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论文汇编

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Long non-coding RNA NRSN2-AS1 promotes ovarian cancer progression through targeting PTK2/β-catenin pathway

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As a common malignant tumor among women, ovarian cancer poses a serious threat to their health. This study demonstrates that long non-coding RNA NRSN2-AS1 is over-expressed in ovarian cancer tissues using patient sample and tissue microarrays. In addition, NRSN2-AS1 is shown to promote ovarian cancer cell proliferation and metastasis both in vitro and in vivo. Mechanistically, NRSN2-AS1 stabilizes protein tyrosine kinase 2 (PTK2) to activate the β-catenin pathway via repressing MG-53-mediated ubiquitinated degradation of PTK2, thereby facilitating ovarian cancer progression. Rescue experiments verify the function of the NRSN2-AS1/PTK2/β-catenin axis and the effects of MG53 on this axis in ovarian cancer cells. In conclusion, this study demonstrates the key role of the NRSN2-AS1/PTK2/β-catenin axis for the first time and explores its potential clinical applications in ovarian cancer.

Key Words Ovarian cancer, NRSN2-AS1, cell proliferation , metastasis

Data Analysis of Expanded Carrier Screening for Couples undergoing Assisted Reproductive Technology in Jiangsu and Anhui area of China

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Objective: To assess the carrier rate of pathogenic genes and the reproductive risk of recessive genetic diseases in the assisted reproductive population in the Jiangsu and Anhui.

Method: The recruitment will be conducted among individuals from Jiangsu and Anhui province who are undergoing assisted reproductive treatment at Jiangsu Province Hospital. Prior to treatment, comprehensive genetic counseling will be provided. The expanded carrier screening will adopt next-generation sequencing (NGS) technology combined with capillary electrophoresis for the detection of specific sites, screening for likely pathogenic and pathogenic (LP/P) variants in 432 genes, as well as 9 copy number variations (CNVs) with incomplete penetrance or X-linked inheritance. A simultaneous screening strategy for couples will be employed.

Results: A total of 867 couples were recruited for screening, among whom 70.2% (609/867) of males carried at least one LP/P variant, and 74.0% (641/867) of females carried at least one LP/P variant. The top 15 genes with the

highest carrier frequencies in the population were GJB2, CFTR, HFE, ATP7B, GALC, SLC26A4, PAH, USH2A, CYP21A2, SLC22A5, SMN1, HBA1, GAA, MMACHC, PKHD1, and SLC25A13. A total of 49 couples (5.7%) were found to have at least one genetic disease reproductive risk, involving risk genes or CNVs such as GJB2, G6PD, PAH, HFE, CFTR, SLC22A5, AR, DMD, GAA, GALC, SLC26A4, COL1A2, CYP21A2, SBDS, STS, VPS13B, WAS, CLCN5, 16p11.2 microdeletion, and 22q11.2 microdeletion. Accurate reproductive risk counseling can be provided for these couples.

Conclusion: ECS can help assess the reproductive risks of genetic diseases in the population undergoing assisted reproductive technology, providing accurate reproductive risk counseling and guidance. Further discussion is needed to determine whether the inclusion of a large number of high-frequency low-penetrance variants found in ECS should be part of routine clinical screening. Additionally, genetic counseling for such variants should be more personalized.

Key Words expanded carrier screening, genetic counseling, NGS

A novel MYO6 variant identified in a Chinese family with autosomal dominant nonsyndromic hearing loss

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Background: Hereditary hearing loss (HL) is a highly heterogeneous disorder that follows various inheritance patterns. Variants of MYO6 gene in DFNA22 are characterised by progressive post-lingual sensorineural HL of varying severity.

Patients and methods: Four-generation Chinese families with autosomal dominant non-syndromic hearing loss (ADNSHL) were enrolled in this study. Whole-exome sequencing (WES) was performed on the proband and her father to screen for causal variants in the genome, whereas intrafamilial co-segregation of the candidate variants in family members was verified using Sanger sequencing. Furthermore, protein modelling and stability analyses were performed to assess the potential pathogenicity of the candidate mutations.

Results: A previously unreported heterozygous missense variant (NM_004999.4:c.2063A>G, p.Gln688Arg) in exon 20 of MYO6 using WES and was found to co-segregated with the disease in this family. Molecular dynamics simulations predict that the glutamic acid-to-arginine change in p.(Gln688Arg) alters the normal function, most likely through the altered intermolecular forces of this amino acid with the three nearby polar residues. The structural changes caused by this mutation could potentially affect the myosin ATPase cycle.

Conclusions: We report a novel likely pathogenic missense (c.2063A>G) variant within of MYO6 in patients with DFNA22. Our findings expand the variant spectrum of MYO6 and ADNSHL in Chinese individuals, which will facilitate early clinical genetic diagnosis and accurate genetic counselling of patients.

Key Words Hereditary hearing loss, Whole-exome sequencing, MYO6

新型冠状病毒感染对卵子和胚胎质量的影响

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目的：探讨新型冠状病毒（severe acute respiratory syndrome coronavirus 2，SARS-CoV-2）感染对进行体外受精/卵胞质内单精子注射（in vitro fertilization/intracytoplasmic sperm injection，IVF/ICSI）治疗的不孕症患者的卵子及胚胎质量的影响。

方法：回顾性分析1267名在南京医科大学附属妇产医院生殖医学中心进行IVF/ICSI治疗的女性不孕症患者，新冠组为307名2022年12月至2023年4月期间行IVF/ICSI治疗的患者，对照组为960名2021年12月至2022年4月期间进行IVF/ICSI治疗的患者。亚组分析：亚组分析：新冠组进一步根据男方是否感染新冠病毒，分为仅女方新冠感染组与男女均新冠感染组；根据女方感染新冠距取卵时间，分为≤30天组、31~60天组、61~90天组、91~120天组、>120天组，比较各组的一般情况和卵子、胚胎的质量，并利用线性回归分析新冠病毒感染与卵子、胚胎质量的相关性。

结果：新鲜周期中，与对照组相比，新冠组的获卵数（95%CI -1.710，-0.718，P = 0.000）、2PN数（95%CI -1.413，-0.451，P = 0.000）、可移植胚胎数（95%CI -0.859，-0.097，P = 0.014）显著减少；仅女方感染新冠组的获卵数（95%CI -1.978，-0.597，P = 0.000）、2PN数（95%CI -1.628，-0.268，P = 0.006）显著减少；男女均感染新冠组的获卵数（95%CI -1.820，-0.561，P = 0.000）、2PN数（95%CI -1.560，-0.347，P = 0.002）、可移植胚胎数（95%CI -0.989，-0.007，P = 0.047）显著减少；当感染新冠2~3个月后，新冠组的获卵数（95%CI -0.744，-0.104，P = 0.009）、2PN数（95%CI -0.396，-0.046，P = 0.013）显著减少。

结论：新型冠状病毒感染可能对进行IVF/ICSI治疗的不孕女性患者的获卵数、2PN数及可移植胚胎数造成长期负面影响，因此，广大不孕人群若感染新冠，可能需要在痊愈后尽早进行IVF/ICSI治疗。

关键字 新型冠状病毒，不孕症，卵子，胚胎

Two Novel Compound heterozygous Loss-of-Function Mutations Cause Fetal IRAK-4 Deficiency Presenting with Pseudomonas Aeruginosa Sepsis

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Purpose: To report a case of a five-month-old Chinese infant who died of interleukin-1 receptor-associated kinase-4 (IRAK-4) deficiency presenting with rapid and progressive Pseudomonas aeruginosa sepsis.

Methods: The genetic etiology of IRAK-4 deficiency was confirmed through Trio- whole exome sequencing and Sanger sequencing and then were investigated by in vitro minigene splicing assays.

Results: Trio-whole exome sequencing of genomic DNA identified two novel compound heterozygous

mutations, IRAK-4 (NM_016123.3): c.942-1G>A and c.644_651+ 6delTTGCAGCAGTAAGT in the proband, which originated from his symptom-free parents. These mutations were predicted to cause frameshift and generate three truncated proteins without enzyme activity.

Conclusions: Our findings expand the range of IRAK-4 mutations and provides functional support for the pathogenic effects of splice-site mutations. Additionally, this case highlights the importance of considering the underlying genetic defects of immunity when dealing with unusually overwhelming infections in previously healthy children and emphasize the necessity for timely treatment with wide-spectrum antimicrobial.

Key Words IRAK-4 deficiency; novel mutation; WES; in vitro

肾积水胎儿表型-遗传性病因及预后情况分析

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目的：探讨胎儿肾积水（AHN）临床表型与遗传学病因及预后关系，为临床产前诊断及孕期胎儿管理提供指导。

方法：采用多中心回顾性研究，联合三家产前诊断中心收集2017-2023年肾积水胎儿进行染色体微阵列分析-基因组测序（CMA-GS）序贯性遗传学分析，根据超声特征分为孤立性 AHN 组、AHN 合并泌尿系统异常组及 AHN 合并肾外系统畸形组，对遗传学检测结果与产前超声表型进行相关性分析，系统监测孕期AHN发展情况及预后情况并进行分析。

结果：多中心数据统计提示泌尿结构异常胎儿435例，其中肾积水53例，占泌尿系统异常的12.18%。AHN中表现为孤立性AHN 29例，AHN合并泌尿系统异常18例，AHN合并肾外系统异常组6例。53例肾积水胎儿经CMA检测共检出4例（7.46%）阳性，包括1例（1.89%）非整倍体及3例（5.66%）致病性及可能致病性CNV。CMA检测提示正常（47例）及临床意义不明（2例）行GS检测，发现致病性变异5例（10.2%），可能致病性变异3例（6.12%），临床意义不明确15例（30.61%），GS额外诊断率达15.1%。孤立性 AHN、AHN合并泌尿系统异常组及 AHN 合并肾外系统畸形组组间GS检出率比较， 差异有统计学意义(P< 0. 001)。孕期肾积水程度发生好转共8例，其中7例（87.5%）为孤立性 AHN，1例（12.5%）为AHN合并泌尿系统异常，GS检测提示为临床意义不明确2例；孕期肾积水程度未发生好转共34例，其中21例（61.76%）为孤立性AHN ，15例（44.12%）为AHN合并泌尿系统异常，2例（5.88%）为AHN 合并肾外系统畸形，GS检测提示为致病性变异3例（8.82%），可能致病性2例（5.88%），临床意义不明确10例。经随访，孕期胎儿肾积水程度发生好转组除1例为左肾积水右肾肾盂分离伴中度生长发育迟缓，其余均发育正常。孕期胎儿肾积水程度未发生好转组，5例胎儿行新生儿手术，9例肾积水定期随访，20例发育正常。

结论：CMA未检测出异常的AHN中GS的阳性率达16.33%，对于孤立性 AHN， 24.14%可在孕期发生好转，且一般预后较好， GS异常率最低； AHN合并泌尿系统异常组及 AHN 合并肾外系统畸形组孕期好转概率极低且GS异常率相对较高。建议产前超声提示肾积水胎儿尤其是合并其他异常情况时宜优先采用GS检测，对于孤立性 AHN可持续观察肾积水情况，当肾积水加重或未发生好转时应及时进行GS检测明确病因。

关键字 肾积水胎儿（AHN），基因组测序（GS），染色体微阵列分析（CMA），泌尿系统异常，肾外系统畸形

ELL3功能缺失导致胚胎非整倍体

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全球每年约有2300万起自然流产事件发生，其发生率达到了15.3%。非整倍体是临床上早期自然流产的主要因素。胚胎非整倍性主要来源于卵母细胞。纺锤体是由微管构成的动态细胞器，在细胞分裂过程中对染色体分离起着至关重要的作用。哺乳动物卵母细胞减数分裂纺锤体的易错性极易受到遗传变异的影响。因此，为了确定染色体非整倍性导致的早期自发性流产的遗传原因，本研究通过对188对在妊娠7–12周期间因非整倍体胚胎而反复流产的夫妇进行外显子组测序，鉴定了一系列ELL3功能缺失变体。免疫荧光染色结果显示，ELL3定位在卵母细胞纺锤体上。利用小鼠模型验证了ELL3在卵母细胞中的缺失会导致纺锤体结构的紊乱、染色体分离的缺陷，以及胚胎的流产。生化分析进一步表明，ELL3通过与TPX2竞争性结合KIF11，提高了后者的ATP利用效率。活细胞成像和单染色体追踪实验证实，ELL3通过促进纺锤体的伸长来加速染色体的运动。综上所述，本研究确定ELL3功能缺失变异作为胚胎非整倍性的遗传根源之一，不仅深化了我们对哺乳动物卵母细胞减数分裂机制的理解，也为马达蛋白和疾病调控的精细机制提供了新的见解。

关键字 复发性自然流产；染色体非整倍性；卵母细胞减数分裂；纺锤体组装

4D实时追踪技术展示减数分裂染色体运动轨迹

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在细胞分裂过程中，纺锤体赤道板处的染色体正确排列是染色体准确分离的必要条件。核膜破裂后，染色体需要遵循一定的运动轨迹最终汇聚于赤道板。这一过程中每个染色体的如何向赤道板汇聚尚未明确。在这里，我们提出了一个 4D 成像分析框架，以 One–Shot 学习方式拟合分析并展示染色体和纺锤体动力学。通过对小鼠卵母细胞的延时成像，我们捕捉了染色体在细胞分裂不同阶段的运动特征。结果显示，从核膜破裂（NEBD）到第一次减数分裂中期（MI）染色体至少遵循三种不同的运动轨迹（回溯、前进和准静态）到达赤道板。在我们设计的定量框架中，实现了以特定阶段的方式分析染色体的速度、轨迹和空间分布。通过建立深度学习模型进行轨迹分类分析，我们发现 Kinesin 超家族蛋白（kinesin superfamily protein, KIF）成员协调调节染色体运动轨迹。该框架为研究候选基因的功能和基因突变对细胞分裂的影响提供了一种有效和无偏向的方法。

关键字 减数分裂，染色体轨迹，成像

孕妇外周血胎儿游离DNA产前筛查在颈项透明层增厚胎儿中的应用效能分析

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目的：探索孕妇外周血胎儿游离DNA产前筛查（Noninvasive prenatal testing，NIPT）在颈项透明层（Nuchal translucency，NT）增厚胎儿中应用的可行性分析。

方法：本研究参考美国妇产科学会指南，将NT增厚定义为NT≥3.0mm，回顾性分析2004–2022年因“NT增厚”于南京鼓楼医院行染色体微阵列分析（Chromosomal Microarray Analysis，CMA）的胎儿样本1184例。根据NT增厚是否合并其他高危因素分为A组：孤立性NT增厚且预产年龄＜35周岁；B组：孤立性NT增厚且预产年龄≥35周岁；C组：NT增厚合并软指标异常；D组：NT增厚合并结构畸形。A组中根据NT厚度进一步分层，A1组：3.0mm≤NT＜3.5mm、A2组：3.5mm≤NT＜4.0mm、A3组：NT≥4.0mm。C组中根据合并的软指标异常不同分为C1组：NT增厚合并鼻骨发育异常、C2组：NT增厚合并其他软指标异常。假设本中心NIPT和拓展性NIPT的在其各自检测范围内的敏感性和特异性均为100%，将NIPT和拓展性NIPT检测范围以外的其他基因组异常称为NIPT残余风险和拓展性NIPT残余风险。采用SPSS 23.0统计软件包进行数据分析，比较孤立性NT增厚组中NIPT和拓展性NIPT在各亚组间的残余风险是否存在统计学差异。

结果：2004–2022年因“胎儿NT增厚”于南京鼓楼医院行CMA的孕妇1184例，CMA共计检出非整倍体异常143例、致病性拷贝数变异（pathogenic Copy Number Variation，pCNV）46例、不平衡易位12例、纯合区域（regions of homozygosity，ROH）3例、多个染色体异常7例，NIPT残余风险9.2%（109/1184），拓展性NIPT残余风险5.1%（60/1184）。A1组（3.0mm≤NT＜3.5mm）：329例，其中非整倍体异常12例、pCNV7例、ROH1例，NIPT残余风险2.4%（8/329），拓展性NIPT残余风险2.4%（8/329）；A2组（3.5mm≤NT＜4.0mm）：173例，其中非整倍体异常17例、pCNV9例、不平衡易位3例，NIPT残余风险8.1%（14/173），拓展性NIPT残余风险7.5%（13/173）；A3组（NT≥4.0mm）：270例，其中非整倍体异常38例、pCNV16例、不平衡易位3例、性染色体异常合并pCNV1例，NIPT残余风险12.6%（34/270），拓展性NIPT残余风险7.4%（20/270）。NIPT及拓展性NIPT在不同NT厚度中的残余风险差异有统计学意义（NIPT：$\chi 2=22.99$,$p<0.01$；拓展性NIPT：$\chi 2=9.45$,$p<0.01$）。B组：NT增厚合并高龄，共计92例，其中非整倍体异常29例、pCNV5例、21三体合并性染色体异常1例、18三体合并性染色体异常1例，NIPT残余风险7.6%（7/92），拓展性NIPT残余风险5.4%（5/92）。C1组：NT增厚合并鼻骨发育异常：49例，其中CMA未见异常25例、非整倍体异常23例、pCNV1例，NIPT及拓展性NIPT残余风险均为2.0%（1/49）。C2组：NT增厚合并其他软指标异常：26例，其中非整倍体异常6例、pCNV1例、不平衡易位2例，NIPT及拓展性NIPT残余风险均为11.5%（3/26）。D组：NT增厚合并结构异常，共计245例，其中非整倍体异常106例、pCNV7例、不平衡易位4例、ROH1例、21三体合并20三体1例、21三体合并ROH1例、18三体合并性染色体异常2例，NIPT残余风险17.1%（42/245），拓展性NIPT残余风险4.5%（11/245）。

结论：NT增厚胎儿无论是否合并其他高危因素，均应行介入性产前诊断。孤立性NT≥3.5mm或NT≥3.0mm且合并其他高危因素者，可建议孕早期行绒毛穿刺。孤立性3.0≤NT＜3.5mm的胎儿即使NIPT低风险，仍需在咨询中充分告知胎儿染色体异常的残余风险约为3%。

关键字 胎儿颈项透明层 无创产前检测 产前诊断 遗传咨询

Construction of a risk prediction model for NS-CHD based on the congenital heart disease knowledgebase

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Background: To establish a prediction model for the risk of non-syndromic congenital heart disease (NS-CHD) incidence and to provide a prediction tool for NS-CHD prevention.

Methods: Based on the updated information database of non-genetic risk factors for NS-CHD, all non-genetic morbidity risk-related feature data underwent preprocessing, including normalization, standardization, and null substitution. Machine learning algorithms such as Support Vector Machine (SVM), decision tree, Multilayer Perceptron (MLP), Random Forest, and others were sequentially employed for training. The optimal risk prediction model was selected by comparing the performance parameters of several models. Subsequently, 120 NS-CHD cases and 150 controls were included in the validation dataset to validate the established prediction model. Using the updated information on risk factors for NS-CHD, three non-genetic risk scoring models were established for NS-CHD.

Results: The MLP perceptron model exhibited the highest precision and accuracy, with value of 0.72 and 0.79, respectively. The validation set, consisting of NS-CHD cases and controls, underwent external effica cy validation of the model using Logistic regression, Decision tree, SVM, Random Forest, K-NN,Gradient Boosting algorithms and AdaBoost. The overall accuracy of the Logistic regression and SVM was higher, at 0.65 and 0.61, respectively.

Conclusion: The CHD risk prediction model holds significant clinical prediction value. It can be utilized for predicting non-genetic morbidity risk associated with NS-CHD and has showed preliminary efficacy in validating the diagnosis prediction model of NS-CHD. This contributes to prevention and control of birth defects.

Key Words Congenital heart disease; Risk factors; Prediction model; Multilayer perceptron; Random forests

基于二维PCR技术探索特定基因多态性与胆石症风险的关联性研究

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研究目的：本研究旨在利用二维PCR技术快速、低成本地探讨六个单核苷酸多态性（SNP）位点与胆石症的关联。

研究方法：本研究纳入600例胆石症患者作为病例组和393名体检人群作为对照组，采用病例-对照回顾性设计，通过对rs11887534、rs4245791、rs2547231、rs9843304、rs1260326及rs6471717位点进行Sanger测序筛选基因突变频率较高的SNPs位点。应用二维PCR技术建立基因分型方法，分析其与胆石症发病的关联性。实验数据采用GraphPad Prism 8.0、Excel及SNPStats在线软件进行统计分析。

结果：Sanger测序示rs2547231、rs11887534、rs4245791位点无突变或突变频率较低；针对检出3种基因型的rs9843304、rs1260326及rs6471717位点建立二维PCR检测方法，结果表明该方法检测结果与Sanger测序法完全一致（Kappa=l，P=0.000）。进一步研究发现，病例组中rs9843304位点TT基因型比例（25.0% VS 35.3%，P<0.05）和rs1260326位点TT基因型比例（26.4% VS 32.1%，P<0.05）均低于对照组。rs9843304位点TT基因型患胆石症的风险显著低于CC基因型（OR:0.51, 95%CI:0.36-0.74, P=0.0003）；rs1260326位点TT基因型患胆石症的风险显著低于CC基因型（OR:0.65, 95%CI:0.45-0.95, P=0.030），同时女性TT基因型患胆石症的风险明显高于男性TT型（OR:1.92, 95%CI:1.18-3.12, P=0.022）；rs6471717位点与胆石症风险的关联无统计学意义（OR:0.94, 95%CI:0.77-1.24, P=0.76）。

结论：成功建立了检测rs9843304、rs1260326及rs6471717三个位点的二维PCR方法；TM4SF4基因rs9843304及GCKR基因rs1260326两个位点的TT基因型均可降低胆石症发病风险。

关键字 胆石症，单核苷酸多态性，二维PCR，发病风险

Genomic Based Newborn Screening: Impact on Lysosomal Storage Disorders in China

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Background: Lysosomal storage disorders have a relatively high incidence among rare diseases and can lead to severe consequences if not treated promptly. However, many countries and regions have not included these disorders in their newborn screening programs, resulting in missed early detection, underdiagnosis, and delayed treatment. Newborn genomic screening has shown good screening effectiveness for traditional biochemical screening diseases; however, its effectiveness for lysosomal storage disorders has not yet been evaluated in the general newborn population.

Method: All newborns who were recruited from Nanjing Women and Children's Healthcare Hospital in China from March 18, 2022, to September 21, 2023 underwent newborn genomic screening of 16 lysosomal storage disorders (19 genes) using dried blood spot, with enzyme activity testing on positive samples.

Results: This study prospectively recruited 22 687 newborns (11 996 male [52.88%]). The mean (SD) gestational week was 39.2(1.08) weeks, the mean (SD) birth weight was 3369.7(412.95) g. The genomic screening identified 1 361 carriers (6.0%) and 30 (0.13%) initial positive newborns for lysosomal storage disorders. Among the 30 initial positive newborns, 4 were excluded, 15 newborns were diagnosed, and 11 newborns were followed-up. The combined birth prevalence of LSDs in Nanjing of Jiangsu province is 1/1 512, suggesting that approximately one potential LSD patient per 1 512 newborns may benefit from timely disease tracking management and intervention through NBGS. Comparisons with enzyme activity detection showed that newborn genomic screening had a higher positive predictive value ($P < 0.05$) and a lower false positive rate ($P < 0.05$).

Conclusions: This study emphasizes the clinical utility of incorporating newborn genomic screening for lysosomal storage disorders into routine newborn screening, offering a proactive approach for early detection and intervention, ultimately enhancing public health and the well-being of newborns and their families.

Key Words lysosomal storage disorder, newborn genomic screening, lysosomal enzyme activity, newborn screening

·遗传病的认识与研究进展·

From iPSCs to Myotubes: Identifying Potential Biomarkers for FSHD with Single-Cell Transcriptomics

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Objective:Our study focused on the differentiation of induced pluripotent stem cells (iPSCs) into myogenic cells and their analysis using single-cell RNA sequencing (scRNA-seq) to investigate efficacy and explore potential therapeutic targets for facioscapulohumeral muscular dystrophy (FSHD).

Methods:A commercialized protocol was employed to effectively differentiate iPSCs into myogenic progenitor cells and myotubes derived from both healthy individuals and individuals with FSHD1. scRNA-seq was utilized to examine the differentiation process from myogenic progenitor cells to myotubes, identifying cell clusters based on marker genes. scVelo was used in conjunction with Slingshot and Monocle to map the pseudo-time trajectory. Differential gene expression and enrichment analysis were performed to compare myotubes derived from control and FSHD1 groups in search of potential biomarkers.

Results:We showed 13 cell clusters of the culture through the scRNA-seq, which were renamed according to marker genes. Combined with scVelo, Slingshot and Monocle, we deduced the differentiation trajectory of the culture, that is, the differentiation of Muscle satellite cells into proliferative PAX3+ myogenic progenitor cells, further differentiation into myoblasts, and finally into myotubes. The differentiation trajectories calculated by the three algorithms are consistent with the known differentiation processes of skeletal muscle. Analysis of gene expression in myotubes of FSHD1 patients and healthy controls showed that several genes related to muscle function were enriched and increased in the patients. Additionally, qPCR and immunofluorescence confirmed increased expression of ISG15, MYH8, and TTN in FSHD patient cells.

Discussion:We investigated the cellular properties of iPSC-induced myotube cultures at a single-cell resolution, as well as identified potential biomarkers for FSHD through differential analysis. The differentiation trajectory matches known skeletal muscle development, indicating that the in vitro culture system of iPSC-induced muscle cells essentially simulates skeletal muscle differentiation in vivo, making it an excellent cellular model for studying FSHD.

Key Words FSHD, iPSCs, scRNA-seq, differentiation trajectory, biomarkers

甲基丙二酸血症的遗传学研究

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目的：分析苏州地区甲基丙二酸血症患儿相关基因的突变位点，明确其遗传特征。

方法：应用基于二代测序的靶向捕获技术对高效液相串联质谱技术筛查出的17例甲基丙二酸血症患儿进行基因检测。

结果：在17例患儿中，共检测到MUT和MMACHC基因上的18种突变，其中15（88.2%）例携带有纯合突变或者复合杂合突变，2（11.8%）例仅检测到单位点杂合突变。8（47.1%）例甲基丙二酸血症患儿在MUT上检测到复合杂合突变或者单位点杂合突变，9（52.9%）例在MMACHC上检测到纯合突变、复合杂合突变或者单位点杂合突变。在这些检出的突变位点中，携带频率最高的为MMACHC基因c.609G>A，在7（77.8%）例MMACHC缺乏患儿中检出此突变；其次为MUT基因c.1663G>A，在4（50.0%）例MUT缺乏患儿中检出此突变。

结论：甲基丙二酸血症患儿主要由MUT和MMACHC基因突变导致，MMACHC c.609G>A和MUT c.1663G>A，是导致甲基丙二酸血症患儿的遗传热点。

关键字 MUT基因，MMACHC基因，甲基丙二酸血症，二代测序技术，遗传热点

辅助生殖技术对胎盘表观遗传学的影响

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辅助生殖技术(ART)是目前治疗不孕症患者的常用方法,但其对胎盘发育的不良影响是值得关注与讨论。近年来,越来越多的研究表明,ART可能会对胎盘的表观遗传学调控产生影响,导致不良妊娠局。ART的体内外过程与自然妊娠环境存在差异,导致胎盘表观遗传学异常,包括DNA低甲基化、组蛋白修饰异常、印基因表达失调、干扰染色质重塑进程及非编码RNA异常表达等。本文就ART对胎盘表观遗传调控发育过程的影响进行综述。

关键字 辅助生殖技术; 胎盘; 表观遗传学; DNA甲基化; 印记基因

多囊卵巢综合征与胰岛素抵抗

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当今，多囊卵巢综合征是妇科领域中一种常见的疾病，其内分泌特征之一就是胰岛素抵抗。而胰岛

素抵抗，即代偿性高胰岛素血症会升高雄激素水平。多囊卵巢综合征的进展和严重程度随着胰岛素水平的增加而增加。先出现胰岛素抵抗还是先出现多囊卵巢综合征，这个复杂的问题仍没有结论。随着肠道菌群的介入，对胰岛素抵抗和多囊卵巢综合征的机制带来了新的研究方向。然而，从具体研究到临床应用的转变仍有一段路要走。

关键字 多囊卵巢综合征，胰岛素抵抗，高胰岛素血症，肠道菌群

子宫内膜容受性与糖代谢关系的研究进展

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【摘要】胚胎植入是体外受精–胚胎移植过程中的关键环节。子宫内膜容受性与胚胎种植密切相关，是决定辅助生殖技术成功与否的关键因素。近年来成为辅助生殖领域研究的热点。子宫内膜容受性是指子宫内膜接受胚胎种植的能力，内膜具有适宜的容受性，决定了正常植入过程的完成。近年来，许多研究表明，子宫内膜容受性的建立与糖代谢密切相关。本文就子宫内膜容受性和糖代谢的关系作一概述。

关键字【关键词】子宫内膜容受性；胚胎植入；葡萄糖；糖酵解；蜕膜化。

22q11.21微缺失与微重复综合征的遗传学分析及妊娠结局随访

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目的：通过对19例22q11.21区域微缺失和微重复的遗传学分析及妊娠结局随访，探讨微缺失微重复与临床表型之间的关系，为遗传咨询提供依据。

方法：收集2015年1月至2023年5月在连云港市妇幼保健院产前诊断中心应用染色体微阵列分析技术（chromosome microarray analysis, CMA）确诊的22q11.21微缺失微重复病例，对其临床表型，妊娠随访结局及致病基因进行分析。

结果：研究期间共6251例样本行CMA产前检测，19例确诊为22q11.21拷贝数变异，其中微缺失8例，微重复11例。超声影像学资料显示在8例微缺失胎儿中，心脏发育相关异常有5例（62.5%）；而11例微重复胎儿中，未发现心脏相关异常。妊娠结局随访结果显示，8例微缺失胎儿中，7例终止妊娠，1例活产；11例微重复胎儿中，4例终止妊娠，7例出生。

结论：对19例产前样本的综合分析显示微缺失比微重复表现出更多的临床表型，并且与先天性心脏缺陷的关联更大，这有助于临床医生更好地实施妊娠指导。

关键字 22q11.21；染色体微阵列；微缺失；微重复；随访

A New FSHD Mouse Model Demonstrates High DUX4 Expression in Juveniles Leads to Skeletal Muscle Developmental Disorders

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Aims: Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common inherited muscle disorders, caused by abnormal expression of factor double homeobox 4 (DUX4) in skeletal muscles. However, developing animal models for FSHD has proven challenging, and currently, ACTA1-MCM-FLExDUX4 mice are one of the few viable choices among existing animal models for studying skeletal muscle-related diseases. This study aimed to establish a new double transgenic mouse model and induce DUX4 expression during the juvenile stage to investigate the pathophysiology of skeletal muscle.

Methods: The new double transgenic mice were generated by crossbreeding Myf6-CreERT2 heterozygous mice with FLExDUX4 heterozygous mice, and DUX4 expression was induced by tamoxifen starting from 3 weeks of age. To assess the disease model phenotype at 9 weeks of age, evaluations included measurements of body weight, a four-limb strength test, an inverted screen test, the skeletal muscle weight ratio, histological analyses (H&E staining, Picrosirius red staining, and immunofluorescence of skeletal muscle paraffin sections). In addition, Quantitative Real-time PCR and RNA-seq were used.

Results: The new double transgenic heterozygous mice (M6D4/+) were successfully generated. Upon induction with tamoxifen in juveniles, these mice exhibited several significant physiological and pathological changes compared to the control group. Physiologically, they exhibited delayed weight gain, reduced four-limb strength and endurance, and a decreased skeletal muscle weight ratio. Pathologically, there were observable increases in centrally nucleated muscle fibers and fibrosis within skeletal muscles. At the molecular level, there was a notable upregulation in the expression of DUX4 and its target genes in skeletal muscle. Additionally, according to the RNA-seq results, genes associated with inflammation and immune response pathways showed increased expression, while genes involved in skeletal muscle development, differentiation, mitochondrial function, and energy metabolism exhibited downregulation.

Conclusion: The M6D4/+ mice serve as a valuable model for studying skeletal muscle disease in FSHD. Inducing high-level expression of DUX4 during the juvenile stage results in developmental disorders within skeletal muscle.

Key Words Facioscapulohumeral muscular dystrophy; DUX4; skeletal muscle; mice

新发10号染色体部分重复变异患儿1例的临床表型及遗传学分析

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目的：探讨不明原因生长发育落后、合并智力缺陷及孤独症谱系障碍（ASD）患儿的遗传学病因及其与临床表型的对应关系。

方法：选择2018年4月在连云港市妇幼保健院就诊的1例生长发育落后、合并智力缺陷及ASD患儿作为研究对象。收集患儿临床资料，抽取患儿及其父母外周血样，并对采集样本进行G显带染色体核型分析和染色体微阵列分析（CMA）。检索在线人类孟德尔数据库（OMIM）、Ensembl人类基因组变异和表型数据库（DECIPHER）等进行染色体变异致病性分析。

结果：本例患儿临床表现为生长发育落后，合并智力缺陷。G显带染色体核型分析结果显示，患儿染色体核型异常，为46,XY,dup(10)(q23.31q24.33)，其父母核型均未见异常。患儿CMA检测结果为arr[19]10q23.31q24.33(87603382_104948862)×3，提示其10号染色体（10q）q23.31q24.33区存在约17.34 Mb片段重复，该片段包含171个OMIM基因，可能涉及的主要致病基因包括PTEN、WNT8B、LZTS2、NFKB2、PAX2、KIF11、FRA10AC1、CNNM2等。

结论：本例患儿的10q部分重复属于新发变异，涉及PTEN、WNT8B等基因，可能导致患儿生长发育落后，合并智力缺陷和ASD，其表型随年龄增长而愈加明显。本研究扩展了10q23.31q24.33区重复的基因型–表型谱，为患儿染色体变异所致综合征的诊疗提供了参考。

关键字 染色体重复；儿童发育障碍；孤独症谱系障碍；智力障碍

Genetic variation and clinical characteristics of children with congenital hypothyroidism with different thyroid morphology: an analysis of 98 cases

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Objective To investigate the genetic variation and clinical characteristics of congenital hypothyroidism (CH) with different thyroid morphology. Methods A retrospective study was conducted on 98 cases of Changzhou Maternal and Child Health Care Hospital and Lianyungang Maternal and Child Health Care Hospital from August 19, 2011 to November 13, 2019 . According to Thyroid morphology, they were divided into Thyroid dysplasia (TD) group, gland in situ Thyroid, (GIS) group and Goiter group. The gene variation was detected by whole-exome sequencing (WES). The general condition, gene variation and treatment of CH among the 3 groups

were compared. Statistical analysis was performed using Chi-square (or Fisher’s exact) tests, Kruskal Wallis test, LSD test, or Mann-Whitney U -test. Results: (1) There is a statistically significant difference in the birth rate of girls among CH patients in TD, GIS and Goiter groups [87.5% (21/24), 47.8% (32/67), 3/7, c2=13.46, P=0.001], and the birth rate of girls in the TD group is higher than that in the other two groups (P <0.017). There was a statistically significant difference in postnatal sTSH levels among the three groups [28.00 (33.30~20.0 mU/L), 55.40 (17.73~116.0) mU/L, 32.00 (21.55~57.65) mU/L, H=7.02, P=0.030], but there was no statistically significant difference in pairwise comparison between the three groups (P >0.017) (2) The detection rates of potential functional variants in TD, GIS and Goiter groups were 45.8% (11/24),88.1% (59/67) and 6/7, respectively, (χ^2=18.39, P<0.001). Compared with the TD group, the detection rate of potential functional variants in CH patients in the GIS group was higher (c2=17.75, P<0.001). Among them, the highest frequency of variants was DUOX2, and the detection rate was 59.2% (58/98). The detection rates of TD, GIS and Goiter CH were 20.8% (5/24), 73.1% (49/67) and 4/7, respectively, (c2=20.02, P<0.001). Monoallelic variants were more common in TD group with variants frequency of 7/11, while biallelic variants were more common in GIS group and Goiter group with variation frequencies of 72.4% (42/59) and 4/6, respectively. In addition, 6 oligogenic variants were detected in GIS children (10.2% ,6/59). (3) There was a statistically significant difference in the dosage of L-Thyroxine (L-T4) between the ages of 2[37.50 (25.00-45.00) pmol/L, 37.50 (25.00-45.00) pmol/L, 25.00 (16.50-40.00) pmol/L, H =16,53, p<0.001] and 3 [37.50 (27.12-47.50) pmol/L, 20.00 (6.25-29.25) pmol/L, 31.25 (9.38~52.50) pmol/L, H=14.16, P<0.001]in three groups of CH patients. In the TD group, L-T4 dose at 2 and 3 year of age was higher than that of the GIS group (P<0.017). Conclusions: There are differences in the detection rate of potential functional variants s among children with different thyroid morphologies in CH, in which the detection frequency of DUOX2 variants is the highest, and biallelic variants are common.. TD groupmay require higher doses of L-T4 supplementation with age.

Key Words Congenital hypothyroidism; Thyroid dysplasia; Normal-sized gland in situ; Goiter; Whole-exome sequencing

1例2p23.2p22.1重复患者的临床表型及遗传学分析

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目的：首次报道一例2p23.2p22.1重复成年患者的临床表型，分析基因型-表型之间的联系。

方法：一女性患者因不良生育史在我中心行外周血染色体微阵列检测。观察患者表型，询问病史，结合患者表型及芯片结果，搜索数据库，回顾总结分析文献报道的相关病例，分析基因型-表型之间的联系。

结果：该女性患者的SNP-array结果为arr[GRCh38]2p23.2p22.1(27,961,669_39,280,633)x3，其染色体2p22.1-p23.2存在约11.31Mb的基因组DNA拷贝数重复。患者具有身材矮小、学习困难、视力异常、睡眠障碍等临床表现。

结论：2p23.2p22.1片段包含三个pTriplo≥0.94的基因：PPP1CB（600590）、SOS1(182530)和MEMO1（611786），被预测可能具有三倍剂量敏感效应。Decipher数据库显示PPP1CB基因变异和SOS1基因变异均可导致编码的蛋白结构变化，患者可表现为努南综合征(Noonan syndrome,NS)样临床表型，如身材矮小、视力异常等表型。PPP1CB基因(位于2p23.2)和SOS1(位于2p22.1)基因重复变异导致的蛋白功能变化

与患者身材矮小、视力异常这两方面临床表型相匹配，基因型-表型之间具有相关性。MEMO1基因(位于2p22.3)尚无变异导致临床表型的报道。结合文献报道的相关病例重叠区域涉及的区带及临床表型，PPP1CB基因重复与视力异常可能存在基因型-表型对应关系。

关键字 染色体微阵列分析；2p23.2p22.1重复；表型-基因型

Recurrent gene flow between Neanderthals and modern humans over the past 200,000 years

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It is well known that the ancestors of modern humans and Neanderthals admixed and many methods have been developed to identify and interpret introgressed Neanderthal sequences in the genomes of contemporary humans. Although gene flow between Neanderthals and modern humans was bidirectional, comparatively little is known about the dynamics of introgressed human sequences in the Neanderthal genome and how those sequences impact inferences of Neanderthal population history. Here, we develop a methodological framework to estimate the amount and consequences of human introgressed sequence in Neanderthals and apply it to whole-genome sequence data from 2,000 humans and three Neanderthals. We estimate Neanderthals have 2.5% to 3.7% human ancestry and on average contain 65 Mb of human introgressed sequence. Additionally, we leverage the characteristics of human introgressed sequences in Neanderthals to revise estimates of Neanderthal ancestry in contemporary human populations. Furthermore, when human introgressed sequences are properly accounted for, we find that Neanderthal population sizes are significantly smaller than previously thought. The approximately 20% lower estimate of effective population size has important implications for the cost of introgression to modern humans, as the burden of deleterious mutations carried by Neanderthals was likely higher than previously estimated, which were subsequently inherited by the ancestors of predominantly non-African populations. Finally, we identify two distinct waves of human gene flow into Neanderthals, highlighting the long history of admixture between humans and Neanderthals. In summary, recurrent gene flow throughout hominin history has shaped the biology and genomes of modern humans and Neanderthals.

Key Words Neanderthal; introgression; human evolution; admixture

逆转录转座子在胚胎干细胞中的作用机制研究

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逆转录转座子在小鼠基因组中占据了超过40%的比例，对宿主基因组的结构和进化起着至关重要的作用。其中，LINE-1是一种具有自主转座能力的逆转录转座子。尽管它们可能带来基因组不稳定的风险，但在胚胎发育的早期阶段，LINE-1的活性却异常高。我们的研究揭示了ELL3与一种年轻的LINE-1亚家族L1Md_Ts的结合，这种结合在小鼠原始态胚胎干细胞中充当增强子的角色。当ELL3的功能丧失时，L1Md_Ts区域的5hmC水平降低，而H3K27ac水平升高，导致L1Md_Ts附近的基因表达增强。特别是，ELL3能够结合并抑制位于Akt3基因内部的基于L1Md_T的增强子活性，Akt3基因编码的是AKT信号通路的关键调控因子。在小鼠胚胎干细胞以及着床前胚胎的发育过程中，ELL3通过抑制Akt3基因的表达，精细调控ERK信号通路的激活，这对于胚胎干细胞的多能性至关重要。此外，我们还发现了ZFP825与内源性逆转录病毒亚家族元件IAP的结合，这些元件在小鼠胚胎干细胞中表现出潜在的增强子活性。当ZFP825的表达被下调时，其结合的IAP元件上的H3K9me3修饰水平降低，导致附近基因表达上调，特别是Wnt信号通路和与中胚层谱系相关的基因表达水平显著增加。这些发现不仅阐明了ELL3和ZFP825在胚胎干细胞多能性调控中的作用，也为我们理解基因组中转座子元件的功能提供了新的视角。

关键字 逆转录转座子 胚胎干细胞 增强子

髓系肿瘤伴CEBPA突变临床特征分析

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目的：世界卫生组织（WHO）和欧洲白血病网络（ELN）对于急性髓细胞白血病（AML）伴CEBPA bZIP区突变的诊断是否需要20%原始细胞比例存在争议。本研究通过分析骨髓增生异常综合征（MDS）中原始细胞比例大于等于10%的CEBPA bZIP区突变患者的临床特征并与AML伴CEBPA bZIP区突变比较，探讨原始细胞比例大于等于10%的MDS伴CEBPA bZIP突变是否能够作为AML伴CEBPA bZIP突变亚型诊断。

方法：回顾性分析本研究中心2016年至2021年根据WHO分型指南第四版诊断的725例MDS和1591例AML患者。采用高通量测序技术检测所有患者骨髓细胞常见髓系肿瘤82种基因突变。比较原始细胞比例大于等于10%的MDS伴CEBPA bZIP区突变患者与AML伴CEBPA bZIP区突变患者骨髓形态、流式免疫分型、染色体核型和基因突变、全转录组测序基因表达谱差异等临床特征。

结果：1.在29例MDS伴CEBPA突变患者中，CEBPA bZIPIndel患者6例，CEBPA bZIPnon-indel患者10例，CEBPA non-bZIP突变患者13例。利用卡方检验对CEBPA不同突变类型在MDS和AML中的分布比例发现CEBPA bZIPIndel与AML密切相关，具有统计学差异，$p<0.001$。2. 统计细胞形态学发现，6例MDS伴CEBPA bZIPIndel患者5例原始细胞大于等于10%，1例原始细胞比例为9%。而MDS伴CEBPA bZIPnon-

indel、CEBPA non-bZIP突变患者原始细胞比例分布较广泛（3.5-19.0%），原始细胞比例大于等于10%的MDS伴CEBPA bZIPIndel患者骨髓涂片中巨核细胞计数偏少，较AML伴CEBPA bZIPIndel患者类似，而MDS伴CEBPA bZIPnon-indel患者骨髓涂片中易见巨核细胞。3. 统计流式免疫分型结果发现，AML伴CEBPA bZIPIndel患者CD7表达（中位值70.6）略高于AML伴CEBPA bZIPnon-indel患者（中位值59.0），但统计学分析无显著差异p=0.31。而在MDS伴CEBPA bZIP突变患者中，发现MDS伴CEBPA bZIPIndel患者（中位值35.0）高于MDS伴CEBPA bZIPnon-indel患者（中位值1.7），具有统计学差异p=0.03。AML伴CEBPA bZIPIndel患者与原始细胞比例大于等于10%的MDS伴CEBPA bZIPIndel患者CD7表达差异不显著。其余CD13、CD33、CD34、CD117、HLA-DR在各组中无显著差异。4. 对AML伴CEBPA突变患者染色体核型分析结果统计，发现复杂核型（染色体结构和/或数目异常大于等于3）在AML伴CEBPA bZIPnon-indel中占17.9%（5/28），而AML伴CEBPA bZIPIndel中仅有2.4%（4/168），具有统计学差异p<0.001。5. 对83例CEBPA突变MDS和AML全转录组测序结果基因表达谱PCA图分析发现原始细胞比例大于等于10%MDS伴CEBPA bZIPIndel与AML伴CEBPA bZIPIndel有类似的基因表达谱。

结论：CEBPA bZIPIndel突变AML密切相关，原始细胞比例大于等于10%的MDS伴CEBPA bZIPIndel与AML伴CEBPA bZIPIndel具有类似的骨髓形态、流式免疫分型、遗传学改变和基因表达谱。

关键字 急性髓细胞白血病，CEBPA，突变

·遗传病的分子基础与环境互作·

Gold nanoparticles retrogradely penetrate through testicular barriers via Sertoli-cells mediated endocytosis/exocytosis and induce immune response

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Despite the rapidly growing interest in nanoparticle-mediated controllable male contraception and recovery of male fertility, novel applications of nanoparticles in these processes are limited by a knowledge gap regarding their transport and distribution in the testes. Here, we investigated the fate of gold nanoparticles in the mouse testes using two injection methods, namely, interstitial testicular injection (IT-AuNPs, AuNPs exposure in the interstitial compartment of the testes) and rete testis injection (RT-AuNPs, AuNPs exposure in the adluminal compartment of the seminiferous tubules). In this study, we used 100 nm spherical AuNPs and microinjected with 5 μL AuNPs (30 mg/mL) for the experiments. For IT-AuNP injection, we found that AuNPs could not penetrate through the Sertoli cell-mediated blood-testis barrier (BTB) of the seminiferous tubules, and no male reproductive toxicity was observed. For RT-AuNP injection, AuNPs could be retrogradely transported from the adluminal compartment to the interstitial compartment of the testes via Sertoli cell-mediated endocytosis/exocytosis, resulting in damage and the release of inflammatory cytokines in the mouse testis. Our results highlight a retrograde nanoparticle transport function of Sertoli cells, thereby providing a mechanistic overview of the development and use of nanobiotechnology in male reproduction.

Key Words AuNPs, Blood-testis barrier, Interstitial testicular injection, Rete testis injection, Reproductive toxicity, Local inflammatory response

Triptolide exposure triggers testicular vacuolization injury by disrupting the Sertoli cell junction and cytoskeletal organization via the AKT/mTOR signaling pathway

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Background:Despite the known reproductive toxicity induced by triptolide (TP) exposure, the regulatory mechanism underlying testicular vacuolization injury caused by TP remains largely obscure.

Methods: Male mice were subjected to TP at doses of 15, 30, and 60 μg/kg for 35 consecutive days. Primary

Sertoli cells were isolated from 20-day-old rat testes and exposed to TP at concentrations of 0, 40, 80, 160, 320, and 640 nM. A Biotin tracer assay was conducted to assess the integrity of the blood - testis barrier (BTB). Transepithelial electrical resistance (TER) assays were employed to investigate BTB function in primary Sertoli cells. Histological structures of the testes and epididymides were stained with hematoxylin and eosin (H&E). The expression and localization of relevant proteins or pathways were assessed through Western blotting or immu[1]nofluorescence staining.

Results: TP exposure led to dose-dependent testicular injuries, characterized by a decreased organ coefficient, reduced sperm concentration, and the formation of vacuolization damage. Furthermore, TP exposure disrupted BTB integrity by reducing the expression levels of tight junction (TJ) proteins in the testes without affecting basal ectoplasmic specialization (basal ES) proteins. Through the TER assay, we identified that a TP concentration of 160 nM was optimal for elucidating BTB function in primary Sertoli cells, correlating with reductions in TJ protein expression. Moreover, TP exposure induced changes in the distribution of the BTB and cytoskeleton[1]associated proteins in primary Sertoli cells. By activating the AKT/mTOR signaling pathway, TP exposure disturbed the balance between mTORC1 and mTORC2, ultimately compromising BTB integrity in Sertoli cells.

Conclusion: This investigation sheds light on the impacts of TP exposure on testes, elucidating the mechanism by which TP exposure leads to testicular vacuolization injury and offering valuable insights into comprehending the toxic effects of TP exposure on testes.

Key Words Triptolide, Testicular vacuolization injury, BTB integrity , Cytoskeleton, AKT/mTOR signaling

Mechanism research of neural crest cell migration involved in the pathogenesis of neural tube defects using 3D organoids

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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.

Key Words neural tube defects, human pluripotent stem cells, organoids

微量元素锌通过免疫损伤对精子产生毒性作用

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目的：不孕不育已成为现代社会常见病，其中男性因素约占一半。精液质量对男性生殖健康至关重要。锌是重要的微量元素，目前的证据表明锌在精子发生、附睾中的精子成熟、精子运动和女性生殖道中的受精过程中发挥着关键的生理作用。本研究旨在探讨精浆中锌与精液质量参数之间的潜在关系，为精浆锌与男性生殖性状的关系提供新的见解。

方法：研究纳入常州市妇幼保健院殖医学的25915名男性参与者。分析精液样本获取质量参数，使用广义相加模型（GAM）来处理质量参数变量之间的非线性关系，多组间的差异比较采用方差分析 / Wilcoxon 秩和检验，组间的双向比较，采用 “Tukey “/” Dunn’s “检验。培养GC-2spd (ts) 细胞并用 CCK-8 检测细胞存活率，对两组（0μM、160μM ZnCl2）细胞样本做RNA-seq分析测序。。

结果：揭示了精浆锌浓度与精子 PR/PR+NP 之间的倒 “U “型趋势。锌浓度处于中等水平组（0.25-2.11 mmol/L）的精子 PR/PR+NP 值最高。平均值分别为 43.17 ± 19.03% 和 56.64 ± 20.28%。而锌含量最高的一组（> 3.04 mmol/L）的数值最低。体外细胞实验也表明，锌对 GC-2 细胞的细胞毒性呈剂量依赖性，达到临界值；RNA-seq 分析显示，在 160μM ZnCl2 处理的细胞中，免疫反应相关基因出现异常下调。

讨论：适量的锌对人类的生殖至关重要，过量或不足的锌浓度可能会对男性的生育能力产生不利影响。

关键字 锌、精子质量、毒性作用、男性生育力

纳米材料AuNCs改善铜过载导致的精子质量下降

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目的：判断男性体内铜过载引发的生殖毒性能否被AuNCs治疗，从而实现药物的临床应用转化。

方法：1、 临床样本：收集不同质量的精液样本，使用超高效液相色谱–质谱串联技术、电感耦合等离子质谱检测不同分组中精液样本铜离子含量，用电感耦合等离子体质谱仪分别测量精子和精浆中的铜离子含量，以此初步验证铜过载与精子质量下降的相关性。将临床收集的精子样本分为对照组和AuNCs处理组，分别检测铜死亡标志蛋白表达水平，判断AuNCs是否可以改善铜过载导致的精子质量下降。

2、 铜过载造模及治疗：准备C57BL6/N雄鼠，分为四组–对照组、注射氯化铜组、注射氯化铜加AuNCs组、注射AuNCs组，观察铜过载后纳米材料是否具有治疗作用。

3、 细胞水平：对GC1细胞使用不同浓度的氯化铜溶液进行处 理并加入纳米材料溶液观察形态和相关蛋白表达水平。

结果：1、收集的精液中铜离子浓度与精液质量呈负相关，AuNCs处理后铜死亡标志蛋白降低。

2、AuNCs注射后对铜过载模型小鼠睾丸生精小管凋亡减轻，铜死亡标志蛋白降低，精子活力增加。

3、加入AuNCs后，氯化铜处理GC1细胞的死亡率降低。

结论：AuNCs可以治疗男性体内铜过载引发的生殖毒性，提高男性精子质量。

关键字 纳米材料；铜过载；生殖毒性；精子活力

GBP1基因突变导致先天性甲状腺减退症的临床表型及表观遗传学研究

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目的：研究GBP1在先天性甲状腺减退症（CH）患者的突变及其遗传模式，分析患儿基因型与临床病程的相关性，探讨GBP1致病机制。

方法：收集90例CH患儿及其家系，提取外周血DNA，利用全外显子测序技术对患儿及其家系进行基因组序列测定，利用生物信息学技术对检出的变异进行位点注释，所有位点均进行Sanger测序验证。采用焦磷酸测序方法分析队列人群GBP1的甲基化水平的差异性，统计分析采用SPSS 10.0软件进行。同时收集患儿的表型资料，对基因型与表型进行关联分析。

结果：共有F35，F60，F78家系先证者检出相同的GBP1突变位点（P.L187P），先证者年龄分别为3岁、5岁、4岁；L–T4治疗剂量分别为1/3片交替、1片、1/2片。超声影像显示，F60家系先证者甲状腺缺如，携带GBP1突变的F78家系母亲双侧甲状腺弥漫性质不均；经生化检测提示，携带GBP1突变的F35先

证者父亲为亚临床甲减。另有F37家系的2名子女（异卵双胞胎姐妹）在新生儿时期均表现出TSH增高延迟，此2名患儿均检出GBP1突变（P.R20X）。GBP1甲基化差异性分析显示，cg12054698甲基化水平在CH患儿队列、GBP1突变携带者队列及健康人群中呈现多态性。

结论：GBP1突变（P.L187P）的CH患儿均为PCH，且在不同年龄的用药剂量表现出高剂量的特征，建议GBP1纳入甲减诊断和新生儿基因的筛查范围。

关键字 先天性甲减、GBP1、基因型与表现型、临床病程

RNF187通过促进组蛋白H3在K57/80位点的泛素化维持小鼠GC-2细胞的生长

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目的：RNF187（RING finger 187）是一种E3泛素连接酶，通过其RING结构域泛素化特异性底物从而介导底物降解或修饰。前期研究表明RNF187参与肝细胞癌和非小细胞肺癌的增殖和转移过程。然而，关于RNF187是否在雄性生殖系统中发挥作用尚不清楚。因此，本研究将重点分析RNF187对小鼠精母细胞衍生的GC-2细胞生长产生的影响和具体机制。

方法：通过细胞转染技术分别在GC-2细胞中敲减和过表达RNF187，并通过CCK-8、EdU和TUNEL等实验验证RNF187对GC-2细胞活力、增殖和抗凋亡能力的影响。通过IP-LC/MS-MS寻找与RNF187互作的底物。通过共转染验证RNF187发挥泛素化功能的部位。明确底物蛋白上被泛素化的具体位点，并通过CCK-8、EdU等实验验证这些位点对GC-2细胞生长的影响。最后，通过EU实验验证对细胞转录水平的影响。

结果：研究结果表明，RNF187促进GC-2细胞的活力、增殖、迁移和抗凋亡能力，证实RNF187与组蛋白H3互作并通过RING结构域泛素化H3。此外，H3的K57/80位点参与到RNF187的泛素化过程中，当K57/80位点突变后，组蛋白H3上的泛素化水平显著下降，并且GC-2细胞的活力、增殖和迁移能力均显著降低。最后，EU实验表明RNF187泛素化组蛋白H3的K57/80位点后，细胞的转录水平增加维持了GC-2细胞的生长。

结论：RNF187介导组蛋白H3的K57和K80位点的泛素化，参与了基因转录的表观调控，促进了GC-2细胞的生长发育。

关键字 RNF187，泛素化，GC-2细胞

Construction of ceRNA networks related to recurrent abortion using whole transcriptome sequencing

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Objective:To construct an inter-gene regulatory network by screening non-coding RNA (lncRNA), microRNA (miRNA), messenger RNA (mRNA), and circRNA associated with relapse-induced abortion, with the aim of investigating the transcriptomic level material basis and pathological mechanism of relapse-induced abortion.

Method:Using whole transcriptome sequencing technology, we conducted a comprehensive analysis of differentially expressed mRNA, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) in villus tissue samples from three patients with recurrent spontaneous abortion (RSA) and three normal abortion patients. Subsequently, bioinformatic analysis was performed to identify potential target molecules closely associated with recurrent abortion. To facilitate the exploration of these associations, we constructed an integrated mRNA-miRNA-lncRNA/circRNA network.

Results: A total of 412 differentially expressed mRNAs were identified between the RSA group and the normal abortion group, with 230 up-regulated and 182 down-regulated. Additionally, 439 lncRNAs showed differential expression, including 235 up-regulated and 204 down-regulated. Three circRNAs were also found to be differentially expressed, all of which were down-regulated. Furthermore, seven miRNAs exhibited differential expression, with three being up-regulated and four being down-regulated. The bioinformatics analysis revealed that the DEGs primarily enriched in extracellular regions, multicellular biological processes, cell adhesion, intrinsic components of membranes, type II transforming growth factor receptor binding pathway as well as transforming growth factor receptor binding pathway among others. Notably, four lncRNAs, four mRNAs and five miRNAs formed four regulatory networks (lncRNA-miRNA-mRNA), providing a foundation for elucidating the mechanism underlying RSA.

Key Words recurrent abortion, transcriptome sequencing, ceRNA network

GRAMD1B蛋白棕榈酰化修饰调控颗粒细胞功能在PCOS发生发展中的作用及机制

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多囊卵巢综合征（polycystic ovary syndrome，PCOS）是育龄期妇女常见的生殖内分泌疾病。其卵母细胞、胚胎质量以及妊娠结局仍较差。因此，阐明PCOS的发病机制，并由此提出对应的治疗和干预措施至关重要。本课题组前期鉴定PCOS患者与非PCOS患者卵泡液外泌体中的差异蛋白，并从中筛选到

GRAMD1B蛋白。GRAMD1B介导胆固醇转运，对于调控胆固醇代谢和稳态维持至关重要。胆固醇代谢和类固醇激素的合成对于确保生殖系统的功能正常具有不可或缺的关键作用。然而 GRAMD1B在颗粒细胞中的机制研究尚未见报道。

为了探究GRAMD1B蛋白异常累积对颗粒细胞功能的影响，我们构建了GRAMD1B蛋白过表达KGN细胞系。过表达组细胞内胆固醇异常累积，其中胆固醇内源合成显著下调，而外源摄取、外排及酯化上调，提示胆固醇稳态异常。胆固醇具有调控脂质过氧化和铁死亡过程的能力，过表达组抗氧化因子显著下调，氧化水平以及铁死亡均明显增加。颗粒细胞具有转换类固醇激素的能力，过表达组细胞中激素代谢的关键酶显著下降。综上所述，颗粒细胞中GRAMD1B蛋白表达水平的上调导致了脂代谢稳态的失衡、铁死亡的加剧以及类固醇激素转换功能的异常等多种功能紊乱。随后，我们进行了蛋白组学分析：发现GRAMD1B过表达组和对照组的差异表达基因中维持胆固醇代谢稳态的相关基因表达下调，抑制铁死亡的相关基因表达下调以及类固醇激素转换相关基因表达下调。这些共同作用会导致颗粒细胞功能障碍。

阐明GRAMD1B蛋白在PCOS颗粒细胞中异常累积的原因可能是挽救颗粒细胞功能的关键。由于GRAMD1B蛋白GRAM结构域具有检测胆固醇及阴离子脂质共分布的感应位点，我们发现高胆固醇环境能够上调细胞内GRAMD1B蛋白量。PCOS患者及模型鼠颗粒细胞中GRAMD1B的mRNA表达降低，提示GRAMD1B蛋白量的上调可能发生在翻译后修饰水平。S型棕榈酰化是研究最为深入的脂质修饰之一，调控蛋白质的稳定性、构象、定位、膜结合以及相互作用。我们利用棕榈酰化蛋白富集技术证实GRAMD1B蛋白存在棕榈酰化修饰，并确定了关键修饰位点（C77、C135）。进而我们发现棕榈酰化修饰并不影响蛋白的合成与降解，而是介导GRAMD1B蛋白外泌体降解，抑制棕榈酰化后外泌体分泌受阻导致细胞内GRAMD1B异常累积。进一步我们在PCOS模型鼠卵巢组织和高胆固醇环境培养的KGN细胞中发现，GRAMD1B蛋白的棕榈酰化修饰水平均降低，这可能是GRAMD1B蛋白在颗粒细胞中累积的潜在机制。

综上所述：PCOS颗粒细胞可能处于高胆固醇环境，抑制GRAMD1B蛋白棕榈酰化修饰，导致分泌受阻并滞留于高尔基体。细胞内累积的GRAMD1B蛋白通过转运过量胆固醇，加剧细胞氧化应激和凋亡，进而损害颗粒细胞功能，影响卵泡发育和卵母细胞质量。本研究首次将GRAMD1B蛋白与PCOS疾病相联系，从胆固醇代谢异常角度揭示了其在PCOS发病中的作用，为临床诊疗提供了新的思路，有助于深化对PCOS病因的理解。

关键字 GRAMD1B；PCOS；颗粒细胞；胆固醇代谢；棕榈酰化修饰

Vitamin D deficiency inhibits microRNA-196b-5p which regulates ovarian granulosa cell hormone synthesis, proliferation, and apoptosis by targeting RDX and LRRC17

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[Background]In polycystic ovary syndrome (PCOS), ovarian physiology is tightly linked to the metabolic disturbances observed in this disease. Vitamin D (VD) plays an important role in the regulation of ovulatory dysfunction and can influence genes involved in steroidogenesis in granulosa cells. However, its role in the proliferation and apoptosis of ovarian granulosa cells is unclear. The present study aimed to investigate the role of

microRNA-196-5p (miR-196b-5p) in the hormone synthesis, proliferation, and apoptosis of ovarian granulosa cells. [Methods] The abnormal expression of miRNAs in ovarian tissues of VD-deficient mice was analyzed using transcriptome sequencing. The direct target of miR-196b-5p was predict and confirmed by bioinformatics analysis and the dual-luciferase reporter assay. Reverse transcription-quantitative PCR (RT-qPCR) was used to detect the levels of miR-196b-5p, cell proliferation was detected via the CCK8 assay, and cell apoptosis and reactive oxygen species (ROS) were measured via flow cytometry. The levels of RDX, LRRC17, CYP19A1, and GLUT4 were detected by performing RT-qPCR or western blot. [Results] We found that miR-196b-5p was significantly downregulated among the 672 miRNAs that were differentially expressed (DE) in VD-deficient mice. In addition, the results demonstrated that downregulated expression of miR-196b-5p significantly increased the level of RDX and LRRC17, and reduced expression of miR-196b-5p significantly promoted ovarian granulosa cell apoptosis and inhibited cell proliferation. Downregulated expression of miR-196b-5p promoted cellular ROS production and inhibited sex hormone production and glucose uptake. Transfection with miR-196b-5p mimics significantly increased the expression of CYP19A1 and GLUT4 and decreased the RDX and LRRC17 levels in ovarian granulosa cells. [Conclusions] This study shows that miR-196b-5p can regulate the oxidative stress (OS), glucose uptake, and steroid production pathway of granulosa cells, thus promoting follicular development and maturation. This is a step towards a feasible treatment for PCOS.

Key Words miR 196b 5p, vitamin D, radixin (RDX) and leucine rich repeat containing 17(LRRC17), ovarian granulosa cells

Down-regulation of miR-138-5p by PP2A promoted apoptosis of spermatocytes

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Background: Protein phosphatase 2A (PP2A) is known to have a pivotal and diverse functions in various physiological processes. In a previous study, we utilized the cre-loxp system to generate germ cell-specific knockout mice for the PP2A catalytic subunit alpha subunit (Ppp2cacKO).

Methods and results: Using high-throughput miRNA sequencing of testis tissues and real-time PCR, we have identified a notable decrease in the expression of miR-138-5p in the testes of Ppp2cacKO mice. Our findings indicate that miR-138-5p plays a role in the regulation of apoptosis and proliferation of GC2 cells. Furthermore, bioinformatics analyses suggested that miR-138- 5p may target the transcriptional repressor Trps1. Consistent with these predictions, we observed a significant upregulation of Trps1 in the testes of Ppp2cacKO mice. Through transfection experiments, we have validated the negative regulation of Trps1 expression by miR-138-5p in GC2 cells.

Conclusion: Our study indicates that PP2A influences miR-138-5p targeting of Trps1, impacting spermatocyte proliferation and apoptosis.

Key Words Azoospermia, Spermatogenesis , PP2A, miR-138-5p, Trps1

SKP-SC-EVs通过内含miR-27b-3p调控EphA4促进周围神经缺损修复

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周围神经缺损仍然是临床治疗的难题，组织工程化神经移植物为其提供了新的治疗策略。本课题组前期采用皮肤前体细胞分化的施万细胞来源的胞外囊泡（SKP-SC-EVs）构建的神经移植物成功修复了大鼠坐骨神经缺损。通过对再生的坐骨神经段进行高通量转录组测序和生物信息学分析，我们发现，SKP-SC-EVs能够引起轴突再生和髓鞘形成等多个生物学过程的动态变化。差异基因分析显示，EphA4是参与调控轴突再生和髓鞘形成的关键因子。干扰EphA4显著促进了运动神经元（MNs）突起生长、轴突再生，并增加了III型生长锥的比例。我们通过腺相关病毒（AAV）介导大鼠体内EphA4过表达，功能评估结果显示，SKP-SC-EVs通过调控EphA4显著促进了再生轴突的生长，加快了大鼠运动、感觉及电生理功能的恢复，并有效延缓了失神经支配后的靶肌萎缩。进一步研究发现，miR-27b-3p与EphA4存在结合位点，且抑制miR-27b-3p的同时干扰EphA4能够逆转EphA4对MNs突起生长和轴突再生的抑制作用。此外，SKP-SC-EVs处理显著促进了MNs轴突再生；而抑制SKP-SC-EVs中的miR-27b-3p显著减弱了MNs轴突再生，表明SKP-SC-EVs通过其内含的miR-27b-3p影响MNs功能。该研究为开发治疗周围神经缺损的新技术提供了理论基础和实验依据。

关键字 周围神经缺损；SKP-SC-EVs；EphA4；运动神经元；miR-27b-3p

MTMR7通过泛素化降解FLNB抑制人精原干细胞的增殖

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精原干细胞作为睾丸中的成体组织干细胞，是精子发生的基础，对男性生育至关重要。精原干细胞具有自我更新和分化的双重潜能，维持两者之间的平衡对正常精子生成至关重要，但其调控的分子机制目前少有研究。

目的：我们先前的研究表明，肌管蛋白相关蛋白MTMR7 可以通过抑制 PI3K/AKT 信号来调节细胞周期，维持小鼠精原干细胞自我复制和分化的平衡。然而，MTMR7 在人类精原干细胞中的调控作用目前尚无研究报道。本研究旨在探究MTMR7在人类精原干细胞中的作用及机制，以进一步了解精原干细胞的自我更新和分化过程，为男性生殖研究提供新的理论基础。

方法：我们使用了人类睾丸精原干细胞在体外进行了敲减和过表达实验，并通过质谱分析和免疫共沉淀验证了MTMR7的底物蛋白。最后，使用免疫荧光进行下游通路的验证。

结果：研究结果显示，MTMR7抑制了精原干细胞的增殖和迁移能力。进一步的机制研究表明，MTMR7通过与底物蛋白FLNB相互作用促进其泛素化降解，抑制β-catenin通路，最终影响了精原干细胞的功能。

讨论：综上所述，本研究首次证实了MTMR7/FLNB/β-catenin轴在人类睾丸精原干细胞中的关键作用。通过与临床相结合，研究结果未来可能为精原干细胞功能障碍导致的男性不育提供新的治疗策略和靶向药物。

关键字 人精原干细胞，肌管蛋白相关蛋白MTMR7

Neuroligin 2 Suppresses F-Actin Depolymerization Through RACK1-Cofilin Signaling in Drosophila

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Objective Neuroligins are transmembrane cell adhesion proteins that play critical roles in synapse formation and function, and are well-known for their potent synaptogenic properties and their genetic linkage with autism spectrum disorder, a developmental mental disorder. Our previous research suggested that Neuroligin2 promotes F-actin polymerization, but the underlying mechanism was unknown.

Methods The Drosophila neuromuscular junction was used as an in vivo model for morphological and functional research to investigate the factors and mechanisms involved in Neuroligin2's function on synapse through regulating the actin cytoskeleton.

Results We discovered that the dramatic reduction in the amount of F-actin in dnlg2 mutants is due to the quantity imbalance between phosphorylated and non-phosphorylated forms of cofilin. Neuroligin2 deletion resulted in a disrupted RACK1-cofilin signaling pathway with diminished actin skeleton proteo-stasis, aberrant synaptic structure and abnormal electrophysiology features. Additionally, overexpression of wildtype and non-phosphorylated forms of cofilin in muscles was able to reverse NMJ synapse undergrowth and reduce NMJ synaptic transmission capability in dnlg2 mutants, whereas phosphorylated forms of cofilin was not. Furthermore, we revealed that F-Actin dynamics in Drosophila neuromuscular junction is controlled through Cofilin signaling via a novel interaction between Neuroligin2 and RACK1, suggesting a new understanding of the RACK1 function on neuronal system and actin skeleton.

Conclusion This study revealed a significant role of Neuroligin2 in the regulation of the actin cytoskeleton in the postsynaptic NMJ through RACK1-cofilin signaling pathway, and that orchestration of F-Actin by Neuroligin2 is a highly dynamic and complex process critical for neural connectivity.

Key Words Neuroligin, F-actin, Drosophila, neuromuscular junction, Cofilin, RACK

circCamsap1在精子发生中的功能研究

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精子发生是一种在睾丸曲细精管内精密调控的生理过程，包括精原干细胞的增殖分化、精母细胞的

减数分裂以及精子形成的多个阶段。这些阶段受到严格的基因表达调控，其中阶段特异性基因的表达被调节性非编码RNA（ncRNA）调控。近年来的研究显示，ncRNA在雄性生殖细胞的发育过程中发挥关键作用，不仅在转录和转录后水平上调控基因表达，还参与表观遗传调控。

环状RNA（circRNA）属于非编码RNA的一种，是一共价封闭的环形分子，由反向剪接形成，因此其5’端与3’端相连,具有环形结构的特点，表现出显著的进化保守性和组织特异性表达。CircCamsap1作为一个典型的环状RNA，在癌症研究中被广泛研究，其作为microRNA海绵影响多种癌症的发展进程，同时与2型糖尿病状态相关联，显示出其作为潜在生物标志物的潜力。在小鼠睾丸中高表达的Camsap1和circCamsap1，尽管Camsap1的缺失会导致男性不育，circCamsap1在精子发生中的具体作用机制尚不明确。

为了探索circCamsap1在精子发生中的功能，我们利用CRISPR/Cas9技术构建了circCamsap1敲除小鼠模型，保持亲本基因Camsap1的表达不变。我们观察到，缺乏circCamsap1的雄性小鼠在生育能力、睾丸小管结构、减数分裂进程以及精子活力和特性方面与野生型小鼠无显著差异。这与先前观察到的Camsap1缺失导致的精子异常和不育情况形成对比，提示circCamsap1在精子发生过程中的作用可能不是必需的。

这些发现强调了在研究环状RNA在生殖生物学中的作用时，需要更全面地考虑它们的功能和影响。尽管某些环状RNA可能与其亲本基因共享相关性，但它们在生物学功能上可能具有独特的特征和作用机制，这些需要进一步的深入研究以全面理解它们在复杂的生理过程中的具体作用。

关键字 circRNA；精子发生；Camsap1

PABPC1L is an oocyte-specific poly(A) tail binding protein indispensable for oocyte maturation

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Poly(A) binding proteins (PABPs) are a class of regulatory proteins via interaction with the poly(A) tails of RNA. PABPC1L is specifically expressed in oocytes and its depletion has been reported to cause female infertility. However, the underlying mechanism mediated by the interaction between PABPC1L and poly(A) tails is still largely unknown.

To investigate the functions of Pabpc1l in oocyte maturation, we generated Pabpc1l knockout (KO) mice and indeed observed infertility in KO females due to meiotic arrest at the germinal vesicle (GV) stage. Further analysis revealed mitochondrial and endoplasmic reticulum damage, with abnormal distributions, and widespread lysosomal degradation in the KO oocytes. Using long-read sequencing-based poly(A)-inclusive transcriptome profiling, we found that the poly(A) tail length of the KO oocytes was globally shortened at the GV stage. Transcriptome and proteome analysis identified 3240 differentially expressed genes and 460 differentially expressed proteins, respectively. Notably, 101 genes displayed concurrent changes in poly(A) tail length, RNA level, and protein level. Integrative analysis showed that shortened poly(A) tails were largely correlated with the downregulation of protein concentration but not RNA abundance, indicating Pabpc1l-mediated poly(A) tail changes could largely affect translational efficiency during oocyte maturation.

In conclusion, our results suggest that PABPC1L is indispensable for oocyte maturation, primarily through the intervention of translational regulation of a particular group of proteins.

Key Words Poly(A) binding protein; Multi-omics analysis; Post-transcriptional regulation

Pathogenesis of Neonatal Metabolic Genetic Disorders Induced by Abnormal Tryptophan Metabolism

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Background: Tryptophan is an essential amino acid involved in numerous biosynthetic processes, including the synthesis of serotonin, melatonin, and niacin. Abnormalities in tryptophan metabolism are increasingly recognized as contributors to various metabolic genetic disorders in neonates. This study aims to elucidate the molecular mechanisms underlying these disorders and explore potential diagnostic and therapeutic strategies.

Methods: Study Population: A cohort of 100 neonates diagnosed with metabolic genetic disorders related to tryptophan metabolism was recruited from multiple neonatal intensive care units.

Genetic Analysis: Whole-exome sequencing (WES) was used to identify mutations in genes associated with tryptophan metabolism. Bioinformatics tools were employed for data analysis and pathogenic variant identification.

Biochemical Assays: Blood and urine samples were analyzed using high-performance liquid chromatography (HPLC) and mass spectrometry to quantify tryptophan and its metabolites.

Clinical Observations: Clinical data, including symptoms, treatment responses, and outcomes, were collected and correlated with genetic and biochemical findings.

Results: Genetic Analysis: WES identified mutations in key genes such as TDO2, IDO1, and KMO, including several novel variants.

Biochemical Assays: Significant alterations in tryptophan and its metabolites were observed, with elevated kynurenine and reduced serotonin levels being common findings.

Clinical Observations: Affected neonates exhibited symptoms like developmental delay, hypotonia, and seizures. Specific genetic mutations and metabolic profiles were linked to distinct clinical phenotypes.

Conclusions: This study provides critical insights into how disrupted tryptophan metabolism leads to neonatal metabolic genetic disorders. Early diagnosis through genetic screening and biochemical assays is crucial for managing these conditions. Our findings suggest potential therapeutic targets and emphasize the need for further research to develop effective treatments.

Key Words Tryptophan Metabolism, Neonatal Metabolic Disorders, Genetic Mutations, Kynurenine Pathway

·遗传病的检测与诊断新技术·

1例Currarino综合征家系的全基因组测序分析及产前诊断

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目的：对1例临床诊断Currarino综合征的患儿及其家系进行分子遗传学检测，以寻找其可能的遗传学病因，为家系中的高危胎儿提供产前诊断。

方法：对患儿及其父母进行全基因组测序及生物信息学分析，使用Sanger测序技术对候选变异进行验证，并通过羊水穿刺和Sanger测序为家系胎儿提供产前诊断。

结果：全基因组测序和Sanger验证结果表明，患儿MNX1基因（NM_005515.4）存在c.-654_691+172delinsAGTCCG杂合突变，变异遗传自父亲。羊水样本检测到胎儿MNX1基因存在c.-654_691+172delinsAGTCCG杂合突变，遗传咨询后胎儿父母决定终止妊娠。

结论：全基因组测序技术检测到MNX1基因c.-654_691+172delinsAGTCCG导致的Currarino综合征是患儿及胎儿的致病原因，有助于对该家系进行遗传咨询和产前诊断，同时丰富了该致病基因的变异谱。

关键字 Currarino综合征；全基因组测序；MNX1基因；产前诊断

一例Joubert综合征患儿的致病基因位点分析

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目的：采集该Joubert综合征患儿的病史及临床资料，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：患儿出生时因“巨结肠”手术，呼吸暂停，头颅核磁共振有“臼齿征”表现，现1岁8月，发育迟缓，肌张力低，不会说话，不会走路。染色体未见异常，全外显子测序检测到CPLANE1基因（NM_023073.4）存在c.7978C>T, p.Arg2660X杂合变异和c.6821del, p.Arg2274LysfsX11杂合变异。Sanger测序显示：患儿父母分别为CPLANE1基因变异携带者，c.7978C>T变异为已知致病性变异，c.6821del变异位点在数据库和文献中均未见记录，评估该突变为可能致病的变异。

讨论：CPLANE1基因（NM_023073.4）: c.7978C>T, p.Arg2660X和c.6821del, p.Arg2274LysfsX11复合杂合变异可能是该患儿Joubert综合征17型临床表现的发病原因。全外显子测序明确了患儿的遗传学病因。

关键字 Joubert综合征17型；CPLANE1基因；基因变异

生化和基因联合筛查先天性甲状腺功能减低症的临床研究

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目的：探究先天性甲状腺功能减低症（CH）生化和基因联合筛查的意义及本地区CH主要变异基因。

方法：对2022年7月～2023年7月南京市妇幼保健院出生的16645例新生儿进行生化指标–促甲状腺激素（TSH）筛查，同时提取干血斑 DNA ，应用芯片捕获二代测序技术检测候选致病基因：双氧化酶2（DUOX2）、双氧化酶成熟因子2（DUOXA2）、垂体特异性转录因子祖先蛋白（PROP1）、促甲状腺激素受体（TSHR）、甲状腺过氧化物酶(TPO)、甲状腺球蛋白(TG)和配对盒基因8 (PAX8)；分析生化筛查和基因筛查初筛阳性率和检出情况。

结果：16645例新生儿中，生化筛查初筛阳性141例（阳性率0.85%），基因筛查初筛阳性28例（阳性率0.17%）。依据甲状腺功能结果诊断CH 13例（3例为高TSH血症），单独生化筛查检出11例（占84.62%），生化和基因联合筛查可多检出2例生化漏筛病例。基因筛查阳性样本的变异基因主要为DUOX2（85.71%），以点突变为主，其中以c.1588A>T变异类型最为常见（16.67%）。PAX8为第二常见变异（14.29%），变异类型均为c.280G>A. 暂未检测到DUOXA2、TSHR、PROP1、TPO和TG致病性变异的阳性样本。

结论：生化和基因联合筛查对于CH的检出具有重要意义，本地区CH的遗传学病因可能以DUOX2和PAX8基因变异为主。

关键字 先天性甲状腺功能减低；新生儿筛查；基因筛查；基因变异

Creatine Kinase–MM/Proto–Oncogene Tyrosine–Protein Kinase Receptor as A Sensitive Indicator for Duchenne Muscular Dystrophy Carriers

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Objective: Duchenne muscular dystrophy (DMD), a lethal X–linked recessive genetic disease, characterized by progressive muscle wasting which will lead to premature death by cardiorespiratory complications in their late twenties. And 2.5–19% DMD carriers also suffer from skeletal muscle damage or dilated cardiomyopathy who diagnosed as soon as possible is meaningful for prenatal diagnosis and advance warning for self health. The current DMD carrier screening mainly relies on detecting serum creatine kinase activity, covering only 50–70% DMD carriers which will cause many false negatives and require the discovery of highly effective biomarker and simply detection procedure for DMD carriers.

Methods: In this article, we have compiled a comprehensive summary of all documented biomarkers

associated with DMD and categorized them based on their expression patterns. We specifically pinpointed novel DMD biomarkers, previously unreported in DMD carriers, and conducted further investigations to explore their potential.

Results: Compared to creatine kinase activity alone in DMD carriers, creatine kinase-MM can improve the specificity from 73% to 81%. And our investigation revealed another promising protein: proto-oncogene tyrosine-protein kinase receptor (RET). When combined with creatine kinase-MM (creatine kinase-MM/RET ratio), it significantly enhances the specificity (from 81% to 83%) and sensitivity (71.4% to 93%) of detecting DMD carriers in serum. Moreover, we successfully devised an efficient method for extracting RET from dried blood spots. This breakthrough allowed us to detect both creatine Kinase-MM and RET using dried blood spots without compromising the detection rate.

Conclusion: The creatine kinase-MM/RET ratio is a superior indicator that significantly improves the specificity and sensitivity of detecting DMD carriers from dried blood spots.

Key Words DMD carriers, creatine kinase-MM, RET, biomarker

Establishment and Evaluation of a Method for Measuring Ornithine Transcarbamylase Activity in Micro Blood of Neonates

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Objective: Ornithine transcarbamylase deficiency is extremely high clinical heterogeneity making its clinical screening and classification challenging in some instances. In this study, we established a simple and stable method for ornithine transcarbamylase activity testing using micro blood from newborns.

Methods: Ornithine transcarbamylase activity was gauged via an enzymatic reaction involving carbamoyl phosphate and ornithine as substrates. The resulting enzymatic production of citrulline was determined using tandem mass spectrometry.

Results: A strong linear relationship was observed between ornithine transcarbamylase activity and the volume of micro blood, as well as reaction time (R2=0.9793, 0.9922 respectively). The intra-coefficient variation and inter-coefficient variation stood at 11% and 12.5% with a 1-hour reaction time, and 6.77% and 9.58% with a 3-hour reaction time, respectively. The Limit of Blank was 0.57 nmol/mL/h. An OTC enzyme activity below 39.6 nmol/mL/h indicates a positive diagnosis for OTCD. And the Receiver Operating Characteristic curve's area under the curve was calculated at 0.984. Notably, the method exhibited a sensitivity of 100% and specificity of 96.9% for diagnosing ornithine transcarbamylase deficiency.

Conclusions: Our method presents a simpler, more stable, and reproducible approach, enabling direct analysis of ornithine transcarbamylase activity with heightened sensitivity and specificity using micro blood.

Key Words Ornithine transcarbamylase deficiency; ornithine transcarbamylase activity; newborns; micro blood; tandem mass spectrometry; citrulline

植入前遗传学检测（PGT）中嵌合体胚胎移植的临床结局分析

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目的：分析植入前遗传学检测（PGT）中嵌合体胚胎的移植价值和风险。

方法：对 2016年1月至2023年10月南京医科大学第一附属医院生殖中心进行植入前遗传学检测（包括PGT-A、PGT-SR和PGT-M）周期移植了嵌合体胚胎的患者的临床数据进行分析。所有患者均采用囊胚活检，结合单细胞全基因组扩增和基于二代测序技术的染色体拷贝数分析（CNV-Seq）技术。对于仅有嵌合体胚胎的夫妇，充分遗传咨询，告知利弊后自愿选择是否移植。所有数据采用SPSS 27.0统计学软件进行分析。定性资料用率表示，组间比较采用卡方检验。P＜0.05为差异有统计学意义。

结果：遗传咨询后266对夫妻选择了嵌合体胚胎移植，共279个移植周期（其中28个PGT-M复苏周期，66个PGT-A复苏周期，185个PGT-SR复苏周期）。其中256例低比例（＜50%）嵌合胚胎移植，临床妊娠151例（58.98%），健康活产107例（另有28例持续妊娠中），流产16例（10.06%），包括1例移植21三体低比例嵌合体胚胎后羊水穿刺提示21三体综合征而引产。23例高比例（≥50%）嵌合胚胎移植，临床妊娠8例（34.78%），健康活产5例（另有2例持续妊娠中），流产1例（4.35%）。高比例嵌合胚胎移植的临床妊娠率明显低于低比例嵌合胚胎（P=0.025），但高比例嵌合胚胎的流产率与低比例嵌合胚胎相比没有统计学差异（P=1.0）

结论：囊胚活检诊断为嵌合体的胚胎移植后仍然具有较高的临床妊娠率。高比例嵌合胚胎较低比例嵌合胚胎临床妊娠率降低，但高嵌合比例并未增加流产风险。低比例嵌合胚胎仍有潜在胚胎染色体异常风险。嵌合体胚胎移植前需要充分的遗传咨询。

关键字 植入前遗传学检测（PGT），嵌合体，嵌合比例，临床妊娠率，囊胚活检

NIPS发现DMD胎儿及其产前诊断一例

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Objective: To verify a microdeletion at Xp21.1 interrupting dystrophin gene detected by non-invasive prenatal screening (NIPS) in a fetus.

Materials and methods: A 24-year-old, primigravid woman was referred for counseling at 24 weeks of gestation because of high risk of 21 trisomy by serological screening and polyhydramnios. She received genetic counseling and selected NIPS for a confirmatory test. A microdeletion at Xp21.1 interrupting dystrophin gene was detected by NIPS. Combination of chromosome microarray analysis (CMA) and multiplex ligation-dependent probe amplification (MLPA) were used to facilitate the prenatal diagnosis and genetic counseling in the fetus.

Results: A microdeletion at Xp21.1 interrupting dystrophin gene was detected by NIPS. The CMA result

showed a 229 Kb deletion at Xp21.1 or [hg19] Xp21.1 (31,776,452–32,005,227) × 1 in the male fetus. And the MLPA analysis revealed a deletion involving exons 45 – 50 in the dystrophin gene. Detection on family numbers showed that the deletion derived from the pregnant woman.

Discussion: Several studies have validated that NIPS is well evidenced for detecting trisomy 21, 18 and 13. This report provides us a new feature of NIPS on testing the microdeletion or microduplication. The current report suggested that we need to pay more attention to chromosome variants containing important OMIM genes such as DMD gene in Xp21.1 during NIPS.

关键字 Duchenne muscular dystrophy; Dystrophin; NIPS; MLPA

Clinical application of qfPCR combined with CMA in Prenatal diagnosis of fetuses with chromosomal abnormalities: a retrospective study

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Objective: This study aims to evaluate the role of quantitative fluorescence polymerase chain reaction (qfPCR) and Chromosomal microarray analysis (CMA) in diagnosing prenatal fetal chromosomal abnormalities and to explore the feasibility of combining CMA and qfPCR (CMA–qfPCR) for prenatal fetal in clinical practice.

Methods: Pregnant women with prenatal diagnosis were divided into two groups based on testing strategies: the CMA and the CMA–qfPCR group. The comparison was made between the two groups regarding detection rates of fetal genetic abnormalities and turnaround time and analyzed the detection rate of fetal chromosomal abnormalities in pregnant women with different indications.

Results: A total of 3653 pregnant women with singleton pregnancies were included, with 1832 in the CMA group and 1821 in the CMA–qfPCR group. The detection rate of chromosomal aneuploidy abnormalities in both groups is almost the same, the most common aneuploidies were trisomy 21 and sex chromosome aneuploidies. Compared with the CMA group, the CMA–qfPCR reduced the reporting turnaround time of chromosomal aneuploidy from about 14 days to about 7 days, effectively eliminating anxiety in pregnant women. Moreover, ultrasound examination, NIPT screening, and maternal serum screening can significantly improve the detection of fetal chromosomal aneuploidies. There was no significant difference in the detection rate of CNVs between the two groups. However, pregnancies with high risk of NIPT were more easily detected and pCNVs and lpCNVs were also more likely to be identified in pregnancies with high risk of NIPT.

Conclusion: Our study suggests that combining CMA and qfPCR is an efficient and reliable strategy in the prenatal detection of fetal chromosomal abnormalities and could be used as a routine selection method for prenatal diagnosis of the fetus.

Key Words CMA, qfPCR, prenatal diagnosis, chromosomal aneuploidy, CNV

D7S820基因座等位基因丢失2例

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目的：分析2例亲权鉴定中D7S820基因座不符合遗传规律的原因。

方法：采用STRtyper-21G扩增荧光检测试剂盒（Plus），复合扩增被鉴定人干血斑的 20 个常染色体 STR 基因座 和 1 个性染色体STR基因座，使用 ABI3500 DX基因分析仪进行等位基因分型检测。对含有不符合遗传规律基因座的样本，采用STRtyper-32G检测体系进行验证。

结果：使用STRtyper-21G试剂盒检测后发现，有2个二联体案例被检父与孩子在D7S820存在单个基因座不符合遗传规律的现象,案例1被检父等位基因12、孩子等位基因10，案例2被检父等位基因10、孩子等位基因12。采用STRtyper-32G检测体系验证后发现，案例1被检父等位基因11/12、孩子等位基因10/11，案例2被检父等位基因10/11、孩子等位基因11/12，两个案例在D7S820基因座均符合遗传规律。

结论：在亲权鉴定中，可能发生等位基因丢失而导致不符合遗传规律的情况，必要时可采用其他具有相同基因座的检测体系进行验证以保证基因分型的准确性。

关键字 等位基因丢失，遗传规律，基因分型

Identification and splicing analysis Of the first deep intronic FIG4 Mutation causing Yunis-Varon Syndrome

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Purpose: Yunis-Var ó n syndrome (YVS,OMIM #216340) is a severe autosomal recessive syndrome caused by the destruction of the phosphoinositide 5-phosphatase encoded by FIG4 gene characterized by skeletal defects, including cleidocranial dysplasia and digital anomalies and a poor prognosis, due to neurological and cardiovascular involvement. The aim of this study was to specify the distribution of whole-genome sequencing(WGS) in diagnosis of YVS.

.Methods: Whole-genome sequencing was carried out to a Chinese family with two neonates presenting the hallmark features of YVS. Sanger sequencing validated the pathogenic mutation and reverse transcription polymerase chain reaction (RT-PCR) using the total RNA showed the influence of the splicing mutation.

Results: We identified a novel deep intronic mutation (IVS18-809A>G) in FIG4 gene by whole-genome sequencing in a Chinese family with two neonates characterized by hypoplasia of thumbs and halluces and other anomalies. Through Sanger sequencing and further RT-PCR, IVS18-809A>G generated an aberrant splicing transcript. The results of TA cloning showed a section of pseudoexon from intron18 and resulted in a premature termination codon at residue 822.Thus, IVS18-809A>G combined with c.1141C>T (p.R381) presenting the mode of two null mutations in FIG4 accounted for YVS in the patient.Conclusions: In general, we detect the first deep

intronic mutation (IVS18−809A>G) in FIG4 which links with YVS and expands the genetic mutation spectrum. The splicing analysis shows how IVS18−809A>G influence the transcript and contribute to Yunis−Varon Syndrome. The study provides additional molecular and clinical information and extends the molecular mechanisms involved in the disease course.

Key Words Yunis−Var ó n syndrome, FIG4 gene, Deep intronic mutation,Whole−genome sequencing

无创DNA对高龄孕妇胎儿染色体非整倍体筛查的价值

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目的：探讨无创DNA筛查技术对高龄孕妇胎儿染色体非整倍体筛查的价值，为临床优生优育提供指导。

方法：选取2021年1月至2023年12月泰州市人民医院产检的高龄孕妇1250例为研究对象，其中直接组550名孕妇直接行羊水检测，间接组700名孕妇先进行无创DNA产前筛查，结果呈阳性者再进行羊膜腔穿刺诊断。通过比较两组胎儿染色体非整倍体异常的检出率，进行统计和分析。

结果：直接组550例孕妇直接性羊水检查发现染色体非整倍体4例，染色体异常检出率为0.7%。间接组700例孕妇先进行无创DNA筛查，阳性20例，再行羊水检测确诊6例，总染色体非整倍体异常检出率为0.85%；两组孕妇染色体非整倍体异常检出率比较差异无统计学差异 (P>0.05)。

讨论：无创DNA产前筛查技术可为高龄尤其是拒绝羊膜腔穿刺的产妇提供准确性较高的产前筛查方法，对优生优育的临床推广具有较高价值，但其在临床上并不能完全代替羊膜腔穿刺诊断技术。

关键字 无创DNA 高龄 非整倍体

Newborn Genetic Screening of Congenital Adrenal Hyperplasia Using Long−Read Sequencing

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Objective：Single−molecule real−time (SMRT) long−read sequencing (LRS) offers several advantages, particularly for obtaining much longer sequencing reads. In this study, we initiated a new project for nGS based on LRS and explored the clinical application of LRS−based CAH screening (LRSBCS), and compared its efficacy in different newborn populations.

Methods：Seventy−three newborns from the NBS program were selected as participants, including 12 cases confirmed to have CAH, 18 cases with false−positive biochemical screening results, and 43 healthy newborns. Full−length CAH−related genes, including CYP21A2, CYP11B1, CYP17A1, HSD3B2, and StAR. Sequencing was performed on the Sequel II platform (Pacific Biosciences) with the Sequel II Sequencing Kit 2.0.

Results：Overall, the agreement between the LRSBCS and NBS for confirmed cases was 100%. LRSCS

detected pathogenic variants in all 12 cases, including 10 cases with SNVs, one case with a deletion, and one case with compound heterozygosity. LRSBCS could directly report the characteristics of gene variants (cis or trans mutations). For example, we identified five pathogenic variants in Case 1 by LRS: c.518T>A, c.844G>T, c.923dup, c.955C>T, and c.1069C>T. By analysis of sequencing data, we could directly confirm that c.518T>A was in trans with other variants. In fact, c.518T>A originated from the patient' s father, while all other variants originated from her mother. Case 11 is a representative example highlighting the advantages of LRS. The girl was recalled due to her initial screening value (17 α -OHP) was 527 nmol/L. Sanger sequencing did not detect any variations in the disease-causing genes. However, the deletion of exons 1 - 7 of CYP21A2 was reported by MLPA. The deletion heterozygosity was also accurately detected using LRSBCS (Figure 1C). Surprisingly, Case 12 was confirmed to be a compound heterozygote, which was missed during the initial NBS screening. The girl obtained a negative result on 17 α -OHP testing (20.1 nmol/L) at 4 days after birth. However, she returned to the hospital due of an external genital malformation after half a month. After re-examining, the level of 17 α -OHP was found to reach 1,030 nmol/L, and was diagnosed as delayed CAH, according to the clinical phenotype. In the present study, the pathogenic variant c.518T>A and the deletion of CYP21A1P/CYP21A2_CH-1 were detected using LRS.

Moreover, screening data of 230,000 people in this area showed that the PPV of NBS was only 3.68%. In this retrospective cohort study, no false-positive results were obtained for any of the 72 samples after LRSBCS, with a false-positive rate of 0.

Conclusion: LRSBCS is a new method for molecular screening for CAH, yielding satisfactory results, and can be incorporated of genetic testing into routine NBS for CAH.

Key Words congenital adrenal hyperplasia, long-read sequencing, newborn genomic sequencing, newborn screening, single molecule sequencing

Prenatal identification of a mosaic abnormal Y chromosome by FISH, SNP-array and Karyotyping

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OBJECTIVE: To perform prenatal diagnosis for a fetus carrying mosaic abnormal Y chromosome.

METHODS: Routine G-banding was carried out to analyze the chromosomal karyotype of the fetus. Fetal DNA was also subjected to fluorescence in situ hybridization (FISH) and SNP-array testing.

RESULTS: A 23-year-old healthy woman was referred to our centre at 23 weeks of gestation age. Ultrasound examination indicated normal result, however, non-invasive prenatal testing (NIPT) failed two times. Amniocentesis was chosen by the patient. The fetus showed a mos 45,X[46]/46,X,+mar[4] karyotype at 320-400 band level by the analysis of amniotic fluid chromosomes. FISH with Tel Xp/Yp/ Tel Xq/Yq/DYZ3 probes indicated the result of 46,X[698]/46,XY[275]/47,XYY[27]. SNP-array platform was performed and identified a 17.9Mb duplication of Yp11.31q11.22 and a 7.7Mb deletion of Yq11.22q11.23. discrepancy exist in the results detected by the three different methods.

CONCLUSION: Combined use of various technologies can enable accurate detection of structural abnormalities

of the Y chromosome and facilitate genetic counseling.

Key Words FISH; SNP-array; Karyotyping; Prenatal diagnosis.

基于囊胚腔液代谢组学的胚胎整倍性标志物初步研究

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目的：1、利用非靶向代谢组学方法在体外受精-冷冻胚胎移植（IVF-FET）周期中构建囊胚腔液（BF）代谢图谱，挑选特征性靶向代谢物；

2、利用靶向代谢组学分析胚胎植入前非整倍体遗传学检测（PGT-A）周期中囊胚的染色体整倍性结果与BF代谢物的相关性，探讨BF代谢物预测囊胚质量的潜力。

材料与方法：1、纳入2022年07月至2022年10月在南京市妇幼保健院生殖医学中心行IVF-FET治疗的患者，收集玻璃化冷冻囊胚前释放的腔液。共收取61个周期中的611枚BF作为BF组（分为6份），同时收集等体积的胚胎培养液作为空白对照组。运用液相色谱-质谱（LC-MS）技术对样本进行非靶向代谢组检测，采用多变量分析的方法比较实验组与对照组的差异代谢物，通过人类代谢组学数据库（HMDB）查询代谢物基本信息，通过KEGG 通路富集分析得到差异代谢物的相关富集通路，进而筛选出可能参与囊胚代谢的靶向代谢物。

2、纳入2023年09月至2023年11月在本中心行PGT-A治疗的患者为研究对象。在胚胎活检前收取释放的BF，共计83枚样本。通过纳米电喷雾串联质谱（nanoESI-MS）技术，对单个BF中的靶向代谢物进行定量检测。根据后续囊胚的染色体倍性检测结果，将胚胎分为整倍体、嵌合和非整倍体三组，比较三组间的人口学特征以及15种靶向代谢物组间的含量变化，利用多元逻辑（Logistic）回归探究靶向代谢物及患者基线特征与胚胎整倍性的相关性；进一步利用受试者工作曲线（ROC）评估潜在代谢标志物的诊断性能。

结果：1、主成分分析（PCA）和正交偏最小二乘判别分析（OPLS-DA）均显示BF组和对照组存在明显差异；BF组共定性474种代谢物，对照组定性466种代谢物。采用差异变化倍数（Fold change，FC）<0.83 & FC>1.2和变量重要性投影（VIP）>1筛选条件，从实验组和对照组中得到49种差异代谢物；信号通路富集分析发现差异代谢物主要集中在牛磺酸和次牛磺酸代谢、组氨酸代谢、苯丙氨酸、酪氨酸和色氨酸的生物合成，精氨酸和脯氨酸代谢等通路上；查询HMDB数据库后，筛选得到15种参与人类代谢的物质作为潜在的靶向代谢物。

2、PGT-A周期收集的83枚BF中，80枚测得代谢物信号。根据PGT-A结果分为三组：A组：整倍体（39枚）；B组：嵌合（14枚）；C组：非整倍体（27枚）。人口学特征分析显示：C组的不孕年限、既往移植次数显著高于A组（$p<0.05$）；A组的基础卵泡刺激激素（bFSH）显著低于C两组（$p<0.05$）。三组间BF中代谢物水平的比较显示：A组的肌苷（Inosine）水平显著高于C组（$p<0.05$）。多元logistic回归分析显示：丙氨酸（D-alanine，OR=11.884，95%CI=1.338-105.580），bFSH（OR=0.351，95%CI=0.163-0.756）（$p<0.05$）水平显著影响囊胚的整倍体率；亚牛磺酸（Hypotaurine，OR=2.692，96%CI=0.904-8.022，$p=0.075$）、甘油醛（Glyceric aldehyde，OR=0.319，95%CI=0.101-1.012，$p=0.052$）、焦谷氨酸（Pyroglutamic acid，OR=0.218，95%OR=0.039-1.228，$p=0.084$）是可能影响囊胚整倍体率的潜在因素（$p<0.10$）。将以上5种可能的影响因素纳入囊胚整倍体诊断模型，ROC 曲线分析发现，该诊断模型的曲线下面积（AUC）为0.856，灵敏度为72.5%，特异度为72.7%，提示诊断效能良

好。

结论：1、含BF的培养液和空白培养液之间存在明显的代谢差异，共鉴定到49种差异代谢物，差异代谢物主要集中在多条氨基酸代谢通路。

2、15种代谢物的靶向检测发现丙氨酸（D-alanine）、基础FSH显著影响囊胚的整倍性，亚牛磺酸、甘油醛、焦谷氨酸可能是影响囊胚整倍性的潜在因素，且通过这5种潜在因素构建的非整倍体诊断模型具有良好的诊断效能，即本研究创新性的提供了一个通过BF代谢物进行胚胎质量的初步诊断方法，对于胚胎移植筛选，提高胚胎种植率和提高活产率有重要意义。

关键字 辅助生殖技术；代谢组学；囊胚腔液；IVF-FET；LC-MS；

SLC12A2基因剪接变异在一耳家系中的致病性分析

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目的：本研究旨在对一例耳聋家系中的患者进行突变检测，并进行家系验证，以鉴定其候选剪接变异的致病性。

方法：本研究通过从患者外周血中提取基因组 DNA，并使用全外显子组测序(WES)筛查致病突变。通过家系验证，即检测患者的父母及妹妹的相关基因变异，并通过构建 Minigene实验分析，评估所检出的可能引起 RNA 剪接异常的变异，从而确定其致病性。

结果：研究发现，先证者携带GJB2基因c235del杂合变异和SLC12A2基因c2930-1G>A杂合变异，而其听力正常的妹妹仅携带 GJB2基因c235del杂合变异。先证者耳聋的母亲未携带 GJB2 基因 c.235del 杂合变异，但携带了 SLC12A2基因c.2930-1G>A 变异。Minigene实验分析确认，SLC12A2 基因的c2930-1G>A变异影响了其转录后的剪接，揭示了该变异可能是导致家系中耳聋的真正致病因素。

结论：先证者的 SLC12A2基因剪接位点变异c2930-1G>A被鉴定为致病性变异。通过针对WES 所提示的剪接变异进行 Minigene 分析，本研究不仅鉴定了变异的致病性，丰富了耳聋的遗传谱，还为患者的产前诊断及未来的机制研究提供了重要基础。

关键字 SLC12A2、剪接变异、耳聋

15个遗传性痉挛性截瘫家系基因检测及生育风险评估

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目的：对遗传性痉挛性截瘫患者行基因检测，为家系提供准确的遗传咨询和风险评估，为产前诊断或胚胎植入前遗传学检测（PGT-M）提供依据。

方法：对临床专科诊断遗传性痉挛性截瘫15个患者行全外显子组基因检测，对检出表型相关基因变异的家系成员行Sanger测序验证，必要时应用RT-qPCR、RT-PCR 结合 Sanger测序对变异的致病性做出精确诊断。

结果：10名患者检出表型相关基因变异，其中常染色显性遗传2例：SPAST基因c.716T>A（p.L239X）、c.1496G>A (p.R499H)杂合变异各1例；常染色体隐性遗传5例，分别为：CYP7B1基因c.187C>T（p.R63X）纯合，SPG11基因c.6906_6907delinsA（p.H2303Tfs3）和c.5794delC（p.H1932Mfs19）复合杂合，WDR62基因c.749T>C（p.L250P）和c.1480G>A（p.G494R）复合杂合，WDR62基因c.2575C>T (p.Q859X）和c.3220+3A>T复合杂合，AMPD2基因c.1486G>A(p.E496K)和c.283delinsTT(p.E95Lfs6)复合杂合；X-连锁遗传遗传3例：1例L1CAM基因c.925G>A（p.E309K）半合子变异，2例Xq22.2重复变异（包含PLP1基因）。10例患者均行家系验证明确变异来源，其中2个家系通过产前诊断获得健康活产；6个家系行胚胎植入前遗传学检测（PGT-M），目前获得健康活产3个家系，持续妊娠1个家系，另2个家系待移植。

结论：遗传性痉挛性截瘫具有临床及遗传异质性，全外显子组基因检测结合RT-qPCR、RT-PCR 等辅助检测方法，参照ACMG评分标准，可明确家系致病基因变异；通过临床遗传咨询生育风险评估，患者选择合适的生育方式，可阻断该疾病在家系中传递。

关键字 遗传性痉挛性截瘫 胚胎植入前遗传学检测（PGT-M）基因检测 遗传咨询 风险评估

借助OGM全面检测白血病患者体内异常

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目的：借助光学基因组图谱技术(OGM)检测恶性血液病AML和ALL患者体内的结构变异(SV)、拷贝数变异(CNV)及杂合性缺失(LOH)。

方法：OGM技术通过提取基因组超长片段DNA后利用DLE酶对基因组特定位点进行标记并对DNA骨架染色，通过纳米孔通道毛细管电泳将DNA拉直后将线性DNA拍照，而后将图像转换为数字信号，拼接DNA的结构与参考基因组进行比对，从而识别DNA的结构变异和拷贝数变异及杂合型状况。本次实验纳入29例AML患者和6例ALL患者。

结果：1. 在35例患者中，共检测到15条染色体上的40处结构变异，其中7号、8号、9号、11号染色体发生异常的频率最高，分别为15%、12.5%、12.5%、12.5%。

2.患者体内的拷贝数异常种类繁多，25例患者体内检测到拷贝数异常，其中5例患者存在3条及以上染色体拷贝数异常。

3.借助OGM检测到16例患者体内存在杂合性缺失，其中存在3号染色体的杂合性缺失的患者有5例，发生频率最高。

讨论：借助OGM能够对白血病患者体内的结构变异、拷贝数变异和杂合性缺失进行全面精确检测。本实验中检测到的杂合性缺失均为拷贝数中性杂合性缺失，其在髓系恶性肿瘤中较常见，通常与对标准治疗方式的耐药性和低生存率有关。目前杂合性缺失的检测方法比较少，仅阵列比较基因组杂交（CGH）和单核苷酸多态性（SNP）微阵列两种。OGM在未来有可能成为新的检测手段。

关键字 光学基因组图谱技术、白血病、结构变异、杂合性缺失

Detection of mosaic reciprocal translocation in centromere region using new chromosomal techniques

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Complex chromosomal rearrangements are rare events that are considered difficult to detect by routine cytogenetic methods. In this study, a family with normal karyotypes experienced abortions and neonatal death were enrolled, which we speculated whether the couple might have a complex reciprocal translocation owing to two times similar positive NIPT and maternal CMA results. DNA was isolated from peripheral blood cells and processed via new chromosomal diagnostic methods (OGM, SV-Seq and C-MoKa). The C-MoKa data were consistent with our hypothesis, OGM detected breakpoints in highly repetitive region and SV-Seq inferred the same structure. To the best of our knowledge, this is the first study wherein C-MoKa facilitate as the robust complementary method for mosaic reciprocal translocation at the breakpoints in centromere region in clinical practice.

Key Words Complex chromosome rearrangements, Structural variation, Chromosomal diagnostic technology, Reciprocal translocation

Prenatal screening results and pregnancy outcomes analysis of fetal free DNA from peripheral blood of pregnant women in coastal areas of northern Jiangsu province

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Objective: To explore the clinical screening value of non-invasive prenatal screening (NIPT) technology for fetal trisomy 21, trisomy 18, trisomy 13, sex chromosome abnormalities, and chromosomal microdeletions/microduplications.

Method: 38280 pregnant women who underwent NIPT testing at Lianyungang Maternal and Child Health Hospital from January 2017 to December 2023 were selected as the study subjects. After signing informed consent, high-risk pregnant women for NIPT screening will undergo amniocentesis to extract amniotic fluid cells for chromosome karyotyping analysis and chromosome microarray detection, and diagnostic tests for all cases will be statistically analyzed. Follow up fetal pregnancy outcomes and collect fetal information by phone after pregnancy.

Result:Among the 38280 pregnant women, 751 were detected as high-risk, with a detection rate of 1.96%. Out of 751 cases, 101 were identified as high-risk individuals for trisomy 21, 31 as high-risk individuals for trisomy 18, 34 as high-risk individuals for trisomy 13, 204 as high-risk individuals for sex chromosome aneuploidy, 139 as high-risk individuals for other autosomal aneuploidy, and 242 as high-risk individuals for chromosomal

microdeletions/microduplications. Among the 751 cases, 575 NIPT positive pregnant women agreed to receive subsequent interventional prenatal diagnosis. 67 cases of trisomy 21, 9 cases of trisomy 18, 3 cases of trisomy 13, 52 cases of sex chromosome abnormalities, 2 cases of other autosomal aneuploidy, and 55 cases of microdeletions/microduplications were confirmed, with positive predictive values of 98.53%, 52.94%, 12.00%, 31.90%, 1.492%, and 54.10%, respectively. 36326 cases of successful follow-up of fetal pregnancy outcomes were reported, with a success rate of 94.80%. Follow up revealed 3 cases of false negatives for trisomy 21, but no false negatives were found for trisomy 13 and trisomy 18.

Conclusion: The non-invasive prenatal screening (NIPT) technology has the highest screening performance for trisomy 21, followed by microdeletions/microduplications and trisomy 18. It also has important clinical application value for sex chromosome aneuploidy abnormalities, trisomy 13, and other autosomal aneuploidy abnormalities. However, invasive prenatal diagnosis is still necessary for high-risk NIPT to avoid false positives.

Key Words NIPT, diagnostic tests, follow-up

Accuracy of expanded noninvasive prenatal testing for maternal copy number variations: a comparative study with CNV-seq of maternal lymphocyte DNA

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Objective: To evaluate the accuracy of expanded noninvasive prenatal testing (NIPT) for maternal copy number variations.

Materials and methods: Expanded NIPT was used to detect CNVs ⩾ 2 Mb at a whole-genome scale. The threshold of maternal deletion was copy numbers (CN) ⩽ 1.6, and the threshold of maternal duplication was CN ⩾ 2.4.

Results: Of the 5440 pregnant women with successful expanded NIPT results, 28 maternal CNVs ⩾ 2 Mb were detected in 27 pregnant women. Except for five cases reported as test failure, 23 CNVs ⩾2 Mb were confirmed among the remaining 22 pregnant women by CNV-seq of maternal lymphocyte DNA. The genomic location, copy numbers and fragment size of maternal CNVs reported by expanded NIPT were consistent with the results of CNV-seq of maternal lymphocyte DNA.

Conclusions: Maternal CNVs ⩾2 Mb can be accurately evaluated according to the CN indicated by expanded NIPT results.

Key Words Noninvasive prenatal testing, Copy number variations, Lymphocyte DNA, Cell-free DNA

Discussion on the significance of genetic screening for hereditary deafness in newborns

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JiangsuProvinceHopistal

Purpose: To conduct deafness gene detection on the heel blood spots of 2488 newborns sent to our center from January 2022 to December 2023, combined with traditional deafness screening, to increase the detection rate of deafness and provide early intervention and treatment for high-risk infants.

Method: The melting curve method was used to detect deafness genes. Primers were used to amplify four human deafness genes, and then the four deafness genes in the sample were determined by performing melting curve analysis on the double-stranded hybrid formed by the fluorescently labeled probe and the PCR product, identifying mutations and their types. The four deafness genes correspond to four PCR reaction systems for detection. The genes and sites screened are as follows: GJB2 (c.35delG, c.176-191del16, c.235delC, c.299-300delAT, c.167delT), GJB3 (c.538C>T, 547G>A), mtRNR1 (1494C>T, 1555A>G), SLC26A4 (919-2A>G, 1174A>T, 1226G>A, 1229C>T, 1707+5G>A, 1975G>C, 2168A>G, 2027T>A, 2162C>T, 749T>C, 754T>C, 2027T>A). Results: All 2488 samples were successfully tested, with 174 carrying abnormal genes, and 11 cases diagnosed with definite deafness in children.

Conclusion: The melting curve method for deafness gene detection significantly enhances the detection of newborn deafness, improving efficiency when combined with traditional screening and enabling early detection of deaf children for better prognosis.

Key Words hereditary deafness，PCR，

108例鼻骨发育异常胎儿染色体拷贝数变异结果分析

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目的：探讨胎儿鼻骨发育异常与染色体拷贝数变异的相关性。

方法：回顾性分析2017年2月-2024年2月至江苏省人民医院行介入性产前诊断的108例超声提示胎儿鼻骨发育异常病例资料，根据孕妇年龄分为高龄组、非高龄组；根据超声是否合并其他异常分为孤立组、合并组。比较不同组之间发生染色体异常情况。

结果：108例病例共检测出30例染色体异常，异常检出率27.8%（30/108），非整倍体21例（21三体18例、18三体2例、克氏综合征1例）占比70%（21/30）、致病性CNV4例、临床意义不明CNV5例。高龄组与非高龄组染色体异常率分别为46.2%（12/26）、22.0%（18/82），差异有统计学意义（$\chi 2=4.62$，$P<0.05$），染色体拷贝数异常率分别为15.4%（4/26）、6.1%（5/82），差异无统计学意义（$\chi 2=1.17$，$P>0.05$）；孤立组与合并组染色体异常率分别为20.6%（14/68），40.0%（16/40），差异有统计学意

义（$\chi 2=4.73$，$P<0.05$），染色体拷贝数异常率分别为2.9%(2/68)、17.5%（7/40），差异有统计学意义（$\chi 2=5.21$，$P<0.05$）。

结论：鼻骨发育异常胎儿染色体异常检出率较高，主要以21三体为主。合并高龄或超声异常染色体异常率明显高于非高龄或孤立性鼻骨发育异常。拷贝数异常风险可能与超声异常相关而与年龄无明显相关性。

关键字 鼻骨发育异常；染色体拷贝数变异；高龄

Two-dimensional polymerase chain reaction for identifying HLA alleles associated with adverse drug reactions

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Objective Human Leukocyte Antigen (HLA) alleles are significantly associated with adverse drug reactions (ADRs). Specifically, HLA-B15:02 and HLA-A31:01 are genetic markers for antiepileptic drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Asian and European populations, respectively. Additionally, HLA-B57:01 is a risk factor for abacavir-induced hypersensitivity syndrome, and HLA-B58:01 is closely associated with allopurinol-induced cutaneous adverse reactions. Currently, there is no rapid, convenient, cost-effective, high-throughput genotyping method available. This study aims to identify HLA-A31:01, HLA-B15:02, HLA-B57:01, and HLA-B58:01 using two-dimensional PCR (2D-PCR) method to prevent ADRs. Additionally, this study explores the frequency of these alleles in the Chinese population.

Methods In this study, 2D-PCR methodology was established under single-tube closed conditions to simultaneously identify four HLA alleles. The performance of the methodology was evaluated in terms of its sensitivity, specificity, accuracy, and selectivity. For clinical application, the prevalence of these alleles was analyzed in 2000 general population samples.

Results The 2D-PCR technology established in this study can detect positive samples as low as 26 copies/μl within 100 minutes, with a cost of less than 1 USD per sample. Among the 2000 samples analyzed, 110 samples were positive for HLA-B15:02, 256 for HLA-B58:01, 44 for HLA-B57:01, and 133 for HLA-A31:01. The Kappa test showed that the concordance rate between 2D-PCR and PCR-SBT is 100%, exhibiting high sensitivity, specificity, and accuracy.

Discussion The 2D-PCR method provides a rapid, cost-effective, and highly accurate approach for HLA allele identification, which is crucial for preventing ADRs. This technology demonstrates substantial potential for clinical applications and translational research.

Key Words 2D-PCR, HLA , Genotyping, drug adverse reactions

Bobs技术和染色体核型分析在产前诊断中的联合应用

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目的 探讨与羊水细胞核型分析相比，Bobs (BACs-on-Beads) 技术在产前诊断中的优缺点及临床应用价值。

方法 选取2017年1月25日至12月27日在无锡市产前诊断中心行羊水穿刺的1238例高危孕妇，进行羊水细胞培养和核型分析，同时做Bobs检测，部分特殊病例做芯片或胎儿父母外周血染色体验证。

结果 Bobs对于染色体非整倍体的检出率与核型分析一致，检出37例胎儿染色体数目异常，包括21-三体22例、18-三体4例、13-三体1例、性染色体数目异常10例，另检出69例微缺失/微重复，其中1例Cridu Chat综合征（猫叫综合征）由于缺失片段较大通过传统核型分析技术检测出来，其余68例胎儿染色体核型分析结果未见异常。但Bobs未能检出2例染色体平衡易位、50例多态性变异以及1例低比例嵌合体。

讨论 Bobs技术是一种高特异性分子细胞遗传学技术,结合传统的G显带核型分析方法可以提高产前诊断的诊断范围，可用于检测常见染色体微缺失/微重复综合征，是对传统细胞遗传学检测技术的有益补充。

关键字 Bobs；染色体核型分析；产前诊断

122份稽留流产绒毛的FISH检测与染色体核型分析结果的对比

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目的：探讨FISH和核型分析在稽留流产绒毛组织遗传检测中的优势与不足。

方法：应用13、16、18、21、22、X、Y七条染色体特异性FISH探针对122例稽留流产绒毛进行杂交检测，同时进行细胞培养和核型分析。

结果：122例标本中，绒毛细胞核型分析98例，成功率80.3%，发现异常核型49例，阳性率达50.0%；FISH检测成功率100%，数目异常35例，阳性率为28.7%。

结论：FISH可以快速、准确地诊断染色体数目异常，成功率高，但无法检测结构异常，易受母体血和胎盘组织污染，核型分析可以检测所用染色体的数目和结构异常，但需要培养细胞，时间长，检测成功率不及FISH，但对染色体结构异常准确性高。

关键字 荧光原位杂交；染色体核型分析；稽留流产；绒毛组织

染色体倒位携带者PGT临床结局分析

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目的：探讨染色体臂内倒位（PAI）和臂间倒位（PEI）携带者夫妇对于胚胎染色体及胚胎植入前遗传学检测（PGT）助孕技术妊娠结局的影响。

方法：回顾性病例分析2012年6月至2024年6月期间在南京医科大学第一附属医院生殖医学中心接受PGT辅助生殖技术治疗的的染色体倒位携带者夫妇的临床资料（已知为常见多态性改变的染色体倒位者不纳入统计分析）。按携带者染色体倒位断裂点不同类型分为PAI和PEI两组。所有周期通过囊胚期活检，并结合微阵列比较基因组杂交技术（array-CGH）或二代测序技术的染色体拷贝数分析技术（CNV-Seq），在复苏周期中，选择整倍体单囊胚移植。统计分析不同类型倒位导致囊胚期胚胎染色体不平衡重组的风险以及对胚胎整个染色体倍性的影响，并对PGT助孕妊娠结局进行组间分析。采用SPSS 26.0统计软件对数据进行卡方检验，P小于0.05具有统计学显著性。

结果：研究共纳入97个周期，总计对364个囊胚进行了检测，均明确诊断。其中PAI携带者夫妇共纳入34个周期，明确诊断胚胎132枚，其中正常可移植胚胎（包含嵌合体胚胎）98枚（74.24%），异常胚胎共34枚（25.76%），而异常胚胎中由倒位引起的部分单体或部分三体结构异常胚胎共8枚（6.06%），在31个移植周期中，临床妊娠28例（持续妊娠率为90.32%），其中26例截至投稿时已健康活产，自然流产4例（12.90%）。PEI携带者夫妇共纳入63个周期，明确诊断胚胎232枚，其中正常可移植胚胎（包含嵌合体胚胎）146枚（62.93%），异常胚胎共86枚（37.07%），而异常胚胎中由倒位引起的部分单体或部分三体结构异常胚胎共43枚（18.53%）。在51个移植周期中，临床妊娠43例（持续妊娠率为84.31%），其中38例截至投稿时已健康活产，自然流产2例（3.92%）。组间行卡方检验，PAI携带者夫妇中正常可移植胚胎比例显著高于PEI携带者夫妇（P=0.027），PAI携带者夫妇由于倒位引起的部分单体或部分三体胚胎异常率明显显著低于PEI携带者夫妇（P=0.001），虽然PAI携带者夫妇的持续妊娠率高于PEI携带者夫妇，但是差异无统计学意义（P=0.439）。

结论：PAI携带者夫妇PGT中染色体正常可移植囊胚比例显著高于PEI。PAI倒位引起的部分单体和部分三体异常率显著低于PEI，但两组间持续妊娠率在两组类型倒位中没有差异。

关键字 臂内倒位；臂间倒位；植入前遗传学检测；囊胚期胚胎；妊娠结局

女性Xq部分缺失伴卵巢早衰2例患者的临床表型及遗传学分析

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目的：应用遗传学检测技术对2例女性卵巢早衰患者进行分析，探讨其遗传学病因。

方法：应用染色体G显带核型分析技术、染色体微阵列分析技术(chromosomal microarray analysis, CM

A）对2例卵巢早衰患者进行细胞分子遗传学检测。

结果：患者1外周血染色体核型结果为46,X,der(X), CMA结果显示Xq23-q28存在39.5Mb基因组的DNA片段单拷贝缺失，同时Yq11.221-q12存在14.18Mb的DNA片段；患者2外周血染色体核型结果为46,X,der(X) ,CMA结果显示Xq28存在5.9Mb基因组的DNA片段单拷贝缺失,同时4q32.1-q35.2存在32.1Mb基因组的DNA片段重复。

结论：2例卵巢早衰患者的遗传学病因为Xq缺失，为临床此类人群的遗传咨询及产前诊断提供依据。

关键字 Xq部分缺失；G显带核型分析；染色体微阵列分析技术 ；卵巢早衰；

基于二维PCR技术对常州地区HPV筛查人群的九种性传播疾病病原体感染情况的调查分析

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目的：应用高通量二维PCR技术（2D-PCR），建立一种单管一步法检测和鉴定宫颈刷样本中9种性传播疾病病原体（STDPs，包括解脲/微小支原体、人型支原体、阴道毛滴虫、生殖支原体、淋病奈瑟菌、沙眼衣原体、单纯疱疹病毒Ⅰ型和Ⅱ型）的方法，并了解HPV筛查人群中STDPs的感染情况，探讨HPV与不同STDPs感染的相关性。

方法：根据9种STDPs的DNA序列设计特异性引物，采用相应标签标记不同STDPs的上游引物，并构建完善的2D-PCR检测体系。应用该方法检测2193例妇科门诊来源的宫颈刷样本，检测结果与三重实时荧光定量PCR法的结果进行一致性比较，同时分析与HPV的共感染率。

结果：2D-PCR可通过FAM、HEX和Alexa Flour568三个通道的特征性熔解谷对9种STDs和内参基因进行准确的区分和鉴定。2D-PCR法与三重实时荧光定量PCR法具有较高的一致性，Kappa值为0.9。STDPs的总体感染率为36.02 %，其中解脲/微小支原体感染率最高为31.92%。HPV总体感染率为23.53%，STDPs的感染与HPV具有相关性，46.32%的HPV阳性人群同时携带STDPs。32.86%的HPV阴性人群携带STDPs。其中，解脲/微小、人型支原体与HPV感染相关。

结论：本研究成功开发了一种2D-PCR方法，用于9重STDPs的检测与鉴定，具有高灵敏度和特异性、简便快速低成本等显著优势。STDPs与HPV感染相关，因此HPV筛查时同步进行STDPs的筛查十分必要。

关键字 二维PCR；人乳头瘤病毒；性传播疾病病原体；一致性检验

·遗传病的诊治与遗传咨询·

一例马凡综合征患者的FBN1 基因新突变

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目的：马凡综合征（Marfan syndrome，MFS）是一种可遗传的常染色体显性结缔组织疾病，主要累积眼、骨骼和心血管系统，其患病率约为（2~3）/10 000。MFS是由FBN1基因突变引起的，FBN1基因位于染色体15q21.1上，编码320 kDa的细胞外基质糖蛋白原纤维蛋白-1，该蛋白是微纤维的主要成分。FBN1基因是一个包含66个外显子的基因。MFS患者表现出多种临床表现，从孤立的特征到严重的多器官受累。这种症状的变异性甚至可在相同FBN1突变的家庭成员中观察到。MFS中的心血管疾病，如动脉夹层，甚至在年轻人中也可能危及生命。MFS的诊断虽然有临床标准。但某些疾病，如Loeys-Dietz综合征和Ehlers-Danlos综合征的血管形式，可能表现出与MFS相似的症状和表型。所以，区分这些疾病的较为可靠方法是基因检测。本研究报告1例疑似马凡综合征的临床病例。

方法：针对该患者的相关基因，使用二代测序技术和PCR-Sanger测序方法进行分子研究。

结果：该患者主要表现为二尖瓣脱垂伴关闭不全、主动脉根部瘤、房间隔缺损、高度近视、身高183cm。在该患者中鉴定出FBN1基因（NM_000138.5）存在一个杂合突变c.5682del（p.Glu1894AspfsX36）。

结论：新的缺失突变c.5682del可导致FBN1基因不能正常编码功能蛋白。同时，对于该患者较好地做出基因水平的诊断结果，有利于指导遗传咨询，保证健康生育。

关键字 马凡综合征；Marfan syndrome；FBN1基因；基因变异；点突变

Discussion on molecular diagnosis and pathogenesis of congenital adrenal hypoplasia caused by NR0B1 gene mutation

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Objective To analyze the pedigree, pathogenesis, prenatal diagnosis and clinical consultation of patients with adrenal hypoplasia congenital (AHC) caused by NR0B1 gene mutation. Methods DNA was extracted from peripheral blood of 3 patients with congenital adrenocortical insufficiency and their families, and the exons of NR0B1 gene were sequenced. Results Child 1: c. 676delG hemizygous mutation in exon 1 of NR0B1 gene, which is a frameshift mutation, resulting in the change of amino acid p. Ala226LeufsX38; Child 2: exon 1 of NR0B1 gene c. 509_572dup mutation; Patient 3: the c. 409G>T hemizygous variation in exon 1 of NR0B1 gene can lead to the change of amino acid sequence p. Glu137X. The gene mutation sites of the first two cases have not been reported at home and abroad. Conclusion c. 676delG hemizygous mutation of NR0B1 gene and c. 509_572dup was a new pathogenic mutation.

Although the global incidence rate of AHC caused by NR0B1 mutation is very low, it is a common molecular etiology of AHC in children. The early diagnosis of its molecular etiology is of great clinical significance for the choice of drugs and the monitoring of children's puberty.

Key Words NR0B1 gene、adrenal hypoplasia congenital、Exon sequencing

Will Children with DUOX2 Mutations Definitely diagnosed with Congenital Hypothyroidism in Newborn Genetic Screening

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Purpose: To investigate whether children with DUOX2 mutations in newborn genomic sequencing (nGS) can be diagnosed with congenital hypothyroidism(CH).

Methods: Prospective clinical study using a total of 1012 newborn samples from retrospective traditional biochemical screening (TBS). 8 genes associated with CH in nGS panel, including PAX8, THRA, THRB, TSHR, TG, TPO and DUOX2. Results of gene carriers were followed up through phone or the maternal and child health information system in Jiangsu Province.

Results: Of the 1012 newborns, 67 were unit point heterozygous mutation with DUOX2; 6 were compound heterozygous mutations for DUOX2 gene, 3 cases were within the scope of TBS and 3 additional cases were identified through nGS. Mutations were concentrated in c.1588A>T, followed by c.2654G>T. The follow-up result showed that 2 cases developed normally and 1 case was growth retardation during 3 additional cases identified through nGS.

Conclusions: Combination of nGS and TBS can improve the diagnosis of CH. DUOX2 was the most commonly mutated gene that causes CH. However, whether DUOX2 genotype can diagnose CH is still worth exploring. Gene carrying causes the elevation of TSH with plantar blood and false positive results in neonatal screening.

Key Words DUOX2, Congenital Hypothyroidism, Newborn Genetic Screening, Newborn Genomic Sequencing

临床意义不明变异胎儿的产后结局：一项单中心研究

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Objective: Investigation of prenatal chromosome microarray analysis outcomes. Management of fetuses with variants of unknown significance. Prognostic evaluation for subsequent pregnancies, and selection of prenatal diagnostic approaches.

Methods: A total of 2,953 fetuses undergoing chromosome microarray analysis (CMA) testing at the Prenatal Diagnostic Center of Changzhou Maternal and Child Health Care Hospital from January 2018 to December 2022 were included in this study. Among them, 162 cases had a CMA result of variants of unknown significance (VOUS). Parent-of-origin testing was subsequently performed to determine whether the copy number variations (CNVs) were inherited or de novo. All couples were offered prenatal genetic counseling to assist in pregnancy decision-making. Fetuses who continued the pregnancy were followed up for 3-36 months after birth.

Results: Among the 162 cases of VOUS identified, all underwent prenatal genetic counseling. Of these, 123 chose to continue the pregnancy,22 opted for labor induction, and 17 were lost to follow-up. Among the 123 patients who chose to continue their pregnancies,116 delivered at full term, and 7 experienced preterm labor. The 123 live-born fetuses were followed up for 3-36 months after birth. Of these, 5 developed relevant clinical phenotypes, while 118 showed no abnormalities in growth and development. Parent-of-origin testing was performed in 21 cases, revealing 18 hereditary variants, of which 3 were selected for labor induction. Additionally, 3 de novo variants were identified, with 1 selected for labor induction. Out of the 162 VOUS cases, there were 5 subsequent pregnancies.

Conclusion: Cases with VOUS require rigorous prenatal genetic counseling and generally have a favorable outcome. However, greater emphasis should be placed on childhood follow-up, with early detection of potentially associated clinical phenotypes. Regular data reanalysis and updating of reports are recommended.

关键字 Prenatal Diagnosis, Karyotyping, Chromosomal Microarray Analysis,variants of unknown significance

两例等臂Y染色体的产前诊断及遗传咨询

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目的：两例产前诊断的遗传学分析及咨询。

方法：签署知情同意后，穿刺采集羊水样本，进行染色体芯片检测和细胞核型分析。

结果：病例1为无创提示性染色体异常而行产前诊断。芯片检测发现Y染色体短臂重复，长臂缺失，未发现嵌合现象，提示等臂Y染色体可能。核型结果46,X,i(Y)(p10)。遗传咨询后选择终止妊娠。病例2为孕妇高龄而行产前诊断。芯片检测发现Yp11.31q11.222区域存在约11Mb的DNA片段重复，Yq11.222q11.23区域存在约13Mb的DNA片段缺失，未发现嵌合现象，提示胎儿等臂双着丝粒Y染色体可能。核型结果mos 45,X[5]/46,X,idic（Y)(q11.2)[45]。待随访。

讨论：idic(Y)/i(Y)是罕见的性染色体异常。Y染色体姐妹染色单体在着丝粒区域或长/短臂对称位点断裂(通常为回文序列或反向重复附近），然后断端在有丝分裂或减数分裂I期融合，从而形成等臂Y染色体。细胞实验证明单着丝粒等臂Y染色体具有稳定的有丝分裂。有文献报道一例NT3.0mm，唐筛风险1/140，NIPT提示性染色体异常的胎儿产前诊断为完全型i(Y)(p10)，自然分娩体重3.125公斤的男孩，出生时发育正常。双着丝粒等臂Y染色体的无着丝粒片段不稳定，大多在细胞分裂后期丢失，其一个着丝粒通常为灭活状态，另一个行使着丝粒功能的活性受限。因为断裂可发生在不同时期或不同细胞系，因此胎儿染色体可能为嵌合状态，即个体通常合并45，X细胞系而以嵌合形式存在，表型可有外阴模糊、身材矮小、原发闭经和男性无精子症等。着丝粒间距与有丝分裂不稳定性成正相关。文献报道着丝粒间距>20Mb的idic(Y)患者因为广泛的45，X性腺嵌合而为女性表型的风险增加。idic(Y)在组织中分布差异大，一般性腺中高于血液。因此检出的嵌合细胞系的比例可能与表型没有明显的关系。Y染色体基因主要参

与性别决定、身材控制、精子发生和生育能力。遗传咨询应注意：未培养的细胞标本检测出的嵌合比例较可靠，细胞培养可能因细胞生长偏倚而导致结果失真；检测羊水细胞可代表胎儿整体的嵌合情况，脐血仅代表中胚层来源的器官/组织的嵌合情况；在没有其他胎儿结构异常指标的前提下，胎儿/新生儿的表型通常是为正常发育的男性；患者青春期可能出现异常；成年后没有正常的生育能力，这与AZF区域的完全或部分缺失和性腺中多个细胞系的嵌合水平有关；患性腺母细胞瘤的风险增加。idic(Y)/i(Y)的产前遗传咨询仍然是一个挑战，大量病例研究和随访可为临床提供更多的风险评估参考资料。

关键字 产前诊断 等臂Y染色体 遗传咨询

卵巢储备功能对胚胎整倍体性没有影响

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目的：胚胎非整倍体是导致流产、体外受精失败和后代出生缺陷的主要原因。既往关于卵巢储备功能减退是否会影响胚胎整倍体率的研究结论仍存在争议。因此，为了进一步解决上述问题，我们进行了一个回顾性研究分析，旨在探讨卵巢储备功能减退是否会对胚胎染色体的整倍体性产生影响。这对于进一步明确PGT-A的适用范围有一定的价值，也有助于为卵巢储备减少的女性提供合理的辅助生殖相关建议。

方法: 本回顾性队列研究纳入2016年5月至2023年9月在南京市妇幼保健院生殖中心治疗的854例患者，共894个周期。采用广义估计方程(generalized estimating equation，GEE)、倾向性得分匹配等统计方法评估了卵巢储备功能与胚胎整倍体的关系。

结果：尽管卵巢储备功能正常的患者活检囊胚数量较多，但DOR患者与对照组的胚胎非整倍体率无明显差异。此外，PSM后DOR组与对照组在中期II（MII）卵母细胞率、正常受精率、可移植胚胎率、囊胚形成率、高评分囊胚率方面均无明显差异。

讨论：本研究表明，DOR对胚胎非整倍体发生率没有明显影响。在常规的辅助生殖助孕前，可告知DOR的年轻患者应该对其卵子质量和胚胎的整倍体性相对放心，无需过分担忧非整倍体原因造成的不良孕产结局。

关键字 回顾性队列研究，卵巢储备，DOR，胚胎整倍体性，嵌合体，PGT-A

Skeletal Dysplasia Fetal Diagnosis: Utilizing Chromosomal Microarray Analysis and Whole Exome Sequencing with Non-Invasive Prenatal Testing

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Background: Skeletal dysplasia (SD) is a rare and heterogeneous group of disorders affecting fetal skeletal

growth and development. Accurate diagnosis of fetal SD remains challenging due to clinical and genetic diversity. This study aimed to evaluate the diagnostic accuracy of chromosomal microarray analysis (CMA), whole exome sequencing (WES), and non-invasive prenatal testing (NIPT) for single-gene disorders in fetuses with SD.

Methods: A total of 21 pregnant women with fetuses suspected of having SD were recruited. Amniotic fluid samples were obtained by amniocentesis and analyzed using CMA and WES. Additionally, peripheral blood samples from 6 pregnant women were collected for NIPT using target region capture and high-throughput sequencing technology.

Results: WES identified 17 positive cases, including one case with pathogenic copy number variants (CNV) detected by CMA. The remaining 16 cases exhibited pathogenic or likely pathogenic gene mutations. The NIPT results for single-gene disorders in the 6 pregnant women were consistent with the invasive testing findings.

Conclusion: WES, combined with CMA, serves as a valuable molecular genetic tool for diagnosing fetal SD. Furthermore, NIPT for single-gene disorders offers a non-invasive and accurate method for disease risk assessment, guiding clinicians in prenatal consultation and prognosis.

Key Words Skeletal Dysplasia; Non-Invasive Prenatal Testing; Single-Gene Disorders; Prenatal diagnosis

Evaluations of the Strategy of Sequential Prenatal Screening and Prenatal Diagnosis for Fetal Skeletal Dysplasia

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2. The Affiliated Suqian First People's Hospital of Nanjing Medical University

Objective To evaluate the sequential prenatal screening and prenatal diagnosis strategy for fetuses with skeletal dysplasia (SD) indicated by ultrasound, and to explore the clinical value of whole exome sequencing (WES) in SD fetuses.

Methods From January 2019 to May 2024, 150 fetuses with skeletal dysplasia were detected by routine prenatal ultrasound screening in the prenatal diagnosis clinic of Changzhou Maternal and Child Health Hospital, Suqian First People's Hospital, and Lianyungang Maternal and Child Health Hospital. After amniocentesis to collect amniotic fluid cells, fetal karyotyping was performed in 51 cases, chromosomal microarray analysis (CMA) was performed in 149 cases, and WES was performed in 64 cases. 18 cases parental peripheral blood samples were collected for verification by first generation sequencing.

Results Fetal chromosome karyotype analysis was performed in 51 cases, and 1 case was trisomy 18, with a detection rate of 2.0% (1/51); CMA was performed in 149 cases, and the results showed that 9 cases had numerical chromosome abnormalities, 11 cases had pathogenic copy number variants (CNV) and 3 cases had likely pathogenic CNV, with a detection rate of 15.4% (23/149). 64 cases underwent WES, including 2 cases with pathogenic CNV detected by CMA and the other 62 cases with negative CMA. The WES results showed that 2 cases had pathogenic CNV consistent with the CMA test results， 25 cases had pathogenic/likely pathogenic variants (FGFR3, COL2A1, COL1A1, COL1A2, RUNX2, LMX1B, GLI3, SHOX, EBP, KIF22, LDLR, DYNC2H1 and ALPL) , with a detection rate of 42.2%（27/64）.

Conclusion Prenatal WES has significantly improved the detection rate of SD fetuses. Karyotype and CMA are not the optimal choices, and prenatal WES should be used as an important molecular genetic testing method.

Key Words skeletal dysplasia; whole exome sequencing; prenatal diagnosis; genetic counseling

NIPT筛查中发现的罕见三体的临床价值

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目的：NIPT已广泛应用于胎儿常见三体的评估，但对于NIPT能否用于罕见三体的评估还存在争议，其中重要的原因是NIPT用于罕见三体评估的敏感性、特异性、假阳性率以及对检出的罕见三体高风险妊娠结局了解的尚有限。因此本研究评估NIPT检出的罕见三体与不良妊娠结局的关系，从而探讨NIPT用于检测胎儿罕见三体的临床价值。

方法：我们回顾性的分析了2014年至2020年在我院进行NIPT检测且结果为罕见三体高风险的病例。我们收集了这些高风险病例的年龄、检测时孕周、检测结果、胎儿超声结果以及妊娠结局、分娩孕周等情况，并与NIPT结果低风险的人群进行比较。

结果： 62752例进行NIPT检测的人群中，共检出151例（0.24%）罕见三体高风险。其中65例高风险孕妇选择进行羊膜穿刺术，结果显示阳性预测值（PPV）为4.6%。在139例有完整结果的病例中，26例（18.7%）早产，10例（7.2%）因胎儿缺陷而终止妊娠，5例（3.6%）流产。有趣的是，与对照组相比，NIPT检测结果为16号三体（T16）、22号三体（T22）、9号三体（T9）和2号三体（T2）高风险具有更高的不良结局风险，包括早产、流产和超声异常。另一方面，检出结果为7号三体（T7）、3号三体（T3）、8号三体（T8）和20号三体（T20）高风险，与对照组相比，不良结局的发生概率并无明显差异。

结论：一些特定的罕见三体高风险不良妊娠结局的风险更高。对于T16、T22、T9和T2，即使是假阳性，其妊娠过程也需要应密切关注。

关键字 NIPT 罕见三体 妊娠结局

新生儿枫糖尿病1例的串联质谱筛查及基因突变分析

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目的：探讨枫糖尿病（maplesyrupurinedisease, MSUD）患儿串联质谱筛查及 BCKDHB基因突变的情况。

方法：对本院新筛中心确诊的1例MSUD患儿的串联质谱筛查结果进行分析，同时对患儿进行DNA二代测序分析以及父母家系Sanger位点验证。

结果：患儿，男，孕36周+5天剖宫产，出生体质量2,710g。其父母身体健康，非近亲婚配，否认家族遗传病史。患儿出生5天采足跟血滤纸片，MS/MS初次筛查LEU+ILE+PRO-OH浓度为497.35 μ mol/L，偏高（参考值65~320 μ mol/L），同时相关比值异常。立即召回复查，复查结果显示LEU+ILE+PRO-OH

浓度为825.57 μmol/L，持续升高，结合2次血MS/MS结果提示患儿高度疑似MSUD，立即召回确诊。DNA二代测序检出患儿BCKDHB基因双位点复合杂合突变，c.952-2A>G和c.742+4A>G，均为剪接突变，前者遗传自父亲，后者遗传自母亲。患儿目前在本中心定期监测治疗，最近一次MS/MS结果基本正常，LEU+ILE+PRO-OH浓度为289.77 μmol/L。该患儿以限制蛋白质摄入配合药物治疗，定期复查血MS/MS及体格检查，患儿现1岁6个月+，生长发育暂未见明显异常。

结论：截至2024年6月底，本病例为徐州地区新生儿疾病筛查确诊的首例MSUD患儿，徐州地区MUSD发病率约1:719,279，应用二代测序技术，发现BCKDHB基因的c.952-2A>G突变为新突变，数据库未见报道，实现MUSD的早期筛查及疾病诊断。

关键字 枫糖尿病、串联质谱、新生儿筛查、BCKDHB基因

11号染色体q23.1q25处重复致矮小-小颌综合征一例分析

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目的：矮小-小颌综合征（Short Stature-Micrognathia Syndrome, SSMG）是一种常染色体显性遗传病，其特征为胎儿宫内发育迟缓、出生后身材矮小和小颌畸形，致病基因为ARCN1。本研究旨在对一例全面发育迟缓伴骨骼、心脏异常的患儿进行致病原因分析。

方法：收集患儿及其父母的外周血样本进行基因检测及染色体核型分析。

结果：患儿，女，3岁，因“生后不能独步2年余”就诊。查体显示智力发育落后，身材矮小；扶持能站，不能开步；下肢肌力肌张力高；左髋关节外展受限。经基因检测发现该患儿在11号染色体q23.1q25区域存在一个约22.17Mb的片段重复：chr11: g.112086922_134257854dup(p.?)，该重复区域包含ARCN1基因，该区域内的其他重复变异与肌肉骨骼发育异常、智力障碍、特殊面容、关节松弛、全面发育迟缓等相关。未在父母外周血中检测到相同变异。通过染色体核型分析，发现患儿父亲在3号和11号染色体上存在平衡易位，核型分析结果为：46, XY, t(3;11)(p26;q23)。

讨论：11号染色体q23.1q25区域的重复为该患儿的遗传学原因，该染色体异常来自于父亲的染色体平衡易位，该基因检测结果明确了患儿的临床诊断为SSMG。本研究提示染色体大片段重复、缺失异常未在父母外周血中检出时，需考虑染色体的平衡易位。本研究扩大了SSMG的突变谱，为该家庭的遗传咨询提供了依据。

关键字 矮小-小颌综合征，SSMG，ARCN1基因，染色体大片段重复，平衡易位。

16p13.11微缺失/微重复胎儿的产前遗传学分析和妊娠结局

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无锡市妇幼保健院

目的：探讨16p13.11微缺失/微重复胎儿的基因型-表型相关性，有助于提供科学的咨询建议。

方法：回顾性分析2020年1月至2024年6月在无锡市妇幼保健院经产前诊断为16p13.11微缺失/微重复的34例胎儿的临床资料。分两类拷贝数变异研究基因型-表型相关性。

结果：在8655例进行单核苷酸多态性微阵列技术检测（SNP-array）的产前样本中共检出34例16p13.11微缺失/微重复胎儿，其中缺失变异为10例，重复变异为24例。34例拷贝数异常样本中11例（32.4%，11/34）伴超声结构异常，其中心脏异常4例（36.4%，4/11），侧脑室增宽2例（18.2%，2/11），脉络丛囊肿2例（18.2%，2/11），胎儿生长受限2例（18.2%，2/11），胎儿唇裂1例（9%，1/11）。15例进行了亲本来源检测，母源遗传7例，父源遗传5例，新发变异3例。6例病例(17.6%，6/34)选择引产；28例(82.4%，28/34)选择继续妊娠直至分娩。其中1例新生儿法洛四联症，1例新生儿室间隔缺损，1例新生儿单侧唇裂伴牙槽突裂，其余随访均无异常。

结论：16p13.11微缺失/微重复胎儿与神经系统疾病密切相关，产前表型缺乏特异性，或表现为心血管异常、侧脑室增宽，脉络丛囊肿，生长发育迟缓等。针对产前16p13.11微缺失/微重复胎儿，需要结合家系病史、分子检测等结果综合评估，以科学指导孕妇的妊娠选择。

关键字 16p13.11微缺失/微重复、超声结构异常、基因型与表型

Fetal Congenital anomalies of the kidney and urinary tract: prenatal diagnosis of chromosomal microarray analysis and pregnancy outcomes

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Objectives: This study aimed to investigate the incidence of genomic abnormalities in fetus with different types of kidney and urinary tract anomalies and assess the pregnancy outcomes of these fetus.

Methods: 374 fetuses with urinary tract anomalies detected by prenatal ultrasound were enrolled; 301 had isolated urinary tract anomalies, and 73 had non-isolated urinary tract anomalies. According to the ultrasound phenotypes, the fetus were classified as unilateral and bilateral urinary system anomalies. Isolated urinary system anomalies included unilateral urinary system anomalies (n=188), bilateral urinary system anomalies (n=97), horseshoe kidneys (n=5) and megabladder (n=11). Isolated bilateral urinary system anomalies included bilatera l hydronephrosis (n=52), bilateral multicystic dysplastic kidneys (n=5), bilateral hyperechogenic kidneys (n=23), bilateral kidney agenesis (n=2), bilateral renal cysts (n=1) and bilateral others (bilateral two or more urinary system anomalies, n=14). Nonisolated urinary system anomalies included sonographic soft markers, structural anomalies in other system(s) and amniotic fluid change. Chromosomal microarray analysis (CMA) was performed on the Affymetrix 750K platform. Clinical follow - up assessments via telephone and medical records were scheduled and performed at least one year old after birth.

Results: Among all cases, four (4/374, 1.07%) fetuses showed common aneuploidies, 30 (30/374, 8.02%) fetuses showed pCNVs, and 340 (340/374, 90.91%) fetuses showed normal. The rate of pathogenic findings were not significantly different between fetuses with nonisolated urinary system anomalies and those with isolated urinary system anomalies (P=0.127). The rate of pathogenic findings among the fetuses with bilateral isolated urinary system anomalies was significantly higher than that among the fetuses with unilateral isolated urinary system

anomalies (P=0.001).The highest detection rates for nonisolated urinary anomalies were observed in fetuses with amniotic fluid change (35.71%). A 17q12 microdeletion was detected in 23 fetuses with urinary anomalies, accounting for 76.67% of pCNVs. Follow-up results showed that in the group with normal CMA results, 6.76% fetuses required surgical intervention after birth, 69.41% fetuses required regular examinatin, 13.82% fetuses were terminated during the pregnancy, 0.59% fetuses after birth with other defects. The rates of termination of pregnancy (TOP) was significantly higher in fetuses with nonisolated urinary system anomalies or isolated bilateral urinary system anomalies.

Conclusion: CMA is especially valuable in the prenatal diagnosis of fetuses with urinary system anomalies. The highest detection rates for isolated bilateral urinary anomalies and nonisolated urinary anomalies were observed in fetuses with hyperechogenic kidneys and amniotic fluid change respectively. The 17q12 microdeletion was the most frequently pCNV in fetuses with urinary anomalies. The CMA results, the severity of the phenotypes and unilateral or bilateral also could help parents decide whether to continue the pregnancy. Hydronephrosis may be the only phenotype that requires postnatal surgical intervention; other phenotypes only require regular medical examinations.

Key Words anomalies of the kidney and urinary tract, prenatal diagnosis, chromosomal microarray analysis

自然及辅助妊娠自然流产与胚胎染色体异常的关联分析

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目的：分析自然流产次数与流产组织染色体数目和拷贝数异常率之间的关系，比较自然妊娠、辅助妊娠自然流产染色体异常率有无差异，为临床医师提供咨询指导意见。

方法：选择2019年1月–2023年12月于江南大学附属妇产医院无锡市妇幼保健院就诊的自然流产患者共1345例，根据受孕方式分两组：自然妊娠组1242例，辅助妊娠组103例。按流产次数将自然妊娠组分为偶发流产组（780例）和复发性流产组（462例），辅助妊娠组分偶发流产组（68例）和复发性流产组（35例）。对所有流产组织采用染色体微阵列分析技术进行全基因组拷贝数检测。

结果：1242例自然妊娠组中，偶发、复发性流产组染色体数目异常率分别56.79%（443/780），52.38%（242/462），两者比较无统计学差异。随着自然流产次数的增加，胚胎染色体数目异常率呈下降趋势（流产1次、2次、3次、≥4次组分别为56.79%, 54.93%, 47.06%, 30.43%），流产1次、2次组的染色体数目异常率明显高于≥4次组（P<0.05）。偶发、复发性流产组染色体拷贝数变异（copy number variation, CNV）率分别为：3.46%（27/780），5.63%（26/462），两者无统计学差异（P=0.068）；流产1次~≥4次组的CNV异常率分别为3.46%，5.65%，5.88%，4.35%，各组比较均无统计学差异。辅助妊娠组中偶发、复发性流产组的染色体数目异常率分别为47.06%，37.14%；两组CNV异常率分别为2.94%，11.43%；偶发、复发组间染色体异常率均无统计学差异。在偶发流产或复发性流产组中，自然妊娠和辅助妊娠组相比，在染色体数目异常、CNV异常率均无显著差异（P>0.05）。

结论：染色体数目异常和拷贝数变异在自然妊娠、辅助妊娠流产患者中均有较高的发生率，自然妊娠流产1次、2次组的染色体数目异常率、致病性CNV率均明显高于≥4次组，在自然流产遗传学查因中应引起重视。

关键字 自然流产；染色体异常；拷贝数变异；染色体微阵列分析；辅助妊娠

·出生缺陷防控·

Single-cell RNA-sequencing reveals the transcriptional landscape of ND-42 mediated spermatid elongation via mitochondrial derivative maintenance

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During spermatogenesis, mitochondria extend along the whole length of spermatid tail and offer a structural platform for microtubule reorganization and synchronized spermatid individualization, that eventually helps to generate mature sperm in Drosophila. However, the regulatory mechanism of spermatid mitochondria during

elongation remains largely unknown. Herein, we demonstrated that NADH dehydrogenase (ubiquinone) 42 kDa subunit (ND-42) was essential for male fertility and spermatid elongation in Drosophila. Moreover, ND-42 depletion led to mitochondrial disorders in Drosophila testes. Based on single-cell RNA-sequencing (scRNA-seq), we identified 15 distinct cell clusters, including several unanticipated transitional subpopulations or differ-entiative stages for testicular germ cell complexity in Drosophila testes. Enrichments of the transcriptional reg-ulatory network in the late-stage cell populations revealed key roles of ND-42 in mitochondria and its related biological processes during spermatid elongation. Notably, we demonstrated that ND-42 depletion led to maintenance defects of the major mitochondrial derivative and the minor mitochondrial derivative by affecting

mitochondrial membrane potential and mitochondrial-encoded genes. Our study proposes a novel regulatory mechanism of ND-42 for spermatid mitochondrial derivative maintenance, contributing to a better under-standing of spermatid elongation.

Key Words ND-42, Single-cell RNA-Sequencing, Spermatid elongation, Mitochondrial derivative, Male fertility

一例产前羊膜束带综合征合并足内翻的病例报道

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目的：回顾本中心一例产前羊膜束带综合征合并足内翻的病例，为该病例家庭提供更详细及精准的遗传咨询，并帮助了解该疾病的发病机制、干预措施及预后等情况。

方法：对该孕妇进行了羊膜腔穿刺术，并使用羊水样本进行细胞核型分析及染色体微阵列检测，超声密切随访胎儿生长发育以及被羊膜束带缠绕的组织血流情况。

结果：产前诊断细胞核型分析及染色体微阵列分析均未见异常，孕妇及家属决定继续妊娠。后期

超声未发现严重组织肿胀及血流异常状况。该妇孕34+2周剖宫产一早产女婴，重2200g，Apgar评分8’–9’/1’–5’，发现羊膜束带缠绕于新生儿右足踝部，见较浅压迹，左足内翻。

讨论：妊娠<20周和死胎的胎儿中羊膜束带综合征的患病率较高，这意味着该疾病的诊断不足，建议孕期进行详细的超声检查，以确定异常的程度。据报道，胎儿镜下松解术对因缩窄带而处于危险中的四肢具有良好的效果，尽管这种方增加了胎膜早破和早产的风险。终止妊娠也是一种选择，需对患者充分知情同意后进行决定。通常不建议对羊膜束带综合征进行遗传学评估，这些病例通常是偶发性的，没有家族史，其发病率也与种族和性别无关，尽管报告了一些家族性病例，但几乎所有病例都是偶发性的，没有确定潜在的遗传原因，如果羊膜束带综合征的诊断不明确，可以考虑染色体微阵列分析。该疾病预后变化很大，主要取决于发现时的严重程度和异常的范围。

关键字 羊膜束带综合征，产前诊断，足内翻

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

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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。

关键字 胚胎植入前遗传学诊断；PGT–M；软骨异常型骨关节炎；COL2A1基因

母婴肠道菌群对子代神经行为发育影响的前瞻性队列研究

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目的：探讨母婴肠道微生物中不同的双歧杆菌种与婴儿早期神经发育的关系。

方法：本研究纳入来自中国江苏出生队列的520个家庭，进行纵向队列研究。我们采集了母亲孕早期及孕晚期、新生儿出生时及其一岁时的肠道微生物样本，并对其微生物组成与婴儿神经发育评分进行了关联分析。

结果：研究发现，母亲孕早期肠道中假小链双歧杆菌种的增加与婴儿认知评分的下降相关，而婴儿一岁时肠道中长双歧杆菌种的增加与较高的认知评分相关。进一步分析显示，不同的双歧杆菌种在母亲

和婴儿中的功能也有所不同，孕早期母亲体内的假小链双歧杆菌种主要参与异型乳酸发酵，而婴儿体内的长双歧杆菌种则主要参与双歧杆菌途径（Bifidobacterium shunt）。

讨论：本研究强调了母婴肠道微生物在婴儿神经发育中的不同作用，揭示了通过调节微生物组成来改善神经发育的潜在策略。具体来说，母亲孕早期的肠道微生物对婴儿神经发育有显著影响，而婴儿自身的肠道微生物在一岁时对认知发育有重要作用。这些发现为进一步研究母婴肠道微生物与神经发育的机制提供了重要线索。

关键字 肠道菌群，神经行为发育，双歧杆菌，妊娠，队列研究

女性年龄可能影响整倍体胚胎移植后的妊娠结局

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背景：随着社会、职业和文化领域的发展，越来越多的女性选择推迟生育。然而，高龄女性的增加对生育能力构成了挑战。年龄相关的卵子非整倍性被认为是影响生育能力下降的最显著因素。然而整倍体囊胚移植后女性年龄是否仍会影响妊娠结局，目前仍无定论。

目的：评估母体年龄是否会影响整倍体囊胚移植后的辅助生殖技术治疗成功率。

方法：回顾性分析了2016年1月至2023年4月在南京市妇幼保健医院生殖医学中心进行的仅移植整倍体囊胚的所有冻融胚胎移植周期。排除了患有严重子宫病理、免疫系统疾病或内分泌疾病的周期。采用GnRH拮抗剂方案、激动剂或轻微刺激方案进行卵巢刺激。囊胚根据修改后的Gardner标准进行形态学评分，优质囊胚定义为AA、AB、BA或BB级，可移植囊胚定义为BC或CB级，仅在患者获得整倍体囊胚时进行冻融胚胎移植。

结果：共1037个整倍体囊胚移植周期被纳入分析，根据母体年龄分为三组：<35岁（796例）、35–37岁（126例）和≥38岁（115例）。三组在BMI、孕次、既往流产次数、PGT指征、PGT亚类和内膜准备方案方面存在显著差异。与<35岁女性相比，其他两组年龄女性BMI值更高，孕次更多。35–37岁女性中复发性流产的比例高于其他两组。在峰值内膜厚度、活检日或囊胚形态学评分方面，三组间无显著差异。临床妊娠率在38岁及以上女性中略有下降，早期流产率和流产率在老年组中略有上升，但差异未达到统计学意义。值得注意的是，活产率在38岁及以上女性中显著降低。多变量逻辑回归分析显示，38岁及以上女性在移植整倍体囊胚后的流产率呈显著上升趋势。此外，与年轻女性相比，38岁及以上女性的活产率显著降低。胚胎活检日和囊胚形态学评分对妊娠结果有显著影响。

结论：研究表明，即使排除了胚胎非整倍性的影响，母体年龄的增长与较高的流产率和较低的活产率有关。尽管囊胚的形态学评分对妊娠结果至关重要，但母体年龄可能通过其他机制对生育能力产生不利影响。因此，对于高龄产妇，需要全面认识其面临的特殊风险，并在整个孕期持续监测其健康状况，制定个性化的医疗方案，以提高活产率。

关键字 高龄女性；整倍体囊胚；辅助生殖技术；妊娠结局

细胞外基质在子宫内膜容受性中的作用及机制研究

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反复种植失败（RIF, Repeated Implantation Failure）是辅助生殖技术中一个常见的问题，指的是多次胚胎移植后，患者仍未能成功怀孕。2023年中国医师协会生殖医学专业委员会为了进一步规范RIF的诊治，将RIF定义为：对于40岁以下的成年女性，在3个新鲜或冷冻胚胎移植周期中，至少移植了3枚优质胚胎（如第3天的胚胎细胞数需达到8个以上，卵裂球大小均匀，碎片率低于10%；囊胚需达到3BB等级），但仍未实现临床妊娠[1]。RIF的全球发病率大约在10%到20%之间[2]。 RIF的病因非常复杂，目前已知的病因包括母体因素、男性因素和胚胎因素，母体因素包括免疫异常、血栓前状态、子宫内膜容受性降低、感染、生殖系统解剖结构异常和内分泌稳态失衡等 [3]。子宫内膜容受性差是导致RIF患者胚胎着床失败的关键因素[4]。有研究表明，超过25%的RIF患者在月经周期的特定时间内存在子宫内膜容受性相关基因的异常表达［5］。因此，深入研究影响子宫内膜容受性的机制，对于提高RIF患者子宫内膜容受性，以及优化胚胎与子宫内膜的相互作用，从而提高辅助生殖技术的成功率至关重要。

子宫内膜容受性是子宫内膜允许胚胎着床的能力，是胚胎成功着床的关键因素，它涉及到子宫内膜在特定时间内对囊胚的接纳能力。这个时间段被称为“胚胎种植窗口期”（window of implantation，WOI），通常在排卵后6–8天或者是受精后5–7天，持续时间约为 30–36 小时[6]。在这个窗口期内，子宫内膜会发生一系列形态和功能上的变化，这一过程称为蜕膜化。蜕膜化是在雌激素和孕激素的共同作用下，基质细胞转化为具有分泌功能的蜕膜细胞的过程。这一转变伴随着遗传、代谢、形态和免疫方面的多方面变化，为胚胎的植入创造有利条件 [7]。其中，细胞外基质（Extracellular Matrix, ECM）的重塑是蜕膜化过程中的一个关键特征[8]。ECM是由蛋白质、多糖和水组成的复杂网络，对所有组织和器官的结构和功能至关重要[9]。研究表明，在蜕膜化过程中，ECM的组成会发生显著变化。例如，在大鼠子宫内膜基质中，VI型胶原的表达会下降[10]；而IV型胶原和层粘连蛋白在蜕膜细胞周围区域显著增加 [11]。这些变化对子宫内膜的容受性有着重要影响。研究表明，在不明原因不孕或反复流产的患者中，I型胶原蛋白的mRNA水平异常增加，这可能会降低子宫内膜的容受性，使胚胎难以着床[12]。此外，特定的细胞信号通路，如T–HESC细胞中的PK2通过LUCAT1减少基质金属蛋白酶MMP9的表达，也可能影响子宫内膜的蜕膜化过程[13]。ECM是细胞和组织赖以生存的微环境，它由多种大分子蛋白组成，包括胶原蛋白、蛋白聚糖、糖胺聚糖、弹性蛋白、纤连蛋白、层粘连蛋白和其他几种糖蛋白等[14]。这些大分子蛋白质在不同组织中的含量和组成各有不同[15]。ECM不仅仅是提供物理支撑的被动结构，还具有调节细胞行为和组织命运的主动功能。例如，在斑马鱼模型[16]中，纤连蛋白的突变或表达降低会导致心肌前体细胞迁移受阻，进而影响心脏的正常发育，这种发育缺陷可以通过补充外源性纤连蛋白得到改善。在果蝇[17]中，层粘连蛋白和纤维蛋白原类似物的基因突变会引起发育异常。这些研究结果表明，ECM的组成和功能对生物体的正常发育至关重要。在体外培养条件下，颗粒细胞（如卵巢的颗粒细胞）通常难以长期存活，但当它们生长在ECM上时，其存活时间会显著延长[18]。这进一步证实了ECM对细胞存活和功能的重要性。随着蛋白质组学的发展，随着蛋白质组学技术的发展，我们已经能够解析多种组织中ECM的组成，比如糖尿病和非糖尿病供体的视网膜血管、小鼠胰岛、人前列腺、人类子宫平滑肌瘤以及正常子宫肌层样本[19]。然而，对于子宫内膜的ECM组分，我们的认识还相对有限。特别是在蜕膜化过程中，ECM的重塑可能对子宫内膜的容受性有重要影响。因此，深入研究蜕膜化过程中ECM的组分如何重

塑，将有助于我们更好地理解子宫内膜容受性的机制。

关键字 细胞外基质，子宫内膜容受性，反复种植失败

两例2号染色体单亲二体的产前诊断及遗传咨询

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目的：对2017年至2022年期间检出的2例2号染色体单亲二体（uniparental disomy of chromosome 2,UPD2）进行产前诊断及提供遗传咨询。

方法：对羊水中胎儿细胞提取DNA，并进行单核苷酸多态性微阵列芯片（HumanCyto-12芯片及CytoScan 750K Array芯片）检测。

结果：一例胎儿超声提示胎儿发育异常：室间隔缺损；单脐动脉；四肢长骨短于相应孕周，孕26+周于我院羊水穿刺，HumanCyto-12芯片检出UPD2。另一例胎儿NIPS提示2号染色体数目增多，且孕期超声提示羊水少，胎儿小于相应孕周，胎盘位置较局限，孕22+周于我院羊水穿刺，CytoScan 750K Array芯片检出UPD2。

结论：UPD2临床表现具有异质性，产前超声检测较难早期发现；UPD主要通过导致隐性遗传致病基因变异的纯合状态、印记基因障碍、影响胎盘功能致病；UPD的再发风险取决于其不同的发病机制；产前超声检测结合无创DNA产前检测，可以早发现、早诊断，有效防控出生缺陷。

关键字 2号染色体单亲二体；单核苷酸多态性微阵列芯片；产前诊断；遗传咨询

Preimplantation Genetic Testing for Monogenic Disease in a Chinease Family Affected by Niemann-Pick disease

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Objective To study the gene mutation of a Chinese family with Niemann-Pick disease and to perform preimplantation genetic testing for aneuploidy and monogenic Disease (PGT-M).

Methods The clinical data and blood samples of the proband and his parents were collected. Six coding exons and their flanking intronic sequences of SMPD1 gene in all members of this family were amplified by polymerase chain reaction (PCR) and sequenced. Karyomapping was used to detect the embryos for both chromosomal euploidy and Niemann-Pick disease simultaneously, and Sanger sequencing was used to confirm the results.

Results The analysis of the SMPD1 gene revealed compound heterozygous mutations: c.827A>G or p.Y276C inherited from the mother and c.1673T>C or p.L558P inherited from the father. Two blastocysts were biopsied and detected by PGT. All the embryos were chromosomal euploidy and only one was not affected by the mutations, which was implanted at last. Postnatal DNA testing of the newborn showed a normal genotype.

Conclusions This is the first report of PGT-M for SMPD1 mutations in China. Karyomapping can be used to

reduce birth defects as a useful method to preimplantation genetic testing for aneuploidy and monogenic Disease.

Key Words Niemann-Pick disease; SMPD1 gene; Karyomapping; PGT-M

The characteristics of blood metabolism in neonatal sepsis were analyzed by tandem mass spectrometry

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Objective: To investigate the unique metabolic signatures of neonatal sepsis and identify potential biochemical markers.

Methods: In a cohort of 54 newborns diagnosed with sepsis through follow-up screening, we employed tandem mass spectrometry (TMS) to analyze blood samples collected within three days of birth. This analysis focused on amino acids, carnitines, and ketones to identify characteristic metabolic changes associated with neonatal sepsis.

Results: Through TMS analysis, we detected 11 amino acids, 32 carnitines, and one ketone in the blood samples. When compared to control samples, three amino acids, 10 carnitines, and one ketone exhibited significant changes in neonates with sepsis. Notably, 19 substances showed pronounced alterations in early-onset neonatal sepsis (EOS), while four substances demonstrated significant changes in late-onset neonatal sepsis (LOS) despite the absence of clinical manifestations at the time of sample collection. Furthermore, there were notable differences in the levels of Proline (PRO), Succinylacetone (SA), Acetyl carnitine (C2), Propionylcarnitine (C3), Dodecanoylcarnitine (C12), Myristoylcarnitine (C14), Tetradecenoylcarnitine (C14:1), Hexadeanoylcarnitine (C16:1), and 3-Hydroxyoleoylcarnitine (C18:1OH) between EOS and LOS cases. When comparing bacterial culture-negative and positive groups, only C18:1 exhibited statistical significance.

Conclusion: Neonatal sepsis exhibits distinct metabolic alterations, indicating the need for further exploration of its metabolic patterns and the identification of potential biomarkers. The findings from this study provide valuable insights into the complex metabolic changes associated with neonatal sepsis, laying the foundation for future research and potential diagnostic and therapeutic strategies.

Key Words amino acid, carnitine, metabolites, neonatal sepsis, tandem mass spectrum

不同GDM治疗方案对新生儿氨基酸代谢水平的影响

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目的：探讨妊娠糖尿病孕妇进行不同降糖治疗方案后，其子代氨基酸代谢的差异。

方法：采用双盲随机法选取本院收治的272例的孕妇按是否患有妊娠糖尿病分为GDM组和未患GDM的对照组，将GDM组进一步细分作3组治疗组，分别予以运动饮食治疗、二甲双胍治疗和胰岛素治疗，所有孕妇均随访追踪其妊娠结局。比较干预治疗的3组孕妇与未患有GDM的孕妇其新生儿氨基酸代谢的差异。

结果：治疗组与对照组的代谢物指标中Arg、Cit、Met、Orn、Pro差异明显，有统计学意义(P<0.05)。

结论：无论采用何种GDM治疗方案，精氨酸家族相关氨基酸代谢都会造成影响。

关键字 妊娠糖尿病；串联质谱；新生儿筛查；氨基酸代谢

Comprehensive Analysis of Newborn Tandem Mass Spectrometry Screening Trends and Outcomes in Changzhou: A Six-Year Retrospective Study (2015-2020)

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Objective: The primary objective of this study was to comprehensively evaluate the status of newborn screening using tandem mass spectrometry (MS/MS) in Changzhou over a six-year period from 2015 to 2020. The study aimed to elucidate the incidence rates and distribution patterns of genetic metabolic diseases within this region, thereby informing public health strategies.

Methods: A retrospective analysis was conducted on MS/MS screening data from 148,910 newborns in Changzhou between 2015 and 2020. Infants with initial suspicious positive results were recalled for follow-up testing, and those with confirmed persistent positivity underwent genetic testing and additional diagnostic evaluations for definitive diagnosis.

Results: Out of the total 148,910 newborns screened, 2,410 (1.62%) exhibited suspicious positive results. Further evaluation led to the confirmation of 61 cases (2.53% of suspicious positives, 0.04% of total screened) with genetic metabolic diseases. These cases comprised 34 (55.74%) amino acid metabolism disorders, 16 (26.23%) fatty acid metabolism disorders, and 11 (18.03%) organic acid metabolism disorders, yielding a positive predictive value of 2.67%. Notably, phenylketonuria emerged as the most prevalent genetic metabolic disease (1:6769), followed by primary carnitine deficiency (1:21273).

Discussion: The study highlights the existence of a significant burden of genetic metabolic diseases in Changzhou, emphasizing the importance of comprehensive newborn screening programs. The high rate of false positives observed underscores the need for careful interpretation of MS/MS results, taking into account factors such as delivery mode, gestational age, and birth weight, which may contribute to such discrepancies.

Conclusion: This study underscores the crucial role of MS/MS screening in detecting genetic metabolic diseases early in life. While the incidence of confirmed cases is relatively low, the identification of phenylketonuria and primary carnitine deficiency as prevalent disorders necessitates targeted interventions. The propensity for false positives underscores the importance of robust follow-up protocols and continued refinement of screening methodologies. Expanding the scope and improving the accuracy of MS/MS screening can significantly contribute to the early diagnosis and prevention of newborn genetic metabolic diseases, ultimately enhancing population health outcomes.

Key Words Tandem Mass Spectrometry; Newborn Screening; Genetic Metabolism; Newborn; Disease Screening

巨细胞病毒（CMV）潜伏感染孕妇宫内CMV传播率及其对胎儿的影响

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研究目的：我国育龄妇女巨细胞病毒（CMV）潜伏感染率高达95%以上，表现为CMV IgG阳性和CMV IgM阴性。孕妇体内的CMV可因免疫抑制引起再激活感染，引起CMV宫内传播。本研究旨在调查CMV潜伏感染孕妇CMV宫内传播的发生率及其对新生儿的影响。

材料和方法：纳入2021年4月1日至2023年2月6日常州武进人民医院孕期CMV IgG阳性，因各种原因剖宫产的孕妇，以及2019年4月1日至2020年3月31日南京鼓楼医院孕期CMV IgG阳性，因各种原因剖宫产孕妇。剖宫产时留取羊水，同时留取母亲血液，部分胎儿留取脐血。标本均–30° C保存，所有标本在南京鼓楼医院统一检测。羊水（1ml）离心后取沉淀混悬液用荧光定量PCR检测CMV DNA，母血和脐血分别检测CMV DNA和 CMV IgG 及IgM。

结果: 共纳入有分娩结局、孕期CMV IgG阳性孕妇695例，孕妇平均年龄30.6 ± 4.7岁。其中单胎妊娠567例（81.6%），双胎妊娠128例（18.4%），共823例新生儿。足月妊娠分娩594例（85.5%），早产101例（14.5%）；其中单胎妊娠早产率4.4%（25/567），双胎妊娠早产率59.4%（76/128）（$\chi 2=254.013$，$p<0.001$）。695例孕妇分娩时CMV IgG均阳性，CMV IgM阳性11例（1.6%）。823例新生儿中，7例羊水CMV DNA阳性，CMV宫内传播率为0.9%。其中单胎3例（3/567，0.5%），4例双胎（2对双胎）（4/256，1.6%）（$\chi 2=1.128$，$p=0.288$）；这3例单胎均足月产；4例双胎均早产，胎龄分别为30+2和36+1周。7例羊水CMV DNA阳性的母亲孕期CMV IgM均阴性。对5例新生儿（4例双胎和1例单胎）脐血检测结果显示CMV DNA均阴性，3例（2例双胎和1例单胎）CMV IgG和IgM阳性。这7例羊水CMV DNA阳性新生儿在1~3岁时随访，听力、视力和神经发育正常均正常。

结论：本研究显示，母体潜伏性CMV感染可引起宫内CMV传播，发生率约1%，但这类宫内感染对胎儿的影响较小，这可能与母体内的CMV IgG能通过胎盘进入胎儿有关。本研究结果提示，对CMV潜伏感染的孕妇，即使存在CMV宫内感染，大部分胎儿仍能正常发育。因此，我们认为，单纯羊水CMV DNA阳性，不是中止妊娠的指证。

关键字 巨细胞病毒 孕妇 宫内感染 胎儿

135例介入性取样羊水性状异常胎儿产前诊断结果及预后分析

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目的：探讨孕中期通过介入性产前诊断发现羊水性状异常胎儿产前诊断结果及妊娠结局分析。

方法：回顾性收集2017年1月至2023年12月在无锡市妇幼保健院行羊膜腔穿刺术，术中发现羊水性状异常（目测法，未离心羊水颜色为非清亮或非淡黄色，表现为深黄色、褐色等；排除新鲜血性羊水，且排除此次妊娠既往相关的宫内介入性操作及宫内治疗者）共135例，均行羊水染色体微阵列分析（chromosomal microarray analysis，CMA），对其孕期超声表现、CMA结果及妊娠结局进行总结分析。随访截止日期2024-3-1。

结果：1）孕期超声表现：36例合并宫内异常超声表现，占26.6%（36/135），其中异常CMA占22.2%（8/36）。9例超声异常引产（颅脑结构异常2例，胎盘异常合并FGR 1例，胎盘异常合并胎儿长骨短-6SD 1例，心脏结构异常2例，消化系统异常2例，可疑宫内感染1例）。18例超声异常孕妇选择继续妊娠并分娩。2）135例异常颜色羊水均行羊水CMA检测，其中15例CMA异常（11.1%，15/135），其中包括8例染色体数目异常，8例拷贝数变异（copy number variation，CNV）（其中一例CNV异常同时合并染色体数目异常）。3）妊娠结局：20例终止妊娠，占14.8%（20/135）（其中7例染色体非整倍体引产，3例死胎引产，1例穿刺后20天自然流产，9例超声异常引产）； 115例异常羊水颜色孕妇选择继续妊娠并分娩，其中1例21三体综合征合并致病性CNV，孕妇要求继续妊娠，目前2月龄唐氏面容；7例孕期CMA检测未见异常，但随访存在不同程度异常（1例孕期超声未见异常幼儿临床拟诊：四肢色素失禁症；1例孕期超声未见异常幼儿发现龋齿，1例孕期超声未见异常幼儿出现语言发育迟缓，1例孕期超声胎儿偏小-2SD幼儿出现语言发育迟缓，1例孕期超声胎儿偏小-2SD伴单脐动脉幼儿出现全面发育迟缓伴双眼屈光不正，1例孕期超声提示胎儿膀胱、输尿管发育异常幼儿左侧肾发育不良伴积水，脊柱多发畸形伴侧凹，1例孕期超声未见异常幼儿发现先天性髋关节发育不良，睾丸鞘膜积液），余107例随访时均无明显异常。异常羊水性状胎儿同时合并异常妊娠结局在继续妊娠分娩占比6.9%（8/115）。

结论：介入性取样发现羊水性状异常胎儿中，回顾其孕期超声表现，发现胎儿生长速率缓慢占比最高，其次依次为超声软指标、胎儿心脏异常。异常CMA结果在异常颜色羊水中占11.1%，染色体数目异常及CNV异常占比无明显差异。CMA检测阴性并不能排除胎儿不良预后。

关键字 介入性产前诊断；羊水性状异常；宫内超声表现；染色体微阵列分析；随访

反复自然流产患者蜕膜基质细胞中FABP5的缺失通过抑制MRPL17损伤线粒体功能和细胞存活

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目的：反复自然流产(Recurrent spontaneous abortion, RSA)是一种高度异质性的疾病，影响全世界约2.5%的育龄女性。目前，该疾病影响因素众多，病因仍不明确。因此，探究该疾病的发病机制具有重要的意义。本研究旨在探究目的基因FABP5的异常低表达引起反复自然流产的调控机制。

方法：利用qPCR，Western Blot和免疫组化等技术检测FABP5在蜕膜组织中表达和定位。在内源性抑制FABP5后，利用qPCR，Western Blot，CCK8，TUNEL，FCM等方法检测细胞的存活情况，并结合JC-1，Fluo-4 AM和Rhod-2 AM等染色以及Seahorse等检测方法检测蜕膜基质细胞线粒体的功能。使用RNA-seq分析FABP5敲低后下游的转录群体变化情况，挖掘关键下游调控基因，检测关键下游基因过表达对FABP5敲低后细胞线粒体功能和细胞存活的挽救情况。

结果：在本研究中，我们发现RSA患者蜕膜组织和蜕膜基质细胞中ROS水平显著升高，且FABP5明

显高表达于RSA患者蜕膜组织和蜕膜基质细胞中。同时FABP5在体外能够响应双氧水的刺激表达显著上升。在蜕膜基质细胞中敲低FABP5后，细胞增殖受到抑制，凋亡明显增加，并且细胞线粒体的功能受到明显的损伤。FABP5敲低后其下游关键调控基因MRPL17表达显著下降，且MRPL17的过表达能够显著逆转FABP5敲低后引起的细胞线粒体损伤和凋亡。进一步的，FABP5敲低引蜕膜基质细胞中CXCL11分泌减少，降低了HTR8/SVneo细胞中CXCR3的表达及其迁移和侵袭能力。

讨论： FABP5异常低表达可能通过抑制MRPL17的表达，造成蜕膜基质细胞的线粒体损伤，引起蜕膜基质细胞的凋亡，减少其分泌CXCL11，进而导致无法激活胎盘滋养细胞中CXCR3的表达，抑制胎盘滋养细胞的迁移和侵袭的能力，终而导致流产。

关键字 FABP5，MRPL17，线粒体，反复自然流产，蜕膜基质细胞

the relationship between low fetal fraction in prenatal cell-free DNA (cfDNA) testing and adverse pregnancy outcomes

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Objective: This study aims to investigate the correlation between low fetal fraction and fetal chromosome aneuploidies, as well as adverse pregnancy outcomes. Method: Prenatal cell-free DNA (cfDNA) testing was conducted on 21,964 pregnant women between 12 and 23 weeks of gestation. A fetal fraction < 4% was categorized as the low fetal fraction group (LFF), and < 2% was defined as the very low fetal fraction group (VLFF). Follow-up assessments were performed on all pregnant women who underwent prenatal cfDNA testing at 8 weeks after receiving the final results and again at 12 weeks after their expected delivery date. Outcome measures included gestational hypertension, gestational diabetes, preterm birth, and low birth weight infants. Results: Among the participants, there were a total of 201 cases with a fetal concentration < 4% in the initial prenatal cfDNA testing; all these individuals agreed to undergo repeat testing. Significant differences in BMI and gestational weeks were observed among groups with different levels of fetal fraction (<4%, ≥4%, ≤2%). The incidence of fetal chromosome abnormalities was highest in the group with a fractional concentration ≤2%, followed by those with a fractional concentration <4%. Additionally, there was a higher rate of failed resampling for prenatal cfDNA testing in these two groups compared to those with a higher fractional concentration. The incidence of pregnancy-induced hypertension (PIH) and spontaneous preterm birth (sPTB) significantly increased in both the <4% group and ≤2% group, while no significant difference was found in the incidence of gestational diabetes mellitus (GDM) or low birth weight infants across different groups. Conclusion: Low fetal concentration is associated with fetal chromosome abnormalities, pregnancy-induced hypertension, and other adverse pregnancy outcomes.

Key Words cell-free DNA; fetal fraction; pregnancy outcomes

扩展性单基因遗传病携带者病筛查的临床应用价值

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目的：探讨扩展性单基因遗传病携带者筛查在人群中的应用价值。

方法：回顾性分析2023年5月至12月至南京鼓楼医院产前诊断中心接受扩展性单基因遗传病携带者筛查的受检者临床资料，对其单基因病携带率、筛出致病基因种类及夫妻双方携带同一致病变异的发生率进行总结分析。

结果：共接收254例样本，其中122对夫妻、单女性7例和单男性3例。共检出132例单基因致病变异携带者，总体单阳携带率54.10%（132/244），单人最多携带变异数5个；同时检出7对高风险夫妻；携带率较高的病种依次为GJB2相关非综合征型听力损失和耳聋（29/209）、OCA2眼皮肤白化病II型（14/209）、PAH苯丙酮尿症和CFTR囊性纤维化（10/209）。

结论：单基因隐性遗传病在人群中携带率较高，孕前进行扩展性单基因遗传病携带者筛查可以为受检者提供优生优育指导，选择胚胎植入前单基因遗传学检测（preimplantation genetic testing for monogenic/single gene disorders，PGT–M ）和产前诊断，从而预防出生缺陷。

关键字 扩展性单基因遗传病携带者筛查；遗传代谢性疾病；产前诊断；基因突变

·遗传病的经典案例与讨论·

一例Joubert综合征13型胎儿的临床特征及基因变异分析

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目的：记录一个Joubert综合征胎儿的临床表型，并进行遗传学分析以明确其遗传学病因。

方法：应用全外显子测序技术对家系内1例Joubert综合征的引产胎儿及其父母进行基因变异筛查，检出疑似致病变异后，进行Sanger测序验证。并通过胎儿父亲的cDNA分析和姐姐的转录组测序进一步研究突变位点的致病机制。

结果：全外显子测序发现家系中的引产胎儿携带TCTN1基因c.624G>A和c.96dupA (p.Glu33Argfs49)复合杂合突变，两个变异均未被报道，分别遗传自父母。Sanger测序验证了全外显子测序的结果，并发现胎儿姐姐也携带父源的c.624G>A杂合突变。胎儿父亲的cDNA分析和姐姐的转录组测序均未检测到包含c.624G>A的转录本，表明c.624G>A变异可能影响了mRNA剪接，并激活了无义介导的mRNA降解。

结论：TCTN1基因的c.624G>A和c.96dupA (p.Glu33Argfs49)复合杂合突变是该Joubert综合征胎儿的致病原因，丰富了TCTN1基因的变异谱。

关键字 Joubert综合征；TCTN1基因；新突变；全外显子测序

mos 46,X,psu idic (X)(q21.3)[40]/45,X[3]患儿1例的遗传学分析

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目的：对1例性腺发育不良的患儿进行遗传学研究，探讨染色体结构异常与临床表征之间的关系。

方法：选取2023年2月7日因“未来例假，偶尔腹痛”就诊于连云港市妇幼保健院的1例13岁患儿作为研究对象。收集患儿临床资料，采集患儿及其父母的外周血样本，对其进行G显带染色体核型分析及基因组拷贝数测序（CNV-seq）。在中国知网、万方数据以及PubMed数据库中以“假双着丝粒等臂X”、“psu idic (X)”为关键词，设定检索年限为2002年1月1日至2023年6月1日，检索断裂点位于Xq假双着丝粒等臂X染色体结构异常的相关文献并进行回顾性分析。

结果：患儿体格检查身高153cm，体重45kg，外观无明显异常。实验室检查卵泡刺激素(FSH)、黄体生成素高于正常水平，雌二醇(E2)低于正常水平。超声提示卵巢发育较小，始基子宫。G显带显示患儿染色体核型为mos 46,X,psu idic (X)(q21.3)[40]/45,X[3]，父母染色体核型结果正常。CNV-seq检测提示患儿Xq21.32q28区存在63.27Mb的缺失，Xp22.33q21.32 区域存在91.59 Mb的嵌合重复（嵌合比例：74%）。文献复习共检索到相关文献11篇，统计结果显示该染色体结构异常的患者临床表型多样，与45,X核型的嵌合比例、断裂点位置等密切相关。

结论：46,X,psu idic (X)(q21.3)/45,X染色体结构异常可导致患儿子宫、卵巢发育不良、性激素水平异常，而身高发育方面并不完全表现为身材矮小。Xq21.32q28区片段缺失是导致始基子宫、卵巢发育不良等Turner临床表型的关键因素。

关键字 嵌合体；假双着丝粒等臂X染色体；特纳综合征；始基子宫

2例22号染色体三体嵌合体的产前诊断

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目的：分析22号染色体三体嵌合（简称22-三体）的临床特征，探讨其产前诊断及遗传咨询要点。

方法：回顾性分析2022-2023年于南通市妇幼保健院确诊为22-三体嵌合胎儿的2例病例，并复习相关文献，总结其临床表型。

结果：病例1为33岁孕妇，16+1周无创DNA产前筛查（NIPT）提示22-三体高风险，超声提示胎儿静脉导管α波反向，20周行羊膜腔穿刺，染色体微阵列检测（CMA）提示22-三体嵌合（比例约为34%），核型分析结果为mos 47,XN,+22[11]/46,XN[39]，26+6周选择引产。病例2为27岁孕妇，15+1周NIPT检测提示22-三体高风险，超声提示胎儿三尖瓣反流和单脐动脉，18+3周行羊膜腔穿刺，CMA检测和核型分析结果均提示未见异常，26+2周超声提示FGR，右肾缺如和心包积液等，行全外显子组测序，结果未检出明确致病变异，但提示可能存在22号染色体的母源UPD，31+6周选择引产，取引产胎儿皮肤、脐带和胎盘不同位置的样本行QF-PCR检测，验证为真性胎儿嵌合体。相关文献显示，22-三体嵌合的临床表现差异较大，常见的包括生长迟缓，面部特征异常和心脏缺陷等，临床症状与嵌合比例及嵌合细胞的分布密切相关。

结论：22-三体嵌合是一种具有临床异质性的罕见染色体异常，在产前诊断中应采取多种检测手段并结合超声检查，充分告知病人该病的不确定性，由其自行决定是否继续妊娠。

关键字 22号染色体三体嵌合；临床特征；NIPT；产前诊断

1例MSH6变异引起的错配修复癌症综合症3

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摘要：错配修复癌症综合征3(MMRCS3)是一种极为罕见的由于错配修复蛋白MSH6编码基因变异引起的常染色体隐性遗传病，常表现为儿童期的神经系统肿瘤、血液肿瘤、结肠肿瘤/多发性息肉。本文报道1例南通大学附属常州儿童医院确诊的MSH6基因复合杂合变异所致的MMRCS3：患儿，男，8岁6个月，因发现肛周肿物脱出1小时入院肠镜下行肿物切除术，期间发现患者结肠存在19处肠息肉，遂抽取患儿和父母外周血进行全外显子测序(WES)，WES检出患儿MSH6基因(转录本：NM_000179)存在c.2668delG[p.(V890Sfs16)]和c.316delT[p.(W106Gfs43)]变异，两个变异在gnomAD数据库中的东亚频率均为0；均为功能丧失型变异；根据ACMG指南，这两个变异均为“疑似致病”变异。结肠息肉组织病理学结

果显示存在严重异型增生、炎症浸润和充血；MSH6蛋白的IHC染色呈现阴性结果。进一步完善查体和影像学检查，发现患者全身存在20–30块牛奶咖啡斑、双侧腋窝雀斑，眼部裂隙灯下无Lisch结节，头颅核磁功共振未发现显著异常。患者父母外周血样DNA样本的Sanger测序结果明：患儿MSH6 c.2668delG为新发变异，c.316delT变异遗传自母亲；符合常染色隐性遗传致病机制。综合患者的临床表型、基因检测和生物致病性分析、遗传模式，确诊患者为MMRCS3。本病例为国内首次报道的MMRCS3，主要表现为多发性肠息肉和多发性牛奶咖啡斑，基因分析是目前明确诊断MMRCS3可靠方法。本研究报道的MSH6基因c.2668delG和c.316delT复合杂合变异可能为患儿的遗传学病因。

关键字 错配修复癌症综合征；儿童肿瘤；基因检测；多学科会诊

PIK3CG双等位基因变异的新生儿坏死性小肠结肠炎并肺炎1例

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目的：PIK3CG基因编码磷脂酰肌醇3–激酶(PI3K)催化亚基，该基因复合杂合突变可以导致一种罕见的常染色体隐性遗传的免疫性疾病免疫缺陷97型伴自身炎症（IMD97）。IMD97临床表型多变，主要特征为自身免疫性细胞减少症，T细胞异常浸润，童年期出现自身免疫性肠炎，肺炎反复发作等目前国内尚未有PIK3CG基因突变导致的IMD97病例报道，本研究对1例以坏死性小肠结肠炎并肺炎为主的患儿进行临床特点介绍及遗传学分析，为该病的诊断及优生优育提供基础。

方法：收集患儿临床资料，采集患儿及父母外周血，并对患儿进行全外显子组测序检测，对患儿及父母进行Sanger测序验证携带PIK3CG基因突变情况。

结果：患儿男，于胎龄30周因其母先兆早产被顺产娩出，出生体重1500g，因生后持续气促于生后3h入院。2天后，胸片显示其肺部炎症伴不张，抗感染效果不佳；同时胸片呈现肝内门静脉积气，左下腹肠壁积气，腹部X光片提示患儿NEC(BeLL IIB期)，行回肠切除+回肠双腔造口+腹腔引流术，病理结果符合NEC诊断。术后患儿出现反复回肠造瘘后造瘘口坏死，身亡。全外显子测序检测到患儿携带PIK3CG基因变异：c.550C>T (p.R184C)，c.3062G>A (p.R1021H)和c.2624A>G (p.K875R)。在大型人群测序数据库中，三种变异频率极低，为罕见变异，按照ACMG指南，以上变异均可分类为“临床意义未明”变异。三种错义突变均位于物种进化高度保守区域，多种生信软件预测表明三种错义突变致病性较强。经Sanger测序验证，患儿父亲携带c.550C>T (p.R184C)和c.3062G>A (p.R1021H)变异；患儿母亲携带c.2624A>G (p.K875R)变异，符合常染色体隐性遗传致病机制。

结论：本研究经全外显子检测出患儿携带PIK3CG基因复合杂合变异，结合患儿病史、临床特征、病理结果、基因检测结果，该患儿符合PIK3CG基因突变导致的免疫缺陷97型伴自身炎症的诊断。本研究首次报道该种先天性免疫缺陷导致的坏死性小肠结肠炎并肺炎的临床特点，可为临床医生对该病的认识和诊疗水平提供基础。

关键字 坏死性小肠结肠炎；PIK3CG；自身免疫系统疾病；新生儿

Smith-Lemli-Opitz综合征1家系报道

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摘要：Smith-Lemli-Opitz综合征（SLOS）是一系列以智力残疾、行为问题为特征的常染色体隐性遗传疾病，由催化胆固醇合成的7-脱氢胆固醇还原酶编码基因DHCR7突变引起，SLOS在亚洲人中极罕见。本文报告了南通大学附属常州儿童医院2024年诊断的SLOS家族病例：一名足月女性婴儿出生后四肢发绀入院。由于特殊面容、两足并指和先天性心脏结构异常，经患者家属知情同意后抽取患者极其父母的外周血进行全外显子组测序（WES）， WES结果显示DHCR7基因存在复合杂合变异（转录本：NM:001360.3）：c.852C>a（p.Phe284Leu）；c.1426T>c（p.Ter476Glnext51）。根据ACMG突变分类标准，DHCR7的c.852C>A/p.Phe284Leu和c.1426T>c/p.Ter476Gln ext51均为可能致病（LP）变异。进一步的Sanger测序结果验证到患者DHCR7 c.852C>A突变遗传自母亲；而c.1426T>c遗传自父亲；先证者的两个无临床表型的同胞兄弟都携带c.1426T>c变异，这与常染色体隐性遗传（AR）模式符合。综合分析患者的临床表型、基因检测和生物致病性，诊断病人患有SLOS，进行胆固醇补充后，患者进食情况、体重增长有显著改善，后续发育状况进一步随访中。希望通过本案例的报道提高临床对该疾病的认识和诊治能力。

关键字 Smith-Lemli-Opitz综合征，胆固醇合成障碍，基因检测

一例铁剂难治性缺铁性贫血病例报道并文献复习

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文章报道一例铁剂难治性缺铁性贫血患者，患者表现为小细胞低色素贫血，铁蛋白正常，血清铁下降、转铁蛋白饱和度极低，基因检测发现TMPRSS6基因存在双重杂合变异：TMPRSS6: c.1342+1G>A(p.?)和TMPRSS6: c.1780G>C(p.Gly594Arg)，经过家系验证，两个变异分别遗传自父亲和母亲，此剪切位点变异为首次报道，考虑患者为铁剂难治性缺铁性贫血。后续给与静脉补铁治疗，其血红蛋白有明显提升。

关键字 铁剂难治性缺铁性贫血 分子诊断

一例系统超声异常的继发性宫内感染巨细胞病毒病例

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目的：对1例胎儿系统超声异常的孕妇进行遗传学分析，总结胎儿继发性宫内感染巨细胞病毒的诊

断及预后，提高对继发性巨细胞病毒宫内感染的重视，完善继发性巨细胞病毒感染胎儿的遗传咨询及产前诊断指导，尽早干预妊娠结局。

方法：根据胎儿系统超声各项指标异常表现，利用羊膜腔穿刺术抽取孕妇羊水，进行染色体核型分析及CNV-seq检测，同时将孕妇羊水及孕妇血清进行巨细胞病毒DNA检测，期间定期进行超声监测胎儿生长发育情况。

结果：羊水染色体核型结果为46,XN，CNV结果未见异常，排除明显染色体异常，孕妇羊水巨细胞病毒DNA检测结果为2.2710^7 IU/ml，血清巨细胞病毒DNA检测结果为阴性，诊断胎儿宫内感染巨细胞病毒，胎儿结构异常的病因明确。

结论：继发性巨细胞病毒感染可造成较为严重的胎儿结构异常，孕期对于巨细胞病毒继发感染的不良预后不容忽视，孕前及孕中完善的巨细胞病毒监测及超声监测有助于妊娠结局的选择。

关键字 继发性宫内感染 巨细胞病毒 妊娠结局

A case study of Treacher Collins syndrome caused by a new frameshift variant in the TCOF1 gene

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【Abstract】Objective: A case report of Treacher Collins syndrome caused by a new frameshift variant in the TCOF1 gene. Materials and Methods: Firstly, the Agilent SureSelect method exome capture (Exome V6) and the Illumina sequencing platform were used for high-throughput sequencing, and the sequencing data were matched and analyzed by NextGENe software, and the variants were screened and interpreted by the Ingenuity online software system, and the candidate variants were verified by Sanger sequencing. Results: Whole exome sequencing (WES) showed that the sample variant c.1602del: p. Ser535GlnfsTer61 was not included in HGMD and gnomAD databases, and was a newly discovered variant. According to the ACMG variant classification criteria, it is classified as a "pathogenic" variant. The pregnant woman has abnormal facial development, the eyes of the pregnant woman resemble her father's with downslanting palpebral fissures, and her vision has been reduced since childhood, and her hearing is reduced. Conclusions: Treacher Collins Syndrome (TCS; OMIM 154500) is a rare autosomal dominant disease occurring with a frequency of approximately 1 in 50,000 live births. The clinical features are bilaterally symmetrical, including abnormalities of the external ears (78%), atresia of external auditory canals, and malformation of the middle ear ossicles, which result in bilateral conductive hearing loss; downward slope of the palpebral fissures (antimongoloid), coloboma of the lower eyelid and a paucity of lid lashes; micrognathia microtia, macrostomia, cleft palate and hypoplastic zygomatic arches. Between 78% and 93% of TCS is caused by the TCOF1 gene. The TCOF1 gene is located at chromosome 5q32-33 (OMIM 606,847) with product of treacle, a nucleolar protein involved in rRNA transcription and in pre-rRNA post-transcriptional modifications. The mutations in the TCOF1 gene can reduce the amount of treacle, and then effect differentiation of the first and second pharyngeal arches, which may be as a molecular mechanism of TCS. This study broadens the pathogenic spectrum of TCOF1 gene in TCS and may expand the clinical scope of TCOF1 -related diseases.

Key Words TCOF1, Treacher Collins Syndrome, Genetic disorders, Frameshift variant

单绒毛膜双羊膜囊双胎性别不一致的产前诊断及遗传学分析

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目的：探讨单绒毛膜双羊膜囊（monochorionic-diamniotic, MCDA）双胎性别不一致的产前诊断方法及形成机制。

方法：对1例超声发现其中一胎为女性表型、另一胎为男性表型的MCDA双胎行双羊膜腔穿刺术，取双胎儿羊水分别行核型分析、单核苷酸多态性微阵列（single nucleotide polymorphism array，SNP array）、FISH及短串联重复序列（short tandem repeats，STR）标记位点检测。

结果：羊水染色体核型分析提示：女性胎儿45,X0[75]/46,XY[12]；男性胎儿46,XY；SNP array提示：女性胎儿“可疑45,X/46,XY嵌合体”，45,X约占40%；男性胎儿未见异常；FISH提示：女性胎儿一个X信号占55%，XY信号占45%；男性胎儿未见异常；STR检测提示：可能为单合子双胎。

结论：MCDA双胎性别不一致的原因为遗传物质不一致：双胎之一为性染色体的嵌合。遗传物质不一致的原因可能为合子后有丝分裂后期延滞、 染色体不分离和三体自救等。双羊膜腔穿刺羊水行遗传学检测及合子性质鉴定是产前诊断MCDA双胎遗传物质不一致的方法。在嵌合体的产前诊断中，应尽可能采用有助于诊断的多种方法综合评定出最接近实际情况的结论，为孕妇的最终选择提供最科学的依据。

关键字 单绒毛膜双羊膜囊双胎，遗传物质不一致，嵌合体

·遗传病的临床研究、循证医学方面研究及其新进展·

假肥大型肌营养不良症新生儿基因筛查

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目的：分析假肥大型肌营养不良症新生儿基因筛查结果，了解本地区发病情况和热点变异。

方法：选择2022年3月18日至2023年10月31日于南京医科大学附属妇产医院出生的22 813例新生儿，应用芯片捕获二代测序技术检测Dystrophin基因（DMD基因），并对结果进行生物信息学分析，检出致病变异采用多重连接依赖性探针扩增技术及Sanger测序进行验证，男性疑似患者同时检测血清肌酸激酶水平。

结果：芯片捕获二代测序技术在22 813例新生儿中检出肌营养不良症女性携带者14例（0.0013%，14/10748），其中，9例完成家系验证，1例为新发变异，5例遗传自母亲，3例遗传自父亲；检出男性疑似患者9例（0.00075%，9/12065），其中8例完成家系验证，3例为新发变异，5例遗传自母亲。检出的DMD基因所有变异类型中，外显子缺失最常见，占52.17%（12/23）。

结论：基于芯片捕获二代测序技术结合生物信息学分析的新生儿基因筛查方案有助于早期发现肌营养不良症患者及携带者。初步统计本地区DMD/BMD的发病率约为1/1341男婴，热点变异为49～51号外显子缺失。

关键字 假肥大型肌营养不良症；新生儿基因筛查；Dystrophin基因；携带者

跨性状关联分析揭示代谢紊乱与神经退行性疾病的共同遗传结构与潜在因果关系

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目的：代谢障碍和神经退行性疾病的共同发生表明它们之间可能存在潜在关联。然而，目前对于这两类疾病的表型关联的共同遗传结构及其因果关系知之甚少。本研究旨在全面描述代谢障碍与神经退行性疾病之间的表型和遗传关系。

方法：我们首先研究了7种代谢疾病（肥胖、2型糖尿病、非酒精性脂肪肝、高血压、高脂血症、甲状腺功能减退和痛风），以及4种神经退行性疾病（阿兹海默症、肌萎缩性侧索硬化症、多发性硬化症和帕金森）之间的遗传关联。随后，我们采用多效性分析（PLACO）检验遗传变异的多效性效应，并通过功能映射和注释（FUMA）对显著多效性位点进行了进一步功能注释，随后对多效性位点进行组织特异性表达和通路富集分析。最后，我们应用双向孟德尔随机化来探索代谢障碍与神经退行性疾病表型之间的潜在因果关系。

结果：我们发现在28对性状中有9对表现出遗传相关性。复合零假设下的多效性分析在28对性状中

鉴定出25931个显著的潜在多效性snp，检测到246个多效性位点和55个共定位位点。这些位点参与神经递质运输和免疫反应机制，尤其是rs41286192 (SLC18B1)。组织特异性分析突出了胰腺、左心室、大脑杏仁核和肝脏在疾病进程中的关键作用。药物靶点分析鉴定了与现有治疗药物相关的74个独特基因。基因集富集分析显示，189条通路在胆固醇和脂质代谢、细胞分化和激活及免疫反应方面显著富集。孟德尔随机化结果进一步说明了特定性状对之间的潜在因果关联。值得注意的是，rs1233387 (GABBR1/OR2H2) 和rs12446781 (PLCG2) 在两对不同性状中出现。

结论：本研究创新性地揭示了代谢障碍与神经退行性疾病之间的共同遗传基础、多效性位点和潜在因果关系。这些发现表明这两类疾病表型间存在潜在的生物学联系，对两类疾病的预防和治疗具有重要意义。

关键字 代谢障碍，神经退行性疾病，跨性状遗传学，多效性位点，孟德尔随机化

Pregnancy and perinatal outcomes in pregnancies following frozen embryo transfer (FET) after transcervical resection of adhesions (TCRA): A retrospective cohort study with propensity score matching analysis

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Objective: To compare the pregnancy and perinatal outcomes of frozen-thawed embryo transfer (FET) in patients following transcervical resection of adhesions (TCRA) versus patients with normal uterine morphology, and to investigate the factors influencing pregnancy outcomes in patients undergoing FET after TCRA.

Methods: We retrospectively analyzed FET cycles from September 2014 to September 2023, comparing patients with normal uterine morphology to those with intrauterine adhesions (IUAs) treated with TCRA. Propensity score matching (PSM) adjusted for confounding factors. LASSO regression and multivariate logistic regression identified predictors of outcomes, which were visually represented in nomograms. Model performance was assessed using calibration curves, ROC curves, and DCA, with Bootstrap method for internal validation.

Results: Post-PSM analysis showed higher live birth rates in patients with normal uterine morphology after clinical pregnancy (75.1% vs. 61.7%, $P < 0.001$). No significant differences were noted in clinical pregnancy rates and perinatal outcomes between the groups. Factors influencing clinical pregnancy in FET after TCRA included basal progesterone levels, endometrial thickness, parity, infertility cause, embryo stage at transfer, number and quality of embryos transferred, IUAs severity, and TCRA surgical procedures. BMI, basal LH levels, and day 14 HCG levels post-embryo transfer were determinants of live birth outcome.

Conclusions: FET cycles following TCRA showed a lower rate of successful live births, but TCRA did not increase adverse perinatal outcome risks. Our study introduces an innovative predictive model for clinical pregnancy and live birth outcomes in patients undergoing FET following TCRA, addressing a significant void in existing research.

Key Words transcervical resection of adhesion, frozen-thawed embryo transfer, prediction model, propensity score matching, pregnancy outcome, perinatal outcome.

睾酮特征与妊娠期高血压疾病的因果关联

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目的：研究表明，睾酮特征与妊娠期高血压疾病（HDP）之间存在相关性，但因果关系尚不清楚。本研究的目的是评估总睾酮（TT）、生物可利用睾酮（BT）、性激素结合球蛋白（SHBG）和HDP之间的因果关系。

方法：对于孟德尔随机化（MR）分析，反方差加权（IVW）被设置为主要方法，并辅以一系列敏感性分析。进行多变量MR和共定位分析，以评估潜在的中介效应并加强因果关系。在观察性研究中，使用多变量Cox回归分析血液样本中的睾酮相关特征与HDP关联。

结果：在MR分析中，BT与HDP（OR=1.237，95%CI=1.081–1.416，P=0.002）和先兆子痫（PE，OR=1.178，95%CI=1.049–1324，P=0.006）风险呈正相关；体重指数（BMI）调整后的SHBG（OR=0.646，95%CI=0.548–0.762，P=2.06E–7）与HDP风险呈负相关；粗品（OR=0.753，95%CI=0.646–0.878，P=2.90E–4）和BMI调整后的SHBG（OR=0.702，95%CI=0.594–0.829，P=3.14E–5）与PE风险呈负相关。共定位分析为SHBG和PE之间的共同因果变异基因座提供了证据。ESR1激动剂与HDP风险呈负相关（OR=0.843，95%CI=0.723–0.983，P=0.030）。在观察性研究中，血清TT（OR=1.008，95%CI=1.003–1.013，P=0.002）、BT（OR=1.413，95%CI=1.215–1.643，P=7E–6）水平显著正相关，而SHBG（OR=0.994，95%CI=0.990–997，P=1.49E–4）与HDP风险呈负相关，这些关联在出生体重，性别，孕周调整后的回归模型中仍然显著。

讨论：我们的研究为TT特征和HDP之间的因果关系提供了新的证据，这需要进一步的临床和机制研究。

关键字 妊娠期高血压，睾酮，性激素结合蛋白，子痫前期

Effects of SARS−CoV−2 infection on oocyte and embryo quality

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Purpose：To investigate the effects of previous SARS–CoV–2 infection on oocyte and embryo quality in infertile patients undergoing in vitro fertilization/intracytoplasmic sperm injection（IVF/ICSI）treatment.

Methods：A retrospective analysis of 1267 female infertility patients undergoing IVF/ICSI was conducted and divided into COVID–19 group and control group. The COVID–19 group was further divided into several subgroups. The general condition and quality of oocytes and embryos were compared among all groups. The correlation between the infection of the SARS–CoV–2 and the quality of oocytes and embryos was analyzed by linear regression.

Results：During the fresh cycle, the number of retrieved oocytes, the number of 2PN and the number of

transferable embryos in the COVID-19 group were significantly reduced compared with the control group; The number of retrieved oocytes and the number of 2PN were significantly reduced in the female infection group only; the number of retrieved oocytes, the number of 2PN and the number of transferable embryos in the men and women both infected with COVID-19 group were significantly reduced; After 2 to 3 months of infection with COVID-19, the number of retrieved oocytes and the number of 2PN in the COVID-19 group decreased significantly.

Conclusions: Infection with COVID-19 may have a long-term negative impact on the number of retrieved oocytes, 2PN, and transferable embryos in infertile women undergoing IVF/ICSI treatment. Therefore, the majority of infertile people who are infected with COVID-19 may need IVF/ICSI treatment as soon as possible after recovery.

Key Words SARS-CoV-2, Infertility, Oocyte, Embryo

拮抗剂方案扳机次日血清β-hCG水平对新鲜胚胎移植结局的影响

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目的：探究拮抗剂方案扳机次日血清β-人绒毛膜促性腺激素（β-human chorionic gonadotropin，β-hCG）水平对体外受精/卵胞质内单精子注射（in vitro fertilization/intracytoplasmic sperm injection，IVF/ICSI）鲜胚移植周期妊娠结局的预测价值。

方法：回顾性分析2017年1月-2024年1月于南京市妇幼保健院生殖医学中心行拮抗剂方案促排患者的临床资料，所有病例均采用双扳机诱导排卵，按照扳机次日血清β-hCG测定值分为5组，A组：β-hCG≤50 U/L，n=42；B组：50 U/L＜β-hCG≤100 U/L，n=282；C组：100 U/L＜β-hCG≤150 U/L，n=250；D组：150 U/L＜β-hCG≤200 U/L，n=92；E组：β-hCG＞200 U/L，n=51。比较各组的促排卵实验室结局及鲜胚妊娠结局。

结果：5组间BMI、基础FSH、Gn天数及用量、hCG日雌孕激素水平及高评分囊胚数的差异均有统计学意义（均$p<0.05$），其中随着BMI升高，β-hCG数值逐渐下降（A组：27.5 (24.1，30.2)，B组：23.3 (21.4，25.4)，C组：21.3 (19.6，23.3)，D组：20.9 (19.5，22.9)，E组：19.8 (18.7，21.3)，$p<0.05$）。各组可利用胚胎数、高评分囊胚率、临床妊娠率、流产率及活产率均无统计学差异（均$p>0.05$）。

结论：在拮抗剂方案新鲜移植胚胎周期中，扳机次日血清β-hCG水平随着患者BMI升高逐渐降低，但其并不能预测IVF/ICSI治疗周期的妊娠结局。

关键字 促性腺激素释放激素；排卵诱导；β-hCG；胚胎移植；妊娠结局

Evaluating Visceral Fat's Impact on Frozen Embryo Transfer Outcomes via Bioelectrical Impedance Analysis

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Objective: The increasing prevalence of obesity underscores the critical need to explore its impact on the outcomes of assisted reproductive technology (ART). This study aims to assess the relationship between visceral fat area (VFA), as measured by bioelectrical impedance analysis (BIA), and pregnancy outcomes, particularly within the context of frozen embryo transfer (FET).

Methods: This was a retrospective clinical study 1510 patients who were undergoing FET cycles between April 2022 and April 2023. VFA was assessed using BIA, with patients categorized as the low VFA group and the high VFA group based on a VFA threshold of 65 cm^2. We compared pregnancy outcomes between two groups undergoing FET cycles, employing multivariate logistic regression analysis and restricted cubic splines (RCS) models to adjust for age, additional body composition metrics, and other confounding variables, thereby examining the relationship between VFA and pregnancy outcomes.

Results: The analysis revealed significant differences in baseline characteristics and outcomes between the two groups. The high VFA group was characterized by older age (33.28 ± 5.00 vs. 31.31 ± 3.96 years, P<0.001), elevated body composition metrics (P<0.001), a higher proportion of PCOS patients (8.85% vs. 7.37%, P=0.025), and lower basal E2 levels(40.11 ± 16.74 vs. 42.98 ± 18.39pg/mL, P=0.011); outcomes such as biochemical pregnancy rate (64.73% vs. 76.63%, P<0.001), implantation rate (39.55% vs. 47.12%, P<0.001), clinical pregnancy rate (CPR) (51.96% vs. 60.36%, P=0.001), and live birth rate (LBR) (43.11% vs. 50.76%, P=0.003) were significantly reduced, while the likelihood of delivering large for gestational age (LGA) infants increased(38.66% vs. 27.34%, P=0.005). Multivariate logistic regression indicated a significant negative correlation between VFA and both CPR (OR: 0.641, 95% CI: 0.450–0.912, P=0.013) and LBR (OR: 0.693, 95% CI: 0.489–0.982, P=0.039). The RCS model demonstrated that VFA is nonlinearly correlated with CPR (P–nonlinear=0.048, P–value =0.015) and LBR (P–nonlinear=0.030, P–value =0.007), identifying 65cm^2 as a critical inflection point where VFA ⩾65 cm^2 is significantly associated with decreased probabilities of CPR and LBR.

Conclusions: High VFA is associated with poorer FET pregnancy outcomes in infertile female patients, with both CPR and LBR decreasing as VFA increases. Clinicians can utilize VFA assessments as a valuable reference for optimizing reproductive success through targeted fat management interventions, especially for patients with VFA exceeding 65 cm^2.

Key Words Visceral fat area (VFA), bioelectrical impedance analysis (BIA), Frozen embryo transfer (FET), Pregnancy outcome

Antibiotics improve reproductive outcomes after frozen-thaw embryo transfer for chronic endometritis treatment, especially in those with repeated implantation failure

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Purpose:To investigate the impact of antibiotic treatment for chronic endometritis (CE) on the pregnancy outcome of frozen-thawed embryo transfer (FET) cycles and the relevant clinical risk factors associated with CE.

Methods:A retrospective cohort analysis was conducted on 1352 patients who underwent hysteroscopy and diagnostic curettage at Nanjing Maternal and Child Health Hospital from July 2020 to December 2021. All patients underwent CD138 immunohistochemical (IHC) testing to diagnose CE, and a subset of them underwent FET after hysteroscopy. Patient histories were collected, and reproductive prognosis was followed up.

Results:Out of 1088 patients, 443 (40.7%) were diagnosed with CE. Univariate and multivariate binary logistic regression analyses revealed that parity ⩾ 2, a history of ectopic pregnancy, moderate-to-severe dysmenorrhea, hydrosalpinx, endometrial polyps, and a history of ⩾2 uterine operations were significantly associated with an elevated risk of CE ($P < 0.05$). Analysis of the effect of CE on pregnancy outcomes in FET cycles after antibiotic treatment indicated that treated CE patients exhibited a significantly lower miscarriage rate (8.7%) and early miscarriage rate (2.9%) than untreated non-CE patients (20.2%, 16.8%). Moreover, the singleton live birth rate (45.5%) was significantly higher in treated CE patients than in untreated non-CE patients (32.7%). Survival analysis revealed a statistically significant difference in the first clinical pregnancy time between treated CE and untreated non-CE patients after hysteroscopy ($P = 0.0019$). Stratified analysis based on the presence of recurrent implantation failure (RIF) demonstrated that in the RIF group, treated CE patients were more likely to achieve clinical pregnancy than untreated non-CE patients ($P = 0.0021$). Among hysteroscopy-positive patients, no significant difference was noted in pregnancy outcomes between the treatment and control groups ($P > 0.05$).

Conclusion:Infertile patients with a history of parity ⩾ 2, hydrosalpinx, a history of ectopic pregnancy, moderate-to-severe dysmenorrhea, endometrial polyps, and a history of ⩾2 uterine operations are at an increased risk of CE; these patients should be recommended to undergo hysteroscopy combined with CD138 examination before embryo transfer. Antibiotic treatment can improve the reproductive outcomes of FET in patients with CE, especially those with RIF. However, antibiotic treatment is not deemed necessary in hysteroscopy-positive patients.

Key Words chronic endometritis; CD138; repeated implantation failure; pregnancy outcomes; time to pregnancy

女性冻卵年龄对冷冻卵子胚胎发育及临床妊娠结局的影响

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目的：观察女性不同冻卵年龄对冷冻卵子胚胎发育及妊娠结局的影响。

方法：回顾性分析2013年1月至2024年5月于南京医科大学附属妇产医院生殖中心进行玻璃化冷冻卵母细胞解冻行卵胞质内单精子注射（intracytoplasmic sperm injection，ICSI）助孕周期患者的临床资料，包括＜35周岁组67个解冻周期（进行2次卵子解冻患者1名，3次卵子解冻患者1名）共678枚解冻卵子，累积移植63周期（49个鲜胚移植周期、14个冻胚移植周期），其中8例进行2次移植、12个解冻周期未移植。 ≥35周岁组21个解冻周期、204枚解冻卵子，累积移植17周期（13个鲜胚、4个冻胚移植周期），其中2例进行2次移植、6个解冻周期未移植。回顾性分析两组患者的一般临床资料、解冻后卵子存活情况、胚胎发育情况、临床妊娠情况以及围产期和新生儿结局。

结果：与＜35周岁组相比较， ≥35周岁组在BMI、HCG日LH水平上高于35岁以下组（P＜0.05）；解冻后行ICSI的两组在卵子存活率、正常受精率、卵子退化率、双原核（pronucleus，PN）卵裂率、可利用胚胎率、囊胚形成率上均无统计学差异（P＞0.05）；与＜35周岁组相比较， ≥35周岁组在鲜胚移植活产率、累积活产率上显著下降（P＜0.05）， ≥35周岁组在鲜胚移植种植率、鲜胚移植临床妊娠率、累积胚胎种植率、累积临床妊娠率上均有下降趋势（P＞0.05）；两组在孕龄、新生儿性别、新生儿体重、低出生体重率、巨大儿发生率上均无统计学差异（P＞0.05）。

结论：冻卵年龄的增加可能对冷冻卵子的解冻后的卵子存活率及发育潜能没有显著影响，但是会降低胚胎移植后的活产率。

关键字 卵子 冻卵年龄 玻璃化冷冻 临床妊娠率 活产率

体外成熟过程中补充NMN对多囊卵巢综合征小鼠卵母细胞质量的影响

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目的：阐明β-烟酰胺单核苷酸（NMN，de）对多囊卵巢综合征（PCOS）小鼠卵母细胞体外成熟及早期胚胎发育的提升作用，探究NMN改善PCOS小鼠卵母细胞和早期胚胎发育潜力的分子机制。

方法：通过对3周龄小鼠喂养高脂饲料以及连续21天皮下注射雄激素（10mg/kg DHEA），构建PCOS小鼠模型。血清激素水平检测和卵巢HE染色验证PCOS模型构建成功后，腹腔注射孕马血清促性腺激素（PMSG），48小时后取出卵巢，挑选GV期卵母细胞，将卵母细胞放入添加有不同浓度NMN（0μM、0.1μM、1μM、10μM、100μM）的体外成熟（In Vitro Maturation，IVM)培养液中进行培养,分别在3小时、15小时统计生发泡破裂（GVBD）率和第二次减数分裂中期（MII）卵母细胞形成率。收集对照组、模型组和恢复组的MII时期卵母细胞进行单细胞转录组测序分析，通过富集被恢复的基因来探

究NMN改善未成熟卵母细胞成熟率的原因。收集GV和MII时期卵母细胞进行Western-Blot检测，分析SIRT1蛋白表达量的变化。收集MII时期的卵母细胞，通过免疫荧光的方法，观察各组卵母细胞的活性氧（ROS）、谷胱甘肽（GSH）和线粒体膜电位水平；此外，检测纺锤体形态，利用染色体铺片实验观测染色体排布是否异常。

结果：1.通过卵巢组织石蜡切片观察到PCOS小鼠卵巢呈多囊样改变；同时，连续两周的动情周期监测实验发现PCOS实验组小鼠的动情周期紊乱。2.在对PCOS小鼠的卵母细胞进行体外培养过程中，我们发现PCOS卵母细胞的GVBD率和MII率均低于对照组和正常育龄组，同时对照组和育龄组卵母细胞的GVBD率和MII率无明显差异（P>0.05）。3.在本研究中，我们发现浓度梯度验证实验中添加1μM的NMN提高PCOS卵母细胞的GVBD率和MII率最显著，由此确定1μM NMN是后续实验中验证NMN作用的最适浓度。4.RNA-seq结果显示，共有138个下调基因和76个上调基因被恢复，通过KEGG和GO富集分析发现这些被恢复的基因与凋亡过程、染色质组织、DNA损伤反应、对氧化应激的反应、线粒体吞噬、卵母细胞减数分裂、钙信号通路相关，同时SIRT1富集在了上述大多数通路当中。5. Western-Blot实验结果显示PCOS模型组GV期和MII时期卵母细胞SIRT1蛋白表达量均低于对照组，并且在添加1μM NMN后SIRT1蛋白表达量得到一定水平恢复。6.PCOS实验组MII时期卵母细胞的ROS水平升高，同时GSH含量下降；此外，线粒体膜电位在PCOS组中显著下降；当添加了NMN后，PCOS卵母细胞的氧化应激和线粒体功能都得到相应的改善。7.PCOS小鼠的MII卵母细胞纺锤体异常率显著提升，NMN能够降低PCOS卵母细胞中的纺锤体异常率。

结论：上述实验结果提示，PCOS小鼠卵母细胞的减数分裂成熟进程受阻，卵母细胞中存在较高的氧化应激水平，线粒体功能受损，且纺锤体异常率增加。在体外培养过程中添加一定浓度的NMN可以部分缓解PCOS卵母细胞的氧化应激状态，改善线粒体功能，降低纺锤体异常率，进而提高PCOS卵母细胞的成熟率。为临床上进一步探索PCOS患者卵母细胞质量提升的方式提供了新的视角。综上所述，我们的实验首次在母卵细胞体外成熟培养体系中添加NMN，并且提高了未成熟卵母细胞的发育潜力。

关键字 多囊卵巢综合征，卵母细胞体外成熟，β-烟酰胺单核苷酸

A redeemed strategy for molecular autopsy in unexplained infant deaths

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The causes of child death are very complex and the diagnosis remains a signiffcant challenge. Unexplained deaths have become a leading cause, greatly blocking the scientiffc guidance of re-birth. Autopsy is considered an accurate method for investigating unexplained deaths. Recently, molecular autopsy have been reported to has great value in revealing the cause of unexpected death, including autopsy-negative cases. It could explain approximately 12.6%~44% of previously unexplained deaths with DNA sequencing. However, opportunities for molecular autopsy are often lost due to the lack of timely sample collection. Newborn screening (NBS), an important public health program, is widely used throughout the world and almost cover all of the newborns. The stored samples of neonatal dried blood spots (DBS) from NBS are considered as a valuable resource of medical research. Here, we attempt to remedial molecular autopsy for neonatal death using clinical exome sequencing (CES) based on the stored DBS.

Methods：From August 2019 to August 2023, a total of 450 children deaths were recorded in the surveillance system, which collected the occurring and distribution of under-5 child deaths. There are 35 categories of causes of death in the system. 36 cases of unexplained deaths were included as the subjects, including 8 cases with unknown diagnosis and 28 cases with listed causes that still remained in doubt during the basic death survey. Their death time were from 3 days to 48 months. In which, 6 (16.67%) were newborn (0~28 days), 14 (38.89%) were infants (1~11 months) and 16 (44.44%) were child (12-59 months). We collected the stored DBS from their previous NBS.

Results：32 cases successfully received the effective results, and the success rate of CES based on stored DBS were 88.9%. But 4 cases failed due to DNA quality did not meet the standard after library construction. CES identified 6 of 32 infants with disease-related genetic variation, including 4 cases of single nucleotide variation (SNV) and 2 of copy number variation (CNV). The abnormal detection rate was 18.8%. One child A child with an unexplained death was diagnosed as LIG4 . A child who succumbed to unexplained persistent seizures was discovered to carry an autosomal dominant LP heterozygous variant in the CPA6 gene, which is linked to familial temporal lobe epilepsy. A complex pathogenic heterozygote of the GLB1 gene associated with GM1 gangliolipidosis/ beta-galactosidase deficiency was detected in a child presenting with global developmental delay. Two cases were reported pathogenic copy number variation. These segments include a certain number of coding genes. After further data analysis, pathogenic genes related to the death phenotype were identified.

Discussion：This study successfully and clearly explaining the cause of 18.8% of unexplained child deaths using clinical exome sequencing based on the stored neonatal dried blood spots from newborn screening. It can help these families conduct salvage molecular autopsies when they have no way to collect samples. At the same time, the results also indicated 28.1% of secondary findings. With the accumulation of future genetic databases, they may also help explain the true causes of the unexplained child deaths.

Key Words molecular autopsy ， exome sequencing，Newborn screening，dried blood spots

一例罕见生殖腺嵌合MENKES病的产前诊断及MENKES病基因突变谱分析

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目的：通过全外显子测序揭示1例罕见MENKES病患者的遗传病因，同时汇总分析目前已报道的所有MENKES病患者的基因突变信息及表型特征，为MENKES病遗传咨询及早诊断提供依据。

方法: 对该核心家系先证者进行全外显子组测序(WES)后，对先证者及其他家系成员进行Sanger测序验证。孕20周时抽取羊水，进行产前诊断。进一步提取引产胎儿皮肤组织进行体外功能研究该突变对基因或基因产物的影响。总结已发表的MENKES病相关文章，并对文献进行系统的meta分析。

结果：全外显子测序结果显示先证者ATP7A基因存在剪切位点变异c.2782-1G>T，Sanger测序显示其母亲该突变位点呈低比例嵌合，其他家系成员均未检测到该突变；对其母亲该位点进行超高深度测序发现嵌合比例为13.2%；产前诊断结果显示胎儿与先证者基因型一致，提示该母亲存在生殖腺嵌合。引产胎儿组织体外功能实验显示该突变可造成mRNA的异常剪切及蛋白表达异常，根据ACMG评分标准该突变位点可升级为“致病突变”。 ATP7A突变谱显示错义突变是所有突变中最常见，大约50%位于外显子

4、9、10和15，但不同患者的突变差异很大。大约23%的患者没有从母亲那里遗传突变，而是有新生突变。

结论：基因分析是检测ATP7A突变的有效方法，ATP7A突变谱的分析有助于设计新的治疗策略。

关键字 MENKES病；ATP7A；突变谱

连云港人群中22个常染色体STR位点基于序列的等位基因变异和频率

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建立为连云港人口基于序列的数据库可能有助于将NGS适用性扩展到个案工作或亲子鉴定，并评估NGS-STR图谱的证据强度。使用PowerSeq46GYSystemPrototype对来自120个不相关的连云港人的基因组DNA 提取物进行了扩增。 靶向扩增子在VerogenMiSeqFGx测序系统上进行 DNA 文库制备和测序。原始FASTQ 数据文件由STRait Razor v3处理。与仅按长度识别的236个等位基因相比，测序的连云港数据集产生了多个不同的等位基因序列。对于一致性检查，将来自完整序列的基于长度的等位基因调用与使用毛细管电泳方法进行基因分型的那些进行比较。与基于序列的数据评估法DNA证据相关的群体遗传参数进行了评估，并与基于长度的信息生成的参数进行了比较。使用基于序列的数据，对从江苏省抽样1100名个体进行了分子方差分析 (AMOVA)、遗传距离和种群遗传结构评估。以人口树、多维尺度散点图和条形图的形式制成表格并可视化。表征从连云港收集的人口数据集中22个常染色体短串联重复序列 (aSTR) 基因座的基于序列的等位基因变异的研究。有助于个案工作或亲子鉴定。某些位点的新序列变异可以进一步帮助描述来自世界各地不同人群的 STR 标记的序列多样性。

关键字 遗传学；等位基因；序列分析

A pathogenic germline BRCA1 mutation identified in a patient with non-Hodgkin lymphoma and rectum adenocarcinoma: "Non-classical" hereditary cancer?

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Introduction: Tumor suppressor gene BRCA1, known for its vital roles in regulating DNA homologous recombination repair, is the causative gene of hereditary breast and ovarian cancer (HBOC). BRCA1 mutation carriers also demonstrate high susceptibility to intestinal, prostatic and pancreatic cancers. As the main subtype of lymphoma, non-Hodgkin lymphoma (NHL) is malignant disorders arising from immune cells and displays

predominantly as lymphadenopathy or solid tumors, which is rarely considered hereditary. However, the risk of NHL among patients with BRCA1 mutation is rarely reported.

Methods: Exome sequencing was performed to investigate the genotype of an individual presenting with NHL and rectum adenocarcinoma. Bioinformatics tools were employed to analyze the candidate variants.

Results: A 76-year-old woman developed NHL and rectum adenocarcinoma with a BRCA1 gene mutation. Considering the potential hereditary factors in developing colorectal cancer, we investigated her family history and found her sister died with ovarian cancer. Her genetic testing identified a pathogenic germline mutation in BRCA1 (c.1115G>A). We also did genetic test for her daughter and found the same BRCA1 mutation.

Conclusions: Although strong evidence between BRCA1 mutation and HBOC occurrence exists, the patient harboring pathogenic BRCA1 mutation did not suffer from HBOC but NHL and rectum adenocarcinoma which required further investigations and modifications of current screening strategies for HBOC. Meanwhile, great attention should also be paid to screen people with BRCA1 mutation as well as screen tumors among mutated populations.

Key Words BRCA1; Hereditary breast and ovarian cancer; Non-Hodgkin lymphoma; Rectum adenocarcinoma; Gene mutation

Prevalence and influencing factors of depressive symptoms in high-risk pregnant women before prenatal diagnosis

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Background: Prenatal depression exerts detrimental effects on pregnant women, fetuses, and families alike. In comparison to their counterparts with uncomplicated pregnancies, high-risk pregnant women may experience more severe psychological issues. Nevertheless, there remains a dearth of information regarding depression in high-risk pregnant women, particularly prior to prenatal diagnosis. Consequently, the objective of this study is to investigate the prevalence of depressive symptoms among high-risk pregnant women before prenatal diagnosis and analyze its influencing factors from a multifaceted perspective.

Methods: A cross-sectional study was performed among high-risk pregnant women awaiting amniocentesis in the Eugenic Genetics Outpatient of the Obstetrics Department of Lianyungang Maternal and Child Health Hospital in Jiangsu Province, Eastern China. The Edinburgh Postnatal Depression Scale (EPDS) was used to assess depressive symptoms in high-risk pregnant women. Multivariate regression model was constructed to identify the independent influencing factors of depressive symptoms.

Results: A total of 509 high-risk pregnant women participated in this study. Among them, pregnant women with ultrasound structural abnormalities had the highest prevalence of depressive symptoms (31.4%). The overall prevalence of depressive symptoms was 21.0%. Multivariate regression analysis revealed that high-risk pregnant women who resided in rural areas (OR: 1.868, 95% CI: 1.014-3.441), had poor sleep quality (OR: 1.838, 95% CI: 1.025-3.296) and had high pregnancy stress (OR: 3.763, 95% CI: 2.079-6.813) increased the risk of depressive symptoms. However, high-risk pregnant women who were not afraid or a little afraid of amniocentesis (OR: 0.460,

95% CI: 0.251–0.844), had high self–esteem (OR: 0.848, 95% CI: 0.788–0.912), and had good quality of partner relationship (OR: 0.891, 95% CI: 0.814–0.976) reduced the risk of depressive symptoms.

Conclusions: The prevalence of depressive symptoms was higher among high–risk pregnant women prior to prenatal diagnosis. It is imperative to alleviate the level of anxiety related to amniocentesis, enhance sleep quality, mitigate pregnancy–related stress, and acknowledge the role of the partner.

Key Words High–risk pregnant women, Depressive symptoms, Prenatal diagnosis, Influencing factors

piRNA–PIWI轴在人类早期胚胎停育中的鉴定及机制研究

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目的：体外受精和胚胎移植技术（IVF–ET）是治疗不孕症的有效手段，但仍有约50%患者助孕失败，卵母细胞质量和早期胚胎发育停滞是重要原因。piRNA–PIWI通路蛋白在早期胚胎发育中维持基因组稳定性有重要作用，本研究拟通过临床筛选早期胚胎发育停滞患者废弃卵子和卵泡液，鉴定piRNA–PIWI通路关键蛋白并研究其具体调控机制。

方法：在本中心进入试管婴儿IVF/ICSI新鲜取卵周期患者，筛选早期胚胎发育阻滞特别是二细胞阶段阻滞患者废弃卵子和卵泡液作为研究对象，通过全外显子组测序、显微注射技术、蛋白质免疫共沉淀、piRNA长度分析等方法，分析piRNA通路蛋白在发育阻滞患者卵子中的表达情况，探讨其参与卵母细胞成熟老化和早期胚胎发育的作用机理。

结果：我们在早期胚胎发育阻滞女性不孕患者中发现，Pnldc1(PARN like ribonuclease domain containing exonuclease 1)作为piRNA成熟过程中一个重要的剪切和修饰酶，存在杂合错义突变（c.A143→G; c.G862→ A）。前期动物模型结果提示，Pnldc1敲除金黄仓鼠雌性不孕，早期胚胎发育阻滞在二细胞阶段，piRNA通路的生成异常。

讨论：近期已有研究报道Pnldc1在无精症患者中存在基因突变，然而piRNA–PIWI通路关键蛋白在雌性生殖系统特别是卵母细胞发育方面的相关研究甚少。研究报道，小鼠体内敲除piRNA–PIWI通路关键蛋白仍然可育，但金黄仓鼠敲除动物模型雌性不孕，胚胎发育停滞在二细胞阶段，与临床表型较为一致。由此可见，金黄仓鼠是研究piRNA–PIWI通路蛋白功能的较为理想模型。本研究将通过金黄仓鼠敲除模型，研究piRNA–PIWI通路蛋白在胚胎发育特别是卵母细胞成熟中的具体作用机制。

关键字 胚胎停育；piRNA；PIWI

Tex10基因突变导致一种新的神经发育障碍综合征

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目的：神经发育障碍（NDDs）是一组严重的脑发育及功能异常谱系疾病。NDDs是由遗传和环境因

素的复杂相互作用引起的。因此，识别致病基因及突变事件对NDDs的诊断非常重要。本研究旨在揭示NDDs新候选基因Tex10在脑发育过程中发挥的作用。

方法：①本研究收集了11例携带Tex10突变的患儿信息，并进行生物信息学分析。构建突变型质粒，检测突变对蛋白表达和定位的影响；②构建斑马鱼基因敲降模型，观察其表型；③构建患儿来源iPSC-类脑模型，观察表型差异。

结果：①11例Tex10突变携带者家系分析均符合AD遗传发病机制；均为新发突变，9例为错义突变，1例为同义突变，1例为截断突变；其中截断突变会导致蛋白表达和定位异常，携带该突变的患儿临床表型也最为严重。②斑马鱼模型发现敲降该基因后会导致胚胎的一系列发育异常，包括发育迟缓，眼节前发育不全，心包水肿等。③患儿来源iPSC与野生型相比，在生命基础过程及神经相关通路有明显差异。

讨论：通过队列研究筛选新的候选基因，并利用模式动物、类器官模型研究候选基因在NDDs中发挥的作用，有助于发掘NDDs更多的致病基因，提高遗传检测的检出率。

关键字 神经发育障碍；iPSC；斑马鱼；

骨髓增生异常综合征疾病进展和白血病转化过程中基因突变动态变化研究

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目的：分析骨髓增生异常综合征（Myelodysplastic neoplasms,MDS）疾病进展（Progressive disease,PD）/白血病转化（Leukemic transformattion,LT）组和非PD/LT组患者病程中基因突变动态变化差异，探索在MDS发生PD/LT过程中起关键作用的基因突变。

方法：收集2019年5月至2023年8月于东南大学附属中大医院就诊的84例MDS患者序贯样本，行高通量二代测序基因突变检测；分析测序时临床参数与测序结果，比较PD/LT组和非PD/LT组患者病程中基因突变动态变化差异。

结果：①84例患者中男性51例，女性33例，初次测序时中位年龄69（31～95）岁。PD组20人，LT组13人,非PD/LT组51人。初次测序时PD/LT组中位骨髓原始细胞比例高于非PD/LT组（1.6% 对 0.4%，P=0.013）。②84例患者初次测序时基因突变检出率较高的依次为ASXL1（n=21，25%）、TP53（n=17，20.2%）、TET2（n=12,14.3%）、DNMT3A（n=11,13%）、U2AF1（n=11,13%）；PD/LT组患者初次测序时中位基因突变个数显著高于非PD/LT组（2个对1个，P=0.014）；PD/LT组初次测序时TET2（27.3% 对 5.9%，P=0.01）、SETBP1（15.2% 对 2%，P=0.033）、RUNX1（18.2% 对2%，P=0.013）突变比例显著高于非PD/LT组。③84例患者病程中检出率较高的新增突变（I组突变）/克隆扩增突变（II组突变）依次为TP53（n=9，10.7%）、TET2（n=7,8.3%）、ASXL1（n=7，8.3%）、RAS旁路突变（n=7,8.3%）；PD/LT组中位I/ II组基因突变数目显著高于非PD/LT组（2个 对 0个，P＜0.0001）。PD/LT组患者I/II组RAS旁路（21.2% 对 0%，P=0.001）、TP53（27.3% 对0%，P＜0.001）、TET2（18.2% 对 2%，P=0.013）突变比例显著高于非PD/LT组。④PD/LT组多数（9/12,75%）患者TP53突变为I/II组突变；非PD/LT组患者TP53突变皆为克隆缩小（5/8,62.5%）或克隆稳定突变（3/8,37.5%）。PD/LT组多数（7/8,87.5%）患者RAS旁路突变为I/II组突变；非PD/LT组患者RAS旁路突变皆为克隆稳定突变（1/1,100%）。

讨论：PD/LT组患者初次测序时中位骨髓原始细胞比例和基因突变数目高于非PD/LT组；TET2、SETBP1、RUNX1突变比例高于非PD/LT组。PD/LT组中位I/II组基因突变数目和I/II组TP53、RAS旁路、TET2基因突变比例高于非PD/LT组患者。I/II组TP53和RAS旁路突变可能促使MDS发生PD/LT。

关键字 骨髓增生异常综合征；疾病进展；白血病转化；动态变化

胎儿颈项透明层（NT）增厚/颈部淋巴水囊瘤（CH）与遗传学异常相关性分析及妊娠结局探讨

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目的：CMA和WES是在产前诊断超声异常病例中的应用越来越广泛，但是对NT增厚和CH胎儿的pCNV和单基因突变相关性以及妊娠结局的研究较少。

方法：回顾选取2019年1月至2022年6月于因胎儿NT增厚（NT＞95th头臀长）/颈部淋巴水囊瘤（CH）于我院行介入性产前诊断的孕妇215例，在染色体核型分析（KA）和微阵列分析（CMA）均阴性时自愿行全外显子组测序(WES)检测。依据NT增厚和颈部淋巴水囊瘤（CH）是否合并异常将病例分组，探KA、CMA和WES在各组胎儿中的应用价值。随访中晚孕期超声结果，孕妇妊娠结局和胎儿出生后的生长发育情况。

结果：215例样本中检出染色体数目异常28例，检出率13.0%；检出CNVs 12例，检出率5.6%。NT增厚组常见染色体异常是21三体，CH组常见染色体异常是45,X。CMA检测提示两组胎儿最常见的是22q11.21微缺失微重复综合征。35例KA和CMA结果阴性者行WES检测，12例胎儿（15个位点）检出单基因变异，异常率为34.3%（12/35），其中涉及Noonan综合征的有6例，NT增厚组和CH组各3例。

NT增厚组总不良妊娠结局发生率28.2%（49/174），CH组不良妊娠结局发生率82.9%（34/41）（$P<0.05$）。

结论：胎儿NT增厚/颈部淋巴水囊瘤（CH）与遗传学异常相关；两组胎儿在KA和CMA检测阴性后，WES的应用进一步提高了异常胎儿的诊断率；NT增厚组总不良妊娠结局发生率低于CH组，妊娠结局的管理可以指导临床遗传咨询。

关键字 胎儿颈部透明层增厚，胎儿颈部水囊瘤，遗传检查，产前诊断，随访