解释(Sequence Varia-nt Interpretation，SVI)专家组对指南标准的应用建议，以及对人类表型本体数据库（HPO）、在线《人类孟德尔遗传》（OMIM）、遗传学参考（GHR）等公共数据库查找与白化病、无精症、附睾异常等表型或疾病相关基因变异进行筛查，提示 TYR 基因的 c.929dup 为致病突变位点。
结论 经全外显子测序及 Sanger 测序验证，确诊先证者为白化病，致病突变为 TYR 基因 c.929dup（p.R311Kfs*7）。测序结果可为该家庭遗传咨询提供依据。

214 例 DSD 患者分子遗传学分析

杨季云
四川省人民医院

目的 通过对 214 个性发育异常（disorders of sex development，DSD）病例进行分子病因学分析，以期明确其遗传病因。拓展 DSD 致病基因变异谱并发现新的候选基因，为 DSD 人群的预防、诊断和治疗提供遗传病因学依据。
方法 在四川省人民医院招募诊断为 DSD 的病例 214 例。其中 203 例 46,XY DSD，11 例 46,XX DSD。MLPA 方法检测 SOX9，NR5A1，WNT4，CXorf21，NROB1 基因拷贝数。靶向性捕获高通量测序检测与性发育相关基因，共计 219 个基因。通过生物信息学方法筛选候选变异，并使用 Sanger 测序或 QPCR 进行家系验证。
结果 在 23 个 DSD 致病基因中筛选出 109 个变异位点，其中致病和疑似致病变异占 72.48%（79/109），临床意义未明变异占 27.52%（30/109）。总体确诊率为 **36.9%。其中** 46,XY DSD 确诊率为 **38.9%，**46,XY DSD 确诊率为 0，有 3 例 46,XY DSD 检出临床意义不明变异。
结论 DSD 基因诊断率较低，仍有大量的新致病基因有待发现；基因诊断有助于疾病诊断、性别再分配及选择更合理的长期治疗方案，并提供准确的遗传咨询信息；体外功能实验有助于 VUS 致病性的判断。内分泌检查和评估不应局限于先证者，应包括其父母。

FECH 基因变异的白塞病患儿 1 例

祝紫葳 姜红堃
中国医科大学附属第一医院

目的 白塞病是以血管炎为基本病理改变的系统性自身免疫性疾病。实验室检查缺乏特异性，诊断依赖临床表现。病初临床表现不典型且症状复杂多变，容易漏诊、误诊。白塞病存在地域及种族差异性，儿童患者较为罕见，较成人有更显著的家族聚集分布现象。病因、发病机制及确切的致病基因目前尚不明确，本研究对 1 例临床诊断白塞病患儿进行高通量全外显子测序，以期发现白塞病的遗传学病因及发病机制，为白塞病的基因诊断治疗提供理论依据。

方法 对 1 例临床诊断白塞病的患儿行血常规、血生化检验，收集患儿及其父母外周血标本，采用高通量测序技术进行全外显子检测。
结果 未检测到该患儿存在既往已报道的白塞病相关基因变异。但发现该患 FECH 基因的 1 号内含子和 3 号内含子存在杂合变异 c.68-23C>T、c.315-48T>C，其父母 FECH 基因相应位点均为杂合携带。既往有报道此两种变异可引起 FECH 基因所转录的 mRNA 剪接水平的异常，使其编码的 FECH（亚铁螯合酶）活性降低，引起红细胞生成性原卟啉症（EPP）。该患儿临床及实验室检查均无相应表现。
结论 我们推测 FECH 基因的变异可能与白塞病有关，具体发病机制有待进一步探究。

Screening LncRNA-SET2-1 related to ABAT gene based on integrated regulatory network analysis and its effect on cell proliferation and apoptosis in myelodysplastic syndrome

qian wang
Department of Hematology, Huashan Hospital, Fudan University

Objective By constructing an integrated regulatory network with the characteristics of myelodysplastic syndrome (MDS), we screened out the long non-coding RNA (LncRNA) that regulates the ABAT（4-aminobutyrate aminotransferase）gene, and explored its expression and function in MDS preliminarily.
Methods The differential genes of bone marrow samples collected from MDS patients and controls were screened by methylation microarray and whole genome expression profile microarray. Integrated analysis of the differentially expressed genes (DEGs), differentially methylated genes (DEMs) and differentially expressed LncRNAs (DELs) was conducted for constructing a co-expression regulatory network. The LncRNA-SET2-1 correlated with ABAT gene was screened from the integrated regulatory network. The expression levels of LncRNA-SET2-1 and ABAT in bone marrow samples of MDS patients and controls were detected by qRT-PCR. The expression level of LncRNA-SET2-1 was detected in MDS transformed leukemia cell line SKM-1, acute leukemia cell line THP-1 and control cell line HEK-293T. The SKM-1 and THP-1 cell lines with stable overexpression of LncRNA-SET2-1 were established. In these cell lines, the expression of ABAT was detected by qRT-PCR, the cell viability by CCK-8 and apoptosis by flow cytometry. The expression changes of LncRNA-SET2-1 were also detected in ABAT knockdown SKM-1 and THP-1 cells.
Results Through the analysis of co-expression regulatory network, LncRNA-SET2-1 had the highest correlation with ABAT. The expression levels of LncRNA-SET2-1 and ABAT in MDS patients, SKM-1 cells and THP-1 cells were significantly down-regulated ($P < 0.0001$). Overexpression of LncRNA-SET2-1, the expression level of ABAT was significantly increased ($P < 0.01$). While ABAT was knockdown, the expression of LncRNA-SET2-1 did not change significantly. When LncRNA-SET2-1 was overexpressed, the cell viability of SKM-1 and THP-1 cells was reduced significantly, and the cell apoptosis was increased significantly.
Conclusions LncRNA-SET2-1 may be the upstream regulator of ABAT. LncRNA-SET2-1 with functions of cell proliferation inhibition and cell apoptosis induction was aberrantly down-regulated in MDS patients and MDS transformed leukemia cell lines.

The inhibitory effect of the downregulation of TUBB2C and its promotion of apoptosis in SKM-1 cells

qian Wang
Department of Hematology, Huashan Hospital, Fudan University

Background Myelodysplastic syndrome (MDS) comprises a varied group of diseases that originate in hematopoietic stem cells, but its pathogenesis is still uncertain. This study aimed to

explore whether the downregulation of *TUBB2C* could affect the biological function of *TUBB2C* in the leukemic transformation of MDS by reducing the viability of SKM-1 cells.
Methods A previous nested control study was conducted and six genes that could differentiate the leukemia group and the control group were screened. *TUBB2C* showed a higher expression level in the leukemic transformation group. SKM-1 cell line was a malignant MDS/acute myeloid leukemia (AML) cell line established in the leukemic phase.
Results *TUBB2C*-specific siRNAs were used to down-regulate the expression of *TUBB2C* in the SKM-1 cell lines. After the transfection, the analyses of cell morphology, cell cycle, cell apoptosis, and viability were performed both in vitro and in vivo. The down-regulation of *TUBB2C* was able to inhibit SKM-1 cell mitosis and the proliferation of SKM-1 cells in the G1/S restriction point, inducing the early apoptosis of SKM-1 cells and inhibiting cell viability and tumor formation in NOD/SCID mice.
Conclusions *TUBB2C* gene silencing could inhibit the growth of SKM-1 cells and promote its apoptosis, which could further decrease cell viability both in vitro and in vivo. This signifies that *TUBB2C* might play a significant role in the transformation of myelodysplastic syndrome (MDS) into MDS/acute myeloid leukemia (AML). It might be a biomarker of leukemic transformation and a potential target of this MDS/AML cell.

Comprehensive analysis of LncRNA-miRNA-mRNA ceRNA network in Down syndrome based on bioinformatics analysis

Zhipeng Zeng Zhiyang Hu Wei Shi Wenlong Hu Xi Wang Wanxia Cai Mei Ye Jun Zhou Pingping Ye Fang Yuan Yong Dai Donge Tang
Shenzhen People's Hospital

Background Down syndrome (DS) is a typical chromosomal disease caused by an extra copy of all or part of chromosome 21, and its clinical phenotype is complex and various including autoimmune disease, Alzheimer’s disease, congenital heart defects, leukemia, etc., which seriously harms people's health. However, there have been fewer reports revealing the competing endogenous RNA (ceRNA)-mediated regulatory mechanisms in DS.
Methods In this study, we collected umbilical cord blood and separated the PBMC and analyzed the expression profiles of lncRNAs, miRNAs and mRNAs between DS individuals and normal people by using deep RNA sequencing (RNA-Seq).
Results We identified 216 differentially dysregulated miRNAs, 651 differentially dysregulated lncRNA transcripts, and 15789 differentially dysregulated mRNA transcripts between the DS group and the NC group. KEGG pathway enrichment analysis showed that DEmRNAs were involved in pathways such as Huntington's disease, Alzheimer's disease, Parkinson's disease, NF-kappa B signaling pathway, etc., which are closely related to DS. Then 11 hub mRNAs (RPS27A, UBA52, UBC, RPL11, RPS27, MRPS7, RPL23, RPL9, NFKB1, RBX1, and RELA) with the highest degree in the PPI networks, which may play an important role in the occurrence of DS. Finally, we constructed up-regulated and down-regulated lncRNA-miRNA-mRNA ceRNA sub-networks consist of 197 lncRNAs, 5 miRNAs, and 4 mRNAs. MIAT, RBX1, and RELA may be underlying biomarkers for DS. In addition, we found several pairs of ceRNAs that might be involved in DS. MIAT may serve as a ceRNA to sponge hsa-miR-378c and ultimately co-regulate the expression of RBX1 together with other lncRNAs causing trisomy 21 by affecting the cell cycle.
Conclusions In this study, we comprehensively analyzed the gene regulation in the progression of DS by the lncRNA-miRNA-mRNA ceRNA network. The lncRNA-associated ceRNA might contribute to the diagnosis and treatment of DS.

一种基于三类属性来预测颈动脉斑块的方法

蒋鹏[1] 李建敦[2] 蒋伏松[1] 刘丽梅[1]
1.上海交通大学附属第六人民医院
2.上海电机学院

目的 针对颈动脉斑块（Carotid Plaque）诊断效率不高的问题，本文旨基于真实数据集开展横断面研究，以建立能有效识别的有监督分类器。
方法 基于上海交通大学附属上海市第六人民医院 5993 例糖尿病患者（2012 年～2018 年）的脱敏数据来开展研究。根据已有的研究成果，聚焦其中的 10 个属性来训练分类模型，包括性别、年龄、糖尿病病程、甘油三酯（Triglyceride，TG）、低密度脂蛋白、高密度脂蛋白、总胆固醇（Total Cholesterol，TC）、空腹血糖（Fast Plasma Glucose，FPG）、糖化血红蛋白、空腹胰岛素（Fast Insulin，FINS）。在传统机器学习模型基础上，如线性回归、逻辑回归、支持向量机、决策树等,我们采用更多的有监督模型拟合。模型由 Weka（v3.8）实现，且经 10 折交叉验证（10-fold Cross Validation）。
结果 实验表明，随机森林在精度（0.808）、召回率（0.806）、F1 值（0.805）、曲线下面积（Area Under Curve, AUC）(0.897）等方面均优于其他模型。结论：根据对预测贡献的大小排序，年龄、脂蛋白标记物（如低密度脂蛋白、高密度脂蛋白）和血糖指数（如糖化血红蛋白和空腹血糖）三类属性最高，且仅此三类属性已足以预测颈动脉斑块病患（AUC=0.853）。
结论 实验表明，脂蛋白、血糖和年龄三类属性，已足以从糖尿病人群中预测颈动脉斑块。

HADHB 基因突变致线粒体三功能蛋白缺乏症一例

张光业 杨露 律玉强 马健 高敏 盖中涛 刘毅
山东大学齐鲁儿童医院

目的 线粒体三功能蛋白缺乏症(Mitochondrial trifunctional protein deficiency, MTPD)是一种罕见的常染色体隐性遗传的脂肪酸氧化障碍性疾病，是由于 HADHA 或 HADHB 基因变异导致其编码线粒体三功能蛋白缺陷、阻碍身体某些脂肪转化为能量的一种罕见疾病，每年新生儿发病率为 20 万分之一。该病可在婴儿期或儿童早期发病，婴儿期发病典型症状为喂养困难、嗜睡、低血糖、肌张力减退及肝脏问题。本文对 1 例 MTPD 患儿进行临床特点和基因突变分析，探讨其分子遗传学发病机制，明确诊断。
方法 对一例患儿临床表现、实验室检查及病史进行回顾性分析；同时采用全外显子组测序技术对患儿进行基因突变检测，并对疑似致病性突变进行患儿及其父母的 Sanger 测序验证及生物信息学预测，用 REVEL，SIFT、PolyPhen_2、MutationTaster 、GERP+软件对突变进行致病性分析。
结果 先证者，男，5 月，因呕吐，肝功异常入院，后表现出低酮性低血糖，脂肪酸代谢异常、肝脏肿大、转氨酶升高、严重酸中毒、呼吸衰竭，基因检测发现 HADHB 基因有 c.181C>T(p.R61C)及 c.1389+5G>A(splicing)复合杂合突变，分别来自先证者母亲和父亲。其中 c.181C>T(p.R61C)突变为文献报道的已知致病性突变；c.1389+5G>A(splicing)目前未见文献报道，生物信息学预测为临床意义未明突变。
结论 患儿可能为 HADHB 基因复合杂合突变所致 MTPD。本文丰富了 MTPD 基因突变谱，并为家系遗传咨询及产前诊断提供了依据。

FARS2 基因变异导致联合氧化磷酸化缺陷 14 型的临床表现及遗传学分析

马健 张洪伟 律玉强 高敏 王东 盖中涛 刘毅
山东大学齐鲁儿童医院

目的 联合氧化磷酸化缺乏症 14 型（Combined oxidative phosphorylation deficiency 14,COXPD14）是一种核 DNA 变异导致线粒体氧化磷酸化功能障碍从而引起的代谢性疾病，呈常染色体隐性遗传模式。其特征是新生儿期开始出现持续性癫痫发作、躯干肌张力减退，发育迟缓和乳酸性酸中毒，病变主要集中于中枢神经系统，属于线粒体脑病一种。应用二代测序技术（NGS），我们对一惊厥发作，生长发育迟缓，体内血乳酸值升高的 2 月龄患儿行全外显子组和线粒体环基因检测，探讨其分子遗传学病因。
方法 对患儿进行临床和实验室检查，并抽提患儿及其家系成员外周血基因组 DNA 行 NGS 检测，对可疑致病性位点进行 Sanger 测序验证，依据 ACMG 指南对疑似位点进行致病性分析。同时检索 PubMed，万方数据库和中国知网数据库中 COXPD14 的病例报道，对国内外已报道的所有 COXPD14 患儿临床资料进行回顾性总结并绘制 *FARS*2 基因突变谱，对该病临床表型及遗传学病因进行探讨分析。
结果 患儿出生体重 3.1kg，身长 52cm，2 月龄因癫痫发作、发育迟缓入院治疗。神经系统检查发现四肢肌张力减退，眼神接触不良（不会追视，与人眼神无交流）。头颅 MR 提示脑内多发异常信号，双侧额叶、颞叶、枕叶和皮层下白质区出现病变，胼胝体发育不全，部分脑液间隙较宽；MRV 示左侧横窦、乙状窦较对侧略细。血乳酸值高于正常水平，且随着惊厥发作加重，谷丙转氨酶(ALT)和谷草转氨酶(AST)高于正常水平。3 月龄时因呼吸窘迫夭折。全外显子测序提示患儿 *FARS2* 基因携带 c.925G>A（p.G309S）和 c.405C>A（p.H135Q）复合杂合变异，分别遗传自母亲和父亲。依据 ACMG 指南，c.925G>A 变异定义为疑似致病性变异（PM3-Strong +PM2-Supporting +PP1+PP3）；c.405C>A 预测为疑似致病性变异（PM3-PM2-Supporting+PP3+PP4）。文献检索发现 30 例 COXPD14 患者 (共 31 例)，均以癫痫发作，血清乳酸升高及新生儿期生长发育迟缓作为典型表现，且病死率高。HGMD 收录 *FARS2* 变异类型包括：错义突变、剪切位点改变、读码框内碱基缺失和编码区域微缺失，以错义突变最常见（占 80%）。
结论 我们通过遗传学检测发现 *FARS2* 基因 c.925G>A 和 c.405C>A 复合杂合变异是导致患儿发病的原因。该病起病早，因此对 COXPD14 患儿首次诊断后的发育评估及长期随访研究是必要的，以便于明确患儿的发育轨迹以及药物治疗的效果，同时基因学诊断可以为家庭的遗传咨询及再次生育时产前诊断提供依据。

一例 ADNP 基因变异导致 Helsmoortel-van der Aa 综合征患儿的临床及遗传学分析

马健 马海霞 张开慧 律玉强 高敏 王东 盖中涛 刘毅
山东大学齐鲁儿童医院

目的 Helsmoortel-van der Aa 综合征(HVDAS)是一种罕见的先天性颅面畸形伴自闭症谱系障碍综合征，呈常染色体显性遗传，多数患者是由 *ADNP* 基因 3’端最后一个外显子上移码或无义变异导致。该病患儿可见不同程度的面部畸形(前额突出，前发际线高，上睑下垂，眼距宽，宽鼻梁，人中平滑，上唇薄)，智力障碍（轻度/中度/重度），自闭症谱系障碍（强迫性/刻板行为、多动），身材矮小，睡眠障碍，低张力症，先天性喂养困难，视觉障碍（远视/斜视），先天性心脏缺陷，手畸形（小手），癫痫等特征。本研究中，我们对 1 例面容异常，智力低下，语言发育迟缓，自闭症谱系障碍的先证者进行了全外显子组测序，对先证者及其父母突变位点行 Sanger 测序验证，通过对先证者家系临床表型及遗传学病因进行探讨分析，为该病的诊断和遗传咨询提供依据。
方法 对患儿进行临床和实验室检查，并抽提患者及其家系成员外周血基因组 DNA,应用二代测序技术对患者外显子组基因序列进行检测，Sanger 测序验证家系可疑致病位点，依据 ACMG 指南对

疑似致病性变异位点进行分析。对已报道的 HVDAS 患儿的临床特征进行总结，试图探讨该病基因型-表型间相关性。

结果 患儿面容特殊，表现为前额宽大，额头凸出，眼距宽，双眼斜视，外耳廓畸形，鼻根扁平，人中平滑，薄上唇。自幼运动及语言发育落后，理解认知能力差。存在轻微自闭症谱系障碍，牙齿萌发过早（3 月龄即可见乳牙萌出）。全外显子测序提示患者 *ADNP* 基因 5 号外显子上携带 c.568C>T (p.Q190X)杂合变异，该无义突变可导致蛋白质翻译的提前终止。依据 ACMG 指南及现有临床证据，c.568C>T 被评定为致病性变异（PVS1:功能丧失型突变+PS2:新发变异+PM2:该变异未见大规模人群数据库报道）。我们对已报道病例的临床表型与基因型相关性进行总结，发现无义和移码变异的先证者运动及语言发育更为缓慢，颅面部特征更加典型。位于 C 端核定位信号结构域上的基因变异个体上睑下垂和运动障碍发生的频率更高。

结论 该患者被诊断为 *ADNP* 基因变异导致的 Helsmoortel-van der Aa 综合征，这是迄今国内该病的第二例报道。目前，已报道的 HVDAS 先证者发病年龄相对较小，因此长期的随访研究是必要的，以确定 ADNP 变异个体的发育轨迹以及康复治疗的效果，为后续该病的诊治提供更宝贵的经验。

基于 Nanopore 三代测序技术的全线粒体测序在 Leber 视神经病变诊断中的应用研究

王攀峰 张清炯 贾小云
中山大学中山眼科中心

目的 近年来二代测序技术以及广泛应用于遗传病的主流临床研究和检验方法，但由于二代测序技术的读长短，对结构变异等复杂技术的检测常常力有不逮。长度长测序技术（也称第三代测序技术），具有超常读长、GC 偏好低等优势，有效弥补二代测序的不足，在结构变异、串联重复序列的检测中表现优异。但其对点突变的灵敏性和准确性尚未获得广泛认可。人类线粒体基因组是一个长约 16569 bp 核外基因组，线粒体组的遗传缺陷会导致机体能量来源不足而出现线粒体病。本文探讨基于 Nanopore 三代测序的全线粒体测序在 Leber 视神经病变诊断中的应用价值。

方法 将携带 m.11778G>A 的 Leber 视神经病变患者外周血 DNA 同该位点正常的对照外周血 DNA（n=3），在相同浓度的情况下（40ng/ul）进行 8 个不同比例的混合，浓度范围从 100%-0.1）。进行长片段 PCR 扩增全线粒体后建库，在 Oxford Nanopore GridION 上机测序收集测序 1 小时、2 小时和 4 小时的测序结果，生物信息学分析后，统计不同条件下突变检出情况。

结果 数据量和测序深度随着测序时间的延长而增加。该方法可有效检测出杂合异质比 20%及以上的 m.11778G>A 突变，但更低比例的突变，因为 Nanopore 测序固有的错误率而无法从背景噪音中滤出。

结论 基于 Nanopore 三代测序技术的全线粒体测序可谨慎用于嵌合比较高的 Leber 遗传性视神经病变检测。

Compound heterozygous mutations in TMC1 and MYO15A are associated with autosomal recessive non-syndromic hearing loss in two Chinese Han families

Pengcheng Xu[1,2,3] Tao Yang[1,2,3] Jun Xu[1,2,3]
1.Department of Otorhinolaryngology-Head and Neck Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
2.Ear Institute, Shanghai Jiao Tong University School of Medicine, Shanghai, China
3.Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China

Genetic hearing loss is a common sensory disorder and its cause is highly heterogeneous. In this study, by targeted next-generation sequencing of 414 known deafness genes we identified

compound heterozygous mutations p.R34X/p.M413T in *TMC1* and p.S3417del/p.R1407T in *MYO15A* in two recessive Chinese Han deaf families. Intrafamilial co-segregation of the mutations with the hearing phenotype was confirmed in both families by Sanger sequencing. Auditory features of the affected individuals are consistent with that previously reported for recessive mutations in *TMC1* and *MYO15A*. The two novel mutations identified in this study, p.M413T in *TMC1* and p.R1407T in *MYO15A*, is classified as likely pathogenic according to the guideline of ACMG. Our study expanded the mutation spectrums of *TMC1* and *MYO15A* and showed that next-generation sequencing in combination with genotype-phenotype correlation can provide more accurate genetic diagnosis for deafness.

Familial 22q11.1-q11.21 duplication: a two generation family with a 1.35-Mb duplication and a de novo 2.54-Mb duplication

Yang Lu Bo Shen
Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University

Background Cat-eye syndrome (CES) and 22q11.2 duplication syndrome are induced in duplications in the 22q11.1-q11.21 region. While the genetic transfer from CES to 22q11.2 duplication syndrome, that not previously reported.
Methods The proband and her father were diagnosed with cat-eye syndrome, and the proband's sister was diagnosed with 22q11.2 duplication syndrome. Karyotype analysis and CNV-seq was detected in the family members. An ophthalmologic examination performed in proband and father, included: orbits routine scan, fundus examination, single field analysis and eyeball pull test.
Results We reported a Chinese family with cat-eye syndrome (CES) with a 1.35-Mb tetrasomy on 22q11.1-q11.21 (17.25 Mb-18.60 Mb) in two generations. Prenatal diagnosis of the fetus who is the couple's third child using CNV-seq revealed a 2.54-Mb trisomy on 22q11.21 (18.90 Mb-21.44Mb), suggesting that 22q11.2 duplication syndrome. Following up the baby, the clinical symptoms were consistent with the disease. We hypothesized a model of genetic transmission from CES to 22q11.2 duplication syndrome. In addition to these reported symptoms of CES, family members appeared a novel clinical symptom of extraocular muscle dysfunction, their eyeballs can barely move.
Conclusions Our findings revealed the first genetic case of from CES to 22q11.2 duplication syndrome and broadened the understanding of CES syndrome.

中国新生儿外显子组基因测序包（NeoExome）设计与 3430 例多中心新生儿样本的早期验证研究

曹紫阳[1,2] 余朝文[3] 何晓燕[3] 王冬娟[3] 伍建[4] 李木明[4] 顾茂盛[5] 强荣[6] 王晓华[7] 曹东华[8] 邹琳[1,2,3]
1.上海市儿童医院临床研究中心
2.上海交通大学医学院儿童感染免疫与重症医学研究院
3.重庆医科大学附属儿童医院临床分子医学中心/新生儿筛查中心
4.北京迈基诺基因科技股份有限公司 5.徐州市妇女儿童医学中心
6.西北妇女儿童医学中心 7.内蒙古妇女儿童医学中心
8.大连市妇女儿童医学中心

目的 新生儿筛查（新筛）是出生缺陷三级预防中的最后一道防线，目前常用生化方法进行筛查，病种有限且存在假阳/阴性。近年高通量测序技术（NGS）在产前诊断、肿瘤靶向基因与病原体检测应用广泛，在新筛应用前景广，但仍存在系列挑战。本研究旨在初步探索 NGS 在中国新筛中的应用潜能。

方法 基于 NGS 中外显子组测序技术，以中国高发遗传病、明确致病基因与变异位点为靶标，参照经典数据库，设计中国新生儿外显子组基因测序包（NeoEXOME），先回顾性验证，再在中国 5 个新筛中心收取样本，利用基因捕获技术，初步验证合理性。
结果 结合多个遗传病数据库（Clinva、HGMD、dbSNP 等）、可防可治的新筛防控要点，设计出适合中国新生儿 NeoExome，涵盖 542 种单基因遗传病，602 个基因；以 ACMG 指南为依据，结合算法，分别制定出适合高危新生儿基因检测和普通新生儿筛查数据的解读规则；利用千人基因和 10 万人遗传病测序数据库，回顾性分析和理论验证基因与位点；在重庆、陕西、内蒙古、大连、徐州 5 个新筛中心收集到的 3430 例样本与信息，分析与验证了 NeoExome 对中国新筛的应用场景与合理性。
结论 NeoExome 对于可防可治的中国高发遗传病新筛设计合理，应用前景良好，可进一步优化方案与入组更多受试者。

PTCH1 可能不是 CTD 的潜在候选基因

李璐璐 傅启华 梁斐 王波
上海交通大学医学院附属上海儿童医学中心

目的 通过对先心病人和正常对照人群靶向测序结果的突变富集测试分析，以及心脏组织特异性 *Ptch1* 敲除小鼠模型，探究 *PTCH1* 是否为一个新的先心病致病基因。方法对 300 例圆锥动脉干畸形（Conotruncal defects, CTD）患儿（排除染色体核型异常和 22q11.2 微缺失）及 1447 例健康人群外周血 DNA 样本进行 23 个先心病（Congenital heart disease, CHD）候选相关基因和 80 个已知 CHD 致病或相关基因进行靶向测序，所得结果经多种生物信息学手段分析；同时利用心肌细胞和第二心域特异性表达 Cre 小鼠与 $Ptch1^{flox/flox}$ 小鼠，制备心脏组织特异性敲除小鼠模型，通过心脏组织石蜡切片和 HE 染色观察 *Ptch1* 敲除对小鼠心脏结构的影响。结果遗传学上经过多重假设检验校正表明 *PTCH1* 非同义罕见变异在 CTD 病人中并没有显著富集（$q \approx 0.2$, ）。心肌细胞和第二心域 $Ptch1^{-/-}$小鼠，尽管前者在 E14.5 时胚胎全部死亡或被吸收，但后者可以存活到出生且心脏外观和血管连接方面没有明显异常。CTD 占到 CHD 病人的 30%，患者主要为动脉锥和动脉干异常，表现出流出道缺陷，而第二心域细胞是流出道延长分离成主动脉和肺动脉干的最主要细胞群来源。综上，研究结论表明 *PTCH1* 可能不是 CTD 的潜在候选基因。

Adverse Glycemic Events Detection Analysis based on CGM Neural Network Predictive Models

Jiang Fusong[1] Tao Li[1] Ting Chen[1] Li Wei[1] Mengling Wang[2] Limei Liu[1]
1.Shanghai Jiao Tong University Affiliated Sixth People's Hospital
2.East China University of Science and Technology

BACKGROUND Base on the real-time blood glucose data through Continuous Glucose Monitoring (CGM), diabetics can take efficient measurements to deal with adverse glycemic events (AGE) by hyper or hypoglycemia in time. Since CGM monitoring instrument cannot be embedded in human body all the way, and for a certain economic factor, it's hard to totally rely on real-time CGM data for AGE detection.
METHODS In this paper, four indictors of AGE detection analysis are proposed based on predicted blood glucose from 328 type 2 diabetic patients' CGM data. The neural network predictive models are proposed to achieve accurate predicted BG values which provides clinical meaning for understanding and alerting future AGEs.
RESULTS In this paper, 75% CGM data collecting from each individual sample is used for training and the rest 25% data is used for testing. Based on NN predicted values, especially GRU prediction values, it shows accurate duration of hypoglycemia events through TO and TD analysis. And four metrics are proposed to indicate the AGE detection's effectiveness and viability based on the NN predicted value. False Negative (FN) and False Positive (FP) are defined, which prove

the validity for detecting the AGE based on predicted value. The Temporal Overlap (TO) and Time Difference are proposed to represent the effectiveness of counting duration of AGE based on the predicted value. FPR values of five prediction models are within acceptable range except Holt-Winter. Especially for the severe hyperglycemia event, NN models have lower FPR. Comparatively, False Negative rates are higher than False Positive rates. And FNRs for hypoglycemia events detection is even worse than the FNRs for hyperglycemia events detection. Basically, it has very low FPRs for defined severe hyperglycemia and hypoglycemia events. False Negative rates are higher in comparison. But it can achieve a good indication after tuning to an acceptable boundary.

CONCLUSIONS The results show that the proposed predictive NN models can be used for effective AGE detection helping to represent the future dynamics of blood glucose.And it helps doctor and patients to better comprehend the future events' temporal behavior and to make reasonable decisions in advance.

新冠疫情下基于微信公众号的眼遗传病患者病历资料收集情况

龙雨希 张清炯
中山大学中山眼科中心

背景 全国新冠疫情防控形势日益严峻，为了适应防控疫情需要，降低因医务人员与患者接触造成院感风险，需要寻找新的病历资料收集随访途径。

方法 搭建"中山大学眼科医院小儿遗传"微信公众号平台，该平台具有签署知情同意书、上传病历资料、查询报告功能。通过该平台，中山大学中山眼科中心临床基因检测实验室收集患者知情同意书与病历资料方式，由以往患者前往临床基因检测实验室现场扫描改进为患者通过微信公众号自行上传。患者在抽血前，由护士指导关注绑定信息，工作人员后续通过平台与患者联系。

结果 2021 年 4 月该平台接待患者共 136 人，其中关注并绑定信息 131 人、签署知情同意书 131 人、上传资料 122 人。资料缺失原因为患者仅关注平台但未完成信息绑定步骤（0.7%），导致后续无法与患者取得联系。疫情前同样存在患者抽血后未到实验室扫描资料的情况（0.6%），两种收集方式病历资料缺失率相近。

结论 通过微信公众号自行上传病历资料能够降低医务人员与患者接触的院感风险，方便患者更新资料，检测报告可永久查看。

Partial thyroxine‐binding globulin defciency in a family with coding region mutations in the TBG gene

Lidan Chen[1] Huijie Lu[2] Yanling Gan[1] Shuwang Pang[3] Que Zheng[2] Demei Ye[2] Xiaoyan Huang[1] Huana Qi[2] Wenbin Xu[2] Xiaozhen Wen[2] Linhai Li[1] Liang Li[2]
1.Department of Laboratory Medicine, General Hospital of Southern Theater Command of PLA
2.Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University
3.Zhengzhou Yihe Hospital

Purpose T4-binding globulin (TBG) is the main thyroid hormone (TH) transporter present in human serum. Inherited thyroxine-binding globulin (TBG) defciency is caused by mutations in the *TBG* (*SERPINA7*) gene, which is located on the X chromosome. This study was performed to report and evaluate coding region mutations in *TBG* gene for partial thyroxinebinding globulin defciency.

Methods A pedigree spanning four generations is described in this study. The proband is a female with partial TBG defciency. All members of this pedigree underwent thyroid function tests, while Sanger sequencing was used to identify the *TBG* gene mutations. Bioinformatics databases were used to evaluate the deleterious efects of the mutation(s). Two hundred and seven unrelated individuals were used to evaluate the thyroid function of individuals with diferent

TBG mutations. A one-way ANOVA was used to analyze the impact of the *TBG* mutations on thyroid function.
Results *TBG* gene sequencing results revealed that the proband had a novel mutation in codon 27 leading to alanine to valine substitution (p.A27V). This mutation was associated with lower serum T4 levels (p<0.0001) when compared to the groups that did not carry the mutation. The previously reported p.L283F mutation was also found in the proband. The hemizygous p.L283F individuals presenting with lower T4 serum and TBG levels (p<0.001) when compared to wildtype males and females. Both mutations were deleterious upon SIFT and PolyPhen-2 evaluation.
Conclusion Associated with partial thyroxine-binding globulin defciency, this study reports a novel p.A27V mutation in the *TBG* gene.

Functional CYP3A variants affecting tacrolimus trough blood concentrations in Chinese renal transplant recipients

Dina Chen[1] Huijie Lu[1] Weiguo Sui[2] Liqing Li[1] Jian Xu[3] Tengfei Yang[1] Siyao Yang[1] Ping Zheng[4] Yan Chen[4] Jiejing Chen[2] Wen Xue[2] Qingping Li[5] Que Zheng[1] Demei Ye[1] Sadee Wolfgang[6] Danxin Wang[7] Wanying Qian[1] Liusheng Lai[2] Chuanjiang Li[5] Liang Li[1]
1.Department of Medical Genetics, School of Basic Medical Sciences, Southern Medical University
2.Guangxi Key laboratory of Metabolic Diseases Research, Nephrology Department of Guilin NO. 924 Hospital
3.Department of Organ Transplantation, Nanfang Hospital, Southern Medical University
4.Department of Pharmacy, Nanfang hospital, Southern Medical University
5.Department of Hepatobiliary Surgery, Nanfang Hospital, Southern Medical University
6.Center for Pharmacogenomics, Department of Cancer Biology and Genetics, College of Medicine, The Ohio State University
7.Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida

The aim of this study was to identify novel genetic variants affecting tacrolimus trough blood concentrations. We analyzed the association between 58 single nucleotide polymorphisms (SNPs) across the CYP3A gene cluster and the log-transformed tacrolimus concentration/dose ratio (log (C0/D)) in 819 renal transplant recipients (Discovery cohort). Multivariate linear regression was used to test for associations between tacrolimus log (C0/D) and clinical factors. Luciferase reporter gene assays were used to evaluate the functions of select SNPs. Associations of putative functional SNPs with log (C0/D) were further tested in 631 renal transplant recipients (Replication cohort). Nine SNPs were signifificantly associated with tacrolimus log (C0/D) after adjustment for CYP3A5*3 and clinical factors. Dual luciferase reporter assays indicated that the rs4646450 G allele and rs3823812 T allele were signifificantly associated with increased normalized luciferase activity ratios ($p < 0.01$). Moreover, CYP3A7*2 was associated with higher TAC log (C0/D) in the group of CYP3A5 expressers. Age, serum creatinine and hematocrit were signifificantly associated with tacrolimus log (C0/D). CYP3A7*2, rs4646450, and rs3823812 are proposed as functional SNPs affecting tacrolimus trough blood concentrations in Chinese renal transplant recipients. Clinical factors also signifificantly affect tacrolimus metabolism.

母系遗传的特殊类型糖尿病——MODY3 和线粒体糖尿病各 1 例

崔巧丽 苗青 何敏 张烁 鹿斌 李益明 叶红英
华山医院

目的 通过对临床表现为青年起病、非酮症倾向并有母系遗传家族史的青少年起病成人型糖尿病（MODY）3 型和线粒体糖尿病患者的临床病例报道及文献回顾，提高特殊类型糖尿病的鉴别能力及诊治经验。
方法 通过临床病史采集、体格检查、实验室检查、高通量核基因及线粒体基因组检测和分析，明确患者的糖尿病分型诊断，并总结 MODY3 和线粒体糖尿病的临床特征。

结果 两例患者均为青年起病，体型偏瘦（BMI 均为 20kg/m^2），糖尿病病史长（分别为 5 年及 30 年），非酮症倾向，均有母系遗传糖尿病家族史，其中一例患者合并双耳神经性听力下降。基因检测分别发现肝细胞核因子 1（HNF1）α 基因 c.872dupC 杂合突变，导致氨基酸发生移码突变（p.G292Rfs*25）及 MT-TRNL1 基因杂合变异 m.3243A>G。结合既往文献和病例报道，明确诊断分别为 MODY3 和线粒体糖尿病，且后者合并线粒体心肌病。
结论 临床工作中对于起病年龄轻的非胰岛素依赖及酮症倾向的糖尿病患者，尤其合并明确糖尿病家族史者，应考虑特殊类型糖尿病可能，建议完善核基因和/或线粒体基因组检测分析，助力临床诊疗。

PPP3CA 基因变异所致智力障碍一例报道-单氨基酸变异的临床异质性

舒荔[1,2] 田畦[1,2] 鄢慧明[1,2] 席惠[1,2] 彭莹[1,2] 毛翛[1,2] 王华[1,2]
1.湖南省妇幼保健院
2.国家卫生健康委出生缺陷研究与预防重点实验室

目的和方法 通过进行全外显子组测序（WES）并进行 Sanger 测序验证，对一个智力障碍家系明确遗传学病因。
结果 在该智力障碍家系中发现位于 PPP3CA 基因的新发突变 c.450T>A（p.N150K），p.N150K 基因突变在之前文献中有报道，我们的患者和既往报道患者携带相同的单氨基酸变异（SAV），虽然单碱基变异不同。然而，先证者表现出明显的临床表现，如智力残疾伴多发畸形。
结论 我们的研究为进一步研究 SAV 水平上的临床异质性提供了线索。

LAMC3 基因复合咂合突变致枕叶皮质畸形一例及功能验证

钱晓杭[2] 曹立[1]
1.上海交通大学附属第六人民医院
2.上海交通大学医学院附属瑞金医院

目的 报道一例由 LAMC3 基因复合杂合突变所致枕叶皮质畸形，探讨该患者的临床症状、体征、影像学特征以及该突变所致的潜在致病机制。
方法 对患者临床症状与体征评估与总结，完善脑电图、肌电图和头颅 MRI 检测；通过全外显子组测序和 Sanger 测序鉴定相关基因突变位点。细胞功能实验验证上述突变检测蛋白亚细胞定位与蛋白结构改变。利用生物信息学技术构建 LAMC3 基因的蛋相互作用网络，并对其进行功能富集分析探讨潜在致病机制。
结果 患者，女性，24 岁。13 岁时无明显诱因下出现癫痫失神发。每次发作持续一至几分钟，每月发生一至两次；至今全身强直发作 5 次。自 20 岁起服用丙戊酸钠（500mg，3 次/天），仍偶有发作；至 22 岁时调整丙戊酸钠用量（100mg，2 次/天）。3 月后逐渐改服左乙拉西坦（200mg，2 次/天），至今失神发作两次。查体未见明显异常。脑电图示双侧背景区为 10-40uv 8 ~ 9 Hz α 波为主，各导有较多 10-35uv 5 ~ 7 Hz θ 波。头颅 MR 未见异常。基因检测发现该患者的 LAMC3 基因存在 c.G470A 和 c.4030+1G>A 复合杂合突变，而其母亲和父亲的 LAMC3 基因分别存在 c.G470A 和 c.4030+1G>A 突变。根据 ACMG 指南评判上述两突变位点均为“致病”。细胞功能性实验证实两个突变位点均导致 LAMC3 基因翻译的提前终止产生截短蛋白。生物信息学分析预测得出 10 个与 LAMC3 存在潜在相互作用的蛋白（P 值= 1.0e-16）。这些蛋白主要位于基底膜和细胞外基质成分中，并通过含蛋白复合体结合、信号受体结合等方式发挥生物学作用。最后，KEGG 通路富集预测 LAMC3 基因突变最有可能通过 ECM 受体相互作用和 PI3K-Akt 信号通路参与疾病发生发展。
结论 本研究首次报道了中国人口中一例由于 LAMC3 基因复合杂合突变所致枕叶皮质畸形的患者，并对其临床特征进行总结。细胞功能研究证实上述突变均导致截短蛋白的产生。生物信息学分析筛

选发现 ECM 受体相互作用和 PI3K-Akt 信号通路可能是 LAMC3 基因突变所致枕叶皮质畸形的作用途径。

1 例低比例嵌合 12 三体伴多发畸形胎儿的产前遗传学分析

尹婷 王雷雷
连云港市妇幼保健院

目的 对 1 例低比例嵌合 12 三体伴多发畸形的胎儿进行遗传学研究，探讨该染色体嵌合与超声异常表征之间的关系。
方法 整理分析患儿的临床资料，应用 G 显带染色体核型分析及染色体微阵列分析(chromosomal microarry analysis,CMA)技术对该患儿进行遗传学检测，并对其父母进行外周血染色体核型分析。同时，选取相关文献复习比较。
结果 胎儿超声检查结果为心包腔少量积液，主动脉弓部局部内径狭窄，右心室一血管连与腹部，脐静脉肝内段分支异常等。遗传学检测结果显示胎儿染色体核型为 47,XX+12[1]/46,XX[73],嵌合比例为 1.35%。CMA 检测结果提示胎儿 12 号染色体存在约 18%三体型嵌合。其双亲染色体核型正常。
结论 低比例的 12 号染色体三体嵌合可能会导致胎儿心脏先天发育异常等其他多发畸形。

CACNA1A 相关共济失调 3 例并文献复习

曹立[1] 黄啸君[2] 王诗格[1]
1.上海交通大学附属第六人民医院
2.上海交通大学医学院附属瑞金医院

背景 *CACNA1A* 编码分布于脑部和神经肌肉接头的 Cav1.2 蛋白。*CACNA1A* 基因突变引起以共济失调为主要临床特征的神经系统和/或运动系统障碍的一类疾病。
目的 了解 *CACNA1A* 相关疾病的表型、基因型-表型相关性以及临床治疗，进一步掌握 *CACNA1A* 基因突变谱及表型, 提高对 *CACNA1A* 相关疾病的早期认识以及对该类疾病施行有效的治疗策略。
方法 本文描述了 *CACNA1A* 相关的 3 例先证者，通过其临床表型、影像学特征，分析基因型-表型相关性及临床治疗效果并进行相关文献复习。
结果 3 例先证者的 *CACNA1A* 基因突变不同，其临床表型具有异质性，表现为多种症状叠加，其中 2 例先证者发病年龄较小且症状较重；其影像学表现早期一般无明显异常，随着疾病的进展小脑萎缩逐渐表现出来；其对药物的反应也不同，仅存在发作性共济失调的先证者对醋甲唑胺较敏感，而存在多种症状叠加的患者对醋甲唑胺不敏感。通过相关文献复习发现 *CACNA1A* 基因突变多数为新发突变。在 *CACNA1A* 基因突变中，尚未发现基因型-表型明确相关性，仅发现功能缺失突变与发作性共济失调有关而功能获得突变与发作性共济失调有关。
结论 本研究报道了 3 例由 *CACNA1A* 基因突变所致以共济失调为主要特征的一类疾病，尚未发现基因型-表型之间存在相关性。发病年龄是否与基因型有关有待进一步研究。醋甲唑胺可用于治疗以发作性共济失调为特征的 CACNA1A 相关疾病。

SYNE1 基因纯合突变致常染色体隐性遗传小脑共济失调 1 型一例报道

曹立[1] 田沃土[1] 郑浩然[2]
1.上海交通大学附属第六人民医院 2.安徽理工大学附属第一人民医院

目的 报道一例 *SYNE1* 基因纯合移码突变所致常染色体隐性遗传小脑性共济失调 1 型（*ARCA-1*）病例，并对遗传学检出的 *SYNE1* 突变进行致病性评估，进一步总结和探讨该病的临床表型特点。
材料与方法 对该患者的临床资料进行采集，采用国际合作共济失调评定量表(ICARS)进行评估、完善影像学检查，并进行二代测序，通过家系共分离和一代测序对所检出的突变进行验证。
结果 患者，男，44 岁，因“进行性行走不稳 9 年”就诊，患者自 35 岁起出现行走速度慢，易摔倒，并伴有语言含糊不清，旁人难以理解，病情随时间逐渐加重。六年前，患者出现书写笨拙；五年前，出现进食流食后频繁呕吐。现上下楼梯需搀扶，否认长期服用和接触酒精或药物史，否认感染和卒中史等。体格检查：一般检查及心、胸、腹部查体未见异常，神志清，吐词欠流利，眼震不明显，视力粗测正常，四肢肌力 5 级；腱反射：双上肢(+++),双下肢（++）；病理征（-），无高弓足，感觉正常，双侧指鼻试验、跟膝胫试验和轮替试验均欠稳准。患者出生自近亲婚配家庭，父母为两代以内堂兄妹，家族中无相似共济失调症状。患者时隔一年来我院分别进行首诊和随访时进行国际协作共济失调评估量表（ICARS）评分如下：一年前后肢体共济失调（15/52 vs 15/52）、言语障碍（3/8 vs 3/8）和动眼功能（1/6 vs 1/6）均未见明显恶化，而姿势和步态障碍（3/34 vs 5/34）略有进展。辅助检查：血、尿、便常规正常，肝肾功能、维生素浓度以及眼底镜检查正常。头颅 MRI 显示中度弥漫性小脑萎缩，其余未见明显异常。遗传学检查：运用遗传性共济失调 Panel 进行二代测序，结果提示患者存在 *SYNE1* 基因（NM_182961）纯合移码突变 c.9347delA（p.N3116Mfs*6），家系共分离和一代测序验证提示父亲为相同突变的杂合携带者（母亲因已去世未获得标本进行基因检测）。根据 ACMG 评估和分级指南，该变异被评为致病变异（PVS1+PM2+PP3）。
结论 本研究中，患者表现为晚发性、缓慢进展的的单纯型小脑性共济失调并伴有构音障碍，不伴感觉及泌尿等其他系统功能受累。患者出生自近亲婚配家庭，结合其临床表现、辅助检查结果以及家系共分离结果，综合考虑其诊断符合 ARCA-1 型。本病为常染色体隐性遗传性疾病，迄今，尚未发现明确的基因型-表型相关性。在 *SYNE1* 的突变谱中，移码突变相对少见。本研究报道的 *SYNE1* 基因新的致病性突变 c.9347delA（p.N3116Mfs*6）可导致编码一错误截短型蛋白，后者丢失 64.5%的正常氨基酸序列。因此，该移码突变很可能通过无义介导的 mRNA 降解机制（NMD）导致本病的发生。

CAPN1 基因新突变致痉挛性截瘫 76 型一例报道

曹立 朱泽宇 柯慧怡 田沃土
上海交通大学附属第六人民医院

目的 报道一例遗传性痉挛性截瘫 76 型（SPG76）病例的临床表现和对所发现的新突变进行功能验证，探讨该病的临床特点以及评估该突变的致病性。
方法 对该例患者的临床表现及家系资料进行采集，全外显子组测序（WES）明确病因，并经 Sanger 测序验证。构建野生型及突变型 CAPN1-GFP 质粒，并转染入 HEK293T 细胞，利用共聚焦显微镜观察荧光蛋白表达及定位情况。
结果 男，48 岁，因“步态异常、行走不稳 26 年，进行性加重 6 年”就诊。26 年前家人发现其步态异常，但自己并未觉得行走困难和下肢乏力，故未予重视。后逐渐开始出现行走不稳、容易摔倒，双下肢动作不利，伴乏力，以双侧小腿明显，足底擦地，向左右侧轻度摇晃，上、下楼梯困难。近 6 年自觉腰背部活动不佳，肌肉僵直。家族史：父母为近亲结婚，患者哥哥有类似症状。体格检查：言语清晰，颅神经检查正常。双上肢肌张力稍高，左侧高于右侧，双下肢肌张力正常。双上肢肌力正常，双下肢髂腰肌肌力 IV 级，远端肌力 V 级。腱反射亢进，双侧髌阵挛及踝阵挛阳性，双

侧病理征阳性，痉挛步态。基因检测结果显示，患者 *CAPN1* 基因存在纯合移码突变 c.231dupG（p.D72Gfs*95）。*CAPN1* 基因编码蛋白 calpain-1 催化亚基。免疫荧光显示野生型 calpain-1 在细胞内与微管蛋白共定位，而突变型截短蛋白则异常沉积于细胞核周围。依据美国医学遗传学与基因组学会（ACMG）的基因变异解读标准和指南，该变异被评为“致病”。

结论 该患者 22 岁起病，表现为单纯型痉挛性截瘫，结合临床与遗传学特点考虑诊断为 SPG76。SPG76 为常染色体隐性遗传性痉挛性截瘫。目前，已有 37 例 SPG76 病例被报道，本例为中国第 3 例。同时，根据功能验证结果，本研究发现新的 *CAPN1* 致病性突变，其可能通过影响 calpain-1 的亚细胞定位，从而导致疾病的发生，而具体机制尚待阐明。

ERLIN1 基因新突变致痉挛性截瘫 62 型 1 例报告

曹立 朱泽宇 李资益 田沃土
上海交通大学附属第六人民医院

目的 报道中国首例 *ERLIN1* 基因相关痉挛性截瘫 62 型（SPG62）患者的临床表现以及对所发现的新突变位点进行功能分析，探讨该病的临床特点以及评估该突变的致病性。

对象与方法 分析评估该患者的临床资料，抽提患者的外周血 DNA 进行全外显子测序，利用生物信息学方法预测突变对基因转录表达等的影响，应用 Minigene 技术在体外构建突变型及野生型表达载体，转染 HEK293T 细胞，并通过 RT-PCR 和 Sanger 测序技术分析基因突变对 pre-mRNA 剪切的影响。

结果 男，23 岁，因“进行性行走困难 11 年余”就诊。患者于 12 岁时开始出现双下肢走路困难，表现为一摇一摆，一脚深一脚浅，易摔倒。13 岁起不能跑步，13~14 岁时上下楼梯需要扶，近 2~3 年，行走时需要扶。无饮水呛咳、吞咽困难。患者否认颅外伤史，否认父母近亲结婚，父母及姐姐均无类似症状。体格检查：双上肢肌力 5 级，双下肢肌力 5-级，双上肢肌张力正常，双下肢肌张力升高，双上肢腱反射（+++），双下肢腱反射（++++），双侧巴宾斯基征（-），霍夫曼征（-），双侧持续性踝阵挛，持续性髌阵挛。全外显子测序结果提示 *ERLIN1* 基因存在剪切位点 c.504+1G>A 纯合突变，生物信息学工具（BDGP、NetGene2、HSF）预测结果均提示该突变可能影响 *ERLIN1* 基因转录产物的剪切，Minigene 体外功能实验结果表明该突变造成突变型 *ERLIN1* 基因转录产物 mRNA 中 7 号外显子缺失。

结论 该患者表现为单纯型 HSP，结合临床与遗传学特点综合考虑诊断为 SPG62，目前世界范围内仅有 3 个家系 7 名患者被报道，其中 6 例于婴儿期起病，1 例于 13 岁起病。同时本研究发现新的 *ERLIN1* 致病性剪切位点突变，其可能通过错误切除 mRNA 中 7 号外显子而改变 ERLIN1 蛋白保守结构域 PHB 并影响 ERLIN1/2 复合体的功能，从而导致疾病的发生。对于表现为迟发型、隐性遗传的单纯性 HSP 的患儿，应当考虑 SPG62 的可能。

IBA57 基因突变引起的多发性线粒体功能障碍综合征 2 例报道

曹立[1] 詹飞霞[1] 刘晓黎[2]
1.上海交通大学附属第六人民医院
2.上海市奉贤区中心医院

目的 报道 2 例经基因检测明确的多发性线粒体功能障碍综合征 3 型（Multiple mitochondrial dysfunction syndrome 3, MMDS3），以探讨 *IBA57* 基因突变致多发性线粒体功能障碍综合征患儿的临床、影像特征及基因变异特点，提高对疾病的认识。

方法 对 2 例患儿进行详细的病史资料采集及全面检查，并进一步应用全外显子测序进行基因检测。

结果

病例一：患儿，男，10 月，因“发现运动倒退半年，加重 1 月余”就诊。患儿 6 月余能抬头，偶会翻身，不能独坐，会主动伸手抓物。近 1 月余不能翻身、抬头，不能主动伸手抓物，偶有点头拥抱发

作，四肢僵直。家族史：否认家族史，父母非近期结婚。查体：手中线位活动少，双下肢稍硬直伸展；俯卧位:辅助肘支撑短时抬头 45°，无手支撑，无四点支撑，不会翻身、爬；坐位:不能独坐，各方平衡未建立。追视追听能引出，能逗笑出声。原始反射残存，病理反射巴氏征阳性，四肢肌张力增高。辅助检查：遗传代谢性项目：血氨基酸、酰基肉碱和琥珀酰丙酮未见异常。头颅 MRI：脑内白质弥漫性信号异常，考虑脑白质营养不良可能（图 1A）。脑电图：正常婴儿脑电图。二代测序示患儿存在 *IBA57* 复合杂合突变：c.189delC 和 c.286T>C，共分离示其父亲和母亲分别为杂合携带者（图 1B）。c.189delC 为新发突变，而 c.286T>C 有相关致病性报道，经 ACMG 评估均为“致病”。

病例二：患儿，女，1 岁，因“发热后发现精神运动倒退 20 天”就诊。患儿在 20 天前出现发热，体温 37℃左右，伴声音嘶哑，胸片考虑“支气管肺炎”，抗感染治疗一周后，发现目光呆滞，头下垂，并出现肢体无力，站立时右下肢不自主抖动，活动差，伴言语减少，反应差。顺产，7 月时会爬，9 月时能扶站，10 月龄能发双音。既往多次高热病史，体温最高 39.3℃，曾用抗生素治疗。家族史：否认家族史，父母非近期结婚。查体欠配合，偶见双眼球上翻，肢体有规律不自主抽动，四肢肌张力增高，角弓反张样。辅助检查：头颅 MRI：颅内双侧额顶叶及半卵圆中心白质弥漫多发斑片状异常信号（图 2A）。二代测序示患儿存在 *IBA57* 复合杂合突变：c.580A>G 和 c.286T>C，共分离示其父亲和母亲分别为杂合变异携带者（图 2B）。c.580A>G 为新发变异，经 ACMG 评估均为“可能致病”。

结论 MMDS3 是一种罕见的以弥漫性空泡性脑白质病变为主要特征的线粒体病。由线粒体内铁硫蛋白装配异常引起，以脱髓鞘、空泡化和星形胶质细胞增生为主要病理改变。患者多于婴幼儿期发病，多表现为喂养困难、精神萎靡、癫痫发作、急性精神运动倒退、认知障碍、痉挛性瘫、肌张力低下、广泛肌无力、原始反射消失和小头畸形、关节弯曲等，可引起早期死亡，诊断需与遗传代谢病及其他线粒体病相鉴别。精神运动发育迟滞伴广泛性脑白质病变的患儿临床需考虑多发性线粒体功能障碍综合征的可能。

UBAP1 杂合突变致痉挛性截瘫 80 型一家系报道

曹立[1] 朱啸巍[1] 钟平[2]
1.上海交通大学附属第六人民医院
2.安徽医科大学附属宿州人民医院

目的 报道一个 *UBAP1* 基因杂合突变所致痉挛性截瘫 80 型（SPG80）家系，并对遗传学检出的 *UBAP1* 基因突变进行致病性评估，进一步探讨该病的临床表型特点。

材料与方法 对一例患者的临床表现进行分析评估，并进行全外显子测序及家系共分离和一代测序验证。

结果 先证者，女，34 岁，因“进行性行走困难 26 年”就诊，8 岁起出现行走时双下肢肌肉僵硬、紧绷和肿胀感；逐渐出现行走时双下肢易乏力，抬腿费力；随后下肢乏力进行性加重，约行走 10 分钟即需要休息，易摔倒，需要他人搀扶，不能独立行走。无上肢肌肉僵硬、肌痛、肌萎缩、吞咽困难、饮水呛咳、构音障碍等。体格检查：双上肢肌力 5 级，下肢内收肌力 5 级，外展肌力 4⁻级，双下肢肌张力增高，下肢腱反射（+++），双侧踝阵挛持续性（+），共济和轮替动作可，行走呈剪刀步态。全外显子测序结果及一代测序验证提示该先证者存在 *UBAP1* 基因 c.371dupT（p.L124Ffs*15）杂合变异。家族史：否认父母近亲婚配；先证者之母亲具有相似症状：于 6 岁起出现行走困难，12 岁时下肢乏力明显加重但仍可独立行走，13 岁起走路需人搀扶，现年 60 岁行动依赖轮椅。母亲查体提示：神清，双上肢肌力 5 级，下肢内收肌力 5 级，外展肌力 3 级，双下肢肌张力增高，下肢腱反射（+++），双侧踝阵挛（+），共济和轮替动作可，目前丧失独立行走能力。家系共分离和一代测序验证结果显示其母亲也存在相同位点的杂合变异。先证者父亲无临床症状亦未见相同变异。根据 ACMG 评估和分级指南，该变异可评为“疑似致病”（PVS1+PM2）。

结论 本研究中，先证者及其母亲仅有运动功能障碍，感觉、泌尿及视力等其他系统功能暂未累及，表现为单纯型 HSP。结合临床特点、遗传学检测以及家系共分离结果，综合考虑诊断为 SPG80。本病为常染色体显性遗传性疾病，常在青少年期发病，其特征是出现进行性痉挛和反射亢进，主要影响下肢，导致行走困难或丧失独立行走能力，部分患者可同时存在小脑症状和轻度认

知障碍，但大多数患者仅表现为步态异常。迄今，在全球共计报道的 33 个诊断为 SPG80 家系（包括本报道）的 84 例患者中男女比例为 2.11(57:27)，并鉴定出 18 种 *UBAP1* 突变。其中 69/84 为单纯型 HSP 患者，平均起病年龄约为 11 岁；12/84 为复杂型 HSP 患者，平均起病年龄约为 6 岁。本研究报道的 *UBAP1* 致病性突变 c.371dupT（p.L124Ffs*15）为一新的移码突变，可导致编码一错误截短型蛋白，后者丢失 72.6%的正常氨基酸序列。该移码突变很可能通过无义介导的 mRNA 降解机制从而引起 UBAP1 蛋白功能异常以及细胞凋亡等神经退行性改变，然而具体发病机制仍需进一步功能学验证方可得出确切结论。

非典型 Charlevoix-Saguenay 常染色体隐性遗传痉挛性共济失调二家系报道

曹立 李资益 田沃土 沈隽逸
上海交通大学附属第六人民医院

目的 报道具有非典型临床表现的二例 Charlevoix-Saguenay 常染色体隐性遗传痉挛性共济失调（ARSACS）家系，并对遗传学检出的 *SACS* 基因突变进行致病性评估，总结和探讨该病的临床表型特点。

材料与方法 对两家系患者的临床表现进行分析评估，完善影像学、电生理等辅助检查，并进行二代测序及家系共分离和一代测序验证。

结果 家系 1：先证者（PA1067），女，37 岁，因“进行性走路不稳 5 年余”就诊，患者自幼体育成绩不佳，于 5-6 年前开始出现走路不稳，并进行性加重。目前患者下楼需扶梯，尚可于平地独立行走，伴有语速慢、言语含糊。先证者之姐姐（PA1068），40 岁，为早产儿，运动里程碑发育较同龄儿童迟，自幼行走不好，易摔跤。近年，走路不稳症状进行性加重，并伴有肢体僵硬、共济失调、语速慢、言语含糊等，癫痫发作史阳性，幼儿期便有失神发作及脑电图检查可见棘波。患者 PA1068 自幼有便秘史，一周 2-3 次排便。否认父母近亲婚配和阳性家族史。体格检查：两患者双上肢肌张力正常，双下肢肌张力增高，患者 PA1067 双下肢肌力减弱，上肢腱反射正常，下肢腱反射亢进；患者 PA1068 肌力均正常，上肢腱反射减退，下肢腱反射亢进；双下肢病理征阳性，双下肢痉挛，高弓足（+）。双侧指鼻、轮替和跟膝胫试验均欠稳准，闭目难立征（+）。二代测序结果提示两位患者均存在 *SACS* 基因双杂合突变（c.7276C>T（p.R2426X）和 c.8053_8056delTATC（p.Y2685Wfs*53））。家系共分离结果显示 c.7276C>T 来自父亲，而 c.8053_8056delTATC 来自母亲，提示两患者为复合杂合突变。家系 2：先证者（PA1336），男，12 岁，因“进行性共济失调 7 年”就诊，患者于 5 岁时首次出现走路不稳，此后 2 年内症状进行性加重；自 6 岁起，学习能力及记忆能力逐渐减退。目前，患者上楼需扶梯。偶有睡眠时出现全身阵挛发作及意识丧失，脑电图提示中度异常脑电活动，双侧大脑半球轻度异常伴 θ 波（6-7Hz）电活动。父母为近亲结婚，无相似临床症状。体格检查：四肢肌力和肌张力正常，无痉挛，四肢腱反射减退，左下肢病理征阳性，无高弓足；双侧指鼻、轮替试验均欠稳准，闭目难立征（+）。二代测序结果提示患者 PA1336 存在 *SACS* 基因纯合突变 c.8107C>T（p.R2703C），其祖母为该突变的杂合携带者。上述两家系 3 位患者的颅脑 MRI 均显示小脑萎缩，尤以小脑蚓部萎缩为重，肌电图均提示外周神经存在轴索变性以及脱髓鞘变性。

结论 本研究所报道的两个家系总计 3 名患者，结合其临床表现、辅助检查以及基因检测结果，综合考虑诊断为 ARSACS。本病为常染色体隐性遗传性疾病，多于儿童时期起病，其核心临床表现包括下肢痉挛、小脑性共济失调、构音障碍、眼球震颤、上运动神经元功能障碍、周围神经病变等。本研究中 2 名患者癫痫史阳性，1 名患者并无痉挛症状，此均为 ARSACS 相对少见的非典型临床表型。在家系 1*SACS* 复合杂合突变中，已知突变 c.7276C>T 和新突变 c.8053_8056delTATC 均可导致编码蛋白截短；而家系 2 中的 *SACS* 错义突变 c.8107C>T 导致 2703 位精氨酸突变为半胱氨酸，该位点在不同物种之间呈高度保守。根据 ACMG 评估和分级指南，c.7276C>T 和 c.8053_8056delTATC 两变异均为可能致病（PM2+PM4+PP1+PP4），c.8107C>T 变异亦为可能致病（PM2+PM6+PP3+PP4）。

中国 CSF1R 相关性白质脑病的临床及遗传学特点

曹立 邬静莹
上海交通大学附属第六人民医院

目的 *CSF1R* 相关性白质脑病是一类罕见的青年起病、具有严重致残致死性的遗传性脑白质病。本研究对中国 *CSF1R* 相关性白质脑病患者临床资料进行总结及分析，以期明确中国患者的临床及遗传学特征，为进一步规范该疾病的诊断及治疗提供依据。
方法 本研究收集了 2021 年 1 月 31 日前在全国 21 家医院神经内科确诊的 CSF1R 相关性白质脑病患者，纳入标准如下：（1）至少以下 2 种临床症状和体征：认知障碍；精神症状；锥体系受累体征；帕金森病；癫痫；（2）常染色体显性遗传或散发；（3）头颅 MRI 示双侧脑白质病变；（4）确证有 CSF1R 基因突变，且 ACMG 评级为“致病”或“可能致病”；（5）排除引起脑白质病变的其他原因。本研究详细记录了患者病史资料及简易精神状态检查量表（MMSE）蒙特利尔认知评估量表（MoCA）、磁共振严重性评分。不同性别患者的组间比较采用 SPSS 26.0 软件进行统计学分析。
结果 本研究共纳入患者 64 例，其中男性 21 例，女性 43 例，男女比例 1:2.05。平均起病年龄为 40.44±8.78 岁，平均病程为 2.53±1.90 年。首发症状中，运动症状最为常见（59.7%），其次为认知障碍（40.3%）。病程中，大多数患者出现认知障碍（79.0%）、运动症状（75.8%）及性格行为改变（67.7%）。体征上，锥体束受累最为常见，包括病理征阳性（71.4%）、反射亢进（67.9%）、肌张力增高（62.5%）。患者 MMSE 平均得分为 18.97±7.20 分，MoCA 为 14.04±7.23 分。其中，男性 MMSE 及 MoCA 评分分别为 22.06±5.31、18.08±5.600，显著高于女性（15.69±7.62、10.00±6.51）（$p<0.01$）。最常见的影像学特征为双侧非对称的白质改变（100.0%）。磁共振严重性评分平均为 27.00±11.56 分，其中白质病变得分为 20.63±8.93 分，萎缩评分为 5.65±3.14 分。其中，女性患者的白质病变评分（22.55±8.63）显著高于男性（17.62±8.74）（$p<0.05$）。部分患者可伴肌电图（10/20，50.0%）、脑电图（9/24，37.5%）及脑脊液（10/29，34.5%）异常。本研究共发现 36 个 *CSF1R* 致病或可能致病突变，其中 18 个为未报道突变。根据突变类型，可分为错义突变（24/36，66.7%）及无效突变（12/36，33.3 %）。突变多位于酪氨酸激酶结构域（28/36，75.7%）。c.2381T>C/p.I794T 突变最为常见，56 位先证者中，共有 10 位（17.9%）携带该突变位点。
结论 中国 *CSF1R* 相关性白质脑病患者在临床表现上以进行性运动和认知障碍为主，影像上以双侧非对称的白质改变为核心特征。表型上存在性别差异，女性患者认知障碍及影像改变较男性更为严重。遗传学上，中国患者热点突变为 c.2381T>C/p.I794T。

不伴卵巢功能衰竭的 AARS2 相关性白质脑病一家系报道

曹立 邬静莹
上海交通大学附属第六人民医院

目的 AARS2 相关性白质脑病是一类青年起病的以卵巢功能衰竭、进行性认知、运动和精神障碍为主要表现的常染色体隐性遗传线粒体病。其起病隐匿、进展极快，具有极高的致残致死性。本文报道 1 个不伴卵巢功能衰竭的 AARS2 相关性白质脑病家系，对其临床、影像、病理及遗传学特征进行分析及总结，以拓宽对该罕见疾病的认识。
方法 收集 1 例确诊为 AARS2 相关性白质脑病的患者及其家系的临床资料、体征、实验室检查、影像学检查、脑组织活检病理及基因检测结果，并结合文献复习进行分析。
结果 先证者，女，31 岁，因“反应迟钝、记忆减退 1 年，行动缓慢 10 个月”入院，头颅 MRI 平扫示 T2-FLAIR 及 DWI 序列双侧侧脑室前角旁白质及胼胝体不对称高信号，脑萎缩，脑室扩大，胼胝体变薄。脑活检示电镜下神经纤维密度减低，伴薄髓鞘形成，可见个别巨大轴索及轴索肿胀，其髓鞘变薄、髓鞘断裂或缺失，个别轴浆内可见大量神经丝及线粒体、溶酶体、囊泡等少量细胞器。遗传学分析提示 *AARS2*:NM_020745:exon3:c.T452C:p.M151T 及 *AARS2*:NM_020745:exon22:c.G2893A:p.G965R 复合杂合突变。结合其临床、影像、病理及遗传学特征，该患者被确诊为 AARS2 相关性白质脑病。回顾家族史，该患者有一哥哥 3 年前因车祸行

颅脑外伤手术，术后出现脑积水，行体内腹腔分流术，术后无明显好转，CT 平扫提示双侧侧脑室旁白质不对称异常低信号，脑室扩大，脑萎缩，已于 2 年前去世。家系验证提示其姐姐携带相同复合杂合突变，查头颅 MRI 平扫示双侧侧脑室旁广泛异常信号，目前认知、运动功能正常，无神经精神表现。此外，尽管既往报道中几乎所有女性患者均存在卵巢功能衰竭，且该症状往往早于其他神经系统症状，此家系中先证者及姐姐妇科 B 超及卵巢功能相关激素检测均无显著异常。[18F]DPA714-PET 提示先证者双侧侧脑室前角旁放射性摄取异常增高，而姐姐尚无异常增高的摄取信号。

结论 AARS2 相关性白质脑病是一类罕见的常染色体隐性遗传线粒体脑病。临床上对于青年起病，表现为快速进展的认知、运动和精神障碍、且伴有 T2-FLAIR 及 DWI 序列双侧白质不对称高信号的患者需进一步进行遗传学分析，无论是否存在卵巢功能衰竭，均需要考虑该疾病的可能。[18F]DPA714-PET 或有助于该疾病的早期诊断。

以内分泌障碍为首发症状的线粒体神经胃肠脑肌病一家系报道

曹立 詹飞霞 王诗格 栾兴华
上海交通大学附属第六人民医院

目的 报道一家系经基因检测明确的线粒体神经胃肠脑肌病（MNGIE），以探讨该病的临床特点，提高对疾病的认识。

方法 对先证者进行详细病史及家系资料采集，并行神经活检和基因测序，进一步检测血浆脱氧核糖核苷浓度及胸苷磷酸化酶活性（TP）以评估突变影响。

结果 先证者，女，21 岁，因“皮肤变黑 6 年，体毛增多 5 年，闭经 3 月余”就诊。16 岁时全身多处皮肤变黑，17 岁时体毛增多，外院发现血脂和胰岛素升高，且头颅 MRI 示弥漫性脑白质病变，未重视。2016 年因月经不调，发现多囊卵巢综合征，予甲羟孕酮及英达 35 治疗；2017 年因腹痛诊断高脂血症性胰腺炎。2018 年皮肤变黑（手背部、后颈部）明显加重，面部雀斑，脂肪粒及体毛增多，并出现闭经，就诊于我院内分泌科，头颅 MRI 示弥漫脑白质病变，随后转诊至神经内科进一步明确病因。**家族史：**父母非近期结婚。弟弟体型消瘦（身高 178cm，体重 34kg，BMI:10.7kg/m2），腹部和臀部脂肪减少（图 1G），四肢腱反射减弱，余体征阴性。**查体：**先证者身高 166cm，体重 47.4kg(BMI:17.2 kg/m2)。全身多处皮肤粗糙变黑，角化过度（图 1A）。颈部、胸部、背部和下肢见浓密体毛。腹部和臀部脂肪减少。四肢腱反射消失，余体征阴性。**辅助检查：**甘油三酯 15.71mmol/l↑，总胆固醇 6.42mmol/l↑，低密度脂蛋白 0.99mmol/l↑，高密度脂蛋白 0.62mmol/l↑，游离脂肪酸 0.72mmol/l↑，载脂蛋白 E 18.7mg/dl↑，甲状腺素 54.92nmol/l↓，游离甲状腺素 8.81pmol/l↓，促黄体生成素 2.57mIU/ml↓，促卵泡激素 3.93mIU/ml↓，雌二醇<10pg/ml↓，性激素结合球蛋白 6.10nmol/l↓；血清胰岛素: (禁食-30min-1h-2h-3h): 28.95（2.6-24.9）-144-269.9-348.8-465.6（uIU/ml）。余检验未见异常。头颅 MRI 示进行性融合对称性弥漫性皮质下白质病变，并向胼胝体延伸（图 1B 和 1C），磁共振波谱未见异常（图 1D）。腹部 CT 示严重脂肪肝、肝肾肿大（图 1F）。肌电图示周围神经变性，轴索受累为主，伴脱髓鞘性改变。腓肠神经活检显示有髓和无髓神经纤维密度降低，轴突萎缩，脱髓鞘，Schmidt-Lanterman 切口变宽，线粒体肿胀和空泡化（图 1E）。弟弟肌电图示周围神经变性改变。头颅 MRI 示双侧白质弥漫性改变（图 1H）。基因检测示姐弟均存在 *TYMP* 复合杂合突变：c.356G>T 和 c.433G>A，共分离示其父亲和母亲分别为杂合变异携带者（图 2）。c.356G>T 为新发突变，c.433G>A 有相关致病性报道，经 ACMG 评估均为“可能致病”。血浆脱氧核糖核苷检测显著升高，其父母均未检测到脱氧核糖核苷水平。此外，先证者成纤维细胞中残留的胸苷磷酸化酶活性(52.3±35.8，14.3-95.2nmol/h/mg)较对照组(142.9±70.8, 61.9-276.0nmol/h/mg)显著降低。

结论 MNGIE 是一类罕见的进展性线粒体疾病，由编码 TP 的基因突变引起酶活性部分或全部丧失，致血浆和组织中核苷积累及线粒体功能障碍。我们报道了一家系经基因明确，先证者以内分泌障碍为首发症状的 MNIGIE，通过总结临床、生化、神经病理和遗传学特点，扩展了表型-基因型谱。临床上对于存在神经系统、胃肠道症状及各种内分泌代谢障碍等可疑患者，应考虑到此病的可能，必要时行基因检测明确。

以 1 型糖尿病为首发症状的血浆铜蓝蛋白缺乏症 1 例报道

曹立 詹飞霞 栾兴华
上海交通大学附属第六人民医院

目的 报道 1 例以 1 型糖尿病为首发症状的血浆铜蓝蛋白缺乏症（ACP）病例，分析其临床表现、实验室检查及影像学特点，结合文献复习，以提高对该病的临床认识。
方法 对患者进行详细的病史及家系资料采集，全面的实验室检查及影像学评估，并进一步行铜蓝蛋白（*CP*）基因测序分析。
结果 患者，男，45 岁，17 岁参加军训出现严重体力不支，伴口干、多饮、多尿，易饥、多食、消瘦，数月内体重下降约 20 斤，并发现血糖增高（具体不详），住院予胰岛素治疗，诊断 1 型糖尿病，此后治疗过程中血糖波动较大，时有心悸、出汗、饥饿感等低血糖症状。近 2 年开始出现记忆力下降，如反复遗忘银行卡密码、时常丢东西。1 年前记忆下降明显加重，并伴言语含糊、语速慢，走路迟缓，逐渐无法胜任工作。入院前 4 天无明显诱因出现头晕，伴有视物旋转、恶心，约 2-3 分钟后自行缓解，共发作 2 次，近 1 年体重下降约 14 斤。个人史：自幼学习成绩优异，大学本科学历。家族史：父亲有房颤病史，母亲高血压病，父母为近期结婚（患者祖母及外祖母系亲姐妹，图 B），妹妹体健，妹妹育有 2 子，均体健。查体：身高 165cm，体重 63kg ，血压 104/62mmHg。神清，精神可，时间、地点、计算力粗测正常。言语含糊、缓慢，余颅神经（-），四肢肌力肌张力正常，腱反射（++），针刺觉对称，共济稳准，闭目难立征（-），病理征及脑膜刺激征（-）。辅助检查：血红蛋白 133g/L，平均红细胞体积 82.2↓fl（83.9-99.1fl），尿葡萄糖（++++）↑，糖化血红蛋白 7.6↑%，糖化血清白蛋白 21.19↑%。铁代谢：铁蛋白 1095.2↑ng/mL（80-130ng/mL），血清铁 4.1↓μmol/L（9-29μmol/L），铁饱和度 8.9↓%（20-55%），总铁结合力 45.9↓μmol/L（45-72μmol/L），转铁蛋白 236mg/dl（220-400mg/dl）。铜蓝蛋白<2.00↓mg/dl（20-40mg/dl）。肝肾功能、血脂、电解质、肿瘤标记物，叶酸、维生素 B12 未见明显异常。头颅 MRI 示双侧基底节区灰质核团对称性短 T2 信号灶，考虑铁质沉积改变，伴双侧壳核及尾状核尾部信号异常（图 A. a-c）。脑电图：额颞区较多段状慢波活动。腹部 MR 示肝脏、胰腺重度铁质沉积（图 A.d）；脂肪肝，胰腺脂肪浸润；胰腺轻度萎缩。神经电生理检查正常。眼科检查：糖尿病 I 期眼底病变，无 K-F 环，未见视网膜变性。*CP* 基因一代测序发现第 4 号外显子 c.643C>T 纯合突变(图 C)，致 215 位精氨酸变成终止子（p.R215X），经 ACMG 评估为“致病”。
结论 ACP 是一种罕见的与铁沉积有关的常染色体隐性遗传疾病，由编码铜蓝蛋白的 *CP* 基因突变所致，临床上表现为胰岛素依赖型糖尿病，视网膜变性导致的视力减退，及中枢神经系统表现，如锥体外系症状：不自主运动，肌张力增高等；进行性记忆力减退，可发展为痴呆，多数患者可有轻度贫血。对于 1 型糖尿病伴贫血，认知障碍、共济失调或运动障碍等神经系统症状的患者，应注意血浆铜蓝蛋白缺乏症的可能，早期诊断予铁螯合剂治疗，可能缓解症状或延缓疾病进展。

FGD4 基因新突变致腓骨肌萎缩症 4H 型一例报道

曹立 詹飞霞 栾兴华
上海交通大学附属第六人民医院

目的 报道一例由 *FGD4* 基因突变所致的腓骨肌萎缩症 4H 型（CMT4H），探讨 CMT4H 患者临床和基因突变特点。
方法 对该例患者的病史及临床表现进行全面评估，并进一步行遗传学检测分析。
结果 患者，男，12 岁，因“步态异常 1 年余”就诊。自上中学后，发现跑步变慢，偶尔行走时摔跤，穿鞋时觉足部紧迫感。1 年前，发现行走步态异常，呈摇摆步态，右脚跟不能着地，弓形足，易摔跤，且症状逐渐加重。出生史正常，从小精神运动发育同一般人。否认家族史，父母非近期结婚。查体：神清，颅神经阴性；四肢肌力、肌张力正常，四肢腱反射消失，四肢肌肉未见明显萎缩；双足高弓畸形，右侧明显，行走时步态不稳，右脚尖着地，脚跟悬空，躯干左倾。辅助检查：肌电图示上下肢多发感觉、运动神经损害，上肢运动神经神经脱髓鞘为主，伴轴索损害可能，可见传导阻滞。全外显子测序发现患者存在 *FGD4* 基因复合杂合突变：c.1951C>T

(p.Q651X) 和 c.1688C>A (p.T563K)，均为未报道的新突变，共分离示其父亲和母亲分别为杂合变异携带者。经 ACMG 指南评估， c.1951C>T 为“致病”，c.1688C>A 为“可能致病”。
结论 腓骨肌萎缩症是一类具有高度临床和遗传异质性的遗传性周围神经病，多为儿童和青少年期起病，主要表现为进行性，对称性肢体远端肌无力和肌萎缩，感觉障碍和腱反射减退或消失，常伴高弓足、爪形手和脊柱侧弯等骨骼畸形。根据本例患者临床、肌电图等特点，结合文献复习，提示除上述典型临床表现外，CMT4 更有发病年龄早、疾病进程快、破坏范围大等特征，且近亲婚配的子女患病率更高。综上，我们报道了一例经基因检测明确的腓骨肌萎缩症 4H 型病例，扩展了中国人群 *FDG4* 基因突变谱。

一例 17q21.33-17q22 微缺失导致的综合征型耳聋

王际平 吴红敏 周慧群 陈正侬 于栋祯 时海波 殷善开
上海市第六人民医院

目的 对一 2 岁综合征型耳聋患者进行遗传学病因分析。
方法 对先证者进行全面的体格、听力学及影像学的检查。提取其中核心家庭成员外周血有核细胞基因组 DNA，行全外显子测序和染色体 100K 检测及相关生物信息学分析。
结果 先症者出生后发育迟缓、中度智力、自闭、左耳极重度听力损失，右耳重度听力损失；颞骨影像学无明显异常；双侧第五指斜位；外耳轻度畸形；全外显子组测序未发现可疑突变，染色体 100K 检测显示先症者第 17 号染色体长臂有 6.25M 的一个拷贝缺失（46,XY,del(17q21.33q22).(49,145,834-55,409,832)×1），先症者父母无该缺失突变提示为新发突变。该区域包含 OMIM 收录的致病基因 *NME1*、*DGKE*、*NOG*，患者部分表型复合 *NOG* 单倍剂量不足导致的近端指间关节融合综合征。
结论 第 17 号染色体长臂的一个拷贝微缺失导致该患者综合征表型。

三个 MYO15A 基因剪切位点新突变导致遗传性耳聋

王际平 吴红敏 周慧群 陈正侬 于栋祯 时海波 殷善开
上海市第六人民医院

目的 MYO15A 突变导致 DFNB3 型耳聋，听力表型呈现出多样性。本研究对前期收集的三个耳聋家系进行了病因研究，以期揭示耳聋患者的遗传性致病因素。
方法 对先证者进行全面的体格、听力学及影像学的检查。结合家族史，提取其中核心家庭成员外周血有核细胞基因组 DNA，行全外显子测序及相关生物信息学分析，阳性位点经一代测序验证。
结果 三个家系先症者均表现为先天性双侧极重度感音神经性聋。全外显子测序和遗传分析显示家系 1 先证者携带 MYO15A 基因 c.10258_10260delTTC（p.Phe3420del）和 c.7395+6T>G 两个复合杂合突变；家系 2 先证者携带 MYO15A 基因 c.10250-10253delCCT 和 c.4487-7 T>A 复合杂合突变；家系 3 先证者携带 MYO15A 基因 c.10250-10253delCCT 和 c.7654+1 G>A 复合杂合突变。突变位点均与耳聋表型共分离。
结论 通过基因序列和遗传分析，明确了 3 个家系耳聋的由于复合杂合突变导致 DFNB3 型耳聋，发现三个新的 MYO15A 致聋剪切突变。

德朗热综合征致病基因 NIPBL 剪切位点突变分析

庞秀红
江苏省泰州市人民医院

目的 德朗热综合征(Cornelia de Lange Syndrome，CdLS)是一种罕见的常染色体显性综合征性耳聋，其特征性表型包括听力障碍、独特的颅面部畸形、骨骼肌肉系统畸形、生长发育及智力发育迟

缓等。*NIPBL* 基因为 15 个 CdLS 候选基因中最为常见的致病基因。本研究拟对前期收集的 1 例中国汉族散发疑似德朗热综合征患者的遗传性病因进行探查。
方法 利用二代测序技术对所有 406 个已知耳聋基因和 15 个德朗热综合征候选基因进行筛查，利用 PolyPhen-2、Mutation Taster、SIFT、PROVEAN 等工具软件进行生物信息学预测，Sanger 测序进行家系内验证。
结果 先证者具有典型德朗热综合征特征性表型，包括双侧先天性极重度感音神经性耳聋、CdLS 经典面容、足趾短小、生长发育和智力发育迟缓等。先证者同时携带 *OTOG* 基因 c.6941A>G（p.N2314S）和 c.7126 G>A（p.D2376N）双等位基因杂合错义变异，其正常表型父母各携带一个杂合变异，工具软件预测这两个变异很可能为良性改变。另外，先证者携带 *NIPBL* 基因已报道剪接位点 c.6763+5G>T 杂合突变，而表型正常父母不携带该突变。
结论 本研究第二次在中国汉族疑似 CdLS 患者中筛查发现既往已报道与 CdLS 相关的 *NIPBL* 基因剪接位点 c.6763+5G>T 杂合突变，该突变在本研究家系中很可能为 *de novo* 突变。本研究再次证实了 *NIPBL* 基因剪接位点 c.6763+5G>T 突变的致病性，为临床遗传咨询及婚育指导进一步提供了理论依据。对该家系二胎及先证者后代患病风险进行预测，提供遗传咨询及婚育指导，从而实现综合征性耳聋的一级预防。

Maffucci syndrome complicated by giant chondrosarcoma in the left ankle with an IDH1 R132C mutation: case report

Haiyan Lv Rangteng Zhu
Taizhou Hospital affiliated to Wenzhou Medical University

Objective Maffucci syndrome is rare, nonhereditary congenital mesodermal dysplasia characterized by multiple enchondromas and hemangiomas. At present, there are few studies on MS with giant chondrosarcoma and whole exome sequencing analysis. We present a case of 45-year-old man with Maffucci syndrome to supplement the clinical manifestations and explore the molecular mechanism of Maffucci syndrome.
Methods Physical, imaging and laboratory examinations were performed on the patient. Furthermore, the whole exome of peripheral blood embryogenic and chondrosarcoma tissue DNA were analyzed by next generation sequencing.
Results Physical examination showed a giant lump of about 35 cm × 30 cm × 30 cm in the left ankle, with local skin ulceration and evident purulent secretions discharge. Imaging examination indicated local spherical expansive bone destruction with multiple calcifications at the left tarsal, multiple chondromatosis with bone deformity, and multiple hemangiomas. Laboratory indicators implied severe bone destruction and inflammation before surgery. Finally, the patient was underwent amputation surgery to inhibit tumor development and diagnosed as Maffucci syndrome with 1-2 grade giant chondrosarcoma in the left ankle. In addition, the whole exon analysis revealed isocitrate dehydrogenase 1 R132C chimeric mutation in chondrosarcoma lesions but not in blood DNA.
Conclusions This case report presents the genetic evidence for the inclusion of chondrosarcoma among tumors characterizing Maffucci syndrome. Consequently, it is suggested that patients with Maffucci syndrome should be followed up more actively to exclude neoplasms due to IDH1 R132C somatic chimeric mutation.

Genetic spectrum and clinical features of NMNAT1-associated retinal degeneration

Zhen Yi[1] Shiqiang Li[1] Siyu Wang[2] Xueshan Xiao[1] Wenmin Sun[1] Qingjiong Zhang[1]
1.Zhongshan Ophthalmic Center, Sun Yat-sen University
2.Li Chuan People's Hospital

Objectives To systematically analyse the *NMNAT1* variant spectrum and frequency, the associated phenotypic characteristics, and potential genotype-phenotype correlations based on our data and literature review.
Methods Biallelic potential pathogenic variants (PPV) in *NMNAT1* were collected from our in-house exome sequencing data. Whole-genome sequencing was conducted subsequently for patients with only one heterozygous PPV detected in *NMNAT1*. The clinical data were reviewed and evaluated in detail. Furthermore, the literature was reviewed for reports of *NMNAT1* variants and their associated phenotypes.
Results Eleven *NMNAT1* variants, including two novel variants, were detected in 8 families from our cohort. All of the 9 available patients showed generalized tapetoretinal dystrophy at an early age (88.9% in the first decade), and disciform macular atrophy was identified in six patients from five unrelated families. Among a total of 125 patients from 8 families of our cohort and 91 families reported by the available literature, 92.9% patients showed onset of disease at no later than 1 year of age, and 89.0% patients showed a visual acuity of 0.05 or lower. All of the 39 patients with fundus photos available presented disciform macular atrophy with generalized tapetoretinal dystrophy. Most (54/80, 67.5%) of causative *NMNAT1* variants were missense. The most frequent variants in Caucasian population and in Asian population are p.E257K and p.R237C, respectively.
Conclusions Early onset age, disciform macular atrophy with generalized tapetoretinal dystrophy, and poor visual acuity are the typical features of *NMNAT1*-associated retinal degeneration. Different variant hot spots of *NMNAT1* were observed in different populations.

NIPT 在不同血清学筛查风险值及不同年龄孕妇中检测染色体异常的效果分析

裴元元
龙岗区妇幼保健院

目的 探讨无创产前检测（NIPT）技术在不同血清学筛查风险值及不同年龄孕妇中检测染色体异常的价值。
方法 回顾性分析 2018 年 1 月至 2019 年 12 月在深圳市龙岗区妇幼保健院同时进行了早期血清学筛查与 NIPT 的单胎妊娠孕妇 11517 例,按孕妇年龄及血清学筛查与 NIPT 结果将研究对象分组:组 1：血清学筛查与 NIPT 均高风险组、组 2：血清学筛查临界风险且 NIPT 阳性组、组 3：血清学筛查低风险但 NIPT 阳性组，各组内再分高低龄组。对血清学筛查高风险及 NIPT 提示结果异常的孕妇，建议进行产前染色体核型分析、染色体微阵列分析进一步明确诊断。
结果 11517 例孕妇，血清学筛查高风险率为 3.98%，NIPT 阳性率为 1.81%。产前血清学筛查检测 21 三体的阳性预测值（PPV）为 42.86%，检测 18 三体的 PPV 为 28.57%；NIPT 检测 21 三体的 PPV 为 84.62%，检测 18 三体的 PPV 为 33.33%，检测其它染色体异常的 PPV 为 17.19%。组 1 及组 2，血清学筛查、NIPT 检测 21 三体和 18 三体的 PPV 的差别无统计学意义，组内高低龄孕妇间两种技术检测 21 三体和 18 三体的 PPV 的差别也无统计学意义。相较于产前血清学筛查，通过 NIPT 异常结果提示，额外确诊 21 三体 3 例；性染色体数目异常 8 例；微缺失微重复 8 例；22 三体嵌合体 1 例；性染色体结构异常 2 例，16 号染色体部分片断杂合性缺失 1 例。
结论 NIPT 筛查各类染色体异常的灵敏性与准确性明显高于产前血清学筛查，NIPT 可有效降低血清学筛查的漏诊。实际工作中，需充分利用信息化大数据平台，加强产前筛查结果异常人群的追踪随访，做到闭环管理。

一例 SON 基因杂合变异引起 ZTTK 综合症患儿的病例报道

辛红美 赵建设 律玉强 杨亚楠 李子龙 盖中涛 刘毅
济南市儿童医院

目的 ZTTK（Zhu-Tokita-Takenouchi-Kim，OMIM：617140）综合征是一种以智力缺陷，脑、面部以及内脏的畸形，骨骼肌肉异常等为特征的罕见的先天性异常综合征，由 *SON* 基因的杂合突变引起，呈常染色体显性遗传。我们探讨了 1 例足月小样儿伴有发育落后、面部畸形、心脏缺陷及脑发育不良患儿的遗传学病因。
方法 对患儿进行临床和实验室检查，应用二代测序技术进行测序分析，对可疑致病基因位点进行患儿及其父母的 Sanger 测序验证。
结果 患儿临床表现为足月小样儿，存在宫内发育迟缓；毛发增多，低位耳，额头窄的面部畸形；头颅核磁共振显示胼胝体发育不良；心脏彩超显示动脉导管未闭、卵圆孔未闭和三尖瓣轻度反流。二代测序结果显示，患儿 *SON* 基因存在一个 c.5751_5754del 变异，导致氨基酸发生移码变异（p.V1918Efs*87），属于极强的致病性证据，患儿父母在该位点均无变异。结合患者的临床表现，判断该变异为致病性变异。
结论 *SON* 基因的杂合变异是导致该例患儿 ZTTK 综合征的遗传学病因。上述发现丰富了 *SON* 基因的变异谱，为临床决策和遗传咨询提供了依据。

非典型早老综合征患者 LMNA p.Pro4Arg 诱导性多能干细胞系模型

戴礼猛[1] 武岩[1] 张丹妍[2] 赵乐天[2] 李嘉[1] 白云[1] 郭洪[1]
1.陆军军医大学
2.重庆市人口与计划生育科学技术研究院

目的 LMNA 基因突变患者会引起早老样表现，除典型 Hutchinson-Gilford 早衰症外，部分患者表现非典型早老综合征表现，其中机制并未完全阐明。本研究通过构建患者来源的诱导性多能干细胞模型，用于探索 LMNA 致病变异引起非典型早老综合征的致病机制。
方法 本研究患者携带 LMNA p.Pro4Arg 突变，呈现非典型早老综合征表现，临床特征包括鸟样相脸，四肢脂肪营养不良，以及四肢和躯干皮肤色素沉着。知情同意后采集患者外周血，分离及扩增红系祖细胞；采用电转方法导入 Episomal 重编程载体后进行低密度细胞接种；采用干细胞培养体系诱导细胞重编程；观察干细胞克隆形成过程，挑取优质克隆传代扩增；采用核型分析、免疫荧光染色、拟胚体形成、胚层分化等实验对传代细胞进行干细胞鉴定。
结果 患者红系祖细胞经过重编程获得的干细胞克隆能成功扩增，第 10 代细胞核型正常，免疫荧光染色提示表达 Nanog、SOX2、OCT4 干性标记基因产物，定量 PCR 实验证实干性标记基因产物表达量与 H9 胚胎干细胞系相当。细胞能成功形成拟胚体，免疫荧光实验证实拟胚体随机分化过程能生成三个胚层标记基因产物 Nestin、cTnT 及 AFP。
结论 本研究成功建立 LMNA p.Pro4Arg 突变非典型早老综合征患者诱导性多能干细胞系，该细胞模型可为 LMNA 基因突变引起的非典型早老综合征发病机制研究提供重要实验材料。

脊髓性肌萎缩症的三级预防研究进展

覃瑶 陈钢 肖辉 刘俊娇
深圳会众生物技术有限公司

脊髓性肌萎缩症(spinal muscular atrophy，SMA) 是一种以脊髓前角运动神经元退化变性和丢失所致的肌无力和肌萎缩为主要临床特征的常染色体隐性遗传病，位居 2 岁以下儿童致死性遗传病的首位。开展 SMA 三级预防，即在孕前、产前、新生儿三个阶段进行 SMA 筛查，对于降低有缺陷人

口出生率、提高患者生存期具有重要的意义。本文针对国内外脊髓性肌萎缩症的三级预防进展情况，重点围绕一级预防、二级预防的 SMA 携带者筛查和三级预防的新生儿筛查进行了总结和分析。分析发现，在 SMA 携带者筛查方面，国内近年来取得了较大进展，但人群接收度相比国外还比较低；在新生儿筛查方面，相比美国、德国等西方发达国家，国内进展还比较缓慢，有待于社会各界来共同努力推动。

KMT2A 基因新发无义变异致 Wiedmann-steiner 综合征 1 例

刘宁
山东大学齐鲁儿童医院

目的 Wiedmann-steiner 综合征（Wiedmann-steiner syndrome, WDSTS，OMIM# 605130）是一种罕见先天性生长发育障碍综合征，以肘部多毛、身材矮小及特殊面容为主要特征，属于常染色显性遗传病。本文总结分析 1 例由 KMT2A 基因突变所致 WDSTS 的临床特点和基因型，提高对该病的认识。
方法 对 1 例到我院儿保所会诊的 WDSTS 患儿的进行临床和实验室检查。对患者进行全外显子测序筛选符合表型的可能致病基因变异，Sanger 测序验证患者及其父母突变基因位点，并利用在线软件 Mutation Taster 预测蛋白功能损伤。
结果 患儿男性，G2P2，足月刨宫产，3 岁 3 个月，因'语言发育迟缓'就诊。头颅外形正常，营养良好，神志清楚，精神反应好，心肺正常，脊柱四肢无畸形，特殊面容，鼻梁高，眼睑裂下斜。基因检测结果发现患儿携带 KMT2A 基因第 27 号外显子新发杂合无义突变 c.8501C>A，导致氨基酸提前终止(p.S2834X)，父母均未携带。ExAC 数据库，千人基因组数据库(1000G)，人类基因突变数据库（HGMD）及疾病相关基因变异（Clin var）数据库，均未见该变异报道。Mutation Taster 预测该位点有害，根据 ACMG 遗传变异判定为致病性变异（PVS1+PS2+PM2）。
结论 临床对发育迟缓，特殊面容的患者应进行基因筛查以明确致病原因，提高对罕见遗传病的诊断。本例患儿临床表型由 KMT2A 基因 c.8501C>A 变异所致，为新发无义变异，该病例的发现丰富了 *KMT2A* 变异数据库。

A Chinese neonatal case of Adams-Oliver syndrome with one novel heterozygous mutation Gly204Ser in DLL4 gene

Yanxin Wang Xiaoying Li Yuqiang Lv Min Gao Zhongtao Gai Yi Liu
Qilu Children's Hospital of Shandong University

Purpose Adams-Oliver syndrome (AOS) is an extremely rare genetic disease with an estimated incidence of 1/225 000. Various clinical manifestations have been observed, which are well characteristic by aplasia cutis congenita of the scalp and terminal transverse limb defects. Here we reported one novel missense mutation of DLL4 gene causing AOS in a Chinese neonate.
Methods In this study, the phenotype and genotype of the proband and her parents were studied. Whole genome sequencing (WES) was performed for the proband, and Sanger sequencing was used for verification of the variant in the proband and her parents. To further identify the predicted effect of missense variant on protein function, we applied different in silico prediction models, such as SIFT, PolyPhen-2, Mutation Taster, and GERP+.
Results The proband, a 2-day-old girl, suffered from defects of the scalp vertex, cutis marmorata, and ankyloglossia when she was born, while her parents were normal. The 3-dimensional reconstruction imaging of brain CT validated the existence of defects around the left parietal bone further. The Doppler echocardiography exhibited crack-like patent ductus arteriosus and slightly patent foramen ovale, while other important internal organs were not involved, namely liver, spleen, kidney, and adrenal gland. There also were no markedly abnormal findings in amino acid and acylcarnitine screening of blood and urine. WES analysis displayed that a heterozygous

variant of c.610G>A (p.Gly204Ser) was detected in DLL4 gene on chromosome 15. The transversion from G to A in exon 4 of DLL4 resulting in the replacement of Gly by Ser at the position of 204 was identified in the proband. Whereas identical substitution was not found in her parents via Sanger sequencing, indicating the heterozygosis was a de novo mutation. Additionally, in silico prediction models revealed that the missense mutation of c.610G>A in DLL4 gene was predicted to be damaging.

Conclusions This study detected one novel loss-of-function mutation in DLL4 gene from a neonatal girl presenting phenotypes of AOS which contributed to exploring phenotype-genotype correlations further. Meanwhile, this work also expanded the spectrum of DLL4 gene variants of human beings. Nevertheless, it was likely that other underlying phenotypes had not yet emerged due to the proband was in the early stage of growth and development, implying a long term follow-up was essential.

FGF21-脂联素信号通路与糖代谢紊乱的相关性

刘丹 贾伟平 吴量 高琼媚 龙晓雪 李华婷
上海交通大学附属第六人民医院

目的 通过一项前瞻性队列研究探讨 FGF21-脂联素信号通路与糖代谢紊乱的相关性。

方法 选取 2013 年 4 月至 2018 年 9 月，上海泥城队列随访的 6361 名受试者，测定基线血清 FGF21、脂联素浓度。通过多元 logistic 回归分析，探讨基线 FGF21/脂联素比值与血糖恶化的相关性，并采用 C statistics、净重新分类改善指数 (NRI) 以及综合判别改善指数 (IDI) 评估 FGF21/脂联素比值的临床应用价值。

结果 基线时，血清 FGF21、FGF21/脂联素比值随着血糖恶化的程度逐渐升高，而血清脂联素浓度随之递减 (p for trend 均 < 0.001)。经过 4.6 年随访 (4.3 ~ 4.8 年)，在 4797 名无基线糖尿病的人群中，195 名受试者发展为糖尿病，351 名受试者发展为糖尿病前期。与非新发糖尿病受试者相比，新发糖尿病患者的基线血清 FGF21、FGF21/脂联素比值更高，血清脂联素浓度更低 (p 均 < 0.001)。多元 logistic 回归分析显示，在校正传统危险因素后，基线 FGF21/脂联素比值是新发糖尿病的独立危险因素，尤其是在基线糖尿病前期人群中 (OR = 1.367，p = 0.001)。此外，FGF21/脂联素比值与新发糖尿病前期的发生风险显著相关 (OR = 1.185，p = 0.021)，而血清 FGF21、脂联素水平均不能独立预测糖尿病前期的发生 (p 均 > 0.05)。值得注意的是，NRI 及 IDI 分析结果显示，与 FGF21 或脂联素相比，FGF21/脂联素比值可显著提高传统危险因素构建模型对糖尿病风险的预测效能 (NRI = 27.1%，p < 0.001; IDI = 0.7%，p = 0.020)。

结论 FGF21/脂联素比值与新发糖尿病前期、新发糖尿病的发生风险密切相关，FGF21-脂联素信号通路的紊乱参与糖尿病发展的病理生理机制。

A family segregating lethal primary coenzyme Q10 deficiency due to two novel COQ6 variants

Na Wang
Taizhou Hospital of Zhejiang Province, Taizhou Enze Medical Center (Group)

Objective Primary coenzyme Q10 deficiency-6 (COQ10D6) is a rare autosomal recessive disease caused by COQ6 mutations, primarily manifesting as infantile onset progressive nephrotic syndrome (NS) resulting in end-stage renal failure and sensorineural deafness. The clinical value of an accurate diagnosis of primary coenzyme Q10 deficiency is that this disease is considered as the only treatable mitochondrial disorder, since many patients respond well to oral coenzyme Q10 (CoQ10) supplementation. To date, seven mutations of COQ6 including missense, indels and frameshifts have been reported in Human Gene Mutation Database (HGMD), exhibiting the autosomal recessive inheritance pattern for nephrotic diseases in a homozygous or heterozygous state. Herein, we describe a new presentation of the disorder

including NS, growth retardation and hypotonia, due to the combined effects of two novel potentially recessive pathogenic variants of COQ6 gene in a compound heterozygous state.
Materials and methods We performed whole exome sequencing to analyze the genetic cause of infantile NS in a Chinese affected family, and used Sanger sequencing to assess the segregation of the identified variants. The clinical symptoms, molecular biological characteristics and family history of the affected individuals were analyzed retrospectively.
Results The two infants diagnosed with COQ10D6 were conceived by a healthy, non-consanguineous Chinese and Vietnamese couple, who denied hepatitis, tuberculosis, diabetes, allergic diseases and hereditary disease history. The two patients both showed the characteristic NS and growth retardation and died at an early stage of infancy. Besides, we also found that the female proband exhibited a novel extrarenal manifestation such as hypotonia, previously not reported. We also exposed two recessive nonsense mutations of COQ6 gene segregating with disease in the Chinese family: COQ6(NM_182476.3):c.249C>G(p.Tyr83Ter) inherited from the father and COQ6(NM_182476.3): c.1381C>T (p.Gln 461 Ter) inherited from the mother. Genetic analysis indicated that the pathogenic nonsense mutation in exon 2 of COQ6 gene (p.Tyr83Ter) contributed to the deficiency of COQ6 protein function, which might eventually affect the pathway of CoQ10 biosynthesis. Meanwhile, there was a difference of the secondary structure and sovlent accessibility between COQ6 wild type and the candidate variant COQ6 p.Gln461Ter, which might break the protein-protein interaction of COQ complexes comprised of human PDSS2, COQ3, COQ4, COQ6 and COQ7 in human mitochondria, thus inducing progressive renal injury.
Conclusion Our study provides the first report of two novel nonsense mutations in COQ6 gene: c.249C>G (p.Tyr83Ter) and c.1381C>T(p.Gln461Ter), which in a compound heterozygous state resulted in two siblings with severe COQ10D6 that manifests mainly as typical NS, growth retardation and hypotonia that had never been reported previously. Our cases expanded the phenotypic spectrum of COQ6 mutations and the genotypic spectrum of COQ10D6. Based on the molecular analysis, we speculated that the two COQ6 variants may destruct the COQ complexes leading to a disruption of CoQ10 and eventually a severe mitochondrial disease. Thus, there is an essential to perform an early detection of COQ6 mutations in such patients with clinical presentations suggestive of COQ10D6, especially those with neurological manifestations such as growth retardation, because treatment with CoQ10 in the early period can help in improving COQ10D6-related NS and neurological symptoms.

新生儿筛查确诊 538 例 cblC 型甲基丙二酸血症患者预后分析

韩连书
上海交通大学医学院附属新华医院

目的 分析新生儿筛查确诊 cblC 型甲基丙二酸血症（methylmalonic acidemia, MMA）患者预后及影响因素。
方法 将 2004 年 1 月至 2020 年 12 月来自我国不同省、市、自治区经新生儿筛查确诊的 538 例 cblC 型 MMA 患者分为预后良好组及预后不良组，回顾性研究分析其临床特点、生化资料、基因测序结果及预后影响因素。采用单因素分析比较两组间各因素差异及多元 Logistic 回归方程分析新生儿筛查确诊 cblC 型 MMA 患者预后不良的独立危险因素。
结果 538 例 cblC 型 MMA 患者男 280 例，女 253 例。298 例预后良好（55.39%），240 例预后不良（44.61%），其中智力落后 234 例（43.49%），运动障碍 104 例（19.33%），眼部受累 31 例（5.76%），脑积水 9 例（1.67%），死亡 9 例（1.67%）。单因素分析显示预后良好组与预后不良组患者间新生儿筛查结果、临床表现、随访生化结果、治疗早晚及基因测序结果均有统计学意义（均 P<0.05）。多因素 Logistic 回归分析显示，临床症状的出现(OR=12.07, 95%CI：5.18～28.14，p=0.000)及 *MMACHC* 基因 c.609G>A 变异(OR=2.15, 95%CI：1.23～3.75，p=0.007)是预后不良特别是智力落后的独立危险因素。
结论 新生儿筛查通过早期干预管理可明显改善患者预后。

X/Y 染色体不平衡易位一家系临床分析

丛潇怡
龙岗妇幼保健院

目的 探讨 X/Y 染色体不平衡易位患者的临床特征。
方法 利用高分辨染色体 G 显带技术、染色体 C 显带技术以及微阵列比较基因组杂交技术（array-CGH），结合患儿的临床表现，探讨此类患者以及家系中其他成员的临床特征。
结果 患儿染色体 G 显带结果为 46,X,der(X)t(X;Y)(p22.3;q11.21)pat；C 显带结果提示异常 X 染色体末端深染，为异染色质区；array-CGH 结果提示在 X 染色体 Xp22.33-pter 位置发生杂合缺失，片段大小约 2.7Mb，Y 染色体 Yq11.21-qter 位置片段存在，片段大小约 14.2Mb。
结论 X 染色体异常可引起女性生长发育迟缓、原发或继发性闭经、性腺发育异常等。Array-CGH 在染色体微小拷贝数变异中具有更高的分辨率和检出率，对明确疾病的诊断发挥重要作用。

右位主动脉弓的产前诊断、临床分析及预后

曲晓星 孙路明 吴凤钰 邢娅 杨颖俊 邹刚
同济大学附属第一妇婴保健院

目的 总结产前超声发现的右位主动脉弓（Right Aortic Arch， RAA）主要超声表现，细胞及分子遗传学检测结果及预后，探讨孤立的右位主动脉弓的适宜产前流程。
方法 回顾性分析了从 2016 年到 2021 本单位产前超声筛查出的 66 例右位主动脉弓病例，综合分析了合并超声表现，芯片及核型分析结果，临床预后。
结果 66 例产前诊断右位主动脉弓病例：52 例为孤立性右位主动脉弓，大多数（49 例，94.2%）预后良好；6 例合并心内异常；5 例合并其他心外异常。孤立性 RAA 中，其中有 4 例诊断出有拷贝数变异阳性病例，3 例为 22q11.2 微缺失综合征，2 例决定终止妊娠；在心内和心外异常组另外发现 4 例拷贝数变异阳性病例，1 例为 22q11.2 微缺失综合征。在所有发现的 8 例拷贝数变异阳性病例中，7 例为致病性拷贝数变异，1 例为和神经精神发育相关的临床意义未明拷贝数变异，其中 6 例选择了终止妊娠。
结论 所有的右位主动脉弓病例均需要进行详细的超声评估，大多数（94.2%）孤立性右位主动脉弓预后良好，最常见的基因组变异为 22q11.2 微缺失综合征。

羊水同型半胱氨酸检测在甲基丙二酸血症合并同型半胱氨酸血症产前诊断中的应用

韩连书
上海交通大学医学院附属新华医院

目的 甲基丙二酸血症（methylmalonic acidemia, MMA）合并同型半胱氨酸血症 cblC 型是甲基丙二酸血症中辅酶钴胺素代谢缺陷最常见的一种类型。本文旨在建立一种可靠的产前诊断 cblC 型 MMA 的方法以帮助存在生育此疾病患儿的高危家庭选择是否继续妊娠。
方法 本研究对 248 名高危孕妇的产前数据进行了回顾性分析。通过循环酶法测定羊水中的 Hcy 浓度，通过液相色谱质谱联用技术和气相色谱质谱联用技术分别对羊水中的酰基肉碱及有机酸代谢物进行生化分析，通过鉴定羊水中 DNA 的致病变异进行基因分析。
结果 248 例高危胎儿中，63 例被诊断为 cblC 型 MMA 胎儿，其余 185 例为非 cblC 型 MMA 胎儿。63 例 cblC 型 MMA 胎儿中的 Hcy 浓度为 13.20 (6.62–43.30) μmol/L，显著高于 185 例非 cblC 型 MMA 胎儿（2.70 (0.00–5.80) μmol/L），且两组 Hcy 结果无交叉。羊水 Hcy 检测方法的灵敏度和特异度分别为 100%和 92.05%，羊水 Hcy 检测结合酰基肉碱和有机酸代谢物检测方法的阳性预测值为 100%。本研究中 16 例胎儿的 *MMACHC* 基因突变结果不明确，其中 7 例胎儿羊水中

Hcy、C3、C3/C2 以及甲基丙二酸的结果异常，分别为 18.50 (6.70–43.30) μmol/L，8.53 (5.02–11.91) μmol/L，0.77 (0.52–0.97)，8.96 (6.55–40.32) mmol/mol Cr，因此被确诊为 cblC 型 MMA 胎儿，其余 9 例羊水代谢物指标正常的胎儿被认为未患此病。

结论 Hcy 可作为 cblC 型 MMA 产前诊断中的另一个敏感性较高的代谢标志物，羊水 Hcy 检测联合酰基肉碱以及有机酸代谢物的检测可快速、灵敏、可靠的进行 cblC 型 MMA 产前诊断，且该联合方法可弥补基因检测的不足，有助于先证者基因突变不明的孕妇进行产前诊断。

MUT 型甲基丙二酸血症患者基因不同突变类型 VitB12 疗效相关性分析

韩连书
上海交通大学医学院附属新华医院

目的 分析 mut 型甲基丙二酸血症（Methylmalonic acidemia，MMA）*MMUT* 基因不同突变类型与 vitB12 治疗效果的相关性，总结 vitB12 治疗完全有效型、部分有效型及无效型相关 *MMUT* 基因突变位点。

方法 回顾性分析 266 例基因检测确诊的 mut 型甲基丙二酸血症患者的临床资料、质谱检测结果、VitB12 负荷试验结果、智力测试结果及预后。

结果 完全有效组、部分有效组及无效组分别纳入患者 81 例、27 例和 158 例，发病率分别为 30/81 (37.0%)、 21/27 (77.8%) 和 131/158 (82.9%)，有统计学差异（P<0.0001）。三组治疗后血丙酰肉碱（C3）、丙酰肉碱与乙酰肉碱比值（C3/C2）及尿甲基丙二酸水平均低于治疗前，完全有效组治疗后 C3 水平[0.20 (0.06-0.95) μmol/L）降至正常范围，三组间治疗前后血 C3、C3/C2 及尿甲基丙二酸水平差值有统计学差异（P<0.0001）。266 例患者共检测到基因突变 144 种，其中无效型突变 95 个，部分有效型突变 8 个，包括 c.599T>C（p.I200T）、c.1630_1631GG>TA（p.G544*）及 c.1741C>T（p.R581*）等，完全有效型突变 26 个，包括 c.1663G>A（p.A555T）、c.2080C>T（p.R694W）及 c.1880A>G（p.H627R）等。完全有效型和部分有效型患者中发育及智力落后者较无效型患者少，差异具有统计学意义（P<0.001）,预后佳。

结论 VitB12 治疗对部分 mut 型 MMA 患者有效，每例确诊患儿均需行 vitB12 负荷试验，依据结果给予对应治疗，治疗有效患者长期预后佳。

cblC 型甲基丙二酸血症 c.80A>G 突变患者的临床、生化表型及预后分析

韩连书
上海交通大学医学院附属新华医院

目的 探讨甲基丙二酸血症（methylmalonic acidemia，MMA）MMACHC 基因 c. 80A>G 突变患者的生化、临床表型及其与 c.609 G>A、c.658_660delAAG 突变患者的比较。

方法 回顾性分析 1154 例在本中心诊治的 cblC 型 MMA 患者，根据不同的基因突变位点，筛选出 5 组患者进行基因型-表型相关性的研究。A 组 40 例患者，均携带 c.80A>G 突变且不携带 c.609G>A、c.658_660delAAG、c.482G>A 突变；B 组 88 例患者，携带 c.80A>G 及 c.609G>A 复合杂合突变；C 组 24 例患者，携带 c.80A>G 及 c.658_660delAAG 复合杂合突变；D 组 496 例患者，均携带 c.609G>A 突变且不携带 c.80A>G、c.658_660delAAG、c.482G>A 突变；E 组 104 例患者，均携带 c.658_660delAAG 突变且不携带 c.80A>G、c.609G>A、c.482G>A 突变。

结果 与携带 c.609G>A 或 c.658_660delAAG 突变且不携带 c.80A>G 突变的患者相比，携带 c.80A>G 突变患者的血丙酰肉碱、尿甲基丙二酸值较低，肺动脉高压发生率较高，惊厥发生率较低，预后较好（*P*<0.05）。与携带 c.80A>G 突变且不携带 c.609G>A 或 c.658_660delAAG 突变的患者相比，携带 c.609G>A 或 c.658_660delAAG 突变患者的运动障碍发生率较高。新生儿筛查能

改善携带 c.609G>A 或 c.658_660delAAG 突变患者的预后，而对携带 c.80A>G 突变且不携带 c.609G>A 或 c.658_660delAAG 突变的患者无显著影响。

结论 携带 c.80A>G 突变的患者表现出相对较轻的临床及生化表型。新生儿筛查可改善携带 c.609G>A 或 c.658_660delAAG 突变患者的预后，对 c.80A>G 突变患者的预后无显著影响。

720 例甲基丙二酸血症 MMACHC 基因 c.609G>A 突变患者临床资料及随访分析

韩连书
上海交通大学医学院附属新华医院

目的 了解甲基丙二酸血症（methylmalonic acidemia，MMA）MMACHC 基因 c.609G>A（p.W203X）突变患者临床表现、治疗效果及预后。

方法 回顾性分析 720 例携带 c.609G>A（p.W203X）突变 MMA 患者的临床表现、质谱检测结果、治疗效果、神经心理学评估结果及长期预后。

结果 720 例患者中 306 例（42.5%）来自新生儿筛查，其中 156 例发病；414 例未筛查患者中 10 例因同胞确诊而检测后诊断本病，未发病，余 404 例均为临床病例。560 例（77.8%）发病患者中，发病年龄中位数为 1.2 月（3d~20 岁）。所有患者均为维生素 B12 有效型，治疗后患者血中丙酰肉碱、丙酰肉碱与乙酰肉碱比值、尿中甲基丙二酸、甲基枸橼酸及血同型半胱氨酸水平均下降。经新生儿筛查确诊患者中 50.6%患者发育正常。发病患者中 12.3%经治疗发育正常，其余患者遗有不同程度的智力和（或）运动障碍。筛查与未筛查、发病与未发病患者预后及神经心理学评估结果的差异有统计学意义（均 P<0.01）。

结论 MMACHC 基因 c.609G>A（p.W203X）突变与早发型 MMA 相关，新生儿筛查有助于患者预后。

血浆葡糖鞘氨醇检测在戈谢病患者治疗随访中的应用

张惠文
上海交通大学医学院附属新华医院

目的 探索血浆葡糖鞘氨醇（Glucosylsphingosine, lyso-Gb1）水平在戈谢病患者治疗随访中的应用。

方法 收集在 2017 年 1 月至 2020 年 7 月上海交通大学医学院附属新华医院规律使用伊米甘酶治疗的戈谢病患者，分两组，组 1 为 6 例初治患者，包括 1 例壳三糖酶缺失型，年龄 10~43 岁，女 4 例，男 2 例，分析治疗前后患者血常规、壳三糖酶活性和血浆 lyso-Gb1 水平；组 2 为 6 例长期接受特异性治疗的戈谢病患者，其中包括 3 例壳三糖酶缺失型，年龄 17~32 岁，女 2 例，男 4 例，分析 2017 年 1 月至 2020 年 7 月治疗期间患者血浆 lyso-Gb1 水平。

结果 组 1 患者治疗 12 个月后血小板升高（P<0.05），治疗 30 个月血红蛋白升高（P<0.05）；治疗 18 个月后 5 例患者的壳三糖酶活性降低（P<0.05），治疗 30 个月壳三糖酶活性中位数下降 7 278 $nmol \cdot ml^{-1} \cdot h^{-1}$；6 例患者治疗前血浆 lyso-Gb1 水平均显著升高，为 349.1（85.2~1 188.9）μg/L，在治疗仅 3 个月后 lyso-Gb1 水平即开始降低（P<0.05），治疗 30 个月 lyso-Gb1 水平中位数下降 259.7μg/L；组 1 患者血浆 lyso-Gb1 水平变化与壳三糖酶活性呈正相关，Spearman 相关系数为 0.863，P<0.001。组 2 患者外周血血常规正常，肝脾未及肿大，2017 至 2020 年血浆 lyso-Gb1 水平较首次测定值均下降（均 P<0.05），末次检测值中位数下降 23.4μg/L。

结论 戈谢病患者 lyso-Gb1 水平治疗后显著降低，与血常规指标和壳三糖酶活性的变化比较，lyso-Gb1 在戈谢病的随访监测中具有更好的敏感性，能够更早证明药物的有效性，增强患者坚持治疗的信心；lyso-Gb1 水平在携带壳三糖酶缺失的戈谢病患者血浆中显著升高，治疗后下降，提示其可用于伴有壳三糖酶缺失的戈谢病患者的疗效评估；长期治疗的戈谢病患者血常规相关指标和肝脾体

积基本正常，然而随治疗推进患者 lyso-Gb1 水平仍显著降低，提示 lyso-Gb1 检测可用于长期治疗的戈谢病患者的疗效评价。

NGS 在 RB 肿瘤组织中的分子遗传学研究

刘梦楚 张清炯
中山大学中山眼科中心

研究目的 视网膜母细胞瘤（retinoblastoma, RB）是一种婴幼儿时期易患的眼内恶性肿瘤。本研究将高通量靶向测序技术应用到瘤体的致病基因 RB1 基因突变筛查。
研究方法 参照 Roche 的文库构建试剂盒（KAPA HTP Library Preparation Kit）操作手册进行 DNA 文库构建。用包含 RB1 基因编码区及外显子内含子交界处序列的靶向芯片在 Nextseq550 测序平台，对 20 例视网膜母细胞瘤眼球摘除术获得的肿瘤组织 DNA 进行了测序深度为 400 乘的高通量测序，并进行生信分析找到可能的致病突变。
研究结果 病例纳入 20 例，检测结果为在 75%的组织中检测到致病突变（15/20）。各位点的杂合突变频率是 c.392del(p.Phe131SerfsTer5)， 0.9612； c.1498+2T>C， 0.9482； c.1072C>T（p.Arg358Ter）， 0.4631； c.1333C>T（p.Arg445Ter）， 0.4864； c.138del， 0.9887； c.2359C>T(p.Arg787Ter)， 0.9954； c.772_776del(p.Asn258GlufsTer11)， 0.4864； c.1735C>T(p.Arg579Ter),0.4517； c.1363C>T(p.Arg455Ter),0.9699； c.2725A>G(p.Thr909Ala),0.9764； c.1215+4del， 0.9777； c.1695+1G>A， 0.9692； c.861+1G>A， 0.9858； c.2172del(p.Ile724MetfsTer2)， 0.9690； c.763C>T(p.Arg255Ter),0.9773；c.763C>T(p.Arg255Ter),0.9672；c.1420_1421+30del,0.3259；c.1848dup(p.Gly617ArgfsTer36),0.4477；c.1363C>T(p.Arg455Ter),0.9841。NGS 肿瘤突变检测会受很多因素的影响，比如肿瘤的纯度、异质性，对于大片段的缺失、位于内含子深处的剪接信号，测序深度等，这些都可能是某些 RB1 基因突变未检出的原因。
研究结论 基于高通量测序的眼遗传病致病基因靶向芯片，能在 75%的患者肿瘤组织中有效检出 RB1 基因突变，检测肿瘤组织时需要特别关注 LOH 和启动子甲基化，有报道显示这两种改变的出现比例分别高达 60%和 10%。如果未检出突变，可再选择恰当的针对较大片段缺失重排的技术进行检测。

两例散发性先天性无虹膜症致病基因突变筛查及分析

邢雪莎 罗萍 邹梦蝶 王述森 罗阳
中国医科大学医学基因组学教研室 教育部医学细胞生物学重点实验室 沈阳 110122

目的 先天性无虹膜症（Conginital Aniridia，OMIM #607108）是一种罕见的先天性双侧全眼畸形，为常染色体显性遗传疾病，发病率为 1:96000~1:40000。该病最主要的临床特征为虹膜部分或完全消失，但病变又不仅仅局限于虹膜，还常伴有其他眼部异常，包括白内障、青光眼、角膜病变、黄斑发育不全、眼球震颤和视力受损。先天性无虹膜症已报道的致病基因有 *PAX6* 、*FOXC1*、*PITX2*、*CYP1B1*、*FOXD3* 和 *TRIM44*。目前，位于染色体 11p13 上的 *PAX6* 基因杂合突变是最主要的致病原因。本实验室收集到两个散发性先天性无虹膜患者，旨在明确患者致病基因及突变，为该病的基因诊断和遗传学咨询提供依据。
方法 经知情同意后采集家系成员外周静脉血，提取基因组 DNA，应用二代测序分别对两个散发性先天性无虹膜症患者进行相关致病基因筛查，明确两个患者的致病突变。根据突变类型选择不同的真核表达载体，进行突变致病性分析和功能验证。
结果 二代测序结果显示两个患者分别在 *PAX6* 基因存在突变 IVS4-1G>T 和 c.957_960delCACA（p.Asp319fs）突变，为国际尚未报道的突变。对 PAX6 基因 IVS4-1G>T 突变进行体外剪切位点分析结果显示 IVS4-1G>T 会导致 *PAX6* 基因编码的 mRNA 在剪接过程中发生外显子跳跃，导致第 5 外显子缺失，造成读码框改变，形成只有 24 个氨基酸的突变型蛋白，失去野生型蛋白的大部分

结构。对 *PAX6* 基因 c.957_960delCACA 进行功能分析，构建真核表达载体，qPCR 与 RT-PCR 分析结果均显示 c.957_960delCACA（p.Asp319fs）突变导致 mRNA 表达量减少，即发生无义突变介导的 mRNA 降解。

结论 *PAX6* 基因突变 IVS4-1G>T 和 c.957_960delCACA（p.Asp319fs）为导致两个散发性先天性无虹膜症患者的致病突变，均为 *PAX6* 基因新的碱基变异，丰富了 *PAX6* 基因突变数据库，为先天性无虹膜症的临床诊断和遗传学咨询提供依据。

CAD 基因复合杂合变异致早期婴儿型癫痫性脑病 50 型的遗传学分析及产前诊断

王舒月
河南省人民医院

目的 通过家系全外显子检测方法对胎儿及其父母进行基因突变分析，为临床咨询及产前诊断提供理论依据。

方法 使用全外显子测序技术对胎儿及其父母进行致病基因筛查，根据既往妊娠史和本次胎儿超声表型进行分析，锁定候选基因致病位点，通过 Sanger 测序对存在的非多态性突变进行验证。

结果 检测到胎儿羊水标本 CAD 基因复合杂合突变，包括 c.2665-2666insCG(p.Lys889fs) 插入移码杂合突变和 c.6055G>A（p.Asp2019Asn）的错义突变，分别来源于表型正常的父亲和表型正常的母亲。CAD 基因变异，为可能致病性变异，与早期婴儿型癫痫性脑病 50 型相关。

结论 目前早期婴儿型癫痫性脑病 50 型主要依赖于基因诊断，该基因突变位点的发现丰富了 CAD 基因突变谱，对优生优育有很大的指导意义。

Etiological analysis of no call results of cell-free DNA-based noninvasive prenatal testing

Linbei Deng Luming Sun
Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine

Objective With a high sensitivity and specificity, cell-free DNA-based non-invasive prenatal testing (NIPT) is an incomparable component of clinical practice for fetal chromosomal abnormalities. However, NIPT has limitations and complexities, in some cases, no evaluation can be made for a variety of reasons. The aim of this study is to analyse all "test failures" from our department and identify possible causes for these no call results.

Methods Retrospective analysis of all NIPT results (n = 30590) in our center from Jan 2, 2019 to May 31, 2021. Traditional chromosome karyotype, chromosome microarray analysis, whole exome sequencing, and adult tumor-related screening (Tumor markers CA125, CA199, CEA, CA153, SCC; Epigastric ultrasound, urinary ultrasound and faecal occult blood testing) were used to further investigate possible NIPT no call reasons.

Results In this period, there were a total of 75 (2‰,75/30590) no-call NIPT results in our center. Among of which, 74 cases showed low fetal fraction (＜3.5%), and only one case was detected with complex abnormalities. Further invasive diagnosis were performed in 30 cases and 4(13.33%,4/30) were detected with chromosomal diseases or genomic diseases (one with mosaic trisomy 13, two with P/LP microdeletions on 2q23.1 and 2p16.3, one with 20q11.21q13.12 region AOH). The mothers of 30 cases underwent chromosomal karyotype analysis and tumor-related testing, and all with negative results of karyotype but one was confirmed with breast cancer.

Conclusion The reasons for a non-evaluatable sample are multifold and show the limitations of the test options. And the most common cause for NIPT no call is still low fetal fraction. Further invasive prenatal testing is recommended for cases of no call in order to rule out possible genetic variations.

低深度全基因组测序检测孕早期流产物染色体异常的临床价值

牛宏艳
深圳市龙岗区妇幼保健院

目的 探讨与传统 G 显带核型相比较，低深度全基因组拷贝数变异测序技术(Copy number variation sequencing, CNV-Seq)在检测孕早期流产物中染色体异常的临床应用价值。
方法 对 2018 年 6 月至 2020 年 7 月因自然流产或胚胎停育来我院行终止妊娠术取样的流产物标本，同时进行 G 显带核型分析和 CNV-Seq 检测，结合 STR 进行母体污染鉴定和图谱分析。
结果 396 例流产物样本中，核型检出染色体异常 178 例(非整倍体异常 152 例、结构异常 10 例、5 例平衡易位/倒位、7 例多倍体和 4 例嵌合体)，218 例核型正常。178 例核型异常病例中，CNV-Seq 检出与核型异常一致病例 171 例(96.1%, 171/178)，5 例平衡易位/倒位 和 2 例低比例嵌合体 CNV-seq 未能检出。218 例核型正常病例中，CNV-Seq 检出致病性或可能致病性拷贝数变异 12 例，其中 9 例涉及相关微缺失/微重复综合征，包括 2 例 DiGeorge 综合征和 2 例 16P 微缺失综合征。
结论 与传统 G 显带核型分析相比较，CNV-Seq 除可检出流产物中涉及 CNV 的常见染色体数目和结构异常外，还能有效检出 5-10Mb 以下的致病性 CNV，可作为传统核型分析的替代方案，更系统全面的揭示自然流产的遗传学病因。

Aicardi-Goutières 综合征（AGS）3 型 1 例和基因分析

曾兰 王锦 邓艺 陈春 汪雪雁
四川省妇幼保健院

目的 探讨一例 Aicardi-Goutières 综合征（AGS）3 型家系的临床及影像学特点，并检测其致病基因的突变情况，为该家系遗传咨询提供可靠的遗传学依据。
方法 回顾性分析一例 2018 年 11 月于四川省妇幼保健院医学遗传与产前诊断科门诊的 AGS 3 型家系的临床资料及采用人类外显子组高通量测序（WES）基因突变结果。
结果 （1）临床资料：患儿，男，患儿母亲 34 孕周 MRI 扫描：双侧脑室轻度扩张，双侧脑室体部、三角区、颞角室管膜下多发大小不一囊性灶，室管膜下囊肿可能性大。出生 7 天诊断：颅内感染，新生儿败血症，颅内出血，双侧脑室管膜下囊肿，新生儿肺炎，头颅血肿，卵圆孔未闭，粒细胞缺乏症。出生 81 天 MRI 扫描：双侧脑室室管膜下囊肿；双侧脑室旁白质和半卵圆中心多个小斑点和小结片样异常信号，多系小钙化灶，提示颅内先天感染可能；脑部髓鞘化成熟明显延迟。现 1 岁 3 月，颅缝闭合，耳朵大，上睑浮肿，生长发育迟缓，肌张力高，头围小（39cm，<-3SD）。（2）基因突变分析：患儿 RNASEH2C 基因发现两个杂合错义变异，chr11:65487592（c.392(exon 3)T>A）和 chr11:65487550（c.434(exon 3)G>T），经 Sanger 测序验证，分别遗传于父母，为复合杂合突变。其中 c.434(exon 3)G>T 在 ClinVar 数据库中已有收录。这两个变异按照 ACMG 指南评估均为临床意义不明（PM1+PM2+PP3）。
结论 Aicardi-Goutières 综合征 3 型 [MIM: 610329]，一种常染色体隐性（AR）遗传疾病，其特征为脑萎缩，白质脑病，颅内钙化，脑脊液（CSF）淋巴细胞增多症，CSFα-干扰素增高。严重的神经功能障碍在婴儿期表现为进行性小头畸形，痉挛，肌张力障碍和严重的精神运动迟缓。 结合患者临床症状及基因变异情况，RNASEH2C 的 c.392(exon 3)T>A 和 c.434(exon 3)G>T 突变可能是先证者患病的分子基础，这两个变异的致病性有待进一步的功能研究。

PAX6 基因突变导致的合并多种眼部异常及全身系统缺陷患者一例

郭东炜[1] 郑丹莹[1] 靳光明[1] 郭奕斌[2] 连章凯[1]
1.中山大学中山眼科中心 2.中山大学医学院医学遗传学教研室

目的 报告一例由 *PAX6* 基因突变导致的合并多种眼部异常伴全身系统缺陷患者的基因型及临床表型，以探究 *PAX6* 基因突变在先天性无虹膜患者中的基因型—临床表型关联。
方法 对患者眼部及全身体征进行全面检查。通过裂隙灯显微镜、主觉验光、IOL Master、Itrace 等检查采集患者的最佳校正视力、眼轴、角膜曲率、角膜散光、中央角膜厚度等眼部情况。通过提取患者基因组 DNA 进行全外显子测序， Sanger 测序验证所有家系成员可能携带的突变，并对患者的基因型—临床表型关联进行分析。
结果 全外显子测序检测出患者 *PAX6* 基因的第 6 号外显子上存在无义突变(c.760C>T(p.R254X))，家系验证提示该突变为患者自发突变。患者合并了包括双眼虹膜缺损、先天性白内障、先天性晶状体脱位并伴有眼球震颤、角膜形态不规则及外斜视等多种眼部异常，全身系统异常表现为智力发育迟缓及肥胖体征(BMI=31.2)。
结论 本研究报道了一例罕见的合并多种眼部及全身系统异常的病例，补充了 *PAX6* 基因突变相关的眼部及全身系统的临床表型，完善了 *PAX6* 突变的基因型—临床型之间的关联，为后续研究及疾病诊疗提供基础。

一例常染色体亚显微相互易位致反复不良妊娠的遗传学分析

何烟蓉 杨元
四川大学华西校区

目的 对一个孕中期反复出现结构异常胎儿的家系进行遗传学分析，为该家系的遗传咨询和产前诊断提供依据。
方法 应用染色体 G 显带、*拷贝数变异测序（*Copy number variation-sequencing, CNV-seq）及荧光原位杂交（fluorescence in situ hybridization，FISH ）技术对胎儿组织及双亲的外周血染色体进行分析鉴定。
结果 CNV-seq 显示胎儿基因组存在一段 6.59Mb 重复（7p22.3-p22.1）与一段 3.81Mb 缺失（4p16.3）；双亲 G 显带未见明显异常；FISH 结果显示父亲 4 号染色体短臂末端与 7 号染色体短臂末端存在微小片段的相互易位。
结论 7p 微重复与 4p 微缺失是导致该家系胎儿发育异常的原因，这些染色体组的微小结构畸变源于父亲存在的隐匿染色体平衡易位。在常规染色体检查无特殊且反复出现不良妊娠的夫妻中，应该考虑到亚显微染色体相互易位的可能，并经 FISH 等检测技术予以确认。

甲基丙二酸血症合并原发性肉碱缺乏症一例临床及遗传学分析

毋盛楠 陈永兴 陈琼 卫海燕
郑州大学附属儿童医院、河南省儿童医院、郑州儿童医院 内分泌遗传代谢科

目的 甲基丙二酸血症（MMA）是我国最常见的有机酸血症，目前已发现至少 10 种基因与该病相关，在我国最常见的是 *MMACHC* 基因突变所致的合并型 MMA（合并同型半胱氨酸血症），患者临床表型复杂，虽为维生素 B12 治疗有效型，部分仍可遗留神经系统损害后遗症。原发性肉碱缺乏症（PCD）是我国较常见的脂肪酸 β 氧化缺陷病，由于 SLC22A5 基因突变引起高亲和力钠依赖性肉碱转运体（OCTN2）功能缺陷，导致尿中肉碱排出增加，血液、组织、细胞内肉碱缺乏，从而引起一系列生化代谢紊乱及临床症状。MMA 和 PCD 均为可治疗的罕见遗传代谢性疾病，国内外

进行了较为深入的临床与基础研究，但尚未见共患两病的病例报道。本研究报道我国 1 例合并型 MMA 共患 PCD 的病例，并对其临床诊疗及遗传性特点进行分析。
方法 回顾性分析 1 例合并型 MMA 共患 PCD 患儿的临床诊疗及遗传学特点。
结果 患儿 1 月 17 天，因新生儿筛查提示血酰基肉碱谱异常来诊，无其它不适主诉，人工喂养，母孕史、既往史、出生史、家族史无异常。新筛提示血丙酰肉碱（C3）为 11.42，丙酰肉碱增高/乙酰肉碱比值（C3/C2）为 1.07，均明显增高，游离肉碱（C0）8.1，偏低，余无异常。入院后查尿甲基丙二酸 23.9，尿甲基枸橼酸 0.8，均轻度增高；血同型半胱氨酸 43.2umol/l，明显增高。结合病史及实验室检查结果，临床拟诊合并型 MMA，行 MMACHC 基因（NM_015506）测序检出复合杂合变异：c.482G>A/p.R161Q 和 c.567dupT/p.I190fs，分别源于父亲和母亲，ACMG 评级均为致病性。确诊 MMA 后予肌注羟钴铵、口服左卡尼汀治疗，1 月后复查血 C3、C3/C2、C0、同型半胱氨酸，尿甲基丙二酸均恢复正常范围。既往报道携带 c.482G>A/p.R161Q 变异位点患者羟钴铵治疗效果显著，该患儿各项指标均正常且无不适症状，随访期间逐渐减量羟钴铵及左卡尼汀口服液，监测各项指标均正常。8 月龄起停用左卡尼汀口服液，3 个月后复查血 C3、C3/C2、同型半胱氨酸，尿甲基丙二酸均正常，但 C0 3.83，明显降低，与 MMA 临床及生化指标均好转不相符，怀疑合并其他疾病造成肉碱缺乏。故完善全外显子测序提示 SLC22A5 基因（NM_003060）检出复合杂合变异：c.1400C>G/p.S467C 和 c.1195C>T/p.R399W，分别源自父亲和母亲，ACMG 评级均为致病性。确诊为合并型 MMA 共患 PCD，再次规律口服左卡尼汀口服液，定期监测血 C0 恢复至正常范围。
结论 共患两种罕见隐性遗传病的概率很低，但对于复杂的临床病例，仍需提高警惕。本例患儿新生儿筛查确诊合并型 MMA，病初血 C0 即降低，但误诊为继发于 MMA 所致，期间甚至因 MMA 相关指标控制良好停用口服左卡尼汀，发现血 C0 再次明显降低后得以进一步诊断和治疗。正确的病因诊断是指导治疗的关键，早期诊断是改善预后的根本措施。

SECISBP2 基因变异致甲状腺激素代谢缺陷

侯丽萍
深圳市儿童医院

目的 提高临床医生对硒半胱氨酸插入序列结合蛋白 2（*SECISBP2*）基因变异致甲状腺激素代谢缺陷的认识。
方法 报道国内首例由 *SECISBP2* 基因复合杂合变异致甲状腺激素代谢缺陷男童的临床表现、基因检测报告并复习文献。
结果 患儿，男，18 月龄，因“生长迟缓、运动发育落后 15 月”就诊，查体：特殊面容（长人中、小下颌、鼻梁塌陷、小头）矮身材、低体重及肌张力低下，甲状腺功能检测显示促甲状腺激素（TSH）水平正常，甲状腺素（T4）升高、三碘甲状原氨酸（T3）下降。脑干听觉诱发电位示左侧听觉反应阈值位于可疑范围。全外显子测序示：*SECISBP2* 基因存在复合杂合变异：Exon4 c.458delC p.(Thr153fs)移码突变，源自母亲；Exon17 c.2562_2563del p.(*855Arg ext*30)移码突变，源自父亲，根据美国医学遗传学与基因组学会对变异进行致病性分析，判断为致病性变异。
结论 临床上对生长迟缓、运动发育落后的患儿，如甲状腺功能检测示 TSH 正常或轻度升高，而 T4 升高、T3 下降，应考虑甲状腺激素代谢缺陷。

柳州地区不明原因智力障碍儿童脆性 X 综合征基因分析

钟青燕 严提珍
柳州市妇幼保健院

目的 对柳州地区不明原因智力障碍儿童进行脆性 X 综合征基因检测分析，调查本地区脆性 X 综合征的发病率。

方法 利用 PCR 微流控毛细管电泳技术对 2017 年 12 月到 2020 年 5 月来柳州市妇幼保健院就诊的 180 例不明原因智力障碍儿童进行脆性 X 综合征 *FMR1* 基因分析，阳性病例进行家系基因分析，并利用 Southern 印迹杂交法进行验证。
结果 PCR 微流控毛细管电泳技术能够较准确的计算出患者的 CGG 重复数，其中最常见的 CGG 重复次数是 28 次（43.9%）和 29 次（20.6%），在 180 例不明原因智力障碍儿童中共检出 4 例全突变，检出率为 2.2%（4/180）。家系 1 先证者 CGG 重复数为 190 ，248 ，370 次，母亲为 25 和 134 次，妹妹为 39 ，148 ，218 ，554 次，姨妈为 29 和 29 次；家系 2 先证者 CGG 重复数为 859 次；家系 3 先证者 CGG 重复数为 529 次，母亲为 31 和 76 次，姐姐为 29 和 130 次；家系 4 先证者 CGG 重复数为 525 次。4 例阳性样本经 Southern 印迹杂交法验证，结果都显示有>5.8kb 条带（全突变条带），两种方法基因分型结果完全一致。
结论 PCR 微流控毛细管电泳技术高效、快速，可以准确区分正常、灰区、前突变、全突变，适合智力障碍大规模人群筛查，生育过脆性 X 综合征患儿的家庭再发风险高，应进行遗传咨询和基因检测，避免该病患儿的出生。

脆性 X 综合征家系的 FMR1 基因 CGG 重复及甲基化状态分析

钟青燕 严提珍
柳州市妇幼保健院

目的 利用脆性 X 综合征的两个分子生物学标志：FMR1 基因 5’端(CGG)重复序列的异常扩增和该基因 CpG 岛的异常甲基化,对脆性 X 综合征家系进行基因分析。
方法 应用 PCR 微流控芯片毛细管电泳方法对一个大家系中 22 个成员进行 FMR1 基因的 CGG 重复数进行检测,判断 FMR1 基因型(正常型、灰区、前突变型、全突变型)。用甲基化特异性多重链接探针依赖扩增（MS-MLPA）技术,检测 FMR1 基因启动子区域 CpG 岛的甲基化情况和 FMR1 基因缺失重复情况,并用 Southen 印迹技术对全突变患者进行验证。
结果 22 个家系成员中检出正常型 9 例（1 男 8 女），检出前突变携带者 8 例(0 男 8 女)，其中 7 例均为 III 代的女性成员，其突变的 CGG 重复数为 100 到 133 之间，其母亲（II:2 和 II:4）为正常型；8 例女性前突变携带者中，有卵巢早衰 1 例，占 12.5%，出现月经紊乱 5 例，占 62.5%；检出脆性 X 综合征患者 4 例(4 男 0 女)，全突变女性携带者 1 例，均由前突变携带者母亲动态突变传递而来。MS-MLPA 分析，均未发现 FMR1 基因缺失、重复，男性正常型甲基化比值为 0，女性正常型和前突变携带者甲基化比值范围为 0.25~0.48 和 0.33~0.46，两组差异无统计学意义（p=0.095>0.05），一例女性全突变携带者甲基化比值为 0.52 高于正常型和前突变携带者均值（0.33，0.38），4 例男性全突变患者 CpG 岛为异常基化状态，甲基化比值均>0.64，其中中度和重度智力障碍之间甲基化比值差异无统计学意义（p=0.58>0.05）。
结论 女性前突变和全突变的 FMR1 基因 CGG 重复数会发生动态突变递增传给子代，生育全突变的脆性 X 综合征患儿，应尽早对脆性 X 综合征患儿进行基因诊断，同时对家系成员进行基因分析，提供遗传咨询和生育指导，避免患儿的出生；脆性 X 综合征临床表型与甲基化有关，但非正相关性。

一个遗传性卵巢癌家系的高通量测序分析

姜惠琴 张丽 陈馨宁 黄斐 郁俐 史庭燕 沈敏娜 张春燕 王蓓丽 郭玮
复旦大学附属中山医院

目的 明确 1 个遗传性卵巢癌家系的遗传学病因，为家系的遗传咨询提供理论依据。
方法 应用高通量测序技术进行遗传性肿瘤相关基因检测；应用甲基化特异性多重连接探针扩增(methylation-specific multiplex ligation-dependent probe amplification，MS-MLPA)方法验证拷贝数变异 (copy number variation，CNV)。Sanger 测序对变异位点行家系验证。生物信息学分析变异对蛋白质功能及蛋白质结构的影响。

结果 先证者 61 岁确诊卵巢癌，其母亲 52 岁时确诊卵巢癌，其父亲无肿瘤家族史。先证者 4 个兄妹中，1 名姐姐于 80 岁时确诊乳腺癌，另 1 名姐姐于 52 岁时确诊卵巢癌，其余 1 名姐姐及 1 名哥哥无肿瘤家族史。高通量测序结果显示先证者检出 BRCA1 基因的 c.3841C>T（NM_007294.3）致病变异。该变异为功能丧失性变异（Loss Of Function, LOF），在编码区 1281 位提前引入终止密码子，导致截短蛋白产生。检测中未发现先证者染色体致病 CNV。Sanger 测序验证结果显示先证者、先证者的 1 名外甥女携带该位点杂合突变。
结论 先证者外甥女携带该致病变异，提示罹患乳腺癌、卵巢癌、胰腺癌等肿瘤的风险高于普通人群，提示需要进行针对性的随访以及预防措施。

多方法联合检测应用于脊髓性肌萎缩症基因检测和产前诊断

钟青燕 罗世强
柳州市妇幼保健院

目的 探讨多方法联合检测对脊髓性肌萎缩症患者及家系进行基因诊断和产前诊断的临床应用价值。
方法 应用 MLPA 技术对 2011 年至 2020 年在柳州市妇幼保健院就诊的具有典型症状的 31 例患者及其有需要的家系成员进行 *SMN1* 基因 7、8 号外显子及 SMN2 和 NAIP 拷贝数变异检测，同时对部分家系中夫妻双方为携带者或者有生育患儿史的孕妇进行产前诊断，用基因测序和靶基因相关 STR 连锁分析技术对部分家系进行辅助诊断及验证。
结果 31 例患者中 30 例为 SMN1 基因 7、8 号外显子纯合缺失（96.8%），SMN1 基因 7 号外显子纯合缺失 8 号外显子杂合缺失 1 例（3.2%），其中 SMAI 型 17 例，存在 SMN2 基因重复 7 例（41.2%），存在 NAIP 基因缺失 13 例（76.5%），SMAII 型 14 例，存在 SMN2 基因重复 13 例（92.9%），存在 NAIP 基因缺失 8 例（57.1%），SMN2、NAIP 两个基因缺失重复两组数据差异具有统计学意义。27 例产前诊断中，SMN1 基因 7、8 号外显子正常型有 6 例（28.6%），SMN1 基因 7、8 号外显子杂合缺失有 16 例（57.1%），SMN1 基因 7、8 号外显子纯合缺失有 5 例（14.3%）。家系中有 3 个家系均出现父母一方为 SMN1 基因 7、8 号外显子杂合缺失，另一方为 SMN1 基因 7、8 号外显子未见缺失不符合遗传规律，经靶基因相关 STR 连锁分析技术进行家系分析证实为 2+0 型家系。
结论 MLPA 技术能准确、快速、可靠地检测 *SMN1* 基因 7、8 号外显子及 SMN2 和 NAIP 拷贝数变异，适用于脊髓性肌萎缩症的基因诊断及产前诊断，同时基因测序和靶基因相关 STR 连锁分析技术能够弥补 MLPA 技术的不足，三者联合应用能更好更全面的对脊髓性肌萎缩症进行基因诊断与产前诊断，为临床提供诊断依据、阻止患儿的出生具有重要的意义。

一例复杂性心律失常患者 SCN5A 基因变异分析

周年伟 张丽 唐璐 赵维鹏 潘翠珍 张春燕 王蓓丽 郭玮 舒先红
复旦大学附属中山医院

背景 一名中年女性，因劳累后胸闷气促起病，经心电图、心脏超声、心脏电生理检查及心肌活检提示为复杂性室性心律失常伴心衰。该患者存在心脏猝死的家族史，故对其进行高通量测序基因检测，明确其可能的致病原因，进而提供合理的临床诊疗方案。
方法 提取患者外周血基因组 DNA，进行全外显子组测序及生物信息学分析，筛查与心血管疾病发生相关基因的候选致病变异，并用 Sanger 测序进行变异验证。
结果 全外显子组检测及 Sanger 验证发现该患者携带 *SCN5A* 基因致病突变 NM_198056.2:c.2440C>T (p.Arg814Trp)，该变异在 gnomAD 数据库、千人数据库及 EXAC 数据库的东亚正常对照人群中未发现，经多种统计方法预测有害（REVEL score 0.93），已有研究报道会导致心电异常、Brugada 综合征、扩张型心肌病、病态窦房结综合征等多种疾病表型，但未见其与复杂性心律失常相关的临床报道。

结论 *SCN5A* 基因编码心脏电压门控钠离子通道 α 亚基-Nav1.5，Nav1.5 通道参与心脏细胞动作电位的形成及电冲动的传导。患者检出 *SCN5A* 基因的上述致病变异明确了其复杂性心律失常的分子遗传学病因，为其后续临床诊疗提供了重要参考依据。

Novel pathogenic mutations of FERMT1 in two Chinese Kindler syndrome families

Weisheng Li[1] Miao Sun[1] Dan Zhu[1] Likui Lu[1] Jun Guo[1] Jingliu Liu[1] Yajun Shi[1] Hongtao Zeng[1] XI Yu[1] Min Li[1,2]
1.The First Affiliated Hospital of Soochow University
2.Dushu Lake Hospital Affiliated to Soochow University

Object Kindler syndrome (KNDLRS) is a very rare autosomal recessive disorder characterized by bullous poikiloderma with photosensitivity. Loss-of-function mutations in *FERMT1*, which located on chromosome 20p12.3, were responsible for KNDLRS. Numerous mutations in *FERMT1* have been reported to be associated with KNDLRS.
Methods Medical Whole Exome Sequencing V4 combined with Sanger sequencing revealed mutations in *FERMT1* with affected individuals.
Results The present study reported two Chinese KNDLRS families, and affected individuals from both families presented with poikiloderma, palmoplantar hyperkeratosis, and diffuse cigarette paper like atrophy on hands. Skin biopsy of the proband from family 2 showed atrophy of epidermis, hyperkeratosis, dilated blood vessels in upper dermis, and microbubbles at the dermis and epidermis junction. Compound heterozygous nonsense mutations (c.193C>T, c.277C>T) were found with family 1, and a homozygous frameshift mutation (c.220delC) was observed in family 2. According to the clinical features and genetic analysis, KNDLRS was diagnosed in two Chinese families.
Conclusions In summary, we have reported two Chinese Kindler syndrome patients, who had been molecularly confirmed to carry loss-of-function *FERMT1* mutations (c.193C>T and c.277C>T; c.220delC). These findings will expand the mutation spectrum of *FERMT1* and provide a detailed mutation repertoire of *FERMT1* in KNDLRS.

Prader-Willi 综合征阻塞性睡眠呼吸障碍临床特征

杨琴
深圳市儿童医院

目的 分析 Prader-Willi 综合征（PWS）患儿的阻塞性睡眠呼吸障碍（OSA）特征，提高对儿童 PWS 合并 OSA 的诊治认识。
方法 回顾性分析既往确诊 PWS 且行多导睡眠监测（PSG）的 12 例患儿（PWS 组）的病例资料，选取同期年龄、性别、体重指数 （BMI）与研究组相匹配、无 PWS 的 12 例儿童作为对照组。比较两组患儿睡眠呼吸事件，研究 PWS 儿童 BMI Z 值与年龄关系，OAHI 数值分别与肥胖及生长激素（GH）治疗关系。予以 PWS 合并重度 OSA 儿童无创通气治疗。
结果 PWS 儿童 BMI Z 分值与年龄呈线性关系（p=0.02），12 例（100%）PWS 儿童存在 OSA；与对照组相比，PWS 组阻塞型呼吸暂停和低通气事件增加（P<0.05），REM 期和 NREM 期氧减事件显著增多；PWS 儿童 OAHI 值与 BMI Z 分值存在一定的相关性，线性拟合程度较高（R=0.646），两组 OAHI 数值比较差异无统计学意义（4.4±2.5 vs. 6.9±4.1；t=1.241，P＞0.05）；PWS 合并重度 OSA 儿童使用无创通气治疗后睡眠呼吸障碍日夜间症状消除。
结论 肥胖在大年龄 PWS 儿童更常见，PWS 儿童 OSA 患病率高，阻塞性睡眠呼吸暂停低通气在 PWS 儿童普遍存在，氧减持续整个睡眠期，这类儿童肥胖状态与 OSA 存在正相关，GH 治疗期间 OAHI 数值无明显升高，无创通气能改善睡眠呼吸障碍日夜间症状。

全基因组 meta 分析发现两个与癫痫相关的新风险位点

周佳会[1,2,3] 赵长乐[1,2,3] 宋盟[1,2,3] 刘杰伟[4] 杨勇锋[1,2,3] 吕路线[1,2,3] 李文强[1,2,3] 罗雄剑[4]
1.新乡医学院第二附属医院，河南省精神病医院
2.河南省生物精神病学重点实验室
3.河南省精神神经医学国际联合实验室
4.中国科学院昆明动物研究所

目的 癫痫是一种世界范围内常见的神经系统疾病，给社会带来了巨大的经济负担。遗传因素是导致癫痫的重要原因，通过大型全基因组荟萃分析，进一步鉴定风险变异并揭示癫痫的遗传力。
方法 通过整合四个大规模的癫痫全基因组关联研究（GWASs），进行了最大规模的癫痫全基因组荟萃分析（N=80,086）。
结果 1、发现 3 个与癫痫相关的全基因组显著风险位点（$P<5\times10^{-8}$）。其中 7q21.11（最显著的 SNP 是 rs11978015，（$P=9.26\times10^{-9}$）和 8p23.1（最显著的 SNP 是 rs28634186，$P=4.39\times10^{-8}$）是本研究新发现的风险位点。2、rs11978015 位于编码代谢型谷氨酸受体 3 的 *GRM3* 基因的上游。*GRM3* 在神经传递中发挥着重要作用，并且参与大部分正常脑功能。3、另外还鉴定了 3 个基因（*TTC21B*、*RP11-375N15.2* 和 *TNKS*）的顺式调节表达水平与癫痫相关，表明风险变异可能通过调节这些基因的表达增加癫痫的发病风险。
结论 本研究不仅为癫痫的遗传结构提供了新的见解，而且为癫痫新药研发和治疗提供了新的潜在分子靶点（包括 *GRM3* 和 *TTC21B*）。

全基因组关联分析发现四个中国汉族人群早发性精神分裂症的关联基因位点

崔祥正[1,2] 肖洒[1,2] 杨勇锋[1,2] 吕路线[1,2] 邵明龙[1,2] 李明[3] 官方霖[4] 李文强[1,2] 郭素芹[1,2] 罗雄剑[3,5,6]
1.新乡医学院第二附属医院河南省精神病院
2.河南省生物精神病学重点实验室
3.中国科学院/云南省动物模型与人类疾病机理重点实验室
4.西安交通大学医学部法医学院法医精神病学教研室
5.中国科学院动物进化与遗传前沿交叉卓越创新中心
6.中国科学院昆明动物研究所生物资源与疾病分子机理联合实验室

目的 早发性精神分裂症（EOS，定义为 18 岁之前首次发作的精神分裂症）是一种罕见的精神分裂症（SCZ）。虽然全基因组关联研究（GWASs）已经确定了 SCZ 的多种风险变异，但这些 GWASs 中包括的大多数病例并没有按照最初发病时的年龄进行分层。迄今为止，EOS 的遗传结构在很大程度上仍是未知的。本研究的目的就是确定 EOS 的风险变异并揭示 EOS 的遗传基础。
方法 1.本研究在汉族人群中进行了两个阶段的早发性精神分裂症 GWAS。首先在发现阶段（1,256 个 EOS 病例和 2,661 个健康对照）中进行了 GWAS。其次在独立样本（903 例 EOS 病例和 3900 例健康对照）中验证了发现阶段 $P< 1.0\times10^{-4}$ 的遗传变异。2.样本处理：对样本进行 DNA 提取、基因测序，并做到严格质量控制。另外对 EOS 和 SCZ 病例-对照样本库进行对比分析。3.统计分析：采用 GWAS 分析、Mate 分析、eQTL 分析、PRS 分析等方法进行数据处理。
结果 1.本研究在合并样本（2159 例 EOS 病例和 6561 例健康对照）中确定了 4 个 EOS 全基因组显著风险基因位点，包括 1p36.22 (rs1801133, $P_{meta}= 4.03\times10^{-15}$)、1p31.1 (rs1281571, $P_{meta}=4.14\times10^{-8}$)、3p21.31 (rs7626288, $P_{meta}=1.57\times10^{-9}$) 和 9q33.3 (rs592927, $P_{meta}= 4.01\times10^{-11}$)。2.多基因风险评分（PRS）分析显示 EOS 和 SCZ 之间存在大量遗传重叠。
结论 综上所述，这些发现揭示了 EOS 的遗传基础。进一步识别出的风险变异和基因的功能特征将有助于为治疗和诊断提供潜在的靶点。

TRANK1 基因多态性与双相情感障碍的关联研究

李晓静[1,2,3] 刘亚[1,2,3] 蔡欣[4] 李慧娟[4] 杨勇锋[1,2,3] 邵明龙[1,2,3] 李明[4] 吕路线[1,2,3] 李文强[1,2,3]
1.新乡医学院第二附属医院，河南省精神病医院 2.河南省生物精神病学重点实验室
3.河南省精神神经医学国际联合实验室 4.中国科学院昆明动物研究所

目的 在双相情感障碍（Bipolar Disorder，BD）的风险基因中，TRANK1 已经引起关注。本研究主要探讨 TRANK1 基因多态性参与东亚人群双相情感障碍发病的潜在机制。
方法 1.应用病例-对照关联研究设计，招募 1784 例汉族 BD 患者和 2474 例健康对照进行基因型分析；对东亚不同人群中的 BD GWAS 候选 SNP 进行 Meta 分析。2.对 65 个中国汉族人脑样本的杏仁核组织进行表达数量性状基因座（eQTL）分析；对 GWAS 和 eQTL 数据集进行多个 SNP 位点的 SMR 分析。3.构建针对大鼠 TRANK1 基因的短发夹 RNA（shRNA）序列的载体，用 Trank1-shRNA 或对照 shRNA 感染体外培养的 14-15 天的大鼠神经元细胞，取神经元细胞进行 RNA 提取和 RNA-seq 分析。
结果 1.rs9834970 在整个基因组范围内与东亚人群中的 BD 显著相关：在中国大陆 1784 例 BD 患者和 2474 例健康对照的研究中发现，rs9834970 在患者组中的表达高于对照组（P=0.00218，OR=1.149）；在日本两个人群样本的 GWAS 分析报告中显示 rs9834970 与 BD 存在关联性（Ikeda 01:$p=9.41\times10^{-4}$，OR=1.150；Ikeda 02:p=0.0202，OR=1.100）。2. rs9834970 与 TRANK1 mRNA 的表达有微弱的相关性（PeQTL=0.089）。3.对大鼠神经元细胞进行 RT-qPCR 和 RNA-seq 分析证实 TRANK1 mRNA 的表达降低。
结论 本研究证实了 TRANK1 的单核苷酸多态性与东亚人群 BD 的发病相关联，TRANK1 是 BD 的风险基因，并探究了 TRANK1 基因多态性参与 BD 发病的潜在机制，或有望帮助研究人员开发治疗 BD 的新靶点。

5 例 ALK 基因阳性儿童炎性肌纤维母细胞瘤诊治

廖雪莲 蒋莎义 杨静薇 刘江斌
上海市儿童医院

目的 探讨克唑替尼靶向治疗儿童 ALK 基因阳性炎性肌纤维母细胞瘤的有效性和安全性。
方法 回顾性分析 2019 年 1 月至 2021 年 6 月收治的 5 例 ALK 基因阳性炎性肌纤维母细胞瘤儿童病例，男：女为 4：1，年龄 2 岁 3 月~11 岁，中位年龄 7 岁 2 月，其中 4 例给予靶向药物克唑替尼（Crizotinib，280mg/m2.次，q12h）口服，临床密切观察疗效及药物不良反应，另外 1 例因年龄仅 2 岁 3 月，选择术后观察随访。5 例患儿均定期门诊或住院行肿瘤原发部位超声或增强 CT 检查，观察疗效，同时行血常规、肝肾功能、心肌酶谱、心电图、心功能、听力和视力检查等。
结果 5 患儿炎性肌纤维母细胞瘤分别源于肺部、腹腔和单侧眶内，病理免疫组织化学和 FISH 均呈 ALK 基因阳性，4 例均对克唑替尼治疗有较好反应，总随访 6-30 个月，均生存。3 例患儿行肿瘤部分切除或活检后开始口服克唑替尼，均约 2 月后完全缓解，继续口服现持续缓解中；另 1 例源于腹腔的患儿肿瘤完整切除后口服克唑替尼 12 月完全缓解，试停药 1 月时复发，再次手术和继续口服克唑替尼 7 月，目前完全缓解状态中；余 1 例源于肺部的低龄患儿术后仅观察者，随访 6 月完全缓解状态中。2 例服克唑替尼治疗过程中出现一过性心电图 Q-T 间期延长，暂时停药可恢复，继续用药未出现心电图异常。所有患儿均未见血象、肝肾功能、心肌酶谱、心功能、听力及视力等异常。
结论 炎性肌纤维母细胞瘤治疗以手术切除为主，对放疗、化疗不敏感，易复发，对于不能完整切除的病例，目前还没有标准的治疗策略。化学治疗疗效的证据有限，欧洲肉瘤网络工作组指南推荐单用阿霉素作为治疗的首选，或者阿霉素联合异环磷酰胺的化疗方案在国内外尝试或可获得疗效，但是各中心报道疗效不肯定，大多病例经手术和化疗也存在反复复发的情况，故手术和化疗之外的靶向治疗成为炎性肌纤维母细胞瘤的治疗新方向。克唑替尼是 ALK 强效抑制剂，本研究中克唑替尼治疗 ALK 基因阳性炎性肌纤维母细胞瘤患儿 4 例，临床疗效肯定，可作为术前治疗使肿瘤缩小和术后的巩固治疗，治疗过程中未见严重药物相关不良反应。本研究中 4 例炎性肌纤维母细胞瘤患

儿服用克唑替尼治 2 月以上可达完全缓解，监测中除 2 例出现一过性 Q-T 间期延长，总体副作用较少。因此，克唑替尼是目前手术治疗困难和复发儿童炎性肌纤维母细胞瘤的良好选择。

表型为 Galloway-Mowat 综合征的两个家系基因分析

陈剑锋 李月珍 谭宛文
南方医科大学珠江医院

目的 Galloway-Mowat 综合征是一种罕见的常染色体隐性遗传病，临床特征为肾病综合征伴小头畸形、智能和运动发育落后。通过对两个表型为 Galloway-Mowat 综合征的家系进行基因分析，了解基因突变类型，探讨基因突变与临床表现的关系，提高对该综合征的分子遗传学机制的认识。
方法 回顾分析两个表型为 Galloway-Mowat 综合征家系成员的临床资料，采用二代高通量测序技术进行全外显子基因检测。
结果 家系 1 先证者为 3 岁女童，因眼睑浮肿入院。患儿生后肌张力减低，精神运动发育落后，小头畸形，伴有甲状腺功能减退。尿常规：尿蛋白 3+，潜血 3+，红细胞计数 213 个/uL。血清白蛋白 16.4g/L，总胆固醇 8.16mmol/L，甘油三酯 5.59mmol/L。肾脏超声：双肾实质回声稍增强，内部结构模糊。颅脑 MRI 提示脑髓鞘发育未完善，脑白质发育不良。诊断 Galloway-Mowat 综合征。基因检测发现其 *OSGEP* 基因有 2 个杂合突变 c.740G>A(p.R247Q)和 c.300G>C(p.W100C)。c.740G>A 导致第 247 号氨基酸由精氨酸变为谷氨酰胺，根据美国 ACMG 指南该变异判定为疑似致病性变异 PM3_Strone + PM2，ClinVar 数据库对该位点的致病性分析为 Galloway-Mowat 综合征。c.300G>C 导致第 100 号氨基酸由色氨酸变为半胱氨酸，根据 ACMG 指南判定该变异为临床意义未明 PM2 + PM3，生物信息学蛋白功能综合性预测软件 REVEL 预测结果为潜在有害。家系分析显示，杂合变异 c.740G>A(p.R247Q) 来自先证者之母，c.300G>C(p.W100C) 来自先证者之父。先证者弟弟 11 月龄，基因分析发现 *OSGEP* 基因与先证者有相同的双重杂合变异，临床表现为肌张力减低，精神运动发育迟缓伴有尿蛋白阳性。先证者肾病综合征对糖皮质激素治疗无反应。家系 2 先证者为 3 岁半女童，孕 7 月时发现羊水减少，3 月龄诊断婴儿痉挛症，2 岁左右出现颜面浮肿、大量蛋白尿、低白蛋白血症和高胆固醇血症，诊断为肾病综合征。主要临床表现还有精神运动发育迟缓，肌张力减低，难治性癫痫（癫痫发作形式为痉挛发作），无小头畸形。肾脏超声：双肾实质回声增强。基因检测发现先证者 *NUP107* 基因杂合变异 c.460A>G (p.M154V)和 c.1085C>T (p.A362V)。c.460A>G (p.M154V)位点变异来自先证者之母。 c.1085C>T (p.A362V)位点变异来自先证者之父。*NUP107* 基因相关疾病为肾病综合征 11 型和 Galloway-Mowat 综合征 7 型，均为常染色体隐性遗传。*NUP107* 基因 c.460A>G (p.M154V)和 c.1085C>T (p.A362V)变异均未在相关临床病例中报道过，依据美国 ACMG 指南这两种变异判定为“3 类-意义未明”。先证者同时检出 *SCN1A* 基因 c.1499G>A (p.R500Q) 变异，遗传自父亲，该变异在 Dravet 综合征的病例中报道过。*SCN1A* 相关癫痫发作障碍是一个包含诸多癫痫发作类型的谱系障碍，其中包括单纯热性惊厥、全身性癫痫伴热性惊厥叠加症、Dravet 综合征、婴儿痉挛症等。患儿的肾病综合征对糖皮质激素、他克莫司、吗替麦考酚酯等治疗均无反应。
结论 表型为 Galloway-Mowat 综合征的患儿基因型复杂多样，*OSGEP* 基因及 *NUP107* 基因突变可致 Galloway-Mowat 综合征，对于有精神运动发育迟缓伴有蛋白尿的患儿，基因检测有助于该病的早期诊断及预后判断。

新冠肺炎期间基于移动医疗 APP 的延续性护理在中枢性早发育治疗中的应用效果

崔莎
上海市儿童医院

中枢性早发育又称中枢性性早熟, 指下丘脑-垂体-性腺轴功能过早启动导致促性腺激素释放激素分泌,使第二性征及内外生殖器发育。目前国内外的主要治疗方式是使用促性腺激素释放激素类似物

(GnRHa)抑制过快发育,但是，药物治疗期间不仅对患儿身高及骨密度等造成影响，而且还会给患儿家长一定心理压力。中枢性早发育治疗需要不间断完成整个治疗过程，因此患儿的定期随访对治疗效果有着重要意义。
然而，新冠肺炎期间各道路封锁个别城市封城给患儿的入院随访带来了一定的困难。为准确了解患儿用药及发育情况，本研究将采用基于移动医疗 APP 下延续性护理，在减少接触的前提下为患儿及家长提供科学便捷的护理干预，有利于提高临床的治疗效果和满意度。
预期成果 新冠肺炎期间基于移动医疗 APP 的延续性护理在中枢性早发育治疗中，可以对帮助患儿改善身体以及心理健康有积极意义,能够有效控制患儿异常的生长发育,达到良好的治疗效果，而且可以帮助临床医生更加全面快捷的了解患儿每阶段情况，从而可提高护理满意度及患儿家属依从性。
考核指标:患儿家属满意度及依从性、中枢性早发育治疗效果评价

LMNA p.W520R 突变引起家族性房室传导阻滞伴扩张型心肌病患者 iPSC-CMs 钾离子通道基因表达失衡及细胞节律异常

戴礼猛 蒋周芩 李嘉 郭洪 白云
陆军军医大学

目的 LMNA 基因突变会引起家族性房室传导阻滞、扩张型心肌病等心脏疾病，但致病机制并未完全阐明。本研究通过家系患者来源诱导性多能干细胞诱导分化的心肌细胞模型（iPSC-CMs），探索 LMNA 致病变异致心脏疾病的分子机制。
方法 家系患者携带 LMNA p.W520R 突变，疾病早期表现典型房室传导阻滞，疾病晚期合并表现有扩张型心肌病。知情同意后收集其中一名男性患者尿液并进行尿液细胞扩增，采用仙台病毒导入重编程因子将患者尿液细胞重编程，构建出患者 LMNA p.W520R 突变的诱导性多能干细胞系。采用小分子诱导分化获取心肌细胞进行细胞实验，通过荧光显微镜运用 Fluo-8 钙离子荧光探针分析心肌细胞节律，采用 RNA-seq、免疫荧光、蛋白免疫印迹实验及生物信息学分析差异表达基因。
结果 患者来源 iPSC-CMs 重现心脏疾病表型，免疫荧光实验提示患者来源 iPSC-CMs 细胞核异形结构显著增多，钙成像实验记录到心肌细胞异常节律发生。RNA-seq 提示 PI3K-AKT 信号通路为主要影响信号通路，离子通道差异基因分析提示 KCNQ1 及 KCNH2 基因下调显著，定量 PCR 实验及蛋白免疫印迹实验证实其编码的钾通道 hERG 及 KvLQT1 表达下调。
结论 LMNA p.W520R 突变可导致患者 iPSC-CMs 钾离子通道表达失衡，引发心肌细胞异常节律发生，该研究结果拓展了 LMNA 基因致心脏疾病表型的分子机制认识。

一个 X 染色体连锁显性脑室周围结节异位家系的临床及遗传学分析

余雯贤 王华 彭莹 刘静 席惠 杨舒亭
湖南省妇幼保健院

目的 分析 1 个由 *FLNA* 基因变异所致的 X 染色体连锁显性脑室周围结节异位(X-linked periventricular heterotopia，PVNH1)家系的临床及遗传学特点。
方法 先证者 2 岁，女性，先天性动脉导管未闭、扳机指、隐性脊柱裂，头颅磁共振提示灰质异位。提取先证者及家系成员外周血 DNA，应用家系全外显子基因组测序法对基因变异进行检测，并通过 Sanger 测序法验证变异，对变异携带者行头颅磁共振检查。
结果 经家系全外显子基因组测序分析发现，先证者 X 染色体上的 FLNA 基因第 8 外显子存在一个 c.1137delinsGGACGCCAGCAAAGTGACAGCCC (p.Gln387Argfs*26)杂合变异，该变异遗传自母亲，为功能丧失变异，GnomAD 数据库中未收录该变异在人群中频率，根据美国医学遗传学与基因组学学会遗传变异标准与指南判定为可能致病性变异(PVS1+PM2)。对无症状的母亲行头颅磁共

振检查，结果提示双侧脑室旁多发异常信号，考虑灰质异位。对先证者无症状的姨妈行该变异位点验证及头颅磁共振检查，结果均与先证者母亲一致。
结论 FLNA 基因 c.1137delinsGGACGCCAGCAAAGTGACAGCCC 变异可能为该家系脑室周围结节异位的致病原因，其遗传方式符合 X 染色体连锁显性遗传模式，但未导致癫痫发作、智力迟滞等临床表现，新变异的检出丰富了 FLNA 基因的变异谱，分析该家系成员的临床表现有助于提高国内医师对该病的认识。

“2+0 型”脊髓性肌萎缩症家系的胚胎植入前遗传学检测案例分析

李少英 黎青 何健淳 何文智 王燕超 冼嘉嘉 马晓燕 叶国新 张敏聪
广州医科大学附属第三医院

目的 本研究通过夫妻双方一方为“1+0”型脊髓性肌萎缩症（Spinal muscular atrophy，SMA）携带，另一方为“2+0”型 SMA 携带的特殊家系，探讨 PGT-NGS，芯片，荧光 PCR-毛细管电泳法对“2+0 型”SMA 家系的临床应用价值，以期建立“2+0 型”SMA 家系进行 PGT 的方法。
方法 选取 1 对基因型，一方为“1+0”型，另一方为“2+0”型 SMA 携带者，获取先证者以及双方父母对照样本，收集详细的临床信息。本研究共获取夫妻双方、先证者以及双方父母基因组 DNA 及其 11 枚胚胎活检样本，通过对胚胎样本进行单细胞扩增（MDA），采用 PGT-NGS，芯片，荧光 PCR-毛细管电泳法三种方法进行检测。分别采用三种方法的数据对夫妻双方、先证者以及双方父母样本进行连锁分析，获得夫妻双方单体型，然后进行胚胎连锁分析，从而获得胚胎的基因型。比较三种方法的胚胎基因分型结果。
结果 本次研究通过三种不同方法建立夫妻双方单体型同时进行胚胎的基因型分析，芯片，荧光 PCR-毛细管电泳法结果一致；PGT-NGS 方法检测有 5 枚胚胎出现同源重组，与芯片、荧光 PCR-毛细管电泳法结果不一致。
结论 脊髓性肌萎缩症是一组常见的由脊髓前角细胞运动神经元退化变性所导致的常染色体隐性遗传性神经肌肉疾病，夫妻双方均为携带者，其生育的后代有 1/4 的概率为 SMA 患儿，严重影响了患者的身心健康。建立准确的胚胎检测方法是非常必要。因该家系较特殊，“2+0”型区域可能发生串联重复，该区域无法准确知道具体的结构变异大小及方式，造成 SMA 区域存在复杂的结构变异，而 PGT-NGS 的 Panel 由于是针对基因上下游设计，在复杂或者大片段结构变异情况下，导致 SNP 识别不准确，遗传方式与传统的孟德尔遗传方式相违背；无法构建更大范围的单体型 block，这是 Panel 本身的一个局限性。芯片方法可根据需求扩大分析范围，对“2+0”型特殊家系分析有优势。荧光 PCR-毛细管电泳法采用分子标签和 SMN1 联合检测，方法快速、准确。

HBB 基因异常所致类似 CNSHA 表现的溶血性贫血 2 例及治疗

李珊珊 蒋莎义
上海市儿童医院

目的 HBB 基因异常通常与 β-地中海贫血和镰状细胞贫血发病相关，而临床表现为类似先天性非球形细胞性溶血性贫血（CNSHA）的病例罕见报道。本文通过分析 HBB 基因异常所致的、以类似 CNSHA 为临床表现的的 2 例患儿，探讨这类疾病临床表现与突变位点、突变类型的关系及诊断和治疗。
方法 回顾分析 2017 年上海市儿童医院血液科就诊的 2 例 HBB 基因异常的遗传性溶血性贫血的病史特点、临床表现、HBB 基因突变位点及治疗效果。
结果 婴幼儿期发病，慢性反复溶血发作，间断出现茶色尿。查体皮肤、巩膜轻度黄染，肝脾轻度增大。血红蛋白多在 60-80g/L，有时达重度贫血，需要输注悬浮红细胞治疗。血网织红细胞明显升高。球形红细胞、镰状细胞阴性。血间接胆红素增高为主，尿胆红素阳性。红细胞渗透脆性、Coombs 试验、G-6-PD 酶活性、丙酮酸激酶活性、铁代谢检查均正常。骨髓呈增生性贫血。临床表现类似于 CNSHA。本文 2 例均为 HBB 基因第二外显子的杂合突变。分别是 c.G202A：p.V68M

和 c.G295A：p.V99M。2 例患儿父母基因相应位点均呈野生纯合型。其中 1 例输血依赖患儿，接受造血干细胞移植后达到治愈。
结论 HBB 基因突变多样，依突变部位不同，临床表现不同。诊断有赖于基因检测验证。造血干细胞移植可能是有效的治愈方法。

The 46, XX ovotesticular disorder of sex development with Xq27.1q27.2 duplication involving the SOX3 gene: a rare case report and literature review

Jianlong Zhuang[1] Chunnuan Chen[2]
1.Quanzhou women's and children's hospital
2.The second affiliated hospital of Fujian medical university

Background Very few reports are available on human XX ovotesticular disorder of sex development involving *SOX3* gene duplication. Here, we aim to present a rare case of *SOX3* gene duplication in Chinese population who exhibit XX ovotesticular disorder of sex development.
Case presentation A 7-year-old Chinese individual from Fujian province Southeast China was recruited who exhibited 46, XX karyotype, absence of sex-determining region Y and was diagnosed as XX ovotesticular disorder of sex development. Further SNP array detection results demonstrated that the patient had a 2.2-Mb duplication in the Xq27.1q27.2 region (arr[hg19] Xq27.1q27.2:139,499,778-141,777,782) involving *SOX3* genes. Additionally, no *SOX3* duplication was observed in the parents and the sibling who delineated none of clinical feature.
Conclusion In conclusion, we identified the first case of *SOX3* duplication exhibited ovotesticular disorder of sex development in Chinese individual. Our study strengthens the link between the *SOX3* duplication and XX ovotesticular disorder of sex development and indicated that *SOX3* is the evolutionary antecedent of sex-determining region Y.

脊髓小脑共济失调 8 型家系 1 例

陈毅坤 陈万金
福建医科大学附属第一医院

SCA 多为缓慢进展性疾病，其发病机制包括重复序列扩增及点突变导致，临床上以 3 型最为常见。因其表型组合复杂，在临床不易准确识别，易出现漏诊或误诊。本文报道了 1 例 ATXN8 基因 CAG 重复数扩增相关的临床病例。

脊髓性肌萎缩症治疗进展

陈海珠 王柠 陈万金
福建医科大学附属第一医院

目的 脊髓性肌萎缩症(SMA)是婴幼儿期最常见神经系统遗传致死性疾病，病理累及脊髓前角运动神经元导致患者出现进行性肌无力和肌萎缩表现。鉴于脊髓性肌萎缩症严重危害了患者健康甚至危及生命，科学家一直致力于该病的治疗研究，并取得了快速进展。本文将对 SMA 的治疗研究进展进行综述。
材料与方法 通过查阅国内外脊髓性肌萎缩症治疗研究相关文献，对该病治疗研究进展进行总结归纳。

结果 脊髓性肌萎缩症患者由于运动神经元生存基因（*SMN*）1 的纯合缺失，而高度同源的 *SMN2* 基因由于 7 号外显子关键碱基的突变(c.840C>T)导致 SMN2 前体 mRNA 剪接过程中跳跃 7 号外显子，产生了截短的 SMN△7 蛋白，该蛋白不能完全代偿全长 SMN 蛋白功能，因此调节 *SMN2* 基因的选择性剪接是 SMA 治疗的一个靶点。目前 SMA 治疗方式主要包括以下三种：（1）诺西那生钠：该药物为反义寡核苷酸药物(ASO)，通过结合 *SMN2* 前体 mRNA 的 ISS-N1，促进 *SMN2* 基因 7 号外显子纳入剪接，从而达到治疗目的。2019 年该药物获批在国内上市，临床治疗数据显示诺西那生钠能显著改善患者的上肢运动功能，但由于诺西那生钠在血液中的半衰期约 63～87 天，因此需要反复鞘内注射维持药物浓度，这也给严重脊柱畸形的患者带来一定的痛苦。（2）Zolgensma：该药物为以 AAV 为载体递送 *SMN1* 基因，通过直接补充缺乏的 *SMN1* 基因达到治疗效果。该药物被批准用于 2 岁以下 SMA 患儿的治疗，仅需一次静脉注射，但药价昂贵。近期研究表明，在小鼠中长期过表达 *SMN1* 基因导致 SMN 蛋白的异常聚集从而损伤感觉神经环路，此外，在猪和猴子的大动物实验中也表现出毒性作用。（3）Risdiplam：该药物为小分子化合物口服液体制剂，可适用于 SMA I 型/II 型/III 型的家庭治疗，在临床试验中能改善患儿的坐立及上肢功能，目前常见不良反应为上呼吸道感染、发热、腹泻等。

结论 脊髓性肌萎缩症致病基因明确，现有治疗方式通过外源补充 SMN1 基因或通过调节 *SMN2* 前体 mRNA 选择性剪接达到治疗目的，虽在临床试验和真实世界应用中都能改善患者的运动功能和生存期，但尚有改进空间。能否通过基因编辑的方式从源头改造 *SMN2* 基因从而达到一劳永逸的治疗效果仍值得探索。

Novel and recurrent variants identified in fetuses with central nervous system abnormalities by trios-medical exome sequencing

Hu Tan
The Third Affiliated Hospital of Guangzhou Medical University

Background Fetal central nervous system abnormalities often associated with infant death or severe disability.The etiology in fetuses with CNS abnormalities who have normal karyotypes and copy number variants (CNVs) remains unclear, which increases the difficulty in following management and the assessment of prognosis.
Method 11 unrelated fetuses with CNS abnormalities and their parents were enrolled. Genomic DNA was obtained and then trios-medical exome sequencing (trios-MES) including 4000 genes (fetuses and their parents) was performed after both karyotyping and chromosome microarray showed negative results.
Results Pathogenic and likely pathogenic variants were identified in five of 11 cases (5/11, 45.5%), including five novel mutations and two recurrent mutations in ISPD, L1CAM, and GRIN2B genes. Most cases (4/5, 80%) carried one or two recessive mutations, indicating a high recurrent risk.
Conclusion Exome sequencing should be considered for fetuses with CNS abnormalities following negative results of karyotyping and chromosome array. Trios-MES as one of exome sequencing is a potential method for the diagnosis of these fetuses.

隐性遗传腓骨肌萎缩症患者基因型及表型分析

张小蓉 何瑾
福建医科大学附属第一医院

目的 腓骨肌萎缩症也称为遗传性运动和感觉神经病，是一种主要影响周围神经的遗传疾病，目前发病率约为 1/2500。腓骨肌萎缩症的临床特征是慢性对称性进行性远端肌无力和萎缩、远端型感觉障碍、腱反射减弱或消失、弓形足等。腓骨肌萎缩症的致病基因多达 100 多种，其遗传方式有常

染色体显性遗传（AD）、常染色体隐性遗传（AR）、X 连锁显性遗传（XD）和 X 连锁隐性遗传（XR）。本文探讨隐性遗传腓骨肌萎缩症患者的临床与基因型特点。

方法 收集 18 例隐性遗传腓骨肌萎缩症患者的临床资料，包括临床表现、体格检查、临床电生理学表现、基因检测结果进行回顾性分析，结合文献进行讨论。

结果 18 位患者，男 13 名女 5 名，病程在 1-20 年间，起病年龄多大集中在前 20 年；根据肌电图分型，CMT1、CMT2 和中间型 CMT 分别为 5、9 和 4 个,分别约占总数的 27.8％、50％和 22.2％；病情严重程度按 CMTNS 评分为轻(0～10 分)、中(11 ～20 分)和重(21～36 分)及评分不明确的分别为 6、5、1 和 6 例,分别约占总数的 33.3％、27.8％、5.56％和 33.3%；其中 SORD 基因点突变 3 例，GDAP1 基因点突变 3 例，SH3TC2 基因点突变 3 例，MME 基因点突变 2 例，HINT1 基因点突变 1 例，MPV17 基因点突变 1 例，PRX 基因点突变 1 例，IGHMBP2 基因点突变 1 例，EGR2 基因点突变 1 例，MTMR2 基因点突变 1 例，SBF2 基因点突变 1 例。

结论 隐性遗传腓骨肌萎缩症患者在临床上较少见，肌电图表现以轴索型占多数，本文分析了其临床资料及基因型特点

LAMA2 基因突变致 Merosin 缺失型先天性肌营养不良症 1 例报告

李桂河 陈万金
福建医科大学附属第一医院

背景与目的 先天性肌营养不良是一组具有临床和遗传异质性的缓慢进展性肌病，Merosin 缺失型肌营养不良症（MDC1A）是其最常见的亚型，为 *LAMA2* 基因突变所致。其表型谱包括出生时即表现为全身性肌张力低下及肌无力的严重 1A 型和临床表现较轻的迟发型，对于后者临床不易准确识别。本文报道了一例表现为双下肢无力最终确诊为 *LAMA2* 基因突变所致的 MDC1A，对提高临床工作者对该病的认识和拓宽该病突变谱具有一定的意义。

材料与方法 回顾分析 1 例 Merosin 缺失型先天性肌营养不良症的临床资料，包括：详细的病史采集、查体；实验室检查；肌电图；颅脑及肌肉影像；在患儿家属知情同意下为患者行肌肉活检病理检查；采集患儿外周血提取 DNA，并对 195 个神经肌肉病相关基因进行捕获测序，利用 PCR 和 sanger 测序验证捕获测序结果。

结果 ①患儿女性，2 岁 11 月首次以“双下肢无力 2 年”为主诉就诊。主要表现为下蹲起立、爬梯困难，查体略呈鸭步步态，双下肢近端肌力 4 级，四肢肌张力降低，腱反射减弱，余未见明显异常。肌酸激酶 1118U/L，*SMN1* 基因未见纯合缺失，肌电图提示肌源性损害可能。②3 年后该患儿就诊我院，双下肢无力无进行性加重，复查肌酸激酶 1230U/L，肌电图提示轻度周围神经损害累及部分运动神经；轻度肌源性损害。完善双下肢磁共振提示：大腿及小腿肌群脂肪浸润伴水肿，大腿部分肌群萎缩。颅脑 MRI 提示双侧侧脑室旁及额颞顶叶白质及部分灰质信号异常，T1 呈低信号，FLAIR 呈高信号，DWI 呈等信号。肌肉活检提示 Merosin 缺失型肌营养不良。③基因检测结果 :LAMA2:c.A332C,p.Q111P（母源）；LAMA2:c.6628_6639del,p.2210_2213del（父源），HGMD 数据库未见报道，符合家系共分离。

结论 对于临床表现为运动发育落后且肌电图提示肌源性损害的患儿可联合多种手段进行诊断，但最终需要尽早行基因检测以明确诊断。

应用 MLPA 检测鉴定 TSC2 基因大片段缺失的结节性硬化症一例

黄盛文
贵州省人民医院

目的 对于一个疑似多发性结节性硬化症的患者的致病基因进行检测和分析,为该家庭提供遗传咨询依据。
方法 先证者，女，30 岁，临床表现有：面部多处丘疹、结节，右侧腰痛伴全程血尿，CT 示：双肺散在多发肺气肿（考虑淋巴管肌瘤病），双肾错构瘤，结果提示结节性硬化症，家族中未见类似症状的成员。签署书面知情同意书后，采集先证者外周血并提取 DNA，进行全外显子组测序，在发现存在大片段缺失后,进一步行 MLPA 检测验证从而检测患者致病基因及突变位点。
结果 全外显子检测发现 16 号染色体 16p13.3 处缺失长度为 17.74Kb 的区域，覆盖了 TSC2 基因 1-16 号外显子。MLPA 示：TSC2 基因(NM_000548.5)外显子 1-16 区域存在大片段杂合缺失。因 TSC2 基因 1-16 号外显子的大片段缺失（chr16：2047894-2065635），其中缺失片段包含了 TSC2 基因的启动子，起始密码子等与转录相关的基因，缺失链上 TSC2 基因无法转录从而导致其产物马铃薯球蛋白(tuberin)合成的减少。通过对 ClinVar、PupMed、OMIN、UCSC 等数据库的查询，未发现相同缺失片段的报道，根据美国医学遗传学会（ACMG）的遗传变异标准关于 CNV 解读指南提示为致病 CNV。
结论 通过全外显子组测序及 MLPA 检测，确诊先证者为 TSC2 基因大片段缺失的结节性硬化症，丰富了 TSC2 基因的突变谱。检测结果为患者及家属遗传咨询提供了依据。

AGK 在滋养细胞中的表达及其对滋养细胞生物学功能的影响

陈丽君 揭秋玲 马燕琳
海南医学院附属第一医院

目的 模拟胎盘早期低氧环境，研究 AGK 在人滋养细胞中的表达水平及生物学功能，探讨 AGK 在滋养细胞中的调控作用。
方法 通过细胞转染，构建稳定沉默及过表达 AGK 的 HTR8/Svneo 滋养细胞株，并于低氧下（2%O2）培养。以 MTT、Edu 实验检测沉默或过表达 AGK 后滋养细胞的增殖能力，以 Transwell 实验和划痕实验，检测沉默或过表达 AGK 后滋养细胞的侵袭及迁移能力。通过 qRT-PCR 及 Western Blot 检测滋养细胞 EMT 相关因子的 mRNA 和蛋白表达水平。进一步以 Western Blot、Transwell 实验及划痕实验探索 AGK 调控细胞迁移、侵袭能力的机制。
结果 低氧条件下，MTT 实验及 EDU 实验结果表明，与对照组相比，沉默 AGK 后滋养细胞增殖能力受抑制，而过表达 AGK 则促进滋养细胞的增殖能力。Transwell 实验和划痕实验结果表明，沉默 AGK 抑制滋养细胞的迁移及侵袭能力，过表达 AGK 后则相反。沉默 AGK 后，滋养细胞 MMP2 mRNA 及蛋白表达下调、E-cadherin 及 Caspase9 mRNA 表达上调，过表达 AGK 后则相反。目前正以 Western Blot 检测 PI3K/AKT 信号通路中 PI3K、AKT 的磷酸化水平及 MAPK/MEK 信号通路中 MAPK、MEK 的磷酸化水平，以初步探索 AGK 调控滋养细胞迁移、侵袭功能的可能的机制。
结论 低氧条件下，沉默 AGK 抑制滋养细胞增殖、迁移及侵袭能力，过表达 AGK 促进滋养细胞增殖、迁移及侵袭能力，表明在胎盘早期低氧环境下，AGK 在滋养细胞生物学功能中发挥着重要作用，对调控滋养细胞正常生理功能具有重要意义。

Case report of follicular occlusion tetrad concomitant with pachyonychia congenital type Ⅱ with KRT17 gene mutation

Jia Yan Lei Shi Chunxiao Li Yutong Yang Xiuli Wang
Institute of Photomedicine, Shanghai Skin Disease Hospital, School of Medicine, Tongji University, Shanghai 200092, P. R. China

Background The follicular occlusion tetrad is a complex dermatologic syndrome composed of four diseases acne conglobata, hidradenitis suppurativa, dissecing cellulitis of the scalp, and pilonidal sinuses. The follicular occlusion tetrad is a complex dermatologic syndrome which can concomitant with other diseases. In our dermatology clinic, we encountered a male patient with follicular occlusion tetrad in complex condition.
Objectives and Methods In order to confirm the diagnosis, the patient has received comprehensive physical, laboratory, imagological, and histopathological examinations. And even his peripheral blood was collected for genetic examination in order to explore the mechanism. After diagnosis, a comprehensive therapy scheme of photodynamic therapy combined surgery and drug is tried to alleviate his discomfort.
Results Considering the morphologic, histology features, examinations and genetic outcomes, the patient is believed to suffer from follicular occlusion tetrad concomitant with pachyonychia congenital type Ⅱ and ankylosing spondylitis, and the genetic analysis showed the KRT17 gene mutation on exon 1 (c.T284C). Genetic outcomes may indicate the genetic association and we hypothesize that the comorbidities are intrinsically linked to KRT17 mutation which is correlated with the hyperproliferative and undifferentiated state of the keratin.
Conclusions This case indicated the comorbidity of follicular occlusion tetrad, pachyonychia congenital type Ⅱ and ankylosing spondylitis, which may be related to genetic mutation of KRT17 and a comprehensive therapy scheme could do help to such condition.

广东地区正常单胎胎儿孕 11 ~ 14 周颈项透明层厚度的分布

唐斌 黄演林 陈柯艺 钟志成 刘攀 李洁 骆明勇
广东省妇幼保健院

目的 分析广东地区孕 11~14 周整倍体胎儿颈项透明层（nuchal translucency, NT）厚度分布情况，并将其与已报道的欧洲和亚洲数据进行比较。
方法 收集 2015 年 1 月至 2018 年 4 月本院 24892 例 CRL 在 45 ~ 80 mm 的单胎且妊娠结局良好的 NT 数据（随访结果至 2019 年 4 月）。参照英国胎儿基金会的标准超声测量胎儿 CRL 及 NT 厚度。将 CRL 在 45 至 80 mm 的胎儿按每增加 5 mm 为一个组，细分为 7 个组。
结果 CRL 平均值为 62.93±7.26 mm (范围 45 ~ 80 mm)， NT 平均值为 1.49±0.42 mm (范围 0.2 ~ 9 mm)。NT MoM 的第 95 百分位数为 1.5375。
结论 由于不同中心、不同国家的人群和 NT 测量技术的差异，为了更精确地估计风险，最好建立适宜于本地区孕妇人群的胎儿 NT 厚度参考值范围。

1 例成人型神经元蜡样质脂褐质沉积症的病例报告

林晓虹 陈佳颖 王柠 陈万金
福建医科大学附属第一医院神经内科

目的 神经元蜡样质脂褐质沉积症（NCLs)是一组常染色体隐性遗传的溶酶体沉积病，以蜡样质脂褐质在不同的组织和器官中的溶酶体内沉积为特征。根据发病年龄，主要分为 4 型：婴儿型，晚婴儿型 ,青少年型和成年型。成年型神经元蜡样质脂褐质沉积症（ANCL）又称 Kufs 病， 一般在 30 岁

左右发病。本文报道 1 例成年型神经元蜡样质脂褐质沉积症，分析其临床表现和诊断，以期加深临床医师对此病的认识。
方法 收集患者临床资料，完善相关辅助检查，提取患者及家属（父母和弟弟）外周血 DNA，对先证者进行全外显子测序，并通过 Sanger 测序验证及家系共分离验证。回顾其病史结合基因检测结果，分析该病例诊断要点。
结果 （1）35 岁青年男性，以“记忆力减退 6 年，动作缓慢 1 年余”为主诉就诊，6 年前自觉记忆力下降，言语不流利，情绪易波动，夜间睡眠困难。1 年余前出现登楼困难，步伐变小，动作缓慢。2 个月前于对话时突发意识丧失，跌倒在地，伴双眼向上凝视，双上肢屈曲紧握，呼之不应，持续约 10 分钟，自行缓解。7 天前上述症状再发，性质同前。家族史：其弟弟有相似表现。（2）神经系统查体：神清，言语不流利，四肢肌力、肌张力未见异常，双侧腱反射对称，病理征阴性，共济运动正常，深浅感觉未见异常。（3）辅助检查:MMSE：29 分，MoCA：21 分。头颅 MRI：部分脑血管周围腔隙稍大，脑萎缩，交通性脑积水，双侧脑室后角旁白质异常信号。（4）全外显子测序提示：CLN6 基因 c.425C>T 纯合突变，父母均为杂合突变，其弟弟为纯合突变，满足家系共分离。（6）患者 29 岁起病，主要症状结合其影像学特征及基因检测结果，符合 Kufs 病。
结论 通过一个隐性遗传家系鉴定了一例 Kufs 病。临床上以痴呆、癫痫，记忆力减退、动作迟缓，性格改变，咽喉肌麻痹为主要表现的青年患者，结合影像学脑萎缩的表现，需注意此病，容易漏诊。

AARS2 基因突变相关的脑白质营养不良 1 例

王梦文 付莹 陈万金
福建医科大学附属第一医院

目的 成人起病的白质脑病是一组罕见的神经系统疾病，其特征是脑白质退行性变，可出现认知损害、精神行为异常、运动障碍等表现，病因复杂。AARS2 基因为线粒体核 DNA，其基因突变可致 AARS2 基因相关的迟发性脑白质营养不良，目前国内外仅报道 24 例，女性患者多伴有卵巢功能衰竭。本文报道 1 例中国 AARS2 相关脑白质营养不良患者的临床、影像及实验室检查资料，以提高临床医生对该病的认识。
方法 详细采集患者病史和体征，签署知情同意书，采集患者外周血提取 DNA，行 Sanger 测序验证，生物信息学工具预测位点致病性。
结果 患者女性，34 岁，以“左下肢僵硬伴左手麻木 1 年余”为主诉，表现为左下肢僵硬，伴左下肢静止性震颤，行走姿势异常，同时伴左手麻木，症状进行性加重，MMSE 及 MoCA 评分均提示轻度认知损害，神经系统查体提示锥体束损害及共济失调体征，颅脑 MRI 显示双侧脑室前后角旁及胼胝体异常信号灶及脑萎缩，颅脑 CT 提示双侧脑室体旁白质区低密度影及脑萎缩，临床疑诊“遗传学弥漫性白质脑病伴轴索球样变”，经 Sanger 测序发现患者未携带 CSF1R 基因致病突变，而带有 AARS2 基因的纯合突变：NM_020745.3:c.452T>C, 该位点为已报道的致病位点，后完善性激素检测，发现患者的激素水平尚正常，考虑是由于年龄尚轻。基于以上结果，该患者确诊为 AARS2 相关迟发性脑白质营养不良。
结论 AARS2 相关迟发性脑白质营养不良与遗传性弥漫性白质脑病伴轴索球样变在临床表现、影像学及病理上存在极大相似性，应注意鉴别。对临床上磁共振提示脑白质多发异常信号，应警惕迟发性白质脑病的可能，必要时行基因筛查。

儿童腺苷脱氨酶 2 缺乏症 1 例临床特征并文献复习

欧俊斌 李小琳 刘玉玲 孙智才 潘晓芬
中山市博爱医院

目的 总结 1 例腺苷脱氨酶 2 （ＡＤＡ２）缺乏症患儿的临床表型，并进行文献复习，提高临床医生对该病的认识。

方法 对２０21 年 6 月在我院确诊的 1 例ＡＤＡ２缺乏症患儿的临床资料及基因变异进行分析，并复习文献进行讨论。
结果 患儿因发热、抽搐就诊，以高血压、肾损害及皮疹为主要表现，全泌尿系 CTU 检查提示左肾动脉、腹主动脉下段、双侧髂总动脉及髂内动脉改变（血管壁增厚、钙化、毛糙，管腔狭窄、窄后扩张），右肾萎缩，左肾代偿性增大，外周血 ADA2 活性为零，基因检测发现 ADA2 c.753+20C＞T 杂合突变，给予环磷酰胺及甲强龙冲击、阿达木单抗注射及降血压药物治疗，患儿血压下降，肾功能好转。并对其家庭成员进行相关基因检测。
结论 腺苷脱氨酶 2 缺乏症缺乏症（ＤＡＤＡ２）临床少见，掌握 DADA2 临床特点，有助于提高临床诊治水平。

Clinical application of a modified CADASIL screening scale in the Chinese population

Naiqing Cai Mengting Fan Fangwei Hu Mingxia Kang Weijie Xie Ning Wang Bin Cai
the First Affiliated Hospital of Fujian Medical University

Background and Objectives There is a simple and accurate screening tool that allows to select patients with a high probability of being affected by cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). This technique existed even before genetic tests were available but its accuracy varies according to the population under study. Here, we aimed to optimize the scale to which this method can be applied to the Chinese population.
Methods We compared the differences observed between CADASL and CADASIL-like subjects with scores ≥8 in the current scale and derived data from this comparison to modify it. We subsequently applied the modified scale to a different cohort of individuals suspected of potentially suffering from CADASIL to test the accuracy of our method.
Results We applied the current scale on a cohort of 102 subjects (38 CADASIL and 64 CADASIL-like subjects) with scores ≥8 to adjust the weighted scores. Data analyses showed that “TIA or stroke” (p=0.037, OR=0.332), “leukoencephalopathy extended to external capsule” (p=0.002, OR=14.217) and “Family history in at least 2 generations” (p=0.032, OR=3.486) are independent of the gene NOTCH3 mutations. We then applied the modified scale on another 153 subjects (41 CADASIL and 112 CADASIL-like subjects). The newly developed scale showed a sensitivity of 70.7% and a specificity of 62.5%, with an AUC of 0.708 (95%CI 0.611-0.805, p<0.001).
Conclusion We modified and improved the available CADASIL screening scale in order to screen patients with high probability of CADASIL before clinical genetic testing can be performed.

全外显子组测序及等位基因特异 PCR 技术鉴定一个努南综合征家系致病突变

何文智 王燕超 李少英 叶国新 马晓燕 何健淳 冼嘉嘉 王晓蔓 黎青
广州医科大学附属第三医院

目的 努南综合征（Noonan syndrome, OMIM 163950）是一种常染色体显性 (AD) 或隐性 (AR) 疾病，是一种多系统受累的疾病，个体差异大，发病率约为 1/1000-2500 新生儿。迄今为止，至少 15 个基因与 Noonan 综合征相关。*LZTR1* 基因于 2014 年被报道与 Noonan 综合征相关，可导致努南综合征 2 型（MIM#605275）、努南综合征 10 型（MIM#616564）等疾病。努南综合征 2 型临床特征表现为先天性心脏病和身材矮小，眼距增宽、睑裂下裂等特殊面容和胸部畸形。部分患者出现精神发育迟滞，智力发育受损等。亮氨酸拉链转录调节因子 1 (LZTR1) 是一种高度突变的肿瘤抑制基因，参与多种癌症类型和发育障碍的发病机制，因此努南综合征患者罹患特定肿瘤的风险有

所增加。努南综合征的胎儿颈部较短，颈项透明层增厚等，但仅凭超声不易确诊。本研究采用全外显子组测序技术鉴定一个努南综合征 2 型家系的致病突变。

方法 患胎自孕中期起发现 NT 增厚，孕 27 周超声提示前额软组织厚度 6.3mm。羊水基因芯片及染色体核型未见异常。经孕妇及家属知情同意采用留样羊水，并采集该夫妇外周血行先证者及父母 Trio 全外显子测序。QIAGEN DNeasy Blood&Tissue 试剂盒提取基因组 DNA，Agilent SureSelect 技术富集外显子区域序列，HiSeq X Ten 平台对捕获的片段进行测序，目标区域的平均测序深度为 100X。测序数据与人类参考基因组（version: NCBI Build37/hg19）比对后，经变异频率、遗传模式、变异的致病性预测、基因变异与表型之间的已知关系等多个方面对识别的变异进行注释和筛选。采用等位基因特异 PCR 分析两个变异的亲本来源。

结果 全外显子测序得到与患胎表型相关的变异 *LZTR1* 基因 c.2248G>C 杂合突变，源于母亲；c.2325+1G>A 杂合突变，新发突变，有文献报道，在努南综合征 2 型患者中检测到该变异与其他致病性变异构成复合杂合突变（反式位置）。等位基因特异 PCR 确认两个变异分别位于不同等位基因，构成复合杂合突变。

结论 全外显子组测序能够通过一次检测获得所有相关基因的突变，对于亚型较多的疾病更加高效。此外，实验室应建立其他技术辅助判断变异的来源或其他情形，以便提供足够的证据进行变异的致病性评级。

结节性硬化患者的临床表型分布特点、发病机制及治疗方案的研究

王安琪 [1,2] 陈育才 [1,2]
1.上海市儿童医院
2.上海交通大学附属儿童医院

背景 TSC2(TSC Complex Subunit 2)基因是一个蛋白质编码基因，编码的蛋白定位于细胞质和细胞膜外周蛋白，它编码了 tuberin 蛋白，tuberin 蛋白促进了 GTPase 的活动 RAP1A，TSC 患者肿瘤中结节蛋白的丢失导致 RAP1 的结构性激活；tuberin 在体内起 RAB5GAP 的作用，在内吞过程中负向调节 RAB5-GTP 的活性，可能由肿瘤抑制基因 TSC2 编码的 RAB5GAP 活性的丧失可能会干扰内吞途径，导致内化生长因子受体或其他可能发生溶酶体降解的分子分类错误。

目的 探讨 TSC2 基因介导的结节性硬化患者的临床表型分布特点、发病机制及其治疗方案。

方法 我们收集了 24 位确诊为结节性硬化的患儿的临床资料，并对其中一位患儿及家系的外周血进行二代测序、实时定量聚合酶链反应（RT-qPCR）分析 TSC2 基因的表达量以及突变位点的保守性研究。

结果 我们分析了至今为止已经报道的 4330 突变位点的突变特征，其中推测有意义的突变位点有 415，其中推测与 Tuberous sclerosis 2 相关的有 194，无义突变有 245，其中 42 个位点与 Tuberous sclerosis 2 相关；共发现 511 位点的缺失突变，124 个位点都与 Tuberous sclerosis 2 相关，且大部分处于进化的保守位点，分布于 TSC2 编码蛋白的 RAP_GAP 区域。同时我们分析了 24 位确诊为结节性硬化的病人的临床资料并详细追踪了一例汉族女性结节性硬化症患儿以及患儿母亲的临床特征及可能的发病机制，二代测序结果表明 TSC2 基因上发现一个母源未知致病性杂合变异：c.4912_4914delAAG，结果可导致缺失突变（p.Lys1638del），母亲亦为杂合突变。通过定量 PCR 实验表明患儿以及患儿母亲的 TSC2 基因的表达量下降，我们推测可能缺失突变引起了基因无法正常表达。

儿童肿瘤营养评估现状与进展

范夏艳
上海市儿童医院

近年来,我国儿童恶性肿瘤的发病率逐年上升,其造成的死亡仅次于意外伤害,已经占儿童及青少年死因的第二位。随着经济社会的发展，手术、化疗、放疗、免疫、靶向治疗已经成为恶性肿瘤治疗的主要手段，极大地提高了儿童肿瘤患儿的治愈率和生存率。与此同时，恶性肿瘤本身带来的机体高负荷以及治疗的不良反应严重影响了患儿的生活质量。约有 20%-70%的肿瘤患者出现营养不良，严重营养不良会导致体重下降，肌肉萎缩，免疫、身体和精神功能受损等一系列的机体恶病质。有研究显示，20%-50%的肿瘤患者最终会死于营养不良而非肿瘤本身,由于儿童年龄较小，起病隐匿，进展迅速，耐受能力弱且自我表述能力差，营养问题尤为显著。因此，如何准确及时评估患儿的营养情况，给与相应的营养支持，降低肿瘤患儿的死亡率成为临床工作亟待解决的问题。近年来儿科营养支持越来越受到重视，本文就儿童肿瘤营养现状及进展展开综述,以期为肿瘤患儿提供更精准的营养支持。

126 例中国男性先天性低促性腺激素性性腺功能减退症的临床和遗传学特征

王毅 巩纯秀 秦淼 范丽君 张贝贝
首都医科大学附属北京儿童医院

背景：先天性低促性腺激素性性腺功能减退症(Congenital hypogonadotropic hypogonadism, CHH)是由促性腺激素释放激素(GnRH)神经元发育、分泌和功能缺陷引起的，包括 Kallmann 综合征(Kallmann syndrome，KS)和嗅觉正常的(normosmic HH，nHH)。CHH 的诊断、治疗和遗传学特点在成人的研究较多，而在儿童和青少年中的研究较少。
方法：收集从 2008 年−2020 年在我院门诊就诊的 CHH 患者的表型、家族史、分子遗传学等病历资料进行分析。
结果：共有 126 例男性患儿被诊断为 CHH，包括 88 KS (88/126, 69.8%) , 37 nHH (37/126, 29.4%)，1 例 Charge 综合征。7 名患者患有尿道下裂（3 例小阴茎合并隐睾和尿道下裂，4 例小阴茎合并尿道下裂）。在 49 例可追溯到家族史的患者中，青春期延迟、KS/nHH 和嗅觉异常家族史分别占 44.9%、16.3%和 12.2%。65 例患者完成了 HCG 延长试验，其中 24 例 T 水平低于 100 ng/dl，提示至少有 22.9%的患者存在睾丸间质细胞功能障碍，即混合型 CHH。在 95 例完善基因检测的患者中，78 例（82.1%）发现 25 个 CHH 相关基因，23 例发现双基因突变 (23/95, 24.2%)，3 例发现三基因突变(3/95, 3.2%)。最常见的致病基因是 *FGFR1*(20/95，21.1%)、*PROKR2*(17/95，17.9%)、*ANOS1*(12/95，12.6%)和 *CHD7*(12/95，12.6%)。KS 组与 nHH 组 *FGFR1*、*PROKR2*、*CHD7* 基因突变率无显著性差异(P 均>0.05)。常见常染色体显性遗传基因 *FGFR1* 和 *CHD7* 寡基因遗传分别占 50.0%(10/20)和 33.3%(4/12)，常染色体隐性遗传基因 *PROKR2* 寡基因遗传占 47.1%(8/17)，X 连锁 *ANOS1* 占 8.3%(1/12)。在 CHH 患者中，多个基因突变位点存在重复突变，包括 *PROKR2* (5 例 KS 和 nHH 均携带 W178S，*ANOS1* (2 例 KS 患者携带 V560I), *HS6ST1* (3 例 KS 患者携带 H63D) 和 *IL17RD* (各 2 例 KS 患者携带 P191L 和 S671L)。
结论：小阴茎、隐睾联合遗传学检测是儿科诊断 CHH 的重要线索，尿道下裂是 CHH 的少见表型。根据 hCG 延长实验后睾酮水平，22.9%的患者诊断混合型 CHH，后续需进一步结合治疗随访进一步证实。在 CHH 患者中，寡基因遗传占 27.4%。多个基因携带重复突变，提示这些基因对生殖的影响可能相对较轻，本研究进一步加深了对儿科 CHH 患者临床和遗传学特征的认识。

以佝偻病和高血压表现的婴儿全身性动脉钙化症 1 例

任潇亚
首都医科大学附属北京儿童医院

目的 探讨婴儿全身性动脉钙化症的临床表现及诊断。
方法 对 2020 年 10 月在北京儿童医院内分泌遗传代谢科确诊的 1 例婴儿全身性动脉钙化症患儿的临床资料、实验室检查、影像学检查及基因结果等资料进行收集并分析。
结果 患儿，男，6 岁 7 月，主因“双下肢间断疼痛 8 月余”就诊。患儿新生儿期心脏彩超提示心脏射血分数低（41%-50%），生后 25 天复查心脏彩超提示左室扩大，乳头肌水平至心尖左室侧壁后壁及下壁心肌致密化欠佳，左室整体运动幅度减低，射血分数 49%。入院查体四肢血压升高，双侧肋缘外翻，可及肋骨串珠，手足镯阳性，双下肢“X 形腿”。辅助检查：总钙正常，血磷降低，碱性磷酸酶升高。双侧膝关节 X 片提示长骨干骺端“杯口状”改变。血管造影检查发现颈部血管、腹腔干、肝动脉、脾动脉、肠系膜上动脉、双肾动脉、右侧冠脉血管多发狭窄伴瘤样扩张。泌尿系超声提示双肾实质回声增强，髓质边缘少许钙质沉积。全外显子检测发现患儿 *ENPP1*、*ABCC6* 基因为复合杂合突变。
结论 婴儿全身性动脉钙化症（Generalized Arterial Calcification of Infancy，GACI）罕见，主要以动脉和软组织钙化为特征，多由 *ENPP1* 和 *ABCC6* 基因突变引起，大部分患者在宫内或生后几个月即表现出多种心血管症状，还包含一些心外表现，少数患者可能仅有动脉狭窄，并无钙质沉积。此病例提示在多发性动脉狭窄的患者中，即使无影像学提示的钙化灶，也有本病可能。

TH 基因与 Segawa syndrome 的相关性研究

王艺霖
上海市儿童医院

目的 探讨多巴反应性肌张力障碍（DRD）常染色体隐性遗传病患者的临床特点和发病原因。
方法 分析于我院就诊的 7 例无血缘关系的中国汉族散发性 Segawa syndrome 的患儿的临床资料及基因突变，并结合分子生物学实验和国内外相关文献进行分析，从患有 Segawa syndrome 的患者及其父母那里收集了静脉血，进行 TH 基因表达和测序的实时 qPCR（RT-qPCR）分析。在错义突变的迭代线程装配优化（I-TASSER）服务器上的预测蛋白质的结构和功能，并进行蛋白突变位点的保守性研究。
结果 二代测序显示，3 名儿童的 TH 基因突变为报道的纯合突变（c.698G>A）。同时，在其他儿童中发现了 4 个新的 TH 基因突变：c.1004C>T(p.Ala335Val) 、 c.645-2A>G 、c.316_317insCGT、c.832G>A(p.Ala278Thr ）。我们收集了 4 名 Segawa 综合征患者及其父母的静脉血，用于 TH 基因表达的实时 qPCR (RT-qPCR) 分析。我们在错义突变迭代线程组装细化 (I-TASSER) 服务器上预测了蛋白质的结构和功能，并研究了蛋白质突变位点的保守性。结合分子生物学实验及相关文献分析，2 例患者的 qPCR 结果显示，TH 基因的表达低于 10 名正常对照，1 名母亲的 TH 基因表达低于平均水平。推测 TH 基因的突变可能通过影响下游多巴胺和儿茶酚胺的产生而导致相关的临床表现。
结论 在这项研究中，我们详细研究了 7 例汉族 TH 基因突变所致 DRD 的患儿的临床特征及可能的发病机制，通过全外显子检测，我们在 TH 基因中发现了 4 个新的突变位点：c.1004C＞T（p.Ala335Val)，c.645-2A＞G，c.316_317insCGT，c.832G>A(p.Ala278Thr ）。构建了活性位点模型，发现 c.1004C＞T（p.Ala335Val)和 c.698G>A (p.Arg233His)均位于预测的蛋白活性区域附近，丰富了 Segawa syndrome 的基因库，同时通过左旋多巴的应用，有助于 Segawa syndrome 机制的研究及诊断和治疗。

Silver-Russell 综合征一例的早期临床特征和遗传学分析

马俐[1] 孙婧婧[1] 杨帆[2,3] 王娟[2,3] 蔡成[1] 龚小慧[1]
1.上海交通大学附属儿童医院
2.上海交通大学医学遗传学研究所
3.上海市胚胎与生殖工程重点实验室

目的 对一例宫内、外发育迟缓，生后表现为四肢短小，前额突出的患儿进行临床和遗传学分析以明确病因。
方法 应用核心家系医学外显子组序列和拷贝数分析（4681 个基因）对患儿进行医学外显子水平分析，之后运用 DMR H19 甲基化检测分析，检测 DMR 区的 6 个 CpG 位点的甲基化水平。
结果 该患儿在生后 1 月 27 天因肠道感染入住新生儿科治疗，经病史询问和体格检查发现该患儿为小于胎龄儿，经与 fenton 早产儿发育曲线比对，身长和体重均小于 P3，而头围位于 P50。前额突出，单侧上睑下垂，四肢短小，家族史无殊。血串联质谱检查未见异常。甲状腺功能未见异常。下肢全长测量提示双下肢基本对称。头颅核磁提示脑白质髓鞘化未完成。进行染色体核型和核心家系医学外显子测序，结果提示染色体核型正常，未发现和表型相关联的基因位点和拷贝数异常。出院后患儿表现出发育迟缓，矮小，眼睑下垂，发作性不自主运动等症状，头围相对身长和体重增长较快，肢体发育出现不对称增长。相关表型符合 Silver-Russell 综合征，并进行了 DMR 甲基化检测，结果表明其甲基化水平低于正常对照水平 30%，最终确诊为 Silver-Russell 综合征。
讨论 Silver-Russel 综合征患儿早期主要表型鉴别应聚焦于发育迟缓和与身长和体重相比相对正常的头围发育等，并及时进行相关甲基化检测明确病因。

Evaluating Distribution And Prognostic Value Of New Cell Subsets In HCC With CIBERSORTx

Lixing Li
Department of General Surgery, Shanghai General Hospital

Objective This study aims to investigate effective molecular markers to predict the immune cell status of the micro-environment of hepatocellular carcinoma (HCC) and construct an immune risk score model suitable for patients of HCC.
Methods 1) Seven datasets from TCGA, ICGC, and GEO underwent sample screening and data standardization. Using the CIBERSORTx (Cell-type Identification by Estimating Relative Subsets of RNA Transcripts X) platform, this study abstracted the gene signature matrix of 11 tumor infiltrating lymphocytes (TILs) from GSE98638, a scRNA-seq study of HCC. This study evaluated the relative proportion of these cell subsets in HCC samples from the other six cohorts based on the information of the gene signature matrix.
2) The survival analysis was performed in HCC patients from the TCGA cohort according to the infiltrated proportion of different cell subsets to investigate the core cell subtype associated with patients' prognosis. Differentially expressed genes analysis and functional enrichment analysis were conducted in high and low infiltrating groups of the core cell type. Applying Group Mode of CIBERSORTx, the cell-type-specific differentially expressed genes of the core cell type between tumor and normal tissues were analyzed. The pathway enrichment of these genes was analyzed.
3) The cell-type-specific differentially expressed genes related to the prognosis of HCC patients were selected using Univariate Cox hazard analysis. The immune risk model was established using LASSO (Least absolute shrinkage and selection operator) Cox based on these genes. The predictive effectiveness of the model was validated by ROC curve, nomogram, and decision curve analysis in TCGA and ICGC cohorts.
Results 1) This study observed statistically significantly different distributions of seven new immune cell subsets between tumor and normal tissues in six independent datasets. The $CD4^+GZMA^+$ T cell subset had a lower infiltrating proportion in tumor samples. 2) The $CD4^+GZMA^+$ T cell subset showed association with good prognosis (log-rank test, $p < 0.05$) after analyzing clinical information of three datasets. According to the functional analysis, this cell type

might be related to aberrations of growth, differentiation, and organization of cell populations. It might also participate in signal transduction in cytokines like interleukins and the innate immune system. Additionally, pathway enrichment analysis showed the association between cell-specific DEGs and signals involving tumor metabolism and malignant progression. 3) In this study, 19 cell-specific DEGs were associated with the prognosis of HCC patients ($p < 0.05$). The immune risk model was established using LASSO Cox and verified in TCGA and ICGC cohorts. The model showed good predictive effectiveness of prognosis.
Conclusion The distributions of new immune cell subsets in tumor and normal samples from large cohorts differed. The analysis using CIBERSORTx, a “digital cytometry” method, revealed the individual-specific tumor immune cell infiltration. Among these eleven cell types, the $CD4^+GZMA^+$ T cell subset and its molecular features might create benefits during liver cancer immunotherapy. The immune risk score model based on $CD4^+GZMA^+$ T cell-specific gene expression difference might shed new light on the evaluation of the prognosis of hepatocellular carcinoma.

1 例主要表现为震颤的原发性家族性脑钙化症

曾一恒 赵淼 林必玮 姚香平 陈万金
福建医科大学附属第一医院

目的 原发性家族性脑钙化症（Primary Familial Brain Calcification，PFBC）是一组以双侧对称性脑区钙化为特征的神经系统遗传性疾病。PFBC 具有高度遗传异质性和临床异质性。由于临床表现多样，临床常难以确诊。本文通过基因测序对 1 例主要表现为震颤的颅内钙化患者进行基因突变分析以明确其致病基因。
方法 分析 1 例以震颤为主要表现的颅内钙化患者的临床资料，对先证者及其家属进行靶向 PANEL 全长测序、Sanger 测序及家系共分离验证。
结果 患者为男性，青少年期起病，首发症状为“双手不自主抖动”，多于紧张、劳累时加重，饮酒后可见好转，否认头痛、头晕以及行动迟缓表现。神经系统查体发现该患者双手不自主细颤，主要表现为姿势性震颤，饮酒试验阳性。血钙、血磷以及血甲状旁腺素水平均在正常范围。颅脑磁共振平扫示“颅内基底节区、小脑、皮层下多发钙化灶”。追问家族史，母亲曾于体检时发现“颅内钙化”。该患者临床疑诊为原发性家族性脑钙化症。后对先证者进行 PFBC 致病基因靶向全长测序，发现先证者带有 SLC20A2 基因杂合突变：c.1657delA。该位点为移码突变，通过 Sanger 测序对家系成员进行共分离验证成功。基于以上结果，该患者确诊原发性家族性脑钙化症。
结论 颅内钙化是一种神经科常见的 CT 征象。由于其临床表现不典型，易于其他神经系统疾病混淆，因此对颅内钙化的患者行基因检查，有助于颅内钙化病因的确诊。

1 例以发作性脑病为主要表现的神经元核内包涵体病

曾一恒 邱煜森 杨康 陈毅坤 陈万金
福建医科大学附属第一医院

目的 神经元核内包涵体病(Neuronal Intranuclear Inclusion Disease, NIID)是一种罕见的神经退行性疾病,以中枢和周围神经系统内的嗜酸性透明包涵体为特征。神经元核内包涵体病具有高度的临床异质性。由于临床表现多样，临床常难以确诊。通过基因测序对 1 例主要表现为发作性脑病的患者进行遗传分析，明确其致病基因。
方法 分析 1 例主要表现为发作性脑病的患者的临床资料，对先证者进行 NOTCH2NLC 基因的 RP-PCR 与 AL-PCR 验证。
结果 患者为男性，中年起病，主诉为“反复发作性反应迟钝伴发热 5 年”。主要特点为反复发作的意识觉醒度差，甚至昏睡数日，持续数日后自行好转。发作过程中伴发热、尿频。曾有类似癫痫发作，以及右侧肢体无力、言语不能的脑卒中样发作。追问家族史，有 2 个哥哥已故，生前均有“视物幻觉”史。颅脑 MR 示脑白质病变、脑室稍大，DWI 未见绸带征。该患者临床疑诊为神经元核内

包涵体病。后对先证者进行 NOTCH2NLC 致病基因测序，明确 GGC 的重复数为 83/35 次。基于以上结果，该患者分子确诊神经元核内包涵体病。
结论 神经元核内包涵体病临床表现不典型，但以发作性脑病较为常见，影像学 DWI 绸带征也具有提示意义。神经元核内包涵体病确诊有赖于病理活检与基因检测。

Evaluation of intervention strategy of thalassemia For couples of childbearing age in Centre of Southern China

Fan Jiang Liandong Zuo Jian Li Guilan Chen Xuewei Tang Jianying Zhou Yanxia Qu Can Liao
Prenatal Diagnostic Center, Guangzhou Women and Children's Medical Center affiliated with Guangzhou Medical University, Guangzhou, Guangdong Province, People's Republic of China

Background To describe the free intervention strategy of thalassemia for childbearing couples in Guangzhou.
Methods: Routine haematology examinations for 137,222 couples. 37,501 couples one of which had MCV(mean corpuscular volume)<82fL or MCH(mean corpuscular hemoglobin) <27pg were elected for Hb analysis and the deletions of four common α-thalassaemia mutation. Reverse dot blot for common nondeletional α-thalassemia and β-thalassemia was selectively used. 3,022 couples randomly selected were offered all those tests as a control group. Sanger sequencing, Multiplex ligation dependent probe amplification and Next-generation sequencing were used for rare thalassemia. High risk couples were offered prenatal diagnosis at 10–13 weeks' gestation based on informed consent.
Results The carrier rates of α-, β-, αβ- thalassemia and δβ thalassemia/deletional HPFH were 7.7%, 3.02%, 0.5% and 0.059% respectively. 1.37 percent of them were identified as at-risk couples and 345 couples terminated the pregnancy. No severe α- and β-thalassemia births were observed. In control group, two β- thalassemia carriers and 1 case with $–α^{3.7}/αα^{QS}$ were misdiagnosed, but all at-risk couples were found and we could save 1,523,774¥ using our strategy. The cut-off point of 73.46fL and 23.25pg would be useful to find $-α^{+}/α^{T}$ thalassemia.
Conclusion The intervention strategy was cost-effective and offered reference in population thalassemia screening.

First report of Lepore Hong Kong in a Chinese family

Fan Jiang Jian Li Xin Yang Fatao Li Jianying Zhou Xuewei Tang Dongzhi Li
Prenatal Diagnostic Center, Guangzhou Women and Children Medical Center, Guangzhou, Guangdong, China.

Background Hb Lepore is one of hemoglobin (Hb) variants which can cause clinically phenotype. Hb anti-Lepore Hong Kong was rare and only be identified in Hongkong and our laboratory. There were no reports of Lepore Hong Kong which should exit as the the result of an unequal crossover.
Objectives We identified a new δβ configuration within the same fusion region as Anti-Lepore Hong Kong
Methods Six family numbers of the proband were studied. Routine blood examination, Hemoglobin analysis, Sanger sequencing, Gap-polymerase chain reaction (gap-PCR), . Reverse dot blot and multiplex ligation-dependent probe amplification (MLPA) were performed together for obstaining molecular characterization. Quantitative real-time polymerase chain reaction was used to determinate β-globin and γ mRNA
Results Three family numbers had lower Hb A2 and higher Hb F levels. a δβ configuration was revealed within a 54 bp region between Cap site (+22) and codon 8 causing the deletion (NG_000007.3: g.63154_70565del) in those persons. The result of relative quantitative analysis showed that of the β globin mRNA reduced while γ globin mRNA increased significantly comparing to normal controls

Conclusion This is the first time identified the existence of Lepore Hong Kong in the world. We first described the genetic and phenotypic characterization of the the novel δβ configuration, which suggested that it may cause a β^0 thalassaemia phenotype.

一例 NF1 家系的两个杂合 NF1 基因突变鉴定

王雨蒙 李明
上海交通大学医学院附属新华医院

目的 鉴定一例 1 型神经纤维瘤病（Neurofibromatosis type 1, NF1）家系中的 *NF1* 基因突变。
方法 提取先证者、其父母及 100 名正常对照外周血基因组 DNA，应用二代测序检测先证者 NF1 基因的编码外显子及侧翼内含子，寻找可能导致该疾病的变异，应用 Sanger 测序在先证者及其父母血液样本验证可疑致病突变；对先证者父亲进行 *NF1* 基因的 Sanger 测序，并应用 Sanger 测序在先证者及其父母血液样本验证可疑致病突变。
结果 通过对先证者的 *NF1* 基因二代测序，发现了一个复发性突变 c.1063-2A>G(参考序列:NM_000267.3)，该突变导致内含子 7 的剪接异常。在其正常人母亲、患病父亲 DNA 中未检测到该突变。通过对先证者父亲 *NF1* 基因的 Sanger 测序，发现他携带一个杂合突变 c.6143T > G（参考序列:NM_000267.3），该突变在先证者及其母亲 DNA 中未检测到。上述两突变在 100 例正常人对照中均未检测到。
结论 我们的研究提示了一个罕见的现象，即 NF1 父母和他们的患病孩子可能有无关的 *NF1* 突变，即使在临床表型中有明确的家族史。 因此，临床医生需要对家族成员的全长 *NF1* 基因进行测序，而不仅仅是验证突变位点。此外，在 NF1 患者的产前基因诊断中，不仅要检测父母的突变位点，避免其发生突变，还要对整个 *NF1* 基因进行测序，以防止其他 *NF1* 新突变而漏诊。 最后，对 NF1 患者的教育是管理疾病和遗传咨询的重要组成部分。

孕妇血清中 miRNAs 作为生物标志物用于胎儿先心病法洛氏四联症的产前检测

金玉霞
嘉兴市妇幼保健院

目的 筛选孕有先天性心脏病法洛氏四联症胎儿母体血清差异表达的 miRNAs,确定具有潜在意义的无创胎儿先心病法洛氏四联症产前诊断的候选标志物。
方法 收集 2017 年 1 月至 2019 年 10 月，在嘉兴市妇幼保健院行产前超声检查确诊胎儿为先天性心脏病法洛氏四联症的 13 例孕妇为研究对象；同时选取 13 例正常孕妇为对照组，孕周、孕妇年龄与法洛氏四联症组相匹配。应用二代测序对研究组及对照组孕妇血清中差异表达的 miRNAs 进行筛选，进一步应用 qRT-PCR 技术进行差异表达的 miRNAs 的验证，并行生物信息学及统计学分析。
结果 测序结果发现，研究组与对照组差异倍数 2 倍以上的 miRNAs 共 190 个。生信分析显示，GO 通路主要富集在细胞形态发生调节及离子运输上；KEGG 通路主要富集在 MAPK 及肌动蛋白细胞骨架调节。本研究经二代测序及 qRT-PCR 验证，发现 6 个 miRNAs 在先心病法洛氏四联症组中的表达低于对照组，差异具有统计学意义。
结论 孕妇血清中 6 个差异表达的 miRNAs 有可能作为胎儿先天性心脏病法洛氏四联症的无创产前诊断分子标志物，具有潜在的临床应用价值。

PHEX 基因突变 p.Glu145*和 p.Trp749Arg 在 x -连锁低磷性佝偻病家族中的作用及其对 FGF23 启动子转录的负调控机制

甘玉棉 [1,2] 骆杰伟 [1,2]
1.福建医科大学省立临床医学院
2.福建省立医院

目的 X 连锁低磷性佝偻病（XLH）是家族性低磷血症性佝偻病中最常见的类型，临床表型特点是 X 连锁磷酸盐调节内肽酶同系物（PHEX，NM_000444.5）突变导致循环成纤维细胞生长因子（FGF23）水平的升高，肾小管对磷酸盐的再吸收障碍，导致佝偻病和骨矿化受损。我们曾报道了 2 个 XLH 家系，经表型-遗传关联分析，通过第二代测序(NGS)、Sanger 测序发现了 2 个 PHEX 致病突变：4 号外显子 c.433G>T, p.Glu145*和 22 号外显子 c.2245T>C, p.Trp749Arg，本文拟探讨新发现的 2 个突变的细胞功能损害。
方法：通过 PHEX-WT、PHEX-mut、secPHEX-WT、sec-PHEX-mut、FGF-23 基因克隆、质粒构建，单独或与 FGF-23 质粒共转染于 HEK 293T 细胞，应用免疫荧光定位突变蛋白；Western blot 检测蛋白表达及 RT-PCR 检测 mRNA 表达量，应用酶联免疫吸附（ELISA）检测 PHEX 内肽酶活性。用双荧光素酶报告基因检测 PHEX 对 FGF23 启动子的影响。
结果：免疫荧光定位显示野生型 PHEX 蛋白主要定位在细胞膜以及细胞质，而 p.Glu145*、p.Trp749Arg 突变的 PHEX、secPHEX 蛋白在细胞内的定位发生改变，表现为分布有些广泛散漫，突变的蛋白表达显著降低，尤其是 p.145*突变型。而在 PHEX、secPHEX 与 FGF-23 共转染的细胞模型内，野生型 PHEX、secPHEX 与 FGF-23 蛋白分布于细胞膜或者内质网上，而突变型则定位于细胞核膜（可能内质网）和细胞质中。qPCR 检测到 p.Glu145*无义突变导致了细胞内 PHEX、secPHEX mRNA 表达量下降，而 p.Trp749Arg 的 mRNA 表达量无显著性差异。2 个突变型均导致细胞内 PHEX 内肽酶活性下降；Western Blot 检测到突变的 PHEX、secPHEX 蛋白明显下降，在单转染 PHEX、secPHEX 细胞内均未测到 FGF23 蛋白表达；而在与 FGF23 共转染细胞内，发现 PHEX、secPHEX 突变促进了 FGF23 蛋白的表达。双荧光素酶报告基因检测显示 PHEX 过表达后，野生型与突变型萤火虫荧光素酶均活性增强，而且二者间有统计学差异。
结论：本研究揭示了 p.Glu145*无义突变可能通过无义突变介导的 mRNA 衰变（NMD）机制或蛋白截短导致 XLH 发生，p.Trp749Arg 错义突变则可能通过影响蛋白空间结构导致蛋白表达量减少而致病。发现 PHEX 与 FGF23 之间新的调控机制：即突变的 PHEX 可能通过负调控 FGF23 的启动子来影响 FGF23 的表达水平，从而导致低磷血症的发生。

PROS1 基因 Leu607Ser 杂合突变导致蛋白质翻译障碍引起的蛋白 S 缺陷症易栓家系

张艳平 [1,2] 骆杰伟 [1,2]
1.福建医科大学省立临床医学院
2.福建省立医院

目的：遗传性蛋白 S 缺乏症(PSD)是一种常染色体显性遗传性疾病，在 1984 年报道了家族性 PSD 易发复发性血栓。后续的研究证明了杂合 *PROS1* 突变会增加血栓形成的风险，目前已经发现了有 300 多种 *PROS1* 的致病突变，但 PROS1 突变是否会影响蛋白结构，以及为什么它能诱导 PSD 尚不清楚。
方法：收集一个易栓症家系成员临床表型，凝固法测 PS 活性、发色底物法测蛋白 C 与抗凝血酶Ⅲ活性等。对这易栓家系中先证者及其父母进行第二代全外显子测序(NGS)筛查责任突变类型，并构建突变型及野生型的质粒进行转染 HEK293T，检测 *PROS1* 基因的 mRNA 及蛋白表达量。
结果：在本家系中，患有双下肢静脉血栓的先证者、患有双下肢静脉血栓和肺血栓的母亲，和先证者的年少弟弟的 PS 活性明显降低，同时携带有 *PROS1* (NM_000313.3) 的 c.1820T>C:p.Leu607Ser 杂合突变，而正常值 PS 活性的家系成员未发现有此突变。构建的

Leu607Ser 突变型细胞的细胞裂解物和细胞上清 Protein S 表达量减低，而 mRNA 表达水平升高，免疫荧光定位示突变前后蛋白定位没有明显差别。

结论：通过家系表型与基因关联分析，及细胞功能检测，说明 *PROS1* Leu607Ser 杂合突变可能是一个具有致病性的变异位点，丝氨酸的替代导致整个蛋白质的结构不稳定，考虑 PS 翻译合成障碍或可能分泌受损导致是主要发病机制。

先天性鱼鳞病合并囊性纤维化患者一例的基因型和表型分析

马俐[1] 孙婧婧[1] 陈一欢[1] 杨帆[2,3] 蔡成[1] 龚小慧[1]
1.上海交通大学附属儿童医院
2.上海交通大学医学遗传学研究所
3.上海市胚胎与生殖工程重点实验室

目的 探讨先天鱼鳞病（Autosomal recessive congenital ichthyosis-1 ARCI1）合并囊性纤维化（Cystic fibrosis, CF）的患儿基因型与表型的对应关系，并为其进行遗传咨询和随访建议。

方法 运用家系全外显子测序和 sanger 测序技术对生后即出现鱼鳞病样红皮病表现的新生儿及其父母的外周血标本进行检测，并就基因型和表型进行分析。

结果 该患儿生后即出现皮肤的火棉胶样改变，双眼可见黄白色分泌物，外耳廓畸形，出现呕吐治疗后好转。全外显子基因组测序结果显示患儿存在 TGM1 基因复合杂合突变。其中 TGM1 基因的变异之一位于 3 号外显子的 c.463C>T(p.Arg155Trp)遗传自父亲，变异之二位于 5 号外显子的 c.871G>A(p.Gly291Ser)遗传自母亲。患儿表型高度符合因 TGM1 基因缺陷所导致的先天性鱼鳞病-1，且随着时间推移，皮肤鱼鳞状改变逐渐转变为角质化和色素沉着。同时提示患儿中 CFTR 基因也存在复合杂合突变，突变一位于 8 号内含子的 c.1117-1G>A（p.?）遗传自父亲，变异二位于 18 号外显子的 c.2909G>A(p.Gly970Asp)遗传自母亲。两个位点均为致病变异。经随访获知此患儿后续出现了肺部感染和便秘等症状与囊性纤维化的表型符合。经遗传咨询获知父亲有少精和弱精，这可能与携带相关 CFTR 突变有关。

结论 对与初期单以鱼鳞病为主要表现的患者，若行基因检测发现其它基因致病变异需对表型进行综合全面的深入关联分析，以便在遗传咨询出给予最合理化的随访建议。

全外显子测序发现手足裂畸形中一个新的 TP63 基因杂合性错义突变

苗明珠 晋柏 卢守莲 王珏 张国英
南京医科大学第一附属医院（江苏省人民医院）

目的 确定一个中国家系中手足裂畸形（Split-hand/foot malformation，SHFM）患者的遗传原因，为该家系进行遗传咨询和生育指导提供依据。

方法 采集先证者脐带标本和先证者父母、外祖母、舅姥爷的外周血标本，提取 DNA，进行多人家系全外显子测序筛选可疑致病性变异位点，应用 Sanger 测序对致病性位点进行验证。

结果 通过测序后生物信息学分析和 Sanger 测序验证，我们在该家系中发现了 *TP63* 的一个新的杂合性错义突变(NM_003722.5: c.921G>T；p.M307I)导致蛋氨酸被异亮氨酸取代，可能与 SHFM 的发生有关。

结论 确定了 SHFM 中 *TP63* 的一个新的错义突变位点(NM_003722.5: c.921G>T；p.M307I)，该突变的鉴定扩大了已知的 *TP63* 的突变谱，也为 SHFM 家系和患有 *TP63* 相关疾病家系的遗传咨询和产前诊断(植入前遗传学诊断)提供了依据。

家族性肌萎缩侧索硬化症的基因型-临床表型分析

张奇杰 郭祈福 陈万金 王柠
福建医科大学附属第一医院

背景 肌萎缩侧索硬化（ALS）是一种广泛累及大脑、锥体束、脑干及脊髓前角运动神经元的神经变性疾病，其中 5-10%的 ALS 患者存在阳性家族史，称为家族性 ALS，先后发现了 30 余个 ALS 致病或相关基因。本研究旨在开展福建地区家族性 ALS 患者的基因突变筛查，明确不同基因突变患者的临床表型差异。
方法 收集从 2014 年 12 月至 2020 年 12 月就诊于福建医科大学附属第一医院神经内科的家族性 ALS 患者，联合全外显子测序、靶向测序和 Sanger 测序方法，进行基因突变筛查，开展基因型-临床表型分析。
结果 共收集了 30 个 ALS 家系，包括 11 个 SOD1 基因突变家系、8 个 TDP-43 基因突变家系、7 个 FUS 基因突变家系、1 个 ANG 基因突变家系，余下 3 个家系目前尚未发现相关致病基因突变。携带 SOD1、TDP-43 和 FUS 基因突变患者的平均起病年龄分别是 42.0 岁、52.7 岁和 42.2 岁。此外，不同基因突变患者的首发部位也存在差异，TDP-43 突变患者以球部（55%）和上肢（32%）起病多见，而 SOD1 突变患者和 FUS 突变患者以下肢起病多见。在预后方面，与 SOD1 和 FUS 突变患者相比，TDP-43 突变患者病程更为良性，TDP-43 突变患者的中位生存时间为 120 个月，而 SOD1 和 FUS 突变患者的中位生存时间分别为 24 个月和 29 个月。此外，同一基因不同突变位点，其临床表型也差异甚大，其中 SOD1 基因的 p.G148D、p.N87S 和 p.L107F 突变位点患者的临床表型重、进展快，而 p.G38R 和 p.H47R 突变患者则相对较轻。
结论 福建地区家族性 ALS 患者以 SOD1、TDP-43 和 FUS 基因突变最为常见，不同基因突变患者的临床表现、疾病进展速度存在较大的差异。

幕上大量脑出血内镜治疗术后颅内压调控策略

邱伟智
福建医科大学附属第二医院

目的 为了评估神经内镜手术对危及生命的大量脑出血的患者有效性，以及术后颅内压调控策略。
方法 收集 2020 年 01 月至 2021 年 07 月大量颅内出血的患者手术病例 33 例，分成开颅手术+去骨瓣减压组（18 例）和神经内镜组（15 例）。通过手术时间、血肿清除率、术后 GCS、住院时间、术后并发症的出现和术后 6 个月改良 mRS 评分，比较 2 组手术疗效。
结果 所有 33 名患者接受持续随访，随访时间大于 6 个月。2 组病例术前临床资料无明显差异（P＞0.05）；手术时间内镜组为（1.5±0.4）h，开颅组为（3.75±0.61）h（P＜0.05）；术后第 1 天血肿清除率：开颅组为 86.62%±4.45%，内镜组为 87.34%±3.42%，（P＜0.05）；术后第 7 天 GCS 评分分别为：开颅组 11.73±2.48，内镜组 2.90±1.45（P＜0.05）；6 个月改良 mRS 评分在入院时血肿量大于 60ml 的患者：开颅组为 5.13±1.13,内镜组为 3.00±1.25，差异有统计学意义（P＜0.05）。入院时 GCS 评分在 4-8 分的患者：开颅组为 5.25±0.87,内镜组为 3.54±1.56，差异有统计学意义（P＜0.05）。
结论 对于幕上大量脑出血神经内镜治疗与开颅手术相比，可更安全、更有效地清除血肿，术后脑脊液引流，结合颅内压监测，可有效、安全的应对术后脑水肿、颅高压等，对患者预后有一定改善作用。特别是在血肿量在大于 60 mL 或 GCS 评分 4-8 的患者中。

绍兴地区地中海贫血基因突变分析

金晶[1] 金欣[2]
1.绍兴市人民医院血液科 2.绍兴市文理学院医学院基础医学部

目的 分析绍兴地区地中海贫血基因突变的类型和构成比。
方法 选取 2014——2019 年初筛时疑似地中海贫血的 351 例患者，利用跨越断裂点 PCR (Gap-PCR) 技术及 PCR 反向点杂交技术(PCR-RDB)，取外周静脉血 2ml 进行常见的地中海贫血基因类型检测。
结果 351 例患者中，其中 201 例检出地贫基因，总检出率为 57%。其中 α 缺失型检出 59 例（占 16.9%），α 点突变型检出 8 例（占 2%），β 地贫检出 127 例（占 36.3%），αβ 复合型检出 7 例（占 2%）。通过回顾病历和电话随访，发现本地户籍的患者 141 例（其中两例儿童患者，父母双方分别有一方来自浙江温州和广西地区，亦归入本地患者中），占 70%，并且呈逐年上升趋势。61 例为外省市户籍，包括四川、广西、贵州等，5 例失访。7 例 αβ 复合型地贫均为外省市户籍。其中 α 缺失型中最常见的突变型为 αα/--^{SEA}（27 例），占 α 地贫基因的 40%；β 地贫中最常见的突变型分别为 IVS-II-654 突变（51 例）、CD41-42 突变（13 例）、CD17 突变（13 例）、CD14-15 突变（2 例），分布占 β 地贫基因的 40%、10%、10%、1.5%。
结论 本次研究与南方地中海贫血高发的各省地贫基因频率有一定差异，预示绍兴地区人群的地中海贫血的基因类型及构成比有一定的特异性及复杂性，应加强产前诊断与地贫的遗传咨询，制定适宜本地区地中海贫血的人群预防计划。

口轮匝肌手术创伤后修复再生机制及 Wnt7a 干预疗效探究

李京桂[1] 石冰[2]
1.上海交通大学医学院附属第九人民医院
2.四川大学华西口腔医院

口轮匝肌环绕着口周，在维持鼻唇形态、表情形成和语音中发挥重要作用。唇裂手术治疗对口轮匝肌造成创伤，伤口愈合后肌肉组织内瘢痕形成和功能减退。
目的 本研究拟揭示口轮匝肌手术创伤后修复再生过程及机制，探讨 Wnt7a 在口轮匝肌损伤后修复再生中的干预效果。
方法 建立不同手术操作损伤的大鼠口轮匝肌模型，术后分次肌内注射重组人- Wnt7a，不同时间点收集肌肉，检测干细胞增殖、细胞比例、再生肌纤维、胶原纤维量等肌肉再生相关指标及炎症反应。
结果 口轮匝肌手术损伤后 FAPs 扩增程度及时长增加、胶原纤维沉积增多，卫星细胞增殖及融合随着损伤程度递增而抑制更明显，与组织内炎症程度有关。 Wnt7a 刺激了损伤口轮匝肌中卫星细胞扩增，使胚胎型肌纤维表达提前，并抑制了 FAPs 增殖及减少成纤维作用。
结论 口轮匝肌手术损伤修复过程中成肌作用受抑制，成纤维作用增强；Wnt7a 可以有效促进口轮匝肌损伤后修复再生。

成釉细胞源性肿瘤对放射治疗敏感性的临床观察及机制研究

孙强[1] 李紫璇[1] 郑宏雨[1,2] 王攀攀[1] 孙明磊[1] 赵军方[1] 陈万涛[3]
1.郑州大学第一附属医院 2.重庆医科大学附属第一医院
3.上海交通大学医学院附属第九人民医院

目的 观察成釉细胞源性肿瘤对放射治疗的临床敏感性，通过细胞实验研究成釉细胞瘤细胞对放射线敏感的机制。

方法 收集术后复发失去手术指证并经过放射治疗的成釉细胞源性肿瘤患者的基本资料和临床信息。以成釉细胞瘤细胞系 AM-1 为研究对象，分析 AM-1 对放疗的敏感性，以及放疗对细胞生物学行为的影响。
结果 6 例成釉细胞源性肿瘤患者接受了放射治疗，男性 4 例，女性 2 例。1 例患者达到部分缓解，1 例患者达到完全消失，4 例患者疾病无进展。放疗对 AM-1 细胞生长有抑制作用。4Gy 放疗后，细胞凋亡率高于 0Gy 组。4Gy 组经辐照后 72h，处于 S 期的细胞减少(P<0.05)，G1、G2/M 期的细胞增多(P<0.05)。细胞克隆形成能力也受到抑制。
结论 放射治疗成釉细胞源性肿瘤具有良好的临床治疗效果，并且在细胞学水平得到进一步证实，这为放疗的应用提供了实验依据。

中国一例 FLNA 基因突变致 TODPD 的病例报道及文献复习

胡艳秋 何学莲
华中科技大学同济医学院附属武汉儿童医院武汉儿童医院

目的 报道一例伴有色素沉着、虹膜缺失的末端骨性发育不良（TODPD）患儿的临床特征，并对 FLNA 基因突变所致的 TODPD 进行文献复习。
方法 收集一例 3.5 月大的指（趾）骨畸形的患者的临床资料，并进行全外显子家系测序以明确分子诊断，该患儿也进行了手指的 X 线及骨骼的病理检查，我们同时对相关文献进行复习。
结果 患儿双手指关节屈曲，中指及无名指尖出现多个石榴籽样结节，红色，质硬，右脚大拇指内测和左脚小拇指内测也均发现同样结节，约花生米大小，右眼角咖啡斑、散光、虹膜缺失，下牙床缺一小口，漏斗胸。患儿有宫内发育迟缓史。X 线示右手及左足发育畸形。手指骨骼病理检测提示骨骼终端发育不良，基因测序结果提示 FLNA（NM_001110556），c.5217G>A，关联 TODPD。通过查阅文献我们得知 TODPD 是一种 X 连锁显性男性致死性疾病，其特征是四肢骨骼发育不良，皮肤色素沉着，及女性患者婴儿期复发性手指纤维瘤。已有实验证明 FLNA 基因中的 c.5217G>A 突变可以激活一个隐蔽的剪接位点，导致外显子 31 最后 48 个核苷酸被剪切，丢失 16 个氨基酸（p.Val1724_Thr1739del）。除了 c.5217G>A 突变以外，在其他家系中也发现了 c.5850T>C，c.5686+84A>G，c.5814C>T 和 c.5217+5G>C，目前中国只报道过一例类似的病例。
结论 FLNA 基因突变是 TODPD 的主要致病基因，其中 c.5217（exon31）G>A 为突变热点。

Currarino syndrome 患者及其家庭成员的糖尿病患病情况调查研究

刘凌娅 姜茜
首都儿科研究所

目的 Currarino syndrome（CS）是一种以直肠肛门畸形、骶前肿物和骶骨畸形为主要表现的先天性综合征，研究证实 *MNX1* 基因杂合突变与 CS 的发生密切相关。该基因在胰腺 β 细胞的发育中有重要作用，纯合突变携带者多表现为新生儿期糖尿病。本研究拟对 CS 患者家庭成员的相关生化指标进行收集并分析其糖尿病患病及血糖异常升高情况。
方法 针对 2015-2020 年间确诊为 CS 的 13 位患儿及其家庭成员进行问卷调查。问卷由患儿父母填写，分别调查患儿本人、一级亲属及（外）祖父母既往确诊糖尿病或血糖异常升高情况。
结果 13 名患儿中 1 名曾检出空腹血糖受损（IFG）（空腹血糖 6.38），全部家庭均无患儿父母确诊糖尿病，3 名患儿的（外）祖父母曾确诊糖尿病（诊断年龄介于 55-67 岁之间）。总体 CS 患者中 IFG 发生率为 6.6%（1/15），未成年 CS 患者 IFG 发生率为 7.7%（1/13）。
结论 本研究中，未成年 CS 患者的 IFG 发生率为 7.7%，高于我国儿童 IFG 平均发生率（1.95%），提示对于 CS 确诊患儿应加强血糖监测。全部 13 名 CS 患儿的一级亲属未发现明确的糖尿病病史，提示胰岛 β 细胞功能可能与 MNX1 基因存在剂量依赖性关系，未来应进一步探究相关病理、生理机制。

CADASIL 患者合并自身免疫性脑炎 1 例并文献复习

黄惠清 蔡斌
福建医科大学附属第一医院

目的 常染色体显性遗传性脑动脉病伴皮质下梗死和白质脑病（Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy，CADASIL）是 NOTCH3 基因突变导致的最常见遗传性脑小血管病。CADASIL 合并自身免疫性脑炎鲜有报道。在此报道 1 例 CADASIL 合并自身免疫性脑炎。
方法 收集 1 例以“发作性肢体抽搐”为主要表现就诊我院的病例，收集其临床及颅脑影像学等资料。
结果 患者中年男性，4 年前反复发作性肢体抽搐伴意识不清，1 年余前就诊我院，查体未见阳性体征；血清学抗谷氨酸受体抗体 1:100 阳性，脑脊液抗谷氨酸受体抗体 IgG 强阳性，考虑“自身免疫性脑炎”。NOTCH3 基因检测到 R544C 突变，确诊 CADASIL。治疗后认知改善，未再发癫痫。出院 1 年余后，因“突发左侧肢体无力伴情绪易激惹 2 周”再次入院，查体双下肢足背以下浅感觉减退；血清抗谷氨酸受体抗体 1:10 阳性；脑脊液抗谷氨酸受体抗体 1:3.2 阳性，寡克隆蛋白阳性；MRI 示脑白质高信号延伸至外囊及颞极，予艾地苯醌、阿托伐他汀、奥氮平等治疗后，患者情感障碍较前好转。
结论 回顾文献发现部分 CADASIL 患者同时合并多发性硬化，亦有研究报道多个 R169C 突变者存在高滴度血清学 ANA 抗体，可见 CADASIL 患者合并免疫系统疾病并不罕见。为此，仍需进一步探索免疫机制是否为发病的始动因素之一，相关免疫指标能否成为本病的潜在标志物。

CADASIL 脑出血表型相关危险因素及影像特征研究

范梦婷 蔡斌 胡芳炜 黄惠清 谢玮杰 汤莹莹
福建医科大学附属第一医院

目的 脑出血为常染色体显性遗传性脑动脉病伴皮质下梗死和白质脑病（Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy，CADASIL）少见表型，本研究将总结合并脑出血的 CADASIL 患者的临床与影像特点，探讨 CADASIL 脑出血表型的相关危险因素及影像特征。
方法 收集 2014-2020 年就诊于我院，基因确诊 CADASIL 患者的信息，分为脑出血组与非脑出血组，进行组间临床及影像特征方面的比较。
结果
1．在 102 名患者中，有 30 人经病史及影像学检查确认为发生过脑出血，记录症状性及无症状性脑出血事件共 50 次。
2．比较脑出血组与非脑出血组临床特征，两组在高血压病患病率（73.3% VS 30.6%,P＜0.001）、R544C 突变占比（96.7% VS 58.3%,P＜0.001）、颞极受累率（23.3% VS 51.4%,P=0.009）方面有统计学差异；多因素逻辑回归分析提示 R544C 突变（OR=17.722,95%CI:1.911-164.315，P=0.011）、高血压病（OR=5.217,95%CI:1.736-15.680,P=0.003）与脑出血的发生独立相关。
3.比较脑出血组与非脑出血组影像特征，两组在脑叶微出血（83.3% VS 52.5%,P=0.013）、小脑微出血（62.5% VS 30.0%,P=0.011）、基底节微出血（75.0% VS 35.0%,P=0.002）、丘脑微出血（91.7% VS 60.0%,P=0.006）之间差异具有统计学意义。
结论
1.与高加索人群相比，本地区 CADASIL 患者脑出血发生率明显升高。
2. R544C 突变和高血压病为 CADASIL 患者发生脑出血的独立危险因素，发生脑出血的 CADASIL 患者脑叶、小脑、基底节、丘脑的微出血发生率更高。

395 例血红蛋白 Quong Sze 的血液学表型与基因型特征分析

钟泽艳 陈剑虹 官志扬 陈迪娜
惠州市第一妇幼保健院

目的 分析血红蛋白 Quong Sze（hemoglobin Quong Sze，Hb QS）携带者的血液学表型与基因型特征，从而指导临床工作。
方法 使用全自动血细胞分析仪和全自动毛细管电泳仪检测 Hb QS 携带者的血液学参数。采用导流杂交和液相芯片技术检测 77415 例外周血的 α 和 β 地中海贫血基因。对于筛查表型与基因型不符合的样本进一步行珠蛋白基因测序。
结果 395 例 Hb QS 中，检出 14 种基因型。340 例 Hb QS 杂合子几乎表现为 MCH 降低；12 例 Hb QS 复合 α^+-地贫时表现为轻型地贫；21 例 Hb QS 复合--^{SEA}/αα 时表现为 Hb H 病，临床症状轻重不一，重者需要输血，轻者仅为中度贫血；19 例 Hb QS 合并 β 地贫表现为 β 地贫特征；1 例 Hb QS-H 合并 β 地贫表现为 MCV 和 MCH 明显降低，不能电泳出 Hb H 波峰；2 例 Hb QS 纯合子表现为轻到中度贫血，Hb A_2 升高，表现为 β 地贫特征，测序结果阴性，为首次报道。
结论 Hb QS 携带者的基因类型多且临床表现存在特征性个体差异，重者需输血治疗，在遗传咨询和产前诊断上应给予重视，防止漏诊。

惠州地区亚甲基四氢叶酸还原酶基因多态性特征分析

钟泽艳 陈剑虹 陈迪娜
惠州市第一妇幼保健院

目的 调查惠州地区人群中亚甲基四氢叶酸还原酶（*MTHFR*）基因 C677T 位点多态性的分布特征，为个体化指导育龄妇女增补叶酸及降低新生儿出生缺陷率提供科学依据。
方法 2017 年 6 月至 2019 年 12 月，收集门诊就诊的育龄妇女、妊娠期夫妇的外周血样本 765 例。采用 PCR-荧光探针法检测 *MTHFR* 基因 C677T 位点的多态性，并与其他地区或种族人群的数据相比较。
结果 检出 *MTHFR* 基因 C677T 位点分布特征为 CC 野生型占 54.12%、CT 杂合突变型占 38.43% 和 TT 纯合突变型占 7.45%。根据年龄以 30 岁为分界点，将基因型和等位基因分为两组，两组均以野生型为主，依次为杂合突变型和纯合突变型。根据地区与种族差异分析，发现惠州地区分布特征与广东地区、中国南方汉族人群和东亚人群的基因型和等位基因相一致，但与赣南、遵义、云南、郑州、延安和苏州地区存在统计学差异（$P<0.05$），从南方到北方差异呈增大趋势。
结论 惠州地区 *MTHFR* 基因 C677T 位点的分布特征具有该地区与种族的特异性，该基因多态性的检测能够科学地指导叶酸的补充，达到优生优育。

PACS2 基因 c.625G>A 突变所致的发育和癫痫性脑病 66 型一例

张志丹[1] 段丽芬[2] 边成[1] 王晓辉[1] 黄小琴[1] 孙浩[1] 褚嘉祐[1] 杨昭庆[1]
1.中国医学科学院医学生物学研究所
2.昆明市儿童医院癫痫中心

目的 发育和癫痫性脑病 66 型（Developmental and epileptic encephalopathy 66，DEE66）是一种罕见的神经系统疾病，由 *PACS2* 基因突变所致，为常染色体显性遗传，目前报道较少，发病率也不清楚，主要临床表现为癫痫、面部畸形、小脑发育不全、全面发育迟缓等。本研究旨在探讨一例主要临床表现为癫痫、房间隔缺损的患儿的遗传学病因及临床特点。
方法 收集患者临床资料，利用全外显子组测序（whole exome sequencing, WES）筛选患儿的候选致病突变，并利用 sanger 测序对先证者及其父母进行突变位点验证，并分析 DEE66 的基因突变及临床特点。

结果 女性患儿 2 月龄，癫痫发作时脑电检测显示“多灶痫样放电”，颅脑 MRI 示双侧颞部脑外间隙增宽，心脏彩超示房间隔缺损，肝功检测显示肝损害。测序结果显示在患儿 *PACS2* 基因发现一个新发（De novo）杂合性点突变，导致 p.Glu209Lys 发生错义突变，降低了 *PACS2* 基因 FBR 结构域与客户蛋白（client protein）相互作用的能力，进而影响了细胞的功能。结合临床表型及基因检测结果，患儿诊断为发育和癫痫性脑病 66 型（DEE66）。国内外已有 20 余例该基因突变所致患者的报道，均以癫痫起病为特征，其中本研究肝损害为首次出现的表型。
结论 *PACS2* 基因的 c.625G>A 点突变是该患儿罹患 DEE66 的原因，该突变已被多次报道，本研究再次证明了该突变的致病性，并进一步补充了该病的临床表型。

LEOPARD 综合征的临床表现分析——以一例患者为例

吴昊 王旭东
上海交通大学医学院附属第九人民医院

目的 以一例临床患者为例，分析 LEOPARD 综合征的病因、临床表现及治疗方案。
方法 选取上海交通大学医学院附属第九人民医院口腔颅颌面科 LEOPARD 综合征患者一例，通过对其临床病史、照片、影像学资料等临床资料的采集，结合文献与相关医学知识，对 LEOPARD 综合征的临床表现与治疗方案进行总结。
结果 患者性别男，年龄 25 岁，体重 49kg。十余年前发现前牙呈地包天状态，逐渐加重，至成年时稳定。自诉约一岁出现听力损伤，未见听觉系统器质性病变；一周岁行手术治疗动脉导管未闭；十周岁行人工耳蜗植入术；曾行手术治疗隐睾。临床检查与 LEOPARD 经典表现一致：多发性着色斑、心电图传导性异常、眶距增宽、肺动脉狭窄、性功能异常、生长迟缓、神经性耳聋。诊断：LEOPARD 综合征，骨性 III 类错颌畸形，舌肥大。为常染色体显性遗传综合征，致病基因：PTPN11（7/12/13 号外显子）、RAF1（7/14/17 号外显子）、BRAF（6 号外显子），发病率低（尚未统计）。治疗计划：舌体减容术；正畸排齐整平去代偿协调上下牙弓；双颌手术纠正面型及咬合关系；术后正畸精细调节稳定咬合。本次行舌减容术。
结论 患者病史较为复杂且有全身多系统病史时，应考虑颅颌面综合征的可能，并做相应排查，制定多学科治疗方案。

一例少见的 PLS3 基因无义突变致 X-连锁青少年特发性骨质疏松的确诊过程、治疗与转归分析并文献复习

孙之星 李卓 马明圣 邱正庆
北京协和医院

目的 通过对一例 X-连锁、早期起病的特发性骨质疏松的诊治过程和文献复习，了解此类疾病的复杂性、综合评估的重要性以及唑来膦酸治疗的效果。
方法 回顾性分析 2020 年北京协和医院儿科收治的一例最终明确诊断为 *PLS3* 基因无义突变所致的 X-连锁青少年特发性骨质疏松的临床资料、诊断过程、治疗转归。以“*PLS3*”、“骨质疏松”为检索词，检索 Pubmed、CNKI 及万方数据库中建库至 2021 年 7 月报道的病例，结合文献复习总结本病的临床特点、影像学表现、治疗及预后。
结果 患儿男，9 岁，3 岁起病，反复肢体骨折、间断腰背不适。外院曾先后考虑为“外伤、幼年型类风湿关节炎”并予相应治疗。我院全脊柱正侧位片：脊柱椎体骨质密度明显减低，多发椎体形态不规则，不同程度压缩变扁，呈前楔状，T5-7、T9、L1 为著。站立位双下肢全长正位片：骨质结构未见异常。放射骨密度：L1-L4 0.534g/cm^2，符合骨质疏松。β-CTX：2.03ng/ml↑，总 25 羟维生素 D3 25.6ng/ml，24 小时尿钙、尿磷正常范围。甲状旁腺相关：PTH 14.8pg/ml(参考值：12-68)，pH 7.4 时校正游离钙 1.19mmol/L；性腺轴：睾酮 0.12ng/ml，卵泡刺激素 5.24IU/L，促黄体生成素 2.79IU/L；皮质醇相关：血总皮质醇 6.8μg/dl，ACTH：20.7pg/ml；肾小管功能相关：尿 α1、β2 微球蛋白均正常范围。考虑单基因病导致的骨质疏松，即青少年特发性骨质疏松可能性

大。全外显子组测序：X 染色体 *PLS3* 基因无义突变：c.1687C>T，p.Q563X，来自母亲。诊断特发性骨质疏松、重度骨质疏松、多椎体骨折。予佩戴支具，补钙、补 D 等治疗，并予唑来膦酸静脉输注 1 次，6 个月随访时腰背不适症状明显缓解，放射骨密度结果提升，胸腰椎 X 片示骨质疏松及椎体楔形变均有好转。检索到近 10 年全世界范围报道的确诊病例共 10 例，起病年龄 2~33 岁，临床表现以中轴骨骨质疏松、压缩性骨折为主，可伴或不伴有四肢骨骼受累，通常无骨骼系统以外的异常。该病可能与 *PLS3* 编码的一种钙依赖性肌动蛋白结合蛋白(plastin3)对肌动蛋白细胞骨架的异常调控有关。

结论 X-连锁的特发性骨质疏松较为少见，患者男性为主，通常起病早，主要累及中轴骨，血生化指标一般正常。如骨质疏松诊断明确，除外常见的继发因素后，需考虑单基因病导致的骨质疏松，即特发性骨质疏松可能。该病可予唑来膦酸治疗。

22 例鸟氨酸氨甲酰基转移酶缺乏症临床特征及基因突变分析

王明[1] 王冬娟[1] 余朝文[1] 何晓燕[1] 邹琳[1,2,3]
1.重庆医科大学附属儿童医院
2.上海市儿童医院/上海交通大学附属儿童医院
3.上海交通大学医学院儿童感染免疫与重症医学研究院

目的 鸟氨酸氨甲酰基转移酶缺乏症（OTCD）是由 *OTC* 基因突变引起鸟氨酸氨甲酰基转移酶（OTC）酶活性异常的常见尿素循环障碍疾病，其确诊是依靠基因检测。为了解该病的临床特征与基因变异的关系，，本研究回顾性分析了近年来院就诊的 OTCD 患儿临床信息及基因检测数据。

方法 收集 2013 年 1 月至 2021 年 5 月重庆医科大学附属儿童医院确诊为 OTCD 患儿病历资料，回顾性分析 OTCD 患儿发病诱因、临床表现、实验室检查、血氨基酸、尿有机酸及基因检测结果，结合生物学、遗传学和临床特征进行 OTC 基因突变致病性分析，分析基因突变与患儿临床特征的关系。

结果 所收集的 22 例 OTCD 患儿中，男 11 例，女 11 例，平均年龄 3 岁（2 月至 13 岁），均为晚发型 OTCD。22 例患儿中临床表现为 12 例呕吐，9 例意识障碍，4 例烦躁，4 例惊厥；实验室检查结果为 22 例血氨升高，22 例肝酶异常，21 例尿有机酸异常，7 例血瓜氨酸降低；共检测出 17 种 *OTC* 基因突变，查询数据库，发现其中 8 种为新突变，分别为：c.234A>G、c.457A>G、c.793T>G、c.865A>T、c.893G>T、c.78-2A>G、c.367-368delAG、和 c.717+1G>C；经生物学分析和遗传学分析，发现致病性突变 7 种（c.298+5G>C、c.367-368delAG、c.422G>A、c.717+1G>C、c.78-2A>G、c.830G>A 和 c.865A>T），疑似致病突变 6 种（c.119G>A、c.548A>G、c.613A>G、c.793T>G、c.829C>T 和 c.1028C>A），意义不明突变 4 种（c.234A>G、c.457A>G、c.506C>T 和 c.893G>T）。13 例患儿经对症治疗或肝移植后好转（基因突变分别为 c.367-368delAG、c.422G>A、c.422G>A、c.548A>G、c.613A>G、c.717+1G>C、c.78-2A>G、c.78-2A>G、c.829C>T、c.830G>A、c.830G>A、c.893G>T 和 c.1028C>A），4 例反复高氨血症发作待肝移植（基因突变分别为 c.119G>A、c.234A>G、c.793T>G 和 c.865A>T），5 例放弃治疗后死亡（基因突变分别为 c.298+5G>C、c.457A>G、c.506C>T、c.829C>T 和 c.829C>T）。

结论 OTCD 的基因检测可以明确诊断，不同的基因突变与其临床特征、治疗策略和预后等相关联。本研究亦发现 *OTC* 基因新发突变 8 种，需进一步明确各新发突变的致病性。

The clinical application of preimplantation genetic diagnosis for the patient affected by Usher syndrome and Hemoglobin H disease

Tizhen Yan Wugao Li Wenhong Ma Zhetao Li Yongmei Tang Ning Tang Zuxing Qin Dejian Yuan Li Fan Dingyuan Ceng
Liuzhou Maternity and Child Healthcare Hospital

Purpose To investigate the usefulness of preimplantation genetic diagnosis (PGD) for the patient affected by congenital Usher syndrome and Hemoglobin H (Hb H) disease.
Methods Multiple displacement amplification (MDA) was performed for whole genome amplification (WGA) of biopsied trophectoderm (TE) cells. Fluorescence PCR, reverse dot blot（RDB）, STR analysis combined with capillary electrophoresis technology and NGS-based SNP haplotyping was used to distinguish the two genotypes of $\alpha\alpha^{QS}/\alpha\alpha$ and $-^{SEA}/\alpha\alpha$ for PGD of Hb H disease. Direct mutation detection (*CDH23* c.2968G>T and c.1298delC) by Sanger sequencing and next-generation sequencing (NGS)-based single nucleotide polymorphism (SNP) haplotyping were used for Usher syndrome. Unaffected embryos were then subjected to whole-genome low-coverage sequencing and chromosome copy number analysis. Select non-pathogenic and euploid blastocysts for transplantation.
Results In this PGD cycle, fourteen MII oocytes were inseminated by ICSI with testicular spermatozoa. Ten blastocysts were utilized for TE cell biopsy on day 5 after ICSI. After PGD, HMJ-1 was carried $\alpha\alpha^{QS}/\alpha\alpha$ and c.1298delC, HMJ-2 was carried $-^{SEA}/\alpha\alpha$ and unaffected by Usher syndrome, HMJ-3 was affected by Hb H disease and carried c.1298delC, HMJ-4 was carried $\alpha\alpha^{QS}/\alpha\alpha$ and carried c.2968G>T, HMJ-5 was unaffected by Hb H disease and carried c.2968G>T, HMJ-6 was carried $\alpha\alpha^{QS}/\alpha\alpha$ and carried c.2968G>T, HMJ-7 was carried $-^{SEA}/\alpha\alpha$ and unaffected by Usher syndrome, HMJ-8 was carried $\alpha\alpha^{QS}/\alpha\alpha$ and c.1298delC, HMJ-9 was carried $--^{SEA}/\alpha\alpha$ and unaffected by Usher syndrome, HMJ-10 was carried $\alpha\alpha^{QS}/\alpha\alpha$ and c.1298delC. HMJ-1, HMJ-5 and HMJ-8 were unaffected euploid blastocyst.HMJ-5 was transferred into the uterus for the subsequent FET cycle. The accuracy of PGD was confirmed by amniocentesis at 18 weeks of gestation. A healthy boy weighing 3450 g was born by cesarean section at the 39th week of gestation.
Conclusions PGD is a valid screening tool for patients affected of Usher syndrome and Hb H disease to prevent transmission of these genetic diseases from parents to children.

Phelan-McDermid 综合征 5 例临床和遗传特点分析并文献复习

张显凯 何学莲
华中科技大学同济医学院附属武汉儿童医院

目的 探讨 SHANK3 基因杂合突变或 22q13.33 缺失导致的 Phelan-McDermid 综合征（PMS）的临床特点并进行文献复习。
方法 通过收集患儿临床资料，采集患儿及其父母的静脉血行家系全外显子测序和 CNV 检测以明确分子诊断，同时结合文献复习。
结果 5 例患儿 3 例为女性，2 例为男性，均表现为发育迟滞，其中 4 例存在语言缺失，1 例中度语言发育落后；此外，1 例有语言倒退和睡眠障碍，1 例有刻板动作和胼胝体发育不良，1 例伴有异常 EEG。基因检测结果提示 2 例为新发 SHANK3 基因移码突变（p.L1224Lfs*72 和 p.L1251Lfs*29），3 例为 22q13.33 区域缺失，其中 2 例新发的缺失范围包含 SHANK3 的 1-22 号外显子全部区域，1 例缺失范围包含 SHANK3 的 9-22 号外显子且该缺失遗传自智力低下的患儿母亲。PMS 是一种具有异质性的发育障碍疾病，临床表现包括新生儿肌张力低下，全面性发育迟滞，轻度到重度的语言障碍，自闭症行为以及部分病例伴有轻度畸形。SHANK3 基因的杂合突变或 22q13.33 区域的缺失破坏 SHANK3 基因导致 SHANK3 的单倍剂量不足，从而导致突触传递和形态学缺陷是 PMS 发生的分子机制。IGF-1 因子、锂剂以及基因治疗可能是治疗和缓解 PMS 症状的潜在方法。

结论 本文报道了 5 例由 SHANK3 基因杂合突变或 22q13.33 缺失导致的 PMS 的病例，患者或可从 IGF-1 因子、锂剂及基因治疗中获益。

两例 Menkes 病家系的临床表型及基因突变分析

杨昭庆[1] 张志丹[1] 段丽芬[2] 叶磊[2] 孙莹[2] 王晓辉[1] 孙浩[1] 褚嘉祐[1]
1.中国医学科学院&北京协和医学院医学生物学研究所
2.昆明市儿童医院

目的 Menkes 病（Menkes disease, MD）是一种罕见的由铜代谢障碍引起的进行性神经系统变性疾病，属于 X 连锁隐性遗传病，其发病率约为 1：100,000。该病由定位于 Xq21.1 的 *ATP7A* 基因突变所致，主要临床表现为结缔组织异常、精神运动发育迟缓、肌张力低下、癫痫、毛发异常、动脉迂曲、骨骼畸形等。本研究旨在探讨 2 例 Menkes 病患儿家系的临床表型及致病基因突变，明确病因。

方法 收集患者临床资料，提取 2 例无亲缘关系家系中患儿及其父母的基因组 DNA，并对两家系中先证者进行全外显子组测序（whole exome sequencing, WES），对候选致病突变进行生物信息学分析，并利用 sanger 测序对先证者及其父母进行突变位点的验证。

结果 2 例男性患儿临床表现有癫痫、毛发异常及颅脑 MRI 异常，均检出 X 染色体上 *ATP7A* 基因（NM_000052）突变，1 例先证者为 c.2938C>T（p.Arg980Ter）无义突变半合子; 另 1 例为 c.4127_4127delT（p. F1377LfsTer24）移码突变半合子，该突变国内外尚未见报道，在正常人群数据库中也未发现。两患儿的突变均来自母亲。根据美国医学遗传学与基因组学学会遗传突变分类标准与指南，*ATP7A* 基因 c.4127_4127delT 这一新发现突变被判定为可能的致病突变（（PVS1+PM2）。

结论 *ATP7A* 基因上的 c.2938C>T 和 c.4127_4127delT 突变分别是 2 例 Menkes 病患儿的致病原因，本研究进一步丰富了 Menkes 病的基因突变谱。

全外显子组测序诊断 CHARGE 综合征一例

黄盛文
贵州省人民医院

目的 应用全外显子组测序技术，筛查一名智力障碍患者的致病基因。

方法 先证者，男，6 岁。临床表现智力障碍，词不达意。母亲孕期正常，足月顺产，出生无窒息无缺氧。辅助检查提示：患者社会生活能力测试评定结果 8 分（轻度缺陷）。韦氏智力表显示与同年龄组相比，受检者视觉空间的跟踪和预见能力、视觉分析与鉴别能力较差；一般实用知识的掌握程度，语言理解能力，数概念及心算能力，抽象思维与逻辑推理能力，社会理解与适应能力，精神运动速度及协调性，视觉分析与辨别能力，视知觉的分析综合能力极差。构音运动：舌灵活度较差。在取得患者家属的书面知情同意后，采集先证者及父母外周血并提取 DNA，进行全外显子组测序，结果再用 Sanger 测序验证。

结果 发生先证者 *CHD7* 基因 NM_017780.3: c.7013A>T: p.Q2338L 杂合突变，父亲和母亲均未发生突变，为自发突变。*CHD7* 基因突变可导致常染色体显性遗传疾病 CHARGE 综合征。该突变在“神州基因组数据库”、人类外显子数据库(ExAC)、参考人群千人基因组(1000G)和人群基因组突变频率数据库(gnomAD)中没有发现，也未见国内外文献报道。根据 ACMG 遗传变异分类指南，该突变致病等级为可能致病。结合临床表现，该患者符合 CHARGE 综合征诊断。

结论 经全外显子组测序及 Sanger 测序验证，鉴定患者为 *CHD7* 基因 NM_017780.3: c.7013A>T 杂合突变所致 CHARGE 综合征，丰富了中国人群 *CHD7* 基因突变谱。

一个Ⅰ型神经纤维瘤家系致病基因突变分析

李建伟 周永安
山西医科大学第二医院

目的 对一个Ⅰ型神经纤维瘤家系进行基因检测分析，探讨其分子学病因。
方法 采集先证者及其家系成员的外周血标本，应用全外显子测序（Whole-exome sequencing，WES）技术对先证者进行变异筛查，发现可疑的致病突变位点后，对家系中所有成员和 100 名正常对照进行 Sanger 测序验证，确定该家系的致病突变。
结果 测序结果显示先证者 NF1 基因存在致病突变 c.888+1G>A，其表型正常的父母并未检测到该突变。
结论 NF1 基因 c.888+1G>A 突变是该患者的致病原因，且其为 de novo 突变，该位点国内未见相关报道。

A case of SURF1 gene mutation caused Leigh syndrome

Chunmei Wang Yucai Chen
Children's Hospital of Shanghai

Background and purpose The protein encoded by the SURF1 gene is located in the inner mitochondrial membrane and participates in the biosynthesis of the cytochrome c oxidase complex. The most common cause of Leigh syndrome related to cytochrome c oxidase is defects in the SURF1 gene. Through the analysis of the SURF1 gene, we can gain a better understanding of the pathogenesis of Leigh syndrome.
Materials and methods We analysed the clinical features of a female Han Chinese patient with Leigh syndrome. We collected venous blood from the patient and her parents for whole-exome analysis, including real-time quantitative polymerase chain reaction analysis of SURF1 gene expression and intron sequencing.
Results Whole-exome sequencing identified two variants in the SURF1 gene, c.754_755del and c.515+3G>C, in a compound heterozygous state in the female patient with Leigh syndrome. The c.754_755del variant was predicted to lead to a truncated protein with a frameshift (p.Ser252Hisfs*39) mutation and C-terminal loss. Multiple splicing prediction tools predicted that the c.515+3G>C variant would have significantly decreased strength of the exon 5 splicing donor. Further analysis revealed that the intronic variant caused skipping of exon 5, resulting in a shorter protein lacking 64 amino acids. Furthermore, a quantitative analysis indicated that the patient's SURF1 mRNA expression was significantly lower than that of the parents, which might have resulted from nonsense-mediated mRNA decay.
Conclusion In this study, we found a new pathogenic variant in an intron of the *SURF1* gene: c.515+3G>C. We predicted the changes in protein three-dimensional structure caused by the intron variant. The results further enriched the understanding of the genetics of human Leigh syndrome.

Whole-exome sequencing identifies a novel nonsense mutation in EXT1 in a Chinese family with hereditary multiple exostoses

Jianwei li Yongan Zhou
Second hospital of shanxi medical university

Background Hereditary multiple exostoses (HME；OMIM：133700) is an autosomal dominant skeletal disorder characterized by the formation of multiple benign cartilage-capped tumor.HME is generally thought to be associated with pathogenic mutations in the EXT gene family.Besides

suffering complications caused by the pressure of these exostoses on the surrounding tissues, HME patients are at an increased risk for malignant chondrosarcoma.
Objective and Methods The aim of our study was to reveal a possible pathogenic mutation through the investigation of a Chinese family with HME with whole-exome sequencing method.The sequencing results were analyzed by bioinformatics and validated by Sanger sequencing in family members.
Results We identified a novel heterozygous nonsense mutation c.1258G>T(p.E420X) in the EXT1 gene 4 exon exclusively in proband,which introduced the termination codon,results in the truncation of 326 amino acids at the C-terminus of the wild EXT1 protein consisting of 746 amino acids.The lossing portion include the glycosyltransferase domain.Meanwhile,the mutation was not found in other HME members of this familiy,which consistenting with cosegregation genotypes and phenotypes.
Conclusions Thus,the present study identified a novel pathogenic EXT1 mutation in a family with HME , which provides additional evidence for developing quick and accurate genetic tools for HME diagnosis and further enrich the mutation spectrum of HME.

一例 SPAST 基因新突变位点相关的家系报道

江君宜 袁茹莹 邱煜森 林翔
福建医科大学附属第一医院

目的 遗传性痉挛性截瘫（HSP）是一类主要累及皮质脊髓束的遗传性神经退行性疾病，主要以双下肢肌张力进行性增高、腱反射亢进和剪刀步态为特征，具有高度的临床和遗传异质性。目前已明确的致病基因共 83 种，其中 *SPAST* 基因突变所致的遗传性痉挛性截瘫 4 型（SPG4）为最常见的亚型。我们报道了 1 例 *SPAST* 基因新突变位点 c.1047G>C 家系，扩展了 SPG4 的突变谱。
方法 针对一个临床诊断为遗传性痉挛性截瘫的常染色体显性遗传家系，采集先证者及其亲属的外周血样本提取 DNA，先利用 Sanger 测序技术筛选先证者 *SPAST*、*ATL1*、*REEP1* 三个常见显性致病基因的外显子的突变位点，再对其亲属相同的突变位点进行家系共分离验证。
结果 先证者为一名 52 岁的女性患者，主要临床表现为双下肢无力僵硬 10 余年。既往有无特殊病史。育有 4 名子女，小儿子出现类似临床表现，而其余三名孩子均无异常。查体：痉挛步态，双下肢肌张力增高，四肢肌力 5 级，Babinski 征、Chaddokc 征（+），双上肢腱反射（+++），双下肢腱反射（++++），双侧踝阵挛（+），深感觉、浅感觉、复合觉均正常，无明显共济失调体征，轮椅助行。Sanger 测序结果发现先证者 *SPAST* 基因上均出现 c.1047G>C 突变，通过预测软件对突变位点进行保守性及致病性预测，提示该位点高度保守，且因导致错义突变而致病。后续的共分离验证也证实了仅有症状的小儿子具有该突变位点，而其余子女均正常，符合家系共分离。
结论 本例患者通过 sanger 测序发现 *SPAST* 基因上 c.1047G>C 这一点突变，通过生物信息学功能预测、物种间保守性分析以及家系共分离验证，推测该家系患者的临床表现由该致病基因所致，数据库中未见报道。

额外小标记染色体病例两例及回顾分析

苗晨 张欣文
西安市人民医院（西安市第四医院）

目的 对两例患者携带的额外小标记染色体（small Supernumerary Marker Chromosomes, sSMC）进行了遗传学分析，讨论不同 sSMC 所引起的不同临床表现，为遗传咨询提供参考。
方法 外周血染色体核型分析（G 显带法）及外周血基因组拷贝数变异测序分析（Copy Number Variation sequencing, CNV-seq）。
结果 病例 1 核型为 46,XY[40]/47,XY,+mar[60]，家系验证为新发变异，CNV-seq 提示 sSMC 来自 8p12p11.1，患者现两岁半，主要表现为语言发育迟缓；病例 2 核型为 47,XY,+mar，CNV-seq 未发现拷贝数变异，患者不育，伴有严重少弱畸精子症。

讨论 不同患者携带的 sSMC 在临床上的影响是迥异的，我们的病例提示，当 sSMC 包含染色体片段 8p12p11.1 时，会造成发育迟缓，另外，有些 sSMC 即使未检测到拷贝数变异，也可能导致一定的临床症状如精子发育异常，引发男性不育，我们应该重视 sSMC 的功能，利用细胞遗传学和分子遗传学的方法有效诊断相关疾病，明确基因型与临床表型的关系。

CRISPR/Cas9 介导基因敲入的研究进展

江君宜 洪舜彦 郑基坛 陈海珠 林翔
福建医科大学附属第一医院

目的 CRISPR/Cas 9 介导的基因编辑技术继续推动着生命科学的重大进步，该技术极大地促进了基因突变细胞以及组织的原位修复。自问世以来，CRISPR/Cas 9 技术已被广泛应用于外源 DNA 靶向敲入（KI）基因组。然而，通过同源重组（HR）实现精准基因敲入的效率是较低的。至今，已经开发了多种新型的策略来提高靶细胞的基因敲入效率，本文回顾这些新策略以试图指导基因敲入策略的选择。
方法 通过在 pubmed 网站上搜索基因敲入、同源重组、CRISPR 等关键词进行搜索，整理相关文献的报道进行汇总。
结果 与基于非同源末端连接（NMEJ）或微同源介导的末端连接（MMEJ）的策略相比，同源介导的末端连接（HMEJ）表现出更高的编辑效率和更佳的保真度。然而，线性化双链 DNA-CRISPR 靶向整合（Tild-CRISPR）系统相较上述策略具有更明显的优势，同为利用双链 DNA 作为供体，Tild-CRISPR 转基因运用体外供体质粒分离的方式，跳过细胞体内释放的过程，在小鼠胚胎中可以实现更高的 KI 效率。相反，Easi-CRISPR 系统采用单链 DNA 作为供体。该系统已经分别在小鼠胚胎或人类 iPS 细胞中获得了较高的 KI 效率，当获得较低的 KI 效率时，还可适当补充小分子物质治疗来提高靶向整合的效率。但是，由于逆转录酶的限制，供体的大小只能限制在 1-2kb，而且相关的 RNA 聚合酶和逆转录酶缺乏校对能力，可能会导致供体出错。
结论 总之，在进行基因敲入时，需要根据不同策略的特点进行选择。在挑选策略时，目标细胞或目标基因的 KI 效率、策略的简易性和周期以及所致的连接误差和脱靶等标准都应该成为参考的依据。简而言之，考虑到不同的判定标准，目前，Tild-CRISPR 和 Easi-CRISPR 策略在各方面的表现更为突出。

GRIN2A 罕见突变导致癫痫相关性疾病致病机制的研究进展

黄雪晶 王柠 陈万金
福建医科大学附属第一医院

目的 N-methyl-D-aspartate receptors(NMDAR)是谷氨酸门控的钙离子 通道，在神经系统发育过程中发挥重要的生理作用，如调节神经元的存活,树突、 轴突结构发育及参与突触可塑性的形成。目前，编码 N-methyl-D-aspartate receptors(NMDAR)的亚单位的 *GRIN2A* 已被列为局灶性癫痫伴语言障碍 (OMIM:#245570)的致病基因，同时也与早发性癫痫性脑病，癫痫-失语综合征， 罗兰性癫痫等一系列癫痫谱系疾病密切相关。GRIN2A 基因罕见突变引起 NMDAR 功能障碍的机制在近年来受到很大程度上的关注。因此，本文旨在探讨 总结由 GRIN2A 罕见突变导致癫痫相关性脑病的致病机制。
方法及材料 通过查阅国内外与 GRIN2A 突变和癫痫性相关疾病的相关论著 和综述，对其致病机制进行总结。
结果 由于 GRIN2A 突变位点所处结构域位置的不同，致病机制可主要归纳 为：1）位于 N 端（N-terminal domain ， NTD)上的突变，如 Lemke 等报道 的 p.A243V 主要以影响 NMDAR 对内源性负调控因子 Zn^{2+}, proton 的敏感性， 而对 glutamate 和 glycine 亲和力和电流幅度、相对开放状态概率保持不变；2） 位于配体结合域（Agonist binding Domain， ABD)的罕见突变，如 p.D731N 的突变破坏了 Glu2A 与 glutamate 的结合位点，从而导致 NMDAR 对 glutamate 亲和力下降超过

3000 倍，同时降低通道开放频率并且缩短突触样响应时间；3） 位于 ABD 及跨膜结构域（transmembrane domain，TBD）之间的 Link 以及 TMD 上的突变，如 p.A643D 和 p.M817V 突变增加了对 glutamate 和 Glycine 受体激动剂的效力,降低对包括 proton、Mg^{2+}和 Zn^{2+}的内源性负调控因子的敏 感性，增加单通道平均开放时间和增加通道开放概率。4）位于 C 端结构域 （C-terminal domain，CTD)上的罕见突变主要影响蛋白质翻译后修饰途径，p. S1459G 破坏了 CaMKIIa 在 S1459 位点的磷酸化，使得与 SNX27 和 PSD-95 的相互作用中出现障碍，导致了 NMDA 受体运输缺陷,树突棘密度降低和兴奋性 突触传递减少。

结论 通过对 *GRIN2A* 突变以不同的方式影响受体的表达和功能，从而导致癫 痫相关性疾病的致病机制进行探究总结，这将促进 NMDAR 通道疾病的精确治疗干预的发展。

染色体 16q23.2 区域部分纯合缺失致巨轴索性神经病一例

王丽[1,2] 段丽芬[3] 边成[2] 王晓辉[2] 黄小琴[2] 褚嘉祐[2] 杨昭庆[2]
1.昆明医科大学
2.中国医学科学院北京协和医学院医学生物学研究所医学遗传学研究室
3.昆明市儿童医院癫痫中心

目的 巨轴索性神经病（Giant axonal neuropathy，GAN）是一种罕见的常染色体隐性遗传性疾病，由 GAN 基因发生突变或缺失而引起。多于儿童早期起病，主要临床表现包括下肢步态障碍、远端运动无力、共济失调等，可累及周围神经系统及中枢神经系统。我们收集到诊断为巨轴索性神经病的患儿一例，对其致病原因进行分析，旨在为患儿的疾病诊断以及遗传咨询提供依据。

方法 获取先证者及其父母外周血，采用高精度临床外显子组测序（whole exome sequencing, WES）检测，拷贝数变异和 SNP 筛查致病基因变异，并进行实时荧光定量 PCR 检测目标区域基因拷贝数变异。

结果 男性患儿，7 岁 6 月龄，因“发现步态异常 5 年余”入院，头围 55cm，步态异常呈“鸭步”，早期曾有癫痫发作等表现。神经传导检查提示四肢广泛性受检周围神经运动、感觉传导功能异常；拷贝数变异与 SNP 分析发现患儿染色体 16q23.2 区域发生约 115.8kb 的纯合性片段缺失，结合临床表现，该患儿诊断为巨轴索性神经病。该纯合缺失变异分别来自先证者父亲与母亲，患儿父母表型为该片段缺失的杂合子，表型均未见异常，表明该片段缺失呈现隐性遗传模式。

结论 GAN 基因纯合缺失很可能为该患儿巨轴索性神经病的致病原因，基因检测遗传分析有助于提供该病的诊断依据和遗传咨询。

类器官在神经遗传病治疗研究中的应用

林翔 叶子凌 江君宜 陈海珠 陈万金
福建医科大学附属第一医院

背景 类器官是来源于干细胞自我有序分化形成的一种 Ex vivo 模型，能较好的模拟疾病的表型，已被广泛用于多种神经退行性疾病的机制和治疗研究。然而，中枢神经系统类器官的研究多集中脑类器官的构建，包括形成前脑、中脑、海马等。但是，关于脊髓类器官的模型构建尚无系统研究报道。

材料与方法 以健康对照的诱导性多能干细胞（iPS）为模型，遵循鼠、鸡在体胚胎的发育规律，以神经中胚层干细胞（NMP）为分化起源，诱导获得腰段脊髓前角类器官。

结果 在对健康对照 iPS 细胞进行 FGF2（10ng/ml）、CHIR99021（5μM）以及 RA（0.1μM）小分子联合干预 3 天后，可形成表达 SOX2 以及 BRACHYURY 的神经中胚层干细胞。随后，再引入尾化和神经化的小分子化合物 FGF8（100ng/ml）和 Heparin(100ng/ml)后可形成表达 HOXC10 的腰段脊髓。进一步，联合 GDF11（100ng/ml），以及 Matrigel 提供的细胞外基质成分，在腹侧化的小分子化合物 RA（0.1μM）与 SAG（0.50μM）作用下，连续培养过程，可依次表达运动神经元前体细胞标志物 OLIG2、运动神经元标志物 ISLET1 以及成熟运动神经元标志物 ChAT。重要的

是，这种分化方式形成的脊髓运动神经元与单细胞层诱导的脊髓神经元有明显不同，后者无法表达HOXC10。
结论 3 维方式诱导脊髓前角类器官更倾向尾段脊髓特征。这种模型可用于脊髓性肌萎缩症疾病的机制研究，为治疗提供靶点。

WSF1 基因突变——Ala716Thr 致聋家系的基因型及临床表型分析

韦笑宝
柳州市妇幼保健院

目的 研究低频感音神经性耳聋（low-frequency sensorineural hearing loss, LFSNHL）家系的临床特点及其分子遗传学病因，为家系遗传咨询提供依据。
方法 对先证者及其家系成员进行详细的临床检查，完善家族病史信息；采集家系成员的外周血，利用高通量测序技术和 Sanger 测序对此 LFSNHL 家系中的 25 名成员进行检测。
结果 此 LFSNHL 家系中检测出 16 名成员均携带 *WFS1* 基因 c.2146G>A (p.A716T)杂合突变，表现为严重程度不等的低频感音神经性耳聋，Sanger 测序确认该突变与家系耳聋表型共分离，符合常染色体显性遗传特征。
结论 本研究中 LFSNHL 中国家系的致病原因为 *WFS1* 基因 c.2146G>A (p.A716T)杂合突变。与 *WFS1* 基因其他致病位点多导致 Wolfram 综合征不同，该致病突变在中国主要表现为非综合征型 LFSNHL。

一个中国 Hb Stockholm 家系的分子诊断及遗传学分析

袁军鸿[1,2] 杨昭庆[2] 葛世军[3] 易薇[3] 番云华[3] 杨必清[3] 褚嘉祐[2]
1.昆明医科大学
2.中国医学科学院医学生物学研究所
3.云南德宏傣族景颇族自治州人民医院检验科

目的 Hb Stockholm 是一种罕见的异常血红蛋白病，是由 *HBB* 基因 β 链上的一个错义突变（*HBB*:c.24G>T）所导致的，无明显的临床表型。本文对一个 Hb Stockholm 家系进行分子诊断，检测相关变异基因位点，确定其 β 珠蛋白基因簇单倍型并进行遗传学分析。
方法 采用全血细胞计数和毛细管血红蛋白电泳检测血常规指标及异常血红蛋白，并采用 PCR-Sanger 测序检测 *HBB* 基因上的罕见突变位点，通过聚合酶链反应-限制性片段长度多态性（PCR-RFLP）方法进行突变位点的单倍型分析。
结果 先证者的血常规检测指标未见异常，在 *HBB* 基因上检测到错义杂合突变（*HBB*:c.24G>T），血红蛋白毛细管电泳检测出 Z10 电泳区具有异常电泳条带 HbX。通过核心家系分析，先证者 β 珠蛋白基因簇单倍型为（-++++--/+------），突变位点关联的单倍型为（+------）；先证者母亲的血常规检测正常，在 *HBB* 基因上检测到相同的错义杂合突变（*HBB*:c.24G>T），血红蛋白电泳检测出 Z10 异常电泳区带 HbX；先证者父亲的血常规检测及血红蛋白电泳检测结果均正常，在 *HBB* 基因上未检测到异常突变；
结论 本研究发现并鉴定了一个 Hb Stockholm 家系中的基因突变，首次证实了该异常血红蛋白病突变在中国人中的存在，丰富了中国人群中血红蛋白病的基因突变谱和临床表型谱，为该疾病的诊断及遗传咨询等提供了依据，并为该突变的起源提供了线索。

GJB1 基因突变导致 X 连锁显性腓骨肌萎缩症的家系临床表型及基因型分析

韦笑宝
柳州市妇幼保健院

目的 分析 X 连锁显性腓骨肌萎缩症（X-linked Charcot-Marie-Tooth disease, CMTX）家系的临床特征及其致病基因，总结该致病位点的临床表型特点，为该家系遗传咨询提供依据。
方法 对该家系成员进行详细的病史询问及临床体格检查；抽取部分家系成员静脉外周血，利用高通量测序技术进行全外显子检测，并应用 Sanger 测序对此 CMTX1 家系中的 19 名成员进行验证。
结果 该 CMTX 家系为伴 X 染色体显性遗传。先证者表现为进行性腓骨肌萎缩无力；分子遗传学结果显示该家系中 5 人存在 *GJB1* 基因 c.103 G>A (p. V35M) 突变，该错义突变与表型共分离。
结论 *GJB1* 基因 c.103 G>A (p. V35M) 突变为该 CMTX 家系致病原因，此疾病具有不完全外显性。

Wiedemann-Rautenstrauch 综合征一例并文献学习

何子君
北京儿童医院

Wiedemann-Rautenstrauch 综合征（WDRTS，OMIM #264090）是一种罕见的常染色体隐性遗传病（AR），其特征是宫内生长迟缓、发育停滞、身材矮小、早衰面容、低血糖和不同程度的精神障碍。本文报道了一例以生长发育缓慢、发现阴茎、睾丸小为主要表现的 WDRTS。结合患儿临床资料、辅助检查及基因测序结果进行分析，总结 WDRTS 的临床、遗传学特征。此外,本例患儿基因测序检测出 POLR3A 复杂杂合突变：c.3595-32C＞T 剪切变异，c.3467C＞G 错义变异。

成骨不全症伴心脏瓣膜病变一例

梅亚墨 张浩
上海市第六人民医院

目的 心脏瓣膜病变是成骨不全症十分罕见的临床表现。本研究通过分析一例成骨不全症伴心脏瓣膜病变患者的临床表现特点，以期丰富成骨不全症的临床表型谱。
方法 完善相关检查，同时抽取其外周血，抽提基因组 DNA 进行基因检测。
结果 患者，女，36 岁。因“自幼多发脆性骨折史”，于 2021 年 7 月来我科就诊。患者自幼多发多处脆性骨折，包括左侧肘关节、左侧趾骨等处。2020 年 10 月外院就诊，诊断为“骨质疏松症”，予以 5mg 唑来膦酸静滴。家族中外婆、母亲、舅舅、姨妈等人均有相似病史。患者 15 年前因先天性主动脉瓣缺损行瓣膜置换术。查体可见巩膜蓝色，左侧肘关节内翻畸形，心脏听诊主动脉瓣区可听到机械瓣心音。心超示主动脉瓣人工瓣置换术后，各房室大小正常范围。查骨密度示腰椎：Z -1.0SD；股骨颈: Z -0.1SD。基因检测示 COL1A1 的 2 号外显子处发生杂合无义突变，导致 p.Glu90*。
结论 虽然心脏瓣膜病变在成骨不全症中极为罕见，但若合并严重心脏瓣膜病变，则需要行瓣膜成形术或人工瓣膜置换术。临床医生在接诊成骨不全症患者时，需注意其是否合并心脏瓣膜病变。同时，成骨不全症患者行心外科手术时，需谨慎该类患者毛细血管脆性增加、易出血等问题。

染色体核型分析和 AZF 检测在男性不育中的应用

张凤[1] 杨晓玉[2]
1.南京医科大学康本医学检验所
2.江苏省人民医院生殖中心

目的 染色体数目异常和结构异常都可能会导致精子发生异常。Y 染色体长臂上存在控制睾丸发育，精子发生及维持的区域，称为 AZF，AZF 由 AZFa、AZFb 和 AZFc 三个区域构成，AZF 微缺失可导致 NOA 和少精子症，继而引起男性不育。通过分析染色体核型和 AZF 微缺失检测，探讨在男性不育中的应用。
方法 通过对 2017 年 1 月至 2020 年 6 月在南京医科大学第一附属医院生殖医学科就诊的 1899 例少精子症和非梗阻性无精子症男性不育症患者，进行外周血染色体核型分析和 AZF 微缺失检测。
结果 1899 例男性不育症患者检出 225 例染色体核型异常，染色体核型异常率为 11.85%，其中数目异常 100 例（44.44%），结构异常 76 例（33.78%），嵌合体 10 例（4.44%），多态性 18 例（8.00%）；46，XX 性发育异常 21 例（9.33%）。异常染色体核型具体分布见表 1。225 例异常染色体核型病例临床表现为无精子症的有 156 例（69.33%），少精子症的有 69 例（30.67%）。异常核型占比最多的是 47，XXY，共检出 94 例，占 41.78%；其次为 46，XX 核型，检出 21 例，占 9.33%。；AZF 微缺失 215 例，异常率为 11.32%，发生缺失区域最高为 AZFc 区 149 例，缺失率为 69.30%；其次为 AZF b+c 区缺失 25 例，缺失率为 11.63%；AZFa+b+c 区缺失 21 例，缺失率为 9.77%。
结论 通过染色体核型分析和 AZF 微缺失检测二者结合，应用于临床寻找男性不育症的病因，可以提供更加明确的遗传学诊断。

强直性脊柱炎相关的血液来源的 DNA 甲基化表观遗传学标记

肖敏 古洁若
中山大学附属第三医院

目的 大部分（约 90%）强直性脊柱炎的遗传易感位点都位于非编码区域，其功能尚未明确。表观遗传学修饰可以影响基因的表达，并解释一部分“丢失”的遗传度。本研究的目的为发现新的强直性脊柱炎相关的 DNA 甲基化位点，并探索其潜在的发病机制。
方法 纳入 40 例 AS 患者和 20 例健康对照，使用 Infinium® MethylationEPIC 芯片对血液样本进行全基因组 DNA 甲基化检测，并用 R 包 ChAMP 进行分析。
结果 全基因组甲基化分析识别 4794 个差异甲基化位点（DMP），包括 3294（68.7%）个在 AS 中高甲基化和 1500（31.3%）个低甲基化位点（图 A）。DMPs 在 PCA 和非监督聚类上明显的区分患者和对照（图 B 和 C）。KEGG 通路分析显示 DMPs 富集在 T 细胞受体信号通路，TH1 和 TH2 细胞分化通路上。同时，有 1048 个差异变异位点（DVP）被鉴别，其中大部分位点（974，2.9%）在 AS 中变异度升高，这与在其他研究中的观察一致，提示 AS 患者中存在内在的异质性，这可能受到多种因素的影响，例如疾病活动度和治疗等。
结论 AS 患者外周血单个核细胞出现异常的 DNA 甲基化组和升高的 DNA 甲基化变异度，这些结果加强了我们对 DNA 甲基化参与 AS 发病的理解，并可能作为新的治疗靶点。

苏北地区新生儿耳聋基因联合听力筛查及随访研究

孙玉华 王雷雷
连云港市妇幼保健院

目的 分析苏北地区新生儿听力与耳聋基因联合筛查结果，根据听力和突变情况以及随访结果，为早期发现与防治迟发性耳聋和药物性耳聋提供依据。
方法 研究对象为 2018 年 7 月-2020 年 12 月在连云港市妇幼保健院出生的新生儿 7197 例，对其进行听力筛查和遗传性耳聋基因 GJB2、SLC26A4、GJB3 和线粒体 DNA，4 个基因共 13 个位点的筛查，并对筛查阳性新生儿进行 1 月、2 月、3 月龄的随访调查，分析新生儿听力筛查结果、阳性检出率、随访效果。
结果 7197 例新生儿中，听力筛查未通过者占 0.306%（22/7197），耳聋基因总体阳性检出率 5.377%（387/7197），显著高于听力筛查检出率。其中 GJB2 基因最高，为 3.112%(224/7197)，其次由高到低分别为 SLC26A4 基因 1.904%(137/7197)、GJB3 基因 0.222%(16/7197)、线粒体 DNA 基因 0.181%(13/7197)及双基因杂合突变 0.069%（5/7197）。387 例中，5 例有家族史，随访率达到 99.2%（384/387）。
结论 苏北地区新生儿耳聋基因具有较高的携带率，听力筛查通过的耳聋基因携带者也可能出现迟发性耳聋，新生儿遗传性耳聋基因筛查对临床实践中听力障碍的早期诊断、干预和遗传咨询具有重要意义。

Efficient Genomic Correction of Mutations in Compound alpha- and beta- Thalassemia Major iPSCs Using CRISPR/Cas9 System

Hongyan Yi[1,2]
1.Department of Reproductive Medicine, The First Affiliated Hospital of Hainan Medical University, Hainan Medical University
2.Hainan Provincial Key Laboratory for human reproductive medicine and Genetic Research, The First Affiliated Hospital of Hainan Medical University, Hainan Medical University

Objective To repair the β41-42 (-TCTT) and Westmead of complex thalassaemia major gene mutation iPSCs(CAC→CAG) mutation. To identify the pluripotency and the hematopoietic function of iPSCs after the repair of the compound thalassaemia major gene mutation.
Methods In this study, β41-42/β41-42&ααws/αα_iPS derived from amniotic fluid cells were selected as the experimental objects. Firstly, β-sgRNA was designed at about 600bp downstream of the third exon of HBB gene and α2-sgRNA was designed at about 200bp downstream of the third exon of HBA2 gene, Then the constructed plasmids were transfer to 293T cells respectively through calcium transfer method. After transfection， fluorescence microscope observation and flow analysis were used to identify the cleavage activity of β/α2-sgRNA. Secondly, we amplified the first 2kb and the last 1.5Kb of the β-sgRNA targeting site from the normal genome as the left and right homology arms (LA/RA) to construct the HBB-Donor, and the first 800bp and the last 700bp of the sgRNA targeting site from the the normal genome was amplified to construct HBA2-Donor. Finally, we transferred the linearized HBB-Donor and HBB-sgRNA into iPSCs, the sgRNA recognizes the cleavage site and causes DNA damage to induce homologous recombination. After resistance screening, PCR identification and sequencing, βN/βN&ααws/αα_corrected iPSCs are obtained, which we then amplified and transferred linearized HBA2-Donor and HBA2-sgRNA into the cells. Then the final βN/βN&αα/αα_corrected iPSCs was obtained after resistance screening, PCR identification and sequencing. Through teratoma experiments, karyotype analysis, qRT-PCR identification of pluripotency genes OCT4, SOX2, NANOG, and hematopoietic differentiation and colony formation experiments, the function of the repaired iPSCs was further identified.
Results The sequencing after genetic correction showed high efficiency for mutation correction. Hematopoietic lineage differentiation potential was rescued, while the expression of stem cell

markers, genetic stability, and teratoblastoma formation of iPSCs did not show any change after mutation corrected.
Conclusion In our study, we used amniotic fluid-derived iPSCs from patients with complex thalassaemia major as the experimental object, usingThe CRISPR/Cas9 system successfully repaired the β41-42 mutation and Westmead mutation. The repaired cells still maintain pluripotency and the hematopoietic function is significantly improved. Therefore, We demonstrated that iPSCs and CRISPR/Cas9 system can be used as an useful strategy for various thalassemia treatment, even in the case of complex combination of HBB and HBA mutations in the future.

25144 例婚前孕前人群地中海基因检测结果分析

屈艳霞 左连东 马毅敏
广州市妇女儿童医疗中心

目的 了解广州地区婚前和孕前人群地中海贫血的基因突变类型和构成比,并对其防控效果进行探讨。
方法 选取 2020 年参加广州市免费婚前和孕前优生健康检查项目中血细胞检测初筛阳性夫妇 12572 对,进行血红蛋白电泳及基因检测。随访高风险家庭至孕后,并追踪其产前诊断结果。
结果 ①经基因确诊地中海贫血携带者 10 209 例,其中 α-为 7 026 例,β-为 2 805 例,αβ 复合型为 378 例。②α-地中海贫血基因以缺失型为主,基因型以--SEA/αα 为主,占 64.59%,β-地中海贫血基因型以 CD41-42/N 为主,占 38.97%。③在 αβ 复合型地中海贫血携带者中共检出 46 种基因型,以--SEA/αα 和 CD41-42/N 双重杂合子最常见,占 19.84%。④478 个高风险家庭中已孕 197 个,最终确诊重型地中海贫血胎儿 42 例,均知情选择终止妊娠。
结论 广州地区是地中海贫血的高发区,对婚前和孕前人群开展地中海贫血筛查,可更有效预防重型地中海贫血患儿出生。

关于先天性中枢性低通气综合征一例的遗传学临床意义

霍晓青 姚微 高薇薇 苏敏 李海英
南通大学附属医院

目的 提高对先天性中枢性低通气综合征(CCHS) 的临床和基因特征的了解和认识，为家系遗传咨询和产前诊断提供依据，及时处理以改善预后，降低死亡率。
方法 总结分析 1 例 CCHS 患儿的临床表现、诊断和基因检测结果，并进行文献复习，以提高对该病的认识和临床诊疗水平。
结果 足月剖宫产儿，性别男，孕妇 GDM、突发羊水过多，其余无特殊，行剖宫产术，Apgar 评分 1 分钟为 6 分（皮肤、呼吸、反射、张力各扣 1 分），5 分钟为 9 分（呼吸扣 1 分），生后一小时余因生时窒息、生后呼吸不规则伴青紫，面罩吸氧下转至我院新生儿科，入院即告病危，无创呼吸机辅助呼吸，新生儿仍有阵发性呼吸暂停，伴有青紫，氧饱和度降至 76%，气管插管后予呼吸机辅助呼吸。反复撤机困难，撤机后呼吸节律改变，呼吸浅慢，血气分析提示二氧化碳潴留。同时完善相关辅助检查，CT 提示新生儿肺炎，新生儿缺血缺氧性脑病可能，心超提示房间隔缺损、动脉导管未闭，临床诊断为 CCHS 后转至上海新华医院，取患儿及其父母静脉血行 PHOX2B 基因序列检测，显示受检者 PHOX2B 基因 GCN 重复次数为 26 次，超过正常范围，其父母未检出突变，该结果支持受检者为低通气综合征（重复数 26-33 为新生儿发病型，目前最大的已知重复序列长度是 33 个 GCN 重复系列）。住院治疗 1 月余，在觉醒期和睡眠期进行仔细监测，包括血氧（脉搏血氧测定）和通气（如 $PACO_2$）的测定，后携呼吸机出院，现患儿觉醒时呼吸活跃，入睡后依赖呼吸机，自主呼吸减慢，潮气量减小，出现 CO_2 储留。

结论 CCHS 以觉醒时有充足通气，睡眠状态下通气不足为主要表现，行 PHOX2B 基因突变分析可确诊 CCHS。可考虑此孕妇下一胎孕 18-22 周羊水穿刺行胎儿羊水细胞 PHOX2b 基因重复序列分析，为家系遗传咨询和产前诊断提供依据，以及早发现和干预。

Case study and literature review of Phelan-McDermid syndrome caused by a pathogenic mutation in the SHANK3 gene

Quanmei Xu Yucai Chen
Shanghai Children's Hospital, Shanghai Jiao Tong University

Objectives Phelan-McDermid syndrome is a rare genetic disorder resulting from heterozygous deletion of 22q13.3 with the involvement of at least part of *SHANK3* or a heterozygous pathogenic variant in *SHANK3*. We would like to explore the possible pathogenesis and therapeutic direction of PMS.
Methods We identified a child who harbored a *de novo SHANK3* gene mutation and had a speech delay and mental retardation. This pathogenic mutation (c.3679dup, p.A1227Gfs*69) may lead to early termination of protein transcription and is speculated to cause changes in protein function. The gene expression profiles of family members were evaluated by RT-PCR, which showed that *SHANK3* expression was significantly lower in the child than in the other family members. The sites of pathogenic and likely pathogenic mutations in the *SHANK3* gene reported by ClinVar were searched, and the mutation sites were summarized and marked.
Results The relevant literature was reviewed to understand the current state of research progress and possible future treatment directions. Researchers have found that CDPPB is a potent and selective positive allosteric modulator of mGluR5. In addition, it is important to further study whether NMD is involved in the expression of *SHANK3* and to further investigate PTCs.
Conclusions Genetic testing is essential for children with development delay. It's necessary to do further research about the therapeutic direction.

MCV、MCH 联合 HPLC 方法在育龄人群地中海贫血筛查中的价值

屈艳霞 左连东 马毅敏
广州市妇女儿童医疗中心

目的 探讨联合应用血液学指标和高效液相色谱（HPLC）方法对育龄人群进行地中海贫血（简称地贫）筛查的价值。
方法 选取 2013-2015 年参加广州市出生缺陷干预工程的育龄夫妇 4471 例,经地贫基因检测,地贫携带者 2388 例作为地贫组,其余 2083 例为非地贫组,比较 MCV、MCH 和 HbA2 单项指标和联合指标在地中海贫血筛查中的灵敏度、特异度、阳性预测值、阴性预测值和诊断符合率。
结果 ①地贫组的 MCV、MCH 水平低于非地贫组,差异有统计学意义（P<0. 05）。②以 MCV、MCH 和 Hb A2 单独作为筛查指标时，Hb A2 的筛查灵敏度低于 MCV 和 MCH，差异有统计学意义（P <0. 05）；MCV 和 MCH 的灵敏度比较差异无统计学意义（P> 0. 05）；MCH 的阳性预测值和诊断符合率均高于 MCV,差异有统计学意义（P <0. 05）。③MCV+MCH+HbA2 联合筛查，在筛查 β 地贫时灵敏度、特异度、阳性预测值、阴性预测值和诊断符合率均高于 α 地贫，差异有统计学意义（P<0. 05）。
结论 MCV 和 MCH 是筛查地贫的有效方法,简单、经济、有效,适合基层医院开展地贫筛查 MCV 和 MCH 是筛查地贫的有效方法,简单、经济、有效,适合基层医院开展地贫筛查。Hb A2 是地贫分型的主要指标,MCV+MCH+HbA2 是筛查 β 地贫的最佳指标。血液学指标联合 HPLC 方法适合用于大人群筛查。

SUN5 突变致无头精子症辅助生殖结局

房建正 杨晓玉 崔毓桂 刘嘉茵
江苏省人民医院

目的 无头精子症是导致男性不育的一种罕见的畸形精子症，它主要特征为精液中可见大量无头精子尾部和少量无尾的精子头以及一部分头尾连接异常的精子。SUN5 是第一个在人类中发现的无头精子症的致病基因。本文的研究目的是探索由 SUN5 突变导致的无头精子症的辅助生殖结局。
方法 采用 Sanger 测序来证实无头精子症患者是否由 SUN5 突变导致。比较本中心无头精子症与精子鞭毛多发异常患者辅助生殖结局，包括受精率、优质胚胎率、临床妊娠率、流产率等。
结果 本研究共涉及 11 例无头精子症患者，5 例 SUN5 突变，6 例未发现已知突变。其中 5 例被证实由于 SUN5 突变导致的无头精子症。这 5 例患者均通过 ICSI 获得了后代。无头精子症的受精率和优质胚胎率高于精子鞭毛多发异常的患者，并且具有统计学意义（P<0.05）。SUN 突变和未突变的无头精子症他们的 ICSI 结局未见明显差异。
结论 无头精子症通过 ICSI 助孕可以获得良好的妊娠结局。由于样本量较小，这一结论需要更多的数据来验证。仍有部分无头精子症患者未发现 SUN5 突变，提示 SUN5 可能不是唯一的导致无头精子症的基因，可能还存在其他一些基因突变致病可能。

Paternal germline mosaicism of a missense mutation in ELANE in a Chinese boy with severe congenital neutropenia

Yingfen Ying Jinbin Ye Feng Gu Junzhao Zhao
The Second Affiliated Hospital of Wenzhou Medical University

Purpose Severe congenital neutropenia (SCN) is an autoimmune deficiency disease which is clinically characterized by persistent and severe neutropenia. It is typically caused by a heterozygous mutation in ELANE gene, which encodes neutrophil elastase. In this study, through one 3-year-old boy diagnosed as severe congenital neutropenia, we aimed to assess the clinical and genetic characteristics of SCN caused by ELANE mutation, and to test whether the mutation can be corrected by CRISPR/Cas9-mediated gene editing.
Methods The proband underwent extensive clinical assessments, with exome sequencing and bioinformatics analysis to identify pathogenic genes. In addition, Sanger sequencing was used to verify the pedigrees. The cell line, 293-ELANE, harboring ELANE mutation was generated by lentiviral transduction and selection with puromycin from HEK-293. And the mutation was corrected by CRISPR/Cas9-mediated HDR.
Result ELANE gene test in the proband unveiled a heterozygous de novo missense mutation: c. 248T>A (p.V83D), which is not detected on his asymptomatic parents with peripheral blood samples. Surprisingly, we found that 46.01% of his father's sperm cells had the same mutation. These results demonstrated that the proband inherited ELANE mutation from his father, who had a normal neutrophil count but was germline mosaic. In this study, the highest repair efficiency of CRISPR/Cas9-mediated HDR in 293-ELANE is 4.43%.
Conclusions We identified a missense mutation (p.V83D) in ELANE causing SCN, which is the first report on paternal semen mosaicism of an ELANE mutation. Our study also paves a way for the PGD (preimplantation genetic diagnosis) based ELANE mutation birth-defects prevention and clinical treatment.

21-羟化酶缺陷症导致继发性无精子症的病例报告

杨晓玉
江苏省人民医院

目的 探讨 21-羟化酶缺陷症与继发无精子症的关系。
方法 回顾性分析 2 例继发无精子症患者的临床资料和 21-羟化酶基因检测结果，总结临床特征及治疗经验。
结果 2 例患者均表现为继发不育，精液分析结果为无精子症。性激素检测 FSH、LH 明显低于正常，T 正常或偏高，孕酮明显升高，ACTH 正常或偏高，皮质醇正常或偏低。肾上腺 CT 检查提示肾上腺皮质增生，5 例呈腺瘤改变，1 例呈肾上腺髓脂肪瘤。所有患者全部给予地塞米松替代治疗，治疗 3-6 个月后，6 例出现精子或精子浓度升高，5 例妊娠。8 例患者共发现 7 个已知致病突变。
结论 21-羟化酶缺陷症可导致男性睾丸不发育和损害生精功能，通过手术和地塞米松替代治疗可以取得良好疗效。8 例患者均为 21-羟化酶基因复合杂合突变，都携带导致男性化表型的 *p.Ile172Asn* 致病突变。

遗传疾病携带者筛查在供精辅助生殖临床实践中的初步探索

杨晓玉
江苏省人民医院

目的 男方因素不育确诊需要接受供精辅助生殖，同时其妻子为严重遗传疾病患者或携带者。在接受供精辅助生育治疗时，为避免供精生育的子代患上严重遗传疾病或缺陷基因下传，需要对提供精子标本的捐精志愿者进行携带者筛查，以排除其为遗传疾病携带者。为此，江苏省人民医院生殖医学中心和人类精子库协作开展了研究。
方法 一对不孕不育夫妇，男方为克氏综合征，女方输卵管不通拟行供精 IVF。女方前次婚姻生育一个 α 地中海贫血（常染色体隐性遗传疾病）患儿，基因检测提示女方和前夫均系 α 珠蛋白基因的缺失所致。遗传咨询后，建议对捐精志愿者进行地中海贫血基因突变筛查。人类精子库选择符合男性患者血型的合格捐精志愿者备选，知情同意后提供志愿者血样品（标注人类精子库编号：2017****XYZ）。采取全基因组二代测序技术进行地中海贫血基因突变筛查。向人类精子库单独填表申请筛查合格的标本，为该患者夫妇实施 IVF 治疗。孕 17 周取羊水，采用 PCR 技术复核二代测序的结果。
结果 地中海贫血基因突变筛查结果提示，编号为 2017****XYZ 捐精志愿者未发现明确或疑似致病性突变，实施 IVF 后成功生育一个未携带 α 地中海贫血基因的 IVF 子代。孕 17 周取羊水，检测未发现地中海贫血基因明确或疑似致病性突变。
结论 为一些特定的严重遗传疾病患者夫妇提供捐精者携带者筛查，以避免供精生育的子代患上严重遗传疾病或因为 IVF 技术造成缺陷基因下传。该策略还可以在某些特定高发地区进行特定遗传性疾病的携带者筛查和联合 IVF 技术，从而降低此类特殊遗传性疾病的发生率。

梯级检测方案在听力损失家系分子诊断上的应用

曾焙枰[1] 许红恩[1] 汤文学[2]
1.郑州大学 2.郑州大学第二附属医院

目的 听力损失是人类最常见的感觉障碍之一。本研究提出一种多重 PCR 检测、一代测序、MLPA 和全外显子组测序的耳聋基因梯级检测策略，旨在探究梯级检测方案在听力损失家系分子诊断上的应用。

方法 这项研究共纳入 140 个听力损失家系，首先用郑州大学精准医学中心自主研发的高通量测序耳聋基因检测试剂盒，对家系所有成员检测导致耳聋的五个常见基因，分别是 GJB2、SLC26A4、12SrRNA 的编码区域，以及 GJB3 和 USH2A 的热点突变，称之为耳聋基因多重 PCR 检测。其次，对未诊断的携带 GJB2 单杂合突变的家系进行 GJB2 第一外显子的一代测序。再次，对轻中度听力损失先证者使用 MLPA 进行 STRC 基因检测。最后，对未确诊的先证者进行外显子组测序，对阴性结果病例进行 CNV 分析。
结果 在这项研究中，多重 PCR 诊断率为 57%，其中 GJB2 占 33%，SLC26A4 占 23%，12SrRNA 占 1%；用一代测序检测四个 GJB2 单杂合突变家系诊断了其中一家；在轻中度听力损失先证者中，利用 MLPA 分析 STRC 基因 CNV 情况诊断了两个家系；全外显子组测序诊断率为 11%（包含 5%的可能诊断家系），其中 MYO15A 占 3%，CDH23 占 2%，另外还发现了 MITF、POLD1、COL11A2、PTPN11、TRIOBP、MPZL2、USH2A、SOX10、HARS2 等致病基因。本研究耳聋家系队列总体诊断率为 68%。
结论 本研究提高了耳聋家系队列的分子诊断率，并证明了梯级检测方法在基因检测中的优势。

一个常染色体隐性精神发育迟滞 68 型家系的临床特征及遗传学分析

李玛丽
西安市儿童医院

目的 报道一例罕见的常染色体隐性精神发育迟滞 68 型（MRT68）患者的临床及遗传学特征。
方法 以我院内分泌遗传代谢科诊治的 1 例临床表现为大量腹水的婴儿为研究对象，收集患儿及家系成员的临床资料，应用靶向捕获高通量测序及 Sanger 测序进行变异位点分析和家系验证。
结果 该患儿为足月儿，出生体重 2.4kg，临床表现有特殊面容：外耳小、耳位低、鼻梁低平、眼裂小，双眼球内聚等，生长发育明显落后。本次就诊以大量腹水为主要表现，实验室检查提示中度贫血、血小板减少、甲状腺功能减低、低血糖、代谢性酸中毒及肾功能损害，骨髓细胞学除外了血液系统疾病，MRI 提示垂体较薄，垂体后叶高信号影未见显示，垂体柄显示不清。此外，眼底及听力检测也存在异常。基因检测结果发现患儿 *TRMT1* 基因携带 c.454-2del 纯合变异，Sanger 测序证实变异分别来自于父亲及母亲。根据 ACMG 指南，该变异评级为致病性变异。
结论 该患儿临床表型符合 MRT68 特点，*TRMT1* 基因 c.454-2del 纯合变异是其致病的遗传学病因。MRT68 病例目前国际上报道甚少，我国尚无报道，故本病例为我国首例。同时该家系所携带的 *TRMT1* 基因 c.454-2del 变异为国际上未报道的新的致病性变异，拓展了该基因的突变谱。此外，与之前报道的 MRT68 病例相比，该患儿临床表型更为复杂，丰富了该病的临床特征。

以传导性听力下降为表型的遗传性聋相关分子病因机制

吴谢东
中国人民解放军总医院

目的 传导性听力下降是一种广泛发病于人群中，且在不同年龄中可由不同疾病导致的听力下降。从外耳到听小骨的任何部位的缺陷均可导致传导性聋。发生在耳廓、外耳道或听小骨的原发性畸形可能与遗传有关。近年来相关研究增多，但仍未对致病基因有明确解释，以传导性聋为主要表型的遗传性聋的分子机制研究较少，使得临床医生对于以传导性聋为主要表型的遗传性聋的干预及预后的判断较为困难。
方法 通过进行文献检索，以传导性听力下降为表型的遗传性聋大多以家系为研究对象，通过进行连锁分析、微卫星标记等多种方法确定突变位点，部分基因可进一步进行动物实验。通过动物模型，观察动物模型听骨及颅骨形态，明确基因致病作用。

结果结论 根据文献推算可知，美国相关传导性听力损失人群约为 700 万，约占听力损失人群的 14.5%，且具有一定的家族聚集性。关于传导性聋的相关分子病因机制研究仍较少，大多数患者无法通过分子生物学指导临床诊断。

儿童 PTEN 错构瘤肿瘤综合征 1 例报告

余佳 白改改 汪治华
西安市儿童医院

目的 探讨 1 例儿童 PTEN 错构瘤肿瘤综合征（PTEN hamartoma tumour syndrome，PHTS）患儿的临床表现、基因变异特点及预后。
方法 分析我院收治的 1 例 PHTS 患儿的临床资料，同时提取患儿及其父母外周血 DNA，运用二代测序技术对其家系进行相关致病基因测序分析。
结果 患儿男孩，4 岁 2 月，头围 52cm(P90)，表现有精神运动发育落后（1 岁 2 月会坐，3 岁半会走，现只会说简单词语）、面部及躯干可见黏膜皮肤斑点及乳头状丘疹。二代测序结果示患儿携带 *PTEN* c.802-2A>T 剪切突变。上述变异使 PTEN 基因失去了对细胞生长的负调控，导致肿瘤的发生及发展，目前本患儿尚无肿瘤发生依据。患儿父母该位点基因型均正常，提示患儿的突变为新生突变，该变异的致病性已经有文献报道。
结论 本患儿主要临床表现为精神运动发育落后、黏膜皮肤斑点、乳头状丘疹，结合二代测序结果：*PTEN* c.802-2A>T，PHTS 诊断成立。儿童 PHTS 发病率极低，约为 1/20 万-25 万，临床极易漏诊。本病预后不良，罹患良性及恶性肿瘤的风险明显增加，确诊后应长期细致的随访，定期筛查肿瘤，尽可能延长患儿的寿命。

苗勒氏管永存综合征 2 例及其 ICSI 结局分析

杨晓玉
江苏省人民医院

目的 苗勒管永存综合征（persistent Müllerian duct syndrome,PMDS）是一种少见的男性假两性畸形,其特点是存在苗勒管结构或苗勒管退化不全产物,而且染色体核型是正常男性。这类疾病通常由于编码 AMH 或 AMHR2 的基因突变导致。本研究目的是探索苗勒氏管永存综合征的新的基因突变及观察其 ICSI 结局。
方法 我们通过一对苗勒氏管永存综合征合并无精子症兄弟采用全外显子测序的方法寻找新的致病基因，采用 Sanger 测序方法来进一步验证，并采用 Western-blotting 验证蛋白表达,并且记录其 ICSI 结局。
结果 我们通过全外显子测序发现这对兄弟 AMHR2 新的致病突变位点：c.1219C>T [p.R407X] 和 c.1387C>T [p.R463C]，并从他们的父母身上进一步验证。通过 Western-blotting 验证其睾丸 AMHR2 蛋白表达水平降低。病例中哥哥通过睾丸穿刺取精联合 ICSI 成功生育两个孩子；弟弟三次 ICSI 助孕暂未 ICSI 成功。
结论 苗勒氏管永存综合征合并无精子症的患者可以成功通过睾丸穿刺取精获得精子，对于这类病人进行辅助生殖前建议遗传咨询。

COLQ 基因突变导致的先天性肌无力综合征一例

陈佳颖
福建医科大学附属第一医院

目的 先天性肌无力综合征(congenital myasthenic syndrome,CMS)，指一组由基因突变导致的神经-肌肉接头罕见疾病，具有易疲劳及肌无力的共同特征。本文通过二代测序对疑似该病患者及其家系成员进行检测，以明确诊断。
方法 收集患者临床资料，完善相关辅助检查，提取患者及家属（父母和子女）外周血 DNA，对先证者进行全外显子测序，并通过 Sanger 测序验证及家系共分，离验证。回顾其病史结合各项基因检测结果，分析该病例诊断要点。
结果 36 岁青年男性，以“双下肢无力 4 年，再发 3 天”为主诉就诊，表现为反复发作进展性呼吸困难，伴双下肢无力，无法行走。家族史：其弟弟有类似病史，因呼吸衰竭去世。神经系统查体：神清，频繁眨眼，眼睑闭合不全，面部肌肉及舌肌未见萎缩，皱额、闭眼、鼓腮等动作正常，余颅神经查体未见异常。颈肌及四肢肌力 3 级，肌张力正常，腱反射对称活跃。病理征阴性，共济运动正常，深浅感觉正常。辅助检查：神经肌肉疾病谱：均阴性；肌电图：1、重频试验：低频递减 2、肌源性损害。全外显子测序提示：COLQ 基因一条染色体存在 c.175C>T 突变，另一条染色体 14-15 号外显子缺失。其父亲一条染色体存在 c.175C>T 突变，母亲一条染色体 14-15 号外显子缺失，子女无突变，满足家系共分离。结合患者波动性肌无力及呼吸困难表现，肌电图重频试验发现低频波幅递减，神经肌肉疾病谱抗体均阴性，结合其基因检测结果，符合先天性肌无力综合征。
结论 通过该家系鉴定了一例先天性肌无力综合征。临床上以波动性肌无力、呼吸困难为表现的患者，结合肌电图重频试验低频波幅递减的表现，进一步检查神经肌肉疾病谱抗体阴性需注意此病，容易误诊为重症肌无力，明确诊断需依赖基因检测。

Oculoskeletodental 综合征 1 例并文献复习

程明
首都医科大学附属北京儿童医院

目的 通过本篇病例报告报道中国首例表现为无追赶生长的小于胎龄儿，伴有特殊面容，主要表现为生后智力、体力发育落后及牙齿异常，经全外显子组基因检测及家系验证，最终考虑诊断 Oculoskeletodental 综合征，补充了本病复杂杂合致病的病例。
方法 1 例主因“生后发现发育落后”于北京儿童医院内分泌遗传代谢中心门诊就诊的 12 岁男童，该患者伴有身材矮小及特殊面容（面容粗陋，倒三角脸，长颅，前额发际线低，眉毛外 1/3 稀疏；鼻梁宽，小耳，颚弓高，小下颌，上颌门牙宽，下颌齿列不齐并牙釉质不良）及隐睾。对该患者进行全外显子基因检测并家系验证。
结果 最终在 PIK3C2A 上发现两个未报道变异：c.2746G＞A：pA916T（父源）及 c.5006A＞G：pN1669S（母源），上述突变在 ExAC、1000 genomes、ESP6500 等数据库中等位基因频率较低，分别为 0.0001997 和 0.000641，且在疾病数据库 ClinVar 中未曾被报道。
结论 我们报道了 1 例 PIK3C2A 复合杂合致病、具有多种临床表现的 Oculoskeletodental 综合征，由于此罕见病报道全球范围内仅 5 例（该患儿为国内首例）目前认知仍不足，故应用 WES 是诊断不可或缺的手段。希望通过本例报道，增加临床工作者对矮小相关罕见遗传疾病的识别和诊断能力，进一步强化对该疾病的认识。

线粒体脑肌病伴高乳酸血症及卒中样发作（MELAS） 合并血管畸形一例

何琪芳 王志强
福建医科大学附属第一医院

目的 分析 1 例线粒体脑肌病伴高乳酸血症及卒中样发作（*MELAS*）的临床表现、实验室检查及影像学结果，提高对此综合征的诊断率，改善预后。
方法 采集 1 例 2020 年 12 月就诊于福建医科大学附属第一医院的线粒体脑肌病伴高乳酸血症及卒中样发作（*MELAS*）患者，观察该患者的临床表现、实验室检查及影像学结果，总结诊断过程及预后。
结果 患者女性，14 岁，以“头痛伴头晕 5 天”为主诉就诊我院，约 3 天前就诊外院，体温最高达 38.3℃。周围神经病史；查体：身高 140cm，体重 35kg；四肢近端肌力 4 级，远端肌力 5 级，直线行走不能，颈软，双克氏征阳性。患者头痛发热，完善腰穿，脑脊液细胞学正常，颅脑 MRI 提示右额叶-右侧脑室前角旁血管畸形，双侧基底节区钙化灶，排除颅内感染，脑脊液乳酸 4.20↑*mmol/L*；血氨 18.0 *umol/L*，血乳酸 3.20↑*mmol/L*，考虑线粒体病，结合患者直线行走不能，肌电图提示上、下肢周围神经源性损害，考虑线粒体病（神经源性肌萎缩-共济失调-视网膜色素变性 NARP）； 完善眼科检查未见视网膜病变；进一步完善肌肉病理活检及基因检测；神经-肌肉联合活检考虑神经源性肌萎缩；基因检测报告 *mtDNA*3243*A*＞*G*；纯音测听提示双侧感音神经听力受损； 葡萄糖耐量受损；心脏彩超未见异常；MMSE23 分 MoCA 26 分 最终诊断：线粒体脑肌病伴高乳酸血症及卒中样发作（*MELAS*）合并血管畸形
结论 本例患者头痛起病，伴身材矮小，共济失调，周围神经病，感音神经听力、葡萄糖耐量受损，轻度认知功能障碍，临床异质性大，症状及影像学不典型时，进一步完善肌肉活检及基因检测有利于早期诊断，改善患者预后。

一例歌舞伎脸谱综合征患儿的基因新变异致的临床及遗传学分析

卢慧敏
北京协和医学院中国医学科学院医学生物学研究所

目的 歌舞伎脸谱综合征（Kabuki 综合征，KS）是公认的累及多器官多系统的罕见遗传性综合征，KMT2D 基因和 KDM6A 基因已经明确为歌舞伎综合征的 2 个致病基因。KS 患者中先天性心脏病的患病率为 28%–83%。本研究旨在探讨 1 例 KS 患儿的临床表型及致病基因突变。
方法：对先证者进行临床检查，并提取先证者及其父母血液 DNA 进行全外显子组测序（WES），筛选候选致病突变。采用对症治疗方法，患儿经胸骨正中切口采用扩大的端侧吻合法进行主动脉弓部重建，同期矫治心内合并畸形。
结果 患儿为 9 月龄男婴，主要临床表现为特殊面容、主动脉弓离断（A 型）、二尖瓣瓣上隔膜、主动脉瓣二瓣化畸形，卵圆孔未闭等，全外显子组测序结果发现患者 KMT2D 基因一个单碱基缺失性突变，导致移码突变和提前出现终止密码子； Sanger DNA 测序显示患儿父亲、母亲及哥哥均未携带该突变，表明该突变为新发变异。参照 ACMG 遗传变异分类标准与指南，该突变分类为 PVS1+PS2+PM2，属于致病突变，目前尚未见文献报道。根据临床表型和基因突变，该患儿诊断为 KS。结合诊断和表型进行手术对症治疗，患儿复查心脏彩超提示畸形均得到成功矫正。
结论 KMT2D 基因单碱基缺失所致移码变异为该患儿歌舞伎综合征的致病原因，本研究丰富了歌舞伎综合征综合征的基因突变谱和表型谱，为该病的临床诊断和遗传咨询提供了参考依据，为目前采取支持与对症的临床治疗策略提供更多治疗靶点和线索。

一例伴有颅脑钙化的 FGFR1 基因突变相关代谢综合征临床特点和基因突变分析

赵淼 曾一恒 陈万金
福建医科大学附属第一医院

目的：FGFR1 基因编码细胞表面的一种酪氨酸激酶，它作为成纤维细胞生长因子受体，在胚胎发育、细胞增殖、分化和迁移过程中发挥重要作用。目前已报道 FGFR1 基因突变可导致低促性腺激素性性腺功能减退（2 型）伴或不伴嗅觉缺失症、假性软骨发育不良、三角头畸形 1 型、Hartsfield 综合征、Jackson-Weiss 综合征、Pfeiffer 综合征等，均呈常染色体显性遗传。目前国内外对 FGFR1 突变表现为颅脑钙化的病例报道较为罕见，本文将对一例伴有颅脑钙化的 FGFR1 基因突变患者进行临床特点和基因突变分析。
方法：收集 1 例就诊于我院神经内科的 FGFR1 基因突变患者及家系成员的临床资料（症状、体格检查、家族史、头颅影像学资料等），以及外周血白细胞 DNA 进行全外显子测序。
结果：先证者 12 岁，表现为隐睾、短阴茎，高胆固醇血症，重度脂肪肝，贫血，胼胝体发育不良，双侧基底节钙化，父母均无上述症状。全外显子+线粒体基因测序结果显示先证者带有 FGFR1 基因 c.2266T>C（p.Cys756Arg）杂合突变，其父母均不存在该位点突变。
结论：本研究先证者的临床表现和基因突变符合 FGFR1 基因突变导致的代谢综合征。其突变位点 c.2266T>C（p.Cys756Arg）在人群数据库中的发生率极低，蛋白功能预测很可能致病，在现有数据库中尚未报道。由于先证者父母无症状且无该位点突变，因此考虑该位点突变为新生突变。该突变的报道为 FGFR1 基因相关遗传代谢综合征的早期诊断为提供了依据。

开封地区出生缺陷现状及干预措施研究

申华 冯杏琳
开封市妇产医院

目的 了解开封地区近五年出生缺陷儿的基本特征，为采用合适的干预措施以降低本地区出生缺陷发生率提供依据。
方法 对开封市妇产医院 2015 年 7 月至 2020 年 6 月分娩的出生缺陷儿从出生缺陷类别、产母生育年龄、文化程度、居住地、缺陷儿性别等进行回顾性分析。
结果 开封地区出生缺陷以先天性心脏病高居第一位，其次为唇腭裂，神经管缺陷排在第三位。其发生与母亲年龄相关，低龄（＜20 岁）和高龄（＞35 岁）发生率较高；受教育程度较低者出生缺陷儿发生率明显升高，而与胎儿性别、产母居住地关系不大。
结论 针对出生缺陷发生率较高的先天性心脏病、唇腭裂及神经管缺陷进行重点干预，同时加强孕前宣教及孕期产前诊断工作，使更先进的技术应用于临床，降低本地区出生缺陷发生率。

全外显子测序发现远端关节弯曲新的致病基因 CHST3 突变

孔令慧 袁正伟
中国医科大学附属盛京医院

目的 本课题利用全外显子测序技术,检测了 2 个中国患者家系的 DNA 样本,筛选新的致病变异,经过 Sanger 测序验证了突变位点的正确性。并探讨该基因突变的致病机制，为远端关节弯曲寻找新的生物标志物，并为个体化治疗提供新的思路。
方法 利用全基因组外显子测序技术对远端关节弯曲家系的先证者及患者进行基因,经过对比和深入分析,初步确定可能的致病基因,并通过 Sanger 测序验证了突变位点的正确性。针对上述基因突变位点设计 CHST3 突变型和野生型质粒分别转染至 293T 细胞中，通过荧光定量 PCR 和 Western blot 技术检测突变对 CHST3 表达情况的影响。

结果 通过分析患者基因结果,并与参照基因组比对,发现有 CHST3 (p.F434L)新突变,并发现突变可以下调 CHST3 基因的表达。
结论 本课题利用全外显子测序技术,检测了 2 个中国患者家系的 DNA 样本,筛选到 CHST3 (p.F434L)新的致病变异,经过 Sanger 测序验证了突变位点的正确性。此外,我们对 CHST3 的突变蛋白进行检测,发现 CHST3 突变导致 CHST3 蛋白表达量下调。表明 CHST3 可能是远端关节弯曲新的致病基因。

第一二鳃弓综合征患者下牙槽神经相关解剖形态变异与 Pruzansky-Kaban 分型相关性研究

柳稚旭
上海交通大学医学院附属第九人民医院

目的：下颌骨畸形是第一二鳃弓综合征的重要体征。Pruzansky-Kaban 通过对下颌骨畸形分型，为临床治疗提供参考。本研究通过 CT 重建第一二鳃弓综合征患者下颌骨，并描记下牙槽神经走形，分析其经走行变异与 Pruzansky-Kaban 分类相关性，避免治疗导致的神经损伤。
方法：研究纳入 2014 年 11 月至 2019 年 11 月我科就诊且拍摄 CT 第一二鳃弓综合征患者，CT 重建下颌骨，记录分型（I，IIa，IIb，III 型），同时描记下牙槽神经走行，将其与 Pruzansky-Kaban 分型做相关性分析。
结果：纳入患者 97 例（男 57 例，女 40 例），I 型 7 例，IIa 型 33 例，IIb 型 41 例，III 型 16 例。I 到 III 型均可出现下牙槽神经走行异常，包括下颌孔位置异常（乙状切迹下颌孔、颊侧下颌孔）、下颌管走行异常（贴颊侧骨壁走行、近心端分裂为双支、贴下颌支前缘走行），颏孔位置异常（下颌体舌侧、下颌支前缘、颏孔消失）。下牙槽神经异常发生率随下颌畸形严重增加，IIb、III 型相关变异率与 I、IIa 具有统计学意义（$P<0.05$）。IIb 及 III 型患者可出现反向下颌小舌。
结论：Pruzansky-Kaban 分型可提示下牙槽神经异走行异常。

海南南部地区地中海贫血分子流行病学分析

游国岭[1,2] 陆春娇[1] 李翠云[1] 李冬雪[1] 于英[1]
1.上海儿童医学中心三亚市妇幼保健院
2.上海交通大学医学院附属上海儿童医学中心

目的 通过对海南省南部地区内育龄青年进行婚前、孕前及孕期的调查，了解海南省南部地区不同民族、性别地中海贫血基的分子流行病学特征。
方法 对平均红细胞体积(MCV)小于 80fL 的育龄夫妇利用 Gap-PCR 和 PCR-反向斑点杂交技术进行地中海贫血基因突变检测。
结果 对 8988 例样本进行地贫基因检测，检测出未携带地贫基因样本 2634 例，占 29.3%；地贫基因携带者 6354 例，占 70.7%，其中 α 地贫基因携带者 5315 例，占地贫基因携带者 83.6%，最常见的地贫基因型为-α4.2/αα，占全部 α 地贫基因携带者的 18.3%；β 地贫基因携带者 336 例，占地贫基因携带者 5.3%，最常见的地贫基因型为 βCD41–42，占全部 β 地贫基因携带者的 69.3%;β 地贫复合 α 地贫基因携带者 703 例，占地贫基因携带者 11.1%。不同民族中，黎族、苗族和汉族的检出率分别为 50.9%、0.86 和 18.3%，以黎族最高；性别中，女性的检出率高于男性，分别为 37.4%和 33.3%。
结论 海南省南部地区地中贫血的基因型较为复杂多样，应结合本地区基因型分布及民族分布特征，加强本地区地中海贫血产前筛查和诊断，减少出生缺陷，提高优生质量。本研究结果为制订地中海贫血的地域性筛查、诊疗计划和开展优生工作提供参考数据。

BDNF 基因差异甲基化在精神分裂症中的功能机制研究

秦恒伟 秦胜营 沈陆 荚宸汉 唐毓昊 雷超宇 罗诗涵 汤天辰 赵祥语 林云晓 田子钊
上海交通大学

目的 精神分裂症是一种严重的精神疾病，在世界总人口中的发病率约为 0.75%。DNA 甲基化作为一种表观遗传学修饰模式，在精神分裂症患者中发生异常变化。BDNF 基因编码大脑中重要的神经营养因子，它的遗传突变与精神分裂症有关。近年来，BDNF 的甲基化异常也陆续被发现。针对前期研究中通过机器学习鉴定的一个精神分裂症相关 BDNF 调控区 DNA 甲基化异常区域，细胞模型分析了其调控表达的功能机制。
方法 本课题中使用了人肝祖细胞和神经母细胞瘤两种细胞（HepaRG 和 SK-N-SH），采用 Crispr/dCas9 基因编辑系统，通过脂质体转染的方式对于基因组目标区域进行了甲基化、去甲基化、片段敲除。样本提取的 DNA 进行 MassARRAY 检测其甲基化水平。RNA 逆转录后进行 qPCR 和转录组测序，检测基因表达量和下游通路。蛋白质使用 Western-Blot 技术检测其表达量的变化。
结果 HepaRG 细胞系中，对照组中目标区域的甲基化程度高，低甲基化组的目标区域甲基化水平降低，BDNF 表达量有较为明显的提升；SK-N-SH 细胞系中，对照组中目标区域的甲基化程度低，高甲基化组的目标区域甲基化水平升高。
结论 本实验成功从细胞模型上验证了 BDNF 目前区域的甲基化水平与其表达量变化有显著关系。因此，基于我们研究结果的进一步研究可以为精神分裂症发病机制的探索提供新的思路。

SORD 基因致病变异导致的福建省腓骨肌萎缩症临床遗传分析

袁茹莹 何瑾 叶子凌 张小蓉 许柳青
福建医科大学附属第一医院

目的 山梨糖醇脱氢酶(*SORD*)编码基因的双等位基因突变最近被确定为常染色体隐性遗传的 CMT 病患者的常见遗传原因。我们调查了来自中国的 3 名 CMT 双等位基因 *SORD* 突变患者的临床、遗传和电生理特征。在 *SORD* 基因突变的患者在针刺试验中表现出阳性反应并存在血清山梨醇脱氢酶水平降低。我们证实了 *SORD* 突变是 CMT 的致病原因，并进一步扩大了与 CMT 相关的突变和表型谱。
方法 选取来自 CMT 注册队列研究(NCT04010188)共 215 名患者，从外周血提取基因组 DNA。首先用多重连接探针扩增技术（MLPA）检测 17p11.2 拷贝数变异，Sanger 测序检测 *GJB1* 和 *MFN2* 基因外显子突变，排除这些常见突变后，使用全外显子测序（WES）筛选其他与 CMT 相关的致病突变。随后应用聚合酶链反应（PCR）扩增了 *SORD*(NM_003104)基因的 9 个外显子,使用 Sanger 测序验证所有候选突变，并根据美国医学遗传学和基因组学学院(ACMG)的标准和指南进行分类。并且使用山梨醇脱氢酶酶联免疫吸附测定试剂盒对血清山梨醇脱氢酶进行定量。
结果 在该队列中三名患者被发现携带 *SORD*(NM _ 003104)基因的突变。两名患者携带 *SORD*:c.757DelG(p.A253Qfs*27) 纯合突变，一名患者携带 *SORD*:c.757DelG(p.A253Qfs*27)和 c.625C>T (p.R209X)复合杂合突变。到目前为止，这个等位基因还没有在东亚人群中发现。三名患者的临床表现非常相似，发病年龄 14 ~ 16 岁，首发症状均始于下肢。神经系统检查显示双下肢远端明显的无力和萎缩，双上肢无明显无力或萎缩。下肢远端腱反射减弱或消失，上肢则正常。巴宾斯基未引出。患者均未观察到感觉障碍或认知障碍。下肢神经传导显示神经中复合肌肉动作电位(cMAP)波幅降低，运动神经传导速度正常(MNCV)，提示轴索损害。上肢的 cMAP 和 MNCV 均正常；四肢感觉神经传导正常。2 名患者的皮肤划痕实验呈阳性并且发现他们的血清山梨醇脱氢酶水平低于健康对照受试者。

结论 在我们的队列中 *SORD* 突变频率为 1.39%， 为第二大常见突变。并且发现患者存在皮肤划痕实验阳性的体征和血清山梨醇脱氢酶水平的降低。证实了 *SORD* 基因突变会导致 CMT，但其造成的损伤机制尚不清楚。

CpG Site Hypomethylation at ETS1-binding Region Regulates DLK1 Expression in Chinese Patients with Tetralogy of Fallot

Guixiang Tian
Children's Hospital of Fudan University

DLK1 is a non-canonical ligand of the Notch signaling pathway, which is involved in heart development. However, the epigenetic regulation for this gene remains elusive. In this study, we used immunohistochemistry to detect the DLK1 protein expression and measured the methylation status of the DLK1 promoter using bisulfite sequencing PCR (BSP). Dual-luciferase reporter assays were performed to examine the influence of transcription factor ETS1 on DLK1 gene expression. The electrophoretic mobility shift assay (EMSA) and chromatin immunoprecipitation assay, both in vivo and in vitro, were used to verify the binding of the ETS1 transcription factor to the DLK1 promoter as well as the influence of methylation status of DLK1 promoter on this binding affinity. The expression of DLK1 in the right ventricular outflow tract (RVOT) was significantly lower in patients with TOF than in controls ($p<0.001$). Moreover, the methylation level of CpG site 10 and CpG site 11 in the DLK1_R region was decreased in TOF cases, compared with controls ($p<0.01$). The integral methylation level of DLK1_R and the methylation status of the CpG site 11 were both positively associated with DLK1 protein expression in TOF cases. ETS1 was proved to inhibit DLK1 transcriptional activity by binding to the CpG site 11 and this affinity can be influenced by the methylation level of the DLK1 promoter. **T**hese findings demonstrate that the hypomethylation of the DLK1 promoter can increase the affinity of binding of ETS1 transcription factor, which in turn inhibits DLK1 gene transcriptional activity and contributes to the development of TOF.

UGT1A1 mutation association with increased bilirubin levels and severity of unconjugated hyperbilirubinemia in ABO incompatible newborns of China

Liye Yang
People's hospital og Yangjiang

Background Neonatal hyperbilirubinemia causing jaundice is common in East Asian population. Uridine diphosphate glucuronosyltransferase isoenzyme (UGT1A1) glucuronidates bilirubin and converts the toxic form of bilirubin to its nontoxic form.
Method A retrospective study was conducted to review clinical information of ABO hemolysis neonates (ABO HDN) admitted to the Department of Neonatology, referred for neonatal hyperbilirubinemia, in a large general hospital of southern China from 2011 to 2017. Variation status of UGT1A1 was determined by direct sequencing or genotype assays.
Result Sixty-nine ABO HDNs were included into the final analysis. UGT1A1 c.211 G>A mutation (UGT1A1*6, p.Arg71Gly, rs4148323) was significantly associated with the increased bilirubin level in ABO HDNs, after adjusted by age, sex and feeding method (P=0.019 for TBIL, P=0.02 for IBIL). Moreover, heterozygous and/or homozygous UGT1A1 mutations in the coding sequence region were significantly associated with the increased risk of developing hazardous hyperbilirubinemia (as defined by TSB>427 umol/L) as compared those with a normal UGT1A1 genotype (OR_{adj}=9.16, 95%CI 1.99- 42.08, P=0.002) in the study cohort.

Conclusion UGT1A1 variant in coding region is actively involved in the pathogenesis of ABO hemolysis related neonatal hyperbilirubinemia. Genetic assessment of UGT1A1 may be useful for clinical diagnosis of neonatal unconjugated hyperbilirubinemia.

13-三体综合征胎儿脐血和孕妇外周血中 miRNAs 差异表达谱关联分析

马驰宇
深圳市人民医院

为分析 13-三体综合征 miRNAs 表达特征，寻找与 13-三体综合征相关的差异表达 miRNAs。本文收集 13-三体综合征患者和核型正常对照的脐血和外周血，采用 Trizol 提取 RNA，对合格的 RNA 进行高通量测序。对差异表达的 miRNAs 进行筛选，对差异表达 miRNAs 的靶基因进行 GO 功能分析以及 KEGG 信号通路富集分析。本文在脐血中总共筛选到 105 个差异表达的 miRNAs，12 个 miRNAs 均在外周血和脐血中差异表达。脐血中差异表达 miRNAs 的靶基因主要涉及到：包涵体等细胞组成；肺泡发育等生物学过程；硫转移酶活性等分子功能。13-三体综合征脐血和外周血中 miRNAs 表达发生明显改变，这些 miRNAs 能结合 mRNAs，参与 13-三体综合征的发生。

Co-inheritance of G6PD deficiency and 211 G to A variation of UGT1A1 in neonates with hyperbilirubinemia in eastern Guangdong

Liye Yang[1] Jiaxin Xu[2]
1.People's hospital of Yangjiang
2.Chaozhou Central Hospital

Background Glucose-6-phosphate dehydrogenase (G6PD) deficiency, which may manifest as neonatal hyperbilirubinemia, is the most prevalent erythrocytic enzyme-related disease in the world.
Objective To investigate the association between neonatal hyperbilirubinemia and co-inheritance of G6PD deficiency and 211 G to A variation of UGT1A1 in Chaozhou city of eastern Guangdong province, the effects of G6PD deficiency and UGT1A1 gene variant on the bilirubin level were determined in neonates with hyperbilirubinemia.
Method The activity of G6PD was assayed by an auto-bioanalyzer. PCR and flow-through hybridization were used to detect 14 common G6PD mutations in G6PD deficient neonates. 211 G to A variation of UGT1A1 was determined by PCR and sequencing. The data of neonatal peak bilirubin was collected and analyzed retrospectively.
Results 74 cases of the 882 hyperbilirubinemia neonates were G6PD deficiency (8.39%) while 12 cases of the 585 non-hyperbilirubinemia neonates (control group) were G6PD deficiency (2.05%). The rate of G6PD deficiency in the hyperbilirubinemia group was higher than that of the control group. Moreover, the peak bilirubin in the G6PD-deficient group of hyperbilirubinemia neonates was 334.43±79.27μmol/L, higher than that of the normal G6PD group of hyperbilirubinemia neonates (300.30±68.62 μmol/L). The most common genotypes of G6PD deficiency were *c.1376G>T* and *c.1388G>A*, and the peak bilirubin of neonates with these two variants were 312.60±71.81μmol/L and 367.88±75.79 μmol/L, respectively. The bilirubin level of c.1388G>A was significantly higher than that of c.1376G>T. Among the 74 hyperbilirubinemia neonates with G6PD deficiency, 6 cases were 211 G to A homozygous mutation (bilirubin levels 369.55±84.51 μmol/L), 27 cases were 211 G to A heterozygous mutation (bilirubin levels 341.50±63.21 μmol/L), and 41 cases were wild genotypes (bilirubin levels 324.63±57.52 μmol/L).
Conclusion The rate of G6PD deficiency in hyperbilirubinemia neonates was significantly higher than that of the non-hyperbilirubinemia neonates in Chaozhou. For the hyperbilirubinemia group, neonates with G6PD deficiency had a higher bilirubin level compared to those with normal G6PD.

For hyperbilirubinemia neonates with G6PD deficiency, there was a declining trend of bilirubin levels among 211 G to A homozygous mutation, heterozygous mutation, and wild genotype, but there was no significance statistically among the three groups.

Molecular and clinical characteristics of hemoglobin Malay detected in China mainland

Liye Yang[1] Fen Lin[2]
1.Peopls's Hospital of Yangjiang
2.Chaozhou Central Hospital

Hemoglobin (Hb) Malay (HBB:c.59A>G, p.Asn19Ser) was firstly described in Malaysian population in 1989. Up to date, there has been no report of Hb Malay in mainland China. Hb Malay results from an AAC→AGC mutation in codon 19 of the β-globin gene, the carriers do not present any clinical symptoms, only shows with increased HbA2 and decreased MCV, are often diagnosed during thalassemia screening. However, compound heterozygosity for Hb Malay and β^0-thalassemia mutation shows β-thalassemia major clinically. Here, we identified 5 cases of Hb Malay, two cases were compound heterozygosity for Hb Malay and β^0-thalassemia.

Clinical validation of a single tube PCR and reverse dot blot assay for detection of common α- and β-thalassemia in Chinese

Liye Yang[1] Liejun Li[2]
1.People's Hospital of Yangjiang
2.Guangdong Hybribio Limited Corporation

Introduction Thalassemia is one of the most prevalent inherited diseases in southern China. We evaluated a novel reverse dot blot (RDB) assay for simultaneous detection 6 kinds of common α-thalassemia (α-thal) alleles (three deletional and three common non-deletional mutations) and 19 kinds of common β-thalassemia (β-thal) alleles in Chinese for clinical setting. This thalassemia gene assay involved one multiplex PCR amplification system and one time of hybridization.
Method Study samples were collected from one large general hospital and two women and children hospitals in southern China. Each of the clinical validated samples was re-tested by the new multiplex polymerase chain reaction /reverse dot blot assay II (M-PCR/RDB II) in a double-blind manner.
Results A total of 1060 unrelated cases including 829 cases of thalassemia and 231 healthy samples were collected. The whole PCR and RDB procedure could be completed in 2h. All the samples, including heterozygous thalassemia, homozygous thalassemia and compound heterozygous thalassemia, were correctly genotyped, yielding 100% concordance with the reference assays. In addition, HKαα/--^{SEA} and HKαα/−$\alpha^{4.2}$, which were not included in this detection panel, yielded a contradictory result with this new kit, this remind us refer to other alternative methods to diagnose these rare conditions.
Conclusion The developed M-PCR/RDB II assay was simple, rapid, accurate, and cost-effective, which would be applicable for genetic screening and clinical diagnosis of these common α- and β-thalassemia in Chinese population. For rare genotypes such as HKαα, other alternative methods should be used for differential diagnosis.

Human serum albumin variants found in China：molecular epidemiological investigation and literatures review

Liye Yang[1] Jiaoren Wu[2]
1.People's Hospital of Yangjiang
2.Chaozhou Central Hospital

Background Bisalbuminemia is a hereditary or/and acquired abnormality, characterized by a double band of albumin (ALB) compositions on serum protein electrophoresis (SPE). There has been no any epidemiological investigation of ALB variants in Chinese.
Methods 71,963 unrelated subjects from five provinces of southernChinareceived our ALB variants screening by cellulose acetate electrophoresis at pH 8.6. The mutations of the ALB variant were confirmed by PCR-DNA sequencing.
Results and Conclusions The average incidence of inherited bisalbuminemia in southern Chinese population was 0.0264% (19/71,963). 13 cases showed slow genetic variants and 6 cases showed fast genetic variants by cellulose acetate electrophoresis. Four kinds of ALB variants were identified, including proalbumin Lille (p.Arg23His), albumin Castel di Sangro (p.Lys560Glu), albumin Fukuoka-1 (p.Asp587Asn) and a novel ALB Wuxi (p.Lys562Glu). The 0.126% (13/10297) gene frequency in Wuxi region was higher than those of other regions (P<0.05) in southern China. 90.9% (10/11) of proalbumin Lille was also found in Wuxi region of Jiangsu province. Our study firstly described a detailed prevalence and molecular characterization of ALB variants inChina. Comparison with other areas ofChina, Wuxi had a different pattern of ALB variant with a high prevalence of proalbumin Lille.

NPRL2 基因相关遗传性局灶性癫痫 1 例并文献复习

孙于林 万林 李志超 胡琳燕 杨光
中国人民解放军总医院第一医学中心小儿内科

目的 报道 1 例 NPRL2 基因相关遗传性局灶性癫痫的临床特点、诊治过程并文献复习。
方法 回顾性分析 1 例 NPRL2 基因相关遗传性局灶性癫痫的临床资料，检索 PubMed、中国知网、万方数据知识服务平台及在线人类孟德尔遗传数据库等文献检索系统，结合文献报道，总结 NPRL2 基因相关遗传性局灶性癫痫的临床特点，并探讨其与基因型的关系。
结果 该文患儿为 3 岁 11 月龄女孩，主要临床表现为以左侧肢体为主的间断抽搐，脑电图示右侧前颞区放电。遗传学分析结果显示 NPRL2 基因父源性剪接变异：c.933-1G>A，为新报道的变异，根据多种生物信息学软件及 ACMG 标准预测为致病性突变，从而确诊为 NPRL2 基因相关遗传性局灶性癫痫。文献复习发现，NPRL2 基因共报道 11 种变异类型，以错义突变最常见，多数为遗传性变异。癫痫的临床表型以局灶性癫痫为主，亦可见婴儿痉挛症和未分类癫痫，多数为药物难治性。
结论 本例患儿发现的 NPRL2 基因剪接受体突变之前未见文献报道，增加了 NPRL2 基因相关癫痫的表型和基因谱。对于有家族史的局灶性癫痫，应警惕 NPRL2 基因突变可能，必要时完善基因检查，治疗药物可尝试奥卡西平或雷帕霉素，远期预后需长期随访。

In silico analysis of m6A-related single-nucleotide polymorphisms in systemic lupus erythematosus

Shuhong Chen Jieruo Gu
The Third Affiliated Hospital, Sun Yat-sen University

Aim To investigate the effects of m6A-single nucleotide polymorphisms (SNPs) on systemic lupus erythematosus(SLE).
Method We examined the association of m6A-SNP with SLE in a public genome-wide association study. Furthermore, we used the HaploReg database to screen out m6A-SNPs with expression quantitative trait loci (eQTL) effect. Lastly, we validated the eQTL genes by differentially expression analysis on datasets from the Gene Expression Omnibus (GEO) database.
Results Among the 4820 m6A-SNPs detected,45 seemed to be associated with SLE (P <1E-5). 24 m6A-SNPs with eQTL signals were screened out and 10 m6A-SNP-gene expression-SLE trios were identified.
Conclusion The study has identified several SLE-associated m6A-SNPs as potential causal variants and established mechanisms for genetic associations with SLE.

Glucose-6-phosphate dehydrogenase deficiency screening and gene analysis in blood donors of Guangdong province

Liye Yang
People's Hospital of Yangjiang

Background The characteristic of glucose-6-phosphate dehydrogenase (G6PD) deficiency is red blood cell (RBC) destruction in response to oxidative stress. Patients requiring RBC transfusions may simultaneously receive oxidative medications or have concurrent infections, both of which can induce hemolysis in G6PD-deficient RBCs. We intend to investigate the incidence of G6PD deficiency in voluntary blood donors and to evaluate the transfusion risk associated with G6PD deficiency in Guangdong province.
Methods G6PD enzyme was analyzed in 3042 donors and gene mutations were genotyped in G6PD deficient samples.
Results The G6PD deficiency rate of voluntary blood donors was 6.97% (212/3042), 55% blood donors with G6PD deficiency donated blood more than twice. 85 cases of G6PD deficiency were genotyped, and the common types of G6PD mutations were c.1376 G>T, c.1388 G> A, c.95 A>G, c.1024 C>T and c.871 G>A.
Conclusions We recommended that the screening of G6PD deficiency should be carried out for the regular blood donors to ensure the safety of blood users.

The gene spectrum of thalassemia in Yangjiang of western Guangdong province.

Liye Yang[1] Weimin Liang[2]
1.People's Hospital of Yangjiang
2.Maternal and Children Hospital of Yangjiang

Background Thalassemia presents a higher incidence in southern China. However, there is a lack of data on the common mutations among the people of Yangjiang. The objective of this study was to analyze the genotype distribution of thalassemia in Yangjiang, a western city of Guangdong province.

Methods The genotypes of suspected cases with thalassemia was tested by Gap-PCR and reverse dot blot (RDB). Unidentified rare genotype of the samples was further ascertained by PCR and direct DNA sequencing.
Results: 22467 suspected thalassemia cases were tested by a thalassemia detection kit involving Gap-PCR and RDB. 7658 cases were found with thalassemia genotypes. 5313 were α-thal alone, $--^{SEA}$ were the most common α variant, accounting for more than 67% of α-thal individuals, and the following mutations were $-\alpha^{3.7}$, $-\alpha^{4.2}$, α^{CS}, α^{WS}, and α^{QS}. 2032 cases were β-thal, CD41/42 (-TCTT), IVS-II-654(C-T), and -28(A-G) accounted for 80.9% (1644/2032) of all β-thal mutations, and the following mutations were CD17 (A-T), CD71/72(+A), Hb E and -29(A-G). 11 cases of compound heterozygotes of β-thal and 5 cases of β-thal homozygotes were identified in this study, these patients showed β-thal intermedia or β-thal major. 313 cases were identified with α-thal combined with β-thal, showing 57 genotype combinations of the coincidence of both Hb disorders, one extreme patient had a genotype of $--^{SEA}/\alpha^{WS}/\beta^{CD41-42}/\beta^{-28}$.
For those cases suspected with rare thalassemia genotypes could not be identified by PCR and RBD of the kit, they were referred to gene sequencing or Gap-PCR. 18 cases were identified as rare thalassemia genotypes not included in our detection kit, they included 4 types of rare α-globin gene of $--^{THAI}$/αα, HKαα/$--^{SEA}$, $\alpha\alpha^{WS}$ combined with Hb Q-Thailand, and CD31 AGG>AAG/$--^{SEA}$. 6 types of rare β-globin gene were identified, including CD39 CAG>TAG, IVS-Ⅱ-2 (-T), -90(C>T), Chinese $^{G}\gamma^{+}(^{A}\gamma\delta\beta)^{0}$, CD104(-G) and CD19(A>G) (Hb Malay). CD104 (-G) and CD19 (A>G) were firstly identified in China mainland.
Conclusions: This study provided detailed genotypes of thalassemia in Yangjiang of western Guangdong province, reflected the complexity of genotypes of this high prevalent region, and this would be valuable for diagnosis and counseling for thalassemia in this area.

A Novel Missense Mutation in NALCN cause CLIFAHDD Syndrome and Prenatal Diagnosis in China

Jia Tang[1,2] Yuping Li[2] Haihong Shi[2] Chenglong Zhou[2] Yangran Chen[2] Qiang Chen[2] Ning Li[2]
1.Guangdong Provincial Fertility Hospital
2.Jiangmen Maternity and Child Health Care Hospital

Background CLIFAHDD is caused by mutation in NALCN and characterized by facial malformation, hypotonia, and developmental delay. Recently rare mutations in NALCN associated with of CLIFAHDD syndrome have been reported.
Methods Whole exome sequencing (WES) was applied to a diagnosis suspected CLIFAHDD syndrome proband based on clinical symptoms. Blood samples were taken from the parents of the proband for co-segregation analysis using Sanger sequencing. In addition, prenatal gene diagnosis was performed to the family. Finally bioinformatics analysis was utilized to predict the pathogenesis of novel variant.
Result We reported a 24-hour-old proband with a novel missense variant c.3016G>T (p.Val1006Phe) in NALCN by WES. The proband showed clinical symptoms of head abnormalities, neck shortage, thumbs adduction, positional foot deformities and elbows contracture. Prenatal diagnosis revealed that the proband's sibling did not carry c.3016G>T.
Conclusion Our findings indicate c.3016G>T is a novel pathogenic mutation, while extending new phenotype CLIFAHDD syndrome and enriching the mutation spectrum of the NALCN gene.

Deletion of 22q11.2 in a prenatal diagnosed fetus originated from his phenotypically normal mother

Qinghua Wu
The first afdiliated hospital of zhengzhou university

Aim 22q11.2 deletion syndrome (22q11.2 DS) has a history of more than 50 years since it was first reported. It is the most common microdeletion syndrome with overall incidence 1/(3000-6000)

in live births and as high as 1/1000 in fetuses. At present, there are a large number of reports about the phenotype of 22q11.2 DS with a wide range of manifestations. More than 180 phenotypes were reported which are highly variable, including cardiac malformations, palatal dysplasia, characteristic facial features, thymic dysplasia, hypocalcemia and so on. However, in the present study, we described a very rare family in which the fetus was detected with 22q11.2 deletion originated from his phenotypically normal mother.

Materials and method This is a 29-year-old pregnant woman referred for counselling at 17 weeks gestation because of the critical risk of trisomy 21 indicated by serological screening for Down's syndrome. Amniocentesis was performed in July 2020. Copy number variation (CNV) analysis were applied in the fetus and his parents. ***Results:*** The 2.6 Mb deletion at 22q11.2 (18880000-21480000) was detected in the fetus, and the cytogenetic analysis of cultured amniocytes revealed a normal karyotype. Ultrasound scanning was performed for the fetus and showed a single hyperechoic spot and vascular rings formed by left arch and right subclavian artery vagus which are regarded as mild cardiac vascular variations. Parental peripheral blood was collected to trace the source of the missing fragments. The results of CNV analysis showed that a 2.58 Mb deletion at 22q11.2(18900000-21480000) in the pregnant woman with normal phenotype. Her husband did not have such a deletion.

Discussion The chromosome 22q11.2 region contains eight chromosome low copy number repeat sequences (LCRs), LRC22A to LRC22H. The most affected individuals have typical 3 Mb deletion between centromere LCR22A and LCR22D (close to 90%), and the rest are non-classical 1.5 ~ 2.0 Mb deletions between LCR22A and LCR22B or LCR22C (5-10%). In this study, the 2.6 Mb deletion fragment of fetal and maternal 22q11.2 overlaps with the typical deletion fragment mentioned above. The phenotype spectrum of 22q11.2 DS caused by the typical deletion region is extensive, ranging from fatal phenotype (congenital heart disease) to mild abnormality (mild facial abnormality).

The first case of the pregnant woman without any abnormal phenotype in China was reported in this study, which further expanded the clinical significance of 22q11.2 deletion. We can no longer think that the syndrome must be a pathogenic genetic disease, and clinical findings spectrum of 22q11.2 DS should be further extended to normal phenotype. Further work should be done to explore the potential reasons and more clinical data are needed in the future to provide a broader basis for prenatal diagnosis and clinical counselling of 22q11.2 DS.

以转氨酶异常首发的 1 例肌营养不良病例报告及临床分析

张桂霞 胡娇
63600 部队医院

进行性肌营养不良（Progressive Muscular Dystrophy，PMD）是一组儿童期常见的遗传性肌肉疾病，主要包括 Duchenne 和 Becker 型肌营养不良（Duchenne/Becker Muscular Dystrophy，DMD/BMD）两种类型，以 DMD 更为多见，两者均是由于抗肌萎缩蛋白(dystrophin，dys)基因突变所致的 X-连锁隐性遗传病，由于 dys 缺乏导致骨骼肌细胞膜缺陷，细胞内的肌酸激酶等外漏，肌细胞坏死、脂肪组织和纤维结缔组织增生。本文通过 1 例因转氨酶升高为首发表现的肌营养不良患儿，探讨 DMD 的临床表现、实验室检查、基因诊断、治疗等。DMD 的主要临床表现为儿童期发病、缓慢进展的对称性的骨骼肌变性、肌无力和肌萎缩，发病率较低，在存活男婴中的发病率约为 1/3599～1/9337。本例患儿发病时主要表现为转氨酶异常升高，经保肝、降酶治疗后，没有明显改善，后完善血清酶学检查，肌酸激酶超过正常值 56 倍，怀疑肌营养不良，经基因诊断明确。DMD 在婴儿期，临床表现常常不典型，肝功异常有可能是最早的临床表现之一。因此临床医生，在遇到血清酶学异常患儿，首先在排除肝损害、心肌损害等常见疾病后，首先应想到 DMD 的可能，并及早进行相关的血清酶学，包括 CK、CK-MB 等检测，必要时进行肌肉活检或基因检测，以便早期获得正确的诊断，并且及时进行合理的治疗和遗传咨询。DMD 预后差，目前为止，尚没有针对肌营养不良的根治方法，治疗目的主要为延缓发病时间、提高生活质量，尽可能延长生存期。经典的糖皮质激素治疗,结合康复训练、多学科综合管理等可有效延缓病程。基因治疗是目前最有前景的治疗手段。

ATN1 HX 重复区新发变异导致 CHEDDA 的 2 例病例报道

罗素坤 何学莲
武汉儿童医院

目的 *ATN1* 基因关联常染色体显性遗传病 Congenital hypotonia, epilepsy, developmental delay, and digital anomalies （简称 CHEDDA），该病 2019 年正式命名，由 *ATN1* HX 重复区的错义、框内缺失/重复变异引起。本文旨在了解 CHEDDA 的临床表型、诊断及遗传学特点。
方法 回顾分析我院通过 Trio-WES 测序确诊的 2 例 CHEDDA 患儿临床表型及遗传学资料，并进行相关文献复习。
结果 患者 1 为 13 天的新生儿，临床表现为主动脉弓降部局限性膨大、动脉导管未闭、卵圆孔未闭或房间隔小缺损、永存左位上腔静脉、三尖瓣轻至中度关闭不全、右心增大、肺动脉压力升高、先天性舌系带缩短、喂养困难、吸吮能力差、异常新生儿脑电图、睑裂稍小等。患者 2，1 岁 9 个月，临床表现为言语缺失、运动发育落后、走路不稳、轻度面容异常等。基因检测发现，患者 1 的 *ATN1* 基因存在 c.3155A>C 杂合变异，导致 ATN1 第 1052 位 His 变为 Pro。患者 2 的 *ATN1* 基因存在 c.3176-c.3177insGCACCT 杂合变异，导致 ATN1 第 1059Ser-1060His 之间插入 His 与 Leu 两个氨基酸。两个变异均为新发突变，二者父母均为野生型。两个变异位于 ATN1 高度保守的 HX 重复区，确诊为 *ATN1* 基因 HX 重复区新发变异导致的 CHEDDA。
结论 检索文献发现，该报道为 CHEDDA 在中国的首次报道。该病起病年龄早，新生儿期即会起病，临床表现异质性较大，发育迟缓、特殊面容与婴儿肌张力减退为该病的普遍临床特征，癫痫发作与颅脑、心脏、泌尿生殖系统的先天结构异常是 CHEDDA 患儿经常出现的临床症状，但不普遍。此外，CHEDDA 患儿还伴有喂养困难、视力与听力损害等并发症。目前，CHEDDA 尚无有效的针对性治疗方法，只能对症治疗，早期基因诊断有助于疾病的确诊。

江门地区 21541 例孕妇的脊髓性肌萎缩症基因携带者筛查和新筛查方法研究

唐佳[1,2] 石海弘[2] 李秋丽[2] 马巍[2] 李观明[1]
1.广东省生殖医院
2.江门市妇幼保健院

目的 对广东江门地区孕妇进行脊髓性肌萎缩症携带者筛查研究，建立一种新的 SMA 筛查方法，降低脊髓性肌萎缩症的发生率。
方法 选取 2016 年 12 月到 2020 年 12 月 21541 例江门地区孕妇采用实时多重荧光定量 PCR 的方法分别对 SMN1 基因第 7、 8 外显子进行扩增并对拷贝数进行相对定量检测并建立筛查 SMA 的 CRISPR-cas12a 技术方法。
结果 在 21541 例受检者中共检测出 515 例杂合缺失携带者，约占 2.39%，其中 363 例为 SMN1 基因第 7、8 外显子杂合缺失携带者，占 1.68%；25 例为 SMN1 基因第 7 外显子杂合缺失携带者，占 0.12%；127 例为 SMN1 基因第 8 外显子杂合缺失携带者，占 0.59%；即 388 例为致病缺失携带者，携带率约为 1.8%。利用 CRISPR-cas12a 技术成功研发快速、准确、简单的 SMA 筛查方法，可以区分正常人，携带者和患者，可以大规模用于 SMA 筛查。
结论 开展携带者筛查和研发新的筛查方法，为脊髓性肌萎缩症群体防控提供理论和技术支持。

两例伴有感音神经性聋新表型的 Coffin-Siris 综合征病例

王秋权[1,2] 吴婕[1,2] 黄莎莎[1,2] 袁永一[1,2] 戴朴[1,2]
1.解放军总医院耳鼻咽喉头颈外科医学部
2.国家耳鼻咽喉疾病临床医学研究中心

背景 Coffin-Siris 综合征（CSS，OMIM：135900）是一种罕见的先天性疾病，其主要与多发畸形，神经发育异常和发育迟缓有关。导致 CSS 综合征的主要原因是 BAF 染色质重塑复合体编码基因、*SOX11* 或 *PHF6* 基因上发生某些变异。本研究对两名患有 CSS 综合征且伴有感音神经性听力损失及内耳畸形的患者进行了基因检测。
材料及方法 两名被诊断为综合征性耳聋的患者，他们表现出独特的面部特征，智力低下，生长发育迟缓，第五指畸形和感音神经性聋以及不同程度的内耳畸形。两例患者均接受了全外显子组测序，并对他们的听力学、放射学以及生长发育相关检查结果进行分析。
结果 两例患者分别检测到一个 *SOX11* 基因的 *de novo* 突变(c.148A>C：p.Lys50Asn；c.811-814del：p.Asn271Serfs*10)，结合其临床及遗传学检测结果，并根据 ACMG 指南判定为致病性变异，两例患者被诊断为 CSS 综合征。
结论 这是在中国人群中发现由 *SOX11* 基因突变引起 CSS 综合征的首次报告。遗传性 *SOX11* 基因变异可导致感音神经性聋，并伴有不同程度的内耳畸形，这极有可能扩大相关基因致病性变异的表型谱。因此我们建议，在诊断综合征性听力损失时，应同时考虑遗传和临床检测结果相结合，并为患者提供适当的健康管理指导。

1 例 9p 倒位重复伴末端缺失综合征的遗传学分析

郭彩琴
南京医科大学附属无锡妇幼保健院

摘要：目的 联合应用细胞及分子遗传学技术诊断 1 例不明原因智力障碍的儿童。**方法** 应用单核苷酸多态微阵列芯片(SNP array)检测患儿全基因组拷贝数变异(CNV)，G 显带分析患儿及其父母的染色体核型，荧光原位杂交(FISH)鉴定患儿染色体结构变异模式，确认核型结果。**结果** SNP array 发现患儿 9 号染色体 9p24.3p23 区段存在 8.8Mb 缺失且 9p23p21.2 区段存在 18.9Mb 重复，染色体 G 显带核型分析显示患儿存在 1 条 9 号衍生染色体、父母未见异常，FISH 检测明确核型为 46,XY,der(9)del(9)(p23p24) inv dup(9)(p21p23) dn，患儿为新发的 9p 倒位重复伴末端缺失综合征患者。**结论** 细胞与分子遗传学技术的联合应用有助于明确部分智力障碍儿童的病因，并对再发风险评估具有重要价值。

POMT1 基因突变所致先天性肌营养不良症一家系报道

郑富泽 陈龙 邱凉凉 林欣 何琪芳 郑颖 王柠 王志强
福建医科大学附属第一医院

背景与目的 先天性肌营养不良症（Congenital Muscular Dystrophy,CMD）是一组新生儿期或婴儿期起病的遗传性肌肉疾病，以肌张力低下、运动发育落后、关节挛缩并伴血清肌酸激酶升高为主要特征。其中，由蛋白 O-甘露糖基转移酶基因（*POMT1* 和 *POMT2*）致病突变导致的 CMD 相对罕见。在此，我们报道一例 *POMT1* 复合杂合突变病例，通过分析其临床特征以及分子遗传特点，以加深临床医师对此病的认识。
材料与方法 依据规范诊治流程，收集家系临床资料，结合临床病史和体征、实验室检查、影像学、肌肉病理检查，对先证者及其姐姐进行临床诊断。取得家系患者知情同意，取先证者及其姐姐外周血提取 DNA 行全外显子组基因测序，针对所检出的 *POMT1* 基因变异对先证者父母进行 Sanger 测序验证突变。

结果 患者，男性，15 岁，运动能力欠佳伴反应迟钝 10 余年。临床表现为自幼消瘦，走路不稳，易摔倒，不能跑步，伴反应迟钝，记忆力下降，性格内向。症状缓慢进展，近年来出现双手不自主震颤，夜间视力下降。家族史：父母亲无类似症状，姐姐 25 岁，自幼智能略低下，性格内向，活动能力正常。专科检查：四肢近端肌力均 4 级，远端肌力 5 级，肌张力正常，腱反射迟钝，双上肢姿势性震颤。韦氏智能量表示中度下降。辅助检查：血清肌酸激酶（CK）增高 1895U/L，血清肌红蛋白（MYO）增高 182.210ug/L。颅脑 MRI 无异常。左侧肱二头肌活检病理提示总体呈轻度肌源性改变。基因测序结果明确先证者及其姐姐在 POMT1 基因 c.2210_2221del（p.K737_D741delinsN）及 c.2164G>A（p.G722R）均发现致病性复合杂合突变，同时家系共分离验证结果示先证者父亲与母亲各携带一个致病性杂合突变。
结论 由 *POMT1* 致病突变导致的 CMD 相对罕见，临床易致误诊或漏诊，患者常伴有智力障碍注意与精神疾病、先天性肌病等进行鉴别，需综合患者临床表型和基因测序结果确诊。

儿童自闭症患者 miRNA-195 与 BDNF 相关性分析

许华斌
六安市康复医院

目的 通过检测儿童自闭症患者 miRNA-195 和脑源性神经营养因子（brain derivedneuro-trophicfactor， BDNF）水平，探讨 miRNA-195 与 BDNF 的相关性。
方法 选择 2017 年 1 月～2018 年 12 月期间在皖西卫生职业学院附属医院康复医院住院的儿童自闭症患者作为儿童自闭症组，选择同期健康体检的正常儿童作为对照组，检测两组中的 miRNA-195 和 BDNF，同期进行自闭症评价量表（CRAS）评分，并对检测结果进行分析。
结果 自闭症组 miRNA-195 和 BDNF 均显著高于正常对照组（P<0.05），自闭症患者在治疗 6 个月后 miRNA-195、BDNF 和 CRAS 评分均显著降低（P<0.05），相关性分析发现 miRNA-195 与 BDNF 和 CARS 均具有较好相关性（r=0.633，P<0.002；r=0.641，P<0.002），线性回归分析发现 miRNA-195 表达水平与 BDNF 和 CARS 独立相关（β=0.422，P=0.032；β=0.436，P=0.027）。
结论 自闭症患者 miRNA-195 水平明显增高，miRNA-195 随着自闭症治疗后其表达水平随着症状的改善逐渐降低，miRNA-195 可能通过对 BDNF 的调控改善了自闭症的症状，对自闭症的发病机制研究具有一定的参考价值。

A dominant-negative LDHC mutation causing male infertility

Fenghua Lan
PLA 900th Hospital of Joint Logistics Support Force

LDHC4, homotetramer of subunit C, is a lactate dehydrogenase isoenzyme specifically expressed in mammalian testis tissues and spermatozoa. It is a key enzyme in the energy generating system of the sperm, and its role in that system is to convert lactate to pyruvate, or vice versa. In a 33-year-old man with primary infertility, we identified a heterogeneous de novo mutation, LDHC p.L153X, which truncates the subunit C nearly halfway along the polypeptide chain. Model building shows that this truncation eliminates the amino acid residues which participate in the formation of the active site and those directly involved in tetramerization of the enzyme. In vitro assays demonstrated that the mutant LDHC loses catalytic activity when expressed both prokaryotically and eukaryotically. Consistent with this in vitro effect, sperm of the patient showed heavily reduced LDHC4 activity. In routine semen analysis, the patient presents no other abnormalities than decreased sperm motility. Further semen analysis showed that the patient had markedly declined spermatic ATP and lactate levels. Additionally, in vitro catacipation assays demonstrated that most of the spermatozoa from the patient were unable to acquire hyperactivated motility and achieve acrosome reaction, together with a failure to undergo

phosphorylation of sperm protein tyrosine. Finally, evidences were provided that the mutant LDHC subunit can interact with its wild-type counterpart, retarding the execution of normal function of the latter. Our results support two conclusions: mutation of LDHC may be a cause of some unexplained primary male infertility, and heterogeneous non-sense mutation at the middle of subunit C-coding sequence can cause infertility in a dominant-negative manner. The mutation of LDHC provides a opportunity to address the ongoing debate in the reproductive medicine about whether human spermatozoa rely on glycolysis, oxidative phosphorylation or both for their energy production, as well as a chance to investigate the subunit interaction during the formation of active tetramer of LDH as the most canonical isoenzyme superfamily.

KIAA0586 基因所致 Joubert 综合征 1 例临床及基因分析及文献复习

张会婷[1] 廖建湘[2] 刘春艳[3] 方雨[1] 胡俊杰[2]
1.中国医科大学深圳市儿童医院
2.深圳市儿童医院神经内科 3.深圳市儿童医院呼吸内科

目的 丰富我国 Joubert 综合征基因型，分析 Joubert 综合征 23 临床表型，同时对其早期干预、随访提供一定的参考，提高对于潜在有害同义突变评估的意识。
方法 对 1 例 Joubert 综合征女性患儿主要临床表型，影像学特征及基因学检验及验证进行详细描述，对其同义突变进行软件预测，对目前文献库中报道的 Joubert 综合征进行文献总结。
结果 先证者婴儿期间以发育迟缓为主要表现，脑部 MRI 提示“臼齿征”，符合 Joubert 综合征诊断。现 10 岁，智力发育落后，但可与同龄儿童交流，仍伴有反复呼吸道感染，伴有斜视及听力损害，心、肾、肝未见异常，基因检测提示先证者携带 KIAA0586 基因复合杂合变异：c.2724G>A（p.P908P）及 c.3010dupT(p.S1004Ffs*11)，2 个变异均未见文献报道，其中 c.2724G>A 为同义突变。经软件预测致病可能性为 0.9，考虑上述突变为患儿致病突变。
结论 Joubert 综合征是一种罕见的颅脑先天发育畸形，其基因型多，其中 KIAA0586 基因导致的 Joubert 综合征是轻微型，本例先证者是国内首例 KIAA0586 基因导致的 Joubert 综合征患者。早期的康复及长期跟进够取得改善预后。同义突变可以影响转录效率、基因转录的剪接，进而影响蛋白质的功能及丰度，应提高对于潜在有害同义突变的意识。

Predominant Frequency of HLA-B*27 in patients with Ankylosing Spondylitis in Southeastern China

陆娇娇
宁德师范学院附属宁德市医院

Objectives This study was to investigate the polymorphism and distribution of alleles of HLA-B*27 in patients with ankylosing spondylitis in Han population of southeastern China.
Methods A total of 89 peripheral blood samples from southeastern Chinese Han patients with AS that diagnosed according to Modified New York criteria were subtyped using the high-resolution PCR-SSP.Exon 2-3 of HLA-B*27 gene was amplified and sequenced to further confirm the HLA-B*27 subtype.
Results The frequency of HLA-B*27 was 99.87% in AS patients.Three subtypes, B*2704, B*2705 and B*2706,were identified.The frequencies for these three alleles were B*2704 in 84/88(95.46%),HLA-B*2705 in 3/88(3.41%) and HLA-B*2706 in 1/88 (1.13%) of the B*27 positive patients,respectively.
Conclusions Our study shows that B*2704 has an overwhelming frequency in southeastern Chinese Han AS patients.A combined analysis including previous studies of B*27-subtype distributions in Chinese Han populations showed that B*2704 may originate from the

southern Han and then migrate and spread to the northern areas,and B*2705 show the opposite result.

DNA methylation age acceleration is associated with age of onset in a Chinese spinocerebellar ataxia type 3 family

Ming Zhang[1,4] Jiahao Li[1] Anli Shu[2] Wanli Yang[1] Chunling Wan[3] Mingcheng Zhou[1,4]
1.Tongji University
2.Hunan University of Medicine
3.Shanghai JiaoTong University
4.The First Rehabilitation Hospital of Shanghai

Aim Spinocerebellar ataxia type 3 (SCA3), also known as Machado Joseph disease (MJD), is a common dominantly inherited ataxia, and has heterogeneous clinical features and variable age of onset, ranging from 10-78 years. Repeats variability of *ATXN3, HTT*, *ATN1*and *ATXN2* can explain partially but not fully SCA3 age of onset heterogeneity. Aging is a reported modifier of SCA3 severity and closely linked to DNA methylation (DNAm). DNAm age acceleration was associated with disease risk/variable disease phenotypes in several repeat associated neurodegenerative diseases (such as Huntington's disease and Amyotrophic lateral sclerosis). The current study aims to understand if DNAm age acceleration is associated with SCA3 age of onset.
Methods The ataxia family was recruited from Hunan university of medicine (China) in 2004. This family included 9 patients and 48 family members. Age of onset was defined as the time when unsteady gait appeared. Informed consent was obtained from each study participant in accordance with the ethics review boards at Hunan University of Medicine (China).Whole exome sequencing (WES) was performed in three DNA samples from two affected individuals (IV_{32}, IV_{21}) and one healthy control (IV_{17}) at RunningGene Inc. (Beijing, China). We also analyzed the (CAG)n repeatsof fourgenes (*ATXN3*, *HTT*, *ATN1*, *ATXN2*)
using in-house designed FAM fluorescently labeled primers. In addition, we performed a genome-wide DNAm study using the Infinium MethylationEPIC BeadChip (Illumina) at novogene Co. LTD (Beijing, China). We used multivariate linear regression to analyze the link between genetic variations (e.g., trinucleotide repeats) or DNAm age acceleration and SCA3 age of onset, with the adjustment for the pathogenic *ATXN3* CAG repeat number.
Results All patients showed unsteady gait, deterioration of extremities coordination, speech (dysarthria) and swallowing problems (dysphagia, choking on eating/drinking) and oculomotor abnormalities, with variable age of onset ranging from 27 to 52 years. We identified the *ATXN3* CAG repeat expansion (14/72) in the proband (IV_{30}) and other affected individuals. We found that DNAm age acceleration is associated with variable age of onset (p-value=0.0023, B= -1.26) in the current family, suggesting that every 5-year increase in DNAm-age acceleration is corresponding to a 6.3 year earlier disease onset. This association remains significant after the adjustment to *ATXN3* CAG repeats (adjusted p-value=0.0365, B=-0.999). Of note, we found no significant association between DNAm of single-CpG locus/CpG-SNPs and SCA3 age of onset in the current family.
Conclusion Our findings suggested that DNAm age acceleration might be a SCA3 age of onset modifier. Further investigations are encouraged in extended SCA3 cohorts to clarify the role of epigenetic aging in modifying disease onset.

ALG1 基因相关先天性糖基化障碍伴婴儿痉挛症 2 例及文献复习

王秋红
解放军总医院儿科医学部

目的 探讨 ALG1 基因相关先天性糖基化障碍（ALG1-CDG）患儿的临床及遗传学特征。
方法 回顾性分析 2 例 ALG1-CDG 患儿的临床资料及基因检测结果，并复习相关文献。

结果 2 例患儿来自同一家系，其均出生后即存在精神运动发育落后，且均在早期出现痉挛性发作，脑电图呈高峰失律，伴或不伴有小头畸形，肌张力低下，血小板减少症，乳头内陷，眼部异常等。基因检测提示 2 例患儿均为 ALG1 基因复合杂合变异，c.1129 A>C(p.Met377Leu)；c.1263+3A>T，两个位点分别遗传自父母。国内外文献报道的 ALG1-CDG 患儿共 70 例，国内仅报道 2 例。文献复习发现 ALG1-CDG 患儿主要表现为癫痫，精神运动发育落后、肌张力低下及小头畸形等神经系统异常，同时可存在其他多系统疾病。

结论 ALG1-CDG 患儿可表现为婴儿痉挛症，变异位点 c.1129 A>C(p.Met377Leu)，c.1263+3A>T 国内外均未见报道，拓展了 ALG1 表型谱及基因谱。对于不明原因的婴儿痉挛症患儿，当同时存在肌张力低下或小头畸形等神经系统表现，尤其合并其他多系统表现时，需考虑 ALG1-CDG 的可能，必要时行基因检测，有助于下一步的遗传咨询。

Analysis of Glioma Heterogeneity and its Correlation with Clinical Phenotype

Lejin Tian Weidong Tian
Fudan University

Understanding the tumor heterogeneity of gliomas and linking it to clinical relevance are of both theoretical and clinical significance. However, performing large-scale single-cell sequencing on glioma samples with clinical phenotypes is still not yet practical. Given that public databases have already stored a large number of bulk RNA-seq data produced from glioma samples with recorded clinical phenotypes, we can deconvolve bulk RNA-seq data into a combination of tumor cell type-specific expression profiles, and estimate the proportion of each tumor cell type in these samples. Then, we can investigate the link between tumor heterogeneity and clinical phenotypes. However, deconvolution requires the knowledge of tumor cell types and their corresponding cell type-specific expression profiles. Therefore, in this proposal we aim to construct an integrated single-cell resource for glioma by integrating currently available single-cell RNA-seq data. By using the normal developmental lineage of astrocyte and oligodendrocyte as the reference, we will determine the differentiation stage of each tumor cell in the integrated resource, and use it as the annotation. On the basis of classified tumor cells, on the one hand we will investigate the heterogeneity of tumor cells for each type of glioma and explore the possible molecular mechanism. On the other hand, we will conduct tumor cell type deconvolution on glioma's bulk RNA-seq data, to investigate the link of tumor heterogeneity to clinical relevance, and develop a prognostic model based on the clinically relevant tumor cell types.

College Students' Suicidal Early Warning Factor Screening and the Identification of Suicide Risks

Han ke[1,2]
1.Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Shanghai Jiao Tong University
2. Shanghai Key Laboratory of Psychotic Disorders, and Brain Science and Technology Research Center, Shanghai Jiao Tong University

Objective This study was to explore the main influencing factors of suicide risk through screening and establish an early warning model, so as to give interventions on high-risk students.
Methods We collected data from a cohort study of Jining Medical College. The participants in this study were 3630 Chinese college students from 28 provinces. We conducted surveys in the first year and third year of students in college, including basic personal information, family factors, psychological factors, and life factors of college students. Logistic regression models were used to screen the early warning factors and four machine learning models were used to establish early warning models.

Results There were 11 factors related to suicide risk that eventually obtained through screening, which were used for suicide risk early warning. These factors include depression level, life satisfaction, happiness, neurotic personality, academic commitment, relatives' mental illness, parental personality, student political status, and the handling of interpersonal relationships. A random forest model was adopted, and it verified that these 11 suicide risk early warning factors can effectively predict suicide risk within two years with a 0.952 AUC score. Moreover, the factors obtained by screening can be used to identify people with high risk of suicide in the same year, as the random forest model's prediction AUC score reached 0.959.
Conclusion The excavated warning factors showed great effective in predicting and identifying suicide risk of college students. Based on this study, we could suggest some interventions to avoid students going into high suicide risk.

Global Research Trends in Gestational Diabetes Mellitus from 2000 to 2020: A Bibliometric Study

Hongyan Chen[1,2] Fengxiang Wei[1,2] Xiaohang Chen[2] Yingyao Tan[1,2]
1.Guangdong Pharmaceutical University
2.Genetic Laboratory of Shenzhen Longgang Maternal and Child Health Hospital

Aims To analyzing the major research areas and trends in GDM between 2000 and 2020.
Methods Studies on GDM, published between the years 2000 and 2020 were retrieved from the Web of Science Core Collection database. Then, we used Microsoft Excel, VOSviewer, and CiteSpace softwares to analyze publication outcomes, journals, countries/regions, keywords, cited literature, research areas, and research frontiers.
Results A total of 22,713 publications were retrieved, with 21722 publications being included this scientometric analysis. In terms of absolute publication numbers, the USA was the leading country (6145，28. 29%), followed by China (2125, 9. 78%). Overall, the number of studies on GDM are increasing globally. The rapid growth in study numbers begun in 2010, with the highest number of publications being in 2020 (2382). The Journal of maternal-fetal & neonatal medicine (592), Diabetes care (496), and Plos one (434) were the three journals with most publications. Clustering analysis revealed 13 themes across all fields. Physical activity were emerging trends. Co-word analysis showed that subject high-frequency keywords were: risk factor, obesity, insulin resistance, prevalence, association, and birth weight. Moreover, centrality indices identified the most influential keywords to be: body mass index, risk factors, gestational weight gain, obesity, insulin resistance, metformin, and insulin. A total of 134 burst keywords with highest citation strengths were detected. They showed research topics in 7 research fields, of which six were research frontier subtopics.
Conclusion This bibliometric analysis revealed that the number of studies on gestational diabetes mellitus are increasing. For two decades, The United States has been the global leader in the number of published studies. Studies on GDM are mainly from developed countries, with a few from developing countries. An emerging field of research aims at elucidating the association between physical activity and gestational diabetes mellitus.

全外显子组测序的基因检测在肾移植中的应用价值研究

陈若洋 袁晓东
上海交通大学医学院附属仁济医院

背景 目前，我国供肾来源主要来自于公民逝世后器官捐献，但仍有一部分肾脏来自于亲属间供肾肾移植。由于一部分肾病具有遗传性，但是在亲属供肾者体内并未表达，因此，需要在移植前对供受者进行筛查。
方法 我们回顾性纳入 2021 年 1 月 1 日到 2021 年 6 月 30 日在我院拟行肾移植手术的亲属供肾者，并对其外周血进行收集，进行全外显子组测序。

结果 一共有 39 例供受者纳入分析，其中 3 例有特殊性表达，2 例表达为 Alport 综合征，1 例表达为多囊肾，此 3 例未进行手术，避免了肾移植术后供肾肾病的风险。
结论 Alport 肾病综合征和多囊肾有家族遗传性,全外显子基因检测有助于指导临床医师在亲属活体肾移植评估中对相关供者进行选择。亲属活体供者含有遗传性肾病易感基因是肾移植后供者供肾后发生尿毒症的高危因素。

Alström 综合征 3 例报告并文献复习

付东霞[1] 卫海燕[1] 苏畅[2] 杨威[1]
1.河南省儿童医院
2.北京儿童医院

背景 Alström 综合征是一种以多器官受累为特征的常染色体隐性疾病，包括神经感觉视力和听力丧失、儿童肥胖、糖尿病、心肌病、性腺功能减退、肺、肝、肾功能衰竭和系统性纤维化。
目的：分析总结中国 Alström 综合征的临床、实验室检查及遗传学特点。
方法：分析就诊于郑州大学附属儿童医院 3 例 Alström 综合征，并总结既往已报道的中国病例，对临床特征、实验室检查及遗传学特点进行分析。
结果：3 例 Alström 综合征的 ALSM1 基因突变中 c.1894C>T、c.9148_9149delCT 和 c.9154__9155delCT 为未见报道的新变异。共检索到 39 个家系 53 例中国患者，生后第一年大多数出现肥胖、视网膜病变，8 号外显子的 c.2084C>T 为中国人热点变异。中国人 10 号外显子突变患者糖尿病、肾病、矮小症高发，16 号外显子肥胖高发。**结论：**AS 是一种由 ALSM1 基因突变引起疾病，我们发现了未被报道的 3 个新变异，扩大了中国患者基因突变谱。本研究发现热点变异为 c.2084C>T，中国人 10 号外显子变异患者扩张性心肌病、肾病、矮小症高发，16 号外显子变异患者肥胖高发。

非 HLA 抗体在肾脏移植中的应用价值研究

陈若洋 袁晓东
上海交通大学医学院附属仁济医院

背景 肾移植是治疗终末期肾病最有效的方法，肾移植术后的排斥反应会影响肾移植患者的预后和生存。非 HLA 抗体也会导致移植肾的排斥反应。
方法 我们回顾性收集了 2018 年 1 月 1 日到 2021 年 6 月 30 日在我院行肾移植手术的患者，并抽取患者外周血检测患者非 HLA 抗体，分析非 HLA 抗体与移植肾排斥反应的关系。
结果 一共有 1594 例患者纳入分析，其中非 HLA 抗体阳性患者为 788 例，非 HLA 抗体阴性患者 806 例，其中 AT1R 阳性者 420 例，GSTT1 阳性者 475 例，其他抗体阳性者 672 例。其中经穿刺活检发生 AMR 者 15 例，其 PRA 均阴性，非 HLA 抗体阳性，因此诊断为非 HLA 抗体造成的抗体介导的排斥反应。
结论 GSTT1 即谷胱甘肽 S-转移酶 θ1，催化还原型谷胱甘肽与多种亲电和疏水化合物结合，主要在肝、肾中表达，属于次要组织相容性抗原。有些人缺失 GSTT1 基因。受者缺失 GSTT1 基因，供者具有 GSTT1 基因，则受者会产生 GSTT1 抗体，攻击移植物，造成 AMR。41.7%（5/12）的 GSTT1 抗体阳性的肾移植患者发生急性排斥事件，GSTT1 抗体阳性是肾移植患者急性排斥事件的危险因素。

半侧颜面短小畸形患者颞下颌关节发育情况临床研究

薛晓晨 王旭东
上海交通大学医学院附属第九人民医院

目的及背景 半侧颜面短小畸形（Hemifacial Microsomia, HFM），是由第一、二腮弓发育不良引起的颅颌面部先天性疾病。该病发病率仅次于唇腭裂，是第二常见的颅颌面部先天性疾病，多为散发病例，偶有家族聚集病例，多为单侧发病，偶有双侧发病病例。其经典诊断标准包含眶部（Orbit）、下颌骨（Mandible）、外耳（Ear）、面神经（Nerve）及软组织（Soft-tissue），简称为 OMENS 诊断标准。近年来也发展出 OMENS+诊断标准，旨在除经典五项之外增加其他诊断标准，用于进一步对患者进行分类以及指导治疗。

方法 本研究收集了 103 例至我科就诊的 HFM 患者资料，并通过颞下颌关节磁共振检查发现不同患者具有不同程度的颞下颌关节盘发育异常，且该发育异常程度与下颌骨升支及髁突的发育异常程度呈现相关性。

本研究将不同的颞下颌关节盘发育程度进行分型（D 分型），定义如下：

D0：正常关节盘尺寸及形态；

D1：关节盘形态异常，但其长度足以覆盖（重建的）髁突；

D2：关节盘形态异常，其长度不足以覆盖（重建的）髁突；

D3：未见关节盘；

并对纳入样本的 D 分型分布、下颌骨 M 分型分布以及两种分型的相关性进行统计。

结果 纳入样本的 M 分型及 D 分型分布均较为平均，且 M 分型与 D 分型呈正相关。这些结果印证了下颌支与关节盘作为同源且毗邻的组织，其发育受到影响的程度相近，畸形程度相似的猜想。

讨论与展望 半侧颜面短小畸形定义广泛、症状复杂、表现多样，经典的 OMENS 诊断标准为病例的描述和治疗提供了极大的便利，同时我们看到对于 OMENS 诊断标准细化、丰富化的必要性。本研究提出 OMENS+D 诊断标准，期望针对 HFM 患者颞下颌关节盘发育情况做到精确诊断、优化治疗，也期待能为该病的发育学及遗传学研究提供更充分的证据。

应用利拉鲁肽治疗 Prader- Willi 综合征 1 例临床观察

张英娴 卫海燕 马晓翠 陈永兴
河南省儿童医院

目的 介绍 1 例 Prader- Willi 综合征患儿应用利拉鲁肽治疗疗效分析，为临床医师提供治疗指导。
方法 先证者为郑州大学附属儿童医院内分泌遗传代谢科收治 1 例 Prader- Willi 综合征患儿，患儿因贪食明显，合并 2 型糖尿病，病初给予给予胰岛素（甘精胰岛素+门冬胰岛素注射液）和二甲双胍治疗，血糖较前好转，但贪食明显，给予加用 GLP-1 受体激动剂利拉鲁肽治疗进行疗效评价。
结果 病初给予给予胰岛素（甘精胰岛素+门冬胰岛素注射液）和二甲双胍治疗，血糖稳定出院，因平素贪食，体重持续增加血糖波动 4-18mmol/l，血糖控制差，给予加用利拉鲁肽皮下注射，起始剂量 0.6mg，2 天后调整为 1.2mg 皮下注射，二甲双胍片 0.5g 每天 3 次口服治疗，第二天患儿出现明显的饱腹感，食欲明显下降，停用胰岛素治疗，观察三天，血糖稳定，好转出院。1 周、3 周、4 个月、10 个月的电话随访患儿无贪食，食欲明显下降，血糖控制良好。
结论 Prader- Willi 综合征患儿应用 GLP-1 受体激动剂利拉鲁肽后患儿食欲较前明显下降，体重较前减轻，目前停用胰岛素治疗后血糖控制良好。
讨论 Prader Willi 综合征（PWS）1956 年，Andrea Prader、Heinrich Willi 首次报道普拉德-威利综合症 俗称：小胖威利综合征肌张力低下-智能障碍-性腺发育滞后-肥胖综合征，三低综合征。不同年龄段症状有差异：新生儿期肌张力低下并喂养困难、婴幼儿期体格和精神运动发育迟缓、儿童

期贪食、肥胖、身材矮小、精神发育落后，青春期肥胖、性腺发育不良、学习困难和行为异常。目前缺乏有效的治愈 PWS 的方法，早期予以严格饮食控制、增强体育锻炼、应用重组人生长激素等综合治疗，在一定程度上可提高 PWS 患者的运动能力及骨密度、改善终身高等，但不能阻止贪食肥胖、皮肤自损及其他异常行为，且需要长期专人管理，严重影响患儿家庭的生活质量。近年来，对 PWS 贪食肥胖发生机制及干预措施的相关研究取得了较大进展，为改善 PWS 患儿的预后提供了新的治疗方向。GLP-1 受体激动剂 GLP-1 主要在餐后由回肠和结肠的神经内分泌细胞合成，餐后 GLP-1 的分泌异常与肥胖和 2 型糖尿病相关。GLP-1 受体激动剂如利拉鲁肽（liraglutide）和艾塞那肽（exenatide），有延缓胃排空、抑制食欲的作用，从而降低体重。利拉鲁肽与人体 GLP-1 的结构有 97%的相似性，皮下注射后在血浆中的半衰期为 13 小时，每日皮下注射一次，是 FDA 批准的可用于治疗肥胖的 GLP-1 受体激动剂。

半侧颜面短小畸形患者颧骨颧弓发育情况临床研究

薛晓晨 王旭东
上海交通大学医学院附属第九人民医院

目的及背景 半侧颜面短小畸形（Hemifacial Microsomia, HFM），是由第一、二腮弓发育不良引起的颅颌面部先天性疾病。该病发病率仅次于唇腭裂，是第二常见的颅颌面部先天性疾病，多为散发病例，偶有家族聚集病例，多为单侧发病，偶有双侧发病病例。其经典诊断标准包含眶部（Orbit）、下颌骨（Mandible）、外耳（Ear）、面神经（Nerve）及软组织（Soft-tissue），简称为 OMENS 诊断标准。近年来也发展出 OMENS+诊断标准，旨在除经典五项之外增加其他诊断标准，用于进一步对患者进行分类以及指导治疗。

方法 本研究收集了 175 例至我科就诊的 HFM 患者资料，并通过 CT 三维重建发现不同患者具有不同程度的颧骨颧弓发育异常，且该发育异常程度与外耳的发育异常程度呈现相关性。

本研究将不同的颧骨颧弓发育程度进行分型（Z 分型），定义如下：

Z0：颧弓及颞骨颧突形态正常；

Z1：颧弓及颞骨颧突形态异常；

Z2：颧弓或颞骨颧突缺失，伴或不伴其他结构形态异常；

Z3：颧弓及颞骨颧突均缺失；

并对纳入样本的 Z 分型分布、外耳 E 分型分布以及两种分型的相关性进行统计。

结果 纳入样本的 Z 分型及 E 分型分布均较为平均，且 Z 分型及 E 分型呈正相关。这些结果印证了颧骨颧弓与外耳作为同源且毗邻的组织，其发育受到影响的程度相近，畸形程度相似的猜想。

讨论与展望 半侧颜面短小畸形定义广泛、症状复杂、表现多样，经典的 OMENS 诊断标准为病例的描述和治疗提供了极大的便利，同时我们看到对于 OMENS 诊断标准细化、丰富化的必要性。本研究提出 OMENS+Z 诊断标准，期望针对 HFM 患者颧骨颧弓发育情况做到精确诊断、优化治疗，也期待能为该病的发育学及遗传学研究提供更充分的证据。

Novel variant in CHRNA4 with benign childhood epilepsy with centrotemporal spikes and contribution to precise medicine

Neng Xiao
Chenzhou First People's Hospital

Background Benign childhood epilepsy with centrotemporal spikes (BECTS) or benign rolandic epilepsy is the most common epileptic syndrome in school-age children. Genetics is an important factor in BECTS pathogenesis, and <10 genes were associated with BECTS. This study aimed to identify novel genetic causes of BECTS.

Methods We conducted whole-exome sequencing on a patient with BECTS and validated the findings by Sanger sequencing in a pedigree with three patients.
Results CHRNA4 c.1007G>A was identified in three patients with BECTS in a pedigree. Carbamazepine, which should be carefully used in BECTS, was observed to be effective in the treatment of our atypical BECTS proband based on the molecular diagnosis of CHRNA4.
Conclusion This is the first study on CHRNA4 variant in BECTS, which widened the genetic spectrum of BECTS and contributed to precise medicine in BECTS.

A novel mutation in XPNPEP3 of a patient with nephronophthisis-like nephropathy: A case report

Zhen Zhen Yue Yuan Lu Gao Qin Wang Lang Cui Xi Chen Jia Na
Beijing Children's Hospital, Capital Medical University, National Center for Children's Health

Background Nephronophthisis（NPHP）is a progressive tubulointestinal kidney condition that demonstrates an AR inheritance pattern. Up to now, more than 20 various genes have been detected for NPHP, with NPHP1 as the first one detected. XPNPEP3 mutation is related to NPHP-like 1 nephropathy and late onset NPHP.
Methods In this article, we report the case of a 13-year-old female child with mental retardation presented with convulsions and fatigue for 2 years, edema, shortness of breath and paroxysmal nocturnal dyspnea in last 10 days. The examination of cardiac ultrasonography showed left cardiac insufficiency, enlargement of the whole heart, ventricular hypertrophy, a massive pericardial effusion，moderate mitral regurgitation, mild aortic regurgitation, mild tricuspid and pulmonary regurgitation and a severe reduction in ejection fraction (35%). The electrocardiogram showed paroxysmal ventricular tachycardias and ST-T wave changes. After the collection of blood sample from proband and her parents, WES was performed to identify the possible variants in the proband from a consanguineous marriage. The functional importance of variants was estimated by bioinformatic analysis. In the affected proband and her parents, Sanger sequencing was conducted for variants' confirmation and segregation analysis.
Results Using WES, we could detect a novel homozygous splicing mutation in XPNPEP3 (c.970-2A>G). We use ESE finder3.0 to predict the effect of the mutation, and results are showed that the splicing function of XPNPEP3 might be affected by c.970-2A>G for lacking two splicing factors (SRSF2 and SRSF5). A same prediction result was gotten by two bioinformatic softwares, HSF (Human Splicing Finder) and NetGene2 Server that c.970-2A>G in XPNPEP3 might probably affect the splicing of the gene.
Conclusion A novel mutation in XPNPEP3（c.970-2A>G）is the first reported in Chinese family so far. It may cause NPHPL1 in childhood age and had seizures, mental retardation, and hypertrophic dilated cardiomyopathy. Gene sequencing helps us diagnose this disease early.

川崎病合并巨大冠状动脉瘤 1 例超声随访观察

曾海生
东莞市儿童医院

目的 川崎病（KD）是一种病因未明、以全身性中小血管炎为主要病理改变的疾病，易侵犯冠状动脉；冠状动脉瘤是其常见而严重的并发症，是造成儿童后天性心脏病的重要原因。本研究拟通过超声随访巨大冠状动脉瘤 KD，了解其预后及巨大冠状动脉瘤的病变规律，以提高对该类疾病的治疗及管理水平。
方法 2021 年 5 月在我院诊断为 KD 合并巨大冠状动脉瘤（右侧冠状动脉迂曲增宽，呈瘤样扩张，Z 值约 12.5）的患儿 1 例，对其发病各期随诊中的超声心动图进行分析。
结果 患儿在发病Ⅰ期（6 天）超声心动图表现为：三尖瓣返流（轻度），肺动脉压力增高。Ⅱ期（11 天）超声心动图表现为：左冠状动脉内径：2.3mm（Z 值约 0.5）；右侧冠状动脉迂曲增宽，右冠状动脉内径：4.5mm（Z 值约 8.1），考虑右冠状动脉扩张。Ⅱ期（17 天）超声心动图表现：

同 11 天结果，无变化。Ⅲ期（28 天）超声心动图表现为：左冠状动脉内径：2.1mm（Z 值约 0.12）；右侧冠状动脉迂曲增宽，呈瘤样扩张，宽约 6.0mm（Z 值约 12.5），考虑右侧巨大冠状动脉瘤。经过低分子肝素、阿司匹林、泼尼松、华法林、双密达莫等治疗，在Ⅳ期（40 天）复查超声心动图表现为：左冠状动脉内径：2.3mm（Z 值约 0.77）；右侧冠状动脉迂曲增宽，呈瘤样扩张，宽约 4.8mm（Z 值约 8.93）。Ⅳ期（70 天）超声心动图表现为：左冠状动脉内径：2.3mm（Z 值约 0.46）；右侧冠状动脉走行迂曲、增宽，宽约 2.8mm（Z 值约 2.91）。Ⅳ期（100 天）超声心动图表现为左冠状动脉内径：2.2mm；右冠状动脉内径：2.7mm，未见迂曲。

结论 巨大冠状动脉瘤川崎病在早期识别治疗十分重要，其发生主要在发病后 17-28 天，且合并冠状动脉迂曲，采用肝素、激素、阿司匹林等治疗有明显效果，其在治疗 10 天左右缩小，40 天左右明显缩小，70 天左右完全消退。

肾上腺脑白质营养不良疑似患者 ABCD1 基因新突变分析

雷佳凡 许雪青
南方医科大学深圳医院

目的 对 1 例肾上腺脑白质营养不良(ALD)疑似患者及其父母进行 ABCD1 基因突变分析，并排除假基因的干扰。

方法 提取外周血 DNA 对该基因所有外显子进行 Sanger 测序。通过对各个外显子单独进行全基因组序列比对，分析假基因对各个外显子区域的影响。为排除假基因干扰，同时全面分析整个 ABCD1 的突变情况，利用 RT-PCR 技术，结合 Sanger 测序分析 cDNA 突变位点；采用生物学信息的方法对该突变位点进行功能预测分析。

结果 发现第 7 号外显子存在多个突变，包括多个已被报道认为是致病突变的位点。生物信息学分析发现该基因存在多个假基因，特别是在第 7 号外显子，长达 147bp 的片段相似性高达 95%，提示基因组 DNA 的分析可能受到假基因干扰。通过 RT-PCR 结合 Sanger 测序分析疑似患者肾上腺脑白质营养不良基因 ABCD1 外显子 1 上存在 1 个未见报道的错义突变，使原来编码的亮氨酸被脯氨酸取代；生物信息学分析提示该突变是有害的，会导致肾上腺脑白质蛋白的结构发生改变。疑似患者父母均无此突变发生。

结论 在中国人肾上腺脑白质营养不良疑似患者中发现一个新的 ABCD1 基因突变，该突变位于跨膜区，使原来编码的亮氨酸被脯氨酸取代，可能会引起肾上腺脑白质蛋白的结构改变。此外，ABCD1 基因的突变分析可能会受到假基因的干扰，特别是解读读长较短的高通量测序数据时要慎重。

ACTH 预防儿童激素敏感型肾病综合征复发的疗效小样本观察

曾海生 邹贤 陈玉梅 谢明玉 陈婉婷
东莞市儿童医院

目的 探讨促肾上腺皮质激素（ACTH）在预防儿童激素敏感型肾病综合征复发的疗效及肾上腺皮质功能的改善情况。

方法 选取激素敏感型肾病综合征患儿为研究对象,在泼尼松减量至隔天 15 mg 时，将患儿随机分为观察组与 ACTH 组，其中观察组继续规范使用泼尼松治疗，即每月减泼尼松 5mg，三个月后停用；ACTH 组在规范使用泼尼松治疗的基础上加用 ACTH 治疗，剂量为 1U/kg.d（总量不超过 25U），共 5 天，连用三个月，并在治疗前后抽血（早上 8-10 时）检查患儿血中的皮质醇、促肾上腺皮质激素的水平，观察二组半年内复发的次数及肾上腺皮质功能变化。

结果 ACTH 组 7 例半年内复发 4 例（57.1%），治疗前皮质醇 102.51±45.26nmol/L、促肾上腺皮质激素 28.32±14.51pg/ml，治疗三月后皮质醇 115.36±48.18nmol/L、促肾上腺皮质激素 30.61±16.72pg/ml，治疗前后皮质醇、促肾上腺皮质激素水平差异比较无统计学意义

（P>0.05）；观察组 9 例半年内复发 5 例（55.6%），与 ACTH 组复发率比较差异无统计学意义（P>0.05）。

结论 小样本观察 ACTH 预防儿童激素敏感型肾病综合征复发的效果不佳,且皮质醇、促肾上腺皮质激素水平改善不明显，不建议预防性用药治疗。

宏基因组测序分析特发性矮小儿童肠道菌群构成的特征及相关发病机制研究

颜露燕 余永国
上海交通大学医学院附属新华医院

目的 比较特发性矮小（idiopathic short stature，ISS）儿童与健康儿童的肠道菌群差异，分析肠道菌群与 ISS 的相关性及可能的致病机制。

方法 研究对象包括 60 名年龄 3～14 岁儿童，其中 30 例儿童被诊断为 ISS（ISS 组），另 30 名为正常身高健康儿童（对照组）。采用鸟枪法宏基因组测序对两组儿童粪便中的微生物群落进行分析，比较两组之间的差异。

结果 两组间 Alpha 多样性指标无显著差异。Beta 多样性指标显示两组间菌群结构差异较大。ISS 组中 Bacteroides_plebeius、Eubacterium_eligens、Parasutterella_excrementihominis、Megamonas_funiformis、Haemophilus_parainfluenzae、Clostridium_symbiosum 等菌种减少，Bifidobacterium、Anaerostipes 等菌增多。通过对代谢通路注释，发现在特发性矮小儿童中乙酸辅酶 A 转移酶减少，4-氨基丁酸降解途径及 L-赖氨酸降解富集增加，提示特发性矮小儿童肠道丁酸盐产生减少。

结论 特发性矮小儿童肠道细菌群落结构发生显著变化，丁酸产生减少可能与特发性矮小的发生相关。

中国南方 ALS 患者 C9orf72 基因突变的 Repeat-primed PCR 检测分析

黄治中 许雪青
南方医科大学深圳医院

ALS 是一种破坏性的神经退行性疾病，特征为上部和下部脊髓运动神经元的渐进性丧失，已有数十种基因突变被认为与其相关，其中主要为点突变。但这些基因点突变所占病人比例较低，仍有大量 ALS 病人（无论是家族性还是散发患者）未能检测出阳性突变。最近有研究发现 9 号染色体第 72 开放阅读框(C9orf72)的非编码区的 6 核苷酸 GGGGCC 重复扩增会导致 ALS。在正常人群中重复范围是 2~23 次，一些呈现 ALS 或 FTD（并症状（或并发症）患者具有约 700~1600 次重复。在西方人群及其后裔中，该基因突变患者可占家族性 ALS 患者的 39.3%及家族性 FTD 患者的 24.8%，在散发的 ALS 或 FTD 患者中也有 4%~8%携带该突变。这些超大范围高 GC 动态突变普通 PCR 及序列测定分析无法检出。重复引物 PCR 技术(Repeat-primed PCR)结合 7’-脱氮-2’脱氧 GTP(7-deaza-2-deoxy-GTP)的使用实现了高效率检测并提高了检测灵敏度。我们在 Haeusler 等报道的实验方法的基础上做了改进，并成功拼接出了重复次数分别为 70、60、40 和 20 的阳性对照质粒，对 3 名家族性 ALS 患者及 113 名散发 ALS 患者做 C9orf72 筛查，结果未发现有 GGGGCC 6 核苷酸超大范围动态突变。这与之前 Zou 等、Liu 等报道的结果一致，而唐璐等报道在 401 例散发 ALS 患者中筛查到 3 例 C9orf72 基因突变患者。本研究结果提示 C9orf72 重复片段的异常可能不是中国南方人群 ALS 的主要致病突变，研究中获得的不同 GGGGCC 重复次数的阳性质粒将有助于 C9orf72 基因突变的筛查。

A novel heterozygous mutation of XPO5 causes familial focal segmental glomerulosclerosis

HafizMuhammadJafar Hussain Jin Yuanmeng Yu Shuwen Tong Jun Weng Qingjie Fang Zhengying Liu Jian Ma Jun Pan Xiaoxia Ren Hong Chen Nan Xie Jingyuan
Department of Nephrology, Institute of Nephrology, Shanghai Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China.

Objective Focal segmental glomerulosclerosis (FSGS) is a clinically heterogeneous nephropathy that is characterized by segmental scarring histologically which involves a part of the glomerulus and only affects some but not all glomeruli sampled. The clinical manifestations can be nephrotic syndrome or with hematuria, hypertension or renal insufficiency. Both exogenous and endogenous etiologies are involved in FSGS.
Methods To detect pathogenic mutations in FSGS patients, whole exome sequencing (WES) was conducted on a large Chinese cohort that consisted of 40 families and 77 sporadic FSGS patients. Subsequently Sanger sequencing was performed to check segregation of the identified variant(s) and for validation in 200 ethnically matched healthy controls. Moreover, *in-silico* analysis was implemented to characterize the pathogenicity based on predicted structural and stability changes. Inclusion criteria was 1) at least one family member had renal biopsy confirmed FSGS; 2) at least another family member had proteinuria, hematuria or renal failure with unknown reason if only one family member had renal biopsy confirmed FSGS.
Results A novel heterozygous mutation of *XPO5* (c.T1655C; p.V552A) , which is the part of nuclear pore complex (NPC), was identified in 2 families affected with FSGS. Sanger sequencing confirmed segregation of the identified variant with the disease in the families and absent in healthy controls. No other candidate variant was detected in these two FSGS families. Furthermore, *in-silico* analysis revealed that the identified variant is highly conserved and pathogenic based on multiple alignment, predicted structural and stability changes respectively. The onset age of proband (III:2) of FS133 was 22 years, who had proteinuria (4+ g/24h), increased ACR value (119.87 mg/mmol), hypertension (147/90 mmHg) and biopsy confirmed FSGS. The onset age of father (II:3) was 56 years who had proteinuria (3+g/24h), hematuria (1+ rbc/hpf), higher uric acid (611 mmol/L) level and severely increased ACR (74.03 mg/mmol)). While uncle of the proband (II:1) had hematuria (2+ rbc/hpf) and sister of proband (III:3) had moderately increased ACR value (mg/mmol). All these 4 individuals (III:2, II:3, II:1 & III:3) were detected with a heterozygous mutation (c.T1655C; p.V552A) in *XPO5*. On the other hand, mother (II:4) and uncle (II:2) who did not show any kidney related clinical symptoms were wild-type for the identified mutation. In second family (FS005), the proband's (II:3) onset age was 23 years who was detected with heterozygous *XPO5* mutation (c.T1655C; p.V552A), had higher uric acid level (512 mmol/L)& SCr levels (332 umol/L) and biopsy confirmed FSGS. Father of the proband (I:1) had high uric acid (446(mmol/L) and SCr (186 (umol/L). The sister (II:2) showed slightly high uric acid (377 mmol/L) and hematuria (3-7 rbc/hpf).
Conclusion Our study provides the first evidence of familial *XPO5* inheritance in association with FSGS worldwide. Before a homozygous mutation (c.G1654A; p.V552Ile) was reported in a Turkish child affected with steroid-resistant nephrotic syndrome and speech development delay, whose onset age was 2 years. Moreover, this is the fifth *XPO5* variant in association with any disease and first from Asia. Additionally, our findings can expand familial FSGS genes pool.

1 例 Wiedemann-Steiner 综合征使用 rGH 治疗 5 年随访

张英娴 陈永兴 王会贞 李涛
河南省儿童医院

目的 报道 1 例由 KMT2A 基因突变导致 Wiedemann-Steiner 综合征患者，应用重组人生长激素治疗 5 年疗效分析，为临床医师提供治疗指导，同时为遗传咨询和产前诊断提供依据。

方法 先证者为郑州大学附属儿童医院内分泌遗传代谢科收治 1 例矮小症患儿，应用全外显子二代测序技术对先证者进行致病基因筛查，采用 Sanger 测序方法对父母进行验证和遗传分析确诊此病，应用聚乙二醇重组人生长激素注射液（金赛增）治疗治疗 5 年，每三月门诊随访。
结果 基因结果发现受检者 KMT2A 基因上的 1 个杂合变异，KMT2A:NM_001197104.1:exon22:c.5803-3T>G，一代测序结果显示父母均未携带该变异，推测受检者该变异为新发变异或者父母一方存在生殖细胞嵌合。应用聚乙二醇重组人生长激素注射液（金赛增）治疗 0.15~0.17mg/kg/w，治疗 5 年，身高增长 42.1cm，生长激素治疗有效，定期临床随访无发现异常。
结论 Wiedemann-Steiner 综合征患者生长激素治疗有效。
讨论 Wiedemann-Steiner syndrome (WDSTS)（OMIM # 605130）是一种十分罕见的由 KMT2A 基因突变导致染色显性遗传病，1989 年 Wiedemann 等人首次对疾病进行了描述，2012 年 Jones 等通过分子遗传的方法证实了这是一类特殊的综合征，其特征是：身材矮小、多毛、特殊面容（包括长睫毛，浓密或弓形的侧眉，宽鼻梁，向下和垂直狭窄的眼睑裂）及精神发育迟滞为主要临床表现的先天性多发畸形综合征。KMT2A 基因位于 11q23.3 染色体上，有 36 个外显子组成，编码转录辅助激活赖氨酸甲基转移酶 2A，该蛋白包括 3972 种氨基酸， KMT2A 基因共发现 45 个致病变异，包括 24 个错义突变，1 个剪切突变，13 个小片段缺失，4 个小片段插入，大片段缺失 2 个，大片段插入或重复 1 个。治疗:目前本病尚无特殊的治疗方法，均为对症治疗。目前提倡多学科综合治理。对于先天性心脏病的患儿，应在心内科和心外科指导下制定治疗方案；其它复杂的临床症状，需要口腔科、眼科、耳鼻喉科以及心理科等多学科共同参与治疗，制定个体化的治疗方案。关于生长激素的治疗，文献报道无论生长激素缺乏或者不缺乏均建议给予生长激素治疗，且目前报道的已经取得了较好的疗效，目前没有发现应用生长激素后导致肿瘤的发生，但需要定期监测血常规、纵膈彩超等。此患儿应用生长激素治疗 5 年，目前身高增长良好，临床随访，监测血常规、生化、甲状腺功能、血糖及纵膈彩超未发现明显异常。

First report of the spectrum ofβ-globin gene cluster deletions in the Chinese population of Fujian province:A 14-year single-center experience

Meihuan Chen
Fujian Maternity and Child Health Hospital

Background Hereditary persistence of fetal hemoglobin (HPFH) and δβ-thalassemia are relatively rare types of thalassemia caused by large deletions in the β-globin cluster involving δ- and β-globin genes, with or without the $^{A}\gamma$-globin gene, and are characterized by elevated fetal hemoglobin (HbF) in adults. Heterozygotes of HPFH and δβ thalassemia are clinically asymptomatic or have mild hemoglobin (Hb) values. However, when both HPFH and δβ-thalassemia are coinherited with heterozygous β-thalassemia, patients may progress to a clinical phenotype of thalassemia intermedia or thalassemia major.
Methods Subjects with HbF levels ≥10% ,before the blood transfusion,were selected for further investigation. Multiplex ligation dependent probe amplification(MLPA) and Gap-PCR were used to screen for three β-globin gene cluster deletions: Chinese $^{G}\gamma(^{A}\gamma\delta\beta)^{0}$ thalassemia and Southeast Asia HPFH (SEA-HPFH) deletion and 1357 bp deletion (NG-000007.3:g.69997-71353 del 1357).
Results A total of 142 patients with HbF (≥10%) were enrolled to characterize the molecular basis of β-globin gene cluster deletions in our study; 22 cases (0.04% (22/55 001) were definitively diagnosed with β-globin gene cluster deletions. Ten cases were heterozygous for the Chinese $^{G}\gamma(^{A}\gamma\delta\beta)^{0}$-thal mutations, 11 cases were heterozygous for SEA-HPFH, and one case was compound heterozygous for SEA-HPFH and the α-thal mutation. The 1357 bp deletion (NG-000007.3:g.69997-71353 del 1357) was detected in one case.
Conclusion In Fujian Province, the prevalence of common β-globin gene cluster deletions was 0.04%.

FAM111A 基因突变致 Kenny-Caffey 综合征 2 型 1 例

张英娴 卫海燕 王会贞 李涛 付东霞 陈永兴
河南省儿童医院

目的 报道 1 例 Kenny-Caffey 综合征 2 型患儿，为遗传咨询和产前诊断提供依据。
方法 先证者为郑州大学附属儿童医院内分泌遗传代谢科收治 1 例矮小症患儿，应用全外显子二代测序技术对先证者进行致病基因筛查，采用 Sanger 测序方法对父母进行验证和遗传分析。
结果 先证者 FAM111A 基因第 4 外显子 c.1706G＞A：p.R569H 1 个杂合错义突变，受检者的父母均未发现该变异，推测该变异为新发变异。结论：FAM111A 基因 c.1706G＞A：p.R569H 错义变异可能是该该患儿的致病突变位点。
讨论 Kenny-Caffey 综合征（Kenny-Caffey syndrome KCS）是一种非常罕见的畸形综合征，几乎仅在中东人群中报道。临床特征主要包括严重的身材矮小，生长发育迟缓，管状骨皮质增厚伴髓质狭窄，前囟门延迟到闭合，眼部和牙齿异常，以及由于甲状旁腺功能低下而导致的低钙血症等。根据其临床特点和遗传方式可分为 Kenny-Caffey 综合征 1 型和 2 型两类。Kenny-Caffey 综合征 1 型呈常染色体隐性遗传，临床特征为发育迟缓，通常伴有智力落后，精神发育落后和小头畸形。Kenny-Caffey 综合征 2 型呈常染色体显性遗传，临床特征包括生长发育迟缓，精神发育障碍，患者通常智力正常。此患儿临床特点： 7 岁，女孩，身材严重矮小，牙齿错落不齐，头大，前额突出，眼睛内斜视，3 岁时发现视力异常伴弱视，给予生长激素治疗 2 年身高增长良好，目前智力正常，目前门诊定期复诊未发现明显的异常指标。基因诊断 Kenny-Caffey 综合征 2 型。
结论 Kenny-Caffey 综合征 2 型是一种罕见的遗传代谢病，临床表现缺乏特异性。在实际临床工作中，对于合并特殊面容的矮小症要及时行基因检测，早期进行干预治疗，对疾病的诊断及预后具有重要的指导意义。

Prenatal diagnosis of thalassemia in 695 pedigrees from southeastern China: a 10-year follow-up study

Meihuan Chen
Fujian Maternity and Child Health Hospital

Thalassaemia is highly prevalent in southeastern China. This 10-year follow-up study aimed to characterize the genotype and karyotypeof thalassaemia in fetal samples derived from thalassemia carriers in Fujian province, southeastern China. A total of 476 prenatal samples from 472 couples carrying α-thalassaemia traits and 224 samples from 223 couples carrying β-thalassaemia traits were collected for STR analysis and karyotyping. The common deletional α-thalassemias and rare thalassemia genotypes were detected using Gap-PCR assay, and thecommon β-globin gene mutations were detected using PCR-RDBassay. We detected 43.49% prevalence of α-thalassaemia minor, 26.05% prevalence of α-thalassaemia intermediate and major and 1.89% prevalence of rare form among the 476 prenatal samples from couples with α-thalassaemia, and 85 fetuses with β-thalassemiaheterozygote, 16 with homozygote and 21 with double heterozygote，and a rare $\beta^{IVS\text{-}2\text{-}654(C\rightarrow T)}$/Chinese G_γ $(^{A}\gamma\delta\beta)^{0}$ genotype among the 224 prenatal samples from couples with β-thalassemia. Karyotyping showed 7 fetuses with abnormal karyotypes. Totally 153pregnancies were terminated, and genetic diagnosis of thalassemia using fetal umbilical cord blood following induction of labor showed consistent results with prenatal diagnosis.No thalassemia phenotypes were identifiedin normal infants half a year after birth, and the infants with α-thalassemia and β-thalassemiaminor had no or mild anemia symptoms, but normal development, while 15 babies with hemoglobin H disease presented moderate anemia symptoms. Pregestational screening of thalassemia, notably compound and rare forms of thalassemia, is recommended for couples carrying thalassemia traits.

IFITM5 基因突变导致 V 型成骨不全一例并文献复习

贾海亭 刘毅
山东大学齐鲁儿童医院

目的 对 1 例 V 型成骨不全患儿进行临床和遗传学分析。
方法 对患儿进行临床及影像学检查，通过全外显子组测序对患儿进行测序分析，并对其父母进行 Sanger 测序验证。
结果 患儿临床表现为双侧肘部骨性突起，双肘关节活动受限，X 片检查骨间膜钙化并桡骨头脱位，基因检测结果显示定位于 11 号染色体上的 IFITM5 基因 c.-14 C＞T 存在杂合变异，为已报道的致病性变异，遗传自母亲。
结论 IFITM5 基因变异是 V 型成骨不全遗传病因，骨间膜钙化及桡骨头脱位是主要影像学特点。疼痛是儿童期桡骨头切除的绝对适应症，单纯外观不好看以及功能无明显受限可以不做手术。

NEB 基因复合杂合变异导致一例儿童型杆状体肌病临床与遗传学分析并文献复习

贾海亭 刘毅
山东大学齐鲁儿童医院

目的 对 1 例儿童型杆状体肌病患儿进行临床和遗传学分析。
方法 对 2021 年 3 月就诊于山东大学齐鲁儿童医院骨科创伤外科临床诊断为神经肌肉型脊柱侧弯的患儿进行临床及实验室检查，通过全外显子组测序对患儿进行测序分析，并对其父母进行 Sanger 测序验证。
结果 患儿 女，12 岁 8 月，因发现身体向右侧倾斜 2 年就诊，查体发现肌无力，严重脊柱侧弯，伴腭裂；脊柱三维 CT 及脊髓核磁检查发现左侧竖脊肌萎缩伴脂肪浸润；基因检测显示定位于 2 号染色体上的 *NEB* 基因存在两处杂合变异，c.1321C＞T（p.P441S）和 c.18530G＞A（p.R6177H），这两处杂合突变 Sanger 测序的家系验证结果显示分别遗传自母亲和父亲，均为未报道过的新变异，在人类基因数据库中未见有报道，文献检索发现临床表型与已报道的病例相似。
结论 本患儿可能是由于 *NEB* 复合杂合突变导致的儿童型杆状体肌病。

EXT1 基因突变导致遗传性多发性骨软骨瘤一例并文献复习

贾海亭 刘毅
山东大学齐鲁儿童医院

目的 对 1 例遗传性多发性骨软骨瘤患儿进行临床和遗传学分析。
方法 对患儿进行临床及相关辅助检查，手术切除左桡骨远端骨软骨瘤，抽取外周血进行遗传性骨病综合基因检测，并对患儿及其父母进行一代测序验证。
结果 患儿临床表现为全身多处骨性肿物，基因检测显示 EXT1 基因 c.1469delT 杂合突变，为已报道的致病性变异，遗传自母亲。
结论 遗传性多发性骨软骨瘤较为罕见，其诊断主要依靠临床特征和基因检测。当出现肢体畸形或功能活动障碍时需手术切除。

7 例黏多糖 IV 型临床特点分析

张英娴 卫海燕 杨威 陈永兴
河南省儿童医院

目的 分析 7 例黏多糖 IV 型临床特点，为临床医师提供诊断指导。
方法 对 2019 年-2021 年在郑州大学附属儿童医院内分泌遗传代谢科收治 7 例因身材矮小伴多发骨骼畸形黏多糖 IV 型患儿进行临床分析，男 3 例，女 4 例，年龄 3 ~15 岁之间。分别分析了发病年龄，起病特点，酶活性及基因结果情况。
结果：7 例患儿都具有身材矮小、关节畸形、手腕部畸形、脊柱发育不良，脊柱侧弯后凸，X 线片椎体前缘可见鸟嘴装突出，但是智力发育均正常。β-半乳糖苷酶活性极低。
结论 对临床上身材矮小合并骨骼畸形的患儿及时进行溶酶体酶活性检测进行诊断。
关键词：黏多糖贮积症、骨骼畸形、矮小症
讨论 黏多糖贮积症 IV 型，属于常染色隐性遗传病，是由于半乳 β-半乳糖苷酶缺乏所引起，β-半乳糖苷酶缺乏还可导致神经节苷脂沉积神经系统，形成 GMl 神经节苷脂贮积症。因缺乏的酶不同而分为黏多糖贮积症 IVA 和 IVB2 个亚型。IVA 亚型是有半乳糖胺-6-硫酸硫酸酯酶基因突变所导致相应的酶活性缺乏；IVB 亚型是由于 β-半乳糖苷酶基因突变导致相应的酶活性缺乏。两种亚型的临床表现无明显差异，均表现为明显身材矮小、骨骼畸形、关节松弛，但患儿的智力是正常的。本院 7 例患儿中，发病在 1-3 岁，其中 3 例是 1 岁开始发病，以身材矮小，骨骼畸形就诊；2 例 2 岁发病，以髋关节脱位、脊柱后凸首发症状就诊；1 例 3 岁，以身材矮小，骨骼变性就诊；1 例四岁，以身材矮小，脊柱后凸畸形就诊。7 例患儿智力均正常。全部行溶酶体酶活性检测而确诊。其中 1 例患儿背部有大片蒙古斑。4 例患儿有腺样体肥大；7 例患儿都存在胸廓畸形、手腕变性、脊柱侧弯；4 例患儿有关节挛缩；6 例患儿存在爪形手；5 例患儿有腕管综合征；3 例患儿有心脏瓣膜的病变。2 例患儿有肝脾肿大。目前，对于 MPS IV 型疾病，目前尚没有特殊的治疗方法，一般都是对症治疗，需要多学科联合会诊制定治疗方案。这些方法可在一定程度上改善患儿的生活质量，并不能提高患儿寿命或减少病死率。对于黏多糖贮积症 IV，造血干细胞移植(HSCT)和酶替代疗法(ERT)是有效的治疗方法，但对于Ⅳ型酶替代治疗费用昂贵，大部分家庭无法承担昂贵的费用。鉴于该病特点及治疗现状，防止该病危害的最重要的方法即是早期诊断，早期对并发症进行干预；产前遗传咨询尤为重要，通过产前诊断，减少该病患者的出生，减轻家庭及社会的负担。

基于 CNV-seq 技术分析不明原因智力低下、全面发育迟缓及孤独谱系综合征患者基因组拷贝数变异

雷洁 张静 韩璐好 赵刚 黄彦科 龙敏 邓茜 修子涵
深圳市南山区妇幼保健院

目的 评估 CNV-seq 技术在不明原因智力低下、全面发育迟缓及孤独谱系综合征患者病因学分析中的诊断效能。
方法 收集本院儿保科和遗传咨询门诊 2018 至 2019 年诊断为智力低下、全面发育迟缓及孤独谱系综合征的患儿的临床资料, 采集患儿外周血分别进行染色体核型和低深度全基因组测序分析（CNV-seq），利用 ClinVar、DECIPHER、OMIM 等公共数据资源结合生物信息学分析评估拷贝数变异(CNVs)的发生情况。
结果 52 例患者(男/女:40/12)中，智力低下者(ID) 19 例，占比 36.5%；发育迟缓(DD)23 例，占比 44.2%，孤独系谱障碍(ASD)8 例，占比 15.4%。此外, 还包括 ID 合并 DD 及 ID 合并 ASD 的患儿各 1 例。核型分析显示异常核型 5 例，包括 47,XY,+mar、 46,XY inv(8)(p11.2q21.2) 等，占比 9.6%，染色体多态性 2 例, 其余无异常。CNV 分析结果显示：52 例患儿中 26 例检出 35 个 CNVs, 检出率为 50%，明显高于核型分析的检出率。其中发现 11 个致病性 CNVs 来自于 11 名患者，检出率为 21.2%；14 个意义未明 CNV 来自于 11 名患者，检出率为 21.2%；和 10 个良性/可能良性 CNVs 来自于 6 名患者，检出率为 11.5%。

结论 基因组拷贝数变异是 ID/DD 和 ASD 患者重要的遗传学病因之一，CNV-seq 技术可为 ID/DD 和 ASD 的病因学分析提供重要参考。

NTNG2 基因变异导致智力障碍的研究

师良 高燕 余永国
上海交通大学医学院附属新华医院

背景 智力障碍/发育迟缓 (Intellectual disability/Development delay, ID/DD) 是一种常见的神经发育障碍。在临床上，智障患者通常表现出综合征，多伴有癫痫、语言发育障碍、面部畸形等症状，需要投入大量人力物力长期治疗，给患者所在家庭和社会造成了极为严重的心理和经济负担。关于 ID/DD 发生的原因，一直是国内外神经科学领域研究的热点和难点，有 50%的 ID/DD 患者的病因是已知遗传因素导致的。随着全外显子组测序 (whole exome sequencing, WES) 技术的成熟，通过对 WES 结果的挖掘及生物信息学分析，找寻临床上复杂遗传疾病的病因是一大重要手段。
目的 前期运用 WES 在一例 ID/DD 患儿中发现 *NTNG2* 基因的复合杂合变异，并且国内外研究也发现 *NTNG2* 与神经发育有密切的关系，因此本研究拟探讨 *NTNG2* 变异导致 ID/DD 的具体机制。
方法 构建转基因小鼠评价 *NTNG2* 基因复合杂合变异对小鼠神经系统发育的影响。
（1）观察出毛、睁眼、雌性小鼠阴道张开、雄性小鼠睾丸下降等是否在正常发育阶段达到正常发育指标；
（2）各基因型取 6 只小鼠进行转棒实验，评价小鼠的运动能力；
（3）各基因型取 6 只小鼠进行水迷宫、旷场识别实验，判断小鼠的社会属性是否正常，学习记忆水平是否达标。
（4）取小鼠脑部组织，用 qRT-PCR、WB 的方法检测 *NTNG2* mRNA 和蛋白表达水平
结果 携带有 NTNG2 复合杂合的转基因小鼠行为学结果提示神经系统发育异常。
（1）在出毛、睁眼等发育指标以及阴道张开、睾丸下沉等性成熟指针来看，*NTNG2* 复合杂合变异小鼠相比对照组并无显著差异。
（2）转棒实验结果显示，携带有 *NTNG2* 复合杂合变异的小鼠停留时间较对照组短，提示其运动能力较差。
（3）旷场实验结果显示，携带有 *NTNG2* 复合杂合变异的小鼠运动距离稍低，在中心区域停留时间稍短，但没有显示出统计学差异；水迷宫实验结果显示，携带有 *NTNG2* 复合杂合变异的小鼠逃避潜伏期相比对照组显著增长，提示其学习记忆水平较低。
（4）qRT-PCR、WB 的结果显示 *NTNG2* 复合杂合变异导致其 mRNA 和蛋白表达水平下降。
结论 *NTNG2* 基因复合杂合变异会导致其 mRNA、蛋白水平下降，从而影响神经系统正常发育，从而使学习记忆水平以及运动能力下降。

HPDL 缺陷通过损害线粒体呼吸导致神经肌肉疾病

孙昱[1] 尉秀娟[2] 吕建新[2] 方合志[2] 余永国[1]
1.上海交通大学医学院附属新华医院
2.温州医科大学

目的 研究 *HPDL* 双等位基因突变导致的神经肌肉病的致病机制。
方法 通过外显子组与基因组测序发现 *HPDL* 基因双等位基因突变病例。总结这些患者的基因型和临床特点。确定 HPDL 蛋白的亚细胞定位。以患者外周血构建的永生化淋巴细胞，患者皮肤组织成纤维细胞，及 *HPDL* 敲降的 HeLa 细胞为模型，测定细胞氧耗速率、呼吸链复合物表达量及酶活性、ATP 及胞外乳酸水平判断线粒体功能、使用透射电镜观察线粒体形态；并导入野生型及突变型慢病毒颗粒观察 *HPDL* 缺陷细胞氧耗恢复情况。
结果 我们在 4 个患病家系中发现 6 位患者携带 *HPDL* 纯合或复合杂合的致病突变。这些病例共携带 7 个突变，其中 5 种突变未被报道。智力障碍、痉挛性麻痹、肌张力亢进是本病患者主要临床特

点。HPDL 定位于线粒体膜间隙，患者的成纤维细胞及永生化淋巴细胞 HPDL 表达均下降。细胞氧耗速率测定显示患者成纤维细胞基础及最大氧耗、磷酸化耦合呼吸均减少；永生化淋巴细胞磷酸化耦合呼吸不变，基础氧耗显著减少，最大氧耗轻微减少；而 *HPDL* 敲降的 HeLa 细胞基础及最大氧耗均降低，且外源表达野生型 HPDL 可挽救线粒体氧耗量。BN-PAGE 发现在永生化淋巴细胞及 *HPDL* 敲降的 HeLa 细胞中线粒体复合物 I-V 的表达量相较于对照并无差异。线粒体呼吸链复合物酶活性分析显示，复合物 II 在永生化淋巴细胞和 *HPDL* 敲降的 HeLa 细胞中活性均降低；复合物 III 和 IV 在永生化淋巴细胞中活性降低；但在 *HPDL* 敲降的 HeLa 细胞中无显著变化。患者永生化淋巴细胞 ATP 水平显著降低，乳酸水平无变化；*HPDL* 敲除的 HeLa 细胞乳酸水平显著上升。透射电镜可见患者永生化淋巴细胞矩阵电子密度比对照组更高，*HPDL* 敲除的 HeLa 细胞线粒体稍小，其他与野生型相比无显著差异。

结论 *HPDL* 双等位基因突变可致以智力障碍、痉挛、肌张力亢进为主要临床特征的线粒体神经病变。*HPDL* 缺陷导致线粒体呼吸过程受损，可能通过影响氧化磷酸化复合物 II 酶活性影响线粒体呼吸功能，从而导致相应表征，而外源表达野生型 HPDL 可改善线粒体呼吸功能。

Newborns with Compound Heterozygous Mutations in the RYR1 Gene Show Feeding Difficulties and Bilateral Parietooccipital Hematomas：A Case Report

Hongyan Chen[1,2] Fengxiang Wei[1,2] Xiaohang Chen[2] Yingyao Tan[1,2]
1.Guangdong Pharmaceutical University
2.Shenzhen Longgang Maternal and Child Health Hospital

Aim To determine the etiology of feeding difficulties using genetic methods.
Methods Hematological investigation, chromosomal analysis (G-banding), and All exon group detection were performed on a 15-day-old female patient.
Results We reported a 15-day-old female patient. She had an inadequate response to things, a weak sucking reflex, difficulty in oral feeding, bilateral parietooccipital hematoma, scattered bleeding spots on the skin, and low extremity muscle tone. We performed rapid exon sequencing of the patient's gene and found that her RYR1 gene carries the c.1525del (p.Glu509Argfs*10) variant frameshift variant, which is related to congenital myopathy. Besides, we also found a missense mutation c.2365C>T (p.Arg789Trp) in RYR1.
Conclusion Histopathological examination and exome sequencing in cases where the clinical criteria are not sufficient are necessary to make.

中国大陆 29 例 Phelan-McDermid 综合征患者队列:基因型-表型相关性和 SHANK3 单倍不足在重要表型中的作用

徐娜 吕辉 杨婷婷 杜秀娟 孙昱 肖冰 范燕洁 罗小梅 詹永坤 王丽丽 李斐 余永国
上海交通大学医学院附属新华医院

背景 Phelan McDermid 综合征(PMS)或 22q13 缺失综合征是一种罕见的发育障碍疾病，以张力减退、发育迟缓(developmental delay , DD)、智力障碍(intellectual disability, ID)、自闭症谱系障碍(autism spectrum disorder, ASD)和畸形特征为特征。大多数病例是由包括 SHANK3 在内的多种基因的 22q13 缺失引起的。缺乏 SHANK3 突变(或缺失仅破坏 SHANK3)和包含 SHANK3 基因在内的多种基因的 22q13 缺失之间的表型比较。
方法 对 29 例中国大陆患者进行临床和基因分析。数据来源于病历回顾和标准化的病史问卷，畸形评估通过照片评估。我们分析 22q13 缺失和 SHANK3 小突变，并进行基因型表型分析，以确定神经特征和其他重要的临床特征是否与 SHANK3 单倍剂量不足有关。
结果 19 例 22q13.3 缺失的患者缺失大小从 34 kb 到 8.7 Mb 不等，1 例患者存在末端缺失和重复，9 例患者存在 SHANK3 突变。c.3838_3839insGG, c.3088delC, c.3526G > T、c.3372dupC、

c.3120delC 和 c.3942delC 为首次报道。此外，我们证明语言延迟(100%)、DD/ID(88%)、ASD(80%)、张力减退(83%)和多动(83%)是显著的临床特征。最后，100%单基因 SHANK3 缺失的病例存在低张力。并且在低张力、DD/ID、ASD、疼痛耐量增加、步态异常、冲动、重复行为、退化和不停哭泣的患病率方面，单独缺失 SHANK3 与包括 SHANK3 在内的多种基因的 22q13 缺失之间无显著差异。

结论 这是第一个描述中国大陆患者队列的工作，拓宽了 PMS 的临床和分子谱。我们的研究结果支持 22q13 缺失和 SHANK3 点突变对语言障碍和 DD/ID 等临床表现的影响。我们还证明，SHANK3 单倍剂量不足是 PMS 神经表型的主要因素，也是其他重要表型如张力减退、疼痛耐受性增加、冲动、重复性行为、退化和不停哭泣的主要因素。

COMT Val158Met 多态性与抗精神分裂症药物治疗有效性的遗传关联性及 meta 分析

赵明哲 赵明哲 马靖松 李沫 秦胜营
上海交通大学

背景 *COMT* 酶可以催化突触前多巴胺的降解，从而控制多巴胺的浓度。*COMT* Val158Met (s4680) 基因多态性可以改变催化酶的活性，进而导致前额叶皮质和海马中的多巴胺浓度水平发生异常。因此，*COMT* 基因型可以对作用于多巴胺系统的抗精神病药物反应产生重要影响。本研究通过 meta 分析整合已发表的研究进一步探究 *COMT*Val158Met 多态性与抗精神病治疗反应之间的关联。

方法 通过检索 PubMed, Web of Science, EMBASE, OVID, Google Scholar, Baidu Scholar 数据库，经过纳入和排除标准筛查，共得到 30 篇同行评审研究合并样本 6291 例。使用 Lipták–Stouffer Z score 方法进行数据合并，同时根据人种（白种人和亚洲人）进行亚组分析。

结果 合并结果发现 *COMT* Val158Met 多态性与抗精神病治疗反应存在显著关联（Z=6.709, P=9.8✕10^{-12}）。亚组分析结果发现这种关联分别在白种人（Z=3.180, P=7.4✕10^{-4}）和亚洲人（Z=4.487, P=3.6✕10^{-6}）中显著。

结论 研究结果支持 *COMT* Val158Met 多态性与抗精神病治疗反应之间存在关联的研究假设。研究结论应用于临床实践前还需要更进一步的临床试验进行验证。

在一个心源性猝死患者中鉴定到一个影响剪接能力的 MYBPC3 同义突变（c.24A>C/p.P8P）

金介员 董毅 郭亚东 项荣
中南大学

背景 心源性猝死（Sudden cardiac death，SCD）是一种心脏射血突然停止导致的非正常死亡，通常在症状发生一小时内死亡，是最常见的非自然死亡方式之一，在我国的发病率约为 4.18/10000。心肌病是导致 SCD 发生的主要原因之一，其病因多样，包括感染、中毒、遗传因素等。而 *MYBPC3* 突变是最常见的心肌病致病基因之一，突变蛋白通常导致 MYBPC3 表达减少。

方法 死者是一位 29 岁的女性，死因为心脏病变导致的 SCD，心脏切片显示其存在心肌病表型。我们对其保留的外周血样本进行全外显子测序，并利用 minigene 技术、点突变构建技术和免疫组化对突变进行功能分析。

结果 我们在死者中鉴定到一个 *MYBPC3* 同义突变（c.24A>C/p.P8P），其发生于 1 号外显子的最后一个碱基，可能会影响该剪切位点的剪接。我们构建了一个 *MYBPC3* 的 minigene（pcDNA3.1-1 号外显子-内含子-2 号外显子），并进行 c.24A>C 突变。转染 HEK293 细胞发现相较于正常的 *MYBPC3* minigene，c.24A>C 导致该剪接位点失效，致使内含子序列（1061 个碱基）被错误地转录，使得蛋白翻译提前终止。必须指出，由于 1 号外显子过小，minigene 的剪接能力并不强大。

为排除构建突变本身带来的影响，我们构建了 c.10G>A 突变质粒，发现其剪接能力增强。免疫组化显示，死者心肌的 MYBPC3 显著减少。
结论 我们认为 *MYBPC3* 突变（c.24A>C/p.P8P）导致了死者的心肌病，诱发 SCD。

基因确诊的肢带型肌营养不良 2Y 型(LGMD2Y)1 例

林欣 林锋 王志强
福建医科大学附属第一医院

背景与目的 肢带型肌营养不良（LGMD）是一种常见的以近端肌无力为特征的肌肉疾病。其中，LGMD2Y 是一种罕见类型，除了肢带肌无力外，还表现为远端无力、关节挛缩、限制性肺病和心脏受累等。它是由编码核膜蛋白层膜相关多肽 1(LAP1)的 TOR1AIP1 突变引起的，目前对于本病报道甚少。本文报道一例新型纯合子 TOR1AIP1 突变的患者，以期增加对此病的认识。
材料与方法 依据规范诊断流程，取得患者知情同意，采集患者详细病史、体征、实验室检查、电生理、肌肉病理、MRI 等结果进行临床诊断，并行基因检测确诊。
结果 患者男，33 岁，以“四肢无力 30 余年”为主诉就诊我院门诊。患者自幼感四肢乏力，以右侧为重，初仅表现为活动能力稍差，尚能从事各种日常活动；渐进展，20 年前起出现体育运动不如同龄人，跑步、引体向上、仰卧起坐动作均较差；约 10 余年前起双上肢抬举费力明显，右下肢活动无力，登梯、蹲立动作需左腿代偿，症状持续存在，伴双手臂及右大腿肌肉稍消瘦，余无特殊。既往史、个人史、家族史等无特殊。内科查体无特殊。神检：神清，闭眼、示齿、鼓腮、吹哨、吞咽等动作无明显受限。颈屈肌 3+级，颈伸肌 5 级，前侧平举 90°。四肢肌力基本对称，近端较差，双上肢肌力 3-4 级，双下肢 4-5 级，其中腕屈肌、股四头肌、胫前肌、腓肠肌肌力正常。双侧上臂肌群及右侧大腿轻度萎缩，双侧轻度“翼状肩”，仰卧起坐不能。完善心肌酶谱：正常；肌电图示：肌源性损害；双侧大腿 MRI 示：双侧臀部肌群、双侧大腿内、前、后侧部肌群的肌间隙内可见脂肪浸润；肌肉病理：提示肌营养不良。全外显子测序示：TOR1AIP1 基因 c.192dupA（p.E65Rfs*45）纯合变异，为已知致病性变异。诊断为常染色体隐性遗传肌营养不良伴有脊柱强直和远端关节挛缩(LGMD2Y)。
结论 LGMD2Y 临床异质性高，本文报道了 TOR1AIP1 基因 c.192dupA（p.E65Rfs*45）纯合变异所致 LGMD2Y 型患者，主要表现为四肢近端为主以及选择性受累的远端肌无力，进一步扩大 LGMD2Y 和 TOR1AIP1 相关核包膜病的临床表型。

内含子变异干扰 mRNA 剪接并导致 FGFR3 相关骨发育不良疾病

许汀 范燕洁 余永国
上海交通大学医学院附属新华医院

软骨发育不全和软骨发育不良是最常见的不等比例矮小疾病，主要表现为四肢短小、大头畸形等。软骨发育不全和软骨发育不良多为散发，绝大多数病例可归因于 FGFR3 基因的热点错义突变（G380R 和 N540K 等）。已发现的变异几乎均为错义变异，也有罕见的造成框内插入的变异报道。尽管遗传异质性较低，仍有病例未能找到遗传病因。
在对两例具有软骨发育不良特征的患者进行常规全外显子组测序时，发现同一个新发内含子变异 c.1075 + 95C>G，软件预测可能影响剪接。Minigene 体外转录实验显示该变异引起 8 号内含子 5’端 90 个碱基的滞留（c.1075_1076ins90nt），进而导致蛋白胞外区一段 30 个氨基酸残基的插入。此外，对此前编码区未检测到变异的 26 个疑似软骨发育不全、软骨发育不良或其他不明原因矮小患者进行筛查，在一例患者中检测到 c.1075 + 95C>G 新发变异。根据 ACMG 指南，该变异被评级为可能致病变异（PS2，PM2，PP3，PP4）。
c.1075 + 95C>G 这是 FGFR3 相关的骨骼发育不良疾病中发现的首个内含子变异，扩展我们对 FGFR3 基因突变谱的认知。c.1075 + 95C>G 在 3 例无关患者中检测到，均为新发，提示这是一个

复发性变异，应该被纳入 FGFR3 的临床检测中，尤其是对于临床特征不典型且未在编码区发现突变的患者。

中国南方 ALS 患者 ALS 相关基因的定制靶向 panel 的高通量测序分析

王丰[1] 许雪青[2]
1.深圳市宝安区妇幼保健院
2.南方医科大学深圳医院

目的 ALS 是一种破坏性的神经退行性疾病，特征为上部和下部脊髓运动神经元的渐进性丧失，已有数十种基因突变被认为与其相关，其中主要为点突变。但这些基因点突变所占病人比例较低，仍有大量 ALS 病人（无论是家族性还是散发患者）未能检测出阳性突变，有必要对其进行深入研究。
方法 通过文献分析和数据库挖掘，建立一个 ALS 相关基因（含风险基因和致病基因）的靶向测序定制 panel，通过 NGS 测序技术对 143 名中国南方 ALS 患者进行突变检测，按照 ACMG 变异分类标准和指南对突变致病性进行分析。
结果 5 名患者检出 10 个明确已知致病突变。16 名患者检出可疑致病性突变。在 11 个样本中发现 4 个基因（SPG11\ARHGEF28 \CHGB \ATXN2）存在纯合子突变，其中 2 名患者在 CHGB 基因均存在 2 个位点的纯合突变。此外存在多个致病性突变或可疑致病性突变共存于同一患者的现象。
结论 ALS 是一类遗传异质性非常高的神经退行性疾病，现有已知致病基因能解释少量病因，还有新的致病基因有待发现。定制靶向测序 panel 有助于快速明确部分患者致病基因突变，对疾病进行辅助诊断，避免患者四处求医无法明确病因诊断的不便。

Whole-genome sequencing identified novel MSTO1 recessive mutations in a patient without cerebellar atrophy involvement

Yan Dan
xinhua hospital

Objectives To identity the disease-causing variants in a patient, who showed sever growth retardation and global developmental delay.
Methods We extracted whole blood DNA from the peripheral blood leukocytes of the proband and his parent, and then performed whole genome sequencing (WGS) in this patient. Several filters, such as variants' frequency in Exome aggregation consortium (ExAC) and Genome aggregation database, were applied to screen disease-causing variants. And then the pathogenicity of identified variants were assessed by three prediction software (Polyphen2, SIFT and MutationTaster). Finally, sanger sequencing was used to confirm the underlying mutations identified by WGS, followed by mutation analysis in the patient's parent.
Results a missense mutation c.1109C>G and a 3-bp deletion variant c.777_779delAAC were identified in the MSTO1 gene. By segregation analysis, the parents were revealed to be heterozygous carriers, indicating a recessive pattern of inheritance in this family. According to the guidelines of American College of Medical Genetics, the pathogenicity classification of these two mutations both were likely pathogenic.
Conclusions As there is no therapy for vast majority of mitochondrial disease (MD), prevention is critical for families at risk of MD. However, genetic diagnosis of mitochondrial disease is a complicated process due to genetic heterogeneity. Nowadays, improved next generation sequencing, such as WGS, may help to alleviate this issue.

对 1127 例新生儿进行 573 个严重遗传疾病相关基因筛查的初步研究

罗小梅[1] 孙昱[1] 徐烽[1] 郭君[1] 李琳[2] 林志伟[2] 叶军[1] 顾学范[1] 余永国[1]
1.上海交通大学医学院附属新华医 2.南京诺禾致源生物科技有限公司

背景 新生儿筛查主要是检测血液中代谢物的生化水平，可能会产生假阳性/假阴性结果。目前中国的新生儿筛查主要包括血串联质谱（MS/MS）筛查和苯丙氨酸（Phe）、促甲状腺激素（TSH）、17α-羟孕酮（17-OHP）及葡萄糖-6-磷酸脱氢酶（G6PD）的筛查。
方法 本课题设计了 573 个严重遗传疾病相关基因的 panel 并随机选取了 1127 名新生儿作为研究对象，旨在研究与新生儿生化筛查相比，利用新生儿干血片进行高通量测序能否有效检出遗传疾病，以及是否能作为生化筛查的补充来提高生化筛查的检出率。本课题还计算了检测对象的氨基酸代谢，有机酸代谢和脂肪酸氧化有关遗传代谢病的人群携带者频率。
结果 生化筛查结果显示本研究对象中共有四名 G6PD 阳性的男性新生儿，遗传检测结果显示这四名新生儿均携带 *G6PD* 半合突变。此外，遗传检测还发现一名新生儿携带 *SLC22A5* 基因的复合杂合突变，将其召回后重新抽血的 MS/MS 检测结果提示游离肉碱缺乏，可诊断为原发性肉碱缺乏症，提示该例新生儿在出生时的生化筛查结果为假阴性。这些新生儿中，携带者频率最高的前五个基因是 *PAH*（1:56），*ETFDH*（1:81），*MMACHC*（1:87），*SLC25A13*（1：102）和 *GCDH*（1：125）。
结论 本研究将 1127 名新生儿的生化筛查与基因筛查相结合，证明了基因筛查结合生化筛查可提高新生儿的筛查效能。这也是中国第一个研究与氨基酸代谢，有机酸代谢和脂肪酸氧化障碍相关的 77 个遗传代谢病基因的携带者频率的研究。

Genetic analysis of 1109 infants with dried blood spot screening for deafness in Li ethnic area of Hainan Province in China

ZhenDong Zhao Jie Wang
Hainan Medical Center for Women and Children

Objective To understand the prevalence and genetic characteristics of deafness in Li ethnic areas of Hainan Province, and to provide data support for authority decision-making to formulate policies of deafness prevention and control.
Methods A prospective design and random sampling method was adopted. Infants born between October 2010 and June 2021 in The Li ethnic area were selected as the research subjects. Based on the principle of informed and voluntary consent, the samples of dried blood spots were screened for newborn infants, and the fluorescence PCR fusion curve method was used to screen for common deafness loci for Chinese people. According to genetic screening specifications for hereditary deafness, samples with positive genetic screening results and unknown mutations were verified by Sanger sequencing.
Results In 1109 cases of neonatal dried blood spots, 42 cases of site mutations of deafness were detected, and the carrying rate of deafness genes was 3.79% (42/1109). There were 21 carriers of *GJB2* gene (1.89%, 21/1109), 17 carriers of *SLC26A4* gene (1.53%, 17/1109), 3 carriers of *GJB3* gene (0.27%, 3/1109); in addition, 1 homogeneous mutation of mitochondrial M.1508C>T was found, whose carrying rate was 0.09% (1/1109). Among the mutations detected, the C.235delC mutation in *GJB2* gene accounted for 38.10% (16/42) and C. 919-2a >G mutation in *SLC26A4* gene accounted for 26.19% (11/42). There was no significant difference in the distribution of deafness genes between genders (X^2=0.002,P=0.964) and ethnic groups (X^2=0.000,P=0.997). C. 235delC and C. 919-2a >G were the mutation hot spots, which can be used as an effective supplement for neonatal hearing screening. It is necessary to carry out neonatal deafness gene testing as soon as possible in Li areas of Hainan Province to ensure the life quality and population quality of infants.

Analysis of genotypic mutations of thalassemia in Li nationality newborns in Hainan Province in China

ZhenDong Zhao
Hainan Medical Center for Women and Children

Objectives To investigate the genotypic mutation characteristics of thalassemia of Li nationality newborns in Hainan province in China.
Method During the period from January 2020 to April 2021, 1517 Li nationality newborns were born in Baisha county and Wuzhishan city where the Li nationality was mainly distributed. 1438 of 1517 (94.8%) signed the informed consent form and volunteered to participate in the thalassemia genotype screening. The numbers of male and female newborns were 743 and 695, respectively. Dry blood spot samples were tested by real-time PCR multicolor melting curve analysis method. Some of results were verified by PCR plus flow-through hybridization method. Suspected new mutations were found in genetic testing and sent to genetic testing company to look for unknown mutations.
Results A total of 1024 cases of thalassemia gene were detected in 1438 newborns' dry blood samples. The gene carrying rate of thalassemia was as high as 71.2% (1024/1438). Male and female thalassemia gene carrying rates were 70.5% (524/743) and 71.9% (500/695), respectively. There was no statistically significant difference between the gene carrying rates of thalassemia of male and female newborns (c^2=0.352, P=0.553). A total of 31 known genotypes and 2 suspected new genotypes were detected. The 2 suspected new genotypes were -α4.2/HKαα and βCD76 GCT>CCT/βN (c.229G>C) rare type.
Conclusion The gene carrying rate of thalassemia is high in the newborns of Li nationality in Hainan Province. The alpha thalassemia genotype is the most common type. The top three genotypes are: -α4.2/αα, -α3.7/αα and αWSα/αα.

海南省白沙黎族自治县新生儿耳聋基因特征

赵振东
Women and Children's Health Care Center of Hainan Province

目的 了解海南省白沙黎族自治县新生儿人群中耳聋基因发病情况及基因特征型，为政府决策部门拟定适宜的耳聋防控政策提供数据支持。
方法 选取 2020 年 10 月-2021 年 6 月在海南省白沙黎族自治县出生的新生儿 626 例，并收集自愿签署新生儿耳聋基因知情同意书采集足跟血制成干血斑样本 606 例，本次研究参与率 96.8%。使用荧光 PCR 熔解曲线法进行中国人常见的耳聋基因位点筛查。根据《遗传性耳聋基因筛查规范》对基因筛查阳性及提示有未知突变的样本外送基因公司进行 sanger 测序验证。
结果 ①606 例样本中检出有耳聋基因基因位点共计 26 例，耳聋基因携带率为 4.3%（26/606）。所有检出耳聋基因样本中男性 17 例，女性 9 例，男女之间基因携带（X^2=0.014,P=0.094）无统计学意义。②检出耳聋基因试剂盒中 4 个基因 8 种突变位点由多到少顺序排列如下：c.235delC、c.919-2A>G、c.1229C>T、c.547G>A、c.1174A>T、c.229-300del、c.2618A>G 和 c.538C>T 突变。Sanger 测序验证出 A-ROX 熔解峰样本为 c.235C>T 突变，D-HEX 熔解峰样本为 m.1508C>T 均质突变。③按民族划分，在 358 例黎族样本中检出 13 例耳聋基因突变，检出率为 3.6%（13/358），在 248 例其它民族样本中检出 13 例耳聋基因突变，检出率为 5.2%（13/248），黎族和其它民族耳聋基因检出（X^2=0.005,P=0.942）均无统计学意义。
结论 ①海南省白沙黎族自治县新生儿人群中耳聋基因基因携带率高，以 GJB2 基因的 c.235delC 和 SLC26A4 基因的 c.919-2A>G 位点突变常见。因此，建议海南省相应政府部门应该在白沙黎族自治县尽早开展新生儿耳聋基因检测，以保证出生人口生活质量和人口素质。

245194 例串联质谱新生儿遗传代谢病筛查及随访分析

刘双 王雷雷 汤欣欣 郑芹 刘华君 张贵敏
连云港市妇幼保健院

目的 探讨连云港地区新生儿遗传代谢病的发病率、疾病谱、遗传特征及随访情况。
方法 收集 2015 年 1 月至 2021 年 6 月连云港市出生 3-7d 的 245194 例活产新生儿足跟血制成干滤纸血片，应用非衍生化串联质谱法测定干血片 11 种氨基酸、31 种酰基肉碱和琥珀酰丙酮含量，对初筛阳性标本召回复查，复查仍然阳性标本，通过其他生化检测、尿有机酸检测及基因突变检测等技术进一步诊断疾病，对确诊患儿进行治疗并追踪随访。
结果 245194 例新生儿筛查初筛阳性率 2.21%（5415/245194），诊断遗传代谢病患儿 95 例，总发病率 1/2580，其中氨基酸代谢障碍 52 例（1/4715），脂肪酸氧化障碍 23 例（1/10660），有机酸代谢障碍 20 例（1/12260），共涉及 18 种疾病，发病率排在前 4 位的疾病为苯丙氨酸羟化酶缺乏症 38 例（1/6452）、短链酰基辅酶 A 脱氢酶缺乏症 11 例（1/27243）、甲基丙二酸血症 9 例（1/22290）、希特林蛋白缺乏症 7 例（1/35027）。95 例确诊患儿中 85 例进行了基因检测，检出纯合变异 11 例，复合杂合变异 65 例，另外 9 例患儿仅检出 1 个变异，绝大部分变异来源于父母。95 例患儿随访结果，死亡 3 例，其余有症状患儿根据病情分别给与特殊饮食或药物治疗并随访，无症状患儿进行定期随访。
结论 连云港地区新生儿遗传代谢病发病率较高的病种依次为苯丙氨酸羟化酶缺乏症、短链酰基辅酶 A 脱氢酶缺乏症、甲基丙二酸血症，规范治疗和定期随访可阻止病情发展并改善患儿预后。

围产期妇女叶酸基因检测实验室技术专家共识

王洁
三亚市妇幼保健院

在世界范围内，神经管缺陷（neural tube defects，NTDs）是排在第二位的先天性畸形病，仅次于心脏畸形。2009 年原国家卫生部颁发的《增补叶酸预防神经管缺陷项目管理方案》中明确提到，围产期补服叶酸可预防绝大多数婴儿 NTDs 的发生，显著降低 NTDs 的发生率。研究表明，与叶酸及维生素 B12 代谢密切相关的是 5,10-亚甲基四氢叶酸还原酶（MTHFR）和甲硫氨酸合成酶还原酶（MTRR）。编码 MTHFR 和 MTRR 等基因变异引起的酶活性降低可阻抑同型半胱氨酸转化为甲硫氨酸，导致低叶酸血症和高同型半胱氨酸血症，从而增加新生儿神经管缺陷发生或导致自发性流产等风险。遗传异质性导致了机体对叶酸利用能力的差异，叶酸增补应因人而异，避免增补过多或过少给胎儿和孕妇带来不利影响。通过基因检测手段，对叶酸利用能力进行个体化（差异化）风险评估，可以为围产期妇女增补叶酸，预防新生儿出生缺陷提供科学依据和临床询证。为规范叶酸代谢能力基因检测实验室技术环节，加强检测质量管理，国家卫生健康委临床检验中心组织产前筛查与产前诊断实验室室间质评专家委员会，制订本共识。

α 地中海贫血罕见型变异家系分析及验证

高慧 郭辉 王丽娟 宋雅琴 聂锐 马迪 张阮章 胡玉华 林玉梅 王沙燕
深圳市人民医院

目的 通过家系分析，结合 MLPA 和常规地贫基因检测技术，明确诊断 α 地贫罕见型变异携带者的基因型，并分析基因型与表型的关系，为临床诊断和产前诊断的遗传咨询提供指导。
方法 对本院产前诊断中 2 例确诊为-$\alpha^{3.7}$/αα 缺失型（gap-PCR 法）的携带者及家系成员进行基因型和表型分析，结合 gap-PCR 和 MLPA（P140 试剂盒）检测结果，确定检测样本是否发生了的 α 地贫基因的拷贝数变化，并根据 MLPA- P140 试剂盒探针分布对拷贝数变化的片段进行定位。

结果 家系 1，gap-PCR 结果显示孕妇为-$\alpha^{3.7}$/αα 或 HKαα/aa，丈夫为--^{SEA}/αα，脐血样本为--^{SEA}/-$\alpha^{3.7}$。孕妇临床表型为 MCV 92.1fl，MCH 30.7pg，HBA2 比例 2.9%，不符合-$\alpha^{3.7}$/αα 地贫携带者表型。MLPA 结果及家系分析显示，孕妇携带-$\alpha^{3.7}$ 缺失，同时合并 HBA2 基因的拷贝数增加（即 ααα $^{anti4.2}$/-$\alpha^{3.7}$ 或者 Hkαα/αα），但是仅有-$\alpha^{3.7}$ 缺失传递给胎儿，不符合 Hkαα/αα 传递方式（ααα $^{anti4.2}$ 与-$\alpha^{3.7}$ 顺式），确诊家系 1 中孕妇的基因型为 ααα $^{anti4.2}$/-$\alpha^{3.7}$。家系 2，gap-PCR 结果显示孕妇为-$\alpha^{3.7}$/αα 或者 Hkαα/αα，丈夫为 αα/αα，已育有 1 名 8 岁男孩子，为 αα/αα，本次妊娠脐血样本为-$\alpha^{3.7}$/αα 或者 Hkαα/αα。孕妇临床表型为 MCV 84.4 fl，MCH 27.1 pg，HBA2 比例 3.8%，不符合-$\alpha^{3.7}$/αα 地贫携带者表型。孕妇 MLPA 结果显示为 ααα $^{anti4.2}$ 的拷贝数变化，8 岁儿子为 ααα $^{anti3.7}$/aa，脐血为 Hkαα/αα，亲缘关系符合。通过家系中传递模式分析，家系 2 中孕妇基因型确定为 ααα $^{anti3.7}$/Hkαα（ααα $^{anti4.2}$ 与-$\alpha^{3.7}$ 顺式），其两个等位基因分别传递给了大儿子和胎儿。孕妇 HBA2 电泳比例增加考虑为携带的 HBA2 基因拷贝数增加所致。

结论 当 α 地贫缺失型携带者同时合并 α 地贫基因的拷贝数变异时，gap-PCR 结果常常会出现与临床表型不一致的情况。结合 MLPA 检测结果，配合家系中等位基因的传递分析，可以验证并明确携带者的真实基因型。本研究中家系 1 孕妇及家系 2 孕妇与胎儿均认为是-$\alpha^{3.7}$/αα 缺失型地贫携带者（gap-PCR 法），实际却为 ααα $^{anti4.2}$/-$\alpha^{3.7}$、ααα $^{anti3.7}$/HKαα 与 Hkαα/αα 罕见地贫基因型；可见，这类携带者需在基因型明确诊断后，才能对其表型分析及遗传咨询和风险评估提供正确的指导。

α 地贫基因缺失复合罕见型变异的检出及表型分析

高慧 郭辉 王丽娟 马迪 宋雅琴 聂锐 张阮章 胡玉华 林玉梅 王沙燕
深圳市人民医院

目的 研究探讨罕见型 α 地中海贫血基因变异与常规的 α 地中海贫血基因突变共存时，MCV、MCH 及血红蛋白电泳的变化。

方法 收集本院就诊，常规 gap-PCR 方法确诊为 α 地中海贫血基因缺失型的患者 19 例（--^{SEA}/αα 阳性 4 例，αα/-$\alpha^{3.7}$ 阳性 15 例），分析血常规，血红蛋白电泳等表型。针对 HKαα，- -^{THAI}/αα，fusion gene，ααα $^{anti3.7}$，ααα $^{anti4.2}$ 与-$\alpha^{27.6}$/αα 的变异设计探针，应用 PCR-电泳技术进行检测，并用 sanger 测序进行验证。

结果 报告为--^{SEA}/αα 的样本中发现 4 例复合罕见型变异，分别为 ααα $^{anti3.7}$/--^{SEA} 阳性 2 例，ααα $^{anti4.2}$/--^{SEA} 阳性 1 例，-$\alpha^{27.6}$/--^{SEA} 阳性 1 例；αα/-$\alpha^{3.7}$ 携带者中有 14 例为 HKαα/αα，1 例为 ααα $^{anti4.2}$/-$\alpha^{3.7}$ 或者 ααα $^{anti4.2}$/HKαα 阳性；在 19 例样本中，只有 ααα $^{anti3.7}$/--^{SEA} 与 ααα $^{anti4.2}$/--^{SEA} 阳性出现了 MCV、MCH 、HbA2 低于正常值（有 1 例 ααα $^{anti3.7}$/--^{SEA} 的 HBA2 比例为 2.8%），但其 Hb 均大于 122g/L，MCV 大于 73fl，MCH 大于 22pg；其余样本 MCV、MCH 均正常，HbA2 比例大于 2.5%。 sanger 测序显示阳性结果与 PCR-电泳技术检测结果一致。

结论 α 地贫缺失型变异的样本中（常规 gap-PCR 法检出），存在一定频率同时复合罕见型 α 地贫基因的拷贝数变异，如--^{SEA}/αα 携带者复合 ααα $^{anti4.2}$ 与 ααα $^{anti3.7}$ 变异，-$\alpha^{3.7}$/αα 携带者复合 ααα $^{anti4.2}$ 变异；本研究中 HKαα/αα 与 ααα $^{anti4.2}$/-$\alpha^{3.7}$（或 ααα $^{anti4.2}$/HKαα）变异的临床表型均正常， --^{SEA}/αα 携带者复合拷贝数变异出现了 MCV、MCH 、HbA2 偏低情况，但临床表型比--^{SEA}/αα 携带者轻。-$\alpha^{27.6}$/--^{SEA} 阳性一般与 Hb H 病有关，然而本研究中该患者 MCV、MCH、HbA2 均正常，推测仍然有未知情况，需进一步研究分析。可见，研究人群中罕见 α 地贫基因拷贝数变异的携带率，有助于地贫携带者表型分析及遗传风险评估。应用 PCR-电泳技术分析罕见型 α-地中海贫血基因可作为常规地贫检测的补充，但是仍有不足之处，其无法区分 ααα $^{anti4.2}$/-$\alpha^{3.7}$ 与 ααα $^{anti4.2}$/HKαα 基因型，必须利用家系分析才可以进一步确认。

Rapid detection of twenty-nine common Chinese glucose-6-phosphate dehydrogenase variants using a matrix-assisted laser desorption/ionization-time of flight mass spectrometry assay on dried blood spots

Weiqian Dai Yongguo Yu
Xinhua Hospital, Shanghai Jiao Tong University School of Medicine

Background Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common inherited disease. Current neonatal screening methods for G6PD deficiency primarily rely on the use of biochemical tests. However, only 15%–20% of female carriers were estimated to have been detected using these tests. As a better alternative, DNA-based tests could be used for G6PD deficiency screening. We aimed to develop a matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) assay for G6PD variant detection.
Methods A MALDI-TOF MS assay with multiprimer extension (multi-PEX) was developed to rapidly and accurately detect the 29 common G6PD variants in the Chinese population using a dried blood spot as a template. A parallel study screening 571 unrelated neonatal samples using the MALDI-TOF MS and fluorescence quantitative enzymatic assays was performed. All results were confirmed by Sanger sequencing in a blind study.
Results In 571 unrelated neonatal samples, 34 positive samples, including 26 samples from hemizygous males and eight samples from heterozygous females, were correctly identified, yielding a clinical sensitivity of 100%. The results were validated using Sanger sequencing with 100% concordance. In contrast, the fluorescence quantitative enzymatic assay had a 75% false negative and 88.8% false positive rate for the detection of heterozygous G6PD deficient females.
Conclusions We established a reliable MALDI-TOF MS assay for G6PD deficiency screening in the Chinese population maximizing the chance of detection of heterozygous G6PD deficient females and reducing the false negative and false positive rates associated with routinely used newborn screening procedures

PLOD2 基因突变导致 Bruck 综合征 2 型临床特点及基因变异分析

郝会民[1] 卫海燕[1] 沈凌花[1] 张英娴[1] 刘晓景[1] 曹冰燕[2]
1.郑州大学附属儿童医院 河南省儿童医院 郑州儿童医院
2.国家儿童医学中心 首都医科大学附属北京儿童医院

目的 探讨 *PLOD2* 基因变异致 Bruck 综合征 2 型的临床特征及基因变异特点。
方法 回顾分析 2020 年 2 月就诊的 1 例 Bruck 综合征 2 型患儿的临床资料，并复习相关文献。
结果 男性患儿，1 岁 8 月龄，因生后先天性关节挛缩、反复骨折就诊。二代测序提示患儿 *PLOD2* 基因存在 c.1829G>C 和 c.1559dupC 复合杂合变异，分别来源于表型正常的父母。c.1829G>C 为 HGMD 及 ClinVar 数据库未报道过的变异位点，致病性经 ACMG 指南评估为：可能致病。文献检索到 26 例患者，结合本例患儿，共 27 例，男 16 例、女 11 例；常见临床表型依次为多发骨折 27 例，先天性关节挛缩 17 例，脊柱侧凸 16 例，手指屈曲 12 例，畸形足 12 例，身材矮小 10 例，蓝巩膜 9 例，翼状胬肉 6 例；*PLOD2* 基因变异主要集中在 17 外显子，共有 24 种不同的变异位点，17 例为纯合变异，10 例为复合杂合变异，其中 c.1856G>A（3 例）和 c.1559dupC（3 例）可能为热点变异；接受双膦酸盐治疗的 11 例患者，均取得较好疗效。
结论 新的变异位点 c.1829G>C 扩大了 *PLOD2* 基因变异谱，多发骨折、先天性关节挛缩为 *PLOD2* 基因突变导致 Bruck 综合征 2 型主要临床特征，早期诊断并给予双膦酸盐治疗可改善预后。

非综合征型先天缺牙新致病基因 MYF5 和新突变的发现

赵稚宁 李天琪 王慧娟 林师仪 张亲 张婷婷 张向宇
天津医科大学口腔医院

目的 目前报道与非综合征型先天缺牙密切相关的基因不到 10 个，新致病基因有待发现。本课题旨在一非综合征型先天缺牙家系中寻找新致病基因及突变，并研究其遗传机制。
方法 本课题组收集到一个 10 人三代的非综合征型先天缺牙家系，其中有 3 名患者，其他均为正常对照。通过采集家系患者和正常对照的外周血，利用全基因组外显子测序、生物信息学软件分析，初步确定若干候选突变，将候选突变与已知缺牙基因 WNT10A、WNT10B、AXIN2、PAX9、EDAR、MSX1 进行层次聚类分析，进一步确定该家系的致病基因突变，并对其进行保守性分析和二级结构预测。
结果 全基因组外显子测序结果中筛选出若干候选基因突变位点 MYF5 c.G638A 等。聚类结果显示，候选基因中 MYF5 与已知缺牙基因聚为一类，故高度怀疑 MYF5 为可疑致病基因。
可疑错义突变 MYF5 c.G638A 经软件预测，均为致病性突变。该突变氨基酸（p.R213Q）位于高度保守的 Myf5 结构域。软件预测二级结构显示，与野生型相比，突变型蛋白在第 210-220 位氨基酸附近的 α 螺旋缺失，β 片层长度减少；同时，两者在此处的抗原性存在差异。
结论 本研究在一非综合征型先天缺牙家系中发现一个未报道过的新候选基因突变 MYF5（c.G638A），有望进一步扩充非综合征型先天缺牙的基因图谱。

Optimization of Generating Human Blastocyst-like Structure from Pluripotent Stem Cells

Yingying Zhang Yong Fan
The Third Affiliated Hospital of Guangzhou Medical University

Objective We optimize the ways of generation of human blastocyst-like structures from human extended pluripotent stem (EPS) cells induced by bone morphogenetic protein 4 (BMP4), which was reported in our previous work, in order to improve the efficiency of blastoids generation.
Method In the early stage, we developed a BMP4 induction medium combined with a three-dimensional (3D), two-step induction protocol for generating blastocyst-like structures (EPS-blastoids) from EPS cells, whose key cell lineages and transcriptome levels are similar to those of normal human blastocysts. In order to further increase the efficiency of inducing trophectoderm cells and the rate of generating blastoids, we combined the original BMP4 induction culture medium and the composition of the human trophoblast stem cell culture medium to establish an optimized induction medium system, and then use two-step induction protocol induces EPS cells into a blastocyst-like structure.
Result The efficiency of blastocyst-like structure which is induced by optimized induction medium from EPS is 20% higher than that of the original BMP4 induction medium.
Conclusion The optimized induction medium formed by the BMP4 induction medium combined with the components in the human trophoblast stem cell medium is beneficial to improve the efficiency of generating blastoids from EPS.

4 例复发感染型高 IgE 综合征患者的临床及遗传学分析

张蕾 何学莲 赵培伟 刘凡 卢静静 张显凯
华中科技大学同济医学院附属武汉儿童医院

目的 探讨 *DOCK8* 和 *STAT3* 突变引起复发感染型高 IgE 综合征患者的临床表现及遗传学特点。
方法 收集 4 例患者（P1～P4）的临床资料，利用全外显子测序（WES）技术对患儿进行基因突变分析。结合 4 例患者的临床特点并复习相关文献，总结该病的特点。

结果 4 例患儿分别为 1 女（P3）3 男，年龄为 1 岁 5 月到 10 岁 5 月。4 例患儿均存在局部脓肿，皮炎，反复的金黄色葡萄球菌感染、铜绿假单胞菌感染或真菌感染病史。患者 P2 面容异常，既往有肱骨骨折史；其他患者面容未见明显异常。实验室检测均提示轻度嗜酸粒细胞增多（分别为 0.79×10^9/L、0.60×10^9/L、1.14×10^9/L、1.05×10^9/L），患者（P2~P4）IgE 水平显著增高（分别为 21500.00 IU/ml、41200.00IU/ml、10400.00 IU/ml），患者 P1 未行 IgE 检测。淋巴细胞亚群分析发现患儿（P1）T 细胞、自然杀伤细胞减少，患儿（P2~P4）的自然杀伤细胞减少。CT 平扫提示 4 例患儿颌面部、鼻咽部、颈部软组织肿胀增厚。WES 检测发现患者 P1 的 *DOCK8* 基因为存在复合杂合突变(c.5346C>G, p.I1782M; c.36C>G, p.F12L)，且 2 个突变位点未见文献报道。其余患者（P2~P4）发现 *STAT3* 基因存在杂合变异(分别为 c.1907C>T, p.S636F; c.1954G>A, p.E652K; c.1144C>T, p.R382W)，且三个位点均为已报道的致病变异。 结合患者临床表现 4 例患者均诊断为高 IgE 综合征 。

结论 高 IgE 综合征一组是具有遗传异质性的免疫缺陷病，*DOCK8* 和 *STAT3* 基因突变为该病的常见病因。WES 检测有助于临床诊断 且本研究发现 *DOCK8* 基因两个新致病位点，丰富了该基因突变谱。

一例赖氨酸尿性蛋白耐受不良患儿的临床与 SLC7A7 基因变异分析

郝会民 陈永兴 杨海花 沈凌花 卫海燕
郑州大学附属儿童医院 河南省儿童医院 郑州儿童医院

目的 探讨一例赖氨酸尿性蛋白耐受不良患儿的临床及遗传学特点,以期临床医生对疾病早期识别。

方法 回顾性分析一例赖氨酸尿性蛋白耐受不良患儿的临床特点,通过二代测序对患儿家系进行基因检测。

结果 2 岁 2 月，男性患儿，表现为异常哭闹，发育迟缓，身材矮小，厌恶蛋白。二代测序提示 SLC7A7 基因存在 c.625+1G>A 和 c.225_c.226insAGGGTGTGCTCATATACAGTGCCTCCTTTGGTCTCTCTCTGGTCATC（p.W76Rfs*110）复合杂合变异，分别来自于表型正常的母亲和父亲，c.225_c.226insAGGGTGTGCTCATATACAGTGCCTCCTTTGGTCTCTCTCTGGTCATC（p.W76Rfs*110）为未报道过的变异。

结论 赖氨酸尿性蛋白耐受不良临床缺乏特异性，厌恶蛋白是本病的一个明显特征，新位点变异扩展了 SLC7A7 基因变异谱，基因检测是确诊赖氨酸尿性蛋白耐受不良的关键。

Cell-free DNA test for pathogenic copy number variations: a retrospective study

Honglei Duan
Affiliated Drum Tower Hospital, Medical School of Nanjing University

Objective To evaluate the detection rate (DR) by prenatal cell-free DNA test for pathogenic copy number variations (CNVs)＞2 Mb among pregnancies with fetal ultrasound abnormalities.

Materials and methods This was a retrospective study in 29 pregnant women with fetuses diagnosed as microdeletion/microduplication syndromes by prenatal chromosome microarray analysis (CMA). Cell-free DNA from the maternal plasma was sequenced on the NextSeq CN500 sequencer. The quality standard of unique map reads in a single sample was greater than 10M and only gains and losses of more than 2Mb were reported.

Results A total of 24 CNVs were identified by cell-free DNA test among the 21 fetuses with pathogenic CNVs identified by prenatal CMA, including 20 consistent CNVs and 4 inconsistent CNVs. Overall, the DR of cell-free DNA test for pathogenic CNVs ＞ 2Mb was 69%.

Microdeletions or microduplications at 22q11.2 were the most common CNVs, with a DR of 4/5 (80%) and 3/4 (75%) respectively.
Conclusion Cell-free DNA test exhibited a moderate DR for pathogenic CNVs ＞2Mb in fetuses with ultrasound abnormalities. Cell-free DNA test could provide an opportunity for early screening before the appearance of abnormalities on fetal ultrasound, while further clinical data and cost-effectiveness assessment are needed.

自身免疫性多内分泌腺病综合征 I 型 2 例临床特征及 AIRE 基因变异分析

郝会民 卫海燕 李杨世玉 黄爱 刘晓景
郑州大学附属儿童医院 河南省儿童医院 郑州儿童医院

目的 通过对 2 例自身免疫性多内分泌腺病综合征 I 型临床特征及 AIRE 基因变异分析，提高对自身免疫性多内分泌腺病综合征 I 型的认识。
方法 收集 2 例自身免疫性多内分泌腺病综合征 I 型临床资料，采集患者及父母外周血并提取 DNA，通过二代测序对突变位点进行检测，通过生物信息学进行功能预测及致病性分析。
结果 病例 1 12 岁男性，3 岁出现念珠菌感染，11 岁诊断重度贫血，基因检测 AIRE 基因存在 c.44G＞A：p.R15H 和 c.1036C＞T：p.Q346*杂合突变，病例 2 17 岁男性，7 岁诊断甲状旁腺功能减退症，8 岁出现念珠菌感染，15 岁诊断肾上腺皮质功能减退症,基因检测 AIRE 基因存在 c.38T＞C:p.L13P 和 c1400+2T＞C 杂合突变，均符合常染色体隐性遗传。
结论 自身免疫性多内分泌腺病综合征 I 型临床表现多样，临床症状出现时间跨度大，易漏诊及误诊，疑似时需评估其他内分泌腺体功能，并长期随访,尽早完善 AIRE 基因检测，积极寻求诊断和预测自身免疫性多内分泌腺病综合征的新方法。

肿瘤相关性低血磷性佝偻病一例病例报告

李楠 余永国
新华医院

目的 肿瘤相关性低血磷性佝偻病的鉴别诊断，避免在接诊时的误诊误治。
方法 我院接诊了一例肿瘤相关性低血磷性佝偻病的 11 岁儿童，因“右下肢疼痛约半年伴行走困难 2 个月”就诊，疾病呈进展性，发病半年后行走困难，肌无力，身高呈逐渐降低趋势。辅助检查：长期低血磷，血钙正常，尿磷降低，碱性磷酸酶升高，骨骼影像学改变，骨密度降低。
结果 患者最终明确诊断为肿瘤相关性低血磷性佝偻病。肿瘤相关性低血磷性佝偻病(Tumor-induced osteomalacia，TIO)又被称为致癌性骨软化症，是以低血磷、高尿磷及 1,25(OH)2D 正常或低下为特点的一种罕见疾病。现认为磷酸盐性间叶肿瘤(PMTs)是引起 TIO 的主要原因。而 TIO 是获得性 FGF-23 相关低磷血症最常见的病因。
结论 其起病隐匿、发展缓慢，临床上常误诊及漏诊。并且由于症状的非特异性，诊断可能会延迟数年; 由于长时间的低磷血症会导致不可逆转的并发症，对儿童的身体生长造成严重损害，故强调在年轻人群出现相关症状时进行 TIO 鉴别诊断的重要性。此外，引起疾病的肿瘤通常难以检测和定位，因为它们多在隐匿的解剖位置，好发于软组织、骨组织、鼻腔及鼻窦区域，定位这些很小的肿瘤通常是一个挑战，为此，面对接诊的患者，需要制定系统的诊断和治疗方案，与其他疾病鉴别，避免误诊误治，延误患者的病情。

COL11A2 基因新变异鉴定与临床表型特征分析

钟鸣骏
四川大学华西医院

目的 Collagen type XI alpha 2 chain (*COL11A2*)基因编码 XI 型胶原蛋白的两条 α 链之一。该基因变异可以引起多种疾病表型，结合本团队临床表型数据和基因数据，整合公共数据库信息，绘制 *COL11A2* 基因变异图谱和多种疾病临床表型谱，探究该基因的基因型和表型之间的相关性。
方法 以 CDGC（China Deafness Genetics Consortium）大型耳聋队列研究中的 23927 例耳聋样本为基础，收集临床资料，对受试者的血样提取基因组 DNA，进行高通量测序检测，选取所有携带 COL11A2 基因变异的位点和样本信息。根据美国医学遗传学与基因组学学会（ACMG）发布的遗传变异分类标准与指南进行致病性分析。
结果 基于 CDGC 耳聋队列临床表型数据和基因检测结果，本研究明确诊断了 5 个隐性遗传性耳聋家系，1 个显性遗传性耳聋家系，1 个隐性耳-脊椎-骨骺增生性发育不良（OSMED）家系，其中除 NM_080680.2:c.966dupC 为已报道变异外，还有 6 个目前未报道过的新发隐性遗传变异，分别为 c.3512_3528+1del，c.2554C>T，c.4483-1G>C，c.3636+1G>A， c.5191C>A， c.4553G>C 和 1 个新的显性遗传变异 c.3582+2_3582+3del。同时本研究梳理了以往数据库和文献中已报道的位点和临床表型信息。
结论 本研究通过对 CDGC 耳聋队列的患者临床表型和测序基因数据分析，确诊了 *COL11A2* 基因致病性变异导致的 5 个隐性遗传性耳聋家系、1 个显性遗传性耳聋家系和 1 个 OSMED 家系，扩展了 COL11A2 基因致病性变异谱和表型谱，进一步探究了深层次的基因型表型相关性。

马凡综合征家系突变基因检测

杨涛 赵飞跃 尤祎 曹一璇 赵秀丽
中国医学科学院基础医学研究所

目的 马凡综合征（MFS, Marfan syndrome, MIM 154700）是一种以结缔组织病变为基本特征的单基因病，症状累及眼、骨骼、肌肉、心血管等多个器官系统，患者多呈现主动脉瘤/主动脉夹层、晶状体异位等特征症状。该病为常染色体显性遗传，由 *FBN1*（*Fibrillin-1*）基因突变所致。本研究旨在为临床拟诊的马凡综合征患者提供精准分子诊断，以确定其遗传病因并实现临床确诊。
方法 收集 3 个临床拟诊 MFS 患者及家系临床资料及血样，提取外周血基因组 DNA，目标区域捕获测序先证者 *FBN1* 基因全部外显子及其邻接区域，通过 PCR-Sanger 测序对检出的疑似突变进行家系验证，通过候选致病变异的进化保守性分析、人群数据库预测评估及突变蛋白的功能预测等生物信息学手段，确定变异致病性。
结果 3 个家系的先证者均呈现不同程度的 MFS 症状，在其 *FBN1* 基因均检出一杂合致病突变。家系 1 先证者及其父携带 1 个 *FBN1* 稀有变异，c.1426T>C (p.Cys476Arg)，其父罹患视网膜病变，呈高度近视，但无其他 MFS 相关症状。SIFT 和 Polyphen 预测结果均显示该变异有害，该突变已报道为致病。家系 2 和家系 3 先证者均携带一无义突变，分别为 c.6169C>T，(p.Arg2057*)、及 c.6276G>A（p.Trp2092*），其父母无同样变异，提示先证者为新生突变。其中，p.Arg2057* 为已报道 MFS 致病突变，p.Trp2092*尚无文献报道，为本研究新发现突变。
结论 本研究分别在 3 个 MFS 疑似患者中检出 *FBN1* 致病突变，肯定了先证者的临床拟诊结果；可为患者治疗及家系成员再次妊娠产前诊断提供依据；本研究发现一个新致病突变，并为文献报道突变类型的致病性提供了进一步的支持证据。

MLPA 联合 STR 分型技术快速分析流产组织染色体异常

宋雅琴 郭辉 高慧 马迪 王丽娟 聂锐 张阮章 胡玉华 林玉梅 王沙燕
深圳市人民医院

目的 联合应用多重连接依赖探针扩增(multiplex ligation dependent probe amplification，MLPA)技术和短串联重复序列(short tandem repeat，STR)分型技术快速检测流产组织中的染色体异常，建立快速分析流产组织遗传学病因的技术方法。
方法 对医院 2021 年 1 月至 2021 年 8 月的 282 例流产绒毛组织样本取材，提取 DNA ，检测试剂盒包括 MLPA p36、p70、p180 和 p95 试剂盒以及染色体（13/18/21/X/Y）多重 STR 基因分型试剂盒。
结果 282 例流产样本中发现染色体异常 161 例，异常率为 57.09%，其中 144 例为染色体数目异常、14 例为染色体微缺失和/或微重复（其中 6 例同时包含染色体微缺失和微重复，提示染色体结构的不平衡）、3 例单亲二倍体。染色体数目异常涉及 2-22 号常染色体，X、Y 染色体，主要有 16 号染色体三体（22.22%）、20 号染色体三体（13.89%）、三倍体（12.5%）、X 单体（9.03%）、21 号染色体三体（8.34%）、3 号染色体三体（4.17%）等。检出的 3 例单亲二倍体均为父源性，包括 1 例同源单亲二倍体，1 例异源单亲二倍体，和一例单亲二倍体的嵌合体。
结论 MLPA 可检出绝大多数染色体异常，包括非整倍体，三倍体 69,XXY 和 69,XYY，但对 69,XXX 检出有局限性。STR 技术可快速检出 69,XXX 异常，并对同源性单亲二倍体有很好的提示作用。STR 技术结合 MLPA 技术可以有效提高染色体多倍体的检出率，本文的统计数据显示研究流产组织样本中染色体异常率高于目前大部分文献报道的 40%-50%。MLPA 联合 STR 分型检测分析流产组织染色体异常，可作为临床流产组织染色体快速检查的一线手段。

胚胎植入前遗传学检测技术在一 Noonan 综合征家系中的应用

何健淳 黎青 李少英 何文智 王燕超 冼嘉嘉 张敏聪 马晓燕 叶国新
广州医科大学附属第三医院

目的 应用胚胎植入前遗传学检测技术，为一有 Noonan 综合征家族史的患者实行辅助生殖，以阻断该遗传疾病向下一代的传递。
方法 采用单细胞全基因组扩增技术（MDA）、高通量测序技术及 SNP 分型技术，对女方携带 PTPN11 基因致病突变的该家庭进行胚胎植入前遗传学诊断。SNP 分型技术通过选择 PTPN11 基因突变位点上下游 1M 区域内的高密度紧密连锁的 SNP 位点作为遗传连锁标记，二代测序后选择有效 SNP 位点构建夫妻单体型，确定携带致病基因的风险染色体。采用二代测序技术对胚胎 PTPN11 基因直接测序和构建单体型连锁分析进行植入前遗传学诊断，挑选健康胚胎进行移植,在孕中期行羊水穿刺产前诊断基因型。
结果 该患者共获得 5 枚囊胚，其中有 3 枚为 PTPN11 基因野生型，有 2 枚为 PTPN11 基因杂合突变。选择形态较优且为 PTPN11 基因野生型的胚胎进行移植，羊水穿刺结果与胚胎植入前诊断结果一致，足月分娩一健康婴儿。
结论 PTPN11 基因突变所导致的 Noonan 综合征呈常染色体显性遗传，后代有 50%几率患病。应用胚胎植入前遗传学检测技术，能够有效阻断该突变基因在该家系的垂直传播，生育出健康的下一代，为该家庭乃至社会减轻了负担。

染色体多态性对不孕症患者 IVF-ET 妊娠结局的影响

万留霞
郑州大学第三附属医院

目的 探讨在辅助生殖技术助孕过程中染色体多态性对不孕夫妇妊娠结局的影响。

方法 回顾性研究 2018 年 12 月—2020 年 12 月期间在郑州大学第三附属医院生殖医学中心接受体外受精-胚胎移植（IVF-ET）治疗，促排卵方案为长方案行新鲜周期移植的 1390 对不孕症夫妇,根据外周血染色体检测结果，将其分为染色体多态性组（n=410）和染色体正常组（n=980）,比较两组间患者的妊娠结局。
结果 染色体多态性组与正常组患者相比，染色体多态性组早期流产率高于染色体正常组（19.29%vs 15.70%）,且有统计学意义（P<0.05）,而获卵数、受精率、优质胚胎率、种植率、临床妊娠率无显著差异（P> 0.05）。
结论 染色体多态性患者早期流产的发生率高于染色体正常者，有统计学意义，提示染色体多态性对辅助生殖治疗效果可能有一定影响, 应提醒患者更加注重孕期产检。

神经纤维瘤病 2 型 1 例

李苏一 陈义兵
郑州大学第一附属医院

目的 神经纤维瘤病 2 型是一种单基因常染色体显性遗传病，其致病基因为位于常染色体 22q12.2 的 NF2 基因，NF2 约一半以上的病例为散发病例，主要由新发突变导致。本文报道 1 例 NF2 基因 Sanger 测序及 MLPA 检测未检测到 NF2 基因外显子突变以及大片段缺示。
方法 对该患者进行临床、影像和外周血、切片 NF2 基因 Sanger 测序及 MLPA 检测。
结果 .该患者从临床水平确诊为 NF2 患者，引起 NF2 特征性临床表现，包括全双侧前庭神经鞘瘤、颅内多发脑膜瘤、脊髓肿瘤等表现。对该患者及其哥哥血液样本通过试剂盒法提取 DNA，对 2 型神经纤维瘤病相关的目标基因 NF2 进行了 Sanger 测序和 MLPA 检测。该测试者血液样本中 未检测到 NF2 基因外显子突变以及大片段缺失。后患者手术切除标本切片行基因检测，切片：NF2（Q410Afs*33）体细胞突变丰度：45.60%；外周血（NF2 Q410Afs*33）体细胞突变丰度：0.43%。
结论 NF2 基因突变类型多样，NF2 患者临床表现多样，NF2 致病基因可能存在异质性。

Identification of a novel pathogenic splice variation in FBN1 in a family with Marfan syndrome

Yu Xia[1] Rencong Yang[2] Chaojie Wang[1]
1.Guangdong Provincial Hospital of Chinese Medicine
2.The First Affiliated Hospital, Jinan University

Background Marfan syndrome (MFS) is a connective tissue disease involving multiple systems, in which thoracic aortic aneurysm (TAA) is the most common life‐threatening symptom.
Method A pedigree with TAA was investigated, and peripheral venous blood was extracted from eight family members. RNA was extracted from patient's aortic tissue. After whole exome sequencing (WES) for these members, bioinformatics and inheritance analyses were performed.
Result WES revealed a de novo NM_000138:exon40:c.4817-2A>G in splice site of FBN1, which co-segregated with the disease phenotype in the family. This splice variation was confirmed by Sanger sequencing. Reverse polymerase chain reaction demonstrated the presence of a shortened mRNA transcript and revealed skip of exon 39.
Conclusion Our study expands the phenotypic spectrum of the pathogenic variation, associated with MFS, facilitating clinical genetic diagnosis and future genetic counseling for this family.

TP-PCR 在强直性肌营养不良 1 型基因检测及产前诊断中的应用

陈晨
郑州大学第一附属医院

目的 探讨 TP-PCR 技术在强直性肌营养不良 1 型分子检测和产前诊断中的应用。
方法 应用 TP-PCR 结合毛细管电泳的方法，对 48 个家系共 60 人进行 *DMPK* 基因 CTG 重复次数的测定，并为 4 个 DM1 家系提供产前基因检测。
结果 共检出 DM1 患者 40 人，正常等位基因 CTG 重复范围 5-18 次，检出率最高等位基因重复次数为 6 次（30%），其次为 13 次（25%），12 次和 14 次（15%）。异常等位基因 CTG 重复扩增产物均检测到连续降低的毛刺锋，为典型的阳性扩增峰，提示患者 *DMPK* 基因 CTG 异常扩增数>50 次。检出正常个体 20 人，TP-PCR 全长扩增产物检测到一个或者两个扩增峰，对应重复次数范围 6-27 次检出率最高等位基因重复次数为 13 次（42.5%），其次为 12 次（20%）和 6 次（12.5%）。CTG 重复扩增产物的毛细管电泳结果显示为小范围的连续扩增峰，扩增峰末端处有明显的截断。4 个 DM1 患者家系进行产前诊断，一例胎儿为正常，三例胎儿检测到 CTG 异常扩增（>50 次），为患者。
结论 TP-PCR 应用 DM1 型患者基因检测，结果快速、准确，但是对超过 50 次的 CTG 异常扩增，无法得出准确重复次数。

30 例先天性类脂性肾上腺皮质增生症患者临床及遗传学分析

肖冰 段颖 郑婉祺 梁黎黎 张惠文 罗小梅 顾学范 孙昱 邱文娟 余永国
上海交通大学医学院附属新华医院临床遗传中心

目的 探讨儿童先天性类脂性肾上腺皮质增生症(CLAH)的临床生化特点及类固醇激素合成急性调节蛋白(StAR)基因突变情况。
方法 以 2006 至 2020 年于上海交通大学医学院附属新华医院接受治疗的 30 例 CLAH 患儿为研究对象，回顾性分析其临床资料，包括起病/诊断时间、临床表现、生化影像检查、基因突变情况、治疗和随访等。23 例采用 PCR 扩增和 Sanger 测序方法，7 例采用全外显子测序方法。
结果 30 例 STAR 基因突变患者中，26 例散发，其余 4 例来自不同的两个家庭。**起病年龄**：29 例 7 月龄前出现临床症状，1 例晚发（3.5 岁），平均起病年龄为 3.06 ± 7.70 月，平均诊断年龄（基因确诊）为 28.56 ± 47.77 月，从起病到诊断的时间差均值为 25.49 ± 47.14 月。**临床表现**主要包括皮肤色素沉着（93.3%），失盐或电解质紊乱（80%）、呕吐腹泻或腹痛（60%）。**实验室检查结果**： ACTH 水平升高（100%）。93.3%患儿皮质醇降低，低血钠和高血钾均占 70%，仅 4 例合并低血糖。**影像学检查**：7 例双侧肾上腺增粗，呈低密度影。**染色体核型分析**：14 例为 46,XX，16 例为 46,XY。在 46,XY 的患儿中，4 例患儿的外生殖器呈现男性外观，社会性别认定为男性；12 例患儿外生殖器呈女性外观。**基因突变**：突变类型包括 4 种，分别是无义突变（n=20），框移突变（n=13），错义突变（n=10），剪接突变（n=1）。其中， c.772C>T（p.Q258X）为 21.4%（ 12/56 ）， c.707_708delAGinsCTT （ p.K236Tfs*47 ）为 8.9%（ 5/56 ）以及 c.229C>T（p.Q77X）为 7.1%（4/56）。发现十个尚未报道的新突变，分别为 720delG，509C>T，708_709insT，358T>G，179-2A>C，745-1G>A，179-15G>T，125delG 和 744+1G>A。**治疗**：患儿均接受氢化可的松治疗，初始平均治疗剂量为 22.14 ± 12.5 mg/d/m^2；29 例患儿接受了 9α 氟氢可的松的治疗，平均治疗剂量为 0.06 ± 0.03 mg/d。治疗过程中，3 例患儿出现高血压，2 例肾上腺危象发作，卵泡提前发育，身高增长缓慢，性腺发育不良和 FSH 升高各 1 例。
结论 先天性类脂性肾上腺皮质增生症是类固醇生成急性调节蛋白缺乏所致，是类固醇激素代谢中最严重的一种罕见常染色体隐性遗传疾病。多数患儿婴儿期起病，临床表现为肾上腺皮质功能不全症状，水电解质紊乱常见，外生殖器多呈女性外观。基因变异以无义突变为主，其中 p.Q258X 为中国人群热点突变。基因检测有助于 CLAH 的诊断，可为该病的遗传咨询提供参考。治疗采用激素替代疗法，随访过程中应密切关注患儿血压和生长发育情况。

Dual diagnosis of osteogenesis imperfecta and short stature and advanced bone age with or without early-onset osteoarthritis and/or osteochondritis dissecans reveals a cumulative effect on height caused by mutations in COL1A1 and ACAN genes

Xiantao Ye Wenjuan Qiu Yu Sun
Xinhua Hospital, Shanghai Jiao Tong University School of Medicine

Short stature is a feature when a person's height is more than 2 SDS below the corresponding mean height for a given age, sex, and population. It can be influenced by many factors essential to growth plate. Here we report a three-generation family with 13 patients affected by type I osteogenesis imperfecta or short stature and advanced bone age, with or without early-onset osteoarthritis and/or osteochondritis dissecans (SSOAOD) or both. Panel sequencing of the proband revealed mutations in two extracellular matrix related genes: *COL1A1* and *ACAN*. When comparing the quantitative trait, height within the family of different mutation carrier groups, we found an interesting cumulative effect, the ones with both mutations manifest shortest stature. Dual diagnoses of the family also suggest the necessity of a comprehensive molecular diagnosis method, such as panel/exome sequencing, especially encountering patients with novel phenotype or extreme trait.

伴 GATA1 基因新生突变的嵌合型唐氏综合征一例

王珏
南京医科大学第一附属医院（江苏省人民医院）

本文报道了 1 例伴 GATA1 基因新生突变的唐氏综合征嵌合体患儿。该例孕妇于孕 39 周住院待产，B 超提示胎儿肝脏肿大、回声减低，顺产出生。新生儿因出生后腹胀逐渐加重、腹腔积血可能，于出生后 10 小时行剖腹探查术+腹腔冲洗引流术，术后诊断：1.肝大，原因待查 (遗传代谢性疾病? 血液系统疾病?) 2. (左侧)卵巢损伤(伴出血) 3.凝血机能异常 4.先天性感染(特发于围生期感染，NOS) 5.代谢性酸中毒(持续性)6.新生儿低血糖 7.腹腔积血 8.新生儿贫血 9.电解质紊乱 10.心肌损害。患儿于出生后 20 天因"左侧卵巢损伤伴出血术后；多脏器损伤；肝大待查:血液系统疾病?；凝血障碍；腹腔积血"病情过重，家属放弃抢救死亡。患儿外周血染色体核型分析培养失败。患儿外周血行染色体全基因组芯片检测，提示 arr[GRch37]21q11.2qter(15016487_48093361)×3[0.81]，为嵌合型 21-三体（嵌合比例 81%）；患儿外周血送检核心家系临床外显子检测，基因变异分析发现定位于 Xp11.23 上的 GATA1 基因 c.99_c.100insT/p.F34Ffs*6 杂合变异（父母均为野生型），关联疾病有唐氏综合征相关髓系白血病(DS related myeloid leukemia，DS-MI)；染色体微缺失或微重复分析发现，受检者 chr21p-21q(chr21:1-48129895)位置存在约 48.13 Mb 的可能致病性的单倍重复，关联 21 三体综合征。讨论：唐氏综合征相关髓系增殖(DS-related myeloid proliferation，DS-MP)具有一系列独特的临床特征与生物学特征，GATAl 基因突变与 21 三体之间存在特定的协作关系。

46，XY 性发育异常患儿遗传学病因研究：基于中国性腺发育异常儿童的单中心队列研究

范丽君
首都医科大学附属北京儿童医院

背景 性发育异常（Disordersofsexdevelopment，DSD）是指染色体、性腺和解剖性别不一致，是一系列难以分类、难以诊断的复杂性疾病的统称。DSD 异质性强，病因复杂，其中绝大多数是因遗传物质的改变所致。46，XY DSD 在 DSD 中最常见，涉及的遗传背景最为复杂，不同的表型对应的遗传背景不同。然而，目前关于 46，XY DSD 的大样本病因学研究仍较少。
目的 探索 46，XY DSD 的遗传学病因谱。
方法 我们纳入了 2004 年 6 月至 2021 年 5 月就诊于北京儿童医院内分泌科的 46，XY DSD 患者，评估了患者的遗传学检测结果。
结果 该研究共纳入 792 名患者，初诊年龄为 2.25y（1.0~7.62），初诊社会性别：男性 614 名，女性 178 名。68.43%（542/792）名患者有尿道下裂，31.57% （250/792）患者尿道开口正常。基因诊断率为 52.15%（413/792），另有 22.47%（178/792）患者检测到 DSD 相关基因的意义不明的变异。我们在 75 个 DSD 相关基因中共检测到 466 种不同的变异，其中 58.37%（272/466）变异既往未报道。患者中检测到变异频率最高的基因为 *SRD5A2*（24.12%，191/792），其次为 *AR*（12.50%，99/792）、*NR5A1*（7.07%，56/792）、*FGFR1*（4.04%，32/792）和 *CHD7*（3.41%，27/792）。在 6.57%（52/792）的患者中检测到多个 DSD 相关基因的变异。在尿道下裂患者中最常检测到变异的基因分别为 *SRD5A2*，*AR*，*NR5A1*，*CYP17A1*，*CHD7*，*MAMLD1*，*FGFR1*，*HSD17B3*，*KMT2D*，*ANOS1*，*ATRX*，*WDR11* 及 *MYRF*。而尿道开口正常的患者中最常检测到变异的基因除了 *SRD5A2* 外，均为低促性腺激素性性腺功能减退相关的基因（*FGFR1*，*PROKR2*，*CHD7*，*ANOS1*，*IL17RD*，*SEMA3A*，*KISS1R*，*SPRY4*）。
结论 我们的研究拓宽了 46，XY DSD 的遗传学病因谱，报道了新的变异，并且为寡基因致病提供了进一步的证据支持。小阴茎和尿道下裂涉及了不同的遗传背景，临床医生应根据不同的临床表型采取不同的遗传学检测策略。

Xia-Gibbs 综合征伴肌氨酸血症 1 例

杨孝燕 邹丽萍
解放军总医院儿科医学部；解放军总医院第一医学中心儿科；解放军总医院研究生院

目的 探讨 Xia-Gibbs 综合征的临床表现及基因突变特点。
方法 报道 Xia-Gibbs 综合征合并肌氨酸血症一例，并通过文献回顾总结该综合征的临床特点。
结果 患儿女，1 岁 11 月龄，因运动、语言发育落后就诊。患儿 12 月龄时会扶坐，18 月龄独立坐稳，20 月龄会爬，21 月龄扶站、横向挪步，不会发“bama”音，只会发“a”音。可执行拍手、拿东西等简单指令，精细动作差。患儿为 G4P2，其中第 3 胎在孕 8 月时胎停育，母亲生育该患儿时 43 岁。查体患儿面容特殊：左眼裂较右侧小、左眼球轻微内斜视、左侧鼻唇沟较右侧浅、塌鼻梁小鼻头。肌张力肌力正常，病理征阴性。辅助检查示：血代谢 C2、C16 增高，尿代谢肌氨酸明显升高；脑电图未见异常；脑核磁未见明显异常；全外显子基因检测示 AHDC1 新发突变 c.932delG，导致氨基酸发生移码突变 p.G311Afs*141。另外，基因检测还发现 SARDH 基因有两个位点发生错义突变：c.1090G＞A（p.A364T），c.931C＞A（p.R311S），各来源于父母，解释了患者的肌氨酸血症的原因。目前国内外及本例共报道 41 例。
结论 Xia-Gibbs 综合征由 AHDC1 基因突变导致，以移码突变最多见（70%）,不同突变位点所致临床表型有轻微差异。主要临床特点为全面发育落后、肌张力低下、特殊面容、睡眠呼吸暂停，胼胝体发育不良。肌氨酸血症并不是该综合征的表型。

家族性糖皮质激素缺乏症 1 型 1 例

高静 刘晓景 崔岩 卫海燕
河南省儿童医院

目的 对河南省儿童医院郑州儿童医院内分泌遗传代谢科收治的 1 例罕见的新生儿期发病、诊断曲折，于婴儿期确诊的家族性糖皮质激素缺乏症(familial glucocorticoid deficiency，FGD)1 型患儿进行临床及遗传学分析。
方法 回顾性分析 1 例 FGD1 患儿的临床特点，通过全外显子测序对患儿进行基因检测及父母验证。
结果 基因检测结果显示该患儿携带黑皮质素 2 受体（MC2R）基因：患儿为 c.433C>T（p.R145C）和 c.710T>C（p.L237P）复合杂合变异，其中 c.433C>T（p.R145C）遗传自父亲，为已知报道的致病性变异；c.710T>C （p.L237P）遗传自母亲，该变异在正常人群数据库中未收录，ACMG 评分为疑似致病性变异。
结论 FGD1 易与其他疾病混淆造成误诊，基因检测是确诊关键，1 例新发现突变丰富了基因数据库。

Combination of RNA-seq transcriptomics and iTRAQ proteomics reveal a complex ceRNA network in Essential Thrombocythemia

Zhipeng Zeng Haiqing Lin Wenlong Hu Yong Dai Donge Tang
Shenzhen People's Hospital

Background Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterized by elevated peripheral blood platelet count and its clinical consequences can include both hemorrhage and thrombosis. However, there have been no reports revealing the competing endogenous RNA (ceRNA)-mediated regulatory mechanisms in Essential Thrombocythemia.
Methods In this study, we collected peripheral blood from ET patients and isolated the platelet and analyzed the expression profiles of proteins, lncRNAs, circRNA, miRNAs and mRNAs by using RNA-seq transcriptomics and iTRAQ proteomics.
Results In total, we identified 8571 differentially expressed mRNAs (DEmRNAs), 416 differentially expressed microRNAs (DEmiRNAs), 1563 differentially expressed lncRNA (DElncRNAs), 6742 differentially expressed circRNA (DEcircRNAs), and 680 differentially expressed proteins (DEPs). Combined with the results above, 422 DEP-DEmRNAs with common changes were identified. The molecular functions and biological processes of DEP-DEmRNAs were mainly enriched in phosphorylation, neutrophil degranulation, intracellular signal transduction and protein binding. And the pathway of DEP-DEmRNAs were mainly enriched in Metabolic pathways, Synaptic vesicle cycle, Platelet activation, Endocytosis, and Chemokine signaling pathway. The lncRNA-miRNA-mRNA and circRNA-miRNA-mRNA ceRNA networks showed the possible functions of the lncRNAs and circRNAs. Bioinformatics analysis showed that P2RX1, AP2B1, TAOK1, AZIN1-AS1, SLX1B-SULT1A4, has_circ_0009126, hsa_circ_0085604, novel-hsa-miR243-5p, hsa-miR-665, novel-hsa-miR302-5p may play an important role in the pathogenesis of ET.
Conclusions We explored potential biomarkers by combining transcriptomic and proteomic studies. Our study provides new insights into the regulatory mechanisms and may further contribute to the diagnostic and/or treatment for ET.

中国首例 FADD 缺陷新发突变并文献复习

舒洲 毛华伟
首都医科大学附属北京儿童医院

目的 FADD 缺陷（Fas-associated death domain protein deficiency）是 2010 年首次报道的一种人类出生缺陷病，主要表现为自身免疫性淋巴细胞增生症样表现（FAS 介导的淋巴细胞凋亡下降、αβ+CD4-CD8-T 细胞明显升高，可溶性 FASL、IL-10、维生素 B12 升高），不同程度淋巴结、肝脾增大，还可表现为反复发热、脑病、心脏结构异常、肝病。本研究报道国内首例 FADD 缺陷新发突变，分析其临床及分子特征，扩宽该病基因型及表现型谱，提高对该病的认识。
方法 全外显子测序明确患儿 FADD 基因突变。回顾性分析该患儿的临床、分子、免疫学特征及诊治经过并文献复习。
结果 患儿 2 月起病，主要表现为结核感染、反复颅内真菌感染（毛霉菌、库德里阿兹威毕赤酵母菌），αβ+CD4-CD8-T 细胞比例 27.2%，T、B 细胞亚群未见异常，NK 细胞计数下降，免疫球蛋白未见异常；FADD 基因发现 c.350G＞A，p.R117H，纯合，来源于父母，为新发突变；确诊后予异烟肼、利福平、利奈唑胺抗结核治疗 1.5 年，予西罗莫司口服 1 年，无发热、淋巴增殖表现，但随后出现反复颅内真菌感染。目前已积极配型准备行造型干细胞移植治疗。目前全球报道的 FADD 缺陷共 8 例，Bolze et al 首次报道 4 例。该病为常染色体隐性遗传，主要表现为心脏结构异常、不同程度的颅内病变及肝病，ALPS 样表现型，患者 FAS 介导的淋巴细胞凋亡下降、αβ+CD4-CD8-T 细胞明显升高，可溶性 FASL、IL-10、维生素 B12 升高，T 细胞正常，B 细胞及抗体可正常或下降。大部分病例 5 岁前死亡，目前国外有 2 例患者造血干细胞移植成功。
结论 我们报道中国首例 FADD 缺陷新发突变，首次发现 FADD 患儿结核感染及反复颅内真菌感染。虽目前本病的治疗经验匮乏，西罗莫司治疗能较好控制患儿发热、淋巴增殖等表现，造血干细胞移植仍是根治的较好临床选择。

AMMECR1 基因新变异引起身材矮小、面中部发育不全一例并文献复习

王小红[1] 曹冰燕[2] 卫海燕[1] 杨海花[1] 高静[1] 陈永兴[1]
1.河南省儿童医院
2.首都医科大学附属北京儿童医院

AMMECR1 基因新变异引起身材矮小、面中部发育不全一例并文献复习
目的 报告 1 例 AMMECR1 基因引起身材矮小、面中部发育不全患儿（Alport syndrome, mental retardation, midface hypoplasia, and elliptocytosis chromo
somal region gene 1），并进行文献综述，提高临床医生对该病的认识。
方法 分析患儿临床表现，实验室检查并应用全外显子测序及一代测序法对患儿 AMMECR1 基因进行变异检测，以“AMMECR1 gene 及 Xq22.3-q23 deletion”为检索词，在万方、维普、中国知网、PubMed 数据库中检索建库至 2021 年 3 月已报道涉及 AMMECR1 基因变异家系病例并进行文献复习。
结果 患儿测序结果显示 AMMECR1 基因存在 c.474C>A:p.Y158X 半合变异，一代测序验证结果表明该变异遗传自母亲，母亲表型正常，父亲未携带该变异。变异位点未见报道。文献检索未见国内报道，国外文献 6 篇，涉及 11 个家系 15 例病例。
结论 AMMECR1 基因 c.474C>A:p.Y158X 变异为该患儿的致病原因，基因检测结果可为临床诊断，家系遗传咨询提供依据。

一例 PBX1 基因杂合变异致先天性肾和泌尿道异常的遗传学分析

唐娇[1,2] 惠玲[1] 王玉佩[1] 周秉博[1] 张钏[1] 张翀[3] 张庆华[1] 郝胜菊[1] 杨蕊琼[1,2] 李嘉璇[1,2] 赵磊[1,2]
1.甘肃省妇幼保健院医学遗传中心
2.甘肃省中医药大学公共卫生学院
3.甘肃省妇幼保健院临床检验中心

目的 对 1 例肾发育不良、心脏形态异常、隐睾、先天性膈疝的新生儿进行基因变异检测，明确其可能的致病原因。
方法 提取外周血基因组 DNA，应用高通量测序技术对一家三口进行全外显子组测序和低深度全基因组测序（CNV-seq），并对发现的可疑致病位点在家系中进行 Sanger 测序验证。
结果 患儿 *PBX1* 基因第 6 外显子存在 c.863(exon6)G>A(p.Arg288Gln)杂合错义变异，导致其编码的蛋白从第 288 位的精氨酸突变为谷氨酰胺，父母均为野生型,为新发变异，该变异在所有正常人群数据库频率未收录。根据美国医学遗传学与基因组学学会遗传变异解读指南，*PBX1* 基因 c.863(exon6)G>A 变异判定为致病变异(PS2+PM1+PM2+PP2+PP3)。
结论 *PBX1* 基因 c.863(exon6)G>A 变异可能是患儿的遗传学病因，分子遗传学检测是患儿确诊为先天性肾和泌尿道异常综合征(OMIM:617641)的关键，新变异的检出为临床诊断提供依据，丰富了 *PBX1* 基因的变异谱。

GCK 基因内含子新突变导致 MODY2 的致病机理与精准诊疗

陈亚婷 蒋伏松 李鸣 刘婵薇 葛晓旭 张娟 张荣 蒋燕燕 贾伟平 刘丽梅
上海交通大学附属第六人民医院

目的 葡萄糖激酶（GCK）基因杂合失活突变，导致胰岛素分泌和/或肝糖原合成缺陷的特殊类型单基因糖尿病 MODY2（青少年的成人起病型糖尿病，亚型 2）的发生和进展。本研究探索 MODY2 家系中，新发现的 GCK 基因内含子突变导致糖尿病发病的潜在致病机理、基因型-临床表型特点及其精准治疗方法。
方法 采用 Ellard 提出的 MODY2 筛选标准，对临床表型疑似 MODY2 的 56 个家系先证者，通过 PCR-直接测序，筛查 GCK 基因突变。采用 Regsnp 和 dbscSNV 两种剪接位点预测工具，对于内含子突变位点与致病性进行评估。同时，研究突变位点在家系内的遗传-共分离、基因型-临床表型特点。通过三个月前后突变携带者糖化血红蛋白的变化，评估饮食控制而非药物治疗的降糖效果。
结果 （1）在两个家系先证者发现 2 个内含子突变：c.1019+20G>A，为新突变，国际首次报道；c.863+1G>A，曾在高加索 MODY2 家系中被报道，而中国 MODY 人群中首次发现。两突变在各自家系中与高血糖表型呈遗传-共分离。（2）Regsnpintron，即 regsnp -内含子，利用机器学习算法对内含子 SNVs 的致病概率进行优先排序表明，无论是 c.863+1G>A 还是 c.1019+20G>A, 其 FPR 都小于 0.05，二者均为致病位点。（3）dbscSNV 仅用于预测剪接位点，ADA 或 RF 值越接近 1，则可变剪接的可能性越大。C.863 + 1G> A 的 ADA; RF 为 1; 0.938，被证明是经典的剪接位点；而 c.1019+20G>A 则不在剪接位点上，该突变很可能导致“高度保守区域的一个潜在剪接位点被破坏”。（4）非药物饮食控制三个月前后，糖化血红蛋白分别为 6.4±0.3 和 6.3±0.2，二者无显著差异（p＞0.05，n=15）。
结论 推测 GCK 基因内含子新突变可能通过破坏 GCK 剪接位点（如 c.863+1G>A 突变）或潜在剪接位点（如 c.1019+20G>A 突变），生成 GCK 功能缺陷的新突变蛋白，导致葡萄糖刺激的胰岛素分泌减少，进而发生 MODY2。该预测结果的可靠性仍需实验证实。此外，对于 GCK 内含子突变的 MODY2 患者，饮食控制而不是用药治疗，乃为其精准降糖的有效方法。

一例高鸟氨酸血症-高氨血症-高同型瓜氨酸尿症综合征患儿的临床及遗传学分析

高静 刘晓景 陈永兴 卫海燕
河南省儿童医院

目的 探讨 1 例高鸟氨酸血症-高氨血症-高同型瓜氨酸尿症综合征(Hyperornithinemia-Hyperammonemia-Homocitrullinuria syndrome, HHH syndrome）患儿的临床表现及遗传学病因。
方法 收集患儿临床资料，提取患儿及父母外周血基因组 DNA，应用全外显子基因组测序法进行基因检测，并对可疑致病变异位点进行 Sanger 测序验证。通过数据库检索及变异序列分析，预测候选变异的致病性。
结果 患儿，男，2 岁 2 个月，以“发现肝功能异常 3 个月、走路不稳 5 天”来诊。主要表现为精神差、肝酶升高、血氨增高、步态异常。基因检测结果示患儿 SLC25A15 基因存在两个杂合变异:c.535C>T(p.R179*)和 c.165C>A(p.Y55*)，分别遗传自表型正常的父母，前者为已报道致病变异，后者未见报道。根据美国医学遗传学与基因组学学会标准，两个变异均评级为致病性变异。
结论 SLC25A15 基因 c.535C>T(p.R179*)和 c.165C>A(p.Y55*)复合杂合变异为该患儿的遗传学病因。c.165C>A(p.Y55*)位点的检出丰富了 SLC25A15 基因突变谱，为 HHH 综合征的诊疗提供了新的线索和依据。

一家系 Kenny-Caffey 综合征 2 型患者的临床及基因变异分析

王诗琦 卫海燕 付东霞 刘晓景 陈永兴
河南省儿童医院

目的 分析一家系 2 例 Kenny-Caffey 综合征 2 型（简称 KCS2）患者的临床及遗传学特点。
方法 回顾性分析 1 例在郑州大学附属儿童医院就诊的 KCS2 患儿的临床及基因突变特点，并对其家系进行分析总结。
结果 基因检测结果显示先证者携带 FAM111A 基因 c.1706G>A 杂合突变，来自于先证者父亲，先证者母亲无该突变。该变异为已报道的致病变异。先证者及其父亲均患有 FAM111A 基因变异所致的 KCS2，但既往无父子共患 KCS2 的报道。
结论 FAM111A 基因 c.1706G>A 的杂合变异为 KCS2 的常见变异；声调高而尖，颞骨突出，耳位低，耳后旋，小下颌，视网膜色素紊乱，后极部色素浅，可能为 KCS2 的罕见特征；本研究首次报道了 KCS2 的父传子病例，说明 KCS2 成年男性患者有生育的可能性。

ASL 基因变异致精氨酰琥珀酸尿症一例

高静 刘晓景 卫海燕 陈永兴
河南省儿童医院

目的 探讨 1 例新生儿期发病的精氨酰琥珀酸尿症患儿的临床表现及遗传学病因。
方法 收集患儿临床资料，提取患儿及父母外周血基因组 DNA，对遗传代谢性疾病相关基因进行二代测序，并针对可疑变异位点区域设计特异性 PCR 扩增引物，PCR 产物经过 Sanger 测序。
结果 患儿，男，1 月 17 天，因"呼吸困难 4 天，抽搐半天"为代主诉入院。主要表现为精神差、抽搐发作，实验室辅助检查提示肝酶升高、血氨增高，液相串联质谱法血液氨基酸及酯酰肉碱谱分析示瓜氨酸升高。基因检测结果示患儿 ASL 基因（NM_000048）存在两个杂合变异：第 8 外显子 c.556C>T(p.R186W)和第 12 外显子 c.916 C>T(p.R306W)。家系验证结果显示，患儿母亲携带 ASL 基因 c.556C>T(p.R306W)杂合变异，患儿父亲和哥哥在该位点为野生型，父亲携带 c.916

C>T(p.R306W)杂合变异，母亲及哥哥在该位点为野生型。c.556C>T(p.R186W)和 c.916C>T(p.R306W)变异，均为已知致病变异。

结论 该患者基因型能很好地解释其临床表型，ASL 基因 c.556C>T(p.R186W)和 c.916C>T(p.R306W)变异为患儿的遗传学病因，为家系的遗传咨询和产前诊断提供了依据。

Phenotypic variability of syndromic craniosynostosis caused by c.833G>T in FGFR2: clinical and genetic evaluation of eight patients from a five-generation family

Xianda Wei Guori Huang Baoheng Gui Bobo Xie Shaoke Chen Xin Fan Yujun Chen
The Second Affiliated Hospital of Guangxi Medical University

Objective: Craniosynostosis is the result of the early fusion of cranial sutures. Syndromic craniosynostosis includes but not limited by Crouzon syndrome and Pfeiffer syndrome. Considerable phenotypic overlap exists among these syndromes and mutations in *FGFR2* may cause different syndromes. This study aims to investigate the explanation of the phenotypic variability via clinical and genetic evaluation for eight patients in a large pedigree.
Methods For each patient, comprehensive physical examination, cranial plain CT scan with three-dimensional CT reconstruction (3-D CT), and eye examinations were conducted. Whole exome sequencing was applied for genetic diagnosis of the proband. Variants were analyzed and interpreted following the ACMG/AMP guidelines. Sanger sequencing was performed to reveal genotypes of all the family members.
Results A pathogenic variant in the FGFR2 gene, c.833G>T (p.C278F), was identified and proved to be co-segregate with the disease. Some symptoms of head, hearing, vision, mouth, teeth expressed differently by affected individuals. Nonetheless, all the eight patients manifested core symptoms of Crouzon syndrome without abnormality in the limbs, which could exclude diagnosis of Pfeiffer syndrome.
Conclusion We have established clinical and genetic diagnosis of Crouzon syndrome for eight patients in a five-generation Chinese family. Variability of clinical features among these familial patients was slighter than that in previously reported sporadic cases.

半侧颜面发育不全的临床表现及分子遗传学研究进展

娄群 王旭东
上海交通大学医学院附属第九人民医院

半侧颜面发育不全（Hemifacial Microsomia，HFM）是一种相对常见的先天性疾病，与单侧第一二鳃弓的发育缺陷相关。HFM 在儿童的发生率约 1：5000，通常是散发病例，但也有常染色体显性遗传的病例报道。HFM 相关的临床特征广泛，最常见有面部显著和进行性的骨骼不对称，伴有单侧下颌支和髁突发育不全。下颌常见下颌后缩及骨骼不对称导致的咬合面倾斜。面部骨骼常为扁平并且体积减小。骨骼的缺陷常随着面部生长而加重。除面部骨骼外，HFM 还会影响软组织，具体可见：耳廓常为严重畸形或缺失（小耳畸形）；常见有附耳；睑裂变窄并有单侧眼表皮样囊肿。其他不常见的畸形还有唇腭裂，腭肌和舌肌发育不全和腭咽闭合不全。与其相关的病症还有 Goldenhar 综合征，它结合了椎体异常和眼表皮样囊肿以及 HFM 的特征。

HFM 的病因尚未明确，但鳃弓早期发育过程中的中断与其表型一致。杓状动脉的出血是一种可能的机制。在小鼠的 10 号染色体中插入突变基因来进行基因改造，已被证实可以对该综合征进行表型的复制，这只小鼠表现出小耳畸形，咬合不对称及外耳道，中耳和上颌骨的形态异常。人群中的全基因组连锁分析将致病基因定位于 14q32，该区域的 GSC 基因是 HFM 的潜在候选基因，属于同源框基因 PRD 类，其编码的蛋白是胚胎期颅面部和胸腔发育重要的转录因子，缺乏 GSC 基因功能的小鼠有许多颅面缺陷，包括发育不全和下颌骨的骨突缺失，以及上颌骨，腭骨和翼骨缺损。

家族性糖皮质激素缺乏症合并脓毒症相关性脑病一例

陈琼 王小红 杜语慧 杨海花 卫海燕
河南省儿童医院郑州儿童医院

目的 对河南省儿童医院郑州儿童医院收治的 1 例罕见的家族性糖皮质激素缺乏症（Familial glucocorticoid deficiency, FGD）合并脓毒症相关性脑病患儿进行临床及遗传学分析；
方法 回顾性分析 1 例脓毒症相关性脑病合并 FGD 患儿的临床资料，通过全外显子检测技术对患儿进行基因检查并对父母进行验证。
结果 患儿 1 岁 11 月龄，以“发热 1 天，抽搐伴意识障碍 12 小时入院”，查体：浅昏迷，全身皮肤黏膜色素沉着，实验室检查：血气分析、电解质及血糖正常，PCT 36ng/ml（0-0.05ng/ml），脑脊液常规生化及自身免疫性脑病相关检查未见异常，ACTH 465.9pg/ml（0-63pg/ml），皮质醇 0.02ug/dl，血氨基酸肉碱及尿有机酸检测未见异常；头颅 CT 及 MRI 弥漫性脑损害，脑电图示低波幅脑波活动，完善全外显子检测示 NNT c.2622C>G:p.Y874 及 c.777-51C>G 复合杂合突变，其中变异 c.2622C>G:p.Y874，来源于父亲，变异 c.777-51C>G，为父母均未携带的新生突变，两突变均为未报道过的新发突变。
结论 本文首次报道家族性糖皮质激素缺乏与脓毒症相关脑病相关性，提示危重症患者评估肾上腺功能的重要性，NNT 基因 c.2622C>G:p.Y874 及 c.777-51C>G 新发突变丰富了基因数据库内容。

The association between variants of MYRF and abnormal cardiac development

Zhengshan Zhao
Children's Hospital of Fudan University

Objectives Screening the potential pathogenic genes for congenital heart disease, especially the variants of MYRF gene in CHD cases.
Methods We performed whole-exome sequencing on one pedigree of TOF with three generations, and another CHD trio (ASD+PVS) to screen potential pathogenic genes for congenital heart disease. According to the comprehensive analysis of the whole exome sequencing results, and combined with relevant literature review, the potential pathogenic genes were screened. Subsequently, we performed targeted sequencing of the exon region of the potential pathogenic gene in another additional group (1954 unrelated sporadic congenital heart disease cases) and 400 healthy control, screening the pathogenic mutation site of the potential pathogenic gene (with the standard of MAF <0.0001 and CADD score> 10).
Results Whole exome sequencing of the Tetralogy of Fallot pedigree found that the *MYRF* gene mutation (c.3264C>G:p.S1088R) was co-segregated with congenital heart disease. The CHD trio (ASD+PVS) hinted one *MYRF* gene dysfunction mutation c.940_944del:p.I314PfsX22, and combined with relevant literature review, one case report published a similar frameshift mutation (c.1254_1255dupGA:p. T419RfsX14). Compared with healthy control，the additional CHD group showed 23 rare variants in 25 different cases. Surprisingly， both c.217C>T:p.H73Y and c.905C>T:p.P302L variant showed twice in two different cases, what’s more, p.S1088R amino acid variant appeared again.
Conclusion *MYRF* gene might be a susceptibility gene of congenital heart disease. The rare variants of MYRF protein may contribute to the abnormal cardiac development, and further academic work is needed.

11β 羟化酶缺乏症 4 例临床及遗传学分析

杨海花[1] 陈永兴[1,2,3] 陈琼[1,2,3] 卫海燕[1,2,3]
1.河南省儿童医院郑州儿童医院
2.郑州大学附属儿童医院
3.河南省儿童遗传代谢性疾病重点实验室

目的 分析 4 例 11β-羟化酶缺陷症（11β-OHD）患者的临床表现和遗传学特点。
方法 回顾性分析 2016 年-2021 年在河南省儿童医院确诊的 4 例 11-βOHD 患儿的临床表现、激素水平、影像学检查、基因突变特点、随访结果。
结果 4 例患儿中 3 例男性，1 例女性，诊断时年龄分别为 3 岁、5 岁 8 月、2 岁 3 月和 7 岁（平均为 4 岁 4 月）。就诊时身高分别为：130cm、141cm、104cm、149.5cm，骨龄分别为 12 岁、14 岁、6 岁、16 岁。3 例男性患儿均因性早熟就诊，1 例女性患儿因外生殖器畸形就诊。2 例患儿有高血压，1 例患儿有低钾血症，但无乏力、肢体软瘫表现。4 例肾上腺 CT 结果均提示肾上腺增粗，1 例患儿合并睾丸肾上腺残余瘤。4 例患儿激素水平均表现为 ACTH（204-1405pg/ml）、17 羟孕酮（9.0-15.09ng/ml）、睾酮（1.24-3.13ng/ml）、雄烯二酮（6.1-91.49nmol/L）不同程度地升高。基因分析结果分别为：患儿 1 基因结果为:c.1385T>C（p.L462P）和 CYP11B2 与 CYP11B1 基因同源重组，患儿 2 基因结果为 c.1151G>A（R384Q）及 2 号外显子和 5 号外显子杂合缺失，患儿 3 基因结果为 CYP11B1 c.1354G>A(p.G452R)纯合突变，患儿 4 基因结果为 exon1-6del 纯合缺失，exon7-9 杂合缺失。其中 c.1385T>C（p.L462P）、c.1354G>A(p.G452R)未曾报道过。4 例患儿中 3 例予以氢化可的松片口服，1 例患儿因就诊时线性生长已停止，予以口服地塞米松片治疗，。2 例合并高血压的患儿加用螺内酯降压治疗。2 例男性患儿出现继发性中枢性性早熟，予以加用 GnRHa 治疗。随访至今，2 例男性患儿线性生长已停止，终身高分别为 161.8cm、149.5cm，余 2 例患儿复查相关激素水平正常。
结论 11β-OHD 是第二类常见的先天性肾上腺皮质增生症（CAH），易于与 21-OHD 混淆，临床上需加强对 11β-OHD 的认识，使该类患儿能得到及时诊断及早期治疗，本研究发现了 2 个 CYP11B1 新突变，丰富了 11β-OHD 的基因突变谱，且 1 例患儿为 CYP11B1 与 CYP11B2 发生了基因重组，故而基因检测时需注意采用 long-range PCR 方法进行检测，避免漏诊。

2 例 Coffin-Siris 综合征 1 型 ARID1B 基因新发突变病例报道

李嘉璇[1,2] 惠玲[1]
1.甘肃省妇幼保健院医学遗传中心
2.甘肃中医药大学

目的 提高对 Coffin-Siris 综合征 1 型（CSS）ARID1B 基因突变的认识。
方法 回顾性分析 2 例 2020 年于甘肃省妇幼保健院医学遗传中心确诊的 CSS 患儿临床资料，应用全外显子组测序（WES）检测基因突变，并对检测结果进行遗传学分析。
结果 2 例均为男孩，就诊年龄分别为 6 岁和 14 天，均有出生后肌张力弱，MR 均提示大枕大池及胼胝体发育不良。例 1 智力缺陷，全面发育迟缓，蛛网膜囊肿，言语不能，特殊面容（头皮毛发稀疏，鼻梁宽阔，鼻孔前倾，长睫毛，嘴大，唇厚且外翻，牙齿稀疏，上颌上凹，下颌后缩等），第 5 趾甲发育不良及指弯曲等。WES 分析，ARID1B 基因（NM_020732;exon7）c.2371+5G>A（splicing）及 FBXW11 基因（NM_012300;exon6）c.750_752delTGA (p.D250del)。例 2 发育幼稚，体重下降，喂养困难。WES 分析，ARID1B 基因（NM_020732;exon18）c.4159delC (p.H1387Tfs*61)。两例 Sanger 测序患儿父母均未发现 ARID1B 的突变。本文病例 ARID1B 基因突变均无文献报道。
结论 本例患儿符合 CSS 的临床特点，新发现的 ARID1B 基因突变可能是致病原因，高通量测序是首选的检测方法，临床上如发现可疑病例，可及时进行基因分析确诊。

先天性肌营养不良合并心房静止一例

赵翠梅[1] 李丽[2] 彭鲁英[2]
1.同济大学附属同济医院
2.同济大学医学院

32 岁，女性，因间歇性胸闷 5 年，加重 1 周入院
患者于 5 年前无明显诱因下出现胸闷，自觉压迫感，伴心悸、头晕、恶心、反酸、嗳气，胃纳差，夜间大汗，无明显胸痛，无晕厥、黑朦等，遂于我院就诊，心电图提示房颤。予以华法林、胺碘酮口服，后自行停药。2 年前症状加重，急诊查心电图示 1、房扑伴不规则房室传导，心房率 230 次/分，平均心室率 70 次/分 2、QRS 电轴左偏；此次 1 周前胸闷症状加重，伴心悸、头晕，持续时间可达 15 分钟以上，休息后可缓解，伴有右上腹隐痛，恶心，欲吐。门诊查心电图示：1、心房扑动伴Ⅲ度房室传导阻滞 2、房室连接处逸搏心律，为求进一步治疗，收入我科，
发病以来食欲稍差，精神休息稍差，体力稍差，体重无明显变化，大便正常，小便正常。
既往史：该患者幼儿时即已出现下肢活动障碍，曾至外院就诊，行肌电图等检查明确为进行性肌营养不良。现有乏力、双下肢行走无力、肩背部僵硬感，上楼困难。平时服用维生素。
个人史、月经史：无特殊。
婚育史：未婚未育。
家族史：患者母亲有进行性肌营养不良病史，11 年前曾植入心脏起搏器，于 50 岁时因心力衰竭去世。

• 查体：

查体：T：36.0℃，P：48 次/分，R：18 次/分，BP：117/70mmHg。神志清楚，精神状态一般，查体合作，步入病房。全身浅表淋巴结无肿大，口唇无发绀，颈静脉无怒张，肝颈静脉回流征阴性，甲状腺无肿大，双肺呼吸音清晰，双侧肺未闻及干、湿性罗音，心界无扩大，心率 48 次/分，律齐，P2 不亢，各瓣膜听诊区未闻及病理性杂音，无心包摩擦音，剑突下心音未及增强，腹部柔软，无压痛、反跳痛，双下肢无水肿，双侧 Babinski 征阴性。
神经系统查体：颅神经-，双上肢近端肌力 V-，Gower 征阳性，双小腿假性肥大，肱三头肌萎缩，无明显鸭步，余阴性。
入院后检查示肌酸激酶轻度升高，心电图：心房颤动伴 III 度房室阻滞，房室连接处逸搏心律（47 次/分）。心超：右房增大（47mm），左室舒张功能减退（中度），EF 76%。
动态心电图：全程基础心律为心房扑动（最长 R-R 间期为 1.7 秒），伴 III 度房室传导阻滞，房室连接处逸搏心律，平均心室率 45 次/分，单个室性异位搏动 27 次，呈多源性，室性异位搏动成对 2 次，部分见 CMV5 导联 ST 段水平型压低<1.0mm。

• 入院诊断

1.心律失常-阵发性房颤、房扑伴Ⅲ度房室传导阻滞可能，房室连接处逸搏心律
2.进行性肌营养不良
3.胆囊炎、胆囊颈部结石

• 入院后诊疗经过

患者有上腹部不适，右上腹部有轻度按压痛，结合患者症状及体征患者及 MRCP 提示胆囊炎合并胆囊颈部结石可能，伴周围渗出性改变，予以抗炎、保肝、解痉等治疗后上腹部不适明显好转。

进一步行电生理检查

术中诊断：起搏不能带动心房，心房电活动几乎静止、III°房室传导阻滞可能，房室连接处逸搏心律。故予以行单腔起搏器植入术

并行基因分析。

A novel missense mutation c.1768G>A of PHEX in a large Chinese family with X-linked hypophosphatamia (XLH): A Case report

Yanting Yang[1,2] Hongqian Liu[1,2] Ying Shen[3] Mohan Liu[3] Siyu Dai[1,2]
1.Medical Genetics Department/Prenatal Diagnostic Center, West China Second University Hospital, Sichuan University, Chengdu, 610041，China
2.Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, Sichuan University, Chengdu, 610041，China
3.Department of Obstetrics/Gynecology, Joint Laboratory of Reproductive Medicine (SCU-CUHK), Key Laboratory of Obstetric, Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu，610041，China

Purpose X-linked hypophosphatemia (XLH), an X-linked dominant monogenic disorder, refers to the most common hereditary hypophosphoataemia (HH) cause by inactivating mutations in *PHEX*, which is characterized by hypophosphataemia, diminished synthesis of active vitamin D (1,25(OH)2 vitamin D), rickets, osteomalacia, odontomalacia and disproportionate short stature. With about decades explore, the specific pathogenic mechanism underlying XLH is still one of the more important issues remaining to be addressed. Herein we aim to investigate the pathogenicity of the novel mutation we detected in a large Chinese family with typical bowing legs, short statures and bone pain.
Methods After clinical data were collected in this family, whole-exome sequencing (WES) was performed on in all affected individuals, and a heterozygous mutation c.1768G>A in phosphate regulating gene with homologies to endopeptidases (*PHEX*) was screened. To confirm this mutation distribution in this family, Sanger sequencing was performed in whole family. After constructed expression vectors for WT-PHEX (His-tagged wild-type human PHEX) and mutated-PHEX (His-tagged human mutant PHEX with c.1768G>A) and transiently transfected into 293T cells, quantitative real-time PCR (qPCR), and western blotting were used to further investigate the negative effects of the novel mutations we detected.
Results We collected a large Chinese family including 4 patients with obvious clinical phenotype, typical X-ray and the results in biochemical tests which conform to XLH. We evaluated the novel heterozygous mutation c.1768G>A （p.G590S） by WES. The Sanger sequencing suggested that all patients harbored this mutation, while other unaffected family members were identified as wild type. The result of qPCR shows sharply decreased in mRNA level of the mutation compared to wild type. Meanwhile western blotting confirmed that the missense mutation c.1768G>A （p.G590S）resulted in decreased protein production.
Conclusion The heterozygous mutation (c.1768G>A p.G590S) of *PHEX* identified in this study by genetic and functional experiments constituted a novel genetic cause of XLH, and further study will expand its use in the clinical and molecular diagnoses of XLH.

西罗莫司治疗先天性高胰岛素血症单中心经验总结

陈琼 王小红 崔岩 张英娴 卫海燕
河南省儿童医院郑州儿童医院

目的 探讨西罗莫司治疗先天性高胰岛素血症(congenital hyperinsulinemia，CHI)的有效性及安全性，总结西罗莫司治疗先天性高胰岛素血症的单中心经验。
方法 总结我院收治的 5 例二氮嗪及奥曲肽常规治疗无效后应用西罗莫司治疗的 CHI 患儿临床资料，对西罗莫司治疗先天性高胰岛素血症的疗效及安全性进行评估。
结果 研究共纳入 5 例（例 1-例 5）患儿，其中男 3 例，女 2 例，发病年龄 1 至 90 天，起病表现为精神差（2/5）、抽搐（3/5），血糖 1.3-2.3mmol/L，同期胰岛素 3.62-28.18mIU/L，组织学分型 3 例为弥漫型，2 例未知，全外显子基因检测发现 3 例未经报道新突变（ABCC8 c.4451G＞A，ABCC8 exon25-28del，GCK c.589A＞G）。5 例患儿中 4 例应用二氮嗪及奥曲肽无效后应用西罗

莫司治疗，1 例应用二氮嗪及奥曲肽无效并接受胰腺大部分切除术后仍反复低血糖开始应用西罗莫司治疗，5 例患儿开始应用西罗莫司的年龄为 1.5-26 月，西罗莫司最大剂量 1.2-3.2mg/m^2，用药时间 0.5-11 月，其中 1 例（20%）GCK 杂合突变患儿应用西罗莫司无效，其余 4 例（80%）应用西罗莫司有效，出院后单用或联合常规治疗血糖平稳。所有患儿随访中除腹泻及甘油三酯一过性升高外，无其他不良反应。
结论 单中心研究显示西罗莫司在 CHI 患者中应用有一定疗效，短期应用有较好安全性，但远期疗效及安全性尚不明确，临床需谨慎选择使用人群，尚需多中心研究进一步明确疗效及安全性。

NBAS 基因缺陷病 1 例并文献复习

李杨世玉 刘芳 陈永兴 卫海燕
郑州大学附属儿童医院 河南省儿童医院 郑州儿童医院

目的 对 1 例 NBAS 缺陷病病例进行临床分析,并复习国内外文献,以提高对该病的认识。
方法 收集 1 例 NBAS 患儿的临床资料,对先证者及其父母进行全外显子测序,并系统复习相关文献.
结果 患儿女，7 月龄，因反复于发热时出现肝酶异常，给予保肝药物可降至正常，伴生长发育迟缓及特殊面容，身长 60.5cm（＜3rd）,体重 5kg（＜3rd），头发稀疏，前囟未闭，直径 6cm*6cm，颅缝分离，前额突出，双眼落日征，竖头不稳，不会坐，基因检测结果提示 NBAS 基因复合杂合突变,突变位点为 c.4589T>A(p.L1530X) 和 c.5741G>A (p.R1914H)，其中 c.4589T>A(p.L1530X) 尚无报道。通过在万方、知网、pubmed 及 google 搜索后共纳入 44 篇文献复习,包括本文在内的 149 例 NBAS 缺陷病临床表现涉及多个系统，包括肝功能异常占 72.3%（急性肝衰竭，转氨酶持续升高），生长发育迟缓 64.2%，骨骼系统异常 50.7%（骨密度降低，囟门闭合延迟），神经系统异常 30.4%（运动迟缓、智力低下），皮肤松弛 39.9%，免疫功能异常 33.1%（自然杀伤细胞计数减少），眼部异常 23.6%（视神经萎缩，视网膜营养不良），特殊面容 45.3%，Pelger-Huët 异常 36.5%，其他表现还包括小手脚、肌张力降低、短趾畸形；极少部分患儿还可出现急性肾衰竭、癫痫、心肌病、低血糖、神经母细胞瘤或自闭症等，流行病学主要以俄罗斯、中国、德国为主。
结论 临床上反复肝酶异常，伴特殊面容、生长发育迟缓应考虑 NBAS 缺陷病,c.4589T>A (p.L1530X)为新报道的变异,为首次报道。

儿童 Prader-Willi 综合征并发糖尿病的临床特征分析

赏月
深圳市儿童医院

目的 总结 4 例 Prader-Willi 综合征（PWS）合并糖尿病患者的临床特点、诊断策略及随访并进行文献复习，从而提高临床医生对该病的诊疗，探讨新的治疗方案。
方法 回顾性分析深圳市儿童医院自 2014 年 3 月至 2021 年 3 月收治的 4 例 Prader-Willi 综合征（PWS）合并糖尿病患儿的临床资料，分析其临床特点、并复习相关文献。
结果 4 例均在婴幼儿期有喂养困难、精神运动发育落后、特殊面容；4 例均通过分子遗传学检查最终确诊；4 例既往均有多次就诊经历，但临床医生均未重视此病，此次因肥胖就诊，完善糖代谢指标：多次血糖大于 11.1mmol/L、尿糖阳性、糖化血红蛋白大于 6.5%;4 例患者明确并发糖尿病后，1 例予二甲双胍口服，3 例予胰岛素强化治疗联合二甲双胍治疗， 3 例随访患者血糖及糖化血红蛋白水平控制不理想。
结论 儿科医生应加强对 Prader-Willi 综合征的早期诊断，婴幼儿早期予严格饮食管理至关重要；PWS 患儿即便胰岛素强化治疗后血糖仍控制欠佳，与食欲旺盛，体型肥胖，胰岛素抵抗有关，因此更多治疗措施需进一步探究。

三例先天性糖基化异常患儿的诊疗及 PMM2 基因突变分析

王诗琦 卫海燕 陈永兴 刘芳 崔岩 高静
河南省儿童医院

目的 分析先天性糖基化异常-Ia 型（CDG-Ia）的临床特点、诊疗及基因突变特点；
方法 以 2017 年至 2020 年在郑州大学附属儿童医院就诊的 3 例 CDG-Ia 患儿为研究对象,分析其临床特点,总结分析诊疗过程，对其基因结果进行分析并结合文献进行归纳总结。
结果 3 例 CDG-Ia 患儿均有不同程度的生长发育迟缓，智力障碍，低血糖及肝损害。例 1 患儿主要有小头畸形，眼内斜视，脂肪分布异常，严重且不易纠正的低血糖，肝功能异常，该患儿 PMM2 基因中发现两个错义变异 c.G557T（p.G186V）（父源）和 c.G136A（p.G46R）（母源），目前这两个变异均无文献报道，但是这两个变异位于 PMM2 的 HAD-like 结构域，在 ESP 数据库、千人数据库、EXAC 数据库中人群频率为零，且多种生信方法（PolyPhen 2、SIFT、MutationTaster 等）预测为有害变异，结合临床表现、治疗结果及相关文献复习分析，考虑该患儿诊断为“先天性糖基化异常 Ia 型”，该突变可能为新发突变，例 2 患儿主要表现为前额突出，三角脸，眼内斜视，薄嘴唇，乳头内陷，肌张力低下，低血糖症及肝功能异常，该患儿 *PMM2* 基因中发现一处意义不明的杂合突变和一处致病的突变：c.179-6T＞C（父源）和 c.691G＞A（母源）；例 3 患儿主要表现为生长发育迟缓，乳头内陷，全身多处咖啡斑，肝大，腹水，肌张力低下，低血糖，肝功能异常，凝血功能异常，甲状腺功能减退，该患儿 PMM2 基因中发现杂合变异 c.395T>C（父源）和 c.347+5G>C（母源）及 NF1 基因 c.2288T>C 自发突变，根据 ACMG 指南，判定为致病性变异，考虑该患儿诊断为“先天性糖基化异常 Ia 型，神经纤维瘤病 1 型”，先天性糖基化异常 Ia 型合并神经纤维瘤病 1 型较罕见。三例患儿经甘露糖及保肝治疗后，低血糖及肝功能明显改善；
结论 先天性糖基化异常的患儿临床表现复杂多样，当临床中遇到低血糖，肝功能异常，脂肪分布异常，小头畸形等症状的病人时，我们要考虑到先天性糖基化异常的可能性，临床表现及基因检测可以协助诊断，甘露糖对改善低血糖及肝功能异常大有助益。

TNFAIP3 基因新发变异致 A20 单倍剂量不足 1 例并文献复习

杨威 郝会民 杨海花 王小红 吴雪 陈永兴 卫海燕
河南省儿童医院

目的 探讨 A20 单倍剂量不足（HA20）的临床特点、诊断及治疗。
方法 回顾性分析 1 例 HA20 患儿的临床资料、治疗、转归和基因检测结果，并进行文献复习。
结果 患儿 男，1 岁 4 月龄，以反复发热、腹泻、皮疹为主要表现，疾病活动期炎症指标升高，肠镜显示结直肠黏膜可见多发溃疡；基因测序分析显示 TNFAIP3 基因杂合突变，确诊为 HA20。口腔和（或）生殖器溃疡、周期热、消化道症状、皮疹和关节炎是 HA20 最常见的临床表现，可合并多种自身免疫性疾病。实验室检查特点为炎症指标明显升高，部分患者存在低至中等滴度的自身抗体。大部分 HA20 患者存在 TNFAIP3 基因无义突变或移码突变，导致终止密码子提前出现，使 A20 蛋白截短，导致核因子 κB 通路介导的促炎细胞因子表达增多。治疗上目前尚无统一方案，主要采用糖皮质激素、免疫抑制剂及生物制剂，远期预后个体差异大，严重者有死亡风险。本例患儿给予沙利度胺治疗，随访 1 年 2 月，无严重不良反应，发热、皮疹、腹泻较前明显减少，复查肠镜溃疡完全愈合。
结论 HA20 是一种罕见病，临床表现复杂多变，对兼有自身炎症和自身免疫特点的患者，应详细询问家族史，必要时完善 TNFAIP3 基因检测协助明确诊断。

220 例 21 三体先天愚型儿染色体核型探讨分析

王梦雅
柘城县人民医院

目的 本文就先天愚型儿进行细胞遗传学分析，深入研究并积极预防对优生优育提高人口素质提供可参考的意见。
方法 细胞遗传学检查：取患儿及部分父母外周血进行淋巴细胞培养，37℃培养 72 小时，收获前 4 小时加秋水仙素，按外周血染色体常规制片法，G 显带处理，每例计数 30 个分裂相，分析 2-3 个核型。嵌合型加倍计数 50-100 个，然后进行电脑显微摄像相片分析。
结果 染色体核型分析结果，220 例 DS 患者，其中单纯型 208 例占 94.54%。易位型 7 例占 3.18%，其中 2 例来自母源，嵌合型 4 例占 1.82%。性染色体异常 1 例，占 0.45%。
讨论 先天愚型男性高于女性，有人认为其原因可能在于 Y 精子易与不分离的卵子结合。1.单纯型先天愚型是一种常染色体异常性疾病，与母亲妊娠时的年龄关系密切。2.易位型的核型有很多种，最常见的是 Dq21q。与母亲的年龄无关。可以产生正常胎儿，易位型三体患儿及平衡易位携带者三种胎儿。因此，检出平衡易位携带者双亲具有重要的参考意义。3.嵌合型的核型 21 三体患者两个或两个以上的细胞系，而所有嵌合体都有正常的细胞系。

5 例 ACAN 基因变异导致家族型身材矮小家系分析

郭亚楠
河南省儿童医院

目的 分析 ACAN 基因变异导致的家族性矮小的临床表型及基因变异特征
方法 回顾分析 5 个 ACAN 基因变异导致家族性矮小家系的临床资料，并检索相关文献，总结 ACAN 基因变异导致矮小的特点
结果 该 5 个家系的 ACAN 基因均为杂合突变，发现了 5 个变异位点（c.2100G＞A，c.2173delG，c.6530T＞C，c.1962C＞A，c.512C＞T）的变异是导致发生家族性矮小的分子学病因。多数患者仅表现为身长矮小，无明显的面部异常或者骨骼发育畸形，仅有 1 例有脊柱侧弯；患儿生后身长和体重均正常，生长发育速率较同龄儿缓慢；多数患者表现为骨龄超前，生长激素激发试验提示无明显生长激素缺乏。
结论 ACAN 基因杂合突变可导致家族性矮小，多变现为身材矮小，无明显骨骼畸形，一般生后生长发育速率较缓慢，多数患者出现骨龄超前，然而无明显生长激素缺乏表现。

全外显子组测序诊断 1 例 16p13.11 微缺失综合征合并假肥大性肌营养不良

谢波波 陈玉君 范歆 桂宝恒 魏贤达 陈少科
广西医科大学第二附属医院

目的 对 1 例生长发育迟缓、行走乏力的患儿进行全外显子组测序（whole exome sequencing，WES），以期发现其遗传学病因明确诊断。
方法 采集患儿及其父母的外周血样本，根据标准操作流程提取 DNA。针对患儿进行全外显子组测序。测序获得的 Fastq 原始数据通过 GATK(v3.6）、XHMM(v1.0)等软件分析单核苷酸变异（SNV）、小的插入与缺失（indels）和拷贝数变异（CNV）。采用 Sanger 测序对 WES 检测到的阳性 SNV 或 indels 结果进行验证。根据 ACMG/AMP 指南对于基因变异致病性的评估标准，通过查阅 GnomAD、1000 人基因组数据库、ExAC、ClinVar、HGMD、PubMed 等数据库，进行基因变异的致病性评估。同时，根据 CNV 的致病性评估指南，对检出的 CNV 进行致病性评估。

结果 WES 检测到患儿的 *DMD* 基因（NM_004006.2）第 61 号外显子存在 c.9098del (p.Asp3033AlafsTer56)半合变异，来源于母亲。该变异为功能丧失性变异，可能导致无义介导的 mRNA 降解，从而导致疾病的发生。查阅 GnomAD、1000 人基因组数据库、ExAC、ClinVar、HGMD、PubMed 等数据库，均未见该变异的报道，在本地的 688 例 WES 数据中也未见报道。根据 ACMG/AMP 指南，被评估为致病性变异（PVS1+PM2+PP4）。同时，通过对 WES 数据进行 CNV 分析，发现患儿 16p13.11 染色体区域存在约 1.68 Mb 的微缺失（chr16:14805496-16487830, GRCh37/hg19）。该片段缺失涉及 16p13.11 微缺失综合征，为致病性 CNV。
结论 *DMD* 基因 c.9098del (p.Asp3033AlafsTer56)半合变异和 16p13.11 微缺失是该患儿的遗传学病因，其中，c.9098del 为国内外首次报道的新变异，扩展了中国人群 *DMD* 基因突变谱。同时，本研究结果进一步证实了 WES 数据可用于 CNV 的分析。对于临床表现多样化的患儿，其遗传学病因可能不止 1 个，WES 在其基因诊断中有着巨大的优势。

The First case of Setleis syndrome in China with copy number variation and its genetic diagnosis methods

Qiaoyu Cao
Department of Dermatology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Objectives This study aimed to reduce the size of candidate copy number variants(CNVs) of Setleis syndrome patients in China to focus which gene covered is related to Focal Facial Dermal Dysplasias Type III.
Methods Here we described a big consanguinity in China diagnosed with FFDD3 with a chromosome duplication in the 1p36.22p36.21 region, after clinical manifestation and completing a series of complex clinical genetic analyses, including ASACH chip (version: ASACH_20022517X351729_A1), whole exome sequencing, whole genome sequencing, and Sanger sequencing.
Results CNV repeated mutation was really existed, and the breakpoints were Chr1:11695972 and CHR1:11829858 confirmed by Q-PCR. The size of copy number variants was reduced to 134kb and the critical region contains eight genes, including FBXO2, FBXO44, FBXO6, MAD2L2, DRAXIN, AK125437, AGTRAP, Clorf167.
Conclusion our study is consistent with previous research abroad, and further reduces the size of CNVs and focuses on 8 genes. Our study not only further confirms the hypothesis that the duplication on the p arm of chromosome 1(chr1:11,695,968-11,829,873) is a plausible candidate gene for SS, but also may provides diagnosis and treatment ideas, which is beneficial to FFDD diagnosis and typing. Combined with the mechanism of CNVs, which provides a direction for thinking about whether genes in region or other genes effected the expression of regional genes to cause this developmental disease phenotype.

面肩肱型肌营养不良症的治疗研究回顾

陈龙[1,2] 郑富泽[1,2] 王志强[1]
1.福建医科大学附属第一医院
2.福建医科大学

背景和目的 面肩肱型肌营养不良症（FSHD）是最常见的成人型肌营养不良症之一，表现为面肌、肩胛带肌及四肢肌肉不对称进行性受累。根据遗传类型分为Ⅰ型和Ⅱ型，二者在临床表现上难以区分。除了均需存在 4qA 单倍型，共同致病机制是 4q35 上 D4Z4 片段表观遗传抑制下降引起 DUX4 基因获得性表达而致病。近年来，病理生理机制的进展促进治疗的研究，本文将系统回顾相关的治疗进展。
材料与方法 检索近十年来 FSHD 治疗方面的文献，并进行荟萃分析。

结果 目前对于 FSHD 的治疗可分为两个方向：增强改善肌力和抑制疾病进展。通过单车训练等规律的有氧运动能在一定程度上延缓肌力减弱甚至增强肌力，改善日常活动能力。此外，借助肩胛骨固定术可改善严重翼状肩患者的上肢活动能力，但目标人群较受限。一水肌酸作为改善增强肌力的药物，尽管使用效果有争议，但已有相关临床试验在开展。随着 FSHD 致病机制逐渐阐明，干扰 DUX4 表达成为研究焦点。通过增强 D4Z4 片段的甲基化和抑制组蛋白去乙酰化来增强表观抑制以此达到抑制 DUX4 表达的目的，但表观遗传涉及基因较多，其靶向性有待研究。以 p38α/β 抑制剂——losmapimod 为代表的药物，可直接干扰 DUX4 RNA 表达，目前该药已进入Ⅱ期临床药物试验研究。利用 ASO 直接靶向 DUX4 RNA 或 RNAi 的技术若能改善药物的吸收率，相信可以更好地改善 FSHD 患者的症状。同时，靶向缺氧诱导通路等 DUX4 下游通路的研究也在进行中。
结论 近二十年，FSHD 致病机制的研究有了明显的进展。目前较为统一的观点是由于 DUX4 获得性表达引起 FSHD，因此除了传统改善肌力的技术和药物，多种靶向 DUX4 及其上下游的药物也被用于其治疗研究。

GABRG2 基因相关的热性惊厥附加症 1 家系报告

何文 孟岩 王杨阳 张梦娜 刘丽英 卢倩 邹丽萍
解放军总医院儿科医学部第一医学中心

目的 通过对 1 个 GABRG2 基因相关热性惊厥附加症家系的受累成员进行基因分析，为加强医生准确认识和正确诊断该疾病提供依据。
方法 在取得该家系成员知情同意的前提下，收集先证者（患儿）及其家系成员的临床资料以及外周血 DNA，通过高通量测序分析的方法进行基因突变筛查，找到突变的基因位点。
结果 该家系 3 代共有 6 例成员受累，临床表型为热性惊厥附加症，先证者及其他受累成员 GABRG2 基因存在第 11 号外显子的杂合错义突变，c.1523A＞G（p.Y508C）。此突变属于新发现的 GABRG2 基因突变。
结论 该突变的发现为遗传性癫痫伴热性惊厥附加症的基因筛查提供了新的位点及遗传学证据，为 GABRG2 基因突变相关疾病的治疗提供新的可能的路径。

四氢生物喋呤缺乏症合并复杂型热性惊厥 1 例

方雨[1] 廖建湘[2] 张会婷[1] 段婧[2] 操德智[2] 文家伦[2] 路新国[2] 张曼[2]
1.中国医科大学深圳市儿童医院
2.深圳市儿童医院

目的 对 1 例诊断为四氢生物喋呤缺乏症（BH4D）合并复杂型热性惊厥患儿的临床特点、辅助检查及基因检测结果进行分析。旨在提高临床医生对 BH4D 合并癫痫发作患儿的认识和诊治水平。
方法 对深圳市儿童医院神经内科诊断的 1 例 BH4D 合并复杂型热性惊厥患者的临床特点进行分析，并留取患者及其父母血样进行基因突变检测。
结果 1.临床特点：本例为一女性患儿，出生时新生儿足底血筛查提示血清苯丙氨酸（phe）6.07mg/dl，复查 9.9mg/dl（足底血 phe 正常参考值＜2mg/dl）。四氢生物喋呤（BH4）负荷试验阳性，考虑诊断：BH4D，遂开始规律服用四氢生物喋呤、美多巴、5-羟色胺、四氢叶酸，并配合低 phe 饮食。患儿 5 月龄时无明显诱因开始出现抽搐，为局灶性发作，持续约 5-6 分钟缓解。随后多次出现抽搐发作，发作频率为 4-5 次/年，最长持续 30 分钟。除两次无热抽搐外，余均为发热诱发，发作时中高热为主。4 岁前，仅接受中医中药治疗，于 4 岁 1 月时开始加用丙戊酸钠（VPA）抗癫痫治疗，发作未见明显改善。5 岁 11 月时开始加用左乙拉西坦（LEV），其后仍有热性惊厥发作，甚至出现癫痫持续状态，最长持续 25 分钟。上调 LEV 剂量后，至今已有 1 年半未见癫痫发作，目前患儿智力行为发育仅轻微落后于同龄儿童。2.辅助检查：脑电图：生后 5 月及 3 岁 5 月完善脑电图提示界限脑电图。7 月龄的颅脑 MRI：双侧颞极蛛网膜下腔稍增宽；左侧枕大池扩大，双侧侧脑室稍饱满。基因报告：6-丙酮酰四氢蝶呤合成酶(6-pyruvoyltetrahydrobiopterin syntheie

gene, PTS)基因复合杂合突变：NM_000317.3:c.1A>G，p.Met1Val，剪切突变，源于母亲，可能致病突变；NM_000317.3:c.272A>G，p.Lys91Arg，错义突变，源于父亲，致病突变。染色体微阵列检查：未见异常。

结论 新生儿足底血筛查示 phe 升高，对 BH4D 的早期诊断具有重要提示作用，而 BH4 负荷试验结合 BH4D 相关基因检查，对 BH4D 的确诊至关重要。早期给予四氢叶酸、四氢生物喋呤、美多巴、5-羟色胺补充治疗，可防治 BH4D 患儿智力损伤的发生。但 BH4D 患儿运用左旋多巴治疗后仍可有癫痫发作，甚至是合并复杂型热性惊厥，且 BH4D 患者的抽搐发作较难捕捉到癫痫波并对常规抗癫痫药物疗效欠佳，常需要多药联合抗癫痫治疗。

我们对疫苗接种与婴儿痉挛的关系知之甚少以至于不能停止疫苗接种：一项来自中国的前瞻性研究

何文
解放军总医院儿科医学部第一医学中心儿科

目的 接种疫苗是最具成本效益的公共卫生战略。然而，对免疫接种后不良事件的关注从未停止过。一些严重的癫痫综合征如婴儿痉挛（infantile spasms，IS）也有零星报道。因此，本研究旨在探讨疫苗接种与婴儿痉挛的关系。

方法 疫苗与癫痫发作之间的相关性是通过注射疫苗与癫痫发作之间的时间来判断的。我们进一步比较了疫苗相关组和非疫苗相关组在病因构成比上的差异，以确定某种原因引起的婴儿痉挛是否更可能与疫苗有关。

结果 共有 1226 名被诊断为 IS 的患者符合我们的研究条件，最终分析了 711 名患者，包括 59 例疫苗接种相关 IS 患儿与 652 例非疫苗接种相关患儿。疫苗相关 IS 组 26 例在灭活疫苗接种后 48 小时内发病，33 例在减毒活疫苗接种后 2 周内发病。值得注意的是，这些病例中有 37/59（62.71%）涉及含 DTP 疫苗。所有 IS 患儿中，TSC 是最常见的基因，在病因学的结构/代谢中，最常见的四个原因是脑发育不良，HIE，NHE 和 FCD，无论它是否与疫苗接种有关。疫苗接种相关 IS 组与非疫苗接种相关 IS 组之间的病因组成比没有统计学差异（P=0.076）。

结论 疫苗接种不是婴儿痉挛的病因，但它可能是癫痫发作的诱发因素。尽管如此，常规疫苗接种仍然是非常有意义和必要的。

KIF5A 基因新位点突变导致的肌萎缩侧索硬化 1 例

袁茹莹[2] 郁金泰[1]
1.复旦大学附属华山医院神经内科
2.福建医科大学附属第一医院

目的 肌萎缩侧索硬化（ALS）是一种致命的成人发病的神经退行性疾病，主要累及上、下运动神经元，通常预后不良。尽管大多数病例为散发性肌萎缩侧索硬化症，但大约 5%-10%的肌萎缩侧索硬化症患者有肌萎缩侧索硬化症家族史。KIF5A 基因突变位置及突变类型的不同而呈现不同表型，包括遗传痉挛性截瘫（HSP）、轴突感觉运动性周围神经病(CMT2)和肌萎缩侧索硬化（ALS）。其中 C 端罕见的剪切变异体提示 ALS 表型。本文报道了中国 1 例 KIF5A 基因 c.3020+3A>G（NM_004984）突变导致的家族性肌萎缩侧索硬化，该位点既往未曾报道。

方法 收集一例因“行走不稳 1 年于余”为主要表现，于 2021 年 6 月就诊于上海复旦大学附属华山医院神经内科的病例。进行全外显子基因测序，采集患者临床资料和辅助检查结果，查阅文献对突变位点进行致病性预测，进行变异解释，明确诊断。

结果 先证者为 45 岁男性，其主要临床表现为“行走不稳 1 年，加重伴口齿不清 3 月”。既往病史无特殊。否认家族史。查体：轴性共济失调步态，坐起启动困难，双下肢肌张力稍增高，右上肢远端肌力 5-级，双上肢腱反射（++++），双下肢腱反射（++），双侧 Babinski 征、Chaddokc 征（+），双侧踝阵挛（-），双下肢震动觉稍减退，浅感觉、复合觉均正常，双侧跟膝胫欠稳准，闭

目难立征（+）。基因测序提示患者 KIF5A 基因 c.3020+3A>G（NM_004984）突变。通过软件对该位点进行保守性及致病性预测，结果提示该位点高度保守，在 EXAC 及 gnomAD 数据库人群携带率为 0，且软件预测该突变会因影响剪切而致病。肌电图检查提示：1.神经源性损害肌电图改变，累及右上肢 C6-T1 部分支配肌何下肢部分 S1 支配肌，考虑根性或脊髓前角细胞损害可能。2.右上肢感觉神经轴索或神经元损害考虑。

结论 综合患者临床表型及辅助检查分析，考虑患者可诊断为肌萎缩侧索硬化。可进一步对该该位点进行剪切验证。因该基因突变存在 CMT2 表型，其肌电图提示感觉神经受累，不能排除重叠综合征存在可能。后续还需进一步随访该患者并进行家系验证，复查肌电图。

耳聋基因 MARVELD2 复合杂合新变异分析

倪坤 李晓艳
上海交通大学附属上海市儿童医院

目的 分析一 3 岁双侧极重度感音神经性聋患儿遗传学病因。

方法 对先证者进行全面的体格、听力学及影像学的检查。提取其中核心家庭成员外周血有核细胞基因组 DNA，进行医学外显子组序列和拷贝数分析。

结果 先症者出生足月产，无出生窒息缺氧等高危因素病史，出生时听力筛查通过，3 岁时因说话少就诊儿保科，听力检查发现极重度听力损失。听觉脑干诱发电位提示气导双耳反应阈大于 97dBnHL,骨导双耳反应阈大于 50dBnHL,多频稳态检测提示 500Hz-1KHz-2KHz -4 KHz：右耳 110dBnHL-100 dBnHL -120 dBnHL -120 dBnHL，左耳 80 dBnHL -100 dBnHL -100 dBnHL -110 dBnHL；颞骨 CT 及 MRI 均未见明显异常；全外显子组测序发现 *MARVELD2* 基因的两个杂合变异，其中 c.683C>G (p.Ser228*)变异遗传自父亲， c.1346T>G (p.Ile449Ser)变异遗传自母亲，两个变异均为新变异未见报道，未被正常人群数据库 gnomAD 收录。c.683C>G (p.Ser228*)，该无义变异导致了一个提前终止密码子，可能引起蛋白截短或激活无义介导的 mRNA 降解，从而影响 *MARVELD2* 基因编码蛋白产物的功能；另一变异 c.1346T>G (p.Ile449Ser)，经剪接软件预测显示，该变异使外显子内生成一个新的剪接供体位点，可能影响剪接。根据 ACMG 指南，这 2 个变异被归类为疑似致病变异。

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结论 报道的 *MARVELD2* 基因的 2 个新的变异可能为该患儿的遗传病因，需进一步实验验证。

MECP2 重复综合征临床分子诊断技术研究

张丹妍 李练兵 杨柳 马明福 朱一剑
重庆市人口和计划生育科学技术研究院

目的 分析 2 例 MECP2 重复综合征（MSD）患儿的临床特点，应用微阵列比较基因组杂交（aCGH）技术进行分子诊断，为早期诊断该病提出新方法。

方法 MSD 主要累及男性，约占男性中重度智力障碍患者的 1%左右，症状以自闭症、智力障碍、运动功能障碍、焦虑、癫痫、反复呼吸道感染和早期死亡为主。MSD 重复区域在 1999 年被 Lubs 首次报道，主要与 MECP2 基因重复相关。MECP2 基因位于 Xq28，[hg19]153,287,264-153,363,188，大小为 75 925 bp，有 4 个外显子，其侧翼序列区域富含低拷贝的重复序列及微同源序列，易诱发 DNA 双链松解，发生基因结构重排。本研究报告两名男性患儿临床诊断分别为全面发育迟缓和精神发育迟滞，但病因不清。两名患儿染色体核型分析为 46,xy。本研究利用微阵列比较基因组杂交（ArrayCGH）技术，选用 CytoScanHD（Affymetrix 公司，美国）芯片进行比较基因组学杂交。该芯片含有 270 万个探针(195 万个拷贝数探针和 75 万个 SNP 探针)。以 Affymetrix 提供的正常人 DNA 作为对照标准。采用 Affymetrix GeneChip System 3000Dx v.2 芯片系统进行数据采集，结果采用 Affymetrix Chromosome Analysis Suite Software 软件进行分析。通过多重连接依赖探针扩增技术（MLPA）验证可疑片段的来源。

结果 该患儿通过检测发现一名患儿的 chr Xq28 处有 450Kb 片段重复（位于 arr[hg19] Xq28(153,171,615-153,622,204)x3），另一名患儿的 chr Xq28 处有 433Kb 片段重复（位于 arr[hg19] Xq28(153,005,690-153,438,781)x3）。两个罕见 CNV 重复区域均包含 TS 基因 MECP2，为已知综合征 MECP2 重复综合征。对采集到的患儿父母血样进行 MLPA 验证，发现 2 名患者的母亲均检出 MECP2 基因检测异常，父亲结果正常。两例患儿的重复片段均起源于各自的母亲。

结论 ArrayCGH 技术能有效检测出拷贝数变异（CNV），可较好地应用在 MECP2 重复综合征的临床诊断。

结节性硬化症伴斜坡脊索瘤 1 例并文献回顾

杨孝燕 邹丽萍
解放军总医院儿科医学部；解放军总医院第一医学中心儿科

目的 探讨结节性硬化症（TSC）合并脊索瘤的临床特点。

方法 回顾性分析 2018 年 4 月首诊于我院的 1 例合并斜坡脊索瘤的 TSC 患儿的临床资料，并结合国内外文献分析 TSC 合并脊索瘤的临床特征。

结果 患儿男，4 月龄，主因“发现心脏横纹肌瘤”前来我院。患儿无抽搐，皮肤有三块色素脱失斑，脑 MRI 示室管膜下结节、斜坡占位，心脏超声示左右心室多发横纹肌瘤，基因检测示父源 TSC1 基因移码变异，c.1928delA，p.Q643Rfs*30。予雷帕霉素治疗 2 年后，斜坡占位较前增大，遂手术治疗、肿瘤全切，术后病理回报脊索瘤，对手术标本行基因检测也发现 TSC1 基因同一位点的突变。

国内文献无相关报道，国外文献共报道 13 例。发生于 TSC 的脊索瘤较一般性脊索瘤的临床特点不同：①TSC 的脊索瘤的发病年龄更早，很可能是先天性的，②位置更常见于骶骨而不是斜坡，③预后更好、生存期更长，④转移少见，只有 2 例报道发生了皮肤的转移。有研究提出 mTOR 抑制剂可能对治疗脊索瘤有效，但我们的病例并未发现 mTOR 抑制剂雷帕霉素对脊索瘤有治疗作用。

结论 TSC 患者合并脊索瘤的情况常见于小婴儿，当发现 TSC 患者的斜坡有异常占位时，要高度警惕脊索瘤，提高核磁复查频率，密切监测病灶变化，以便掌握手术治疗的最佳时机。

染色体 13q31.1-33.1 区域缺失导致综合征耳聋

倪坤 李晓艳
上海交通大学附属上海市儿童医院

目的 分析一 2 岁综合征耳聋患儿遗传学病因。

方法 对先证者进行全面的体格、听力学及影像学的检查。提取患儿外周血有核细胞基因组 DNA，进行耳聋基因 Panel 检测。

结果 双侧极重度感音神经性听觉丧失、生长发育迟缓、双侧上睑下垂、喉软骨软化（I、II 型）。无家族遗传性或先天性病史。先症者足月产，出生时有窒息病史（具体不详），出生时未行听力筛查，出生后生长发育迟缓，2 岁仍不会站立，不会讲话。一直进行康复训练，2 岁时听力检查发现极重度听力损失。听觉脑干诱发电位提示气导双耳反应阈大于 97dBnHL,骨导双耳反应阈大于 50dBnHL,多频稳态检测提示 500Hz-1KHz-2KHz -4 KHz：右耳 110dBnHL-110 dBnHL -90dBnHL -110 dBnHL，左耳 110dBnHL -110dBnHL -110 dBnHL -90dBnHL；颞骨 CT 双侧蜗神经孔可疑狭窄，耳部 MRI 左侧蜗神经稍细；基因检测结果显示先证者染色体 13q31.1-33.1 区域存在约 19.27Mb 的缺失（chr13:84451319-103719216）。该缺失变异包含 179 个基因，其中包括 46 个蛋白编码基因。该区域基因缺失可以导致多种畸形：如小头畸形、肢体畸形、手足异常、心脏和肾脏畸形、耳聋以及记忆丧失，认知不佳，轻度智力低下，抑郁症、眼睑下垂等。先证者表型与此基本相符。依据 ACMG 指南，将该变异归类为致病变异。

结论 染色体 13q31.1-33.1 区域缺失导致综合征耳聋。

齿状核红核苍白球路易体萎缩症家系 1 例

邱煜森 袁茹莹 陈毅坤 甘世锐
福建医科大附属第一医院

目的 齿状核红核苍白球路易体萎缩症（DRPLA）是由于 *ATN1* 基因中三核苷酸(CAG)重复序列的扩增而导致的一种罕见的常染色体显性遗传性神经退行性疾病。其临床表现多种多样，以肌阵挛、癫痫发作、共济失调、舞蹈症和痴呆的各种组合为特征，临床表现和致病性与 CAG 重复序列的大小有关。在临床上与 HD 和 SCA17 难于鉴别。本文报道了 1 例以“共济失调、记忆力下降”为主要表现的中国齿状核红核苍白球路易体萎缩症家系。
方法 收集 1 例因“行走不稳、发作性记忆力下降”为主要表现于 2020 年 12 月就诊于福建医科大学附属第一医院神经内科门诊的病例。经知情同意并签署血液采集知情同意书后，收集患者临床资料和辅助检查结果，采集先证者及其父亲的外周血提取 DNA。通过聚合酶链式反应（PCR）经琼脂糖凝胶电泳实验，对常见的显性遗传性脊髓小脑共济失调及亨廷顿舞蹈症致病基因进行筛查，经 Sanger 测序验证，估计 CAG 重复数。
结果 先证者为 37 岁男性，临床表现为行走不稳 18 年，进行性加重，近 6 月余出现发作性记忆力下降，表现为不记得吃饭和穿衣，但可记得家人和过去发生的事，持续 1 周自行缓解，近半年共发作 2 次。既往右上肢骨折手法复位史，遗留右上肢肘关节活动不利，余无特殊。家族中父亲、姑姑、堂弟等有类似病史。查体：神清，可见肢体及面部不自主活动，四肢肌力、肌张力正常，上视可见眼震，四肢反射对称正常（++），病理征阴性。指鼻试验、跟膝胫试验欠稳，闭目难立征阳性。认知评估：MMSE：28 分，MoCA:17 分。对常见的显性遗传性脊髓小脑共济失调及亨廷顿舞蹈症致病基因进行筛查，经过琼脂糖凝胶电泳提示 *ATN1* 基因目标扩增片段长度大于正常。经 Sanger 测序验证，推算 CAG 重复数约为 61 个。
结论 我们对先证者父亲的 ATN1 基因进行了验证，家系验证成功。该患者为青年男性，慢性病程，进行性加重，临床表现主要为不自主运动、共济失调、记忆力减退。需要对遗传性显性脊髓小脑共济失调、亨廷顿舞蹈症、齿状核红核苍白球路易体萎缩症进行鉴别诊断。

SAMD12 中 TTTCA 重复扩增的代间稳定性可能是家族性皮质肌阵挛性震颤癫痫的遗传早现的主要原因

岑志栋[1] 罗巍[1] 陈欣辉[1] 王昊天[1] 杨德壕[1] 张帆[1] 陈悠[1] 陈思[3] 王乐博[1] 刘鹏[1] 谢非[2] 王波[1]
1.浙江大学医学院附属第二医院
2.浙江大学附属邵逸夫医院
3.浙江大学附属第四医院

目的 家族性皮质肌阵挛性震颤癫痫 1 型(FCMTE1)是由 *SAMD12* 中的(TTTTA)exp (exp，expansion)和(TTTCA)exp 组成的双重复单元扩增突变引起的多核苷酸重复扩增突变疾病。重复扩增突变的长度与疾病严重程度和发病年龄等临床表型密切相关。本研究拟通过描述和分析 23 个 FCMTE1 家系 78 例患者的基因型与表型特征，进一步研究其关系。
方法 详细分析 FCMTE1 患者皮质震颤和癫痫的发病年龄。对(TTTCA)exp 和(TTTTA)exp 进行靶向长读长测序，以确定其准确长度。采用 Pearson 相关分析发病年龄与重复扩增突变长度的关系。采用配对样本 t 检验分析代间重复序列不稳定性。
结果 在 FCMTE1 患者的(TTTTA)exp(TTTCA)exp 中，只有(TTTCA) exp 长度与皮质震颤的发病年龄(r = 0.322， p = 0.010， n = 62)和癫痫的发病年龄(r = 0.400， p = 0.0044， n = 49)呈显著负相关性，而(TTTTA) exp 长度不具有这一特性。进一步对 25 对亲子代配对分析显示，代间遗传的(TTTCA)exp 长度显著增加了 166±116bp (p = 2.3e-07)，而(TTTTA)exp 长度在代间遗传中相对稳定(p = 0.08313)，且母系遗传中(TTTCA)exp 长度的增加明显大于父系遗传(p = 0.01436)。研究还发现，子代的皮质震颤发病年龄显著早于亲代(p = 0.004379)，亲子代配对的发病年龄与(TTTCA)exp 长度之间的相关性仍然显著。

结论 我们的研究是迄今为止报道的最大的 FCMTE1 患者队列。基因型-表型相关性分析证实了(TTTCA)exp 的致病作用和(TTTTA)exp 的非致病作用。根据发病年龄与(TTTCA)exp 代间重复序列不稳定性的一致性，我们进一步提出(TTTCA)exp 可能是 FCMTE1 遗传早现的主要原因。

染色体相互易位家系临床分析

胡宇慧
深圳市儿童医院

目的 总结一家系三代 7 例染色体相互易位携带者的临床及遗传学特点，探讨相互易位携带者生殖遗传风险。
方法 采集家系临床资料，外周血淋巴细胞培养技术对家系成员进行常规 G 显带核型分析。
结果 一家三代人中有 5 例染色体核型同为 46,XY（或 XX）,t（1;13）(q25.3;q31)，另两例根据遗传学规律可确诊为该核型携带者。家系中 4 对夫妇在 30 岁前各生育一例表型正常的携带者，2 对夫妇 30 岁后经历 4 次失败妊娠。
结论 携带者生育正常后代比例远高于遗传理论值，减数分裂分离模式可能与年龄相关，对携带者夫妇需给予恰当的生殖遗传咨询。

家族性皮质肌阵挛性震颤癫痫 1 型-SAMD12 位点的(TTTTA)exp(TTTCA)exp 与单纯(TTTTA)exp 存在奠基者效应

岑志栋[1] 罗巍[1] 陈欣辉[1] 王昊天[1] 杨德壕[1] 张帆[1] 陈悠[1] 陈思[3] 王乐博[1] 刘鹏[1] 谢非[2] 王波[1]
1.浙江大学医学院附属第二医院
2.浙江大学附属邵逸夫医院
3.浙江大学附属第四医院

目的 在中国、日本、印度、斯里兰卡和泰国等不同国家的家族性皮质肌阵挛性震颤癫痫 1 型(FCMTE1)患者已经报道过在 *SAMD12* 中的(TTTTA)exp(TTTCA)exp (exp, expansion)存在奠基者效应。而在 SCA37-*DBA1* 位点上，报道过类似重复扩增(TTTTA)exp(TTTCA)exp(TTTTA)exp 和单纯(TTTTA)exp 存在共同起源。FCMTE1-*SAMD12* 位点的(TTTTA)exp(TTTCA)exp 与单纯(TTTTA)exp 之间的关系尚不明确。本研究拟探索 FCMTE1 患者在 *SAMD12* 中的(TTTTA)exp(TTTCA)exp 与健康对照者在 *SAMD12* 中的单纯(TTTTA)exp 是否存在奠基者效应。
方法 选用 FCMTE1-*SAMD12* 位点周围的核心单体型，对 11 个已报道的来自 5 个不同国家的 FCMTE1 家系和 29 个未报道的家系进行单体型分析，其中包括 16 个(TTTTA)exp(TTTCA)exp 家系，12 个单纯(TTTTA)exp 家系，和 1 个(TTTTA)13(TTTCA)exp(TTTTA)exp 家系。基于共享区域的长度，我们使用一种利用重组率的算法(Genetic Mutation Age Estimator: https://shiny.wehi.edu.au/rafehi.h/mutation-dating/)来估计不同单体型聚类的最近共同祖先(most recent common ancestor，MRCA)的年龄。基于不同单体型聚类及其 MRCAs 年龄，绘制系统发育树。
结果 所有 40 个单体型，均共享一段核心单体型，支持(TTTTA)exp(TTTCA)exp 和单纯(TTTTA)exp 来自一个起源。单纯(TTTTA)exp 单体型分散在不同(TTTTA)exp(TTTCA)exp 聚类中。其中 27 个(TTTTA)exp(TTTCA)exp 单体型估计的 MRCA 年代约为 550.8 代(95% CI: 421.6 ~ 720.5)，而 12 个单纯(TTTTA)exp 单体型估计的 MRCA 年代约为 636.6 代(95% CI: 425.6 ~ 955.3 代)。
结论 我们的研究包含迄今为止最大的 FCMTE1 患者队列及最大的 FCMTE1-*SAMD12* 位点单纯(TTTTA)exp 健康对照队列。在此，我们提出奠基者效应存在于所有 FCMTE1 患者的(TTTTA)exp(TTTCA)exp 和健康对照的 FCMTE1-*SAMD12* 位点的单纯(TTTTA)exp 之间。然而，(TTTTA)exp 和(TTTCA)exp 之间的演化历史还有待进一步研究。

一远端型遗传性运动神经病Ⅴ型家系分析

陈淑淇 罗巍
浙江大学医学院附属第二医院

目的 报道一个远端型遗传性运动神经病Ⅴ型家系的临床特点并明确其致病基因。
方法 采集部分家系成员的临床及神经电生理资料，对先证者进行全外显子组测序，用 PCR 结合 Sanger 测序对先证者及其家系成员进行变异位点验证。
结果 该家系 4 代中共有 11 例患者，主要临床表现为四肢远端肌肉萎缩和无力，不伴感觉异常，锥体束征阳性或阴性。针极肌电图示神经源性损害，神经传导检查提示运动和（或）感觉神经传导速度减慢及波幅下降。全外显子组测序发现先证者 *BSCL2* 基因的第 3 号外显子存在 c.269C＞T 杂合突变，该突变已被报道为远端型遗传性运动神经病Ⅴ型的致病突变，并在家系中与疾病共分离。
结论 我们报道了 1 个 *BSCL2* 基因突变导致的远端型遗传性运动神经病Ⅴ大家系，家系内临床表现不尽相同，部分患者以上肢远端损害为主，部分以下肢为主；锥体束征阳性或阴性；电生理提示运动神经受累，部分伴有感觉神经受累。既往报道的与本研究同一突变的远端型遗传性运动神经病Ⅴ家系间临床表现也不尽相同，除了四肢远端肌肉萎缩无力，部分家系患者可有感觉神经及自主神经受累的表现；家系间起病年龄跨度大：为 4 到 70 岁。综上，我们的研究提示远端型遗传性运动神经病Ⅴ家系内及家系间存在一定的临床异质性。

以早发型帕金森综合征为主要表现的 PSEN1 杂合突变患者

陈玥婷[1] 罗巍[1] 刘鹏[1] 王波[1] 谢非[2] 林芝汝[1]
1.浙江大学医学院附属第二医院
2.浙江大学附属邵逸夫医院

目的 *PSEN1* 是常染色体显性早发型阿尔茨海默病（EOAD）最常见的突变基因，携带该基因突变的患者可存在广泛的表型。在这里，我们报道一例以早发型帕金森综合征为特征的 *PSEN1* 突变患者。
方法 对先证者进行详细的病史询问、神经系统检查及影像学评估，提取全血 DNA 并进行全基因组测序和分析，并用 PCR 扩增结合 sanger 测序对先证者及其家系成员对该突变位点进行验证。
结果 一名 32 岁的中国汉族男性在 29 岁起病，没有神经退行性疾病家族史，表现为动作慢、肢体僵硬感。在 31 岁时被当地医院诊断为早发型帕金森病，查体发现患者存在运动迟缓、肌强直、吞咽困难和言语含糊，疾病进展较快。虽然该病人无认知功能方面的主诉，但是认知评估仍然显示存在轻度认知障碍。同时在治疗方面，患者对左旋多巴反应良好，存在异动症和剂末现象。头颅磁共振提示额颞叶及海马萎缩。DAT-PET 提示双侧尾状核和壳核多巴胺转运体减低，右侧稍著。FDG-PET 显示双侧尾状核和壳核葡萄糖代谢减低。PIB-PET 提示双侧前额叶、枕叶、后扣带回、丘脑和双侧纹状体区 β 淀粉样蛋白沉积。遗传分析发现先证者携带了一个 *PSEN1* 基因杂合错义突变（c.697A>G，p.M233V），先证者父母未发现突变，提示该突变为新生突变。该突变已被既往文献报道为致病突变。
结论 我们的病例突出了帕金森综合征可作为 *PSEN1* 突变患者的首发及主要症状，在早发型帕金森综合征的患者中，无论是否存在家族史，应考虑 *PSEN1* 的筛查。

隐性遗传早发性帕金森病患者 PINK1 基因突变分析

林芝汝[1] 罗巍[1] 谢非[2] 岑志栋[1]
1.浙江大学医学院附属第二医院 2.浙江大学附属邵逸夫医院

目的 在所收集的早发性帕金森病患者中对 *PINK1* 基因进行突变筛查，明确隐性遗传早发性帕金森病患者 *PINK1* 基因突变率及临床表型特点。
方法 研究对象为来自 114 个符合常染色体隐性遗传模式的早发性帕金森病家系，包括 46 个父母为近亲结婚的家系和 68 个父母非近亲结婚的家系。对所有患者进行详细体格检查。对 114 个家系内先证者采用纯合子定位、cDNA 水平的 PCR 扩增、Sanger 测序结合的方法对 *PINK1* 基因进行突变检测并对突变进行生物信息学分析。
结果 在 3 个父母为近亲结婚的家系鉴定出 3 个 *PINK1* 基因纯合突变，分别为 c.1489A>G（R497G）、c.1474C>T（R492*）和 c.910-911insGAGACCCCATTCTATACAAC（p.His304ArgfsX22）突变。在一个父母为非近亲结婚的家系中鉴定出一对复合杂合突变 c.1474C>T（R492*）/c.1527_1530dupAAGC（L511Gfs*6）。所有突变在家系内共分离。*PINK1* 基因突变是常见的早发性帕金森病的致病原因，呈常染色体隐性遗传模式。*PINK1* 基因编码一种定位于线粒体的丝氨酸/苏氨酸蛋白激酶。它可以保护细胞免受应激引起的线粒体功能障碍。本文所发现的 c.1474C>T、c.1489A>G、c.910-911insGAGACCCCATTCTATACAAC 和 c.1527_1530dupAAGC 突变均位于蛋白激酶结构域中高度保守的氨基酸上，是多个软件预测有害，且正常人群低频的变异。所有患者均表现为对左旋多巴敏感的早发起病单纯帕金森综合征。
结论 *PINK1* 基因突变在隐性遗传早发性帕金森患者中的突变率约为 3.51%，在非近亲结婚隐性遗传早发性帕金森患者中突变率为 1.47%，在近亲结婚隐性遗传早发性帕金森患者中突变率为 6.52%。相对于非近亲结婚家系，近亲结婚家系中突变率更高。本研究中发现的 c.1489A>G 纯合突变、c.910-911insGAGACCCCATTCTATACAAC 纯合突变和 c.1474C>T/c.1527_1530dupAAGC 复合杂合突变为本文首次报道，丰富了 *PINK1* 基因的致病突变谱。

儿童限制型心肌病的分子遗传学特点与预后分析

陈浩 傅立军
上海交通大学医学院附属上海儿童医学中心

目的 探究儿童限制型心肌病（restrictive cardiomyopathy, RCM）的分子遗传学特点并进行预后分析。
方法 入选 2013 年 1 月至 2021 年 8 月于上海交通大学医学院附属上海儿童医学中心住院诊治，根据超声心动图所示心脏形态、功能特点且经全外显子基因测序或 Panel 测序明确诊断的 RCM 患者。采集入选患者的临床资料，随访并记录心血管不良事件，进行预后分析。
结果 共入选携带基因突变儿童 RCM 患者 38 例，其中 35 例（92.1%）患者携带单基因致病突变，最常见基因突变为 TNNI3（23/38），其次为 FLNC（4/38）、MYL2（3/38）、MYH7（2/38），以及 DSG2、TTN、TNNT2 突变各 1 例；3 例（7.9%）患者携带多种基因突变，包括 MYH7、MYPN、DSP、ACTN2。本研究纳入患者男性 24 例（63%），发病中位年龄 3.0（1.9, 5.2）岁，总体随访率为 92.1%，随访时间 2.6（1.0, 4.6）年；随访过程中共 18 例（47.4%）发生心血管不良事件，其中心源性死亡 16 例（42.1%）、心脏移植 1 例（2.6%）、安装心脏起搏器 1 例（2.6%），发病至发生心血管不良事件的中位生存时间为 4.8 年。
结论 儿童 RCM 患者发病年龄较早、预后极差；TNNI3 突变为本研究中最常见的致病基因；全外显子基因测序或 Panel 测序是诊断 RCM 的可靠方法，可为疾病预后及临床决策提供重要参考。

震颤为主表型的神经元核内包涵体病临床及分子遗传学特点分析

杨德壕[1] 罗巍[1] 岑志栋[1] 王乐博[1] 陈欣辉[1] 刘鹏[1] 王昊天[1] 欧阳志远[1] 陈悠[1] 张帆[1] 谢非[2] 王波[1] 吴盛[1] 尹厚民[1] 蒋飚[1]
1.浙江大学医学院附属第二医院 2.浙江大学附属邵逸夫医院

目的 *NOTCH2NLC* 基因 5'端非编码区的 GGC 多核苷酸重复扩增突变被认为是神经元核内包涵体病（neuronal intranuclear inclusion disease，NIID）的致病突变。最近，这种致病突变也被报道与特发性震颤（essential tremor，ET）发病有关。然而，一些有这种致病突变最初被诊断为 ET 的患者，最终被诊断为 NIID。因此，关于这些临床表现为震颤的 *NOTCH2NLC*-GGC 多核苷酸重复扩增突变患者临床诊断仍存在争议。本研究目的是阐明临床表现为震颤的 *NOTCH2NLC*-GGC 多核苷酸重复扩增突变患者的临床表型。
方法 我们在 602 名最初诊断为 ET 的患者队列中筛查 *NOTCH2NLC*-GGC 多核苷酸重复扩增突变，其中阳性先证者及其阳性家庭成员进行系统评估，以确定其临床表型。
结果 在 10 名先证者中检测到 *NOTCH2NLC*-GGC 多核苷酸重复扩增突变，约占我们队列中的 1.66%，其中有 7 名先证者和他们的 4 名基因阳性家庭成员被重新系统评估。7 名患者均表现为腱反射消失、神经传导速度异常和认知功能障碍，其中 3 名在影像学上发现典型的皮质下绸带征。7 人中有 4 名先证者接受皮肤活检均提示存在核内包涵体。根据以上临床表现及辅助检查，他们的诊断均由 ET 改为 NIID。
结论 NIID 震颤亚型与 ET 临床表型类似，极易被误诊。经过我们研究发现，腱反射消失可能是重要的鉴别诊断线索，对这些患者建议进行基因检测和皮肤组织病理学检查以明确是否是 NIID。

Clinical application of MaReCs in preimplantation genetic testing for chromosome balanced translocation carriers

Qiuxiang Huang Zhihong Wang
联勤保障部队第九〇〇医院

Object To explore the application of mapping allele with resolved carrier status (MaReCs) in preimplantation genetic testing (PGT).
Methods A retrospective analysis of 106 cycles of PGT for couples with chromosome balanced translocation was performed, including 69 cycles which MaReCs could be used and 37 cycles MaReCs could not be used. The characteristic of MaReCs for PGT was analyzed. The clinical outcomes of 39 routine PGT carriers and 44 carriers using MaReCs were compared and analyzed in the first single thawing transplantation cycle, matched with age, IBM, intimal thickness and the number of abortion.
Results Compared with the carriers who could not use MaReCs, the carriers using MaReCs were younger, having significantly higher AMH levels, more antral follicles, occytes, mature occytes, biopsied embryos and euploid embryos, and lower risk of de novo chromosomal abnormality ($P<0.05$). It is necessary for the families with fewer oocytes, mature oocytes and balstocyst, to preserve discarded embryos to help performing MaReCs. Carriers using MaReCs had no difference in clinical pregnancy rate and abortion rate comparing with routine PGT carriers. Carriers using MaReCs could preferentially select the embryo with normal chromosome structure for transferring.
Conclusions It is a prerequisite for having a certain number of occytes, biopsied embryos,and using discarded embryos sometimes, thus MaReCs could be fulfilled. MaReCs is an efficient method to detect the translocation carrier status of embryo and obtain higher pregnancy and live birth, which is expected to rewrite the fertility outcomes for families with chromosome translocation carriers.

6 例 Fabry 病患者的临床、病理及基因突变分析

李晶晶 赵干业 孔祥东 王莉
郑州大学第一附属医院

目的 探讨 Fabry 病患者的临床、病理及 α-半乳糖苷酶 A（α-Gal A）基因（*GLA* 基因）突变的特点。
方法 回顾性分析 6 例 Fabry 病患者的临床资料，应用全外显子组测序（WES）技术进行遗传学分析，对致病性变异通过 Sanger 测序验证。
结果 6 例患者确诊年龄中位数岁 43 岁（15 岁~52 岁），5 男 1 女，均表现为不同程度的蛋白尿，24h 尿蛋白量中位数 0.97g/24h[（0.63~8.8）g/24h]，5 例患者出现镜下血尿。肾功能受损（Scr＞133μmol/L）2 例，且合并肾小球滤过率（eGFR）下降。3 例患者表现为高血压，3 例先证者有肾脏病家族史。Fabry 病肾外表现中，发生率最高的为心脏受累（5 例），其次为脑血管病变（4 例）、手足疼痛（3 例）、肺部炎症（2 例）等。肾脏病理光镜下可见足细胞肿胀、空泡变性，肾小管上皮及部分小动脉内皮可见类似改变。多数患者可见肾小球缺血硬化，部分伴有小球节段硬化。3 例患者免疫荧光阳性，均可见 IgM+。电镜下均可见髓磷脂样小体分布于足细胞、肾小管上皮细胞，均可见足细胞足突融合，肾小管上皮细胞空泡变性，溶酶体增多。2 例患者可见块状电子致密物沉积。6 例先证者共检测到 6 种不同的 *GLA* 基因变异。其中，错义变异 5 例 c.335G>A（p.R112H）、c.188G>A（p.C63Y）、c.454T>C（p.Y152H）、c.1025G>A（p.R342Q）、c.109G>A（p.A37T），无义变异 1 例 c.679C>T（p.R227X）。*GLA* 基因 c.454T>C（p.Y152H）为新突变，致病性未见报道。2 例男性患者的母亲均检测到携带与先证者相同的基因变异。
结论 本组 Fabry 病患者均存在尿检异常，常伴心脏受累及脑血管病变，多数患者可见肾脏病理改变，且不同的 *GLA* 基因突变为患者的致病原因。

一例肾脏表现为肾病综合征及快速进展性肾衰的 MYH9 综合征患者

蔡一恺 靳远萌 唐晓晴 马骏 潘晓霞 谢静远 陈楠 任红
上海交通大学附属瑞金医院

目的 MYH9 综合征是一种罕见的遗传性疾病，由编码非肌性肌球蛋白重链 IIA 的 MYH9 基因突变引起。临床变现为血小板减少、巨大血小板及中性粒细胞包涵体的三联征，部分患者可伴有肾炎、听力下降和白内障等非血液系统症状。本研究报道一例误诊为免疫性血小板减少症的患者，临床表现为肾病综合征和进展性肾功能衰竭。
方法 我们入选一例 16 岁男性患者，入院后完善血常规、外周血涂片，骨髓穿刺，TPO，肝肾功能，24 小时尿蛋白定量，家族史调查，和全外显子测序等检查。
结果 该患者 6 岁时因鼻衄发现血小板减少，上呼吸道感染后加重，血小板最低 $5*10^9$/L，先后接受硫唑嘌呤、激素+静丙、脾栓塞术等治疗无效。患者 14 岁（2019 年 10 月）上感后发现泡沫尿，至医院检查发现肌酐 108μmol/L，尿蛋白 7.14g/d，血白蛋白 36.6g/L，肾活检病理示：系膜增生性肾小球肾炎，予甲泼尼龙 48mg 联合厄贝沙坦 75mg/d 治疗，尿蛋白最低降至 2.64g/24h。患者于 2020 年 3 月再次行肾活检示：FSGS（NOS），IV 型胶原染色表达正常，当时肌酐 90μmol/L，尿蛋白 3.78g/d，血白蛋白 30g/L，血小板 $11*10^9$/L。2020 年 4 月起改用他克莫司 3mg/d 口服治疗 11 个月，2021 年 3 月复查肌酐 210.9μmol/L，尿蛋白 6.03g/d，停用他克莫司，厄贝沙坦加量至 150mg/d。2021 年 4 月患者于我科，肌酐 251μmol/L，尿蛋白 7.1g/d，血白蛋白 26g/L，血小板计数 $14*10^9$/L，TPO 197.59pg/mL，骨穿结果显示骨髓增生明显活跃，粒红比 2.65:1，巨系增生明显活跃，可见形态畸形，部分产板巨产板欠佳，血小板散在可见，易见大血小板。全外显子测序显示患者携带有 MYH9（c.2104C>T, p.R702C）杂合突变。ACMG 评分为 LP (PS1+PS2_Moderate+PM2_Supporting+ PP3)。先证者的父母、姐姐均为野生型，提示为 de novel 突变。患者随后接受甲强龙 35mg/d+利妥昔单抗治疗 500mg*4 次+ARB 治疗。治疗 1 月后复

查血小板 21*109/L，白蛋白 37.7g/L，肌酐 360μmol/L，尿酸 568↑μmol/L，24 小时尿蛋白 4.5g/d。
结论 本文中我们报道了一例儿童起病的 MYH9 综合征患者，该患者在发生血液学病变 8 年后出现大量蛋白尿和快速进展性肾功能衰竭。患者常规免疫抑制剂治疗无效，利妥昔单抗疗效尚有待进一步观察。

一例表现为晚发起病的遗传性痉挛性截瘫 11 型

刘鹏 陈玥婷 林芝汝 岑志栋 罗巍
浙江大学医学院附属第二医院

目的 遗传性痉挛性截瘫 11 型的特点是进行性痉挛，年轻发病和胼胝体薄。在极少数情况下，遗传性痉挛性截瘫 11 型晚发起病。这可能导致临床误诊和漏诊。我们报告一例由新型复合杂合 *SPG11* 突变引起的晚发起病患者的临床和遗传发现。
方法 先证者接受了全面的临床和神经影像学评估。同时，先证者进行了全基因组测序。
结果 先证者在 63 岁时出现快速进展的痉挛性截瘫。颈椎磁共振显示轻度颈椎间盘突出和椎管狭窄。先证者在当地诊所被诊断为颈椎病。上肢神经系统检查无明显异常，说明颈椎病没有引起明显的神经系统症状。颈椎病不应作为导致先症者临床症状的主要原因。脑部磁共振显示脑室周围白质高信号，无胼胝体薄。复合杂合突变（c.6193T>C 和 c.6223_6224insGAA）在先证者中被确定为遗传病因。
结论 遗传性痉挛性截瘫 11 型患者可在 60 岁以上发病，同时可无典型的胼胝体薄表现。我们的发现扩展了遗传性痉挛性截瘫 11 型的表型谱和基因型谱。*SPG11* 突变筛查也应考虑用于迟发患者。

Cardiac abnormalities in offspring of a female mouse model with long-term high folic acid intake

Shuyi Guo Geng Xue
Naval Medical University

Objective To establish a female mouse model with multiple generations of high folic acid intake, lay the foundation for the correlation between long-term high folic acid intake and birth defects in offspring.
Methods A control group with folic acid content of 2mg/kg and three high folic acid groups (10 mg/kg, 20 mg/kg and 40 mg/kg) were set. Female mice (G0 generation) were continuously fed with formula feed from 3-week-old and impregnated with male mouse fed with ordinary feed. The female offspring were kept and continued to modeling. Serum folate and red blood cell (RBC) folate of G4 generation female mice were measured. The cardiac morphology and pHH3 positive cells in ventricular myocardium and endocardial cushion of G5 generation fetuses at E11.5 and E13.5 was analyzed.
Results Serum folate and RBC folate of female mice in experimental groups were higher than control group (P<0.001), which was positively correlated with folic acid content in the diet. Compared with the control group, the proportion of pHH3 positive cells in the 40 mg/kg group was significantly decreased (P=0.004), while was no significant change in 10 mg/kg and 20 mg/kg groups. Furthermore, decreased wall thickness, structural abnormalities in right auricle and outflow tract, and atrioventricular septal defect (AVSD) was observed in the 40 mg/kg group fetuses.
ConclusionThe animal model building method used in this study is effective. Maternal long-term supplementation of ultra-high folic acid may cause abnormal cardiac development in offspring.

PRRX1 基因功能缺失性突变导致家族性房颤

杨奕清
复旦大学附属上海市第五人民医院

目的 鉴定新的房颤致病基因并揭示其致病机制。
方法 收集家族性房颤患者和健康对照者，运用微卫星遗传标记全基因组扫描、基因分型、连锁分析和单倍型分析定位新的房颤致病基因座。通过全外显子组测序、生物信息学分析及 Sanger 测序分析定位基因座的候选房颤基因以发现新的房颤致病基因。克隆所发现的房颤致病基因，构建其野生型和突变型真核表达载体，借助脂质体转染工具细胞，运用双荧光素酶报告基因分析、电泳移动性差异分析、免疫荧光分析明确突变基因的功能特性。
结果 将 1 个家系的房颤致病基因定位于 2 个遗传标记 D1S2851 和 D1S218 之间约 3.20-cM（约 4.19 Mbp）区域，即 1q24.2–q25.1，其间遗传标记 D1S452 在重组率(θ)为 0.00 时最大 2 点 LODs 值为 4.8165。测序分析该染色体区域的基因发现 *PRRX1* 基因新突变 NM_022716.4:c.319C>T;(p.Gln107*)。在另外 225 例无血缘关系的房颤患者对 *PRRX1* 基因进行测序分析又在其中 1 例患者发现 *PRRX1* 基因新突变 NM_022716.4:c.437G>T; (p.Arg146Ile)。这 2 种杂合性 *PRRX1* 基因突变均不存在于 908 名对照者。功能分析显示这 2 种突变型 *PRRX1* 对靶基因 *ISL1* 和 *SHOX2*（2 个已经明确的房颤基因）的转录激活作用均显著降低，与 *ISL1* 和 *SHOX2* 基因启动子的结合力均显著降低，但亚细胞分布正常。
结论 本研究首次发现 *PRRX1* 基因功能缺失性突变导致房颤，揭示了房颤新的分子遗传机制，对房颤的精准防治具有潜在的意义。

Performances liking Muir-Torre syndrome in partial offspring of a female mouse model with long-term high folic acid intake

Hanyu Wang Geng Xue
Naval Medical University

Objective As a policy to prevent birth defects，folic acid (folate, FA) supplementation during perinatal period has already been popularized in china among reproductive aged population. However, because of the huge individual differences in FA uptake, the harmfulness of the excessive FA intake induced by long-term supplementation and its mechanism are still not clear.
Methods A control group with folic acid content of 2mg/kg and three high folic acid groups (10 mg/kg, 20 mg/kg and 40 mg/kg) were set. Female mice (G_0 generation) were continuously fed with formula feed from 3-week-old and impregnated with male mouse fed with ordinary feed. In the process of model construction, some offspring had abnormal neoplasms at the end of anus in different generations. We performed pathological analysis on neoplasm and intestinal tissue samples of abnormal mice. Then the expression profile detection and abnormal methylation site screening were also carried out.
Results We found that sebaceous adenoma with intestinal inflammation & potential malignant transformation occurred frequently in offspring female mice, which often occur in patients with Muir-Torre syndrome. Furthermore, DNA mismatch repair (MMR) genes MSH2 & MSH6, associated with Muir-Torre syndrome, were down-regulated in abnormal offspring female mice, which induced by hypermethylation of CpG islands in promoter.
Conclusion The above results strongly suggest that maternal long-term supplementation of ultra-high folic acid may cause performances liking Muir-Torre syndrome in partial offspring. Our results will further reveal the roles of FA involved in growth and development.

1 例 FIG4 基因新发突变致 Yunis-Varon 综合征患儿的遗传学分析及护理

张瑞鹏[1,2] 杨永鹏[1] 卢慧敏[3] 李海鸿[1,3] 徐瑞峰[1]
1.甘肃省妇幼保健院
2.甘肃中医药大学
3.中国医学科学院&北京协和医学院医学生物学研究所

目的 Yunis-Varon 综合征是一种罕见的常染色体隐性遗传综合征，其缺陷涉及骨骼系统、神经系统、心肺系统和外胚层组织(毛发和牙齿)。特征性表现包括严重的产前和产后发育迟缓、大囟门、锁骨发育不全、特征性面部特征、手指、脚趾异常。Yunis-Varon 综合征的预后差，大多数报告的病例都伴有需要人工通气的呼吸问题，有研究表明该疾病迄今为止，极少数存活到新生儿期以后，全世界仅报道了 25 例，到目前为止，据报道只有 5 名患者存活。探讨 1 例 Yunis-Varon 综合征患儿致病基因突变及护理。
方法 对先证者进行临床检查，并提取先证者及其父母血液 DNA 进行全外显子组测序（WES），筛选候选致病突变。对患儿采用对症治疗方法，经 MDT 会诊，制定个性化的专科护理计划。
结果 本例患儿主要临床表现为毛发稀疏，头围小，发育迟滞，纳奶及反应差，反复肺部感染呼吸衰竭。全外显子组测序结果发现患者 FIG4 基因两个变异，c.793C>T 发生杂合无义突变以及 c.1271+4 A>T 剪切变异。 Sanger DNA 测序显示患儿父亲携带 c.1271+4 A>T 突变，其母亲携带 c.793C>T 突变。c.1271+4（IVS11）A>T 剪切变异位点突变目前尚未见文献报道。根据临床表型和基因突变，该患儿诊断为 Yunis-Varon 综合征。结合诊断和表型医护一体化制定个性化的专科护理，提高了护理质量，延长了患儿生命周期。
结论 本研究丰富了 Yunis-Varon 综合征的基因突变谱和表型谱。为该病的临床护理和遗传咨询提供了参考依据。

A case report of the DOCK6 gene related Adams-Oliver Syndrome that blocked by PGT-M with a successful healthy live birth

Xiaoyang Liu
The Third Affiliated Hospital of Zhengzhou University

Adams Oliver syndrome (AOS) is a rare transmitted multiple malformation syndrome. There have been demonstrated six types of pathogenic genes, among which the mutation of DOCK6 gene is caused by autosomal recessive inheritance, with the widest spectrum and nerve system abnormality. Here, we reported a case that a patient with DOCK6 gene mutation got successfully pregnancy through treatment with Intracytoplasmic Sperm Injection (ICSI) and Preimplantation Genetic Testing for Monogenic gene defects (PGT-M) and successfully gave a heathy birth. After controlled ovulation and embryo culture, ICSI embryos was cultured to blastocyst and the trophoblast cells of blastocysts were biopsied on Day5-Day7 were biopsied. Based on the results of PGT-M, an aneuploidy blastocyst was chosen to be transferred, resulting in the birth of a healthy infant. Our work successfully improved the reproductive outcome for the patients with DOCK6 gene mutation and AOS by using PGT-M technology.

ABCB1 rs1045642 T/T 基因型儿童应用伏立康唑致皮肤光敏反应

张越 徐晓琳 韩彤昕 解佳森 王晓玲 毛华伟
首都医科大学附属北京儿童医院

目的 伏立康唑是引起皮肤光敏反应的第二常见药物，而国内相关报道很少。本文描述一例儿童患者使用伏立康唑致皮肤光敏反应，并探讨 ABCB1 基因多态性与伏立康唑药代动力学及不良反应相关性。**方法** 回顾性分析北京儿童医院 1 例 ABCB1 rs1045642 T/T 基因型患儿服用伏立康唑治疗后，出现皮肤光敏反应的病例临床资料，并总结临床特点。查阅 PubMed、CNKI、万方等数据库复习 ABCB1 基因多态性与伏立康唑药代动力学相关性文献进行讨论。
结果 6 岁男性患儿，诊断原发性免疫缺陷病，口服伏立康唑治疗及预防真菌感染，治疗约 3-4 周出现皮肤光分布性红斑及色素沉着，皮肤症状在停用伏立康唑约 1 月后明显减轻。用药基因检查提示 ABCB1 基因 rs1045642 T/T。回顾关于 ABCB1 基因多态性与伏立康唑药代动力学相关性的文献报道，发现 ABCB1 rs1045642 T/T 基因型使伏立康唑药物清除率降低。
结论 本研究报道了一例儿童患者使用伏立康唑导致皮肤光敏反应，提示在临床实践中需要在儿童患者中重视该不良反应。ABCB1 基因多态性可能与伏立康唑药代动力学及不良反应相关。提示需建立个体化用药模型，以期辅助临床个体化精准用药。

肝静脉阻塞伴免疫缺陷综合征:国内首例报道并文献复习

张越 李妍 马靖 舒洲 韩彤昕 毛华伟
首都医科大学附属北京儿童医院

目的 肝静脉阻塞伴免疫缺陷综合征（Hepatic veno-occlusive disease with immunodeficiency，VODI）是一种罕见的重症联合免疫缺陷病，是由 SP110 基因突变导致的常染色体隐性遗传病。文献报道，如不及早进行感染预防和丙球替代治疗，死亡率大于 85%。目前国内尚无病例报道。本文对国内一例 VODI 病例进行报道并文献复习，以期提高广大临床医生对该病的认识。
方法 回顾性分析北京儿童医院免疫科诊断的一例 VODI 患儿的临床资料，并以“immunodeficiency”和“hepatic veno-occlusive disease”为关键词在 PubMed 数据库进行检索，复习国外报道的相关病例，对 VODI 的临床特点、实验室检查、治疗及预后进行总结。
结果 患儿，女，7y2m，2 岁起反复肺炎、中耳炎，痰病原学检查结果提示草绿色链球菌感染，大便肠道病毒检测阳性。血清免疫球蛋白 IgA、IgG、IgM 均低于正常，淋巴细胞亚群分析示记忆 B 细胞比例及绝对值明显降低，T 细胞计数正常。转氨酶轻度增高，肝脏超声及肝脏血管 CT 增强扫描未见异常。基因检查提示 SP110 基因复合杂合突变。5 岁起予规律丙球替代治疗及复方磺胺甲噁唑预防感染，临床症状好转。1 哥生后因肝衰竭夭折。复习文献国外共报道 VODI 病例 45 例，男女比例接近 1:1，起病年龄多小于 6 个月，最早生后即起病，最晚起病年龄 3 岁。临床多以反复感染、机会致病菌感染、生长发育落后、肝脾肿大、腹水为主要表现，7 例患儿存在小头畸形。所有患儿均存在低丙种球蛋白血症，T、B 淋巴细胞计数降低或正常。病原学检查肺肺孢子菌感染多见（15 例）。转氨酶水平多轻度或显著升高，超过一半病例完善肝活检提示肝静脉阻塞，5 例尸检可见淋巴结生发中心及组织浆细胞缺失。个别患儿无肝静脉阻塞证据或在疾病后期出现。多数患儿予丙球替代及复方磺胺甲噁唑预防感染治疗，8 例行造血干细胞移植，4 例接受肝移植。随访 41 例，死亡 26 例，死亡年龄多小于 1 岁。
结论 本研究为国内首例 VODI 病例报道，该病临床主要表现为低丙种球蛋白血症，T、B 细胞联合免疫缺陷和肝静脉闭塞性疾病。个别患儿无肝静脉阻塞证据或在疾病后期出现。对于联合免疫缺陷合并肝脏异常，需警惕 VODI，应及时完善基因检查明确诊断。造血干细胞移植是目前主要治疗手段，规律静脉注射免疫球蛋白及预防性复方磺胺甲噁唑治疗是有效的支持治疗手段。

成骨不全症 V 型 5'UTR 区致病变异案例分享

唐帅男
上海佰臻生物科技有限公司

受检者男性，13 岁
出生 14 天发现骨折，进行简单处理，未就医。带蓝色瞳孔，较明显，阳光下较明显。全身多发性骨折，左右手关节处畸形，盆骨发育畸形。
无近亲家族史。母亲体格检查正常，黑色瞳仁。父亲年轻时多发骨折，眼球和瞳仁有浅蓝色，27 岁时二胎，右手多发骨折畸形，无就诊史。爷爷瞳仁黑色，体格检查正常。
采用全外显子测序，发现受检者的 *IFITM5* 基因的 5'UTR 区域上发生了 1 个致病性变异：c.-14C>T。

GiteIman 综合征 SLC12A3 基因突变分析与案例分享

李顺发
上海佰臻生物科技有限公司

患者发现低钾低镁及醛固醇增高，进行基因检测，发现存在 *SCL12A3* 基因复合杂合变异，从而确诊为 GiteIman 综合征。

Novel compound heterozygous POLH variants cause Xeroderma Pigmentosum, Variant type

Kexin Guo[1] Xiaerbati Habulieti[1,2] Jiawei Liu[3] Rongrong Wang[1] Donglai Ma[3] Xue Zhang[1]
1.McKusick-Zhang Center for Genetic Medicine, State Key Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences Chinese Academy of Medical Sciences, School of Basic Medicine Peking Union Medical College, Beijing,China
2.The First Affiliated Hospital of XinJiang Medical University, Wulumuqi,China
3.Department of Dermatology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, National Clinical Research Center for Dermatologic and Immunologic Diseases, Beijing,China

Objective To identify the pathogenic variant underlying Xeroderma Pigmentosum (XP) in a Chinese male patient and complete precision diagnosis.
Methods One patient clinically diagnosed with XP was enrolled. Clinical information of the proband and his parents was collected. Laboratory tests and histopathological examination of the proband were carried out. Gene mutational analysis was performed by whole-exome sequencing (WES) and subsequent Sanger sequencing on the peripheral blood DNA of the proband was conducted. All participants signed an informed consent form.
Results We report a 24-year-old XP patient with no family history. He presented pigmented freckle-like patches on his skin areas that were prone to expose to UV at the age of four, gradually progressed all over the face, neck, chest V zone, and the extensor side of both upper limbs. Notably, his manifestations aggravated after sun exposure. He was hospitalized with hyperplasia of bridge of the nose surgery at the age of 20. Histopathological examination of the hyperplasia showed that the proliferative cells are squamous epidermal cells with indistinct boundary, and dyskeratosis atypia cells can be seen. There are lymphocytes, histiocytes, and plasma cells infiltrating the stroma, as well as neoplasms in lymphatic vessels. The patient was suspected to be diagnosed as XP. WES results showed two variants in the POLH gene (NM_006502), c.1066C>T (p.Arg356*) and c.2130dupA (p.Leu711Ilefs*34) respectively. Sanger sequencing confirmed that p.Arg356* inherited from his mother, and p.Leu711Ilefs*34 inherited from his father. To our knowledge, p.Arg356* is a known pathogenic variant reported by Broughton et al in 2002. The allele frequency of the variant c.1066C>T (p.Arg356*) is 0.00002410

in the genome aggregation database (gnomAD), and p.Arg356 amino acid residue is highly conserved in mammalian and vertebrate species. p.Arg356* result in severe truncation of the protein. p.Leu711Ilefs*34 is discovered for the first time in XP-V patients, besides, is not included in gnomAD. DNA polymerase eta (pol eta) is a 713 amino acids protein including 11 exons. p.Leu711Ilefs*34 occurs on the last exon, and is predicted to extend the sequence to 743 amino acids. Opletalova et al has verified that c.2141A>G(p.*714Trp), which is predicted to cross the stop codon and extend the sequence to 721 amino acids, will result in the absence of pol eta expression in patient's skin fibroblasts, whether after long or short UV irradiation. Therefore, we suspect that p.Leu711Ilefs*34 extended protein may perform a similar pattern of degradation, whereas experiments are needed to prove it.
Conclusion Combined with patient's medical history, the diagnosis of XP-V caused by compound heterozygous POLH variants were confirmed. We report a new variant of POLH, and enrich mutation spectrum of XP-V patients.

孤独症谱系障碍 CHD8 基因突变分析与案例分享

胡雅潇
上海佰臻生物科技有限公司

孤独症谱系障碍(autism spectrum disorder,ASD)，是一种典型的广泛性多因素相关的脑功能发育障碍，3 岁前多发，多见于男孩，临床表现为言语交流有限或缺乏、缺乏相互的社会互动或回应、以及兴趣和行为的受限、刻板和仪式化模式。近年来 ASD 的发病率逐渐攀升，由罕见病变为常见病。因其对患儿及家庭造成严重危害，近年来关于 ASD 的研究越来越受到重视。ASD 的发病机制复杂多变且涉及的风险基因众多，具有明显的遗传异质性，目前发现了十几个与 ASD 相关的高风险基因，其中染色体结构域解旋酶 DNA 结合蛋白 8(chromodomain helicase DNA binding protein 8,*CHD8*)基因与 ASD 高度相关，*CHD8* 突变频率最高，且具有重复性，是一个重要的孤独症候选致病基因。本研究的目的是通过全外显子组测序，明确 ASD 的致病原因，为 ASD 患者采取针对性的康复方案，同时为患儿家属提示患病风险，争取做到早发现早干预。本案例通过全外显子组测序，发现 *CHD8* 基因发生了无义突变 c.3686C>G(p.Ser1229*)，该突变未有致病报道依据 ACMG 指南，判定该变异为致病的变异。本案例旨在明确 ASD 患者的致病原因，以期为更好的认知和早期干预 ASD 提供参考。

牵引成骨纠正 Nager 综合征患儿一例

魏弘朴
上海交通大学医学院附属第九人民医院

目的 通过牵引成骨纠正伴有睡眠呼吸障碍的 Nager 综合征患儿
方法 患儿是一名 5 岁的男性，出生后即出现轻度睡眠呼吸障碍伴小下颌畸形。随着患者生长发育症状逐渐加重，伴有咬合不良，面型不佳，逐渐出现头颅偏小，外眦下垂以及小下颌症状，同时出现睡眠打鼾加重等症状，于我院门诊就诊，门诊完善相关检查后诊断为"Nager 综合征"。Nager 肢体骨面骨骨发育不全是下颌骨面骨发育不全伴桡骨缺失于 1908 年首次报道，并于 1948 年由 Nager 和 DeReynier 进行描述。其发病率很低，多为散发病例，可能为常染色体显性遗传。通过数字化虚拟手术设计制定双侧下颌骨牵引成骨手术方案，以改善患者气道及面型问题。
结果 在 3D 打印手术导板的引导下顺利进行手术，术后通过了 30 天的牵引，患者气道功能得到了极大的改善。最狭窄处的气道面积由原先的 37.9mm 增加至 76.5mm，睡眠呼吸暂停低通气指数（AHI）由 30.0 次/小时降低至 1.8 次/小时，其重度睡眠呼吸暂停/低通气综合征得到了极大的改善。经过了 8 个月的牵引稳固期，患者在全麻下拆除了牵引器，术中发现牵引部位成骨良好。
结论 通过数字化手术规划辅助下颌骨牵引成骨的实施，同时解决了患者的睡眠呼吸障碍和下颌后缩畸形，术后患者面型及功能恢复良好。

癫痫相关基因之 SCN1A

刘泽华
上海佰臻生物科技有限公司

在Ⅰ型钠离子通道 α 亚基基因(*SCN1A*)突变引起癫痫的患者中，不论是散发病例还是遗传性病例，都已经证明有多种多样的不同表型。全身性癫痫伴高热惊厥附加症 2 型(Epilepsy, generalized, with febrile seizures plus, type 2 ,GEFS+)、早发幼儿癫痫性脑病 6 型(Developmental and epileptic encephalopathy 6B, non-Dravet)以及 Dravet 综合征(Dravet syndrome)都与 *SCN1A* 基因突变有关。*SCN1A* 基因相关性癫痫多于 1 岁左右起病，临床表现为多种癫痫类型，呈常染色体显性遗传，外显率为 70%-90%。*SCN1A* 基因变异导致的癫痫患者使用生酮饮食疗效可能较好。本研究采用全外显子组测序方法，共检测到 5 例 *SCN1A* 基因突变阳性，其中错义突变 3 例(G1618S，F1635S，R393H)，无义突变 1 例(R1645*)，移码突变 1 例(E468fs)。早期诊断有助于选择适当的治疗方案，改善预后。

Genetic anyalysis of a family with brachymetatarsia

Jian Sun
Nanjing Medical University Affiliated Suzhou Hospital

Objective To diagnose and explore the genetic cause of brachymetatarsia in a family.
Methods Peripheral blood was taken from the family which includes proband daughter, affected father and normal mother. Then genetic analysis was conducted using next-generation sequencing (NGS) and Sanger sequencing.
Results Clinical examinations showed brachymetatarsia in father and daughter, mother was normal, all the three persons were carried out with NGS, genetic analysis revealed two most related novel missense mutations which are located in chr12:132786717 T>C (GOLGA3:NM_005895:exon14:c.2882A>G:p.E961G) and chr17:2681785 G>A (PAFAH1B1:NM_000430:exon11:c.1216G>A:p.V406M).
Conclusion Our study provides insights into diagnosis of brachymetatarsia but more experiments are needed for further study.

鸟氨酸氨基甲酰转移酶缺乏症案例分享

胡雅潇
上海佰臻生物科技有限公司

鸟氨酸氨基甲酰转移酶缺乏症(Ornithine transcarbamylase deficiency,OTCD)，又称高氨血症Ⅱ型。该病是由鸟氨酸氨甲酰转移酶(ornithine transcarbamylase, OTC) 缺乏而导致鸟氨酸循环(尿素循环)障碍进而发生高氨血症的一种遗传代谢病。为 X 连锁遗传病，其发病率为 1/80000-1/40000，在成年人和新生儿中均可发病，该病可为新生儿型和迟发型，新生儿型(≤30 天)的男性患儿 OTC 酶活性往往检测不到，死于新生儿期。迟发型(>30 天)在首次发病前生长发育正常，临床表现又缺乏特异性症状和体征，易被误认为胃肠疾患、肝病、食物或药物中毒及颅内感染而延误诊治。而女性杂合子可以表现为无症状或轻度到重度临床症状,这与 X 染色体选择失活有关。由于 OTCD 临床表现复杂，缺乏特异性，极易漏诊、误诊，首次急性发作即可出现昏迷、呼吸衰竭及致死性脑水肿，甚至猝死，因此基因测序成为一种方便快捷的诊断方法。本案例患者因不能听懂、表达，可站立行走，发育迟滞，隐睾就诊，采用全外显子组方法进行测序，发现了 *OTC* 基因发生错义突变 c.C1024A,pLeu342Met，与 OTCD 相关。此病发现早可通过临床干预环节患者症状，低蛋白饮食对于 OTCD 患者临床表型的控制是十分有益的，另外静脉注射苯甲酸钠、苯基乙酸钠和精氨酸等可对高氨血症进行控制，血液透析可以用于难治性高氨酸症的治疗。此案列受检者反馈后续临床干预效果很好。

案例分享：肾性尿崩症

唐帅男
上海佰臻生物科技有限公司

受检者信息
受检者女性，18 岁
临床诊断：肾性尿崩症，垂体瘤。
临床表型：患者自诉从小口渴，尿量增多，每日小便 10 多次，近 1 年加重。近 6 个月月经周期延长，出现闭经，无溢乳。
家族史：受检者两个舅舅也有喝水多情况。
经全外显子测序，发现受检者携带 1 个致病的变异：*AVPR2* 基因 NM_000054.4:c.383A>C 杂合突变

多囊肾病 1 型 PKD1 基因突变分析与案例分享

陆婷婷
上海佰臻生物科技有限公司

目的 确定 1 例多囊肾病家系的致病性突变,为患者家系提供遗传咨询和生育指导。
方法 利用 Long-PCR 和高通量测序分析技术对先证者进行致病基因突变检测,并用 Sanger 测序对先证者及其家系成员样本进行验证,结合先证者家系的临床资料及 ACMG 指南进行新突变的致病性鉴定。
结果 该家系中的多囊肾病患者存在 *PKD1* 基因 c.8311G>A (p.Glu2771Lys)杂合错义突变,根据 ACMG 指南,其变异分类为"致病的"。
结论 *PKD1* 基因 c.8311G>A(p.Glu2771Lys)错义突变为多囊肾病 1 型的致病变异，该杂合变异会导致发病,为该家系的遗传咨询和遗传学诊断提供了依据。

案例分享：甲状腺激素抵抗综合征

唐帅男
上海佰臻生物科技有限公司

受检者信息
受检者女性，28 岁
临床诊断：TSH 不适当分泌综合征
临床表型：体检发现甲功异常 1 年余。
家 族 史：受检者妈妈和外婆甲状腺结节。
经全外显子测序，发现受检者携带 *THRB* 基因的 1 个可能致病的杂合错义变异

案例分享：芬兰型淀粉样变性一例

刘泽华
上海佰臻生物科技有限公司

临床信息
受检者男性，54 岁
临床诊断：格子样营养不良 II 型（Meretoja 综合征），肾病淀粉样变。特殊面容，VOD0.9（矫正），VOS0.3（矫正），双眼角膜基质浅层见线条状混浊，从角膜缘向心性扩展，下方角膜上皮

糜烂，前房深浅正常，瞳孔圆，对光反应存在，晶状体混浊，左眼较明显，眼底：右眼 C/D0.7，左眼 C/D0.4，黄斑区未见明显异常。右眼压：16mmHg，左眼压 19mmHg。泪膜破裂时间：右眼 4 秒，左眼 6 秒，Schirmer Test 右眼 12 毫米，左眼 13 毫米。蛋白尿样，眼角膜病变。
经全外显子测序，发现受检者携带 *GSN* 基因的 1 个致病的杂合错义变异

发作性运动诱发性运动障碍 PRRT2 基因突变分析与案例分享

刘泽华
上海佰臻生物科技有限公司

发作性运动诱发性运动障碍(ParoxysmalKinesigenitDyskinesia，PKD)发病年龄通常在 6-28 岁，由运动、惊吓或焦虑诱发，发作时间短(小于 1 分钟)，发作频率高(有时 100 次/天)，发作时无意识障碍或疼痛。临床表现单侧或双侧不自主运动突然发作(运动障碍可包括肌张力障碍、舞蹈病、颤抽或手足徐动症)、阵发性运动障碍、抽搐和眼球震颤(罕见)。以常染色体显性方式遗传，外显率约为 60-90%，发病率为 1/150,000。目前认为，有家族史的病人约占 PKD 发病总数的 60%。PKD 的主要致病基因是富脯氨酸跨膜蛋白 2 (*PRRT2*)基因。本研究的目的是诊断一个具有常染色体显性遗传的家系，确定其致病原因。通过全外显子组测序，在基因中发现了 *PRRT2* 基因重复突变 c.649dupC (p.R217Pfs*8)。这种突变与疾病共分离。*PRRT2* 基因突变是绝大多数家族性 PKD 患者及部分散发型 PKD 患者的致病原因，c.649dupC(p.P217fs*8)热点突变占到所有突变的 93.75%。*PRRT2* 基因突变阳性的 PKD 患者发病年龄较早，发作更为频繁且发作时症状对称性更高。本案例旨在明确患者的致病原因，以期对 PKD 患者的临床治疗具有潜在指导意义。

A case of a patient with the spontaneous dissolution of zona pellucida in IVF/ICSI-ET

胡继君 管一春
郑州大学第三附属医院

This study aimed to describe a case of a patient with the spontaneous dissolution of zona pellucida (ZP) after in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI).This patient experienced interventional therapy for fallopian tube obstruction recanalization ,a failed AIH cycle and two IVF/ICSI cycles during 29-30 years.Time-lapse monitoring of embryo cleavage and blastocyst culture was performed in the second ICSI cycle, and we found that the ZP of 7 oocytes dissolved gradually during the cleavage stage of embryo development. In the first IVF+RICSI cycle,we observed six embryos with cracked ZP or dissolved ZP without Time-lapse monitor.Then two embryos were transferred on D3 and two blastocysts appearing on D6 and D7 were frozen. However,one fresh embryo transfer and two frozen-thawed blastocyst transfers resulted in no pregnancy.
To our knowledge, this is the second report of ZP dissolution during the cleavage-stage embryo.We could not perform PGT because of no indications,so the exact mechanism remains unknown.However,we speculate that the morphological changes with granular matter appearing in the periocular space was related to the dissolution of ZP through time-lapse observation

案例分享：局灶性节段性肾小球硬化症 7 型或肾性眼缺损综合征一例

唐帅男
上海佰臻生物科技有限公司

临床信息
受检者男性，14 岁 2 个月
临床诊断：慢性肾病 3 期、胡桃夹综合征。患儿 11 年前因尿床于**市中心医院就诊，查尿蛋白 2+，胡桃夹阳性，无浮肿，无血尿，无高血压，无尿频、尿急等，考虑胡桃夹综合征，后未予特殊处理，期间多次于当地县医院查尿常规提示 2+-3+(具体不详，无报告单)，且尿床症状一直未缓解，1-2 次尿床/周，3-4 次小便/晚，并渐出现夜间饮水增多，夜尿增多，家长一直未予重视，2 年前当地医院查肝肾功能，家长诉未见异常(无报告单)，半月前因尿床至我院就诊，门诊查尿素 10.65mmol/L，肌酐 159μmol/L，尿蛋白 3+，泌尿系 B 超提示双肾缩小，遂拟“慢性肾小球肾炎”收入院，查尿素 13.54mmol/L，肌酐 181μmol/L，24 小时尿蛋白 4.01g/24h，考虑慢性肾病Ⅲ期现肾穿刺病理符合局灶性节段性肾小球硬化症。
经全外显子测序，发现受检者携带 *PAX2* 基因的 1 个致病的杂合移码变异

TGF-β1 contribute to the pathogenesis of high-turnover bone disease through cytoskeletal remodeling regulated by the Rho signaling pathway

Chen Qi Yuanming Wu
Air Force Medical University

Background Bone remodeling depends on the precise coordination of bone resorption and subsequent bone formation. Disturbances of this process are associated with skeletal diseases, such as Camurati-Engelmann disease (CED), which is caused by heterozygous mutations in the transforming growth factor beta 1（*TGF-β1*）gene on chromosome 19q13. We describe the clinical and radiographic characteristics of two CED patients in a family, including waddling gait, bone pain, skeletal deformities, and severe scoliosis. Both patients had elevated levels of ALP and PTH, accompanied by anemia. In addition, the PET CT result showed significant unevenness in bone metabolism throughout the body, with the skull, limbs, long bones, left scapula and hip joints being the most significant. The sequencing results showed both of them have the R218C mutation in the latency-associated peptide domain of *TGF-β1*. The functional activation caused by the mutation of *TGF-β1* in CED disease disrupts the dynamic balance of bone remodeling, which makes the excessive enhancement of osteoclast function, which leads to increased bone turnover and decreased bone density in patients. At present, there are many reports of TGF-β1 dysfunction leading to bone diseases including CED, however, the mechanism of action is still unclear. Therefore, exploring the mechanism of TGF-β1 in the differentiation and maturation of osteoclasts may give us a better understanding of CED diseases and hopefully find potential therapy.
Methods The osteoclastogenesis ability of RAW264.7 macrophages treated with TGF-β1 or inhibitor was demonstrated by bone resorption pit, resistant acid phosphatase (TRAP) staining, and osteoclastogenesis specific marker studies. Gene and protein expression were evaluated by quantitative Reverse-Transcription PCR (qRT-PCR) and western blot, respectively. Cell motility was analyzed by transwell-based migration assay. In addition, Actin cytoskeleton dynamics was evaluated by scanning electron microscopy and laser confocal microscopy using fluorophore-conjugated phalloidin.
Results In the current study, our data showed that TGF-β1 promoted RANKL-induced osteoclast formation, accompanied by the significant activation of the main molecules of the MAPK/Rho pathway downstream of TGF-β1, but the use of TGF-β type I receptor inhibitor significantly

inhibited these effects. Besides that, TGF-β1 promoted the migration of pre-osteoclasts through the increase in filopodia mediated by Rho, which leads to increased osteoclast fusion.
Conclusion Our future research will investigated and evaluate whether changes in Rho signaling in peripheral blood PBMCs of CED patients initiate crucial pathogenic impulses. In summary, we propose that elevated TGF-β1 may contribute to the pathogenesis of high-turnover bone disease through cytoskeletal remodeling regulated by the Rho signaling pathway.

Xia-Gibbs 综合征案例分享

刘泽华
上海佰臻生物科技有限公司

受检者男性，8 岁
智力发育落后，运动发育落后，语言发育落后，咬字不清，流涎，龋齿，视力差，体型胖，头围稍大，喜欢扯头发放鼻孔，刻板动作，乳酸脱氢酶偏高。MRI 异常：1、枕大池扩大（蛛网膜囊肿可能） 2、胼胝体体后部纤细，双侧额顶部脑外间隙增宽、双侧侧脑室形态欠规则 3、松果体小囊肿 4、先天性第五、第六脑室形成。EEG 异常。 首次发病：6 个月，无法独立抬头。孕早期一个多月时候，曾吃避孕药，此胎超预产期 9 天，顺产，3.4KG。无家族史。
经全外显子组测序，发现受检者的 *AHDC1* 基因发生了 1 个移码变异：c.1122dupC:p.Gly375fs

家族性甲状腺髓样癌及多发性内分泌瘤病 2 型 RET 基因突变与案例分享

李振义
上海佰臻生物科技有限公司

家族性甲状腺髓样癌（Medullary thyroid carcinoma,MTC）的临床表现为甲状腺髓样癌，无其他原发性肿瘤，呈常染色体显性遗传。多发性内分泌瘤病 2 型（Multiple endocrine neoplasia 2，MEN 2）分为多发性内分泌瘤病 2A 型和多发性内分泌瘤病 2B 型。多发性内分泌瘤病 2A 型占多发内分泌瘤病 2 型的 70-80%，95%的患者会患有甲状腺髓样癌，50%的患者会患有嗜铬细胞瘤，20-30%的患者会患有甲状旁腺腺瘤；多发内分泌瘤病 2B 型占多发内分泌瘤病 2 型的 5%，全部患者均会患有甲状腺髓样癌，50%患者会患有嗜铬细胞瘤，其他临床表现为粘膜神经瘤、角膜神经增厚、厚嘴唇、厚眼睑和高颚穹等，部分患者还有骨骼异常和胃肠道异常。多发性内分泌瘤病 2 型呈常染色体显性遗传。MEN2、MTC 的主要致病基因是原癌基因（*RET*）基因。本案例通过全外显子组测序，发现了 *RET* 基因致病性突变:c.1859G>T(p.Cys620Phe)。本案例既能为遗传性肿瘤患者查找致病基因，又能提示患者家属患肿瘤的风险，协助其积极主动采取针对性的健康方案，早检测早预防，以期有效降低肿瘤发生风险。

多发性内分泌瘤病 1 型案例分享

李顺发
上海佰臻生物科技有限公司

本文报导了两例多发性内分泌瘤病 1 型的携带者，以期早期发现，早期合理积极治疗，降低误诊并改善预后。

案例分享：全外显子检测 17q12 缺失综合征一例

陆婷婷
上海佰臻生物科技有限公司

17q12 缺失综合征临床主要表现为生殖道畸形、男性隐睾症、女性无阴道或子宫、单角子宫、卵巢囊肿、肾囊肿或高回声肾脏、双侧肾盂输尿管交界处狭窄、肾功能异常或无功能肾、终末期肾脏疾病、单侧肾发育不全或肾发育不全、轻度至中度精神发育迟滞、语言发育迟缓、自闭症及癫痫等。个体间临床表现具有差异性。以常染色体显性方式遗传，外显率高，表现度差异大，发病率为 0.000069。本研究的目的是为临床患者提供辅助诊断。通过全外显子组测序，发现受检者第 17 号染色体 q12(34,806,052-36,285,009)区段缺失一个拷贝，长度约为 1.48Mb。此缺失与 17q12 缺失综合征（17q12 Recurrent Deletion Syndrome）有关，本案例旨在明确患者的致病原因，对 17q12 缺失综合征患者的临床治疗具有潜在指导意义。

痉挛性截瘫 4 型案例分享

李振义
上海佰臻生物科技有限公司

受检者男性，65 岁
临床诊断：复杂性痉挛性截瘫、酒精中毒性周围神经病、颈椎病、运动神经病、侧索硬化。
临床表型：患者 2000 年出现双下肢无力，诊断为“颈椎病”，于 2003 年 3 月行颈椎手术，术后症状逐渐加重，后出现排尿困难和便秘。患者剪刀步态，双下肢痉挛性截瘫，双下肢肌张力高，腰 4-5 椎间盘突出。
家族史：患者父亲 40 多岁就不在了，生胃病，年轻时候没有发现这个症状。患者母亲 70 多岁去世，健康时也没有这个症状。患者还有一个亲妹妹，30 岁左右生皮肤病去世。亲姐姐现在快 70 岁了，没有这个症状，患者亲姐姐的儿子，40 多岁了，目前没有出现这个症状。只有患者的亲弟弟，有类似的症状。
经全外显子测序，受检者的 *SPAST* 基因发生了 1 个剪接变异：c.1729-1G>A，可能造成剪切异常，无人群携带记录（数据来源：1000G、ExAC、ESP 和 GnomAD 数据库）。Clinvar 数据库记录此变异为致病变异，Ivanova N 等在一位痉挛性截瘫病人中发现 1 个可能造成相同剪切异常的变异（c.1729-2A>G），Brugman F 等在一位痉挛性截瘫病人中发现 1 个可能造成相同剪切异常的变异（c.1729-2A>T）。Sanger 测序结果显示受检者及其女儿携带此变异（附图）。依据 ACMG 指南，判定该变异为致病的变异。

改良直线法联合口轮匝肌环形重建在轻度面横裂修复术中的应用

王宏伟 陈阳 王旭东
上海交通大学医学院附属第九人民医院

研究目的 总结面横裂患者的临床特点，评价改良直线法修复面横裂的治疗效果。
研究方法 收集 2019 年 2 月至 2021 年 4 月于我科进行面横裂修复治疗的 21 例患儿的临床资料。所有患儿均采用相同手术方法：根据健侧口裂定点，于患侧上唇预定口角点下方设计弧形唇红黏膜瓣，对应下唇部分去除相应唇红黏膜，将上唇瓣插入下唇，分离断裂的口轮匝肌并重建其环形结构，黏膜及皮肤均采用直线法修复。术后进行至少为期 3 个月的随访观察。
研究结果 单侧面横裂 17 例，双侧面横裂 4 例；男性 12 例，女性 9 例；年龄 3 月-7 岁，平均年龄 14 月；裂隙均未超过咬肌前缘。单侧面横裂患者中，13 例伴发患侧附耳畸形，2 例伴发双侧附耳畸形；5 例有显著的半侧颜面发育不全。双侧面横裂患者中，1 例伴发双侧附耳畸形。随访过程

中，所有患者创口愈合良好无感染裂开，无瘢痕挛缩，口角转折自然，两侧口角对称，口唇运动及闭合良好。

研究结论 面横裂患者临床表现多样，附耳畸形及半侧颜面短小为最常见的伴发症状，部分患者出现耳廓发育异常或斜视等症状。应用改良直线法对轻度面横裂进行早期手术治疗能够有效地改善患儿的外观和功能，获得理想的疗效。

单纯腭裂小家系基因突变的初步分析

张进[1] 谢雨琪[1] 李娜[1] 崔人婕[1,3] 胡颖熹[1] 葛润生[1] 姜楠[1] 马端[1,2]
1.复旦大学 2.复旦大学附属儿科医院 3.上海交通大学附属第九人民医院

背景 非综合征型腭裂 (NSCP) 是一种常见的先天性畸形，致病因素复杂，可分为环境因素和遗传因素。

材料方法与结果 本研究收集父母均正常，但后代中出现两个单纯腭裂且不为双胞胎关系的患者。因为亲代正常，但子代中连续两次出现相类似的腭裂表型，所以我们假设在这些罕见小家系的患者中，存在基因的复合杂合或纯合突变，可能是腭裂发生的易感因素。通过对这些家系成员进行全外显子测序分析，排除高频突变(正常人群中，突变频率大于 5%)及已知突变基因后，结果显示，在 1 号家系患者中存在 FBN3 和 KCNV2 基因的复合杂合突变，2 号家系存在 FLG2、RP1L1 、TLR2 基因的复合杂合突变；3 号家系中只存在一个 C19orf71 复合杂合突变；4 号家系中存在 ADAMTSL1 、CFH 、FADS6 、PRKCSH 多个基因的复合杂合突变。在后续研究过程中，我们将在腭裂体外模型中检测这些候选基因，分析它们在腭裂发生中的可能作用。

1 例表观盐皮质激素增多综合征患儿的临床与 HSD11B2 基因分析

丁圆
北京儿童医院

目的 通过对 1 例生后即发现高血压，11 年后获得确诊的患儿及其基因分析，对表观盐皮质激素增多症进行研究。

方法 患儿，女，12 岁时来院，主因“发现高血压、低血钾 11 年，血压控制差 1 月”就诊，对临床表现及血电解质特点进行分析，采取外周血白细胞进行基因分析。

结果 患儿于 6 个月时因“发热”于当地医院救治发现血压升高、血钾降低，予降血压、补钾等对症治疗，出院后一直口服卡托普利片至今，间断 3-6 个月复诊。病程中，患儿多次因“无力、抽搐发作”等就医，间断予口服降压药及螺内酯等治疗，血压控制不佳，波动于 140-180/100-110mmHg。患儿智力正常，易疲劳，体格发育落后，12 岁时身高为 124cm（-2~-3SD），体重 17.5kg(<-3SD)。实验室检查：多次血电解质检查提示血钾降低，最低为 1.23mmol/L（正常值参考范围：3.5-5.5mmol/L）；血气分析：pH 7.543，实际碳酸氢钠 44.3mmol/L，细胞外液剩余碱 21.8mmol/L；高血压四项（卧位）：血管紧张素 I（37℃）0.85ng/ml，血管紧张素 I（4℃）0.27ng/ml，肾素活性（PRA）0.58ng/ml/hr，醛固酮（ALD）64.01pg/ml，ARR11.04Ratio；高血压四项（立位）：血管紧张素 I（37℃）0.88ng/ml，血管紧张素 I（4℃）0.26ng/ml，肾素活性（PRA）0.62ng/ml/hr，醛固酮（ALD）51.56pg/ml，ARR8.32Ratio。尿液醛固酮 7.07ug/day（参考值：3-15）。*HSD11B2* 基因分析显示患儿存在 c.605T>C（p.V217A）纯合变异，父母分别携带一个杂合变异，为未见报道的新变异。

结论 表观盐皮质激素增多综合征是一种罕见的单基因原发性高血压，诊断相对困难。我们报道了一名中国青少年早发型高血压患者的新型纯合子 *HSD11B2* 变异，丰富了 AME 的基因型和表型谱。基因检测有助于早期诊断和治疗 AME 患者，可避免靶器官损伤。

液态浓缩生长因子在进行性半侧颜面萎缩治疗中的临床应用

张天嘉 王旭东
上海交通大学医学院附属第九人民医院

目的 通过对中度半侧颜面萎缩（progressive hemifacial atrophy，PHA）患者进行浓缩生长因子（concentrated growth factors，CGF）混合脂肪注射治疗，采用数字化技术比对患者三维形态的改善，明确 CGF 对促进 PHA 患者脂肪移植的时空效应，以及在注射 CGF 后患者病损区域的局部环境改善情况。

材料与方法 选取已出现较明显的皮下组织及肌肉的萎缩，皮肤与骨面间组织较少，潜在间隙较少的中度 PHA 患者 6 名，采用三维照片设备（3dMD，美国）采取患者面部三维图像，计算所需充填体积。全麻下抽取患者自体脂肪，与 CGF 按 8:1 的比例混合后，按设计注射至缺损区域。术后两周，三个月及半年定期复诊，重新拍摄三维照片，获取颌面部三维影像，与术前形态及手术设计相比较，对比脂肪远期吸收率。

结果 术后即刻患者面型恢复良好，因肿胀等因素较对侧更丰满；3 个月时较术后有较明显的吸收，面部外形基本对称；术后 6 个月自体脂肪吸收趋于稳定，与 3 个月相比基本一致。长期效果较稳定，远期吸收率较单纯脂肪注射患者下降。

结论 CGF 作为自体材料较为安全和可靠，且可以促进面部脂肪移植的成活率，减少患者术后的脂肪吸收率和重复手术次数。在部分严重患者中，可以增加脂肪组织移植量以及软组织厚度和质地，以减小颌骨手术或其他有创手术的必要性或治疗难度，亦可在遗传性综合征患者的颌面部畸形中进行应用。

一例 18q21.1q21.32 杂合缺失患者及其家系的分子遗传学分析

张钰琦 强荣
西北妇女儿童医院

目的 对 1 例因脑瘫伴喉软骨发育不全、先天性心脏病来我院就诊的患儿进行家系染色体核型分析并验证其异常染色体的来源。

方法 对本例患儿及其父母进行外周血 G 显带核型分析及染色体拷贝数变异（CNV）检测，并应用高分辨染色体 G 显带分析定位患儿之父异常染色体的断裂及可能插入区域。

结果 患儿及父亲染色体核型均为 46,XY,del(18)(q21.1q21.3)，母亲染色体核型为 46,XX，并且患儿 CNV 检查结果发现 arr[19] 18q21.2-q21.32 (48401988-58980702) 杂合缺失 1057.871Kbp，父母却均未发现相关拷贝数缺失。经高分辨染色体分析技术进一步研究，结果发现患儿之父 18 号染色体长臂的一部分片段（18q21.1q21.3）插入到了 5 号染色体断臂（5p13.1）。

结论 患儿整体发育迟滞及先天发育异常的表型可能是由于 18q21.2q21.32 杂合缺失所致，且缺失的染色体片段来源于父亲。此外，对染色体核型异常的患者，染色体拷贝数变异检测及高分辨染色体 G 显带分析技术有利于亲缘性染色体异常的明确。

半侧颜面肥大的数字化诊疗模式

沈舜尧 王旭东 张雷
上海交通大学医学院附属第九人民医院

目的 半侧颜面肥大症的临床特点是以面部为特征的不对称发育，全身症状不尽相同，可出现单指、单肢、或单侧面部，甚至累及半侧躯干。本研究的目的是提出结合数字化技术治疗半侧颜面肥大的诊疗流程。

方法 3 例被诊断为半侧颜面肥大的女性患者在术前通过三维 CT 扫描获得颌面部软硬组织的三维重建图像。 首先分析颌骨的不对称，包括半侧下颌骨肥大、 下颌骨偏斜、同侧的上颌和颧骨肥大，

以及眼眶外侧壁及下壁膨隆。 在计算机技术辅助下，逐次设计上颌 Le Fort I 截骨术、 颧骨颧弓内推；同侧髁突切除术、健侧下颌骨矢状劈开术以及下颌骨轮廓修整术。二期手术时， 通过 3dMD 系统计算分析软组织的不对称，并设计面部提升手术。
结果 3 例患者的上颌骨 Le Fort I 型截骨术及下颌骨矢状劈开术均采用数字化导板完成。导航引导下颧骨内推术和患侧髁突切除术也同台手术完成。 3 例患者中有 2 例同期行面部提升术， 1 例于二期行面部提升术。术后随访一年， CT 扫描结果显示出良好的颌骨对称性。
结论 计算机辅助的虚拟规划与导航技术对于半侧颜面肥大的诊治具有良好辅助作用，可以获得良好的临床疗效。

Whole exome sequencing reveals novel MITF mutation in one Chinese patient with Waardenburg syndrome

Xiaodan Liu
Department of Prenatal Diagnosis, The Affiliated Women and Children Hospital, Jiaxing University School of Medicine, Jiaxing, China.

Background Waardenburg syndrome (WS), whose incidence is about 0.0025%, is a generic terms of hearing impairment and color changes of skin, hair, and eyes caused by genetic change. WS has been classified into four subtypes (WS1-4) based on the presence or absence of additional symptoms. 15% of WS2 patients possess heterozygous mutations of MITF, which is a transcription factor with a basic helix-loop-helix leucine zipper (b-HLH-Zip) motif.
Methods Whole exome sequencing (WES) was performed to detect the causative gene mutations in one Chinese patient with WS followed by Sanger sequencing.
Results We identified one novel heterozygous mutation of MITF gene (c.635-2A > T, reference transcript: NM_000248.3) and one known heterozygous mutation of GJB2 gene (c.235delC, reference transcript: NM_004004.5) in the proband. The c.635-2A > T mutation of MITF gene which would produce an abnormal truncated protein was a de novo mutation. The c.235delC mutation of GJB2 gene, which had been reported to be pathogenic, was inherited from the mother.
Conclusion Our study reported one case of WS patient by routine examination and WES, which expands the mutation spectrum of MITF for the diagnosis of WS and deepens understanding for the pathogenesis of WS.

Novel compound heterozygous mutations in SLC25A26 gene cause Combined Oxidative Phosphorylation Deficiency 28 in a Chinese family

Yaxin Zhang
The Third Affiliated Hospital of Zhengzhou University

Objective To identify the the clinical phenotype and the genetic cause of an affected baby borned with combined oxidative phosphorylation deficiency 28 (COXPD-28) in a Chinese family.
Methods The whole exome sequencing was performed in the proband. And sanger sequencing verified the genetic variations identified in this family.
Results Whole exome sequencing and sanger sequencing identified a compound heterozygous mutations of *SLC25A26* gene (c.403G>T(p.E135*) and c.212A>G(p.Y71C)) in the proband, which were inherited from his parents respectively. And his unaffected eldder sister is a heterozygous of c.212A>G(p.Y71C). And his mother has two abortions due to early embryo suspension and once abortion with trisomy of chromosome 16. The proband presented with severe metabolic acidosis, high lactic acid, poor acid correction effect, intractable metabolic acidosis, poor response, sobbing breathing, central respiratory failure, large heart shadow, heart failure, and died 10 hours after admission.

Conclusion We idenfied a first compound heterozygous mutations (c.403G>T(p.E135*) and c.212A>G(p.Y71C)) in *SLC25A26* gene cause COXPD-28 in Chinese.

HNF-1B 新突变导致 MODY5 的致病机理与药物靶向治疗

张荣 李鸣 蒋伏松 陈亚婷 葛晓旭 张娟 蒋燕燕 刘婵薇 刘丽梅
上海交通大学附属第六人民医院

目的 HNF1B 是肝细胞核因子转录因子家族成员，与 HNF（肝细胞核因子转录因子）家族、类固醇受体超家族等共同组成调控网络，参与胰腺早期发育和葡萄糖稳态调节。HNF1B 杂合突变，导致特殊类型单基因糖尿病 MODY5（青少年的成人起病型糖尿病，亚型 5）的发生和进展。本研究探索 MODY5 家系中，新发现突变的致病机理、基因型-临床表型特点，评估药物靶向治疗效果。
方法 （1）采用经典 MODY 家系诊断标准，收集 32 个临床表型疑似 MODY 家系；（2）对家系先证者，通过 PCR-直接测序，筛查 MODY5 基因(NM_000458)外显子、外显子-内含子拼接区突变；（3）对于 HNF1B 反转录区突变，检测 MIN6 细胞突变-转染蛋白的胰岛素基因转录活性；（4）突变的遗传-共分离、基因型-临床表型研究；（5）用多种预测软件对突变位点进行生物信息学致病性分析；（6）评估药物靶向治疗的降糖效果。
结果 （1）在一个家系先证者发现 HNF1B 基因 exon4: c.C988T，p. L330F（Leu330Phe）新突变，位于反转录激活区，系国际首次报道；（2）突变在家系中与高血糖表型呈遗传-共分离；3）突变体荧光素酶报告基因转录活性降低 34.2%（vs. 野生型）；（4）REVEL 软件预测值 0.67，分类为 Disease-causing 致病；（4）该突变携带者发病早期可用口服降糖药；随着胰岛功能减退，则需要胰岛素进行药物靶向治疗。
结论 发现 L330F 新突变的 MODY5 家系，生物信息学显示突变致病有害；体外研究证实该突变导致 HNF1B 的胰岛素基因转录活性下降 34.2%。随着病程延长，突变携带者胰岛功能的减退，则需要胰岛素药物靶向治疗。

De Novo Mutation of c.103G>A (p.V35M) and c.1211T>G (p.F404C) Cause Syndromic Intellectual Disability due to the loss -function in SLC45A1

Chiyan Zhou
Department of Prenatal Diagnosis, The Affiliated Women and Children Hospital, Jiaxing University School of Medicine

Objective To explore the genetic reason to cause the intellectual disability (ID) and research the potential molecular mechanism for the loss-function of SLC45A1 since the missense mutation.
Methods The proband with syndromic ID was analyzed by the whole-exome sequencing (WES). Responding to the mutation, the structure for wild-type and mutant SLC45A1 was predicted through I-TASSER server and visualized by UCSF Chimera software. The recombinant plasmids of wild-type and mutant SLC45A1 were constructed and transfected into COS7 cells respectively. The cellular location was observed by confocal microscopes, and the activity of glucose uptake was assayed and further compared between the mutant and the wild-type SLC45A1-overexpression cells.
Results The SLC45A1 compound heterozygous mutation of c.103G>A (p.V35M) and c.1211T>G (p.F404C) followed the rule of recessive inheritance in the proband family. The hydrogen bonds surrounding the objective amino acid were changed by the missense mutation. The two variants of p.V35M and p.F404C equally affected the SLC45A1 location on the plasma membrane. And the activity for glucose uptake was also significantly decreased in the variants of p.V35M and p.F404C respectively to contrast with the wild-type SLC45A1.
Conclution The compound heterozygous mutation of SLC45A1 was considered as one of genetic cause for syndromic ID. The variants of c.103G>A (p.V35M) and c.1211T>G (p.F404C) were predicted to be pathogenic equally, since both of them probable altered the tertiary structure,

interfered cellular location and reduced the glucose transport to leads to the loss-function of SLC45A1.

一个锌指 C4H2（ZC4H2）基因无义突变（c.352C>T）的鉴定及功能研究

孙婧婧[1,2,3] 蔡勤[1,3] 许淼[1,3] 李婉睿[1] 李娟[2] 马俐[2] 蔡成[2] 龚小慧[2] 任兆瑞[1,3] 曾凡一[1,3]
1.上海交通大学附属儿童医院，上海医学遗传研究所
2.上海交通大学附属儿童医院，新生儿科
3.上海市胚胎与生殖工程重点实验室，国家卫健委医学胚胎分子生物学重点实验室

目的 女性限制型 Wieacker-Wolff 综合征（WRWFFR）是一种严重的 X 连锁显性遗传病，患者表现为智力障碍和多发性关节挛缩等。位于 Xq11.2 的 *ZC4H2* 是该病的致病基因。本研究对一名早产生后发现多发性关节挛缩患儿的致病位点进行鉴定，并探索其功能。
材料方法 我们在临床工作中发现一例 36^{+5} 周出生，有多发性关节挛缩，并且有异常面容、腭裂和喂养困难的女性早产儿，通过其家系的医学外显子组测序来鉴定可能的致病位点。为了研究突变位点对基因功能的影响，我们构建了表达 *ZC4H2* 基因突变位点的表达载体（5'端加入 Flag 标签）及野生型对照载体。转染 HEK293T 细胞后采用 qRT-PCR 和 Western blot 鉴定 *ZC4H2* 基因在转录和翻译水平的表达。最后，利用 RNA-seq 研究突变对基因表达谱的影响，并通过 PCR-array 或 qRT-PCR 验证差异表达基因的表达水平。
结果 患儿的医学外显子组测序结果表明在 *ZC4H2* 基因上有一个目前数据库中未见报道的 c.352C>T（p.Gln118*）无义突变，该突变理论推算会形成长度仅为 118 个氨基酸的截短蛋白。患儿父母中未发现此突变，因此可能为新发突变。qRT-PCR 结果表明，转染野生型和突变型表达载体的细胞中 *ZC4H2* 的 mRNA 表达水平没有显著差异（P=0.72）。表达野生型载体的细胞能检出 ZC4H2 蛋白，而表达突变型载体的细胞中不能检出，这预示着突变型载体表达的截短蛋白可能不稳定甚至不存在。RNA-seq 结果显示，转染突变型 *ZC4H2* 的细胞与野生型 *ZC4H2* 的细胞基因表达谱差异明显。KEGG 分析显示差异基因主要富集在氧化磷酸化信号通路中，相关基因在突变体的细胞中表达明显下调。这与已有的氧化磷酸化通路障碍与神经系统发育异常密切相关的报道相符合。
结论 我们从一例 WRWFFR 患儿中发现了一个新生的 *ZC4H2* 基因无义突变，该突变理论上会产生长度仅为 118 个氨基酸的截短蛋白，该蛋白在分子水平上未能检出，预示着该截短蛋白可能不稳定甚至不存在，因蛋白功能丧失而产生一些列的疾病表型。RNA-seq 结果显示，表达突变体的细胞中氧化磷酸化信号通路相关基因明显下调，其与该综合征智力障碍表型的关系值得进一步研究。

识别 HLA III 类基因区中的强直性脊柱炎关联罕见变异

杨帆[1,2,3] 朱小泉[3] 赵帆[4] 孙亮[3] 霍正浩[5] 张毓洪[6] 宋玉国[7] 杨泽[3]
1.上海交通大学附属儿童医院，上海医学遗传研究所
2.国家卫健委医学胚胎与分子生物学重点实验室，上海市胚胎与生殖工程重点实验室
3.国家卫健委北京老年医学研究所，国家老年医学中心，北京医院
4.中国人民解放军总医院第一附属医院烧伤整形外科
5.宁夏医科大学基础学院 6.宁夏医科大学公共卫生学院 7.北华大学附属医院

目的 强直性脊柱炎（ankylosing spondylitis，AS）是一种的影响脊柱和骶髂关节的慢性炎症，呈现明显的家族聚集性，属多基因遗传性疾病。多次全基因组扫描研究结果均显示 6 号染色体的 HLA 基因区域与 AS 的关联最强。*HLA-B27* 是迄今已知的与强直性脊柱炎关联性最强和最典型的基因，其侧翼的 HLA III 类基因区存在众多与免疫相关的基因。本组前期定位克隆显示，HLA III 类基因区内约 58K 的基因区块与强直性脊柱炎关联。本研究旨在用来自北京，吉林和宁夏的强直性脊柱炎病例和正常对照组识别 HLA III 类基因区中未知的强直性脊柱炎关联位点，探索强直性脊柱炎的遗传病因。

方法 使用 NGS 对 25 例 *HLA-B27* 阳性的强直性脊柱炎患者的 HLA III 类基因区进行捕获重测序，筛选候选的强直性脊柱炎关联变异。应用病例-对照方法，使用高分辨率熔解曲线、RFLP 等方法，在本组收集的中国北方人群强直性脊柱炎病例及对照队列中验证 NGS 发现的候选强直性脊柱炎关联变异。强直性脊柱炎患者的诊断均符合美国风湿病学会 1984 年修订的风湿病分类标准。
结果 本研究队列包括 901 例强直性脊柱炎患者和 956 例年龄性别匹配的正常健康对照人群。其中吉林病例组 136 例，对照组 148 例；北京病例组 269 例，对照组 257 例；宁夏病例组 496 例，对照组 551 例。汇总三个独立群体的结果显示，6 个位于 HLA III 类基因区的新强直性脊柱炎关联变异 chr6.g.31572283 G/A，chr6.g.31582985 C/T，chr6.g.31607213 A/G，chr6.g.31890598 T/G，chr6.g.31931147 G/A，chr6.g.32063200 T/C（p_{range}=1.785×10^{-12}~6.462×10^{-44}，OR_{range}=4.295~18.383）。这 6 个新的强直性脊柱炎均与 *HLA-B27* 阴性的强直性脊柱炎相关。
结论 在中国北方三个独立人群中发现 6 个新的独立于 *HLA-B27* 的强直性脊柱炎关联变异；HLA III 类基因区可能独立于 *HLA-B27* 与中国北方人群强直性脊柱炎关联；HLA III 类基因区中可能存在其他未知的中国北方人群强直性脊柱炎关联罕见变异，它们在强直性脊柱炎发生中的作用机制尚需进一步研究。

海南省新生儿筛查四氢生物蝶呤缺乏症及基因分析

黄慈丹
海南省妇女儿童医学中心

目的 探求海南省新生儿四氢生物蝶呤缺乏症发病情况及基因的分布特征。
方法 收集海南省 2007—2019 年参加新生儿疾病筛查的样本共 1 295 516 例，测定新生儿筛查干血斑样本中的苯丙氨酸的浓度，初筛使用荧光法，复筛使用串联质谱法。诊断为高苯丙氨酸血症的患儿尿样本尿蝶呤谱分析；干血斑样本红细胞二氢蝶啶还原酶活性测定进行鉴别。临床诊断为四氢生物蝶呤缺乏症患者血样进行高通量测序分析，患者双亲血样进行 sanger 测序进一步验证和诊断。
结果 干血斑样本确诊高苯丙氨酸血症 43 例。其中确诊四氢生物蝶呤缺乏症 8 例病例，男女各 4 例，海南省新生儿人群中四氢生物蝶呤缺乏症发病率 6.2/100 万。其中有 7 例病例检测出了 PTS 基因的 6 个突变位点：c.317C>T、c.286G>A、c.259C>T、c.155A>G、c.84+291A>G 和 c.83+1777T>G；1 例病例检出 QDPR 基因的 c.41T>C 位点纯合突变。
结论 海南省新生儿人群四氢生物蝶呤缺乏症发病率较低，且 PTS 基因突变所占比例最大。

一例巨球蛋白血症转 MDS 患者伴有染色体 t(3;3)(q21;q26)异常的临床特征及细胞分子遗传学分析

史沛芹
连云港市第一人民医院

目的 观察 t(3;3)(q21;q26)染色体异常的核型变化在疾病中临床表现及细胞分子遗传学分析。
方法 行骨髓涂片细胞形态学分析及骨髓活检，应用 R 显带技术进行核型分析；用流式细胞仪检测免疫表型；运用基因探针进行荧光原位杂交分析；高通量测序靶向检测相关基因
结果 骨髓细胞形态学 有核细胞增生活跃低水平，全片原始细胞比例增加占有核细胞总数的 19%，POX 染色阴性。粒系可见巨晚幼及巨杆状核粒细胞，易见小巨核细胞病态产板。骨髓活检提示骨髓增生较活跃，原始细胞增多约占 15%，粒系偏少，红系尚佳以中晚幼阶段细胞为主，巨核细胞增多伴病态改变，易见小圆核及多小圆核巨核细胞。核型分析结果显示患者异常克隆，其核型为 46,xx,t(3;3)(q21;q26)[10]。白血病免疫分型：CD34+，CD13+，CD33+，CD117+ HLA-DR11.4%原始细胞表达髓系阳性；应用探针进行 FISH 检测结果 显示 RPN1/MECOM 基因发生断裂重排，高通量测序靶向检测 CEBPA 基因，C-KIT 基因，FLT3-ITD 基因，NPM1 基因突变皆阴性。

结论 涉及 3 号染色体 3q21 和 3q26 异常 inv（3）（q21; q26）和 t（3;3）（q21; q26），包括插入（ins）（3; 3）（q26; q21q26）或重复（dup）（3）（q21- q26）统称为 3q21q26 综合征，存在于大约 1%的骨髓增生异常综合症（MDS）患者和大约 1.7%急性髓系白血病（AML）患者中。通常患有贫血，血小板计数可能正常或增加，骨髓通常显示病态小巨核细胞数量增加和多谱系发育异常。染色体畸变涉及 3q26.2.2 的原癌基因 EVI1 或其更长形式的 MDS1-EVI1（也称为 MECOM）和 3q21 的 RPN1，这导致 EVI1 或 MECOM 和/或 RPN1 / EVI1 融合转录本的过表达。研究发现 GATA-2 过表达促进了异常巨核细胞生成，表明它是与 3q21q26.2 相关的骨髓瘤的靶标之一。 EVI1 参与抑制造血调控抑制细胞凋亡。本例患者诊断巨球蛋白血症给予万珂+美罗华+地塞米松化疗，来那度胺治疗好转。后骨穿复查诊断（MDS-EB-2）。伴 3q21q26 异常的 MDS 和 AML 可以是新发疾病或与治疗有关的 ，MDS 和 AML 在 3q21q26 异常的比例中不仅具有具有共同的独特的临床特征，而且还显示出重叠的分子特征，对常规化学疗法的耐药性和临床效果不佳，通常预后很差和生存期短，尚需积累更多资料，进行更深入地研究 ，积极寻求更为有效的治疗方案。

儿童 Papillorenal 综合征 PAX2 基因新发突变 1 例

孙智才
中山市博爱医院

摘要： 目的 探讨儿童 Papillorenal 综合征的临床特点及基因型，提高对该病认识。 方法 回顾性分析 1 例 Papillorenal 综合征患儿的临床表现、影像学改变及基因型，并查阅文献判断其致病性。 结果 13 岁男性患儿， 以右眼视网膜脱落、贫血、慢性肾脏病（5 期）起病，智力、听力正常，影像检查提示双肾萎缩（<3SD）伴少量小囊肿。基因检测发现患儿 PAX2 基因 c.754>T(p.R252*)无义突变，可能会导致蛋白质合成提前出现氨基酸的终止密码，父母体健、均未携带该致病基因，家系验证其为新发突变。依据美国 ACMG 变异分类指南，该变异类型为 1 类-致病突变，且人群基因数据库（DGV）中未见相关报道。同时检测到 COL4A4 基因 c.4943A>G (p.Y1648C) 变异，来自于父亲，该变异类型为 3 类-意义未明。 结论 PAX2 基因 c.754>T(p.R252*)新发无义突变是 Papillorenal 综合征的致病基因，丰富了本病的基因谱，为该病诊断提供了更多依据。

Characterization and validation of long noncoding RNAs as new candidates in prostate cancer

Chuanyu Sun
Huashan Hospital, Fudan University

Background Long noncoding RNAs (lncRNAs) have been proved to be an important regulator in gene expression. In almost all kinds of cancers, lncRNAs participated in the process of pathogenesis, invasion, and metastasis. Mean- while, compared with the large amounts of patients, there is rare knowledge about the role of lncRNAs in prostate cancer (PCa).
Material/Method In this study, lncRNA expression profiles of prostate cancer were detected by Agilent microar- ray chip, 5 pairs of case and control specimens were involved in. Differentially expressed lncRNAs were screened out by volcano plot for constructing lncRNA-miRNA-mRNA central network. Then, the top ten up-regulated and down- regulated lncRNAs were validated by qRT-PCR in another 5 tumor specimens and 7 para-cancerous/benign contrasts. Furthermore, we searched for the survival curve of the top 10 upregulated and downregulated lncRNAs.
Results A total of 817 differentially expressed lncRNAs were filtered out by the criteria of fold change (FC) and t-test $p < 0.05$. Among them, 422 were upregulated, whereas 395 were downregulated in PCa tissues. Gene ontology and KEGG pathway analyses showed that many lncRNAs were implicated in carcinogenesis. lnc-MYL2-4:1 (FC = 0.00141, $p = 0.01909$) and NR_125857 (FC = 59.27658, $p = 0.00128$) had the highest magnitude of change. The

subsequent qPCR confirmed the expression of NR_125857 was in accordance with the clinical samples. High expression of PCA3, PCAT14 and AP001610.9 led to high hazard ratio while low expression of RP11-279F6.2 led to high hazard ratio.
Conclusions Our study detected a relatively novel complicated map of lncRNAs in PCa, which may have the poten- tial to investigate for diagnosis, treatment and follow-up in PCa. Our study revealed the expression of NR_125857 in human PCa tissues was most up-regulated. Further studies are needed to investigate to figure out the mechanisms in PCa.

Differential expression profiles of circRNAs in human prostate cancer based on chip and bioinformatic analysis

Chuanyu Sun
Huashan Hospital, Fudan University

Background Increasing evidence suggests that circRNAs are involved in the pathogenesis of multiple kinds of cancer. Nevertheless, the differential expression of circRNAs in prostate cancer (PCA) is rarely reported.
Material/Method In our present analyses, circRNAs expression profiles were identified in PCA, based on 5 pairs of PCA and matched non-PCA tissues using circRNA chips.
Results A number of 749 differential circRNAs were expressed between PCA tumor and paracancerous tissues (Fold Change, FC ≥ 2.0 and $P < 0.05$): 261 were up- regulated, whereas 487 were downregulated in PCA tissues. Gene ontology and KEGG pathway analyses indicated that many of the circRNAs are related to carcinogenesis. Circ_0033074 and circ_0016064 both showed changes of maximum magnitude among differentially expressed circRNAs.
Conclusions Our study detected a relative com- prehensive differential map of circRNAs in PCA, which may become novel biomarkers for diagnosis, treatment and follow-up in the future.

A Multi-Omics Study of Human Testis and Epididymis

Chuanyu Sun
Huashan Hospital, Fudan University

The human testis and epididymis play critical roles in male fertility, including the spermatogenesis process, sperm storage, and maturation. However, the unique functions of the two organs had not been systematically studied. Herein, we provide a systematic and comprehensive multi-omics study between testis and epididymis. RNA-Seq profiling detected and quantified 19,653 in the testis and 18,407 in the epididymis. Proteomic profiling resulted in the identification of a total of 11,024 and 10,386 proteins in the testis and epididymis, respectively, including 110 proteins that previously have been classified as MPs (missing proteins). Furthermore, Five MPs expressed in testis were validated by the MRM method. Subsequently, multi-omcis between testis and epididymis were performed, including biological functions and pathways of DEGs (Differentially Expressed Genes) in each group, revealing that those differences were related to spermatogenesis, male gamete generation, as well as reproduction. In conclusion, this study can help us find the expression regularity of missing protein and help related scientists understand the physiological functions of testis and epididymis more deeply.

A Multi-Omics Analysis of Periostin and Its Role in Bone Metastasis of Prostate Cancer

Chuanyu Sun
Huashan Hospital, Fudan University

Bone metastasis is the prime reason for poor prognosis in prostate cancer (PCa). It has been proved that interactions between cancer cells and the bone microenvironment contribute to bone metastases, but the molecular mechanisms involved are still unclear. In previous study, iTRAQ coupled with 2DLC-MS/MS had been applied to characterize the biomarkers of PCa in proteome level, and 46 differential expressed proteins had been screened out by protein-protein interaction network derived from Metacore™ and IPA software. Through the network, we had concluded the integrin $\alpha_v\beta_3$ was regulated by its ligand periostin (POSTN). Other report indicated that the combination of POSTN and integrin $\alpha_v\beta_3$ could regulate the expression of matrix metalloproteinase 2 and activate the downstream signal pathway of FAK/c-src, which regulated the cell survival and invasion in osteoblast. Also, the overexpression of POSTN is associated with PCa aggressiveness. In this study, we discovered the evidence of POSTN related to metastasis in PCa through multi-omics, validated these outcomes by TCGA database, and then observed that osteoblast-derived POSTN promoted proliferation and invasion in PCa cells whilst PCa cell-derived POSTN likewise promoted proliferation in osteoblasts through experiments. Mediated by transforming growth factor-β (TGF-β) signaling, osteoblasts induced POSTN expression in PCa cells. The functions of POSTN in PCa cells and osteoblasts could be blocked by integrin antibodies. The suppression of POSTN inhibited tumor growth in bone as well as metastasis *in vivo*. Moreover, we constructed ^{18}F-Alfatide II the molecule probe of integrin $\alpha_v\beta_3$ for accurately detecting the local and metastatic lesions of PCa by PET-CT. Taken together, our findings elucidated that POSTN was involved in the interactions between PCa cells and osteoblasts via integrin $\alpha_v\beta_3$, possibly contributing to osteoblastic metastasis in PCa, which would be valuable for further diagnosis and therapy.

COL4A1 基因突变导致脑小血管疾病伴脑膜膨出的一例报导

高宏志 周爽
福建医科大学附属第二医院

背景 （伴或不伴眼部异常）脑小血管疾病是一种常染色体显性遗传疾病，因血管基底膜破裂而表现各异，尤其在脑血管系统中。血管系统紊乱导致大脑退化，脑成像通常显示“空洞症”、血铁质沉积、钙化、腔隙性埂塞和白质脑病等。有些患者 MRI 表现有侧脑室白质缺失、小脑萎缩、胼胝体变薄。疾病表现出不同的外显率和表现度，本文报道 1 例伴颅骨缺损暨脑膜膨出的脑小血管疾病患者的临床特征，并对其 COL4A1 基因的遗传特征进行探讨。

病历摘要 患儿女，8 周岁，因“发现头皮肿物 7 年”来院，患儿自出生即发现后枕部头皮肿物，一岁后出现右侧肢体活动不良，未予特殊诊治，肿物略增大，为明确诊治前来我院。入院查体提示右上肢肌力 4 级，肌张力略高于对侧，后枕部正中线上距枕外隆突 4cm 处及头皮局部隆起，约 2.5´1.5´1cm^3, 触软，无压痛。头颅 CT 及 MRI 提示侧旁室白质软化与脑室相通，枕骨皮质连续性中断，骨质缺损，局部小脑镰经缺损处膨出。入院诊断为枕骨颅骨缺损，脑膜膨出，孔洞脑—脑小血管疾病？先天性脑瘫。于静脉麻醉下行局部脑膜膨出松解复位术及人工钛网颅骨修补术，术中见小脑幕局部脑膜经枕骨缺损处与枕部头皮下层相连，未及脑组织膨出，确诊为枕骨缺损并脑膜膨出。术后行局部功能锻炼，患儿切口愈合良好，未再出现局部肿胀膨出等症，右上肢肌力改善为 4$^+$级。

分子诊断及讨论 为进一步明确该患者的致病基因遗传特征，我们采集其外周血标本实施全外显子组测序，针对变异区域，行一代测序进行验证，结果显示患者 COL4A1 基因第 52 外显子存在一个杂合的错义突变——（NM_001845）c.A4988C: p. Q1663P。通过多个蛋白剪接预测软件 REVEL 评分，提示该突变可能影响剪接、该剪接引发的蛋白变异“可能有害”。而 ACMG 致病性评级为“意义不明确的基因变异”。其对应的 OMIM 表型为（OMIM NO.175780）伴或不伴眼部异常的闹小血

管疾病。其遗传模式为“常染色体显性遗传（AD）”。结合临床表现，我们推测 COL4A1 基因 c.A4988C: p. Q1663P 突变很可能是与受检者临床表现相关，为其致病基因，患儿确诊为脑小血管疾病。课题组同时收集其家系病案资料并绘制家系图。该先证者母亲的 COL4A1 基因为野生型，其父亲患肿瘤早逝，无法获知父亲基因型，直系家属中均未检测到该基因突变也并无相关临床表型。推测该突变很可能是新发突变。由于是常染色体显性遗传，该先证者的这一杂合突变有 50%机率遗传给子代，遂建议其家属未来需随诊行遗传咨询。课题组计划后期将进行全基因组测序已排除其它遗传信息异常，同时针对该突变位点进行细胞学和模型动物的基因功能验证，从而进一步明确该“意义不明确”基因变异的临床指导意义。

遗传性痉挛性截瘫的诊断与治疗

陈熠君 王柠 陈万金
福建医科大学附属第一医院

目的 遗传性痉挛性截瘫（Hereditary spastic paraplegia, HSP）是一组以双下肢僵硬无力为主要临床表现的遗传性神经退行性疾病，在婴儿期、儿童期、青春期或成年期均可能发病。根据遗传模式，HSP 分为常染色体显性（AD）、常染色体隐性(AR)、X 连锁(XL)和线粒体遗传四种方式，目前已发现了 83 种亚型。HSP 的诊断主要依据其临床表现和家族史，详细的发育和家族史可以为 HSP 的诊断提供重要线索。HSP 治疗以对症治疗为主，近几年，针对特定亚型的靶向基因治疗的研究也有所进展。因此，本文主要就 HSP 的诊断与治疗的新进展进行综述。
方法 通过查阅国内外有关 HSP 的文献并仔细阅读，对该病的诊断与治疗进行归纳总结。
结果 HSP 的诊断主要依据其临床表现和家族史，详细的发育和家族史可以为 HSP 的诊断提供重要线索，而急性或亚急性病程则可提示获得性病因。HSP 的诊断首先应排除引起进行性痉挛性截瘫的继发性因素，包括动静脉瘘，维生素 B12 缺乏症和铜缺乏症，以及一系列结构，炎性和感染性病因。目前 HSP 的确诊有赖于基因检测，但部分 HSP 亚型具有特征性的临床和神经影像学的特点，有助于鉴别诊断。比如 SPG4 通常表现为中年发病的单纯型 HSP，而 SPG3A 的发病年龄通常小于 10 岁。此外，T2 加权成像上齿状核相对于桥脑白质的中等信号或高信号对 SPG7 的诊断有提示意义，而几乎所有 SPG11 和 SPG15 病例都出现了胼胝体变薄以及脑室周围白质高信号的影像表现。临床实践中通过分析特征性的临床和神经影像特点，有利于针对性选择基因检测技术，提高诊断效率。HSP 总体疾病进展通常较慢，发病年龄较晚者通常伴随较早失去独立行走的能力，其治疗主要包括物理治疗、药物治疗、矫形器、局部注射肉毒杆菌等。近几年，靶向 HSP 致病基因的特殊治疗方法的研究也一直在增加，包括试图解决病理生理机制和基因治疗的方法。SPG5 是目前最可治疗的 HSP 亚型之一，通过降胆固醇药（即阿托伐他汀）的治疗能够降低 SPG5 患者血浆中毒性标志物的浓度。此外，在来自 SPG11 患者的 iPSC 神经元系和基因编辑的神经元模型中，针对病理机制的的药物能够挽救神经变性相关特征。最后，利用靶向基因替代或编辑的方法，针对常见的 HSP 亚型致病基因进行研究，也能让大多数 HSP 患者受益。
结论 HSP 的诊断主要依赖于基因检测，而分子生物学的进步推动了 HSP 亚型的诊断和基因鉴定。在治疗上，HSP 的遗传异质性也意味着研究其通用治疗靶点具有挑战性。因此，HSP 的治疗主要基中在常见亚型的基因特异性治疗上。

IBA57 基因突变一家系分析并文献复习

钟立霖[1,2] 陆妹[1,2] 黄燕茹[1,2] 葛运生[1,2] 马小敏[1,2] 沈彤[1,2]
1.厦门市妇幼保健院
2.厦门大学附属妇女儿童医院

目的 探讨 *IBA57* 基因变异致多发性线粒体功能障碍综合征患儿的临床、影像特征及基因突变特点。

方法 对 1 个家系中姐弟同患 *IBA57* 基因变异所致多发性线粒体功能障碍综合征患儿的临床资料进行分析，并以“*IBA57* 基因”、“多发性线粒体功能障碍综合征”、“*IBA57* gene mutation”、“multiple mitochondrial dysfunction syndromes(MMDS)”为关键词，对中国期刊全文数据库(CNKI)、万方数据知识服务平台、生物医学文献数据库(PubMed)自建库至 2020 年 7 月收录的论文进行文献复习。
结果 G2P2，女孩，5 月龄出现精神运动发育倒退，肌张力增高，头颅 MRI 提示异染性脑白质营养不良可能，芳香硫酸酯酶 A（ASA）活性检测正常，靶向基因测序未发现致病突变。病情逐渐加重，3 岁 5 月龄癫痫持续状态后夭折。G3P3，男孩，8.5 月龄时出现精神运动发育倒退，肌力减低，肌张力不全，血浆氨、血乳酸升高，血 ASA 活性、血清极长链脂肪酸正常，头颅 MRI 提示脑白质病，MRS 中病灶区乳酸峰倒置，予线粒体鸡尾酒治疗后有所缓解，后未坚持用药，病情逐渐恶化。对该家系行全外显子检测，姐弟均携带 *IBA57* 基因 c.286T>C、c.589C>T 复合杂合突变，诊断 MMDS。文献检索共 35 例信息完整的患者，11 例患者表现为痉挛性截瘫，视神经萎缩等，病情进展缓慢；24 例为 MMDS，发病前发育正常的或轻微落后，感染后功能倒退。c.286T>C 突变在我国病例中较多。
结论 *IBA57* 基因突变导致 MMDS 是一种严重致死性疾病，MRI 提示脑白质病变，预后不良，全外显子检测有助于诊断。

SOD2 ameliorates mitochondrial dysfunction in fibroblast cells of Leber’s hereditary optic neuropathy patients

Qingru Zhou[1] Bo Lei[1,2]
1.Zhengzhou University People's Hospital 、 Henan Provincial People's Hospital
2.Henan Branch of National Clinical Research Center for Ocular Diseases, Henan Eye Institute and Henan Eye Hospital, Henan Provincial People’s Hospital

Purpose In Leber’s hereditary optic neuropathy (LHON), MtDNA mutations mediate mitochondrial dysfunction and apoptosis of retinal ganglion cells. Mitochondrial superoxide dismutase 2 (SOD2) is a crucial antioxidase against reactive oxygen species (ROS). This study is to investigate whether SOD2 could ameliorate mtDNA mutation mediated mitochondrial dysfunction in fibroblast cells of LHON patients and explore the underlying mechanisms.
Methods The skin of normal health subjects and severe LHON patients harboring m.11778G>A mutation was taken to prepare immortalized skin fibroblast cell lines (normal-iFB and LHON-iFB). The LHON-iFB were transfected with SOD2 plasmid or negative control plasmid for 48 hrs respectively. In addition, human neuroblastoma SH-SY5Y cells and human primary retinal pigmental epithelium (hRPE) cells were transfected with SOD2 plasmid or negative control plasmid respectively for 48 h, and then were stimulated by H_2O_2 for 24 hrs. The oxygen consumption rate (OCR) was measured with a Seahorse extracellular flux analyzer. ATP production, mitochondrial membrane potential, reactive oxygen species (ROS) and malondialdehyde (MDA) were measured separately with the corresponding assay kits. The expression level of SOD2, inflammatory cytokines and p-IκBα/IκBα was evaluated by using western blot. Assessment of apoptosis in cell lines was performed by fluorescence analysis with TUNEL and flow cytometry.
Results In the LHON-iFB cells, mitochondrial dysfunction was evident. (LHON-iFB cells exhibited lower OCR, ATP production, mitochondrial membrane potential whereas higher level of ROS and MDA than normal-iFB. Western blot revealed a significant decline in the IL-6 expression and the rate of p-IκBα/IκBα in the LHON-iFB cells. Compared with the negative control plasmid group, SOD2 plasmid manifest increased OCR, ATP production and elevated mitochondrial membrane potential, additionally, decreased levels of ROS and MDA. TUNEL assays and flow cytometry suggested SOD2 diminished cells apoptosis. Western blot demonstrated SOD2 reduced the level of IL-6 and the rate of p-IκBα/IκBα. In the SH-SY5Y cells and hRPE cells, compared with the negative control plasmid group, SOD2 plasmid manifest increased ATP production and elevated mitochondrial membrane potential, and decreased levels of ROS and MDA. Flow cytometry suggested SOD2 diminished cells apoptosis.
Conclusions We showed LHON-iFB presented mitochondrial dysfunction mediated by the most common MtDNA mutation. SOD2 ameliorated mitochondrial dysfunction by inhibiting oxidative

stress and prevent oxidative stress-induced cell death. The protective effects appeared associated with reducing inflammatory response and inhibiting of the NF-κB signaling. Our data further support augment of exogenous SOD2 may be a promising therapy for the treatment and prevention of LHON.

由 SLC26A2 基因复合杂合突变引起的骨畸形发育不良（DTD）1 例

吴丹 陈津津
上海市儿童医院

目的 对该骨畸形发育不良（DTD）患者 SLC26A2 基因突变情况的确定。
方法 了解患者病史,充分采集临床信息，抽取患者、患者父母以及异卵双胎（妹妹）的外周血，提取血样中的 DNA, 利用 PCR 扩增技术对 SLC26A2 基因外显子编码区及其侧翼序列进行测序，同时家系分析。
结果 在该患者全血基因组 DNA 的 SLC26A2 基因中检测到 c.1020-1022delTGT 和 c.2144C>T 两个杂合突变，且均为已有文献报道的致病突变。父母均分别携带一个杂合突变，异卵双胎（妹妹）未查及突变。
结论 SLC26A2 基因的 c.1020-1022delTGT 和 c.2144C>T 突变可能为引起该患者临床症状的病因，且以上复合杂合所导致的表型未见报道。

Hypermethioninemia associated with methionine adenosyltransferase deficiency: Not just a benign disease

Mei Lu[1] Yanling Yang[6] Ruxuan He[2] Lulu Kang[3] Yi Liu[4] Yongxing Chen[5]
1.Women and Children's Hospital, School of Medicine, Xiamen University
2.Beijing Children's Hospital, National Centre for Children's Health, Capital Medical University
3.The First Affiliated Hospital，Zhengzhou University
4.China-Japan friendship hospital 5.Henan Children's Hospital
6.Peking University First Hospital

Background and objective Methionine adenosyltransferase (MAT) I/III deficiency, which is characterized by persistent hypermethioninemia. MAT I/III deficiency is often regarded as a benign inborn error of metabolism. Few reports showed clinical abnormalities in individuals with hypermethioninemia, especially neurologic abnormalities. We aim to investigate the diagnosis, treatment and follow-up of patients with MAT I/III deficiency, who accompanied with neurological abnormalities.
Methods A retrospective analysis of MAT I/III deficiency individuals from Department of Pediatrics, Peking University First Hospital was performed, including clinical data, blood amino acid and acylcarnitine profile, total homocysteine, urinary organic acid, gene analysis, imaging findings and treatment.
Results Fifteen Chinese patients with MAT I/III deficiency were observed in our research. Ten patients showed multiple clinical manifestations. The onset age ranges from 1 year 5 months to 5 years. Delayed speech development and learning difficulties were the main clinical features. Eleven cases were identified by newborn screening. Nine patients had special imaging changes in central nerve system. Amino acid and acylcarnitine analysis by tandem mass spectrometry was performed and severe persistent hypermethioninemia was highlighted. In spite of low methionine dietary control, the concentrations of methionine could not recover normal. One patient received liver transplantation, and methionine values decreased from 1200μmol/L to 100μmol/L. Compound heterozygous mutations or homozygous mutation in MAT1A gene were confirmed by targeted next-generation sequencing or whole exon sequencing.

Conclusions Methionine adenosyltransferase (MAT) I/III deficiency is not just a benign disease which can cause brain injury. Brain MRI should be performed in individuals with severe persistent hypermethioninemia. Liver transplantation is effective and expands a new therapy.

典型极长链酰基辅酶 A 脱氢酶缺乏症病例报道 1 例及危险因素分析

杨夕樱 孟岩
解放军总医院

目的 报道 1 例的儿童极长链酰基辅酶 A 脱氢酶缺乏症(very long chain acyl-CoA dehydrogenase deficiency,VLCADD) 典型病例及诊疗经过，探讨影响其病情反复的危险因素。
方法 总结 1 例反复发作的 VLCADD 患儿的临床表现、诊疗经过并结合相关文献进行危险因素分析。
结果 患儿女, 8 岁, 总病程 2 年 5 月。以腹痛、呕吐、抽搐、低血糖起病，血串联质谱及尿有机酸气相质谱检测分析 C14 C14：1，C14：2，C14：1/C16 增高，C0，C0/C16，C8/C10 降低，极长链脂肪酸氧化异常继发肉碱缺乏症；基因检测提示 ACADVL 17 号染色体 c416T>C 母源 17 号染色体 c1349G>A 父源，确诊患儿为 VLCADD。家长未遵嘱定期治疗，此后反复出现腹痛、呕吐、肌肉酸痛，肝酶、肌酸激酶及心肌酶、肌红蛋白升高显著。其同胞弟弟 11 月龄猝死，根据描述推测为 VLCADD 患儿。入院后查肌酸激酶 19007.0U/L↑，肌红蛋白定量 2697.0ng/ml↑，予左卡尼汀、还原型谷胱甘肽及磷酸肌酸钠静点，辅酶 Q10、生玉米淀粉口服等对症治疗，复查肌酸激酶 4103.7U/L↑，肌红蛋白定量 774.3ng/ml↑。入院第 13 天患儿再次出现肌肉酸痛，未诉其它不适，查体患儿咽部稍充血，复查血生化提示肌酸激酶 15572.0U/L↑，肌红蛋白定量 5513.0ng/ml↑,完善呼吸道病原九项及肺炎支原体抗体检查，提示肺炎支原体阳性，予阿奇霉素 2 个疗程及中成药物口服对症 13 天后肝酶、肌酸激酶及心肌酶、肌红蛋白全部降至正常。入院第 20 天患儿因参加节日庆祝活动体力活动显著增加，维持原有治疗基础上，活动后患儿未诉肌肉酸痛，查血生化提示肌酸激酶及肌红蛋白较活动前分别呈 2 倍、2.5 倍增高。
结论 VLCADD 为婴幼儿期潜在猝死性疾病之一, 尤其以反复胃肠道表现为主的，除常规检查外，需要积极行血糖、乳酸、血/尿代谢性筛查等代谢性检查，根据血串联质谱检测血肉豆蔻烯酰基肉碱(C１４：１)增高及尿有机酸气相质谱检测二羧酸可实现早期诊断、早期治疗。劳累、饥饿、感染是诱发反复发作的常见危险因素，根据本病例感染是较劳累、饥饿更隐匿，影响更显著的危险因素。预防感染、防止低血糖等核心治疗原则需重点做好家长宣教，从而实现改善预后的最终目标。

69636 例广西柳州地区人群染色体病检出情况分析

徐玉婵 严提珍 韦朔峰 韦小妮 覃宋强 张美瑜 覃江锋 蔡稔
柳州市妇幼保健院

目的 了解柳州地区人群中染色体病的检出情况，为柳州地区染色体病出生缺陷的防控措施提供参考。
方法 回顾性分析我院 2014 年 1 月至 2020 年 10 月行外周血染色体核型分析的就诊者 69636 名，采集其外周血接种于淋巴细胞培养液,37℃培养 72h 后进行常规染色体制备及 G 显带。根据外周血染色体核型结果并结合其它临床资料分析就诊者染色体病检出情况。
结果 69636 例外周血染色体核型分析中检出异常 1547 例，检出率 2.22%。其中数目异常 916 例，检出率 1.31%，以染色体非整倍体（21-三体综合征，Turner 综合征，超雌综合征,Klinefelter 综合征）及标记染色体多见；结构异常 631 例，检出率 0.91%，倒位，易位多见。0-5 岁就诊者染色体异常 320 例，检出率 0.46%，数目异常 270 例，检出率 0.39%，其中 21-三体综合征 241 例，占 75.31%；结构异常 50 例，检出率 0.07%。

结论 柳州地区人群中染色体病以唐氏综合征、Turner 综合征、超雌综合征、Klinefelter 综合征常见，0-5 岁就诊者以唐氏综合征的检出率最高。因而应加强该地区染色体非整倍体尤其是唐氏综合征的产前筛查和产前诊断，以降低出生缺陷患儿的出生。

CDH2 基因变异所致 ACOG 综合征一例

孟曦
北京儿童医院

患儿 男，1 岁，因“生后小阴茎”就诊。临床表现为特殊面容、发育迟缓、双侧胼胝体缺如、双眼 Peters 异常、小阴茎和右侧隐睾。家系全外显子检测提示患儿为 CDH2 基因 c.1879G>A（p.D627N）杂合变异所致 ACOG 综合征。患儿该变异是新发变异，在国内未见报道，扩大了基因变异谱。

不同性别平衡易位携带者 PGT 相关遗传学分析

何萍
柳州市妇幼保健院柳东分院

目的 探讨不同性别平衡易位携带者植入前遗传学检测后染色体组构成情况及不同亲本来源对子代染色体形成的影响。
方法 选取自 2017 年 1 月起来在柳州市妇幼保健院行外周血染色体检查的不孕不育夫妇进行核型分析，筛选出平衡易位携带者，并对平衡易位携带者夫妇实施辅助生殖技术，对囊胚期胚胎采用高通量测序技术进行胚胎植入前遗传学检测，对不同性别的染色体平衡易位携带者囊胚期胚胎染色体组类型和构成情况进行分析比较。
结果 通过染色体核型分析，共筛选出 113 对双方之一为染色体平衡易位携带者夫妇，女性携带者 42 例，男性携带者 71 例。应用高通量测序行染色体结构重排的植入前基因测试（PGT-SR）检测，共检测 738 个囊胚期胚胎，获得可移植胚胎 166 个，其中来自男性携带者的 124 个，来自女性携带者的 42 个，男性相互平衡携带者获得可移植胚胎率、单纯不平衡胚胎率、散发性异常胚胎率、复杂性异常胚胎率分别为 27.3%、19.7%、41.8%、38.5%；女性相互平衡携带者获得可移植胚胎率、单纯不平衡胚胎率、散发性异常胚胎率、复杂性异常胚胎率分别为 15.2%、25.2%、33.2%、41.6%。不同亲本来源的可移植胚胎率有显著性差异（父源 27.3%，母源 15.2%，c^2=14.152，P=0.000，P 值<0.05），单纯不平衡胚胎率差异不明显（父源 19.7%，母源 25.2%，c^2=2.378，P=0.123，P 值>0.05），不同亲本来源的散发性异常胚胎率有显著性差异（父源 41.8%，母源 33.2%，c^2=4.231，P=0.040，P 值<0.05），不同亲本来源的复杂性异常胚胎率有显著性差异（父源 38.5%，母源 41.6%，c^2=0.546，P=0.460，P 值>0.05）。
结论 女性相互平衡易位携带者获得可移植胚胎率和散发性异常胚胎率显著低于男性携带者，单纯不平衡胚胎率及复杂性异常胚胎率均高于男性携带者。

IRF6 c.742G>T(p.G248C)变异在一个 van der Woude 综合征家系中致病性分析

朱湘玉 曹培暄 李洁
南京大学医学院附属鼓楼医院

目的 对一个 van der Woude 综合征家系进行进行致病基因分析，明确 *IRF6* c.742G>T(p.G248C)变异在该家系中与疾病表型的相关性。

方法 应用全外显子测序对先证者及其父母进行变异筛选，发现 IRF6 c.742G>T(p.G248C)变异位点后对家系中 8 名相关成员（包括先证者一家三口）一代测序验证及基因型表型分析。
结果 先证者及一名党兄表现为下唇凹，父亲表现为下唇凹伴腭裂，此三名患者均携带 *IRF6* c.742G>T(p.G248C)杂合变异。该变异为错义突变，位于重要的蛋白质功能结构区域(Interferon regulatory factor DNA-binding domain)，在正常参考人群基因数据库中未见报道，多种计算机辅助分析预测这个变异影响蛋白质结构/功能的可能性较大。依据 ACMG(The American College of Medical Genetics and Genomics, 美国医学遗传学与基因组学学会)遗传变异分类标准与指南这个变异为意义不明确变异(ACMG: PM1, PM2, PP3)。其余 5 名无表型者均未携带该变异。IRF6 变异相关的 van der Woude 综合征与该家系中患者特异性表型高度相关，因此可将 *IRF6*c.742G>T(p.G248C)杂合变异升级为致病性变异。
结论 结合家系多名成员的基因型表型分析，明确了 IRF6 c.742G>T(p.G248C)杂合变异为该家系的致病变异。

Assessment of the effects on unaffected pregnant women and their pregnancy outcomes during the COVID-19 pandemic in Shunyi, Beijing

Chongyi Hao[1] Feng Jin[2] Chanjuan Hao[1] Xiaofen Zhang[2] Limin Xie[2] Yawei Zhang[1] Xuanshi Liu[1] Xin Ni[1] Wei Li[1]

1. Bei jing Key Laboratory for Genetics of Birth Defects, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China,100045
2.Shunyi Women’s and Children’s Hospital of Beijing Children’s Hospital

Abstract
Objective: COVID-19 has adverse effects on pregnant women and newborns, but there were little researches on the associations between unaffected pregnant women and their pregnancy outcomes during the COVID-19 pandemic. Therefore, we aimed to evaluate the impact of the COVID-19 pandemic on maternal and neonatal outcomes of uninfected pregnant women and related risk factors.
Methods: We retrospectively analyzed the complications diagnosed during pregnancy and at labor on 1,604 pregnant women (including 802 cases in the pandemic group [defined as: delivery time between April-September 2020] and 802 cases in the pre-pandemic group [defined as: delivery time between April-September 2019]) in China Longitudinal Environmental, Genetic, and Economic Cohort (CHALLENGE), and evaluated the health-related behaviours, dietary patterns, depression and other related factors of 311 pregnant with adverse pregnancy outcomes. The impact of the COVID-19 pandemic on maternal and infant pregnancy outcomes and related factors were assessed by using the Chi-square test or Mann-Whitney U. We addditionly appliled a multivariate binary logistic regression model to correct the related confounding factors.
Results: Compared with the pre-pandemic group, the proportion of anemia and vaginitis increased during pregnancy in the pandemic group (OR=1.530, 95%CI=1.246-1.879, P<0.001; OR=3.187, 95%CI=1.868-5.438, P<0.001). At labor, we found that the amount of postpartum hemorrhage and shoulder dystocia increased in the pandemic group (628.57 ml vs 583.14 ml, P=0.008; OR=5.007, 95% CI=2.054-12.206, P<0.001). Moreover, we assessed the adverse pregnancy outcomes between two groups and the pandemic group had higher risk (OR=1.297, 95%CI=1.008-1.668, P=0.043), especially the rate of preterm birth increased significantly (OR=1.994, 95%CI=1.198-3.321, P=0.008). Additionally, we found that the women in the pandemic group with adverse pregnancy outcomes had increased anemia and vaginal candidiasis rate (P<0.05).
Conclusion: Among pregnancy complications, the rate of anemia, vaginitis, postpartum hemorrhage, and shoulder dystocia was increased during the COVID-19 pandemic. And the risk of adverse pregnancy outcomes, especially preterm birth, was also higher. In addition, increased adverse pregnancy outcomes were associated with maternal anemia and vaginal candidiasis.

Clinical characteristics and genetic analysis in 12 pedigrees with autosomal recessive polycystic kidney disease and prenatal diagnosis

Li Wang Jingjing Li Ganye Zhao Ying Bai Xiaofan Zhu Huikun Duan Xiangdong Kong
The First Affiliated Hospital of Zhengzhou University

Background: Autosomal recessive polycystic kidney disease (ARPKD) is a rare genetic disorder caused by *PKHD1* mutation. The phenotype is characterized by collecting duct tubular dilatations and progressively developing renal cysts that result in bilateral massive renal enlargement.
Methods In this study, we collected 12 families clinically suspected of ARPKD. Whole-exome sequencing (WES), Sanger sequencing, quantitative Real-time PCR, in silico analyses and pedigree analysis were performed to analyze their genetic cause. Prenatal genetic diagnosis for the high-risk fetus was performed after genotyping.
Results Totally, 30 individuals (5 fetuses prenatally diagnosed with ARPKD, 12 couples of parents and 1 unaffected sibling) from 12 unrelated pedigrees were enrolled in this study. Five fetuses (including 2 fetuses and 3 aborted fetuses) from 5 unrelated families were prenatally diagnosed with ARPKD due to fetal ultrasonography in the second or third trimester. The gestational age (GA) at clinical diagnosis varied between 22 and 34 weeks, with the median GA at 29 weeks. The most frequent features of prenatal ultrasonography were bilateral hyperechogenic (5/5), enlarged kidneys (5/5), oligohydramnios (5/5), multiple microcysts (4/5) and poor corticomedullary differentiation (3/5) were also common features. 28 mutations in *PKHD1* gene were identified from 5 fetuses and seven couples with the patient died at the time of genetic counseling, including 13 missense mutations, 10 nonsense mutations, 3 frameshift mutations, 1 splicing substitution and 1 duplication covering 4 exomes. Nine fetuses from 7 high-risk pedigrees with ARPKD were performed by chorionic villus sampling or amniocentesis, and the results showed that 4 fetuses were normal, 2 ones only carried one mutation, and 3 ones carried two mutations. Pregnancy outcome were recorded that 6 fetuses with normal or only one heterozygous mutation continued pregnancy, while 3 fetuses with two compound heterozygous mutations were terminated. The phenotypes of 6 fetuses with normal or only one heterozygous mutation were normal at 1year follow-up.
Conclusions The findings provide new references for genotype-phenotype analyses and expands the mutational spectrum of *PKHD1* genes, which were significantly valuable for prenatal diagnosis and genetic counseling.

遗传性肢端骨质溶解症 FAM134B 基因新发突变及致病机制研究

姚艳[1] 陈琪[1] 贺春霞[1,2] 吴元明[1]
1.空军军医大学
2.西省缺血性心血管疾病重点实验室、西安医学院基础与转化医学研究所

目的 探讨 2 例常染色体隐性遗传性肢端骨质溶解症家系及散发病例的致病基因及其潜在发病机制。
方法 采集遗传病家系 1 名患者及其父母外周血进行全外显子组测序，并通过千人基因组计划 2012 数据库比对筛选候选致病基因及突变位点，应用家系共分离分析进行验证，进一步通过突变位点保守性分析、蛋白质结构及功能预测分析其致病性。在体外采用下调 Fam134b 表达的 CD14（+）和 Raw264.7 细胞诱导破骨细胞，检测破骨细胞生成、骨吸收能力及内质网应激和凋亡相关分子表达，初步探讨其分子机制。
结果 全外显子组测序及家系共分离分析表明该家系患者 FAM134B 基因发生 c.1000+1G>T 纯合剪切突变，其父母为杂合突变，该突变位点在家系其他患者及散发病例中均得到验证。该位点突变可导致 Fam134b 发生移码突变而 LIR 域消失。我们在体外细胞水平上发现 Fam134b 敲低可促进破骨细胞分化，骨吸收能力增强。分子水平分析表明 Fam134b 敲低显著促进破骨细胞生成标志物

NFATc1 的表达。分子机制研究表明敲低 Fam134b 表达后，破骨细胞中内质网应激相关分子 ATF6，自噬配体 LC3 以及凋亡因子 JNK 和 cleaved/Caspase3 蛋白表达增高。
结论 FAM134B c.1000+1G>T 位点突变为该遗传性肢端骨质溶解症家系的致病突变，推测其致病机制为 Fam134b 自噬功能缺陷可诱导 ATF6 调控的内质网应激，进而促进破骨细胞分化和凋亡，促进骨吸收，从而导致肢端骨质溶解。

Xp11.4p11.3 微缺失致胎儿生长受限一例

卜秀芬 林彭思远 胡兰萍 李红玉 周世豪 贺骏
长沙市妇幼保健院

目的 分析 1 例孕晚期生长受限胎儿的遗传学病因。
方法 利用染色体微阵列分析(Chromosomal microarray analysis, CMA)技术对胎儿进行全基因组拷贝数变异分析(Copy number variants, CNVs)。对检测到的 CNVs 应用实时荧光定量 PCR(real-time fluorescent quantitative PCR,qPCR)进行验证。
结果 CMA 结果提示为：arr[hg19]Xp11.4p11.3(41,125,677-43,880,590)x1，即胎儿为女性，且 Xp11.4p11.3 区域杂合缺失 2.76 Mb。父母 CMA 结果均正常，确认该缺失为新发变异；qPCR 结果提示缺失区域内的 *CASK* 基因杂合缺失，与 CMA 结果相符。
结论 Xp11.4p11.3 区域内 2.76 Mb 的杂合缺失是胎儿生长受限的原因。CMA 技术可为作为产前诊断排除致病性 CNVs 的有效工具。

产前诊断 15 号环状染色体并缺失重复 1 例

宋医生
四川省妇幼保健院

目的 运用核型和 CMA 联合分析方法，明确产前诊断一例 r15 的患儿，分析了表型和遗传学病因的关系，为孕妇的优生选择提供了可靠临床参考。
方法 1.染色体核型检查和微阵列分析
2.针对性彩超检查
检测结果 胎儿染色体核型为，46，**，r(15)，为一个着丝粒的小环。样本 15q26.2q26.3 约 5.26Mb 的缺失，为致病性拷贝数变异。该缺失在 DECIPHER 和 ClinVar 中查询到大量致病性报道，该缺失包含 15 个 OMIM 基因，ClinGen 数据库查询到 IGF1R 基因存在单倍体剂量不足效应。
结论 本病例宫内生长发育迟缓与 15q26.3 上 IGF1R 基因缺失所致的单倍功能不全有关，我们的病例经核型分析确定为 r15,但不能确定是否存在基因缺失重复，联合 CMA 技术则可以准确鉴定缺失重复基因,明确异常片段的长度及确切的断裂点，我们联合核型分析和 CMA 技术定位了患儿染色体断裂重接位点,核型图给与了直观的证据，芯片检测准确检测出关键基因,结合既往病例资料为临床咨询优生咨询提供了准确的诊断依据。

An intellectual disability-associated compound heterozygous mutation in DPH1 identified by trio-WES analysis

Penglong Chen Jiao Liu Xiaofang Lan Bixia Qian
Lishui Maternity and Child Health Care Hospital

Background Intellectual disability (ID), which is characterized by significant limitations in both intellectual functioning and adaptive behavior, is closely relevant with genetic factors. Based on

previous researches, diphthamide biosynthesis 1 (DPH1) has been identified as the disease-causing gene of ID.
Methods A consanguineous family with two adult siblings both showing ID, short stature, craniofacial, and camptodactyly. The germ line pathogenic variants were identified by whole exome sequencing (WES), and subsequent candidate variants were verified by Sanger sequencing.
Results Two novel compound heterozygous missense variants (p.D236E; p.R349H) of DPH1 were identified in both two adult siblings of the trio by WES, and the former variants was maternal inherited and the other was paternal inherited.
Conclusions DPH1 has been known as one of the pathogenic genes for ID, here we reported two novel compound heterozygous mutation in DPH1 by trio-WES analysis for further clinical screen and diagnosis.

105 例胎儿先天性心脏病产前诊断及妊娠结局分析

蓝小芳 刘姣 张向东 陈鹏龙 胡辉
丽水市妇幼保健院

目的 探讨胎儿先天性心脏病遗传病因学诊断中 SNP array 的应用价值。
方法 对 105 例产前超声诊断为 CHD 的胎儿，根据胎儿超声检查情况分为单纯心脏结构异常组和合并心外结构异常组。对胎儿进行染色体核型分析及 SNP array 检测，对妊娠结局、出生后的生长发育情况进行回顾性分析。
结果 染色体核型异常 16 例。SNP array 明确了 6 例核型异常者染色体精确位点和性质。对核型正常的 89 例 CHD 胎儿，SNP array 额外检测出 9 例为致病性 CNVs，其中 7 例为已知的微缺失 / 微重复综合征。合并心外结构异常组染色体核型异常检出率明显高于单纯心脏结构异常组，致病性 CNV 两组无统计学差异。单纯心脏结构异常组分娩率高于合并心外结构异常组。9 例临床意义不明，5 例良性，继续妊娠 64 例，38 例终止妊娠，3 例失访。所有继续妊娠胎儿出生时外观正常，在 1 周岁时评估，6 例存在不同程度的体格或发育落后，其中 1 例含致病性 CNV。
结论 CHD 合并心外结构异常时遗传学异常的概率增大，临床上要重视 CMA 临床意义不明的病例，除父母验证之外，需加强对妊娠结局的随访，有必要开展进一步的遗传学检测。

69 例室间隔缺损胎儿遗传学检测结果及预后情况

胡辉 刘姣 张向东 蓝小芳
丽水市妇幼保健院

目的 探讨室间隔缺损（VSD）胎儿的遗传学病因及预后情况。
方法 对产前超声诊断为 VSD 的 69 例胎儿，分为单纯型 VSD 组和非单纯型 VSD 组。对所有胎儿开展染色体核型及微阵列分析，通过基因功能富集分析筛选先天性心脏病（CHD）候选基因，并观察所有胎儿的妊娠结局及出生后的体格、心理发育及 VSD 自然闭合情况。
结果 69 例 VSD 胎儿中共检出染色体异常 10 例。在核型检测正常的 VSD 胎儿中，额外检测出 CNVs 11 例：5 例为致病性 CNV；4 例 VOUS、2 例良性 CNV。共筛选出 7 个 CHD 的潜在候选基因。核型异常及各类 CNV 检出率，两组比较均无统计学差异。非单纯型 VSD 组引产率明显高于单纯型 VSD 组。单纯型 VSD 组自然闭合率明显高于非单纯型 VSD 组。VSD 胎儿出生后随访至 1 周岁，仅 3 例存在体格发育落后、2 例智力发育落后，两组比较无统计学差异。
结论 CMA 技术可提高胎儿 VSD 的遗传学病因检出率，有利于 CHD 候选基因的初步筛选，有助于阐明 VSD 的遗传学病因。单纯型 VSD 自然闭合率高。VSD 胎儿出生后体格发育落后和智力低下发生率低。

应用全外显子测序技术对一个 Waardenburg 综合征Ⅱa 型家系进行基因分析及产前诊断

单群达 雷永良 刘姣 陈鹏龙 罗霞 靳春雷
丽水市妇幼保健院

目的 本研究旨在对一例 Waardenburg 综合征患者的临床症状和致病基因的分析，为患者胎儿产前诊断提供依据。
方法 抽取患者的外周血，应用全外显子测序技术进行检测。取先证者羊水标本、家系成员外周血标本，对可疑基因突变进行 Sanger 测序验证。
结果 确定 MITF 基因在 chr3:69951884-69951884 发生突变，该突变位于 3 号染色体 exon6 外显子：c.632T>C，该突变为 nonsynonymous SNV 突变，导致氨基酸改变 p.L211P。Sanger 测序验证其家系，先证者父亲和先证者的胎儿为野生型，先证者母亲与弟弟为杂合型突变。
结论 全外显子测序技术可以高效准确地对 WS 患者进行基因分析及产前诊断。

产前诊断 45,X/46,X,r(X)(p21.1q21.1)嵌合型 Turner 综合征一例

邹多兵 牧启田 石松秋 施瑜波 丁慧青
宁波市第一医院

对孕妇外周血行无创产前检测（NIPT）提示性染色体非整倍体检测区域及精度范围内性染色体数目偏少的一例胎儿进行产前诊断。采用羊膜腔穿刺术，通过对胎儿羊水细胞进行羊水染色体核型分析及染色体微阵列分析(CMA)，确诊了 1 例胎儿核型为 45,X[22]/46,X,r(X)(p21.1q21.1)[8]的嵌合型 Turner 综合征(Turner syndrome)。提示多种方法联合的检测及分析可提高罕见嵌合型 Turner 综合征的检出率，为遗传咨询和产前诊断提供依据。

HBG1-HBG2（AγGγ） 缺失合并 HBB:c.126_129delCTTT 突变产前诊断案例家系分析

罗世强[1] 陈杏园[2] 唐宁[1] 袁德建[1] 钟青燕[1] 严提珍[1]
1.柳州市妇幼保健院
2.广西区人民医院

目的 研究 *HBG1-HBG2* 缺失产前诊断案例家系，并对家系成员中 *HBB*:c.126_129delCTTT 合并 *HBG1-HBG2* deletion 共同遗传基因型的临床血液学表型分析。
方法 家系成员外周血进行血细胞分析及毛细管电泳血红蛋白分析，产前诊断采取羊水样本，同时采用缺口 PCR（Gap-PCR）、反向点杂交法（RDB）检测 α 和 β-globin 基因突变，同时采用 MLPA 技术（Multiplex ligation-dependent probe amplification）对 β 基因簇拷贝数变异进行分析。
结果 *HBG1-HBG2* 基因缺失被确定，*HBG1-HBG2* 表现为血常规参数正常，Hb A2 及 Hb F 含量可表现为正常，也可表现为 Hb A2 降低和 Hb F 含量增高，*HBB*:c.126_129delCTTT 合并 *HBG1-HBG2* deletion 共同遗传均表现为小细胞低色素性贫血。
结论 明确 *HBG1-HBG2* 缺失变异体，及其合并 *HBB*:c.126_129delCTTT 共同遗传对 β-globin 基因表达和对临床表型的影响数据，这有助于指导临床诊断、人群筛查和遗传咨询。

一例 6q 三体嵌合胎儿的产前诊断

张艳萍 周玉侠 高璐 王菊 古晋
山东省妇幼保健院

目的 通过 1 例 6q 三体嵌合胎儿的产前诊断案例探讨产前染色体嵌合的适宜诊断策略。
方法 收集因超声显示胎儿心脏室间隔缺损伴单脐动脉就诊于山东省妇幼保健院产前诊断中心的孕妇 1 例。该孕妇因中孕期血清学筛查提示 21 三体高危，孕 17^{+2} 周于外院行无创产前检测。孕 25^{+5} 因超声异常到我院接受羊膜腔穿刺及胎儿染色体核型分析与染色体微阵列(Chromosome Microarray,CMA)检测，之后补充未培养羊水细胞 6pter/6qter 定制探针荧光原位杂交（FISH）检测,以及引产胎儿胎盘和皮肤组织的 CMA 检测。
结果 外院无创检测提示胎儿 21 三体综合征、18 三体综合征及 13 三体综合征均为低风险。我院羊水细胞核型计数 82 个细胞，核型分析 5 个，结果：47,XN,+del(6)(p21.1) [24]/46,XN[58]。两次直接羊水细胞染色体微阵列检测均未发现异常，但传代培养的羊水细胞 CMA 检测提示 6q 三体嵌合。直接羊水细胞 FISH 检测计数 100 个细胞，89 个为正常二倍体，6 个为 6q 三体，FISH 结果判读无异常。引产胎儿胎盘和皮肤组织的 CMA 检测均未发现异常。
结论 结合胎儿 B 超、核型分析和分子遗传检测结果，判定胎儿可能为 6q 三体极低比例嵌合胎儿。

一例罕见核型的 Emanuel 综合征胎儿的遗传诊断及分析

张艳萍 俞冬熠 刘娜 高璐
山东省妇幼保健院

目的 明确一例罕见核型 Emanuel 综合征胎儿的遗传诊断，并探讨其形成机制。
方法 孕妇 37 岁，因 NIPT 产前筛查提示[Hg19]11q23.3q25(116.51-132.86Mb)x3 进行羊膜腔穿刺，行胎儿染色体 G 显带和染色体微阵列技术（CMA）检测。
结果 胎儿染色体核型结果：47,XN,t(11;22)(q23;q11.2),+der(22)t(11;22),
CMA 检测结果：22q11.1q11.21(116,888,899-20,116,230)x3, 11q23.3q25(116,683,754-134,937,416)x3，提示胎儿为 Emanuel 综合征患儿。
结论 联合应用染色体 G 显带和 CMA 技术对一例 NIPT 产前筛查提示 11 号染色体增多的 Emanuel 综合征胎儿进行了明确诊断，为后续遗传咨询提供了依据。

结节性硬化并巨细胞病毒宫内感染一例

沈雁文[1] 王爱春[2] 姚致雅[3] 吴冬[4]
1.解放军总医院第一医学中心
2.北京市朝阳区妇幼保健院
3.福建医科大学附属省立医院妇产科
4.福建国人民解放军联勤保障部队第九〇〇医院

女，30 岁，G1P0，孕早期有皮疹及低热，均自愈；孕早期产检正常；孕 23-25 周胎儿彩超出现心腔内占位，考虑心脏横纹肌瘤。胎儿心脏病理组织确定心脏多发横纹肌瘤，父母外周血及胎儿组织三人 200×全外显子测序提示胎儿存在 TSC2 新发变异，外周血及精子进一步行深度测序提示无症状父亲为低比例体细胞及生殖腺嵌合体。同时其母外周血巨细胞病毒抗体 IgG 超过检测上限，故对胎儿心脏及脑组织进行检测，发现脑组织病毒包涵体存在，心脏及脑组织病毒 IE1 阳性，证实合并先天性巨细胞病毒宫内感染。胎儿磁共振对早期神经系统损害存在一定敏感性，但特异性不足。结节性硬化散发病例中嵌合体较常见，且可能存在感染等其他因素导致的二次打击，使神经系统出现严重病理损害。

Clinical experience of choosing prenatal diagnostic approach for positive noninvasive prenatal screening results in Southwest China

Xiaosha Jing Hongqian Liu Qian Zhu
West China Second University Hospital, Sichuan University

Objective: To evaluate prenatal diagnostic methods following different positive noninvasive prenatal screening (NIPS) results.
Method: A retrospective cohort study of NIPS-positive women who underwent amniocentesis between May 2015 and June 2019. Based on NIPS results, 904 singletons and 22 twin pairs were divided into three groups: the main target disease (N=309), sex chromosome abnormality (SCA; N=413), and other chromosomal abnormalities (N=204). Diagnostic methods and results were reviewed, including rapid diagnosis tests (quantitative fluorescence polymerase chain reaction [QF-PCR] /fluorescence in situ hybridization [FISH]), traditional karyotype analysis, and copy number variation (CNV) detection technologies (chromosomal microarray analysis [CMA], copy number variation sequencing [CNVseq]).
Results: In the main target disease group, karyotype analysis and CNV detection methods identified 226 aneuploidies, 6 structural abnormalities, and 8 CNVs including 1 pathogenic CNV (<5 Mb); detection rates were 79.81% (174/218) and 71.43% (65/91), respectively. Among 280 cases with simultaneous rapid test results, 214 (76.43%) were confirmed as positive by QF-PCR, including aneuploidies (n=207; sensitivity=100%), structural abnormalities (n=5), and CNVs (n=2), with no false positive results. No significant difference was noted in the detection rate between each pair of diagnostic methods. In the SCA group, 124 (30.02%) cases were confirmed to have sex chromosomal abnormalities, including 116 aneuploidies, 1 structural abnormality, and 7 CNVs. Of these, 16.13% (20/124) cases were related to the sex chromosome mosaic, while inconsistent results between karyotype and FISH were noted in three cases. Twenty cases of autosome CNVs were observed. Specifically, the abnormal detection rates were 27.11% (45/166) by karyotype analysis and 38.46% (95/247) by CNV testing technologies, including 41.54% (81/195) by CMA and 26.92% (14/52) by CNVseq. The detection rate of the SCA group by karyotype analysis was lower than that by the CNV testing methods (P<0.05). Regarding the other chromosomal abnormalities group, 37/204 cases were confirmed to have chromosomal abnormalities, including 2 cases of autosome mosaic, 28 cases of CNVs (16 cases <5 Mb, 12 cases >5 Mb), and 7 cases of absence of heterozygosity. CMA and CNVseq showed no significant differences in the detection rate of the three types of abnormalities indicated by NIPS (P>0.05).
Conclusion: In the cases with a positive NIPS result for common aneuploidy (T21, T18, or T13), QF-PCR can achieve a comparable detection rate to karyotype analysisv and CNV detection methods, and CNV detection methods may reveal additional pathogenic CNVs. When NIPS shows a positive result for SCA or other abnormalities, CMA and CNVseq may have the same effect on increasing the detection rate of pathogenic or potentially pathogenic chromosomal abnormalities. If an SCA is predicted by NIPS, the addition of FISH assay should be recommended to improve the detection rate of sex chromosome mosaicism.

Identification of a novel mutation in MUT gene of a Chinese patient with Methylmalonic acidemia Case report

Siyu Dai[1,2] Hongqian Liu[1,2]
1.Medical Genetics Department/Prenatal Diagnostic Center, West China Second University Hospital, Sichuan University
2.Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, Sichuan University

Background Methylmalonic acidemia is an autosomal recessive metabolic disorder mainly caused by mutations in the methylmalonyl coenzyme A mutase (MCM) gene (*MUT*) and leads to

the reduced activity of MCM. This study aimed to investigate whether a novel missense *MUT* mutation in a Chinese patient has pathogenic significance.
Methods A Chinese patient was identified with a novel mutation in the *MUT* gene: c.554C>T. The novel missense mutation was assessed by bioinformatic analysis. Plasmids carrying the wild-type and mutated *MUT* cDNA were constructed and transfected into HEK 293 cells for analyses. The expression level of MCM protein was determined by Western Blot. The mRNA expression level of MCM was analyzed by quantitative real-time PCR(qPCR).
Results A 3-year-old girl presented at the hospital for the first time at the age of 2 months and 11 days; the main complaints were poor feeding and a reduced level of consciousness. Following a series of relevant examinations, the patient was diagnosed with carnitine deficiency secondary to methylmalonic acidemia.Whole-exome sequencing (WES) was performed on the proband and identified two compound heterozygous mutations: c.554C>T and c.729-730insTT. Bioinformatics analysis predicted that the novel c.554C>T missense mutation will be damaging and that the novel c.554C>T missense mutation will cause structural abnormalities in the MCM protein. Next, we confirmed that the protein level of MCM and the mRNA expression levels of MCM were significantly reduced in the proband (P<0.05).
Conclusions In this study, we identified a novel c.554C>T mutation in the *MUT* gene in a patient that was predicted to be pathogenic. Our findings provide us with a greater understanding of the effects of MUT variants and will facilitate the diagnosis and treatment of patients with MMA.

一例脊髓延髓性肌萎缩症近亲家系分析及产前诊断

李花
湖南省妇幼保健院

目的 对一例脊髓延髓性肌萎缩症（SBMA）家系进行致病基因分析，明确其致病突变类型，为家系遗传咨询和产前诊断提供依据。
方法 应用 PCR+毛细血管电泳对先证者 *AR* 基因 1 号外显子 CAG 三核苷酸重复次数进行检测，明确重复次数后进行家系分析，并对家系中 16 周胎儿抽取羊水进行产前诊断。
结果 先证者基因型为（CAG）$_{45}$/（CAG）$_{45}$ 纯合突变孕妇，致病等位基因分别遗传自近亲婚配的父母，胎儿为女胎，基因型为（CAG）$_{20}$/（CAG）$_{46}$，系突变携带者。
结论 *AR* 基因 1 号外显子（CAG）重复数扩增是该家系的致病原因。

59 个骨骼发育异常胎儿的分子遗传学研究

邬玲仟[1,2] 张丽[1,2]
1.中南大学生命科学学院医学遗传学研究中心
2.医学遗传学湖南省重点实验室

背景 骨骼发育不良（SDs）是一类常见的出生缺陷，由于超声所提供的信息有限，难以对其进行精确诊断。全外显子测序（WES）在胎儿产前诊断中的应用值得进一步去证实和评价。
目的 评估 WES 在胎儿产前诊断中的应用价值；对检出的部分可疑变异进行功能研究，明确其致病性。
方法 收集超声检测 SDs 胎儿行单独或胎儿+父母一家三口 WES，通过基因型-临床表型-超声表型分析，筛选分析潜在变异；利用 minigene 技术构建野生型及突变型质粒，转染 HEK293T 细胞，对剪接位点变异进行研究；采用实时荧光定量 PCR 技术分析转录水平的改变，通过蛋白质免疫印迹研究突变对蛋白表达的影响，通过双荧光素酶分析突变对蛋白酶活性的影响。
结果 共收集了 59 个超声提示 SDs 的产前胎儿家系。1、为 36 个胎儿明确了遗传学病因，诊断率为 61.02%（36/59）；2、鉴定了 15 个不同基因的 46 个可疑致病变异，其中 17 个（36.96%, 17/46）变异为首次报道的新突变；3、证实了 *COL1A1* 基因 c.1202-1G>A 及 *IFT122* 基因 c.1642-

1G>C 两个新的剪接位点突变的致病性；4、突变型 *ARSE* 转录水平及蛋白表达量显著降低，突变型 ARSE 蛋白芳基硫酸酯酶活性完全丧失。
结论 我们的结果表明 WES 可以为 SDs 胎儿的基因型和表型之间的关系提供新的证据，并拓宽检测基因的突变谱，这对产前诊断和遗传咨询具有重要意义。

IGF-1 Reduced against PBDE-209-Induced Neurodevelopmental Toxicity In Vivo and In Vitro

Zhihua Li
The Third Affiliated Hospital of Guangzhou Medical University

Objective This study investigated Neurodevelopmental Toxicity of PBDE-209 and the protective effects of insulin-like growth factor-1 (IGF-1)
Methods Pregnant Sprague-Dawley rats were treated with PBDE-209 and IGF-1 and the offspring were subjected to the Morris Water Maze test. Hippocampal neurons were cultured with PBDE-209 and IGF-1 or PI3K inhibitor or MEK inhibitor for cell viability, apoptosis, immunofluorescence, and Western blot assays.
Results Prenatal PBDE-209 exposure impaired the learning and memory ability of rats by delaying the mean latency to the platform compared, whereas prenatal treatment with IGF-1 treatment improved the learning and memory ability. In vitro, treatment of primary cultured hippocampal neural cells (H-NSCs) with PBDE-209 reduced cell proliferation and differentiation, but induced apoptosis. In contrast, IGF-1 treatment antagonized the cytotoxic effects of PBDE-209 in H-NSCs in vitro. At the gene level, IGF-1 inhibition of PBDE-209-induced cell cytotoxicity was through activation of the PI3K/AKT and MEK/ERK signaling pathways in vitro because the effect of IGF-1 was blocked by the AKT inhibitor LY294002 and the ERK1/2 inhibitor PD98059.
Conclusion Prenatal PBDE-209 exposure impaired the learning and memory ability of rats, whereas IGF-1 treatment was able to inhibit the neurodevelopmental toxicity of PBDE-209 by activation of the PI3K/AKT, ERK1/2 cell pathway.

Genetic testing and pregnancy outcomes of fetuses with congenital anomalies of the kidney and urinary tract

Zhihua Li
The Third Affiliated Hospital of Guangzhou Medical University

Objective To explore the genetic basis and pregnancy outcomes of fetal urinary system anomalies.
Methods We analyzed the ultrasonographic features, prenatal diagnosis results, and pregnancy outcomes of 1197 fetuses with urinary system anomalies identified using prenatal ultrasonography.
Results The main ultrasonographic features of CAKUTs were hydronephrosis, multicystic dysplastic kidney, renal agenesis, and duplex kidney. Of 413 fetuses that underwent prenatal genetic tests, 80 (19.37%, 80/413) had clinically significant abnormal results, including 27 fetuses with chromosome abnormalities and 40 with pathogenic copy number variations (CNVs)/variations of uncertain significance (VOUSs). Chromosome 22q11.2 deletion syndrome is probably the most common pathogenic copy number variation in CAKUT(2.11%, 8/380). Of the 26 fetuses that underwent whole exome sequencing (WES), 13 (50.00%, 13/26) had pathogenic/likely pathogenic /VOUSs results. The incidence of genetic abnormalities was significantly lower for isolated CAKUTs (11.36%, 36/317) than for CAKUTs with additional anomalies (45.83%, 44/96; $p < 0.05$). Among all follow-up cases, there were 755 live births, 331 cases of termination of pregnancy, 10 cases of in utero deaths, and 3 miscarriages; the remaining 98 cases had unknown or missed pregnancy outcomes. The operation rate among live-born children with CAKUT was 6.75% (51/755). The anteroposterior diameter (APD) of the renal pelvis

in the third trimesters was used to predict the necessity of postnatal surgery. When the APD cutoff was 17.5 mm, the predicted sensitivity and specificity were 63.2% and 94.7%, respectively.
Conclusions Fetuses with non-isolated urinary system anomalies are more likely to have genetic abnormalities (11.36% vs 45.83%); 10.53% of the cases had pathogenic/likely pathogenic CNVs. WES can significantly improve the genetic detection rate of CAKUT fetuses with unknown causes in prenatal diagnosis. Fetuses with isolated urinary abnormalities have a good prognosis after birth. The probability of poor prognosis in isolated fetal CAKUT without genetic abnormality was 2.56%. A third-trimester APD ≥ 17.5 mm predicted the necessity of postnatal surgery.

Genetic Etiology and Pregnancy Outcome of Non-immune Fetal Edema Syndrome

Zhihua Li
The Third Affiliated Hospital of Guangzhou Medical University

Objective To investigate the genetic causes and pregnancy outcome of nonimmune hydrops fetalis(NIHF).
Methods Retrospective analysis was performed on the cases of nonimmune hydrops fetalis diagnosed by ultrasound in our hospital from January 2014 to July 2020.Prenatal diagnosis was performed by chromosomal karyotype analysis/CMA/WES, and pregnancy outcome were analyzed.
Result 34 cases are Hb Bart's Fetal Hydrops Syndrome，103 cases of isolated NIHF,45 cases(43.68%，45/103)have clinically significant abnormal results: among which 30 cases had chromosome number and 9 cases had pathogenic/possibly pathogenic copy number variation，11 cases were performed for WES, suggesting pathogenic/suspected pathogenic/Variation Uncertain Significance in 6 cases(54.54%,6/11).Among the 13 cases of twin and multiple pregnancy NIHF, 5 cases had clinically significant abnormal results: all were aneuploidy. There was no statistical difference in pathogenicity between isolated NIHF and non-isolated NIHF (36.59% vs 48.39%,p>0.05). 19 cases of single fetus chose to continue the pregnancy, except 8 cases died in utero, the rest were all live births. Among which 6 cases （54.54%，6/11）were premature，4 cases （36.36%，4/11）received post-birth surgical intervention，of which 3 cases were successful and 1 case died after operation. Among the 6 cases without surgical intervention，1 case had growth retardation and the rest had normal growth and development.
Conclusion Aneuploidy abnormality, CNV abnormality and point mutation is the main genetic cause of NIHF, CMA should be used as a first-line detection method of NIHF，and WES is a valuable tool for the diagnosis of NIHF. The probability of poor prognosis for NIHF in a single pregnancy without genetic abnormalities was 42%.

Clinical evaluation of non-invasive prenatal screening for the detection of fetal genome-wide copy number variants

Fengying Lu Bin Zhang Bin Yu
Changzhou Maternal and Child Health Care Hospital affiliated with Nanjing Medical University

Objective This study explores and discusses the possible factors affecting the positive predictive value (PPV) of non-invasive prenatal screening (NIPS) for the detection of fetal copy number variants (CNVs) in pregnant women.
Methods NIPS was performed for 50972 pregnant women and 212 cases were suspected as fetal CNVs. Post additional genetic counseling for these women, 96 underwent invasive prenatal diagnosis (amniocentesis), following which they received chromosomal microarray analysis (CMA). We analyzed the PPV of NIPS for the detection of fetal CNVs and the possible interference factors that could affect the PPV.

Results Among the 96 pregnant women that received prenatal diagnosis by CMA, 42 cases were confirmed to be true positive for fetal CNVs with a PPV of 43.8%. There was no significant difference between the women categorized into different groups while undergoing NIPS. Depending on the sizes of the CNVs, the PPVs were 53.8% for CNVs< 3 Mb, 44.8% for CNVs falling within 3-5 Mb, 42.9% for the CNVs falling within 5-10 Mb, and 23.8% for CNVs> 10 Mb. The PPV of chromosome group C (9. 5%), based on the chromosomal locations of CNVs, was lower than that of the other groups (42 .9%-66.7%) (p=0.021). However, there were no significant differences in the CNV characteristics, fetal fractions, unique reads, and the Z-scores between the groups.
Conclusion NIPS with a low-coverage sequencing depth can contribute to detection of fetal CNVs with the PPV of 43.8%. Chromosomal locations of CNVs may be the main factor tha influences its effect. This study can contribute to an increased accuracy in genetic counseling and in predicting NIPS results that are positive for fetal CNVs.

NIPT 与 NIPT-plus 在产前诊断中的临床应用比较

令狐丹丹
运城市妇幼保健院

目的 研究对比高通量基因测序产前筛查 (NIPT) 与 NIPT-plus 在产前诊断中的临床应用价值。
方法 将 2017 年 2 月-2019 年 12 月于该院产前诊断中心遗传咨询门诊接受无创产前基因检查的 800 例产妇纳入研究。 按照随机数字表法分成 A 组与 B 组, 每组各 400 例。 A 组予以 NIPT-plus 产前检查, B 组予以 NIPT 产前检查。 同时, 对 NIPT-plus、 NIPT 筛查阳性的产妇 进行羊膜腔穿刺和羊水染色体核型分析。 对 NIPT-plus、 NIPT 筛查阴性的产妇进行出生后随访。 比较不同产前诊断方式的染色 体非整倍体异常检出情况以及诊断准确率。 以受试者工作曲线 (ROC) 分析 NIPT 与 NIPT-plus 诊断染色体非整倍体的能效。
结 果 A 组 21-三体、 18-三体、 性染色体非整倍体检出例数分别为 5 例、 2 例、 4 例, 染色体非整倍体异常总检出率为 2 鄹 75% , 显 著高于 B 组的 0 鄹 75% 。 以核型检测结果以及随访后出生为金标准, NIPT-plus 的染色体非整倍体异常诊断准确率为 64 鄹 71% (11 / 17)、 漏诊率为 35 鄹 29% (6 / 17), 其中 5 例 21 -三体的诊断准确率为 100 鄹 00% (5 / 5), 3 例 18 -三体的诊断准确率为 66 鄹 67% (2 / 3), 9 例性染色体非整倍体的诊断准确率为 44 鄹 44% (4 / 9)。 而 NIPT 的染色体非整倍体异常诊断准确率为 17 鄹 65% (3 / 17)、 漏诊率为 82 鄹 35% (14 / 17), 8 例 21-三体的诊断准确率为 40 鄹 00% (2 / 5), 3 例 18-三体的诊断准确率为 0 鄹 00% (0 / 3), 9 例性染色体非整倍体的诊断准确率为 11 鄹 11% (1 / 9)。 经 ROC 曲线分析发现: NIPT-plus 诊断染色体非整倍体的曲线下面 积、 灵敏度以及特异度均高于 NIPT 诊断。
结论 NIPT-plus 应用于产前诊断中的临床应用价值略高于 NIPT, 值得临床推广应 用。

A Missense Mutation of MED12 in a Chinese Family with Clinical Characterization of Related Disorders

Huiqin Xue[1] Yu Feng[1] Chenyue Zhao[2] Qiaoyin Tang[2] Jinsong Jiang[2] Guizhi Cao[1] Hongyong Lu[1] Xiayu Sun[1]
1.Children's Hospital of Shanxi, Women Health Center of Shanxi, Affiliated Hospital of Shanxi Medical University
2.Shanxi Medical University

Objective MED12 has emerged as a key player in various X‐linked behavioural disorders. The phenotypic spectrum of *MED12*-related disorders, which is still being defined, includes at a minimum the phenotypes of Opitz–Kaveggia syndrome (FG), Lujan-Fryns syndrome (LS), and Ohdo syndrome (XLOS). The aim of this study was to identify causative mutations in a pedigree and to explore the correlation between *MED12* gene variation and micrognathia phenotype.
Methods Whole exome sequencing (WES) was performed in a three-generation family, and the linically relevant findings were confirmed by conventional sequencing. Then, Perform bioinformatics analysis through quality control, variants calling and variants annotation

and pathogenicity prediction. According to the NGS positive report, for Sanger sequencing validation, genomic DNA was amplified by PCR to confirm selected mutations.
Results Here we report three fetuses from a non-consanguineous family presenting with abnormal posturing of hands, micrognathia, talipes and polyhydramnios detected by color Doppler. WES revealed a hemizygous missense variant c.887G >A (p.R296Q) in MED12 carried by two patients. The disease is X-linked recessive inheritance, based on the parents' genetic mutations, suggesting that the harm of the MED12 gene mutation in this family is related to the patient's gender and phenotype.
Conclusions The phenotype of children with MED12 gene mutation is different from that of other MED12 gene induced syndromes, suggesting that it has a specific phenotype and the possibility of embryonic death. This case expands the phenotypic spectrum related to MED12 gene mutations, and has some guiding significance for prenatal diagnosis.

Prenatal diagnosis of complete paternal uniparental isodisomy for chromosome 3: a case report

Xiufen Bu
Changsha hospital for maternal and child health care

Objective To report on prenatal diagnosis and follow up of one patient with complete paternal uniparental disomy(UPD) of chromosome 3.**Methods** Fetal cells were subjected to G-banded chromosomal analysis.DNA samples of the fetus and their parents were also analyzed with single nucleotide polymophism array (SNP array).**Results** The fetus had a normal female karyotype.SNP array analysis showed the fetus has carried complete paternal uniparental isodisomy(isoUPD) of chromosome 3.The neonate had normal physical findings at birth and develops normally after 1.5 years.**Conclusion** Paternal UPD of chromosome 3 is a very rare condition. The case we reported was the second ascertained paternal UPD(3) with no apparent disease phenotype and could provide further evidence to confirm that there was no important imprinted genes causing serious diseases on paternal chromosome 3.The findings provided a reference for the prenatal diagnosis and genetic counseling of UPD(3) in the future.

一例双胎之一消失综合征对无创产前检测影响分析

赵干业
郑州大学第一附属医院

目的 探讨双胎之一消失综合征（vanishing twin syndrome, VTS）对孕妇进行无创产前检测（non-invasive prenatal testing， NIPT）的影响。**方法** 对一例孕 8 周时发现双胎之一消亡的孕妇，分别在孕 17^{+2} 周、19^{+1} 周和 20^{+6} 周进行 3 次 NIPT 检测；对存活胎儿通过羊水穿刺获取胎儿细胞后，进行 QF-PCR、羊水核型分析和染色体拷贝数变异分析；回顾分析相关文献。 **结果** 孕 17^{+2} 周、19^{+1} 周和 20^{+6} 周时 NIPT 结果皆显示排除胎儿为男胎，但 Y 染色体的 Z 值在 17^{+2} 周和 19^{+1} 周时分别为 12.35 和 6.43，超出正常上限值 5，无法出具报告，而 20^{+6} 周时的 Z 值为 2.77，确定胎儿为女胎，同时染色体筛查报告为低风险。QF-PCR、羊水核型和拷贝数变异分析皆显示存活胎儿为正常女胎，与 20^{+6} 周时 NIPT 结果一致。**结论** 双胎之一消失综合征能够影响 NIPT 的检测，其影响至少可以持续到胎儿消亡发生 11 周以后；提高检测孕周可以消除双胎之一消失综合征对 NIPT 检测结果的影响。

扩展性无创产前检测双胎之一 22q11.2 缺失综合征假阴性原因分析

赵干业
郑州大学第一附属医院

目的 探讨一例扩展性无创产前检测（expanded non-invasive prenatal testing， NIPT-PLUS）双胎之一 22q11.2 缺失综合征假阴性的原因。**方法** 对一例 NIPT-PLUS 结果为阴性，后期因超声异常行羊水穿刺的试管双胎样本，获取胎儿细胞后行核型分析和 CNV-seq（copy number variation sequencing, 拷贝数变异测序）检测。收集并分析孕妇的临床信息及检测数据，探讨假阴性的原因。 **结果** NIPT-PLUS 的 uniMap reads 为 11.77Mb，胎儿游离 DNA 浓度为 3.05%。羊水核型结果显示一胎为 46，XY，另一胎儿为 46，XX，均正常。CNV-Seq 结果显示一胎正常，另一胎为缺失大小为 2.58Mb 的 22q11.2 缺失综合征。 **结论** 本例假阴性应该是由较低的胎儿游离 DNA 浓度、较高的 BMI、试管婴儿、双胎以及较小的缺失片断等综合因素共同作用引起；NIPT-PLUS 低风险后续超声检测不可忽视。

甲基丙二酸血症 MMACHC 基因产前诊断一例

梅婷[1] 夏艳洁[2]
1.乌鲁木齐市第一人民医院 2.郑州大学第一附属医院

摘要：目的 对生育过甲基丙二酸血症（methylmalonic acidemia,MMA）患儿的 1 个家系进行基因诊断分型,并在此基础上提供产前基因诊断。**方法** 采用 PCR 结合 Sanger 测序的方法分析先证者，申请人、申请人丈夫、申请人胎儿甲基丙二酸血症相关 MMACHC 基因(NM_015506)c.80A>G(p.Q27R)和 c.566_567insT(p.I190Y)位点的序列变异情况。**结果** 先证者 MMACHC 基因 c.80A>G(p.Q27R)和 c.566_567insT(p.I190Y)复合杂合变异，申请人 MMACHC 基因 c.80A>G(p.Q27R)杂合变异，申请人丈夫 MMACHC 基因 c.566_567insT(p.I190Y)杂合变异，申请人胎儿 MMACHC 基因 c.80A>G(p.Q27R)和 c.566_567insT(p.I190Y)复合杂合变异。**分析** 申请人胎儿为与先证者相同的 MMACHC 基因 c.80A>G(p.Q27R)和 c.566_567insT(p.I190Y)复合杂合变异导致的甲基丙二酸患者的可能性大。**结论** 利用基因检测可为甲基丙二酸血症患者提供确切的临床分型,并在此基础上提供有效的产前基因诊断。

基于低深度测序的 NIPS 在高龄孕妇胎儿 CNV 筛查中的应用研究

王志伟 王雷雷 汤欣欣 杨舒婷
连云港市妇幼保健院

目的：探讨基于低深度测序的无创 DNA 产前检测技术（NIPS）对高龄孕妇胎儿染色体拷贝数变异(CNVs) 的筛查效力及临床意义。
方法： 2017 年 1 月至 2020 年 6 月来本中心选择做 NIPS 检测的 5420 例高龄孕妇人群，通过低深度测序方法对血浆样本进行 NIPS 检测的同时，对全基因组 CNV 进行了评估。其中检测结果为胎儿 CNVs 高风险的病例进行遗传咨询后，建议其通过羊水穿刺术做染色体微阵列分析(CMA)，进行产前诊断。评估低深度测序下 NIPS 对胎儿 CNVs 的检测效能，并对妊娠结局进行随访。
结果：分析了 5420 例高龄孕妇 NIPS 结果提示 28 例存在 CNVs 变异高风险，检测阳性率为 0.52%。均建议遗传咨询，其中 22 例接受穿刺术，进行 CMA 诊断检测。诊断结果与 NIPS 一致 12 例，阳性预测值为 54.55%。其中包括致病性变异 9 例，可能致病性变异 1 例，临床意义不明的

变异 1 例。随访结果显示，引产 7 例，均属于致病性变异；自然流产 1 例，属于致病性变异；其余 4 例出生后体检未见明显异常。

讨论：基于低深度测序的 NIPS 对高龄孕妇胎儿的 CNVs 具有一定的检测效力。在 NIPS 中应用优化的检测和信息分析方法进行高龄孕妇胎儿 CNVs 的产前筛查可得到满意结果，为临床进行介入性产前诊断提供重要提示。

A complete deletion of TFAP2A is associated with nonclassical features of Branchio-Oculo-Facial Syndrome and cystic kidney in a Chinese family

Jia Che Ying Li Ling Liu Hua Zhang Shihong Cui
The Third Affiliated Hospital of Zhengzhou University

Object The whole gene deletion of *TFAP2A* was reported in only three families diagnosed with Branchio-Oculo-Facial Syndrome(BOFS) as far as we know. And none of these patients were found clinical features of renal anomalies, such as renal agenesis, cystic kidney and so on. Correlations between genotype and severity of phenotype of BOFS have not been established. The frequency of partial or whole gene TFAP2A deletion remains unknown but appears to be low. In this report, we report a Chinese family with complete deletion of TFAP2A associated with nonclassical features of BOFS and cystic kidney.

Materials and Methods The family referred to our center of prenatal diagnosis due to a clinical presentation of cystic kidney. Consent for publication of this case was obtained from the family members. They underwent a routine evaluation protocol which included clinical examinations by expert prenatal diagnostic specialist, dermatologist, gastroenterologist, urologist, ear, nose and throat (ENT) specialist, paediatrician, genetic testing. The fetus's amniotic fluid (10 mL) and the parents' peripheral blood (1 mL) were collected, and genomic DNA was extracted using a QIAamp DNA Blood mini kit (Qiagen Inc., Hilden, Germany). Copy number variants (CNVs) of the affected family members were detected using a genome-wide high-resolution SNP array on a CytoScan 750k (Affymetrix, Santa Clara, CA, USA) platform containing 200,000 SNPs and 550,000 oligonucleotide probes. The raw data were analyzed using the ChAS3.0 software (Affymetrix). Genomic DNA extracted from amniotic fluid was also subjected to whole exome sequencing (WES). The exome sequencing was performed with a minimum median coverage of 80× using Illumina Novase6000 (Illumina). The bioinformatic analysis was performed at Berry Genomics Corporation after sequencing. All procedures were performed following the manufacturers' protocols. The location of the chromosome was described based on the genome version GRCH37/hg19. CNVs were classified according to the American College of Medical Genetics (ACMG) guidelines.

Results The proposita's antenatal history was remarkable for renal anomaly on ultrasound scan done at 20 weeks of gestation, which showed cystic kidney on the right side. She was born at term (38 weeks of gestational age) without typical clinical features including branchial, ocular, and facial anomalies of BOFS. The mother has a healthy 10-year-old son with the proposita's biological father and had two miscarriages that were both detected remarkable features including renal and facial anomalies on ultrasound scan. CMA of the proposita revealed a 429kb deletion at 6p24.3(9992451_10421160) (GRCh37) resulting in a complete deletion of *TFAP2A* gene, which is located at 6p24.3(10396916_10419797(GRCh37). The mother who has a cystic kidney on the right also has a deletion at 6p24.3(10047944_10439707)(GRCh37) and the length was 392kb. Exome‐based CNVs of the proposita also detected a deletion about 260kb at 6p24.3(10159621_10419688)(GRCh37), which is consistent with the result of CMA.

Conclusions Renal anomalies have not yet been described in the BOFS resulting from the whole gene deletion of *TFAP2A*. More BOFS cases are needed to be reported and further studies are still needed to elucidate the more detailed molecular mechanisms responsible for its function in mammalian renal development, incomplete penetrance and variable expressivity. Molecular test for structural anomalies due to ultrasound scan is very important for pregnant woman, especially those with family history.

一例 20P13 重复胎儿的产前诊断并文献复习

陶莹
镇江市妇幼保健院

目的 明确 1 例 20 号染色体微重复胎儿拷贝数变异的来源与性质，分析其与表型的相关性。
方法 羊水胎儿细胞染色体微阵列分析技术（Chromosome microarray analysis,CMA）检测出一例 28 岁健康孕妇孕 22 周+2 天的胎儿染色体 20P13 处存在 3363kbp 微重复；同时使用 CMA 技术检测其父母验证来源；查阅文献资料进行遗传学分析。
结果 该胎儿 CMA 结果为 arr[GRCh37]20P13（888522-4251237）×3，判定为 VOUS，后期行 B 超胎儿系统筛查发现胎儿复杂先心伴颈后皮下软组织增厚、双侧侧脑室轻度增宽、单脐动脉等多发畸形，后孕妇于外地引产；该孕妇于丈夫查体及 CMA 结果均无异常，考虑胎儿为新发突变；查阅文献发现 20P13 区段包含 PDYN、PANK2 等可能引起胎儿或幼儿心脏、神经系统等疾病的致病基因，可能引起胎儿或幼儿不同程度的智力与生长发育迟缓。
结论 染色体 20P13 区域重复可能存在致病性风险，应引起重视。

When a vesicular placenta meets a live fetus: a case report of a twin pregnancy with a partial hydatidiform mole

Minhuan Lin[1] Yanmin Luo[1] Jinzhu Chen[2] Bing Liao[1] Zhiming He[1] Shaobin Lin[1]
1.The First Affiliated Hospital, Sun Yat-sen University
2.Quanzhou First Hospital Affiliated to Fujian Medical University

Background Hydatidiform moles are “distinctive” for the gross appearance of multiple vesicles in the placenta. The advancing development of cytogenetic technologies has uncovered novel entities of hydatidiform moles and prompted elaborate diagnoses. However, management of a vesicular placenta with a coexistent live fetus is a bigger challenge beyond hydatidiform moles.
Case presentation We report a rare case of a twin pregnancy of a partial mole coexistent with a normal fetus that resembled a singleton partial molar pregnancy. The patient conceived through double embryo transplantation and first-trimester ultrasonography displayed a single sac. Mid-trimester imaging of normal placenta parenchyma admixing with multiple vesicles and one amniotic cavity with a fetus led to suspicion of a singleton partial molar pregnancy. After confirmation of a normal diploid by amniocentesis and close surveillance, the patient delivered a healthy neonate. Preliminary microscopic examinations of the placenta failed to clarify the diagnosis until fluorescence in situ hybridization showed a majority of XXY sex chromosomes. The patient developed suspected choriocarcinoma and achieved five-month remission after chemotherapy but relapsed with suspected intermediate trophoblastic tumor.
Conclusion We reflected the ambiguous diagnosis of this case and proposed a scheme for refined diagnosis and management of the four conditions of a vesicular placenta with a fetus. We strongly recommend ancillary examinations in addition to traditional morphologic assessment, in cases with a vesicular placenta.

荧光分选、鉴定孕早期妇女宫颈分泌物中的胎儿细胞并用于无创产前诊断检测可行性的临床研究

费鸿君
国际和平妇幼保健院

目前,临床上使用的传统侵入式产前诊断具有周期长、创伤大，胎儿丢失率约为 1%的缺点。本研究通过从孕早期妇女宫颈分泌物中分离出胎儿细胞，对胎儿进行无创性产前诊断。我们首先从要求终

止妊娠的孕早期妇女宫颈分泌物中激光捕获分离胎儿细胞，计算分离效率，然后对所捕获的胎儿细胞进行形态学及免疫组织学等鉴定、分子诊断（荧光原位杂交 FISH 或全基因组测序等），所得结果与传统绒毛活检结果对比，判断两者的吻合度及使用此方法获得的胎儿细胞进行 NIPT 检测可行性。最终实现临床孕妇（包括自然受孕及辅助生殖）均可使用此方法进行无创产前诊断，使得利用此法分离胎儿细胞进行无创产前诊断的技术取代如今临床普遍使用的侵入式产前诊断，成功提早产前诊断的时间、缩短产前诊断的周期、减少侵入式产前诊断导致流产风险的问题、并且提高诊断准确度与精细度。
除此之外，已知胎儿细胞具有其最完整的遗传信息，我们可以利用此方法，进行各种致病基因明确的单基因遗传病检测。

Prenatal Diagnosis in a Fetus with X-linked Recessive Chondrodysplasia Punctata: Identification and Functional Study of a Novel Missense Mutation in ARSE

Li Zhang[1] Haoran Hu[1] Desheng Liang[1,2] Lingqian Wu[1,2] Zhuo Li[1]
1.Center for Medical Genetics & Hunan Key Laboratory of Medical Genetics, School of life sciences, Central South University
2.Hunan Jiahui Genetics Hospital

X-linked recessive chondrodysplasia punctata (CDPX1) is a rare skeletal dysplasias characterized by stippled epiphyses, brachytelephalangy, and nasomaxillary hypoplasia, which is caused by the function loss of arylsulfatase E (ARSE, also known as ARSL).Pathogenic mutations in *ARSE* were usually responsible for CDPX1 in newborns or adults, while there were few prenatal reports. In our study, a novel missense mutation (c.265A>G) in *ARSE* was identified in a fetus with short limbs by using whole exome sequencing (WES).Bioinformatic algorithms predicted that the mutation is harmful, and following RT-qPCR, western blotting and enzymatic assay were performed to further analyze the pathogenicity of variant. The results showed that the variant could lead to reduced transcription and protein expression and the loss of enzymatic activity. To sum up, the novel mutation c.265A>G in *ARSE* was considered to be the genetic cause for the affected fetus. We report a prenatal case in Chinese population with functional analysis of *ARSE*, which not only helps the family to predict recurrence risks for future pregnancies but also provides more information for understanding this rare disease. The research also shows that WES is a feasible method in prenatal diagnosis for those fetuses with CDPX1.

1 例经染色体微阵列分析技术意外检出 DMD 基因变异家系的临床意义探讨

徐燕 王彦林
中国福利会国际和平妇幼保健院

目的 探讨经染色体微阵列分析技术（Chromosomal Microarray Analysis, CMA）意外检出的 1 例携带 *DMD* 基因拷贝数变异家系的临床意义。
材料与方法 孕妇怀孕 14^{+6} 周，38 岁，G2P1，无家族遗传病史。临床因高龄经羊水穿刺行 Affymetrix CytoScan 750K 芯片检查。应用多重连接依赖探针扩增(MLPA)技术对孕妇、丈夫、儿子和当前胎儿进行 *DMD* 基因拷贝数定量检测。
结果 芯片检测结果提示胎儿羊水标本存在 arr[GRCh38]Xp21.1(31633428_32001167)X1 变异，缺失片段大小为 368Kb，涉及 *DMD* 基因部分外显子。该 CNV 区段根据 ACMG 变异指南分类为致病性变异。MLPA 检测结果显示，胎儿 *DMD* 基因 45-55 号外显子框内缺失，遗传自其父亲。孕妇及儿子均未检出 DMD 基因 1-79 号外显子拷贝数变异。追溯胎儿父亲病史，至 37 岁时无肌肉无力及萎缩相关症状，超声心动图提示左心房扩大，肌酸激酶轻微升高。

结论 CMA 可意外检出胎儿临床指征以外的遗传学病因。本例家系经 MLPA 进一步分析，确定胎儿致病性 *DMD* 基因缺失变异来源于父亲，这为进一步明确父亲的临床诊断提供重要依据，对其临床管理、预后及护理也具有重要指导意义。更重要的是，准确的分子诊断可以为该家庭再次妊娠提供准确的遗传咨询、风险评估、生育方案选择及产前基因诊断。

Research Progress on the effects of lead, arsenic, cadmium and mercury on birth defects

Yanan Sun[1,2] Fengxiang Wei[1,2]
1.Longgang District Maternity&Child Healthcare Hospital of Shenzhen City
2.Anhui Medical University

Abstract birth defects are mainly the result of the joint action of environmental factors and genetic factors, in which the pollution of heavy metals to the environment has become a problem of widespread concern. A large number of studies have shown that exposure to heavy metals in the environment during pregnancy (such as lead, cadmium, mercury, arsenic, etc.) will increase the risk of birth defects. In the case of increasingly serious environmental pollution, the author summarizes the relationship between lead, cadmium, mercury, arsenic and birth defects, which provides important theoretical basis and technical support for the prevention of birth defects.

CPLANE1 基因新变异所致 Joubert 综合征产前诊断一例

王俊霞 李娟 杜润璇 尹璐 戎立敏 田海深 高健
河北省人民医院

本文报告了一例超声提示胎儿小脑蚓部发育不良的产前诊断病例。该孕妇 27 岁，孕 20 周$^{+6}$超声发现胎儿小脑下蚓部部分分离（Dandy-Walker 变异型），上下唇不能闭合、多指（趾），初步诊断为胎儿多发畸形。羊水染色体核型及染色体微阵列分析未见异常。经过遗传咨询和深入沟通后再次行胎儿羊膜腔穿刺行全外显子组测序检测，结果提示胎儿 *CPLANE1* 基因第 19 号外显子和第 17 号外显子分别存在 c.3435G>A(p.W1145X)和 c.2941C>G(p.p981A)复合杂合突变，分别遗传自父亲和母亲，且上述突变位点均未见文献报道。孕妇及家属考虑到胎儿除有面部和肢体发育畸形外，出现神经系统异常的风险极大，最终选择引产。

产前诊断 FGFR1 基因突变所致胎儿并指/趾畸形一例

郑宗朋 高健
河北省人民医院

本文报告了一例超声提示胎儿并指/趾畸形的产前诊断病例。该孕妇 27 岁，孕 27+4 周超声发现胎儿双足发育异常，(双足呈 v 型，足指数目减少，似见并指)，左手并指可能(中指，无名指似为并指)，初步诊断为胎儿并指/趾畸形。患儿父亲表现为轻度性腺功能减退及轻微的嗅觉减退，患儿母亲无异常临床表现。羊水染色体核型及染色体微阵列分析未见异常。经过遗传咨询和深入沟通后行胎儿羊膜腔穿刺行全外显子组测序检测，同时抽取患儿父母外周血送检，结果提示胎儿 FGFR1 基因的 6 号外显子存在一个遗传自父亲的杂合变异 c.625C>T(p.209C)为错异突变;上述突变位点所致的相关临床表现尚未见文献报道，因考虑胎儿除有肢体发育畸形外，出现神经系统异常的风险极大，因此在孕 35+周选择在外孕引产。

Identification of a novel heterozygous nonsense mutation in PLA2G6 and the prenatal diagnosis in a Chinese family with infantile neuroaxonal dystrophy

Yongyi Zou Haiyan Luo Huizhen Yuan Kang Xie Yan Yang Shuhui Huang Bicheng Yang Yanqiu Liu
Medical Genetic Center; Jiangxi Provincial Key Laboratory of Birth Defect for Prevention and Control,Jiangxi Maternal and Child health Hospital

Objective We aimed to identify the underlying causative genetic factors of a Chinese family with two children diagnosed with cerebellar atrophy and developmental delay and to provide prenatal diagnosis for the family for prevention of birth defect.
Methods Retrospective clinical information and MRI review of the proband was collected. Trio-WES (Whole Exome Sequencing) was performed to explore the underlying genetic causes of the proband, while Sanger sequencing was subsequently used to validate the variants identified by Trio-WES. Forward and reverse sequencing was employeed to investigate the pathogenic mutations in *PLA2G6* responsible for Infantile neuroaxonal dystrophy 1 (INAD, OMIM#256600) for aminotic cell DNA.
Results The proband was clinically diagnosed with developmental delay and progressively exacerbated. MRI showed typical features of cerebellar atrophy and cerebellar cortex bright FLAIR signal. Trio-WES revealed two heterozygous variants in *PlA2G6* associated with INAD: a novel maternal inherited variant c.217C>T (p.Gln73*) and a previously reported paternal inherited pathogenic variant c.1894C>T (p.Arg632Trp). This novel variant identified is classified as “pathogenic” according to the latest recommendation on sequence variants by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (PVS1+PM2+PP3). These two heterozygous mutations were also detected in the elder brother of the proband affected with INAD. These two mutations identified are considered as the genetic causes responsible for INAD in this family. Prenatal diagnosis suggested compound heterozygous mutations of c.217C>T and c.1894C>T in the fetus.
Conclusion Our study has helped to elucidate the causative genetic factors of this Chinese family with INAD by the emerging Trio-WES strategy, and provided prenatal diagnosis for this family. Our finding has provided reliable evidence for the subsequent genetic counseling and reproductive options to this family. Furthermore, we have identified a novel pathogenic mutation, which broadens the mutation spectrum of *PLA2G6* and will provide clues for molecular diagnosis of INAD.

一例 45,X/46,X,psu idic(Y)(q11.2)/46,XY 产前诊断病例报道

黄宁 刘艳秋 杨必成 邹永毅 卢婉 周吉会
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

患者女，38 岁，G2P1，既往生育一健康女孩，现孕 22 周，因无创产前检测提示性染色体数目异常就诊，患者 B 超监测胎儿发育未见明显异常。经知情同意患者选择羊膜腔穿刺术行胎儿染色体核型分析、羊水荧光原位杂交(FISH)和羊水染色体微阵列分析(CMA)检测，结果提示为 45,X[12]/46,X,psu idic(Y)(q11.2).ish psu idic(Y)(q11.2)(CSPY++).array Yp11.2q11.223×2,Yq11.223q12×0[45]/46,X,ishY (CSPY+)[17]。
idic(Y)有两个着丝粒，是 Y 染色体常见的异常结构，主要原因是父亲精子中的 Y 染色体在减数分裂过程中的着丝粒异常分裂所导致。idic(Y)常常伴有不同比例 45,X 存在，患者临床表现依据不同细胞所占比例大小，可表现为特纳综合征女性，无精或少弱精男性，外生殖器模糊和性腺发育不良。此胎儿 45,X 细胞所占比例相对较少，发育为男性可能性较大，且伴有无精或严重少弱精症，这是由于 Yq11.2 处断裂引起该区域生精相关 AZF 基因缺失所导致。联合胎儿染色体核型分析，FISH 和 CMA 技术，可以提供准确的核型报告，为判断预后及遗传咨询提供可靠依据。

Identification of a novel heterozygous variant in the EVC gene in a prenatal fetus with ELLIS-VAN CREVELD SYNDROME by Trio-WES

Haiyan Luo Yongyi Zou Huizhen Yuan Kang Xie Yan Yang Shuhui Huang Bicheng Yang Yanqiu Liu
Medical Genetic Center; Jiangxi Provincial Key Laboratory of Birth Defect for Prevention and Control,Jiangxi Maternal and Child health Hospital

Objective Ellis-van Creveld syndrome caused by the *EVC* or *EVC2* mutation is an autosomal recessive skeletal dysplasia, which is characterized by short limbs and ribs, postaxial polydactyly, and dysplastic nails and teeth, and in a proportion of patients, by congenital cardiac malformations.
Methods Herein, we presented a prenatal fetal EVC syndrome case with ultrasound structural anomaly at the gestational week of 19w4d. Sequential test, including amniocentesis, chromosomal karyotyping, chromosomal microarray analysis (CMA) and Trio-WES were further performed to explore the underlying causative genetic factors, while Sanger sequencing and real-time quantitative PCR (Q-PCR) were used to validate the variants identified by Trio-WES.
Results Chromosomal karyotyping showed a normal karyotype, and CMA analysis presented a duplication 637kb at 3p21.1 region (52, 554, 279_53, 190, 827), a variant of unknown significance (VUS). Trio-WES revealed a novel heterozygous pathogenic mutation (c.130delC, p.Leu44Phefs*72) and a previously reported pathogenic heterozygous deletion from exon9 to exon11 in the *EVC* gene, both would produce an abnormal truncated protein, which were probably responsible for the disease phenotype in the affected fetus.
Conlusion Our study have helped to elucidate the pathogenesis of this fetal structural anomaly with EVC syndrome by combined routine genetic testing and Trio-WES, which provided reliable evidence for the subsequent genetic counseling and reproductive options to this family. Furthermore, we have identified a novel pathogenic mutation, which broadened the mutation spectrum of EVC and provide clues for molecular diagnosis of EVC syndrome.

联合应用多种检测技术能显著减少胎儿 16 号染色体三体嵌合的漏诊率

潘丽媛
广东省妇幼保健院

目的 通过联合应用无创产前检测（non-invasive prenatal testing ,NIPT）、染色体核型分析、染色体微阵列分析（chromosomal microarray analysis，CMA）以及荧光原位杂交技术(fluorescence in situ hybridization ,FISH)对 2 例嵌合型 16 号染色体三体胎儿进行产前诊断并分析妊娠结局，为临床诊断和遗传咨询提供依据。
方法 分别抽取孕妇外周血进行 NIPT 检测，超声引导下进行羊膜腔穿刺和脐静脉穿刺，抽取羊水和脐血进行染色体和核型分析，ＣＭＡ检测以及 FISH 检测。
结果 病例 1：NIPT 结果提示胎儿 16 号染色体数目偏多，羊水染色体核型结果为 mos 47,XN,+16[1]/46,XN[80]，羊水 CMA 以及未培养 FISH 检测结果提示 16 三体嵌合比例分别为 30%和 47%。脐血染色体核型和 CMA 以及脐血（中期）FISH 结果均未见异常，脐血（未培养）FISH 提示 16 三体嵌合比例 5%，16 单体嵌合比例 9%。胎儿 24 周二级超声表型无异常，最终孕妇选择引产，拒绝尸解。
病例 2：因唐筛高风险行羊水穿刺，外院羊水染色体结果为 mos 47,XN,+16[4]/46,XN[96]，外院羊水 CMA 提示 16 三体嵌合比例为 25%。我院复查羊水染色体结果为 mos 47,XN,+16[1]/46,XN[49]，羊水 CMA 以及未培养 FISH 检测结果提示 16 三体嵌合比例分别为 25%和 19%。超声提示胎儿永存左上腔静脉，室间隔缺损。

结论 （1）以上两个病例羊水核型嵌合比例均小于 5%，如果只行核型分析，按照指南推荐计数的克隆数或细胞数，极易漏诊，因此最好联合应用核型和 CMA 检测。（2）另外，羊水和脐血经培养后，劣势细胞株的生长可能被竞争性抑制，因此未培养的羊水或脐血 FISH 更能揭示胎儿真实的嵌合比例。（3）胎儿羊水细胞和脐血细胞分别来自不同的胚层，当胎儿存在嵌合型三体时，由于取材不同，产前诊断结果可能会不一致。因此，不同取材的嵌合比例和胎儿预后的相关性还需要更多的临床证据。同时，有病例报道产前确诊为 16 三体嵌合的胎儿在出生后无明显异常。因此在产前诊断中发现 16 三体嵌合不能“一引了之”，应通过多种检测手段充分评估后再由夫妻知情自主选择胎儿去留。

超雌综合征的产前表现和预后分析

罗艳敏 夏舒婷
中山大学附属第一医院

目的 超雌综合征是一组性染色体非整倍体疾病，其特征为比正常女性核型额外多了 1 条或以上 X 染色体，但临床表型存在较大差异。本文通过分析产前诊断中发现的超雌综合征的临床表现和预后，为其产前遗传咨询提供帮助。
方法 回顾性收集中山大学附属第一医院胎儿医学中心 2009 年 1 月至 2020 年 4 月产前诊断标本（羊水、绒毛、脐血）及 2013 年 1 月至 2020 年 4 月的流产组织标本的染色体核型检查结果，对不同类型标本 X 染色体数目增加的检出与临床表现的关系进行分析，总结超雌综合征的临床特点。
结果 共收集 1600 例流产组织标本及 16257 例产前诊断标本数据，超雌综合征的检出率分别为 0.125%（2/1600）及 0.111%（18/16257），核型检查主要为 47，XXX 或 46，XX /47，XXX 嵌合体。产前诊断指征 2 例为胎儿畸形，5 例为母亲高龄，8 例为 NIPT 高风险。12 例妊娠结局为引产，6 例早产或足月产。
结论 产前超雌综合征检出率较低，但随 NIPT 的应用，其检出率增高；产前多数无临床表现，但引产比例高，需提高对该疾病的认识。

四川地区 58113 例无创 DNA 产前检测胎儿染色体非整倍体及其妊娠结局分析

曾兰 李运星 邓艺 魏萍 邓光明 陈春 严梦珈 汪雪雁
四川省妇幼保健院

目的 探讨无创 DNA 产前检测（non-invasive prenatal testing，NIPT）在胎儿染色体非整倍体筛查中的临床应用价值及妊娠结局分析。
方法 选择 2015 年 2 月至 2020 年 3 月在四川省妇幼保健院产前诊断中心行 NIPT 的 58113 例单胎孕妇，对 NIPT 提示染色体异常高风险的 756 例作为研究对象，并将 NIPT 与羊水细胞染色体核型分析和染色体微阵列分析（chromosomal microarray analysis, CMA）的结果进行符合情况比较。对 NIPT 发现性染色体非整倍体（sex chromosomal aneuploidy，SCA）阳性孕妇的染色体核型和拒绝介入性产前诊断的妊娠结局进行回顾性分析。
结果 58113 例孕妇筛查出染色体异常高风险 756 例（1.30％），其中 665 例经羊水细胞染色体核型分析确诊胎儿染色体异常 289 例，其中阳性预测值（positive predictive value，PPV）分别为 21-三体 73.0％、18-三体 39.1％、13-三体综合征 10.3％、性染色体异常 30.4％、其他染色体异常 22.1％。173 例 NIPT 检测阳性孕妇同时做了羊水核型和 CMA 分析，发现 72 例 CMA 结果异常。NIPT 发现性染色体非整倍体 253 例，确诊胎儿 SCA 病例 64 例，其中性染色体三体 45 例（47,XXY 21 例，47,XXX 16 例，47,XYY 8 例），45,X 3 例和嵌合体 14 例，47,XX,+mar 1 例，del(X)1 例。

结论 NIPT 作为一种安全、快速的产前检测手段，是胎儿染色体非整倍体异常产前检测较为可靠方法之一，该检测方法对 21-三体综合征的阳性预测较高，对性染色体非整倍体的筛查阳性预测较低，尚需要进一步完善实验方案，具有唐氏筛查不可代替的优越性。

江西地区产前诊断中胎儿性染色体异常的产前诊断指征与妊娠结局

潘璐 刘艳秋 饶慧华 邹永毅 肖惠
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

目的 分析胎儿性染色体异常的产前诊断指征及影响胎儿妊娠结局的相关因素。
方法 选取 2017.1-2020.8 在我院行介入性产前诊断的孕妇，分析胎儿性染色体异常与产前诊断指征关系及影响胎儿妊娠结局的因素。
结果 研究期间共 5498 例孕妇行产前诊断，胎儿性染色体异常共 151 例。47，XXY 在胎儿性染色体异常中最多共 42 例（27.81%），其他依次为性染色体异常嵌合 33 例（21.85%）,47,XXX 26 例（17.22%）、47,XYY 23 例（15.23%）、45,XO 14 例（9.27%）、结构异常 11 例（7.28%）及 48,XXXX 1 例（0.66%）。无创产前筛查（NIPT）是最常见的产前诊断指征，其次为高龄、超声软指标、结构异常、孕妇染色体异常及唐氏筛查高危。在 151 例胎儿性染色体异常中，选择终止妊娠 95 例（62.91%）,继续妊娠 56 例（37.09%），其中 2 例因超声结构畸形终止妊娠，1 例孕期自发性早产，53 例已足月分娩表型正常儿。在分娩的胎儿中，47，XYY 最容易被接受（73.91%），其他依次是 47，XXX（57.69%）、47，XXY（28.57%）、性染色体嵌合（24.24%）、性染色体结构异常（18.18%）、48，XXXX 及 45，XO（0%）。45，XO 与结构异常的胎儿易表现超声结构异常。
结论 对于 NIPT 异常、高龄、超声异常、孕妇染色体异常及唐筛高危时，胎儿存在性染色体异常风险，尤其是 NIPT 异常。性染色体异常类型、嵌合比例及超声表现是影响胎儿去留的主要因素。

NIPT-plus 无创产前筛查一例阳性结果的验证与分析

林立
河南省人民医院

目的 探讨拓展性无创 DNA 产前筛查（NIPT-plus）阳性结果在提示产前诊断结果异常中的价值。
方法 NIPT-plus 检测技术提示胎儿/母亲 19p13.3(1300000-3899999)重复 2.6Mb，随后对孕妇行羊膜腔穿刺，进行羊水染色体的核型进行分析，同时对羊水进行 DNA 抽提，进行产前全基因组拷贝数变异（CNV）检测。
结果 羊水染色体核型分析显示 46，XN；CNV 检查提示于染色体 19p13.3 位置存在 2.6Mb 大小的片段重复；对该孕妇抽外周血进行 CNV 检测，结果亦提示于染色体 19p13.3 位置存在 2.6Mb 大小的片段重复。
结论 NIPT-plus 在传统无创 DNA 产前筛查的基础上，加以胎儿染色体拷贝数变异在胎儿染色体拷贝数变异筛查，对于提示产前诊断在羊水染色体核型分析正常的情况下依然存在小片段结构异常中的重要作用，以此对指导生育产生影响。

Hb Zurich-Albisrieden (HBA2: c.178G>C) 和 Hb Quong Sze（HBA2:c.377T>C）复合杂合突变导致胎儿重度贫血和胎儿水肿

杜丽
广东省妇幼保健院

目的 分析一孕 25+周胎儿重度贫血和胎儿水肿的原因。
方法 全血细胞分析和血红蛋白分析检测胎儿的血液学指标，风疹病毒和巨细胞病毒的 PCR 检测排查胎儿感染因素，胎儿染色体核型分析和染色体微阵列分析排查胎儿染色体异常，地贫基因检测和外显子测序排查胎儿单基因病相关异常。
结果 脐带血穿刺证实胎儿为重度贫血，血红蛋白水平为 37g/L。血红蛋白分析显示，脐带血中 Hb Bart's 为 9%。对该家系进行地贫基因检测和外显子测序发现，母亲为 Hb Quong Sze(Hb QS, *HBA2*: c.377T4C)杂合子，父亲为 Hb Zurich-Albisrieden (Hb ZA, *HBA2*: c.178G>C)杂合子，胎儿为 Hb Zurich-Albisrieden 和 Hb Quong Sze 的复合杂合子。
结论 Hb Zurich-Albisrieden 和 Hb Quong Sze 复合杂合突变可导致胎儿重度贫血和非免疫性胎儿水肿。

NTRK2 基因新发移码变异导致 OBHD 家系分析及产前诊断

刘建兵 李敏，许孟军，郑建丽，周月云
盐城市妇幼保健院

目的 对 1 例原因不明发育迟缓伴智力低下患儿进行分子遗传学分析，明确其致病原因；再次妊娠行产前诊断阻断遗传魔咒。
方法 全外显子组测序(whole exome sequencing，WES)筛选符合表型并可能致病的基因变异，应用 Sanger 测序在患者及其家系中进行变异验证；明确致病性后，再次妊娠进行产前诊断。
结果 WES 结果显示患儿 NTRK2 基因((NM_006180.4))存在 c.1452delC（p.Ser485Profs*37）杂合变异，家系分析发现患儿父亲检测到该变异，爷爷奶奶该位点均为正常基因型，提示该变异可能为新生突变（De novo）；父亲身高 1.75m, 体重 110Kg BMI35.94,语言沟通存在明显障碍，无癫痫发作史，达到肥胖、嗜食症和发育迟缓（OBHD）诊断标准。经检索相关数据库及文献均未见该变异报道，根据美国医学遗传学与基因组学学会遗传变异分类标准与指南，NTRK2 基因 c.1452delC（p.Ser485Profs*37）变异判定为致病性变异(PVS1＋PS2＋PM2)；再次妊娠后行羊水穿刺未发现该变异，新生儿出生后随访 6 个月生长发育正常，建议二岁左右行智力测评。
结论 NTRK2 基因 c.1452delC（p.Ser485Profs*37）变异可能导致 OBHD 家系发病主要病因，新变异的检出扩展了 NTRK2 基因变异谱。同时行产前诊断阻断悲剧重演。

基于深度机器学习的可解释药物-药物相互作用分类预测模型

刘喆[1,2] 袁铠[1,2] 陈秋芬[3] 禹顺英[1,2] 林关宁[1,2]
1.上海市精神卫生中心，上海交通大学医学院，上海交通大学生物医学工程学院
2.上海市精神疾病重点实验室
3.东北师范大学信息科学与技术学院

随着已知的药物数量在不断上升，药物-药物相互作用（drug-drug interaction, ddi）数据也变得越来越庞大，传统的机器学习模型在处理大样本数据时变得心有余而力不足，深度学习便逐渐成为 ddi 分类任务的主流建模方式。然而，由于深度学习的黑盒效应，我们只能看到某条 ddi 被归为某一类，但对于其中的推理依据却完全不知，这无疑会限制对药物相互作用机制的深层解释。

在这项工作中，我们提出了注意力机制强化的多层感知机二叉树（Attention-enhanced MLP-based binary tree, AMBT）模型，为可解释的 ddi 分类提供了可能。经过大量的文献查阅和调研，我们为这项分类任务挑选了 5 种可能有效的特征，并可以随时根据特征贡献进行改动。为了保证模型的特征提取能力，我们在模型的前端使用了多层感知机（Multilayer Perceptron，MLP）。在模型的后端，我们创新性地使用层次聚类方法倒逼模型对 128 类标签生成二分类树，通过对标签关联关系的建模，AMBT 不仅仅提供了 ddi 分类的决策结果，同时还给出了决策过程。这样的架构设计使得 AMBT 兼具深度学习强大的特征提取能力和机器学习的可解释性，同时 AMBT 也具备发掘不同 ddi 类别之间深层关联关系的潜力。

NIPS 在胎儿缺失型 X 连锁鱼鳞病筛查中的应用研究

汤欣欣 王雷雷
连云港市妇幼保健院

目的 缺失型 X 连锁鱼鳞病（XLI）是由 X 染色体 STS 基因区域片段缺失而导致的较为常见的一种隐性遗传病。本文探讨 NIPS 对于胎儿缺失型 X 连锁鱼鳞病的筛查效力及临床价值。
方法 2019 年 1 月至 2020 年 12 月在本中心行 NIPS 检测的人群，收集 NIPS 提示 Xp22.31（覆盖 STS 基因）区域存在缺失的病例。回顾性分析 STS 基因缺失的发生率，利用低深度测序技术（CNV-seq）对孕妇白细胞进行验证，以及染色体微阵列技术（CMA）对胎儿羊水细胞进行分析，并随访孕妇的妊娠结局和胎儿出生后情况。
结果 分析了 11771 例 NIPS 结果，提示 23 例存在涵盖 STS 基因区域的缺失型 CNV（1/511）。23 例均进行母亲白细胞 CNV-seq 验证，结果显示大小和位置与 NIPT 检测出结果基本一致（母源携带率 100%）。其中 4 例女性胎儿未告知孕妇，剩余 19 例男性胎儿均告知孕妇并建议遗传咨询。18 例孕妇进行了遗传咨询，其中 14 例孕妇进行了侵入性产前诊断， 12 例羊水细胞 CMA 检测结果与 NIPT 结果一致（一致率达 85.71%），2 例 CMA 检测结果未见明显异常。对 12 例 CMA 检测确病例进行随访结果显示，2 例后期引产，10 例正常妊娠分娩，出生 3 个月内婴儿均有不同程度的皮肤干燥、泛有白色鳞屑等症状,并且得到了及时的治疗和护理。
结论 NIPS 对于母源携带 X 染色体 STS 基因区域缺失引起的胎儿缺失型 X 连锁鱼鳞病具有较高的筛查准确性，有助于预测胎儿该疾病的发生情况，对孕妇进行妊娠期管理及胎儿出生后特殊护理具有重要的临床指导意义。

Application of whole exome sequencing in fetal cases with skeletal abnormalities

Juan Cao
Ningbo Women & Children's Hospital

Purpose To investigate the role of whole exome sequencing (WES) technology in fetus with skeletal abnormalities (SKA) for establishing an appropriate clinical diagnosis and treatment path.
Methods From April 2019 to August 2020, 8 special cases were enrolled into the study. These cases showed abnormal SKA by ultrasonic testing with the normal results by chromosomal mlcroarray analysis (CMA) of amniotic fluid or abortion. For further diagnosis, whole exome sequencing (WES) was performed to detect the causative gene mutations followed by Sanger sequencing.
Results All of these 8 special cases showed the regularity of monogenic inheritance disease. We identified 6 novel heterozygous mutations in *COL1A1* gene (c.2885G > A, c.994G > A, c.1002+5G > T) , *EFNB1* gene (c.451G > A), *FGFR3* gene (c.1138G > A), and *COMP* gene (c.1417G > C), respectively. And one heterozygous mutation of *COL1A1* gene (c.644G > A) in the proband, which was inherited from the mother. Another heterozygous mutation of *COL1A2* gene (c.2482G > T) in the proband, which was inherited from the father.

Conclusion Our study reported novel heterozygous mutations in *COL1A1*, *EFNB1*, *FGFR3*, and *COMP* genes, which expands the mutation spectrum for the diagnosis of SKA. Most importantly, WES technology is necessary as a routine step of the diagnosis for SKA, combining with the detection of chromosome level.

先天性中胚层肾瘤的产前诊断和产后治疗：经验分享

李东至 钟薇 何秋明
广州市妇女儿童医疗中心

目的 讨论先天性中胚层肾瘤（CMN）病例其产前和产后的临床特征、病理分型及手术治疗结局。
方法 回顾性分析 2015 年至 2019 年在广州市妇女儿童医疗中心接受产前诊断的 11 例先天性中胚层肾瘤（CMN）病人的临床特征，手术结局，组织病理学和随访情况。
结果 病人进行超声诊断的胎龄中位数为 35 周。其中发现四例孕妇羊水过少（36.4%），后均早产。其中 9 名婴儿发现患有高血压。10 例婴儿行根治性肾切除术，1 例行根治性肾切除术和部分肾上腺切除术。术后病理结果显示：6 个先天性中胚层性肾瘤是经典变异，4 个先天性中胚层肾瘤是混合变异，1 个先天性中胚层肾瘤是细胞变异。病理分期显示：**I**期有 3 例，**II**期有 8 例，无**III**期或者**IV**期的诊断病例。截止目前，所有以上患者均在世。在 14 个月的中位数随访期间，未发现有局部复发或者远处转移。
结论 行早期手术的先天性中胚层性肾瘤（CMN）胎儿其预后很好。

4546 例地中海贫血产前诊断病例的回顾性分析

李东至 许莉莉 甄理 杨昕 韩瑾 张丽娜
广州市妇女儿童医疗中心

目的 总结分析地中海贫血产前诊断的变化情况，反映地贫防控效果及可能存在的缺陷，为进一步防控工作完善提供科学依据。
方法 收集本中心近十年临床指征包括双方地贫的产前诊断病例，分别统计 Hb Bart's 水肿胎、非缺失型 Hb H 病（指 Hb H-CS 或 Hb H-QS)、严重 β-地贫每年的产前诊断量的变化。把穿刺孕周划分为四组，分别是孕 10-14 周、15-19 周、20-24 周及≥25 周，统计各类型地贫 10-14 周在每年所占比例的变化趋势。根据胎儿的产前诊断结果，统计早孕周组（10-14 周）及大孕周组（≥25 周）地贫引产的总例数。分析不同地贫的产前诊断指征量的变化及穿刺孕周分布变化，为临床进一步的地贫防控提供参考依据。
结果 研究期间内地贫产前诊断的总例数为 4546 例，占本中心穿刺量的 13.0%。其中穿刺指征 Hb Bart's 水肿胎 2428 例，非缺失型 HbH 病 270 例，严重 β-地贫 1848 例。2010 年至 2019 年，Hb Bart's 水肿胎指征的例数从 98 例增加到 332 例，非缺失型 Hb H 病从 11 例增加到 48 例，严重 β-地贫从 112 例增加到 230 例，均表现为逐年增长的趋势。早孕期穿刺的 α-地贫从 2010 年的 49.3%增加至 2019 年的 67.5%，严重 β-地贫从 27.7%增加至 63.9%，均呈逐年增加的趋势。根据最终的产前诊断结果，11-14 周引产的病例数为 799 例（56.3%），≥25 周引产的严重地贫 82（5.80%）例，总计共 1419 例严重地贫病例及时终止妊娠。
结论 不同地贫指征产前诊断的病例数逐年增加，研究期间内本中心及时阻止例 1419 例严重地贫儿的出生，显著降低了出生缺陷。56.3%地贫高风险家庭能得到早期产前诊断，达到遗传病早期干预的效果。仍有 5.80%地贫高风险家庭产前诊断时间太晚，需要分析原因，为后续地贫防控工作改进提供决策依据。

胎儿运动不能-运动功能减退序列征：临床外显子测序在胎动减少病例中的应用

李东至 曹群 潘敏 甄理
广州市妇女儿童医疗中心

目的 通过研究胎儿运动不能-运动功能减退序列征中的单基因综合征病例，了解其遗传学病因。
方法 从产前超声诊断为胎儿运动不能-运动功能减退序列征且染色体微阵列分析结果正常的 12 例产后病例样本中提取的 DNA 进行临床家系三外显子组测序（ES）。该检查针对的是 4200 个临床相关致病基因的编码外显子。根据美国医学遗传学与基因组学学会（ACMG）颁布的指南对变异进行解读。
结果 12 例进行临床家系三外显子组测序（ES）的病例中，6 例得到了明确的分子诊断。其中 5 例的致病变异为已知的胎儿运动不能-运动功能减退序列征相关基因。1 例潜在的致病变异为已知的致病基因，该基因与之前的胎儿运动不能-运动功能减退序列征不相关。这些病例中，父母终止妊娠的 6 例，继续妊娠到足月的 6 例。
结论 本研究中采用临床家系三外显子组测序（ES）的半数胎儿运动不能-运动功能减退序列征病例由遗传缺陷引起。这些信息将有助于此类疾病的预后和复发风险的遗传咨询。

胎儿 2 号染色体短臂微缺失一例

胡深 王利权
浙江大学医学院附属第二医院

目的 病例个案报道新发现 2 号染色体微缺失的临床意义
方法 孕妇，31 岁，孕 1 产 0，夫妻双方表型正常，非近亲结婚，均否认家族遗传病史，无有害物质接触史、无烟酒嗜好、无特殊用药史。孕 12 周 3 天超声提示 NT 1.2mm，鼻骨可见，早期及中期唐氏筛查为低风险，孕 13 周行无创性胎儿染色体产前检测（Noninvasive prenatal Testing, NIPT），提示 Chromosome 2p12-p11.2 deletion syndrome，缺失片段大小为 5.46Mb，异常区带：2p12-p11.2，异常起始点：2 号染色体（77880225-83343131），提示高风险，B 超检测未发现胎儿结构性异常，经遗传咨询，在患者知情同意下于孕 19 周 4 天行羊膜腔穿刺术、染色体核型分析、人类全基因组 SNP 分型芯片分析，结果显示为 arr[hg19] 2p12(78,065,337-83,154,631)x1，提示胎儿 2 号染色体 2p12 区段存在 5.0Mb 片段的缺失。胎儿羊水细胞全染色体组模拟核型图，可见 2 号染色体旁红色标记的片段缺失。该缺失的片段包括 α-N-连环蛋白（catenin alpha 2, CTNNA2）（114025）等 6 个 OMIM（Online Mendelian Inheritance in Man）基因，该基因的纯合型突变与皮层发育不良复杂型伴有其他脑部畸形 9 型（Cortical dysplasia, complex, with other brain malformations 9，CDCBM9）相关，这是一种罕见而又严重的常染色体隐性遗传疾病，其特征是从婴儿早期就表现为显著的运动和认知发育受损。受影响的个体会出现难以控制的癫痫发作、无法说话或走动。脑部影像学检查显示皮质发育的各种畸形，皮质增厚，前连合缺如，胼胝体发育不良、巨脑回及其他不同程度的脑畸形，小脑发育不全，白质减少。经遗传咨询，该患者于孕 23 周经自主选择行引产终止妊娠，引产儿外观未见明显异常。
结果 在我们的产前筛查中，发现了一例患者的 2 号染色体缺失异常。NIPT 结果显示，2 号染色体上有 5.46Mb 的微缺失。染色体核型分析（很难发现染色体缺陷和重复量小于 5 Mb）和拷贝数变异（copy number variation, CNV）分析再次确认了 2p12 区段存在 5.0Mb 片段的缺失。
结论 我们通过 NIPT 检测发现了一例染色体 2p12-p11.2 缺失综合征并通过染色体核型分析给予确诊，进一步证实 NIPT 技术可以检测胎儿染色体的微重复/缺失。

一个脊髓小脑共济失调 5 型家系的遗传分析及产前诊断

王金铭 廖世秀 杨科 吴东 郭正隆
河南省人民医院

目的 对一个小脑萎缩患儿的家系进行遗传分析，为临床遗传咨询和产前诊断提供依据。
方法 通过染色体核型分析技术、高通量测序技术等对该家系进行检测，同时应用 Sanger 测序验证基因变异位点。
结果 高通量测序分析结果显示患儿 *SPTBN2* 基因 NM_006946:c.1309C>T 错义杂合变异；Sanger 测序验证结果显示患儿父亲和母亲 *SPTBN2* 基因 c.1309 为野生型；羊水标本提示 *SPTBN2* 基因 c.1309 为野生型。
结论 *SPTBN2* 基因 NM_006946:c.1309C>T 错义杂合变异可能为该家系的致病原因，致病性变异的检出有助于家系的遗传咨询和产前诊断。

胎儿 DNA 短片段富集分析法辨别 NIPT 中母体来源的假阳性病例

谢润桂
东莞市妇幼保健院

目的 探究胎儿 DNA 短片段富集分析法在无创产前检测（Non-invasive Prenatal Testing，NIPT）中辨别母体来源的假阳性病例的临床应用价值。
方法 选取 13 例母体染色体异常引起的 NIPT 假阳性标本和 8 例胎盘染色体异常引起的 NIPT 假阳性标本。用半导体基因测序技术测序后，分别用胎儿 DNA 全片段分析法（M 方法）和 DNA 短片段富集分析法（L 方法）分析测序数据，分别获得染色体 Z 值和相应的染色体位置-剂量分布曲线。
结果 在母体来源的假阳性样本中，L 方法与于 M 方法相比较，阳性信号会缩小，表现为 Z 值绝对值变小，在染色体位置-剂量分布曲线上红线较黑线更接近于基线 0。而胎盘来源样本阳性信号则恰好相反。
结论 在 NIPT 中，DNA 短片段富集分析法能准确判断阳性信号的来源，辨别母体来源的假阳性信号，同时不增加额外的实验成本，该方法用于辨别母体来源的假阳性具有重要的临床应用价值。

染色体微阵列分析在轻度侧脑室增宽胎儿中的诊断价值

吴海荣
北京大学第一医院

目的 探讨染色体微阵列分析（chromosome microarray analysis, CMA）技术对妊娠中晚期超声表现为轻度侧脑室增宽(ventriculomegaly, VM) 的胎儿的诊断价值。
方法 回顾分析 2017 至 2021 年于北京大学第一医院产科超声筛查诊断为 VM 的孕妇 279 例。轻度单侧孤立性 VM 组（147 例），轻度单侧非孤立性 VM 组（76 例），轻度双侧孤立性 VM 组（29 例），轻度双侧非孤立性 VM 组（27 例）。使用基因组 DNA 提取试剂盒提取羊水细胞、脐血、胎儿组织 DNA。采用基于微阵列的比较基因组杂交技术和单核苷酸多态性微阵列技术分析 279 例产前样本 CNVs（copy number variations,CNVs）。
结果 （1）279 例产前样本中，染色体非整倍体异常 1 例，嵌合体 1 例。 致病性/可能致病性 CNVs 22 例， 占比 7.89%（ 22/279 ）。临床意义不明确变异（ variants of uncertain significance,VOUS ）18 例， 占比 6.45%（ 18/ 279 ）。可能良性 CNVs 5 例， 占比 1.79%（5/279）;（2）轻度单侧孤立性 VM 组检出致病性/可能致病性 CNVs 5 例，检测率 3.40%（5/147），检出 VOUS 8 例, 检测率 5.44%（8/147）。轻度单侧非孤立性 VM 组检出致病性/可能

致病性 CNVs 8 例，检测率 10.53%（8/76），检出 VOUS 3 例, 检测率 3.95%（3/76）。轻度双侧孤立性 VM 组检出致病性/可能致病性 CNVs 2 例，检测率 6.90%（2/29），检出 VOUS 7 例, 检测率 24.14%（7/29）。轻度双侧非孤立性 VM 组检出致病性/可能致病性 CNVs 5 例，检测率 18.52%（5/27），检出 VOUS 3 例, 检测率 11.11%（3/27）。

结论 CMA 可以检出显微镜下可见的染色体异常以及染色体微小缺失和重复，是用来检测 CNVs 的主要方法。CNVs 在胎儿 VM 的遗传学病因中起重要作用。应建议所有 VM 胎儿进行 CMA 检测，无论其严重程度或是否合并其他结构异常。

NIPT、CMA、高分辨染色体核型制备与分析技术在珠海市产前诊断中的联合应用

赵理平
珠海市妇幼保健院

目的 评估无创产前检测（non-invasive prenatal testing，NIPT）、染色体微阵列分析（chromosomal microarray analysis,CMA）、高分辨染色体核型制备与分析技术在珠海市产前诊断中联合应用的临床价值。

方法 对 26882 例符合 NIPT 筛查指征孕妇进行 NIPT 检测，对其中 205 例 NIPT 高风险孕妇进行羊水高分辨染色体核型分析及 CMA 检测。

结果 205 例 NIPT 高风险确诊 124 例，总阳性预测值 60.5% ；高分辨核型分析检出传统技术易漏检的 3～5Mb 左右结构异常 5 例；CMA 检出正常核型结果中致病或可能致病性微缺失/微重复 3 例，单亲二体（uniparental disomy UPD）2 例，明确不确定染色体结构 1 例，因方法学局限性未检测出核型分析中 4 例倒位、5 例易位、7 例低比例嵌合体。

结论 高分辨染色体核型制备技术较传统技术能有效提高染色体病的检出率。NIPT、CMA、高分辨染色体核型分析三种技术具有互补性，在产前诊断中联合应用，可以有效提高胎儿染色体病检出率，减少出生缺陷。

产前超声足内翻与染色体异常相关性分析

罗晓辉 黄华洁 李怡 卢建
广东省妇幼保健院

目的：探讨足内翻胎儿产前诊断结果，明确足内翻胎儿染色体异常的发生率及基因拷贝数变异情况。

方法：选取 2016 年 1 月至 2020 年 7 月胎儿超声检查提示足内翻，伴或不伴其他异常并接受介入性产前诊断的 154 例胎儿，所有病例均接受染色体核型分析联合染色体微阵列分析。根据足内翻是否合并其他异常，分为孤立性足内翻组（107 例），非孤立性足内翻组（47 例），对所有胎儿进行随访，了解妊娠结局以及产后发育情况。

结果：孤立性足内翻组和非孤立性足内翻组，染色体核型异常发生率分别为 4.7%（5/107），10.6%（5/47），两组比较差异具有统计学意义($p<0.05$),基因拷贝数变异发生率分别为 5.6%（6/107），6.4%（3/47），两组比较差异不具有统计学意义($p>0.05$)。

结论：非孤立性足内翻组染色体核型异常发生率较高。染色体微阵列分析在足内翻病例中能额外检出约 6%的拷贝数变异。对于产前足内翻病例需要重视拷贝数变异的检测。

一例 17p12 微重复家系的遗传学分析及产前诊断

陈云鹏
镇江妇幼保健院

目的 对一例丈夫有家族性遗传病史的孕妇进行遗传学分析，为其提供产前诊断。
方法 采用常规 G 显带染色体核型分析和染色体微阵列分析（Chromosomal Microarray Analysis, CMA）检测对孕妇外周血及其羊水标本进行分析。
结果 孕妇夫妇外周血及羊水样本核型分析均未见异常，CMA 检测提示胎儿携带 17p12 区域的 1.36Mb 的重复，该区域完全覆盖“17p12 复发（HNPP/CMT1A）区域（包括 PMP22）”，数据库查询结果为该区域三倍剂量敏感具有明确致病性，主要由 PMP22 基因重复引起的“脱髓鞘型腓骨肌萎缩症 1A 型（OMIM118220）”，是一种影响周围神经的遗传性神经系统疾病。父亲同样携带该区域 1.41Mb 的重复。
结论 染色体核型分析不能检测微缺失微重复，CMA 检测出父亲和胎儿均携带 17p12 区域微重复，明确筛查结果后对孕妇进行指导再生育。

297 例圆锥动脉干畸形胎儿的产前诊断和妊娠结局分析

曹群 许莉莉 李茹 韩瑾 易翠兴 景象一 张丽娜 李东至 潘敏
广州市妇女儿童医疗中心

目的 通过分析 297 例圆锥动脉干畸形胎儿的产前诊断结果及妊娠结局，探讨圆锥动脉干畸形与染色体病的相关性，并指导产前咨询和预后评估。
方法 收集 2011 年 01 月 01 日至 2019 年 12 月 31 日在广州市妇女儿童医疗中心产前诊断中心因圆锥动脉干畸形进行介入性产前诊断及染色体分析的病例。根据超声诊断将圆锥动脉干畸形分为六个亚型,并根据是否合并心内/心外畸形异常，分为单纯组、合并其他心内畸形组、合并心外畸形组、同时合并心内和心外畸形组、合并超声软指标组五组。回顾性分析各型、各组的染色体检测结果和妊娠结局。
结果 297 例圆锥动脉干畸形胎儿样本中，染色体异常率为 17.5%（52/297）。染色体数目异常 21 例，病理性拷贝数变异 28 例，嵌合体 3 例。圆锥动脉干畸形各亚型中，永存动脉干的染色体异常率最高，大动脉转位的染色体异常率最低。各分组中同时合并心内心外畸形组染色体异常率最高，单纯组染色体异常率最低。单纯型与非单纯型染色体异常率的比较差异均有统计学意义，但单纯组各亚型之间染色体异常率比较无统计学差异。112 例活产病例中，1 例为 22q11.2 微缺失综合征，5 例出生后临床诊断与产前超声诊断不完全一致，5 例出生后夭折。
结论 圆锥动脉干畸形病例的染色体异常几率高，染色体微阵列（CMA）分析技术可以作为圆锥动脉干畸形的首选遗传学检测手段。在排除染色体异常后，大部分圆锥动脉干畸形儿预后良好。

Prenatal Diagnosis of a Pedigree with Developmental Retardation due to Paternal 8q/18q Translocation

Chunyan Jin Tianhui Xu
Taizhou People's Hospital

Objective To provide prenatal diagnosis for a pregnant woman who had already delivered a child with developmental retardation.
Methods Karyotype analysis and chromosomal microarray analysis (CMA) were performed for the proband to identify the genetic pathogenesis. Prenatal diagnosis of the proband’s mother was then conducted based on the testing results of the proband.
Results CMA revealed a 25.6 Mb duplication (dup) of 8q24.12-q24.3 and a 16.5 Mb deletion (del) of 18q21.33-q23 for the proband. Cytogenetic analysis verified a paternal balanced translocation

at the long arms of chromosomes 8 and 18. CMA and cytogenetic analysis of amniotic fluid cells from the mother of the proband indicated that the fetus also carried the same karyotype as that of the proband. The couple decided to terminate the pregnancy after genetic counseling.
Conclusion This research not only provides genetic counseling about reproductive option for this family, but also helps to better understand the clinical manifestations and prognosis of patients with this rare chromosomal abnormality.

Mutational analysis and prenatal diagnosis of hypophosphatemic rickets in a Chinese family

Di Ma Mei Ye Zhiyang Hu Lijuan Wang Hui Gao Yaqin Song Yuhua Hu Shayan Wang Hui Guo
Department of Forensic Evidence Laboratory, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen 518020, Guangdong, China

Background X-linked hypophosphataemic rickets (XLHR) is the most common type of heritable HR, about 85-90% of HR are associated with loss-of-function variants in phosphate-regulating neutral endopeptidase homolog X-linked (*PHEX*) gene. Here, we screened the underlying mutations that caused HR in a Chinese family to provide accurate prenatal diagnosis and genetic counseling of the disease.
Methods We collected and analyzed the clinical genetics data from a family with HR. Six family members including four males and two females participated in this study. Peripheral blood was collected from the proband and exome sequencing was performed to explore the mutations of disease-associated genes. Multiplex ligation-dependent probe amplification (MLPA) was employed to verify the results of the next generation sequencing. Copy number variants of the fetus were detected by Affymetrix CytoScan HD chromosome microarray (CMA) with umbilical cord blood at 26 weeks of pregnancy.
Results The proband was characterized by rachitic changes with leg deformities and short stature, her elder brother and her son had a similar phenotype. We identified a novel heterozygous deletion mutation in *PHEX* encompassing exons 7 to 11 in the proband, which leads to a partial loss of the gene. MLPA confirmed that this mutation co-segregated with HR in the family and were absent in the normal controls. CMA analysis of the high-risk fetus showed a 31Kb (chr: X 22110449-22141865) deletion in *PHEX*.
Conclusion Collectively, our results demonstrated that the HR in this family was caused by a novel gross deletion in *PHEX*, which has implications for genetic counseling and extend the pathogenic mutation spectrum of the *PHEX* gene. This study also suggests the importance of relaxing the cut-off values of CMA assay in prenatal diagnosis when the proband has a definitive genetic diagnosis

Prenatal diagnosis of Sjögren-Larsson syndrome by whole exome sequencing

Chunyan Jin Xiaohan Jiang
Taizhou People's Hospital

Objective To provide prenatal diagnosis for a pregnant woman who had already delivered a child with Sjögren-Larsson syndrome (SLS).
Methods Karyotype analysis, chromosomal microarray analysis (CMA) and whole exome sequencing (WES) were performed for the proband to identify the genetic pathogenesis. Prenatal diagnosis of the proband's mother was then conducted based on the testing results of the proband.
Results The proband was confirmed to carry a homozygous mutation of c.1157A>G (p.Asn386ser) in *ALDH3A2*, which is the cause of SLS. His parents were validated to be

heterozygous carriers of this mutation. Prenatal diagnosis confirmed that the fetus did not inherit the same mutation
Conclusion Our study suggests that it is effective to utilize WES, as well as karyotype analysis and CMA, for the prenatal diagnosis of SLS in the family.

Whole exome sequencing identifies novel AGT variant in two fetuses with autosomal recessive renal tubular dysgenesis

Xiaomei Shi
Guangdong Women and Children Hospital

Introduction Autosomal recessive renal tubular dysgenesis(ARRTD) is a very-rare autosomal recessive genetic disorder with renal tubular development. In this retrospective study, we describe the ultrasound findings and genetic investigations of two fetuses affected by ARRTD.
Methods We enrolled 2 fetuses diagnosed with ARRTD at the Guangdong women and children hospital. Trio-based whole exome sequencing (Trio-WES) was performed on them and their parents. Variants were confirmed with Sanger sequencing.
Results Both fetuses shared the same clinical: oligohydramnios and hyperechogenic kidneys. AGT exon 3-4 (E3_E4 del) homozygous deletion was detected in the fetus 1, indicating parental heterozygosity. In fetus 2, WES showed a heterozygous point variation c.598C>T (p.Q200*) (novel variant) from the mother and the heterozygosity E3_E4 del from the father, forming a compound heterozygosity. Sanger sequencing found both fetuses had the same E3_E4 del, missing 2870bp and 9bp insertion in AGT, which resulted in a trunked protein (1-292 amino acids) caused by the AGT serpin domain encoding exons skipped.
Conclusion WES as a reliable tool for the prenatal identification of ARRTD. Our findings expand the phenotypic and mutation spectra of ARRTD.

染色体微阵列分析联合染色体核型分析应用于产前诊断

邓艺
四川省妇幼保健院

目的 了解染色体微阵列分析是否能取代染色体核型分析，以及染色体微阵列分析联合染色体核型分析应用于基因组病产前诊断的意义。
方法 2019 年 3 月 ～ 2021 年 3 月 3710 例染色体微阵列分析或/和染色体核型分析进行产前诊断的病例。比较染色体微阵列分析联合染色体核型分析发现的异常病例和仅用染色体核型分析或者仅用染色体微阵列分析发现的异常病例。
结果 染色体微阵列分析联合染色体核型分析发现异常病例 352 例；染色体微阵列分析正常，核型分析异常 12 例；核型分析正常，染色体微阵列分析发现异常 139 例。染色体微阵列分析联合染色体核型分析较仅用染色体微阵列分析检出率提高 0.35%，较仅用细胞遗传学技术检出率提高 3.73%。
结论 染色体微阵列分析不能完全取代染色体核型分析，产前诊断仅用染色体核型分析或者仅用染色体微阵列分析存在医疗风险，应联合染色体微阵列分析和染色体核型分析应用于产前诊断一线检查。

一例 22q11.21 微缺失综合征导致胎儿皮肤增厚的产前诊断

王凤阳
河南省人民医院

目的 对一例胎儿颈背部软组织增厚、心脏结构异常(心轴左偏，室间隔缺损，主动脉骑跨，肺动脉显示不清、动脉导管血流反向)的患儿进行遗传学诊断，分析其发病机制
方法 采用二代测序技术分析患儿及其父母的基因组拷贝数变异。
结果 胎儿的测序结果为 seq[hg19] del(22)(q11.21q11.21)chr22:g.18880000_21480000del，即 22q11.21 区存在 2.60Mb 缺失，胎儿父亲并未发现有大于等于 500Kb 缺失或大于等于 1Mb 重复的拷贝数变异，但胎儿母亲测序结果为 seq[hg19] del(22)(q11.21q11.21)chr22:g.18900000_21480000del。该区域的缺失可导致 22q11.2 缺失综合征，该综合征存在外显不全，常见的临床表型有先天性心脏病、腭裂及其他特殊面容、免疫缺陷、听力缺损、生长发育迟缓和智力障碍等，少数患者遗传自无明显表型父母。
结论 该患儿的缺失遗传自母亲，该缺失是导致患儿临床表型的原因。

无创产前检测开展前后羊水染色体核型情况的对比分析

李晓洲 史云芳 孟凡荣 张颖 袁碧波
天津医科大学总医院

目的 通过对 NIPT 开展前后羊水染色体核型情况的分析，探讨 NIPT 时代产前诊断指征、产前诊断效能及产前筛查效能的变化。
方法 分别选取 2275 例 NIPT 开展前（2009 年 10 月-2011 年 9 月）和 357 例 NIPT 开展后（2015 年 10 月-2017 年 9 月）于天津医科大学总医院产前诊断中心行羊膜腔穿刺的孕妇（孕 19-24 周）进行比较，分析产前诊断的指征、产前诊断的效能和 NIPT 的筛查效能。
结果 NIPT 开展前羊膜腔穿刺 2275 例，因血清学筛查高风险行羊膜腔穿刺 2174 例（95.56%）；NIPT 开展后羊膜腔穿刺 357 例，因 NIPT 检测高风险行羊膜腔穿刺 280 例（78.43%）。NIPT 开展前、后分别检出染色体非整倍体和非平衡结构异常 40 例（1.76%）和 168 例（47.06%）。与 NIPT 开展前相比，NIPT 开展后产前诊断病例数下降了约 5.37 倍，染色体非整倍体及非平衡结构异常检出率提高了 25.74 倍。NIPT 开展后对 21、18、13 及性染色体的综合阳性预测值为 60.00%，与 NIPT 开展前的 1.79%相比较，两者差异有统计学意义（P<0.01）。
结论 天津地区将 NIPT 作为一线产前筛查明显提高了产前筛查和产前诊断的效能。建议在政策法规支持下、技术资质满足以及经济条件允许下可以将 NIPT 作为血清学筛查高风险及单纯高龄孕妇的一线筛查。

孕中期 NIPT 技术检出 15q11.2-q13.1 微重复胎儿一例

黄佳 夏晓亮 朱宏杰 林立 吴东 王凤阳 高越 廖世秀
河南省人民医院

目的 对一例血清学筛查唐氏综合征临界风险孕妇行产前胎儿游离 DNA 筛查和诊断。
方法 进行产前遗传优生咨询，签署知情同意书，采集该夫妇外周静脉血和羊水样本。采用北京贝瑞和康生物技术有限公司商品化试剂盒进行母体外周血游离 DNA 和父母、胎儿基因组 DNA 测序文库构建，Nextseq500 测序仪（美国 Illumina 公司）进行序列分析，测序读长 37bp。序列比对参考基因组为 UCSC GRCh37/hg19，利用贝比安、科诺安在线分析系统进行非整倍体和基因组拷贝数变异分析。
结果 外周血游离 DNA 和基因组 DNA 测序数据产出分别为 23Mb、12Mb。母体外周血游离 DNA 检测显示常见三体综合征（21、18、13 三体）筛查均为低风险，检出 15q11.2-q13.1 区域可能存

在 5.6Mb（chr15:22800000-28399999）微重复。胎儿羊水细胞和父母外周血 DNA 样本基因组拷贝数变异检测显示胎儿及其母亲均携带 15q11.2-q13.1 微重复（chr15:22740000_28400000）。该区域重复可导致 15q11q13 重复综合征，该综合征常见临床表型包括自闭症、智力障碍、癫痫等，部分个体遗传自表型正常的父母。

结论 母体外周血游离 DNA 检测可对部分基因组病进行产前筛查，筛查片段大小和适应症还需进一步规范。

一例胎儿 4q 部分三体综合征的无创产前筛查与产前诊断

夏晓亮
河南省人民医院

目的 对一例无创外周血胎儿游离 DNA 产前筛查结果为 4q 部分三体综合征高风险的孕妇进一步产前诊断。

方法 该孕妇孕 2 产 1，单胎，自然受孕，无不良孕产史；末次月经：2020/12/23；身高 161cm，体重 55kg；家族成员患有视力障碍遗传病；超声检查未见异常，孕中期血清学筛查 uE3 MoM 值异常；2021/5/10 该孕妇于孕 20 周行无创外周血胎儿游离 DNA 产前筛查结果为胎儿 4q 部分三体综合征高风险。2021/5/24 在彩超引导下经腹壁行羊水穿刺术，抽取羊水 15ml，后经羊水染色体核型分析以及染色体芯片分析(CNV)检测对其进行产前诊断。

结果 经羊水染色体芯片分析(CNV) 检测到标本 4 号染色体 q31.3-q33 区段存在 19.86Mb 重复，该区域涉及 75 个编码蛋白基因，数据库中部分个体无明显临床表型，部分个体出现智力障碍、发育迟缓等表型，该重复为可能致病性拷贝数变异。羊水染色体核型分析结果：46, XN, der (5) ins (5; 4) (q31; q31.3q33)，与染色体芯片分析(CNV)结果一致。

结论 无创产前筛查高风险病例需进行羊水产前诊断，无创孕妇外周血胎儿游离 DNA 产前筛查与羊水染色体核型分析、羊水染色体芯片分析等产前诊断技术相结合，对产前筛查高风险患者的诊断工作具有重要意义。对于该孕妇检测出可能致病性拷贝数变异，建议结合四维超声检查，夫妻双方染色体核型及 CNV 检查对照分析，做出进一步判断。

NIPT 无创产前筛查 一例假阳性结果分析

朱宏杰
河南省人民医院

目的 探讨无创 DNA 产前检测（NIPT）在诊断染色体异常中出现假阳性的原因。

方法 选择在产前诊断中心做 NIPT 结果提示高风险的一例样本，该样本患着有葡萄胎史，本次 NIPT 结果提示 13 三体高风险（单体或部分缺失）和 18 三体高风险（单体或部分缺失），对该患者做羊水核型分析和拷贝数变异(CNV)检测。

结果 胎儿染色体核型为 46，XN；CNV 分析结果未发现检测范围内染色体微重复微缺失。

结论 在胎儿出生后可以取胎盘组织和母血进行高通量 DNA 测序分析。若胎盘检测结果与 NIPT 结果相符,母血结果正常, NIPT 假阳性来源于胎盘。胎盘和母血中异常游离 DNA 释放入母血是 NIPT 假阳性的主要原因。若母血结果显示异常，则考虑母体患有自身免疫性疾病或肿瘤。

387 例胎儿羊水性染色体异常的遗传学分析

张亚南
湖南省妇幼保健院

目的 分析羊水产前诊断中性染色体异常检出情况，探讨不同产前诊断指征与性染色体异常之间的相关性，评估不同遗传学技术的诊断价值，为临床遗传咨询你提供指导。

方法 收集 2017 年 1 月到 2020 年 12 月因各种产前诊断指征在我院行孕中期羊膜腔穿刺术孕妇的临床资料，对确诊为性染色体异常胎儿的染色体核型分析和染色体微阵列（CMA）分析等遗传学检测结果进行回顾性分析。

结果 研究中的 12164 例羊水产前诊断病例中，共检出胎儿性染色体异常 387 例，其中性染色体核型异常 351 例，性染色体微缺失/微重复 36 例；无创性染色体高风险指征检出率最高，为 74.16%（287/387）。在 351 例核型异常中，数目异常有 258 例，以 47,XXY 和 47,XXX 多见；嵌合体有 66 例，以 45,X 嵌合体多见，并联合 CMA、FISH、超声诊断了 1 例低比例嵌合型 idic(Y)；结构异常有 8 例，以 X 染色体缺失多见，通过 CMA 明确了其中 24 例性染色体断裂点位置和片段范围；在 36 例性染色体微缺失/微重复中，发现了 15 例致病性 CNVs，以 Xp22.31 区域缺失多见。

结论 胎儿羊水性染色体异常中以性染色体数目异常多见，无创性染色体高风险与胎儿羊水性染色体异常检出密切相关，综合运用合适的遗传学检测技术，可明确性染色体异常胎儿遗传病因，为孕妇提供准确科学的遗传咨询，对提高性染色体异常产前诊断的综合效率具有重要临床意义。

Prenatal Diagnosis and Placental Tissues Multi-point Sampling of a fetus with trisomy 15 Mosaicism: case report and literature review

Xiaona Xu Yanlin Wang
International Peace Maternal & Child Health Hospital, Medical College, Shanghai JiaoTong University

Background Up to date, only 19 cases of trisomy 15 mosaicism detected by amniocentesis have been reported. We report a case of a liveborn baby with trisomy 15 mosaicism detected in prenatal period.

Results A woman with a favorable fetal outcome was described in the present study. Conventional karyotype of cultured amniocytes at amniocentesis revealed a normal result of 46,XY, and the CMA analysis revealed mosaicism for trisomy 15 in the uncultured amniocytes. Interphase FISH applied on uncultured amniocytes showed mosaicism for trisomy 15. Samples of urine, oral mucosal cells and placenta revealed mosaicism for trisomy 15.

Conclusion We suggest that molecular testing, such as FISH and CMA, should to performed in cultured and uncultured cells, to make a comprehensive evaluation. We also suggest the importance of multi-point sampling of the placental tissues to detect the mosaic levels of different part of placenta. To the best of our knowledge, our case is the first prenatally detected cases by comprehensive detection methods, including conventional karyotype, FISH, CMA analysis, MLPA and CNV-seq. This case is also the first prenatal case performing the multi-point sampling of the placental tissues.

PEX7 基因突变致肢跟型软骨发育不良 1 型家系的遗传学分析及产前诊断

余舒婕[1,2]
1.河南省人民医院省直第二医院
2.河南省人民医院

目的 明确一个以妊娠期胎儿发育迟缓，肱骨、股骨明显偏短，肩关节、肘关节及髋关节等解剖解构异常，出生后四肢挛缩，婴儿期夭折等为主要临床表现的骨骼发育异常家系的病因，并给予产前诊断指导。

方法 应用全外显子测序技术（Whole-exome sequencing，WES）检测对胎儿羊水组织、胎儿父母亲、胎儿外祖父母及胎儿舅舅进行外周血检测，经生物信息学分析，对发现的可能致病性位点进行

Sanger 测序验证，并根据检测结果建议先证者再次妊娠需行第三代试管婴儿，即胚胎植入前遗传学诊断（PGD）。

结果 WES 检测到胎儿组织标本 PEX7 基因 c.45_52dupGGGACGCC 插入移码杂合变异，PEX7 基因 c.527-1G>C 剪接位点杂合变异；母亲 PEX7 基因 c.45_52dupGGGACGCC 纯合变异；父亲 PEX7 基因 c.527-1G>C 杂合变异；外祖母 PEX7 基因 c.45_52dupGGGACGCC 杂合变异；外祖父 PEX7 基因 c.45_52 位点野生型；舅舅 PEX7 基因 c.45_52 位点野生型。该基因复合杂合突变目前数据库尚未见收录，依据 ACMG 分级该变异属于致病变异。行 PGD 获卵 9 枚，有 1 枚不携带父源和母源突变。

结论 本研究完整分析 PEX7 基因复合杂合突变导致的肢跟型软骨发育不良 1 型（Rhizomedlic chondrodysplasia punctata type1 ）家系的遗传学意义，产前诊断及 PGD 有助于避免患儿出生，为先证者的再次生育明确了遗传咨询方向，同时为妊娠期胎儿发育迟缓、长骨偏短、婴儿期夭折等疾病的临床分析提供了思路和参考。

Prenatal Diagnosis and Genetic Counseling of Co-occurrence of Complex Fetal CNVs

wei wang Bin Yu Jing Wang Jianbing Liu Ye Shi
Changzhou Maternity and Child Health Care Hospital

Background and purpose Nowadays, rather than rare monogenic disease, digenic or co-occurrence CNVs diseases attracted a great deal of attentions resulting from their severe expressivity and variable clinical phenotype, while rare study referred to prenatal diagnosis and counseling. This cohort study aims to provide suggestions of prenatal diagnosis and genetic counseling for these patients to guide their future pregnancies. We hope clinical counseling would be conducted to each patient with rare complex variants to prevent birth defects in the future.

Methods 2746 pregnant women were received prenatal screening using non-invasive Prenatal Screening (NIPS) followed by diagnosis with chromosome microarray (CMA).A total of 12 fetuses were confirmed as complex CNVs, which means a fetus carried two or more CNVs simultaneously. Parental peripheral blood samples were collected to perform parental validation studies with CMA, G-band karyotype analysis and whole genome low-coverage mate-pair sequencing (WGL-MPS) based on the size of imbalances.

Results Of the 2746 cases diagnosed with CMA, fetuses carried complex CNVs were identified as the proportional of 0.4% (12/2746). Follow-up parental validation study were considered and carried out in 8 of 12 complex CNV cases with the permission of patients. The primary results suggested that 62.5% (5 out of 8) fetus carried complex CNVs were parental inheritance, 50% (4/8) of validated cases were derived from maternal or paternal balanced translocation carrier. Habitual abortion was found in balanced translocation carrier family.

Discussion In regard of prenatal diagnosis and CNVs interpretation, CNVs origin analysis is a crucial basis after proband genetic analysis. Half of validated cases in this study were derived from their balanced translocation parents. Individuals carried this translocation are suffered from recurrent spontaneous miscarriage, infertility or birth of an affected child, while carrier themselves are phenotypically normal only with exchanging of genetic segment location in chromosomes. If parents chromosomal translocated region covers dosage sensitive gene, the CNVs transmitted might have association with pathogenic phenotype.

The complexity of microarray technology used in prenatal testing makes a requirement of counseling to patients. In our study, counseling was performed to all patients based on their CMA results and parental analysis. For *de novo* cases, the risk of recurrence of these complex imbalances is estimated 1% (except germinal mosaicism), which greatly encouraged patients to their next natural pregnancy after counseling. Considered with the cases carried complex CNVs transmitted by their balanced translocation parents, the risk of imbalances recurrence is relatively higher than *de novo* cases; therefore, genetic counseling has a guiding significance for these patients' future pregnancies. We recommended preimplantation genetic diagnosis (PGD) to increase the likelihood of successful pregnancy and decrease the genetic risk to offspring.

However, the expensive cost of PGD is a challenge for most families in China, maybe further attempts for natural conception is another way based on their own selection.
In conclusion, prenatal diagnosis and counseling are highly critical to guide patients' future pregnancies. We hope clinical counseling would be conducted to each patient with rare complex variants to prevent birth defects in the future.

6 例单卵双胎遗传学结果不一致及文献复习

蔡璐瑶 孙路明
同济大学附属第一妇婴保健院胎儿医学科& 产前诊断中心

目的 对单卵双胎遗传学结果不一致进行遗传学分析。
方法 回顾性分析 2017 年 9 月至 2020 年 12 月超声诊断为双胎、并在上海第一妇婴保健院经产前诊断为单卵遗传学结果不一致的 6 例孕妇。所有孕妇在超声下行双针法分别对两个羊膜腔进行羊水穿刺，获取双胎羊水进行染色体微阵列（chromosomal microarray analysis, CMA）检测，和（或）进行细胞培养行 G 显带核型分析，并使用短串联重复（short tendom repeat, STR）连锁分析排除隐性母源基因组干扰，同时进行合子性检测。
结果 发现 6 例单卵双胎染色体核型不一致，均为单绒毛膜性双羊膜囊双胎（monochorionic diamniotic, MCDA）。这 6 例病例一胎核型和芯片结果正常，另一胎遗传学结果异常，其中 3 例为 45,X，1 例为 47,XN,+21，1 例为 47,XN,+18，1 例核型 46,X,del(X)(q27)，芯片结果显示 Xq27.1q28 区域存在 15.830 区域拷贝杂合缺失，为致病性变异。
结论 绝大多数 MCDA 双胎为单卵双胎，但也存在双胎遗传学结果不一致的情况，建议分别从两个羊膜腔中抽取羊水进行产前诊断。未来有待进一步探讨其遗传学机制。

Factors Contributing to False Positive Non-invasive Prenatal Testing Results: a pilot study

Wei Liu Jie Li Zhaoxia Li
The Affiliated Drum Tower Hospital of Nanjing University Medical School

Background Non-invasive prenatal testing (NIPT) has been widely used to detect the fetal aneuploidies worldwide. However, false positive results could limit the application and bring psychological stress to pregnant women. We hoped to find the potential biological or technical causes by our study.
Methods Between January 2012 and May 2019, 628 pregnant women underwent prenatal diagnosis tests for positive NIPT results in our center. Among all, 10 participants with false positive NIPT results were enrolled, the general features of participants were documented and then peripheral blood and placental samples were also collected for sequencing analysis.
Results Of the 10 participants, P1 identified a duplicated region on chromosome 21; P2 identified a duplicated region on chromosome X and has systemic lupus erythematosus; growth restriction was noted in P9 at 31 weeks gestation; confined placental mosaicism (CPM) were found in samples from P3, P4, P5, P6 and P7.
Conclusion CPM and maternal conditions, such as copy number variants, autoimmune diseases and medical treatment, could affect the NIPT performance. Whether CPM has an effect on fetal growth remains to be further studied. NIPT is still a screening test and cannot be used as an alternative to invasive prenatal diagnosis.

无创产前筛查技术在除目标染色体以外检测的应用价值分析

何淑凤
无锡市妇幼保健院

目的 分析无创产前筛查技术在除目标染色体以外的意外发现中的应用价值。
方法 2017-01-23 至 2020-09-25 期间行无创产前筛查样本共 31094 例，其中 235 例无创意外发现病例，经咨询后 177 例接受介入性产前诊断，分析其产前诊断结果。
结果 无创性染色体数目异常 102 例接受介入性产前诊断，胎儿性染色体非整倍体阳性检出率 29.41%，嵌合体核型检出率 34.31%。45, X、47，XXX、47，XXY 及 47，XYY 四种核型中，47，XXY 阳性符合率最高，达 81.25%，其次为 47，XYY（55.56%）、47，XXX（45.46%），45，X（22.64%）最低。无创性染色体数目偏多未明确具体非整倍体类型的 13 例，真阳性 3 例，阳性预测值 23.08%；无创性染色体数目偏少 53 例，胎儿非整倍体 2 例，嵌合体 5 例，胎儿非整倍体阳性预测值 3.77%。染色体拷贝数变异额外补充报告并接受介入性产前诊断 75 例，51 例羊水 CMA 结果正常，24 例羊水 CMA 存在阳性结果，阳性预测值 32%。21 例 CMA 结果与无创额外补充报告结果一致，阳性符合率 28%。对 21 例 CNVs 的致病性进行分类，其中致病性 CNVs 占 19.05%（4/21），VOUS 占 80.95%（17/21）。
结论 随着技术的进步，无创产前筛查技术有望作为超声结果正常时的一线筛查技术。

Excluding embryos with two novel mutations in FREM2 gene by the next-generation sequencing-based single nucleotide polymorphism haplotyping

Xiaohui Yang[1,2,3,4,5] Yanlin Ma[1,2,3,4,5]
1.Hainan Provincial Key Laboratory for Human Reproductive Medicine and Genetic Research, The First Affiliated Hospital of Hainan Medical University, Hainan Medical University
2.Department of Reproductive Medicine, The First Affiliated Hospital of Hainan Medical University, Hainan Medical University
3.Hainan Provincial Clinical Research Center for Thalassemia, The First Affiliated Hospital of Hainan Medical University, Hainan Medical University
4.Haikou Key Laboratory for Preservation of Human Genetic Resource, The First Affiliated Hospital of Hainan Medical University, Hainan Medical University
5.Key Laboratory of Tropical Translational Medicine of Ministry of Education, Hainan Medical University

Background Fraser syndrome is a rare autosomal recessive malformation disorder, characterized by cryptophthalmos, syndactyly, urinary tract abnormalities and ambiguous genitalia. This condition is due to homozygous or compound heterozygous mutations in the FRAS1, FREM1, FREM2, and GRIP1 genes.
Purpose To describes a successful case of preimplantation genetic diagnosis (PGD) of Fraser syndrome (FS; OMIM 219000) with two novel FRAS1-related extracellular matrix protein 2 (FREM2) gene mutations. Methods: In the present study, we recruit a Chinese family with Fraser syndrome. Two novel mutations c.7542_7543insG and c.2689C>T in FREM2 gene were detected in this Fraser syndrome family by PCR-based sequencing. The next-generation sequencing-based single nucleotide polymorphism haplotyping was applied to detect these two mutations in 9 blastocysts obtained from the patients.
Results Finally, the patients received an embryo with heterozygous mutation and obtained one healthy baby.
Conclusion In conclusion, we for the first-time report two novel mutation in FREM2 gene associated the risk of Fraser syndrome and described a next-generation sequencing-based single nucleotide polymorphism haplotyping to select the 'right' embryos from patients with Fraser syndrome for in vitro fertilization treatment.

一例 21 号染色体同源罗氏易位胎儿的产前诊断

杨舒亭
湖南省妇幼保健院

目的 运用多种遗传学检测方法对一例 21 号染色体同源罗氏易位胎儿进行产前诊断，探讨其发生机制及生育风险，为遗传咨询及指导生育提供依据。
方法 应用 NIPT、染色体核型分析、SNP-Array 检测对该家系中胎儿进行产前诊断。
结果 孕妇因“NIPT 提示 21 三体高风险，Z 值 16.78”行羊水穿刺产前诊断，羊水染色体核型为 45,XN,der(21;21)(q10;q10)，SNP-Array 提示 21 号染色体长臂存在约 32.8Mb 杂合度丢失（LOH），父母染色体对照未见异常。探讨其发病机制可能为同源罗氏易位型 21 三体发生三体自救后的限制性胎盘嵌合，其生育风险包括同源罗氏易位导致的生育风险，胎盘染色体异常导致胎盘功能不良影响胎儿生长发育，21 号染色体 LOH 增加常染色体隐性遗传病风险等。详细告知孕妇及家属其生育风险，孕妇及家属决定继续妊娠。胎儿出生半年后随访其生长发育基本正常。
结论 运用多种遗传学检测方法进行产前诊断有助于探讨染色体异常的发生机制，综合评估其生育风险，为遗传咨询及决定胎儿去留提供更好的帮助。

基于全外显子组测序技术探讨神经系统遗传病的产前超声表型

房晓华 朱晓帆 朱朝锋 冯银 焦智慧 孔祥东 刘宁
郑州大学第一附属医院

目的 回顾性分析 15 个经遗传学分析已确诊或可疑神经系统单基因遗传病的胎儿产前超声表型，探讨神经系统遗传病的产前诊断线索，为家系遗传咨询提供依据。
方法 对系统超声检查发现与遗传相关指标异常的胎儿收集绒毛、羊水或流产组织标本，应用全外显子组测序（Whole Exome Sequencing,WES）技术对已排除非整倍体和 CNV 异常的胎儿标本及其父母外周血标本进行 Trio-WES 基因变异检测。
结果 胎儿主要超声异常指标包括：羊水过多（8/15）、肢体姿势异常（包括关节挛缩、姿势固定等）（6/15）、胎儿水肿（3/15）、脑部结构异常（2/15）、骨骼畸形（2/15），WES 共检测到 15 种基因（*KCNT2*、*FBXO11*、*ACTA1*、*KMT2D*、*PTPN11*、*SATB2*、*SOX4*、*CTNNB1*、*CIC*、*SPTAN1*、*RYR1*、*ERCC5*、*POLG*、*CAD*、*FGD1*）变异，其中，常染色体显性遗传（10/15），常染色体隐性遗传（4/15），X 染色体隐性遗传（1/15），常染色体显性遗传病例中多为新生变异（9/10），15 个基因共检出 19 种基因变异类型，其中新变异 14 个，根据变异类型及生物信息学软件预测可能均为致病性变异。
结论 神经系统遗传病产前超声主要表现为胎儿羊水多和肢体姿势异常，可为产前诊断提供重要线索；WES 有助于胎儿超声异常的遗传学诊断，能够准确地预测胎儿预后和再次妊娠复发的风险，改善产前管理和妊娠结局，为家系遗传咨询提供依据。

Prenatal diagnosis of skeletal dysplasia by whole exon sequencing

张玢
常州市妇幼保健院

Objective For fetuses with skeletal dysplasia (SD) indicated by prenatal ultrasound, karyotype, chromosomal microarray analysis (CMA) and whole exome sequencing (WES) were used for genetic diagnosis, which provided theoretical basis for prenatal diagnosis and genetic counseling.
Methods From January 2019 to March 2021, 20 fetuses with skeletal dysplasia were detected by ultrasound in Changzhou Maternal and Child Health Hospital affiliated to Nanjing Medical

University. Fetal amniotic fluid was tested by karyotype, CMA and WES at the same time. Sanger test was performed on the peripheral blood of parents.
Results Among the 20 cases of SD fetuses, 1 case was found to be pathogenic copy number variants (CNV), and 15 cases were detected for pathogenic / possible pathogenic gene mutations (*FGFR3*、*COL2A1*、*COL1A1*、*COL1A2*、*RUNX2*、*LMX1B*、*GLI3*、*DYNC2H1* and *ALPL*), of which 8 were *De novo* mutations. And 1 case was *TBX4* gene mutation with variant of uncertain significance. There were 3 cases with no abnormalities after the above detection.
Conclusion Most of the SD fetuses detected by ultrasound due to gene mutations. Therefore, karyotype and CMA are not suitable for first-line prenatal diagnosis. Prenatal WES should be used as an important molecular genetic testing tool for prenatal healthcare to provide accurate prenatal prognosis and management. However, the WES diagnosis of SD fetuses indicated by ultrasound after 24 weeks gestation is facing a big challenge.

父源性染色体单纯性 3q 微重复综合征胎儿产前诊断和遗传学分析

郑来萍 何轶群
广东省妇幼保健院

目的 探讨父源性染色体单纯性 3q 微重复综合征表型特征和遗传咨询。
方法 联合应用胎儿羊水细胞高分辨染色体 G 显带核型分析和染色体微阵列(chromosome microarray analysis, CMA)基因芯片技术对胎儿进行产前诊断，抽取胎儿父母外周血行 CMA 检测以确定遗传来源。
结果 该家系三例胎儿染色体 G 显带核型结果均为 46,XN,dup(3)(q25q26.1)；胎儿与父亲的 CMA 检测结果一致，提示为 arr[hg19] 3q25.33q26.1(159,336,333-166,924,969)x3,即 3 号染色体长臂 q25.33-q26.1 位置存在 7.6Mb 片段重复,涉及 30 个基因，胎儿染色体重复来源于父亲。母亲 CMA 检测结果未发现明显异常。
结论 父源性 3q25q26.1 微重复可能为超声提示胎儿侧脑室增宽、胎儿生长受限和羊水过多的遗传学病因，产前进行高分辨 G 显带核型和 CMA 检测检测可明确诊断,为该家系的临床诊断及遗传咨询提供依据。

常染色体显性多囊肾病 PKD1 基因的检测与产前诊断

李慧君
南京大学医学院附属鼓楼医院

目的 探讨 8 个多囊肾病家系的致病突变位点，为常染色体显性多囊肾病（autosomal dominant polycystic kidney disease, ADPKD)的遗传咨询和产前诊断提供理论依据。
方法 应用全外显子测序和高通量测序技术检测 8 个独立家系中先证者的 *PKD1*、*PKD2* 基因，通过 Sanger 测序进行位点验证和家系分析，结合多囊肾疾病数据库和蛋白变异预测软件进行生物信息学分析。
结果 检测出 8 个 *PKD1* 突变，包括 5 个无义突变和 3 个错义突变。其中 4 个无义突变 *PKD1*：c.7555C>T，c.7288C>T，c.4957C>T 和 c.11423G>A 已报道为 ADPKD 的致病突变，1 个错义突变 *PKD1*：c.2180T>G（p.Leu727Arg）报道为可能致病的变异；3 个突变位点未曾报道过：，c.6781G>T（p.Glu2261*），c.109T>G（p.Cys37Gly），c.8495A>G（p.Asn2832Ser），其中无义突变 *PKD1*：c.6781G>T（p.Glu2261*）为致病突变，错义突变 *PKD1*：c.109T>G（p.Cys37Gly）和 c.8495A>G（p.Asn2832Ser）为可能致病的变异。2 个家系的产前诊断结果显示，家系 1 胎儿携带与先证者相同的突变，家系 2 胎儿未携带与先证者相同的突变。

结论 鉴定出 8 个 ADPKD 家系的 *PKD1* 基因突变，其中包括 3 个未曾报道的新突变，丰富了 ADPKD 基因突变谱。以鉴定出的变异为理论依据，成功对 2 个家系进行产前诊断，为临床 ADPKD 出生缺陷提供咨询。

全外显子测序鉴定一例胎儿致死软骨发育不良基因突变

黄盛文
贵州人民医院

目的 对于一例 B 超提示致死性软骨发育不良的流产胎儿组织及其父母应用全外显子测序技术检测，并进行 Sanger 测序验证，筛查软骨发育不良基因的致病基因，为该家庭提供遗传咨询。
方法 先证者之流产胎儿组织，B 超提示胎儿(孕 21 周)致死性软骨发育不良。胎儿超声结构描述有：胸廓狭小，桡骨短小，弯曲，骨化不良，腓骨短小，弯曲呈“听筒征”。签署书面知情同意后，采集先证者的流产胎儿组织，以及先证者和其丈夫外周血提取 DNA，进行全外显子测序和 Sanger 测序。
结果 先证者之流产胎儿组织 17 号染色体上 FGFR3 基因 7 号外显子的 c.742C>T 发生突变：FGFR3：NM_000142.4:exon1: c.742C>T:p.R248C，父母均未发生突变。根据 ACMG 指南，该变异初步判定为致病突变位点（PS2_VeryStrong+PS4+PM1+PM2+PP3+PS3_Supporting）：该变异为家系样本中经双亲验证的新发变异，文献报道共在 4 例骨骼发育不良疾病患者中检测到该变异为新发变异；文献报道共在大于 15 例骨骼发育不良疾病患者中检出该变异；该变异发生于 Protein kinase domain Serine-threonine/tyrosine-protein kinase; catalytic domain 功能结构域； 该变异在多个人群数据库中没有发现；经多种统计方法（REVEL）预测，结果显示该变异对基因或基因产物造成有害影响；文献报道，二聚化测量实验提示该变异导致基因功能受损。该变异在 Clin-Var 数据库中评定为 P，在 HGMD 数据库中评定为 DM。
结论 经全外显子和 Sanger 测序，确诊先证者为致死性软骨发育不良，致病突 FGFR3 基因，c.742C>T:p.R248C，先证者父母均未发生突变。测序结果可为患者及家属遗传咨询提供依据。

1 例复杂性葡萄胎与三体嵌合胎融（混）合的分子诊断

王永化
广东省人民医院

摘要：患者 24 岁，G1P0，平素月经规则，本孕为自然受孕，停经 4^{+6} 周测血 βHCG 为 7810mIU/mL。停经 7 周妇科彩超提示：宫内可见妊娠囊回声，内可见一大小 3.7×2.8cm 稍强回声光团、边界清、形态不规则、内回声欠均匀、未见明显胚芽及原始心管搏动；同时测血 βHCG 为 92635mIU/mL。清宫取胎儿组织行 CMA 检测，结果为：arr[hg19]（1-6）×2 mos hmz,(7)×2.1~2.3,(8-22) ×2 mos hmz。其 Log2 Ratio 和 Allele Difference 结果提示除性染色体和 7 三体外，所有染色体拷贝数为 2，但均存在 3 条带或 4 条带交替的情况，非常罕见。在排除三倍体和母细胞污染等情况后，结合葡萄胎和双胎融合带型情况，我们得出此胎为：双雄受精的葡萄胎和 7 三体胎的双胎融（混）合胎。其中，Allele Difference 的 3 条带实质为 7 条带的融合带，而 4 条带则为双雄受精的纯合区域。

深圳地区 5563 例地中海贫血携带者基因检测结果及频数分析

李高驰 曹宪振 欧德标 魏凤香 刘维强 裴元元
龙岗区妇幼保健院

目的 了解深圳地区 α 与 β 地中海贫血患者的基因突变类型，为开展深圳地区 α 与 β 地中海贫血的遗传咨询，产前诊断和预防计划提供参考。

方法 回顾性分析 2020 年 7 月至 2021 年 6 月深圳市龙岗区妇幼保健院地中海贫血基因检测阳性的 1863 名地贫携带者的地贫基因突变类型。
结果 1863 名地中海贫血携带者中 1139 名 α 地中海贫血携带者,其中东南亚型缺失(--SEA)947 例，(-3.7)缺失 96 例,左侧缺失 (-4.2)73 例，缺失型 HbH 病(-SEA/-3.7)9 例，缺失型 HbH 病(-SEA/-4.2)14 例。724 名 β 地中海贫血患者,其中 ISV-Ⅱ-654 杂合子 421 例，CD41-42 杂合子 195 例，CD28 杂合子 71 例，CD17 杂合子 19 例，CD29 杂合子 7 例，CD43 杂合子 7 例，βE 杂合子 5 例，15 名 α β 复合型地中海贫血患者。
结论 深圳地区的 α 地贫人群中东南亚缺失型占主导地位，而 ISV-Ⅱ-654 突变与 CD41-42 突变是 β 地中海贫血最主要的基因突变类型。

Regions of homozygosity detected by chromosomal microarrays in prenatal diagnosis in the South of China

Di Ma Mei Ye Wenlong Hu Lijuan Wang Hui Gao Yaqin Song Yuhua Hu Shayan Wang Hui Guo
Department of Forensic Evidence Laboratory, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen 518020, Guangdong, China

PURPOSE Chromosomal microarrays (CMA) incorporate SNPs can detect regions of heterozygosity (ROH) in the genome in addition to copy number variants. Here, we investigate the general occurrence and clinical significance of ROH in prenatal diagnosis.
Methods We recruited 3589 prenatal cases and evaluate the frequencies and implications of ROH detected by Affymetrix 750 K or CytoScan HD array platforms. Cases were reported based on the American College of Medical Genetics and Genomics (ACMG) guidelines. ROH cases with size over 5 Mb were further analyzed. The common ROH and cases with multiple ROH for identity-by-descent (IBD) were reviewed. We assessed potential candidate genes for autosomal recessive disorders in cases with recurrent ROH. We also explored the cases suspected to uniparental disomy (UPD) or imprinting disorders.
Results A total of 18.58% (667/3589) of the cases, at least one ROH on an autosome was detected. We identified 3 common regions where ROH appeared in at least 1% cases as potentially representing ancestral haplotypes in our population. The region most involved with homozygosity was 3p21.31p21.1 (5.1 %), followed by16p11.2p11.1 (4.54%), 11p11.2p11.12 (2.90%). In 2.73% of the cases (98/3589) had multiple ROHs in different chromosomes and for about 0.8% (28/3589) ROH suggested offspring from third to fifth grade, which more likely to have a clinical impact of autosomal recessive diseases. 569 ROH were concentrated on a single chromosome and of those 0.5% (20/3589) findings were suggestive of UPD.
Conclusions ROH are common findings in prenatal diagnosis, knowing recurrent ROHs in the population may provide further identification of the “hotspot” regions for carrier screening. Our data also demonstrate that interpretation of ROH can unravel those cases with potential clinical implications.

Microduplication of 15q13.3 on gene CHRNA7 in a Chinese family with neuropsychiatric symp-toms

Lan Yang
Affiliated Wuxi Matemity and Child Care Hospital of Nanjing Medical University

Objective The study gives prenatal diagnosis of a fetal microduplication of 15q13.3 and presents neuropsychiatric spectrum disorders with human Cholinergic Receptor Nicotinic Alpha 7 (CHRNA7) duplication in a Chinese family.
Methods With a combination of genetic consulting and family-wide chromosome analysis through karyotyping, SNP-CMA and q-PCR analysis.

Results The study showed that the 15q13.3 microduplication is potentially associated with language development delay and neuropsychiatric disorders, which can provide further evidence for psychiatric phenotypes with overdosage of CHRNA7.
Conclusion When molecular testing techniques such as the SNP microarray are employed to diagnose this microduplication syndrome, precise locus diagnosis and proper genetic counseling should be provided.

深圳市龙岗区精子膜功能完整性与精液各参数关系的研究

曹宪振 魏凤香 李高驰 白江涛
深圳市龙岗区妇幼保健院

目的 研究精子膜功能完整性与计算机辅助的精液分析 (CASA)各项参数的关系。
方法 使用精子膜功能检测试剂盒和精子质量检测仪对 45 例生育男性和 131 例不育男性进行精子膜功能完整性检测及精液自动化分析。
结果 生育组与不育组精子膜功能完整性差异有非常显著性 (P <0 .0 1) ;精子膜功能完整性正常组与异常组 CASA 各项参数除精子平均移动角度、精液量、pH 值外 ,其他差异均有显著性。
结论 精子膜功能完整性检测可作为 CASA 的必要补充 ,同时结合 CASA 对于男性不育症的诊断、治疗和科研等方面有重要的临床意义

一例 46,XX, SRY 基因阳性女性胎儿家系的产前诊断与遗传分析

李磊
珠海市妇幼保健院

本文报道了 1 例染色体核型为 46,XX,Y 染色体性别决定基因（sex-determining region on the Y chromosome, *SRY*）阳性的孕妇和女性胎儿。孕 12 周$^{+6}$时，超声显示胎儿颈项透明层增厚，羊水染色体核型和定量荧光聚合酶链反应检测结果显示胎儿核型为 46,XX,*SRY* 基因阳性。但 B 超显示胎儿社会性别为女性，与 46,XX,*SRY* 阳性男性综合征表型不一致。通过荧光原位杂交技术分析结果发现胎儿 1 条 X 染色体长臂 2 区 8 带（Xq28）包含 Y 染色体短臂 1 区 1 带 3 亚带（Yp11.3）片段。同时，染色体微阵列分析技术检出 Yp11.31p11.2 的片段重复，长度约 1 Mb，证实了胎儿 X 染色体含有部分 Y 染色体片段，与孕妇一致。经遗传咨询，胎儿父母选择继续妊娠至足月分娩，婴儿生后随访未见异常。

全外显子组测序技术在胎儿骨骼发育异常产前诊断的应用

崔慧敏
连云港市妇幼保健院

目的 探讨全外显子组测序技术在胎儿骨骼发育异常产前诊断的应用价值。
方法 通过抽取羊水或引产后的胎儿皮肤组织获取胎儿标本，利用全外显子组测序技术对产前超声检查发现骨骼发育异常的胎儿进行遗传学检测。
结果 在 6 个家系中发现了与骨骼发育异常相关的致病或可能致病性变异，涉及 COL2A1、COL1A1、COL1A2、GNAS、BRAF、FGFR3 6 个基因。
结论 全外显子组测序技术可极大的提高骨骼发育异常胎儿遗传学病因的检出率，为临床医生进行遗传咨询及后续诊疗提供了科学依据。

Prenatal features of 16p11.2 recurrent microdeletion syndrome: A retrospective case series

Chengchu Liang
Department of Medical Genetics Center, Guangdong Women and Children Hospital, Guangzhou, China

Objective Fetuses with 16p11.2 deletion presented a wide phenotypic spectrum. Most cases of 16p11.2 microdeletion syndrome (DS) are reported after birth and few studies evaluated the prenatal phenotype; here, for the first time, we investigate these aspects in a series of fetus with different types of 16p11.2DS in order to present the experience on prenatal features of 16p11.2 microdeletion syndrome.
Materials and methods This study retrospectively investigated 26 cases with 16p11.2 microdeletions diagnosed prenatally by chromosomal microarray analysis (CMA) from a cohort of 20,755 pregnancies between May 2016 and December 2020 in a Chinese tertiary healthcare center. The prenatal ultrasound features, inheritance of the CNVs, and their effects on the pregnancy outcome were analyzed.
Results Twenty-six pregnancies with 16p11.2 microdeletion were identified in our center. Most individuals with 16p11.2 deletion presented various ultrasound soft indicators anomalies, we found skeletal (30.77%, 8/26), urinary system abnormalities (23.08%, 6/26) and cardiac abnormalities (15.38%, 4/26) being the most common finding of structure defects, besides, facial cleft deformity, cleft palate, absent radius and anal atresia (n=2) were the newly prenatal ultrasound features finding of 16p11.2DS. Of note, the rate of termination of pregnancy (TOP) in the cases with abnormal ultrasound was significantly higher than that in the cases presented with normal ultrasound (100% vs 31.25%). but the rate of TOP was not significant associated with the inheritance of the deletions (57.14% in the de novo group vs 60% in the inherited group).
Conclusion We retrospectively reviewed the ultrasound findings for a cohort of fetus with different types of 16p11.2DS. Fetuses with 16p11.2 deletion presented a wide phenotypic spectrum, our experience further demonstrated the high correlation between 16p11.2 microdeletion and skeletal, urinary, cardiac abnormalities. Structural anomalies of the facial cleft deformity, cleft palate, absent radius and anal atresia were newly identified phenotypes during prenatal period. This study facilitates a better understanding of the intrauterine phenotypic heterogeneity and might provide some helpful information for the prenatal genetic counseling of 16p11.2 microdeletions.

八例 Wolf-Hirschhorn 征的产前诊断及文献回顾

邢娅 刘勇 曲晓星 邓林贝 周佳 杨颖俊 郭茗 孙路明
上海市第一妇婴保健院

目的 报道八例 wolf - hirschhorn 综合征(WHS)胎儿，探讨 WHS 的产前诊断，通过回顾以往文献对产前 Wolf-Hirschhorn 综合征的临床表型进行分析总结。
方法 对八例 WHS 胎儿的产前诊断指征、产前超声表现、以及细胞及分子遗传学检测结果进行分析。
结果 七例胎儿由于产前超声异常指征进行产前诊断检测，另外一例是由无创产前筛查提示。其中六例通过传统核型分析及单核苷酸多态性（SNP）芯片诊断，两例仅通过 SNP 芯片诊断。结合我们的病例以及 20 篇文献中的 35 例产前病例，WHS 最常见的两个超声特征是宫内生长受限（IUGR）(95%)和典型的面部外观(75.6%); 其他不常见的表型包括：肾发育不全(34.9%)、唇腭裂(27.9%)、心脏畸形(30.2%)、内翻足/内翻手(23.3%)、大脑异常(23.3%)和 NT/NF 增加(16.3%)。
结论 WHS 最常见的宫内表型是严重的 IUGR 和典型的颅面部特征，同时会伴有一些其他非特异性表现。无创产前检查(NIPT)技术可用于 WHS 筛查，SNP 芯片可以提高 WHS 的诊断的准确性，特别是针对一些隐匿性的异常。

Genetic counseling and prenatal decision for hemoglobin H disease caused by the rare α2 codon 30 (-GAG) (HBA2: c.91_93delGAG) mutation and the SEA deletion: case series study

Jianhong Chen
Huizhou The First Women and Children's Hospital

Objective we report a rare mutation on the α2-globin gene, *HBA2*: c.91_93delGAG and its potential functions.
Case report We mainly described four patients with hemoglobin (Hb) H disease caused by the rare mutation and the SEA deletion but diversity in clinical presentation. Two had survived to adulthood with normal physical and mental development, except for mild anemia. However, two were children, who had more severe clinical manifestations. One child had developmental disorders of speech and language and mild growth retardation, and the other child suffered from severe hemolytic crises precipitated by infection and received blood transfusion.
Conclusion This study is of great significance for clinicians to provide genetic counseling to couples at-risk of having offspring with Hb H disease and let them make the pregnancy decision, particularly reduce the occurrence of severe Hb H disease.

子痫前期患者检测孕中期 β-HCG 与孕后期 D-二聚体的临床意义

潘沅
珠江医院

目的 探讨子痫前期孕妇孕中期 β-HCG、孕后期 D-二聚体水平与疾病的发生及轻重程度的关系。
方法 回顾性分析 2015.1-2016.12 在南方医科大学珠江医院接受孕中期筛查并成功随访直至分娩的 54 例单胎孕妇孕中期血清学筛查 β-HCG MoM 值和孕后期血浆 D-二聚体结果与孕妇发生子痫前期及其轻重的情况。
结果 在 54 例患者资料中，39 例为正常孕妇，15 例经诊断为子痫前期患者，两组比较，孕中期 β-HCG MoM 值差异不显著；孕后期血浆 D-二聚体水平具有显著差异（P＜0.001）。患者组按轻重程度分组，重度组与正常组、轻度组具有显著性差异（P＜0.001、P＜0.01）。
结论 孕中期血清学筛查 β-HCG 对孕妇患子痫前期的预测意义不明显；孕后期血浆 D-二聚体水平对判断子痫前期孕妇的严重程度有显著的意义。

孕妇年龄风险与胎儿染色体异常发生率的相关性分析

李辉斌
南方医科大学珠江医院

目的 探讨高龄孕妇各年龄段与胎儿染色体异常的相关性。
方法 回顾性分析 925 例高龄孕妇(≥35 岁)，行绒毛膜穿刺、羊膜腔穿刺和脐带穿刺收集绒毛、羊水和脐血进行培养及染色体 G 显带核型分析，分析高龄孕妇与胎儿染色体异常率及类型的分布情况，按年龄分组(35-37 岁组、38-40 岁组、40 岁以上组)，用 χ2 检验各年龄组的异常率的差异。
结果 在 925 例高龄孕妇的羊水染色体核型分析中，共检出异常核型 66 例(7.13%)，其中染色体数目异常 53 例(6.93%)，占异常构成比 80.3%，其中 21 三体比例最高 29 例(3.14%)，占异常构成比 43.93%，18 三体/13 三体/性染色体数目异常比例分别为 11 例（1.19%)/4 例(0.43%)/9 例(0.97%)。结构异常 13 例(1.05%)，占异常构成比 19.7%，其中易位 8 例(0.86%)，倒位 5 例(0.54%)。从 35 到 37 岁、38 到 40 岁、40 岁以上 3 个年龄组的染色体核型异常率依次为 5.49%、

6.02%和 10.38%，孕妇年龄递增胎儿染色体异常率逐年上升。各年龄组间总体异常率差异有统计学意义($\chi^2=6.436$，$P=0.04$)。
结论 胎儿染色体异常的风险随孕妇年龄的增长而增加，结构异常的分布与母亲年龄因素相关性，40 岁以上胎儿染色体总体异常率显著上升。对高龄孕妇进行产前诊断染色体核型分析是避免染色体异常儿出生的重要手段。

高频超声诊断新生儿 III 型食管闭锁的研究

乞艳华 邬晋芳
西安交通大学第二附属医院/西北医院

目的 通过回顾分析 42 例经手术修复的 III 型 EA 新生儿临床及超声资料，旨在探讨高频超声诊断评估 III 型 EA 的效果。
方法 收集经我院诊治的 III 型 EA 新生儿临床资料及影像学资料，对比高频超声与 CT 及手术诊断的准确率。
结果 42 例 III 型 EA 患儿，IIIa 型 13 例，IIIb 型 29 例。超声正确诊断 39 例，准确率 92.8%，IIIb 型准确率 100%，IIIa 型准确率 76.9%。食管三维 CT 诊断准确率 100%。
结论 高频超声对 III 型 EA 的诊断有较高的准确度，可以测量盲端间距，为手术方案制定提供重要信息。

Study on the correlation between neonatal esophageal atresia and VATER/ VACTERL association and review of prenatal data, a single center study in china

yanhua Qi
Department of Ultrasound, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi Province, China.

Background Most EA+/-TEF neonates were diagnosed after birth. EA+/-TEF is one of the core anomalies of VATER/VACTERL association. So, it is necessary to clarify the probability of EA+/-TEF neonates diagnosed as VATER/VACTERL association.
Methods 70 EA+/-TEF neonates from Shaanxi province and partial regions of northwest China were evaluated against historical and strict definition of VATER/VACTERL association. Their prenatal data were retrospectively analyzed.
Results 44 neonates were isolated EA+/-TEF. The other 26 neonates had at least one defect besides EA. Four cases had multiple malformations that were outside the criteria for VATER/VACTERL association. Among the other 22 cases, 86% (19/22) fulfilled two diagnostic criteria of VATER/VACTERL association, and 14% (3/22) met three diagnostic criteria, which meant only 4% (3/70) EA+/-TEF cases had VATER/VACTERL association according to the strict definition. 19 neonates were premature, and 26 neonates were low birth weight.
Conclusion This study indicates that a neonate with EA+/−TEF has little probability to have VATER/VACTERL association. EA+/−TEF in a neonate should be given fully examination to avoid over-diagnosis of VATER/VACTERL association.

一例 12p 三体伴多发畸形胎儿的产前诊断

钟银环
广东省妇幼保健院

目的 对一例超声发现第三脑室后方无回声声像、心脏增大的胎儿进行临床、细胞遗传学与分子遗传学分析，以明确其可能的遗传学病因。
方法 对胎儿进行影像学检查，抽取胎儿的脐带血细胞进行 G 显带染色体核型分析、单核苷酸多态性微阵列检测(single nucleotide polymorphism array，SNP array)。
结果 超声提示胎儿二尖瓣、三尖瓣轻度返流，心胸面积比增大，核磁共振成像显示胎儿大脑皮质发育异常，符合多小脑回畸形改变，胎儿脐血染色体核型为 46,XX,inv(9)(p12q13),der(12)del(12)(p13.3)dup(12)(p13.3p11.1)，SNP array 结果为 arr[hg19] 12p13.33(173,786-1,169,700)x1,12p13.33p11.1(1,169,859-34,835,641)x3。
结论 该胎儿为完全 12p 三体综合征，12p13.33 区段的缺失及 12p13.33p11.1 区段的重复为该胎儿的重要遗传学病因。胎儿大脑发育异常，多小脑回畸形的改变拓展了 12p 三体的表型谱。在产前诊断中联合多种检测技术，可得出更加精准的检测结果，为产前诊断及遗传咨询提供更准确的遗传学信息。

一例 2-三体和 UPD(2)嵌合的胎儿

周慧 陈亚军 曾宪琪 张鑫荣 伍丽婷
韶关市妇幼保健院

目的 染色体数目异常是胎儿流产中最常见的遗传因素，通过一例 2 号染色体三体和 UPD(2)嵌合胎儿的诊断，对染色体数目嵌合型异常和 UPD 等特殊情况进行分析。
方法 使用胎儿无创产前 DNA 检测对孕妇进行染色体数目异常的筛查，进而通过羊水细胞核型分析和染色体微阵列分析技术进行产前诊断。
结果 胎儿无创产前 DNA 检测结果为 2 号染色体数目偏多，后经羊水穿刺行羊水细胞核型分析结果为 47,X#,+2[2]/46,X#[104]，CMA 检测结果为可能存在 2-三体和 UPD(2)的嵌合体，2-三体比例约为 20%。
结论 低比例 2 三体可存活至孕中期无超声异常；本病例我们认为是由三体自救形成的三体和 UPD 嵌合体。

一例 18p 四体胎儿的产前诊断

周慧 陈亚军 李毅 张鑫荣 伍丽婷
韶关市妇幼保健院

目的 18p 四体综合征发生率为 1/180000-1/140000，通常被认为是缘于母体第二次减数分裂时染色体的不分离以及着丝粒的异常分离。我们通过产检流程发现一例 18p 四体胎儿。
方法 对该孕妇进行常规产检及血清学筛查，结合孕妇高龄行羊水穿刺术，对羊水细胞进行核型分析和染色体微阵列分析检测。
结果 血清学筛查结果为 18 三体临界风险，羊水细胞核型分析结果为 47,X#,+mar，CMA 检测结果为 **18p×4。**羊水细胞核型分析结合 CMA，考虑 mar 来源为 18p，最终结果解释为 **18p** 四体综合征。
结论 细胞核型分析发现 mar 染色体，可通过 CMA 检测进一步确认来源，对病例更准确的进行诊断。

政府主导的出生缺陷防治工程对高龄孕产妇出生缺陷的干预效果研究

何瑶 张丽霞 主桂莲 王志伟 吴海倩 王雷雷 施庆喜
连云港市妇幼保健院

目的 评估政府主导的出生缺陷防治工程（即“健康宝贝工程”）对高龄孕产妇出生缺陷的干预效果。
方法 采用前瞻性队列研究，选择 2018 年 1 月至 2019 年 7 月在连云港市妇幼保健机构建立围产保健手册的高龄孕产妇，根据纳入标准分为工程实施内人群和工程实施外人群队列。采用回顾性队列研究，通过妇幼信息平台选取 2016-2017 年在连云港市建册的高龄孕产妇建立工程实施前人群队列。三组队列均追踪孕期保健、定期检查、妊娠结局等情况，随访至婴儿出生后 12 月龄。使用描述性统计学方法分析实施效果，率的比较采用 c^2 检验，$P < 0.05$ 差异有统计学意义。
结果 （1）本研究共纳入高龄孕产妇 3146 人，失访 158 人，失访率 5%。（2）工程实施后高龄孕产妇孕期保健意识及检查依从性增加。孕期无创 DNA 检查工程实施内 420 人（41.9%）、工程实施外 173 人（19.1%）、工程实施前 161 人（13%），差异有统计学意义（P=0.000）。孕期产前诊断工程实施内 108 人（10.8%）、工程实施外 28 人（3.1%）、工程实施前 128 人（10.3%），差异有统计学意义（P=0.000）。（3）工程实施带动项目开展，新生儿疾病筛查率呈现上升趋势。新生儿遗传代谢病筛查率工程实施内、实施外及实施前分别为 97.0%、94.5%、95.5%，差异有统计学意义（P=0.032）。新生儿听力筛查率工程实施内、实施外及实施前分别为 97.5%、98.8%、94.5%，差异有统计学意义（P=0.000）。（4）阳性个案均及时给与医学指导及干预。工程实施内确诊染色体异常胎儿 8 例，确诊新生儿遗传代谢病 3 例；工程实施外确诊染色体异常胎儿 2 例；工程实施前确诊染色体异常胎儿 2 例。
结论 政府工程的实施对高龄孕产人群的出生缺陷防干预效果显著，有效推动了出生缺陷综合防治工作的开展，极大地减轻了社会和家庭经济负担。

Prenatal diagnosis of a 4.5-Mb deletion at chromosome 4q35.1q35.2: Case report and literature review

Xianrong Qiu Gefei Xiao
Department of Clinical Laboratory (Institute of Medical Genetics), Zhuhai Center for Maternal and Child Healthcare, Zhuhai, China.

Objective Interventional prenatal diagnosis (IPD) was performed in a case with a high risk of chromosome 4q terminal deletion discovered by noninvasive prenatal testing (NIPT). The genes contained in the copy number variation (CNV) regions and their breaking sites were analyzed. Additionally, the genotype-phenotype correlation regarding this CNV was reviewed.
Methods Chromosome karyotype analysis was performed on amniotic fluid cells and peripheral blood lymphocytes of the parents and brother by means of the conventional G-banding technique. Then, chromosomal microarray analysis (CMA) was used to assess the DNA samples of individuals with abnormal karyotypes and determine the CNV status of the overall genome.
Results The results showed that there were no abnormalities in the karyotypes of the brother and father. Conversely, the mother’s karyotype was 46, XX, del (4)(q35.1). The karyotype of chromosome 4 in the amniotic fluid cells was consistent with that in the maternal peripheral blood. The CMA results showed a partial deletion of the 4q terminus in both the fetus and his mother. The deletion region was arr[GRCh 37]4q35.1q35.2(186,431,008-190,957,460)×1, and the loss size of the CNV was approximately 4.5 Mb and involved 38 OMIM genes, including *SORBS2*, *TLR3*, and *CYP4V2*. The father’s CMA result showed no abnormalities.
Conclusion This case and some reviews indicate that the phenotype resulting from 4q terminal deletion is quite variable. To establish more precise genotypic-phenotypic correlations, more detailed genetic analysis is needed to clarify the genetic mechanisms.

政府惠民工程中不同血清学产前筛查方案的卫生经济学研究

毛华芬 王雷雷 江平 郑安舜 冯丹红 汤欣欣 尹婷 王志伟
连云港市妇幼保健院

目的 探讨母血清学产前筛查二联和三联两种筛查方案的卫生经济学成本效益，为政府选择经济合理的产前筛查方案提供参考依据。
方法 以 2018 年 2 月至 2019 年 9 月在连云港市妇幼保健院进行三联血清学产前筛查的 45600 例孕妇为研究对象，分别计算各孕妇在二联筛查方案和三联筛查方案中的风险值，采用卫生经济学的方法比较分析二联筛查与三联筛查在目标疾病中的检出情况及费用性价比等方面的差异，同时结合产前诊断和临床随访结果，根据筛查投入与社会资源成本进行换算，比较两类筛查的卫生经济学成本效益。
结果 参加产前筛查的 45600 名孕妇，三联筛查高风险患者中确诊 21-三体综合征 16 例，18-三体综合征 4 例，二联筛查高风险患者中确诊 21-三体综合征 12 例，18-三体综合征 4 例。综合筛查成本和漏筛病例所造成的经济损失，每例二联筛查的综合费用比三联筛查的综合费用高 11.1%。
结论 虽然母血清产前筛查三联筛查的直接筛查成本高于二联筛查，但卫生经济学成本效益优于二联筛查，适合用于政府惠民工程的出生缺陷筛查。

不同超声指征对产前诊断染色体异常胎儿的预测价值

杨鹏 唐凯
宝鸡市妇幼保健院

目的 探讨不同超声指征在胎儿染色体异常诊断中的临床价值及其对妊娠结局的指导意义。
方法 回顾性收集 1071 例胎儿的临床、细胞分子遗传学、超声检测数据及其妊娠结局。以超声指征为对象，病例分为 4 组，比较染色体异常检出率，分析各组染色体异常与妊娠结局的关系。
结果 染色体异常 54 例，包括 Bobs 检出的 5 例微缺失微重复，异常检出率 5.04%。单个产生软指标组染色体异常检出率最低为 2.50%，多个超声软指标组和单个结构畸形组检出率分别为 5.69%和 5.17%，多个结构畸形组检出率最高为 26.42%。
结论 证实了超声指标作为临床选择侵入性检测的必要性，结合病变发生部位、时间以及遗传学检测结果，给临床医生对预后判断和产前诊断提供依据，同时超声和血清学或 NIPT 筛查的联合，不仅为产前诊断方法的选择提供风险评估，并且对嵌合体的预后评估提供数据支持。

1 例听力障碍患儿的基因诊断及产前诊断

曾成英[1] 万波[1] 陈燕碧[1] 丁红柯[2]
1.南方医科大学第三附属医院（广东省骨科医院）
2.广东省妇幼保健院

目的 对 1 例听力障碍患儿及其父母进行基因突变分析及产前诊断。
方法 患儿女，4 岁半，临床表现为新生儿听力筛查未通过，1 岁半起讲话，部分发音欠清晰，双外耳道正常，鼓膜内陷，双侧听力中轻度异常等；通过二代测序对先证者进行遗传学分析。父母无临床症状，因母亲再次妊娠，考虑先证者听力障碍并本孕唐氏筛查 DS 临界风险，来我中心进行遗传咨询。对患儿及双亲进行外显子测序。发现疑似致病突变后，知情告知行第二胎产前诊断。
结果 发现先证者 USH2A 基因不同位点的双重杂合突变，其中 c.13079delG（p.Ser4360Thrf*13）杂合为疑似致病变异，遗传自母亲，c.10741-9C＞A 杂合为意义不明的变异，遗传自父亲，该位点位于内含子区域。本实验室参考人群基因组数据库中未发现该突变，后者在多个剪接变异预测软件结果中预测都提示很可能影响剪切，在人群变异频率为 0。产前诊断结果提示胎儿基因型同先证

者，夫妇双方了解该疾病之后，选择保留胎儿，目前胎儿已出生，新生儿听力筛查未通过，暂未发现其他异常。

结论 USH2A 基因变异与 Usher 综合征 2A 型等（OMIM ID:276901)相关，呈 AR 遗传。临床表现主要为先天性双侧感音神经性耳聋（轻度至中度低频耳聋、重度高频耳聋）和进行性双侧视网膜色素变性，后者也称为遗传性视网膜变性（Inherited retinal dystrophy, IRD）指一类不可逆的视网膜退行性疾病。本案例先证者目前 4 岁半，双眼 FERG 各波振幅偏低，其余眼底等检查无明显异常，但该病为进行性的突变，可能成人发病并进行性发展；听力障碍目前已存在。结合先证者及新生儿出生后听力筛查未通过及软件预测及人群变异频率为 0，考虑该 c.10741-9C＞A 杂合为意义不明趋向于疑似致病，该推测仍需进一步实验证实。通过基因诊断，丰富了 USH2A 基因突变引起的常染色体隐性遗传的基因突变谱，并为后续 USH2A 基因型-表型分析提供了遗传学证据。

无创 DNA 产前检测对高龄孕妇胎儿染色体异常筛查效能分析

杨鹏 唐凯
宝鸡市妇幼保健院

目的 探讨无创 DNA 产前检测对高龄孕妇胎儿染色体异常筛查价值。

方法 回顾性收集 2231 例在我院产前诊断中心就诊的高龄孕妇（实验组）与 1665 例非高龄无高危风险孕妇（对照组）行无创 DNA 检测，结果异常者进行产前羊水细胞染色体诊断分析。

结果 实验组提示胎儿染色体异常 23 例，其中 14 例 21 三体、3 例 18 三体、1 例 13 三体、6 例性染色体异常，行羊水穿刺后确诊染色体异常 17 例，包括 14 例 21 三体、2 例 18 三体、1 例 13 三体、3 例性染色体异常，总体阳性预测值为 73.91%，其中 21 三体、18 三体、13 三体、性染色体异常分别为 100.00%、66.67%、100.00%、50.00%。对照组检出 4 例，包括 2 例 21 三体、2 例性染色体异常。两组检出率有统计学差异。

结论 无创 DNA 产前检测高龄孕妇胎儿染色体异常阳性预测值高，可以为产前诊断提供更为精准的提示，有效减少高龄孕妇胎儿染色体异常的漏诊，促进我国人口素质的提升。

染色体微阵列分析和高通量测序技术在胚胎停育中的遗传学研究

叶芸
金华市妇幼保健院

目的 通过对胚胎组织遗传学检测分析胚胎停育的遗传学病因以及 CNV-seq 和 CMA 在临床上的应用对比，探究染色体亚显微结构异常对胚胎停育的影响。

方法 选择本院研究期间就诊的胚胎停育患者 271 例，选取无菌清宫术取出的胚胎组织进行 CMA/CNV-Seq 检测。

结果 271 例流产物共检出阳性病例 166 例，阳性率 61.3%，其中染色体数目异常 119 例(71.7%)，染色体结构异常 43 例(25.9%)，染色体数目合并结构异常 4 例，UPD1 例，染色体数目合并结构异常以及 UPD 均为 CMA 检出。

结论 CMA 技术具有卓效，在检出染色体数目、结构异常的前提下可增加 UPD、LOH、嵌合体等情况的检出；考虑经济性，在充分告知患者技术局限性前提下，推荐使用 CNV-Seq + STR 进行胚胎停育流产物分析。

Genome-wide noninvasive prenatal screening using cfDNA to detect uncommon fetal chromosomal variation in a Chinese cohort

Yan Wang
Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University

Purpose The aim of this study was to evaluate the clinical utility of Genome-wide noninvasive prenatal screening (NIPS) to detect fetal uncommon chromosomal variation including copy number variations (CNVs) and mosaicism.
Methods Between March 2017 and February 2020, a total of 43 pregnancies with positive results excluding an increase in chromosome 21, 18 and 13 via NIPS were analyzed using traditional karyotyping and chromosomal microarray analysis (CMA). The performance of NIPS for detecting uncommon fetal chromosomal variation was calculated.
Results In 35 samples with positive results from NIPS only, CMA detected 11 abnormalities , including five CNVs ≥10Mb in three samples , three CNVs＜10 Mb in three samples and five cases of mosaicism. In eight samples with positive NIPS results combined with advanced age or ultrasound abnormalities, CMA detected four abnormalities. including one CNV ≥10Mb in one sample, one CNV ＜10 Mb in one sample , one case of X haploidy and one case of mosaicism. Thus, the true positive rate (TPR) of NIPS for detecting uncommon fetal chromosomal variation was 34.88 % (15/43).
Conclusion NIPS can be performed to detect uncommon fetal chromosomal variation in the first trimester to provide more information. However, it is vital to recommend further invasive diagnosis to patients with positive NIPS results . A variety of comprehensive technological applications can reduce the occurrence of birth defects.

应用 CMA 技术产前诊断五例 Xp22.31 微重复及妊娠结局分析

杨安琪 高宏志
福建医科大学附属第二医院

目的 探讨 Xp22.31 区微重复与临床表型之间的关系，为遗传诊断与咨询提供依据。
方法 利用染色体微阵列分析（CMA）对 5 个 Xp22.31 区微重复病例的产前诊断指征、胎儿超声检查情况、染色体核型、父母溯源、妊娠结局、生长发育情况进行回顾性分析。
结果 Xp22.31 区域微重复片段大小为 0.5—1.6 Mb，临床表型较为多样，两代之间遗传表型可能存在一定差异。继续妊娠的 3 例中，胎儿出生时外观均正常，随访至今生长发育与参照标准相符。
结论 通过回顾 5 例 Xp22.31 区微重复的临床和遗传学研究中，本文认为单纯的该片段重复是良性拷贝数变异（CNVs）的可能性大，但在产前诊断中出现 Xp22.31 微重复可能是异常表型的一个风险因素，应结合父母溯源情况及其他检查结果慎重选择妊娠结局。

无创 DNA 产前筛查对胎儿性染色体异常的效能分析

杨鹏 唐凯
宝鸡市妇幼保健院

目的 探讨无创 DNA 产前筛查在胎儿性染色体异常中的临床效果。
方法 选取本院单胎无创 DNA 产前检测提示性染色体异常者 32 例，收集其临床症状、产前诊断结果、预后等信息。
结果 32 例无创 DNA 筛查提示性染色体异常者，核型确诊 18 例，总体阳性预测值 56.52%。确诊胎儿中 11 例引产。

结论 无创 DNA 产前筛查可以作为性染色体异常的常规筛查手段，减少性染色体异常胎儿的漏诊，筛查高风险病例必须进行产前诊断确诊，并且进行遗传咨询。

早、中孕及其联合筛查在唐氏综合征中的应用价值比较

苏靖娜
无锡市妇幼保健院

目的 比较早中孕联合筛查与早、中孕期血清学筛查方案的筛查效率，探讨联合筛查模式在本地区唐氏综合征(Downs Syndrome, DS)筛查中的应用价值。
方法 回顾性分析在我院行产前筛查且有随访结局的孕妇资料，早孕和中孕期均进行了两个阶段的血清学筛查，利用 Auto DELFIA 全自动时间分辨荧光仪和 LifeCycle 4.0 风险评估软件，早孕期行二联法检测(PAPP-A、free β-HCG)，中孕期行三联法检测 AFP、free β-HCG、uE3；早中孕联合筛查采用多指标联合筛查方案，即将孕妇在孕中期检测的三联数据结合其孕早期的数据，联合计算筛查风险值。以羊水核型分析结果和出生后结局为随访标准，比较几种筛查方案的筛查效率。
结果 早、中孕筛查的初筛阳性率分别为 5.54%(657/11859)，4.85%(639/13170)，早中孕联合筛查的总阳性率为 2.05%（206/10052），血清学整合筛查与早、中孕期独立筛查方案在 DS 为 1:270 截断值时对 DS 的检出率分别为 83.3%(10/12)，75%（9/12）, 66.7%(8/12)；血清学整合筛查对 DS 的假阳性率（1.91%）均明显低于早、中孕血清学筛查（分别为 5.06%，4.14%），差异均有统计学意义（P<0.01）。联合筛查中，在相同的截断值，阶段性序贯筛查比血清学整合筛查可获得更高的筛查效率。
结论 早中孕血清学联合筛查方案，有助于提高唐氏综合征的检出率，可明显降低假阳性率，有效减少侵入性产前诊断操作，但需根据具体情况选择适宜的筛查方案，在本地宜采用 DS 1：300 为截断值，以实现较优的筛查效率。

一例无创产前筛查假阳性病例原因分析

徐咏 吴维青 胡思琪 郝颖 李素丽
深圳市妇幼保健院

目的 探讨一例 NIPT-plus 检测的 21 三体高风险出现假阳性的原因。
方法 对一例 NIPT-plus 检测中提示 21 三体高风险的孕妇进行产前诊断，对羊水进行染色体核型和染色体微阵列分析技术（CMA）检测，对孕妇外周血进行核型分析，对胎盘组织进行染色体分析，并随访新生儿情况。
结果 经羊水染色体核型和染色体微阵列分析技术（CMA）检测，确诊胎儿染色体正常；孕妇外周血核型为 46,XX；胎盘组织染色体分析显示胎盘胎儿面中央、中部、边缘的取样组织均存在 21 三体嵌合，胎盘母体面中央及中部组织存在 21 三体嵌合、边缘组织为 21 三体；新生儿出生无特殊面容，身高体重正常，无出生缺陷。本例 21 三体假阳性是由于限制性胎盘嵌合导致的。
结论 NIPT 技术存在假阳性的风险，其产生的原因可能是限制性胎盘嵌合。因此，对 NIPT 高风险的孕妇不应盲目建议终止妊娠，应建议产前诊断确诊，对假阳性病例建议留取胎盘组织进行原因分析。

无创产前基因检测研究热点及前沿分析

陈红燕[1,2] 魏凤香[1,2] 陈晓杭[2] 姚瑶[2] 谭颖瑶[1,2]
1.广东药科大学
2.深圳市龙岗区妇幼保健院

目的 分析国内关于无创产前基因检测 （NIPT）的研究热点及研究前沿。

方法 用 CiteSpace 软件对中国知网 （CNKI） 建库以来至 2021 年 8 月 23 日发表的无创产前基因检测相关研究文献进行可视化分析。
结果 共纳入 1263 篇中文文献，我国无创产前基因诊断在 2006 开始引起研究者关注，关键词共现、聚类及突现词分析显示，无创产前基因检测主要研究热点领域包括染色体非整倍体、 tnip1 基因多态与系统性红斑狼疮免疫组化，nf-kb 与性染色体非整倍体异常，胎儿染色体非整倍性临界风险值，孕早期胎儿游离 DNA maldi-tofms 分析与胎儿染色体分析、 无创产前基因检测在先天性心脏病中的预防及应用价值， 二代测序检测软骨发育不全基因中的应用、 不同类型地中海贫血基因筛查、 大规模平行测序在染色体核型分析中的应用、高龄孕妇 NIPT 检测准确度及临床检测路径选择， 突显词及关键词聚类分析显示基因拷贝数变异，阳性预测指标，tnip1 基因多态与系统性红斑狼疮免疫组化研究、nf-kb 与性染色体非整倍体异常将成为该领域研究的新趋势。
结论 我国无创产前基因检测起步较晚，目前仍然有巨大的研究空间，提高

Chromosomal microarray analysis in fetuses with high-risk prenatal indications: A retrospective study in China

Xiaomei Luo Hong Zhu Lili Wang Bing Xiao Yanjie Fan Hui Ye Xiaomin Ying Wenjuan Qiu Huiwen Zhang Lianshu Han Xuefan Gu Yongguo Yu Lei Wang
Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University

Objective The present study aimed to determine the diagnostic value of prenatal chromosomal microarray analysis (CMA) for fetuses with several indications of being at high risk for various conditions.
Materials and methods This retrospective analysis included 1256 pregnancies that were prenatally evaluated due to high-risk indications using invasive CMA. The indications for invasive prenatal diagnosis mainly included ultrasound anomalies, high-risk for maternal serum screening (MSS), high-risk for non-invasive prenatal tests (NIPT), family history of genetic disorders or birth defects, and advanced maternal age (AMA). The rate of clinically significant genomic imbalances between the different groups was compared.
Results The overall prenatal diagnostic yield was 98 (7.8%) of 1256 pregnancies. Clinically significant genomic aberrations were identified in 2 (1.5%) of 132 patients with non-structural ultrasound anomalies, 36 (12.7%) of 283 with structural ultrasound anomalies, 2 (4.5%) of 44 at high-risk for MSS, 38 (26.6%) of 143 at high-risk for NIPT, 11 (3.8%) of 288 with a family history, and 7 (2.1%) of 328 with AMA. Submicroscopic findings were identified in 29 fetuses, 19 of whom showed structural ultrasound anomalies.
Conclusion The diagnostic yields of CMA for pregnancies with different indications greatly varied. CMA could serve as a first-tier test for structural anomalies, especially multiple anomalies, craniofacial dysplasia, urinary defects, and cardiac dysplasia. Our results have important implications for genetic counseling.

海南育龄人群孕前地中海贫血筛查及基因分析

王洁
三亚市妇幼保健院

目的 研究海南省不同地区、民族和性别 α、β-地中海贫血基因类型及其分布状况。
方法 采用基于 Gap-PCR 原理的单管多重 PCR 和反向点杂交（RDB）技术对海南省北部海口、中部琼海和南部三亚平均红细胞体积(MCV)小于 80fL 的育龄夫妇进行地中海贫血基因分析，包括 3 种 α 缺失、3 种 α 突变及 17 种 β 突变类型。
结果 从 11552 例样本中筛选出 1881 例 MCV 低于 80fL 的样本进行基因分析，共检出地中海贫血基因携带者 1650 例（14.28%），α-缺失、α-突变和 β-突变分别为 1214 例（10.51%）、262 例（2.27%）和 463 例（4.01%）。海口、琼海、三亚检出率分别为 9.32%、12.54%和 37.02%。不同地区中，α-缺失、α-突变和 β-突变均以三亚的检出率最高，分别达 32.60%、8.15%和 6.73%。

不同民族中，黎族、苗族和汉族的检出率分别为 42.13%、24.02%和 11.02%，以黎族最高；性别中，女性的检出率高于男性，分别为 16.75%和 11.77%。

结论 平均红细胞体积(MCV)在地中海贫血初筛中具有重要意义，海南省地中海贫血基因携带率高，通过大规模基因筛查对降低地中海贫血患儿出生率，提高人口质量具有重要意义。

基于高通量测序的孕妇外周血胎儿游离 DNA 产前检测失败率及原因分析

王皖骏
南京大学医学院附属鼓楼医院 本院

目的 对孕妇外周血胎儿游离 DNA 产前检测的失败原因及妊娠结局进行分析，探讨检测失败病例处理方案。

方法 对 5898 例妊娠 12-22 周的单胎孕妇进行孕妇外周血胎儿游离 DNA 产前检测，设定严格质量控制标准，首次检测不达标的孕妇知情同意下可选择二次采血或直接进行产前诊断。

结果 5898 例孕妇中，初次采血检测失败率 0.5%（32/5898），其中 17 例 cffDNA%未达质控标准，10 例两次建库检测均提示染色体数据波动，5 例可能存在无法鉴别的性染色体异常。32 例初次采血检测失败病例中，2 例直接接受羊水细胞染色体核型分析，结果均未见异常；30 例接受了重新采血，其中 24 例在二次采血后发放了检测报告，最终报告失败率 0.1%（8/5898）。二次采血共报告 21 三体、18 三体、13 三体高风险各 1 例，经羊水细胞染色体核型分析证实均为假阳性。6 例二次采血检测失败病例中，1 例产前诊断未见异常；1 例产前诊断为 mos45,X[32]/46,XY[18]；4 例未进行产前诊断，目前生长发育未见异常。

结论 胎儿游离 DNA 比例低是检测失败的主要原因，但二次采血成功率较高，可以有效的增加最终检测成功率，减少侵入性检测数量，首次检测失败孕妇充分知情下可考虑重新采血检测。

胎儿脉络丛囊肿的产前诊断和临床意义研究

肖钧方 肖惠 邹永毅 黄淑晖 杨必成 刘艳秋
江西省妇幼保健院医学遗传中心，江西省出生缺陷防治管理中心，江西省出生缺陷防控重点实验室

目的 探讨脉络丛囊肿胎儿的产前诊断和孕期管理，为临床遗传咨询及优生优育提供依据。

方法 回顾分析 2019 年 1 月至 2020 年 12 月因胎儿脉络丛囊肿接受介入性产前诊断的 131 例单胎病例，5 例双胎病例，所有病例均行染色体微阵列分析(CMA) 检测及常规 G 显带染色体核型分析，并定期复查胎儿的发育情况，随访妊娠结局及胎儿出生后的生长发育情况。

结果 138 例脉络丛囊肿胎儿中检出致病性染色体异常 17 例(12.3%，17 /138) 。其中单纯性脉络丛囊肿致病性染色体异常发生率为 8.4%,脉络丛囊肿合并其他超声软指标异常伴或不伴高龄的致病性染色体异常发生率为 11.9%，脉络从囊肿合并结构异常致病性染色体异常发生率为 38.4%，经统计分析发现各组比较差异具有统计学意义(x^2=9.39，P＜0.05)。染色体非整倍体 14 例，其中 18 三体 9 例，21 三体 3 例，性染色体异常 2 例(47，XXY；45，X); CMA 结果异常 10 例; 致病性拷贝数变异 3 例及意义不明确异常 7 例, 本研究中 CMA 较染色体核型分析额外检出 2.2%(3/138)的致病性染色体微结构异常。出生的胎儿脉络丛囊肿多于孕 28 周前消失。

结论 脉络丛囊肿胎儿染色体异常的风险增高，当孕妇高龄或合并其他超声异常尤其是结构异常时，胎儿染色体异常风险明显增加; 对脉络丛囊肿胎儿进行产前诊断排除染色体异常及结构畸形后，单纯性脉络丛囊肿胎儿预后良好。

17q12 微缺失胎儿的产前超声表型及遗传学病因分析

蔡美英 黄海龙 苏林涓 吴小青 谢晓蕊 李英 林娜 徐两蒲
福建省妇幼保健院

目的 分析 6 例 17q12 微缺失胎儿的产前超声表型和遗传学检测结果，探讨其超声表型及遗传学病因。
方法 应用染色体微阵列分析（chromosome microarray analysis，CMA），对 2016 年 12 月至 2021 年 5 月在福建省妇幼保健院医学遗传诊疗中心行产前诊断的 6200 例孕妇进行检测。
结果 CMA 检测结果显示 6 例胎儿含有 17q12 区域的拷贝数（chromosomal copy number variations, CNVs）微缺失，涉及片段大小约 1.4Mb，内含 13 个 OMIM 基因。这 6 例胎儿产前超声表型，均存在双肾实质回声增强，其中 4 例胎儿还出现了其他的超声表型。4 例胎儿的父母拒绝家系验证，2 例胎儿的 17q12 区域的 CNVs 的缺失经家系验证均为新发的变异。
结论 17q12 微缺失胎儿的产前超声特征主要为双肾实质回声增强，如胎儿超声检查发现肾皮质回声增强，应考虑选择进行产前 CMA 检测，排除 17q12 微缺失的可能性。

一例 MCDA 一胎合并颈部水囊瘤的产前外显子分析

孔令蓉 [1,2]
1.上海市第一妇婴保健院
2.Tongji University

临床发现一例 MCDA 妊娠中一胎出现颈部水囊瘤。为探讨其遗传因素，我中心对胎儿进行超声序贯监测，穿刺获得异常胎儿羊水细胞，收集父母双方外周血，采用染色体高密度芯片联合外显子组测序的方法对患儿进行基因检测。该母亲为 IVF 受孕，孕 8W 证实为 MCDA。于孕 12 周超声提示 F2 胎儿 NT 增厚（6.2mm）,鼻骨缺如。孕 17 周 6 天超声提示 F2 胎儿颈部囊性占位（4.7*2mm），三尖瓣反流。F1、F2 胎儿 CMA 正常。F2 trio-WES 结果提示 TCOF1 基因（NM_000356.3）发生杂合突变，夫妻双方均未携带该突变。经验证，F1 存在相同突变，但未有特异产前表型。经分析，TCOF1 基因突变可能导致 Treacher-conlin 综合征，可致胎儿颌面部发育不良、吞咽功能不良、牙床狭窄及耳聋等表现。该基因检测结果可以为该家系的遗传咨询及产前基因诊断提供依据。

1 例异卵单绒双羊的病例报道

朱丹 [1,2] 孙路明 [1,2]
1.上海市第一妇婴保健院
2.上海第一妇婴保健院

单绒双羊通常由一个受精卵分裂而成，但偶尔也有异卵单绒双羊的情况发生。本文报道 1 例 38 岁初产妇，ICSI 受孕，移植 2 枚鲜胚，均存活。早孕期超声提示单绒毛膜性双羊膜囊双胎，F1 胎儿 NT 明显增厚，6.96mm,F2 胎儿 NT 增厚，2.79mm。后行双胎羊水穿刺送遗传学检查，STR 提示为异卵双胎，F1 胎儿核型及 CMA 提示 21-三体，孕妇及家属选择行射频消融减胎术减除；F2 胎儿核型及 CMA 结果正常，后门诊随访至孕 38 周 [1天]分娩 1 正常女婴，出生体重 3205g。当单绒双羊双胎超声表型或遗传学检查结果不一致时，需考虑异卵单绒双羊可能，异卵单绒双羊可见于试管受孕女性，必要时行 STR 检查进行验证。

1 例 Noonan 综合征导致的双胎之一水肿并发母体镜像综合征的病例报道

卫星 孙路明
上海第一妇婴保健院

32 岁初产妇，特殊面容，前次妊娠胎儿颈部水囊瘤引产。本次自然受孕后早孕期超声提示为双绒毛膜性双胎妊娠，无创 DNA 筛查低风险。孕 25 周诊断为双绒之一非免疫性水肿、羊水过多，母体镜像综合征。行双胎羊水穿刺送家系全外显子测序，经氯化钾减去水肿胎儿后母体镜像综合征得到缓解，遗传学结果提示母体及减去的水肿胎儿均存在 PTPN11 基因致病性杂合突变，非水肿胎儿遗传学检测正常并期待至 34 周分娩。

Whole genome sequencing incidentally identified intrauterine cytomegalovirus infection in a fetus with fetal growth restriction

Xing Wei Luming Sun
Shanghai First Maternity and Infant Hospital

We report the identification of intrauterine CMV infection by WGS in a fetus with FGR and intrauterine anemia at 23 weeks of gestation. Given the maternal immunity against CMV before pregnancy (IgG+/IgM- was determined in preconception serological screening) and a considerable low fetal transmission risk (0.5%-2%) of CMV nonprimary infection, intrauterine CMV infection was not suspected and diagnostic measurements were not provided in the first place. Due to the non-genetic nature of the pathogenesis, karyotype, CMA, and WES failed to yield a diagnosis. WGS, which detects nearly all forms of genetic variations, was subsequently provided as an “ultimate solution”. However, no chromosomal numerical disorders, pathological CNVs, SNVs, or InDels were determined. Interestingly, we accidentally detected the genetic materials of CMV. Furthermore, the possibility of intrauterine CMV infection was reconsidered and diagnostic tests were offered. Our experience shows WGS is an effective tool for diagnosing fetal intrauterine infection.

双胎颈项透明层增厚的遗传学结果分析

蔡璐瑶 孙路明
同济大学附属第一妇婴保健院

目的 对双胎妊娠中一胎或两胎颈项透明层（nuchal translucency, NT）增厚产前诊断所获得的遗传学结果进行分析。
方法 回顾性分析 2010 年 12 月至 2020 年 12 月超声诊断为双胎，在孕 11~13+6 周接受超声检查、其中一胎或两胎 NT 增厚大于第 95 百分位并于第一妇婴保健院进行产前诊断的孕妇。所有孕妇在超声下行双针法分别对两个羊膜腔进行羊水穿刺，获取双胎羊水进行 G 显带核型分析和（或）染色体微阵列（chromosomal microarray analysis, CMA）检测。
结果 共 172 例双胎妊娠一胎或双胎 NT 增厚大于大于第 95 百分位，其中双绒双羊（dichorionic diamniotic, DCDA）双胎 122 例，单绒双羊（monochorionic diamniotic, MCDA）双胎 50 例。在 DCDA 中，16 例（13.1%）遗传学结果异常，其中核型异常 11 例，致病性 CMA 2 例，可能致病性 CMA 3 例。在 MCDA 中，3 例（6.0%）遗传学结果异常，其中核型异常、致病性 CMA 、可能致病性 CMA 各 1 例。
结论 DCDA 一胎或双胎 NT 增厚出现遗传学异常的概率高于 MCDA，且高于绒毛膜取样技术的胎盘嵌合概率，或可对 DCDA 一胎或双胎 NT 增厚的病人进行更早的产前诊断策略。

ATAC-seq 和 RNA-seq 联合应用探讨神经管畸形的发生机制

付佳琳 顾卉 黄琬淇 袁正伟
中国医科大学附属盛京医院小儿先天畸形实验室

目的 神经管畸形（neural tube defects, NTDs）是一种神经管闭合失败导致的严重的中枢神经系统先天畸形。本研究拟通过 ATAC-seq 和 RNA-seq 技术联合应用寻找关键的转录因子及其下游的靶基因，以研究 NTDs 的致病机制。
方法 ATAC-seq 是利用 DNA 转座酶研究染色质可及性的高通量测序技术，可以识别基因组内开放染色质区域，捕获调控序列的信息。利用全反式维甲酸致畸小鼠 E9.5 天胚胎进行 ATAC-seq 和 RNA-seq，将组学结果联合分析以寻找 NTDs 特异性转录因子及其靶基因。
结果 利用 ATAC-seq 描绘 NTDs 小鼠的差异染色质可及性图谱，发现了 1690 个 NTDs 相关染色质可及性区域，以及 454 个差异表达基因。联合分析两个组学结果得到一个关键转录因子 P57 以及下游靶基因 Ube，并验证二者 RNA 水平在 NTD 胚胎中差异表达。Ube 作为 E2 泛素结合酶，能与 E3 泛素连接酶结合泛素化降解 Hbp，促进细胞增殖。
结论 我们首次应用 ATAC-seq 技术得到 NTDs 染色质可及性图谱。ATAC-seq 和 RNA-seq 技术联合分析找到 NTDs 形成中的关键转录因子 P57 及其下游靶基因 Ube。P57 通过转录抑制 Ube 的表达，促进对 Hbp 的泛素化降解，因而抑制细胞增殖，最终导致 NTDs 的发生。

1 例 CDC45 突变致 Meier-Gorlin 综合征的产前诊断

史达源 孙路明
上海市第一妇婴保健院

Meier-Gorlin 综合征（MGS）是一种罕见的常染色体隐性遗传病，临床主要表现为髌骨发育不良或缺如、小耳畸形、身材矮小三联征。目前已知的 MGS 相关基因突变包括 ORC1/ORC4/ORC6、CDT1、MCM5、CDC6 等。文献报道，96% MGS 患儿智力正常。
现报道 1 例 CDC45 基因突变导致 MGS 的产前诊断和遗传咨询。孕妇 31 岁，自然受孕，G1P0，NT 正常，中唐低风险，大排畸未发现明显结构异常。31+1 周超声提示胎儿头围偏小，-2.585 SD。进行羊水 CMA 和 Trio-WES 检测，结果提示 CMA 阴性，Trio-WES 发现胎儿携带 CDC45 基因复合杂合突变，分别遗传自父亲和母亲。结合宫内临床表现和遗传学检查结果，胎儿诊断为 CDC45 相关 Meier-Gorlin 综合征可能。
产前 WES 检测能够尽早发现胎儿存在的遗传变异，为孕妇提供遗传咨询，为新生儿早期干预提供指导。

产前诊断发现一例 46XX(SRY+)病历报告

曾黎
长沙市妇幼保健院

目的 对 1 例产筛 21 三体高风险、无创检测失败胎儿进行产前遗传学检测，明确其产前诊断结果，以提供合理的遗传咨询。
方法 对胎儿羊水细胞进行 G 显带核型分析，利用染色体微阵列分析(Chromosomal microarray analysis, CMA)技术对胎儿进行全基因组拷贝数变异分析(Copy number variants, CNVs)。对检测到的 SRY 基因应用 PCR+琼脂糖凝胶电泳技术进行验证，同时结合胎儿外生殖器多普勒超声结果进行判断。
结果 G 显带核型分析显示胎儿羊水染色体核型为 46，XX；CMA 结果提示为：arr[hg19] Yp11.31p11.2(2,650,424-6,165,770)x1 ， arr[hg19] Yp11.2(7,251,143-9,525,901)x1 ， arr[hg19]

Xp22.33q28(2,637,229-154,977,448) x2，即 Yp11.2(2.28Mb)和 Yp11.31p11.2(3.52Mb)。位于染色体 Yp11.31 的 SRY 基因是睾丸决定因子。PCR+琼脂糖凝胶电泳技术检测到 SRY 基因，诊断胎儿为 SRY 阳性 46，XX 男性综合征患者。

结论 G 显带核型分析、CMA 等多种技术联合应用，有助于提供准确的产前诊断，对指导再次妊娠，预防出生缺陷有重要作用。

Identify two novel mutations in CDKL5 deficiency disorder (CDD)

Yucen Song
First Affiliated Hospital of Zhengzhou University

Objective CDKL5 deficiency disorder (CDD) is a neurodevelopmental condition characterized by early-onset epilepsy, intellectual disability and severe motor impairments. This study is aim to explore the genotype and phenotype of CDD and expand CDKL5 mutation spectrum.

Methods Two early-onset epileptic encephalopathy cases were diagnosed at the First Affiliated Hospital of Zhengzhou University. Two new CDKL5 mutation sites were identified by PANEL analysis and PCR-Sanger sequencing. Subsequently, we combined clinical manifestations of the patients and related literatures to analyze clinical and genetic characteristics of CDD.

Results Both patients are girls. Their clinical phenotype are epilepsy with spastic seizures, focal or tonic seizures and even different degrees of developmental delay. However, anti-epileptic drugs are less effective in controlling seizures. Mutation analysis revealed that two CDKL5 mutations are nonsense mutations, C.1423C>T (P.Gln475Ter) and C.2596C>T (P.Gln866Ter), and the former is a de novo mutation. According to the ACMG guidelines, both variants are likely pathogenic.

Conclusion We highlight two novel CDKL5 mutations for the first time. According to literature review and clinical practice, we found that CDKL5 is an essential pathogenic gene of CDD. More research for genotype-phenotype correlation of CDKL5 mutations is necessary, as clinical features and prognosis may be related to the location and type of CDKL5 mutation.

围生期低磷酸酶血症的产前诊断和新的突变位点

武雁 张建芳
空军军医大学第一附属医院

目的 通过高通量测序手段全外显子基因检测，筛查出可疑的致病性突变位点并进行体外功能性验证，最终确定不良孕史的致病基因，给予患者遗传咨询和产前诊断提供基因依据。

方法 1 例两次妊娠均提示胎儿骨骼发育异常行引产术，收集到第二次引产的脐带组织和患者夫妇双方血样进行全外显子基因检测。经全外显子组检测和 Sanger 验证显示分析可解释患者表型的可疑/致病性变异。并对尚未报道的基因突变行体外载体合成、质粒转染和细胞培养，最后验证该基因功能。

结果 该患者遗传方式：复合杂合变异。c.648+1G>A 变异来自父亲，致病性已有报道，符合隐性遗传。c.1120G>A 变异来自母亲，该新发突变尚未见文献报道。通过体外功能实验确该基因突变可导致碱性磷酸酶活性降低。

结论 本研究发现新的中国 HPP 患者致病突变位点。同时围生期疾病的诊断有具有特殊性，产前筛查中发现临床表现高度相关基因并确定该基因的致病性，为围生期遗传疾病的诊断提供新的思路。

一个视网膜母细胞瘤家系的基因变异分析及产前诊断

卢嘉琪
广东省妇幼保健院

目的 对一个视网膜母细胞瘤家系进行基因编译分析，明确致病变异，并进行产前诊断。
方法 联合应用高通量测序技术及 Sanger 测序技术，对家系患者进行基因检测，明确患者致病变异及家系成员携带情况。对存在发病风险的胎儿进行产前基因检测。
结果 家系中先证者 RB1 基因 c.763C>T 杂合变异，母亲 RB1 基因 c.763C>T 变异嵌合比例 7.94%，胎儿该位点为野生型。
结论 明确家系中患者的致病变异是单基因病产前诊断的前提，为家系遗传咨询和产前诊断提供了依据。

Two prenatal diagnoses in a family with Spondylo-meta-epiphyseal dysplasia, short limb-hand type and a literature review

Xing Wu Xiangyu Zhu Zhaoxia Li
Nanjing Drum Hospital

Objective To perform mutation analysis and two rounds of prenatal diagnosis in a family with Spondylometaepiphyseal dysplasia, short limb-hand type**.**
Methods Clinical data was collected from the family, and genomic DNA was extracted from peripheral blood samples of the family members. The coding regions of the DDR2 gene was subjected to Sanger sequencing. Prenatal genetic diagnosis was performed by amniotic fluid sampling at 19 weeks of gestation. and chorionic villus samplingat 12 weeks of gestation. The sequencing results were verified by haplotype analysis.
Results DNA sequencing found that both the proband and the prenatal diagnosis from the first fetus carried a homozygous mutation c.2254C＞T in exon 17 of the DDR2 gene. The parents and the prenatal diagnosis of the second fetus were heterozygous carriers.
Conclusion For pedigrees of Spondylometaepiphyseal dysplasia, short limb-hand type, genetic counseling in addition to prenatal diagnosis should be provided through Sanger sequencing and haplotype analysis.

Identification and functional study of pathogenic gene in a Chinese family with Nance-Horan syndrome

Cheng Huang Jiaxue Wei Daihua Lin Xiaoying Lin Rong Li Qiuxian Mao
Guangdong Second Provincial General Hospital

Purpose Congenital cataract is one of the most common cause of blindness in children, which is also a clinical symptoms of nearly 200 syndromic genetic diseases. Nance-Horan syndrome, also known as cataract-dental syndrome, is a syndromic genetic diseases characterized by abnormal dental and craniofacial development. X-linked recessive inheritance can account for its inheritance pattern. To date, more than 50 NHS gene mutations have been reported in families with Nance-Horan syndrome.
In this study, we illuminate the clinical characteristics and molecular genetic mechanisms of a Chinese family cross three-generation with Nance-Horan syndrome. In vitro Cytological functions study of NHS genes are performed to look inside molecular genetic mechanisms of Nance-Horan syndrome.
Methods
1. Affected Individuals and families medical history and physical examination.

2. Next generation sequence and bioinformatics analysis of 4 families (proband, his second sister, the husband and fetus of the second sister) were performed for pathogenic genes screening. The mutation were verified by Sanger sequencing subsequently. There is no any chromosome abnormality were found in karyotype analysis and Chromosome microarray analysis
3. The wild-type plasmid PEGFP-C2-NHS (NHS-EGFP) and mutant plasmid PEGFP-C2-NHS-C.766DELC (NHS-L256F-EGFP) were constructed to express NHS protein. After transfection experiments of three group of plasmid in HEK293T cells and SRA01/04 cells, we investigate the intracellular subcellular localization change of NHS protein and the expression of NHS in mRNA and protein levels.

Results There are 11 families of three generations, including 7 patients with Nance-Horan syndrome in this Chinese family. The proband is a young man who have been diagnosed with congenital cataract and dental malformation since childhood. There are four sisters of proband suffering from similar vision abnormalities and dental deformities. While the main symptoms of their mother is hyperopia and dental deformities. The proband's eldest sister have a healthy daughter. Ultrasound shows enhanced echo of bilateral eyeballs in the 23-week fetus of the proband's second sister, which is suspected to be congenital cataract. C.766delC deletion in exon 3 of the NHS gene on the X chromosome were detected to be the pathogenic mutations of this family after next generation sequencing. This mutation resulting in the synthesis of truncated polypeptide chains, which is 28 amino acids shorter than wide type polypeptide chains (P. Leu256Phefs*28).

Conclusion We report a rare Chinese family of Nance-Horan syndrome whose clinical characteristics and genetic analysis have identified. The deletion (C. 766delC) of the NHS gene on the X chromosome should be the pathogenic mutations. The frameshift of amino acid coding leading to the synthesis of truncated polypeptide chains are predicted to be harmful by several mutation prediction tools. Further experiment of molecular biology are under way to elucidate the molecular mechanisms of Nance-Horan syndrome.

Prenatal diagnosis of a novel inv del dup 8p23 and a paternally transmitted 22q11 microdeletion associated with a Tetralogy of Fallot reproductive history

Shufang Huang Ping Li
Guangdong Provincial People's Hospital

Objective To molecularly and cytogenetically characterize a *de novo* inv dup del(8p23) and a paternally transmitted 22q11 microdeletion in a fetus of a family with congenital heart disease (CHD) reproductive history.

Methods For prenatal diagnosis, routine G-band karyotype analysis using amniotic fluid cells was performed. Chromosome microarray (CMA) was employed for fine-mapping of the aberrant region. In the following study, other family members were screened by G-band karyotype analysis, and CMA results were confirmed by real-time quantitative polymerase chain reaction.

Results Here, we report a prenatal case with a 6.4-Mb deletion in 8p23.3–8p23.1, a 5.2-Mb duplication in 8p23.1, and a 767-kb deletion in 22q11, in which the 22q11 deletion was paternally inherited, whereas the inv del dup 8p23 was *de novo*. Maternal karyotypes and the CMA were normal. The results of CMA analysis of other lineal relatives were normal.

Conclusion Fetuses with inv dup del(8p) may present central nervous system (CNS) abnormalities and congenital heart defects on prenatal ultrasounds. Prenatal diagnosis of concomitant CNS and cardiac abnormalities should thus include a differential diagnosis of chromosome 8p inverted duplication deletion syndrome. No case study on the occurrence of a inv dup del(8p) with del 22q11.12 has been reported to date. While the 8p23 variants are *de novo*, we speculate that the 22q11 deletion was paternally inherited and may be the disease-causing variant in this family.

超声结合 WES 对 Treacher Collins 综合征胎儿的产前诊断

李荣
广东省第二人民医院

目的 通过基因检测及遗传学分析对一例超声提示小下颌合并外耳异常胎儿进行产前诊断。
方法 采集孕妇临床病例资料及羊水标本，应用多重定量荧光 PCR(quantitative fluorescence PCR，QF-PCR)、染色体核型分析、染色体微阵列（chromosome microarray analysis，CMA）及全外显子测序（whole exon sequencing，WES）技术对羊水标本进行检测。
结果 QF-PCR、染色体核型分析、CMA 结果均正常，WES 结果提示胎儿 *TCOF1* 基因存在一杂合缺失突变（c.928-c.931del：P:T310fs），胎儿父母在该区域的全外显子测序分析未检测到该变异，该变异在胎儿中为新发变异，且该突变类型尚未见文献报道。
结论 本例胎儿 *TCOF1* 基因缺失突变使得终止密码子提前出现，导致 Treacle 蛋白截短而丧失功能，这与单倍性不足的致病机制是一致的。依据美国医学遗传学会（American College of Medical Genetics，ACMG）遗传变异分类标准与指南，判断该变异为致病性变异，可导致 Treacher Collins 综合征。本文结合三维超声和全外显子组测序，成功地检测了 TCS 胎儿，为产前诊断及后续遗传咨询提供了可靠依据。

扑朔迷离的染色体世界-------消失的“Y”和失活的“X”

徐玉婵 严提珍 李亚星 袁德健 韦小妮 王文丹 蔡稔
柳州市妇幼保健院

目的 分析一例染色体核型分析与 CNV-seq 结果不一致的性染色体非平衡性结构异常胎儿的产前诊断过程。
方法 联合应用染色体核型分析 G 显带、C 显带，CNV-seq 及迟复制 X 染色体检测技术对胎儿及父母进行家系分析。
结果 胎儿核型为 46,X,der(X)t(X;Y)(p22.3;q11.23)mat，Xp22.33-p22.31 位置发生缺失，Yq11.221-q11.23 位置发生重复。父亲染色体核型正常。母亲染色体核型为 46,X,der(X)t(X;Y)(p22.3;q11.23)，迟复制 X 染色体检测发现母亲异常的 X 染色体失活。母亲除身材矮小，B 超提示双子宫外没有其他临床表现。经产前诊断和遗传咨询后，孕妇继续妊娠并于 35+6 周早产一女婴，自然分娩，体重 2.26Kg,身长 49cm，未见明显异常。
结论 临床诊断不能单看某一项目的报告单，应将细胞遗传学与分子诊断结合，加上其它辅助诊断验证，并结合临床表型综合分析。涉及 X 染色体结构异常的疾病应考虑到 X 染色体失活偏移对临床表型的影响。涉及产前诊断的胎儿，遗传咨询更应慎重。遗传医生及实验室人员应积极沟通配合，为孕妇寻求最适宜措施。

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