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论文汇编

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A study on building an optimized model on predicting euploid blastocysts and the effectiveness assessment on predicting live birth

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Research Question:Model combining female age, developmental dynamics and morphology of blastocysts could predict effectively euploid blastocysts, however this model failed in predicting live birth (LB). This study built an optimized predictive model (OPM) and assess the effectof OPM on predicting LB.Design:We conducted a retrospective analysis of collected data. 1875 blastocysts with pre-implantation genetic testing for aneuploidy (PGT-A) from 682 patients taken in IVF in Xuzhou Maternal and Child Health Hospital from January 2021 to January 2024 were selected to build OPM. Area under the curve (AUC) was used to assess OPM. 506 blastocysts without PGT-A from 455 patients taken in frozen embryo transfer (FET) in Xuzhou Maternal and Child Health Hospital from January 2021 to January 2024 were selected to assess the effect of OPM. LB rate (LBR) was used to assess FET outcomes. Accuracy rate (AR), true positive (TP) rate (TPR), true negative (TN) rate (TNR), false positive (FP) rate (FPR), false negative (FN) rate (FNR) were used to assess the effect of OPM on predicting LB.Results:OPM was effective with AUC of 0.916. LBR was 45.06%. AR, TPR, TNR, FPR, FNR of OPM were 70.61%, 76.26%, 23.74%, 29.39%, respectively. OPM was effective on predicting LB in FET treatments without PGT-A. Conclusion:OPM was effective on predicting euploid blastocysts. OPM performed better than selecting method by morphological grade in predicting LB. This study may provide a potential, noninvasive, effective new method, or a beneficial improvement on the method based on morphological grade to select blastocysts without PGT-A.

Key Words predictive model, euploid blastocysts, live birth, noninvasive and effective, pre- implantation genetic testing for aneuploidy

Cytosine base editing of DUX4: A potential therapeutic strategy for facioscapulohumeral muscular dystrophy

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Objective This study aims to explore the potential of cytosine base editing technology to suppress the expression of the DUX4 gene in FSHD therapy.

Methods In the investigation of cytosine base editing for FSHD treatment, in vitro experiments using a DUX4 conditional overexpression reporter cell line (N2a-iDUX4) were conducted to assess the editing efficiency of the cytosine base editor (CBE) and identify optimal editing sites. In vivo, lipid nanoparticles (LNPs) were used to

deliver the CBE and sgRNA to the gastrocnemius muscle (GAS) of FSHD mice for gene editing. Next-generation sequencing (NGS) was employed to analyze editing efficiency, and phenotypic analyses were performed on the mouse model at physiological, pathological, and molecular levels.

Results In the exploration of cytosine base editing for FSHD treatment, in vitro experiments demonstrated that CBE effectively edited the DUX4 gene and reduced the expression of DUX4 protein. In vivo experiments showed that LNPs delivery of the CBE to the GAS of FSHD mice effectively edited the DUX4 gene, significantly reducing the expression of DUX4 and its target genes. After CBE treatment, the muscle phenotype of the FSHD mouse model was significantly improved, including enhanced grip strength and endurance, reduced muscle inflammation, a decreased proportion of centrally nucleated fibers, and reduced muscle fibrosis. Additionally, RNA-seq analysis indicated improvements in the expression of genes related to skeletal muscle development, glycolysis, and fatty acid synthesis.

Conclusion This study successfully and demonstrated that CBE suppression of the DUX4 gene significantly improved muscle function and pathological manifestations in FSHD mice. This research provides a new option for FSHD animal models and experimental evidence for the application of cytosine base editing technology in the treatment of FSHD. These findings offer a new therapeutic strategy for FSHD treatment.

Key Words facioscapulohumeral muscular dystrophy; DUX4; CRISPR-Cas9; base editing; gene therapy; mouse model

Whole genome sequencing of the dried blood spot-derived DNA identifies the clinically relevant genetic variants in 92 Chinese children with autism spectrum disorder

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Objective Autism spectrum disorder (ASD) is a group of neurodevelopmental disorder with high heterogeneity and heritability. The utility of WGS in ASD research has grown, whereas its application in Chinese cohorts remains scarce and studies on newborn genetic screening via WGS for ASD are absent. We hence to investigate the potential of WGS from dried blood spot samples for the early diagnosis of ASD in the neonatal period.

Methods Our study was conducted based on the retrospective clinical data, with 92 individuals diagnosed with ASD from Changzhou Maternity and Child Heath Care Hospital as subjects. Genomic DNA was extracted from their dried blood spots of the newborns for WGS to integratedly detect candidate variants, including large copy number variations (CNVs), single necleotide variations (SNVs), the mitochondrial DNA (mtDNA) variants, loss of heterozygosity (LOH), as well as structural variants (SVs). Sequencing results were verfied by Sanger sequencing and quantitative PCR. The identified potential risk genes were investigated through biological function enrichment analysis.

Results Overall, total 10.87% (10/92) ASD children were confirmed with the genetic etiologies. Of the 10 positive cases, 2 cases (20.0%, 2/10) were identified with pathogenic CNVs, 7 cases (70.0%, 7/10) were identified with pathogenic or likely pathogenic SNVs/indels, and one case (10%, 1/10) was identified with the chromosomal

translocation t(8;9)(q13.3;q21.13) with a strong candidate RORB gene for neurological phenotype included in breakpoint region. Total 256 variations of 181 known or candidate ASD risk genes were identified, of which 203 variants (79.3%, 203/256) were previously unreported. The CACNA1H (1.95%, 5/256) was the most prevalent potential risk gene, followed by CHD8, KMT2C, MAST1, SHANK3, SPEN, TRRAP (1.56%, 4/256). Moreover, we identified those 181 potential risk genes (P<0.001) were enriched in neuronal regulation and developmental related biological process.

Conclusions Our study was the first to use WGS of the dried blood spot-derived DNA to uncover the associated-ASD risk gene and variants. The introduction of ASD to the newborn genetic screening should be considered, which could enable high risk populations to get the presymptomatic diagnosis as well as advance earlier intervention and precise treatment of ASD.

Key Words Autism spectrum disorder, Whole genome sequencing, Molecular diagnosis, Newborn genetic screening, Early intervention

基因组光学图谱在结构胎儿遗传学病因诊断中的应用

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目的：探讨基因组光学图谱技术（optical genome mapping, OGM）在结构畸形胎儿遗传学病因诊断中的临床应用价值。

方法：前瞻性收集2022年6月至2024年7月因胎儿结构畸形而于南京市妇幼保健院进行介入行产前诊断的病例共204例。利用OGM进行产前诊断，并对OGM的检测结果进行描述性统计分析。根据结构畸形累及的系统以及是否为单纯性单系统结构畸形进行亚组分析。将OGM的检出率与染色体微阵列分析(chromosomal microarray analysis, CMA)以及染色体核型分析的理论检出率进行比较分析。

结果：OGM共在28例（28/204，13.7%）结构畸形胎儿中检出了致病或可能致病性(pathogenic or likely pathogenic, P/LP)的染色体变异，其中包括12例染色体数目变异，14例P/LP的拷贝数变异以及2例平衡性染色体重排。此外，OGM还在11例（11/204，5.4%）病例中检出了临床意义未明的拷贝数变异。当根据结构畸形累及的系统进行亚组分析时，OGM在淋巴水囊瘤组以及多系统畸形组的诊断率显著高于在其它系统结构畸形胎儿中的诊断率（35.7% vs. 10.3%, 调整后P=0.018; 31.3% vs. 10.3%, 调整后P=0.04）。OGM在结构畸形胎儿中的诊断率（13.7%）高于CMA（26/204，12.7%）以及核型分析（15/204，7.4%）的理论检出率，但无显著性差异（P>0.05）。OGM的中位诊断周期为18（16-24）天。

结论：OGM检测全面、分辨率高、诊断周期合理，是一项结构畸形胎儿产前遗传学病因诊断的有力工具。

关键字 基因组光学图谱；结构畸形；产前诊断；结构变异

利用NIPT数据开展的新生儿代谢的全基因组关联研究

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目的：1、探讨NIPT数据是否能进行新生儿代谢影响的研究？

2、那些变异位点对新生儿代谢有显著影响，影响的效果如何？

方法：配对收集2.7万例母体NIPT检测数据以及对应新生儿代谢筛查结果，对43种代谢物浓度和32个代谢物浓度之间的比值，进行全基因组关联分析。研究分三步进行，首先验证NIPT数据在现有算法环境下是否支持开展全基因组关联分析。在确认可以开展后，第二步对现有新生儿数据进行全基因组关联分析，并通过数据分析的方法验证其结果的有效性和合理性。最后通过遗传力分析以及多基因评分评价，结果对新生儿代谢能力的潜在影响。

结果：1、通过NIPT数据检测到2千多万个变异位点，通过对妊娠期妇女身高的分析，发现使用NIPT数据的分析结论于目前发表的关于人类身高的变异位点高度一致，说明在目前样本量的条件下，可以利用NIPT数据可以进行全基因组分析。2、发现与新生儿代谢相关的30个基因组上的位点，其中19个在成人中被报道，11个在新生儿中首次发现。3、从基因组数据中估计出代谢物遗传度在新生儿群体中高达76%，揭示遗传因素的重要影响。

讨论：本研究根据GWAS研究的基本原理出发，通过验证变异频率在代际间的一致性，利用NIPT数据开展对新生儿表型的研究，将NIPT的研究应用范围从母体表型拓展到新生儿表型。为从遗传学数据中评估新生儿代谢物浓度提供可行性依据。研究结果为未来利用NIPT数据分析和用途提供了新的思考，但任期待有基于新生儿全基因组测序开展的新生儿代谢GWAS研究来证实以及矫正当中的结果。

关键字 无创游离DNA，NIPT，新生儿代谢，GWAS研究

颅面部异常的产前调查分析与遗传病因诊断的系列研究

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目的：利用CMA技术明确胎儿颅面畸形的遗传学病因，探讨trio-WES技术在先天性颅面畸形胎儿中遗传学病因诊断的应用。

方法：对颅面部异常胎儿样本326例进行CMA检测。选取结果未见异常的7例复杂型颅面畸形及1例家族性小下颌家系进行全外分析。

结果：1、染色体异常60例（18.4%），非整倍体41例（12.6%），致病性/可疑致病性CNVs19例（5.8%）。2、22q11.21微缺失和15q11.2微缺失在颅面畸形病例中更常见，TBX1基因可能与唇腭裂相关。3、2例家系存在SF3B4基因变异导致的Nager综合征；3例家系FGFR2基因变异导致的Crouzon综合征；1例家系FGFR2基因变异导致的Apert综合征；1例家系PTPN11基因变异导致Noonan综合征。

结论：1、CMA技术可额外增加颅面畸形遗传学病因的检出率，可将其作为一线检测技术。初步确定候选CNVs（22q11缺失/重复）和基因（TBX1），仍需进一步的功能学研究。2、发现1个新的基因变异位点SF3B4基因c.1111_1121del（p.His371fs）杂合变异可致Nager综合征。3、产前胎儿颅面存在两种或两种以上不同特征的超声结构异常，特别是合并其他超声异常时，强烈提示单基因疾病，优先推荐CMA+trio-WES检测方案。

关键字 颅面畸形；全基因组染色体微阵列分析；染色体拷贝数变异；全外显子组测序；单基因遗传病；产前诊断

Two-dimensional polymerase chain reaction for identifying the 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 HLA 2D-PCR SNP

Performance of expanded noninvasive prenatal testing for fetal aneuploidy and copy number variations in a cohort of 12172 cases from a single center in Jiangsu province, China

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Objective: We aimed to evaluate the clinical performance of expanded noninvasive prenatal testing (NIPT-Plus) in screening for fetal chromosomal abnormalities includes aneuploidies and copy number variations(CNVs).

Methods: A total of 12172 singleton pregnant women we recruited in the study from May 2021 to November 2024 at the Department of Prenatal Diagnosis of Wuxi Maternity and Child Health Hospital, Jiangsu, China. Cases with NIPT-Plus positive results were suggested to accept verification test and part of them were further confirmed by chromosomal microarray analysis(CMA) and chromosomal karyotyping after amniocentesis.

Results: A total of 220 positive cases (1.80%) were identified by NIPT-Plus, including 154 chromosome aneuploidies and 66 CNVs. Following genetic counseling, 177 cases (80.5%, 177/220) were validated by amniocentesis, and 82 were verified as true-positive results, comprising 29 trisomy 21, 5 trisomy 18, 22 sex chromosomal abnormalities, 8 other aneuploidy, and 18 CNVs. The positive predictive value for T21,T18, SCAs, CNVs were 96.67%, 41.67%, 52.38% and 35.29%, respectively. For 66 cases with NIPT-Plus positive result of CNVs, the termination rate was 33.3% (6/18) after invasive prenatal diagnosis.

Conclusions: NIPT-Plus showed a good performance in detecting T21, SCAs, but higher accuracy was required in detecting autosomal chromosomal abnormalities and CNVs. In summary, this study provides objective clinical application of NIPT-Plus for screening fetal chromosomal abnormalities. Therefore, NIPT-Plus technology could be widely extensively used in clinical center in association with prenatal diagnosis and genetic counseling.

Key Words expanded non-invasive prenatal testing (NIPT-Plus), chromosome aneuploidies, copy number variations, positive predictive value

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. 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 pathogenetic copy number variations(pCNVs),such as 17q12 microdeletion, 22q11.2 microdeletion, Xp22.33 microdeletion, 16p13.3 microdeletion and 1q43 microdeletion. 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.

Conclusion: 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.

Key Words urinary tract anomalies,CMA,Clinical follow - up

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

Association between genotype and phenotype in children with phenylalanine hydroxylase deficiency in Lianyungang area

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Objective This study constructed the spectrum of gene variants and phenotypes of phenylalanine hydroxylase deficiency (PAHD) in Lianyungang area to explore the associations between different genotypes and corresponding phenotypes in pediatric patients. Methods Blood samples from 80 patients diagnosed with hyperphenylalaninemia (HPA) were collected. Techniques including next generation sequencing (NGS), Sanger sequencing, and multiplex ligation-dependent probe amplification (MLPA) were utilized to detect gene variants, and analyzed the characteristics of PAH variants. Meanwhile, the patients' basic clinical information and phenotypic data were collected to investigate associations between variation distributions, types, and different phenotypes. Results In patients with HPA, 93.75% (75/80) were found to have PAH variants, while 6.25% (5/80) were found to have PTS variants. Of the 75 PAHD patients, a total of 55 types and 152 variants were detected

on the 150 PAH alleles, achieving a 100% variation detection rate. Of the 152 variants, 80.26% were located in exons, with the main types of variants were missense mutations (67.11%). 53.3% of coding sequence variants occurred in the PAH gene catalytic center region, while 19.7% of variants involved non-coding sequences. The phenotypes of the 75 PAHD patients were evenly distributed. The rescreening Phe concentrations and Phe/Tyr ratios of classic-phenylketonuria (CPKU) and mild-phenylketonuria (MPKU) patients were markedly higher than initial screening values (P<0.001, P<0.001; P=0.004, P=0.016), while there was no similar trend in mild-hyperphenylalaninemia (MHPA) patients (P=0.702, P=0.364). The genotypes of the 75 PAHD patients mostly occurred as compound heterozygotes, and different mutation positions and variant types significantly affect the phenotype (P=0.042, P=0.045). APV/GPV genotype-phenotype analysis of 61 patients showed high consistency between predicted and actual phenotypes (κ =0.755, P<0.001). Conclusions PAH variants were detected in the vast majority of HPA patients in Lianyungang area. The location and type of PAH variants were related to the severity of the phenotype, and the non-coding sequence variations and non-missense mutations may aggravate the phenotype, and the APV/GPV model predicted the phenotype was highly consistent with the actual phenotype.

Key Words Phenylalanine hydroxylase; Hyperphenylalanineemia; Phenylketonuria; Genotype; phenotype

纳米材料AuNCs改善铜过载导致的遗传损伤

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目的：探讨纳米材料AuNCs是否能够治疗铜过载引发的遗传损伤，并评估其在遗传学领域的潜在临床应用价值。

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遗传损伤的相关性。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和DNA损伤标志物（如γ-H2AX）的表达水平，判断AuNCs是否可以改善铜过载导致的遗传损伤。

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，并检测睾丸组织中的DNA损伤和修复相关基因的表达水平。

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，观察细胞形态、DNA损伤标志物和相关蛋白表达水平。

结果：1、收集的精液中铜离子浓度与遗传损伤标志物（如γ-H2AX）的表达水平呈正相关，AuNCs处理后铜死亡标志蛋白和DNA损伤标志物表达水平降低。

2、AuNCs注射后对铜过载模型小鼠睾丸生精小管凋亡减轻，铜死亡标志蛋白和DNA损伤标志物表达水平降低，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，DNA损伤标志物表达水平下降。

结论：AuNCs可以治疗铜过载引发的遗传损伤，减少DNA损伤并提高精子质量，具有潜在的遗传学临床应用价值。

关键字 纳米材料；铜过载；遗传损伤；DNA损伤；精子活力

整合单细胞与空间转录组解析第二心区发育——SEU-TCA算法揭示Irx1在室间隔形成中的关键作用

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先天性心脏病（CHD）作为全球新生儿最常见的出生缺陷，其发病根源可追溯至胚胎期心脏发育的时空紊乱。为突破CHD早期防控的瓶颈，本研究聚焦第二心区（SHF）祖细胞动态发育过程，通过开发单细胞与空间转录组整合算法SEU-TCA，系统阐明关键细胞群的时空调控机制。针对现有跨模态数据整合技术的局限性，创新性引入转移成分分析框架，结合WOT谱系追踪算法构建三维发育轨迹，实现单细胞分辨率下细胞演化路径与空间坐标的精准映射。

本研究首先在四个不同生物系统中验证了SEU-TCA的稳定性和适用性，随后将其应用于小鼠E7.5原肠胚数据，解析第二心区（SHF）的早期发育过程。研究鉴定了多个前第二心区（aSHF）祖细胞亚群及其关键调控因子，尤其是Irx家族分子。遗传谱系追踪结果显示，Irx1阳性祖细胞不仅贡献于aSHF谱系，还参与流出道和右心房的形成。进一步的条件性基因敲除实验证实，Irx1缺失导致aSHF发育异常并导致室间隔缺损（VSD），揭示了Irx1在aSHF调控中的关键作用。

SEU-TCA算法在多生物系统的验证中展现卓越性能，为解析器官发育的空间调控规律提供创新工具。该成果不仅阐明心脏发育的关键调控节点，更为CHD的早期分子诊断和靶向干预提供了新理论框架，推动出生缺陷防控向精准医学迈进。

关键字 先天性心脏病，第二心区，单细胞转录组，空间转录组，室间隔缺损

成骨不全VI型的基因型——表型相关性及治疗效果：一项针对36例中国儿科患者的11.5年队列研究

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VI型成骨不全症是由SERPINF1双等位基因突变致使色素上皮衍生因子（PEDF）生成受阻而引发。本项研究目的是探索Ⅵ型成骨不全基因型与表型的关联，与药物治疗的疗效。本实验采用回顾性队列研究对34个家庭的37例儿科Ⅵ型成骨不全患者进行分析，平均随访时间为 11.5 年。通过全外显子基因检测确定SERPINF1突变位点，临床检测骨密度、脊柱正侧位、血清PEDF、β-CTX、PINP、钙、磷、25-OH-VD水平，并评估双膦酸盐或地舒单抗联合钙、维生素D联合治疗的效果。共鉴定出33种SERPINF1变异，包括4种CNV和33种SNV，常见的致病突变有c.907C>T（p.Arg303Ter）、c.271_279dup（p.Ala91_Ser93dup）。70% c.907C>T突变出现在中国华中华北地区，而c.271_279dup突变未发现明显地区聚集。所有患者均进行手术干预（平均3.79次）并配合药物治疗，使用唑来膦酸或地舒单抗治疗比例为19：18，40.5%的患者有其他双膦酸盐使用史，5例使用地舒单抗的患者出现高钙血症。治疗后骨折频

率降低，但脊柱畸形进展和生物标志物变化趋势仍在分析中。该研究明确了SSERPINF1突变基因型和表型严重程度的相关性。双膦酸盐和地舒单抗都能有效减轻骨折负担，但地舒单抗在患儿中引发的高钙血症需严密监测。脊柱侧弯、椎体压缩与骨代谢指标的纵向数据将进一步明确治疗效果，为这一罕见骨病优化管理策略提供指导。

关键字 VI型成骨不全；PEDF；地舒单抗；唑来膦酸；BMD；

·遗传病的认识与研究进展·

卵巢低反应患者卵泡液的非靶向代谢组学研究

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目的：卵巢低反应(Poor Ovarian Response，POR)是指接受体外受精–胚胎移植(In Vitro Fertilization And Embryo Transfer，IVF–ET)人群中卵巢对促性腺激素(gonadotropins，Gn)刺激反应不良的病理状态，因其周期取消率高、妊娠结局差而成为目前辅助生殖助孕发展的难点。本研究基于卵泡液非靶向代谢组学技术，检测卵泡液中的差异代谢物，分析卵泡液代谢状态，揭示与卵巢低反应相关的潜在代谢途径，探究其背后发生的分子机制，并筛选出潜在的生物标志物，为POR患者的治疗和辅助生殖结局改善提供线索。

方法：纳入2023年6月至2024年5月在常州市妇幼保健医院生殖中心接受IVF–ET助孕的60名不孕患者，其中包括30例POR患者和30例卵巢反应正常患者，年龄在25~38岁之间。依据患者自身情况制定个性化的超促排方案。收集取卵当日卵泡液，采用超高效液相色谱–质谱法(UPLC–MS)对两组患者的卵泡液进行代谢组学分析，寻找两组间差异表达代谢物(P<0.05)，对筛选到的差异代谢物进行生物信息学分析，使用京都基因与基因组百科全书(Kyoto Encyclopedia of Genes and Genomes，KEGG)和人类代谢组数据库(Human Metabolome Database，HMDB)进行途径富集分析，使用随机森林和logistic回归模型计算预测概率并进行ROC分析以确定潜在生物标志物。

结果：本研究最终纳入60例患者，其中POR组30例，对照组30例。卵泡液代谢组学分析结果显示，与正常对照组相比，POR组卵泡液中有221种代谢物的差异具有统计学意义(P<0.05)，有40种代谢物在HMBD数据库和KEGG数据库中均有收录，其中，18种代谢物显著上调，22种代谢物显著下调。对差异代谢物进行代谢通路富集分析，共富集到29条代谢通路(P<0.05)，包括甘油磷脂代谢通路、胆碱代谢通路及自噬通路等。ROC曲线分析显示，紫苏醛可作为POR的生物标志物。

讨论：在本研究中，我们对POR患者卵泡液进行非靶向代谢组学研究。结果显示，POR与卵巢正常人群卵泡液代谢谱差异显著，POR患者的卵泡液中甘油磷脂、乳酸、胆绿素、胆红素等浓度发生了变化，提示上述物质可能在POR的发生发展中扮演重要角色。甘油磷脂途径、胆碱途径及自噬通路可能与POR发生发展过程密切相关。紫苏醛可能是影响POR发生发展的关键因素，推测其可作为评估与预测POR发生的潜在生物标志物。然而，相关代谢物在POR中的作用仍有待于进一步研究。综上，本研究基于非靶向代谢组学分析，对POR患者的卵泡液进行研究与探讨，为揭示POR发病机制提供了新的视角，为未来研究POR提供可能的依据。

关键字 卵巢低反应；卵泡液；非靶向代谢组学

ABO血型系统与疾病关联性的研究进展

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目的：该研究旨在综述ABO血型系统与心血管疾病、癌症、糖尿病、COVID-19以及风湿病等多种疾病之间的关联性研究进展，探讨ABO血型在疾病发生和发展中的可能作用，并为未来的研究提供方向。

方法：通过文献综述的方式，收集并整理了关于ABO血型与各类疾病关联性的现有研究成果，对研究数据进行归纳和分析，以揭示ABO血型与不同疾病之间的相关性。

结果：研究发现，非O型血患者的心血管事件风险显著增加，如血栓形成、VTE、心肌梗死、冠心病。在癌症方面，O血型个体患甲状腺癌、恶性黑色素瘤的风险较高；而头颈部癌症、非黑色素皮肤癌、胃癌在A型血人群中易感性较高；B血型个体下咽癌易感性较高。关于糖尿病易感性与ABO血型的关系仍存在争议，但已有研究证明A和AB血型糖尿病患者的并发症发生风险提高；关于COVID-19，O血型的个体感染风险显著低于非O血型；风湿病方面，B型血患者在SLE中更常见，而A型血患者在RA中更常见。

讨论：研究表明血型相关基因的多态性可能与疾病风险相关联。但现有研究多局限于血型的抗原分型，为了更深入地探究这一领域，未来的研究可以引入新兴技术，进行分子分型，如二维聚合酶链反应（2D PCR），以实现对ABO等位基因的快速鉴定和分析。这将有助于揭示ABO血型与疾病之间的具体关联，为疾病的预防和治疗提供新的思路和方法。

关键字 ABO血型；心血管疾病；癌症；糖尿病；COVID-19；风湿病；关联性

PFAPA综合征一例

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目的：梳理周期性发热伴阿弗他口炎、咽炎及淋巴结炎(PFAPA)综合征的诊治过程，探究该疾病的遗传模式，丰富该疾病的遗传学发病机制研究。

方法：调取本院2024-09-26收治的一例确诊为PFAPA综合征患儿的病案资料进行总结归纳，结合目前已有相关研究结论与该患儿基因检测结果相对比。

结果：PFAPA综合征是一种基于临床诊断的具有特定发作周期的自身炎症性疾病，发作期可使用泼尼松进行诊断性治疗；病例中患儿MEFV（家族性地中海热基因）变异。

讨论：PFAPA综合征需与其他周期性发热综合征相鉴别；诊断为PFAPA综合征的MEFV基因变异者发病年龄更小、发热间隔时间更短、发热更不规律，且扁桃体切除术完全有效的可能性更小。

关键字 PFAPA综合征；MEFV基因

一种新型面肩肱肌营养不良症小鼠模型的建立

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目的：利用Myf6-CreERT2小鼠与FLExDUX4小鼠构建面肩肱肌营养不良症（facioscapulohumeral muscular dystrophy, FSHD）转基因小鼠，并采用他莫昔芬诱导构建FSHD疾病小鼠模型。

方法：利用Myf6-CreERT2半合子小鼠与FLExDUX4半合子小鼠杂交获得双转基因杂合子小鼠（M6D4/+），在3周龄时使用他莫昔芬诱导该小鼠表达全长DUX4（DUX4-fl），通过9周龄时小鼠体重变化、四肢抓力、倒置网格实验、骨骼肌占体重比、骨骼肌石蜡切片苏木素伊红染色、天狼星红染色及免疫荧光、实时荧光定量PCR、骨骼肌RNA-seq等实验评估该疾病模型。

结果：成功获得双转基因杂合子小鼠（M6D4/+），9周龄时该小鼠与对照组相比，在生理方面表现出体重增加下降、四肢抓力及耐力下降、骨骼肌比重下降；组织病理方面出现中央核肌纤维增多、肌束纤维化程度增高等骨骼肌受损表现；RT-PCR分析发现DUX4及其靶向基因在骨骼肌中表达明显上调；RNA-seq结果显示免疫调控、白细胞介素6、肿瘤坏死因子相关基因的表达上调，骨骼肌发育和分化相关基因的表达下调。

讨论：M6D4/+小鼠很好地模拟了FSHD的骨骼肌表型，是一种良好的FSHD动物模型，可用于FSHD的致病机制及干预、治疗研究。

关键字 面肩肱肌营养不良症；DUX4；Myf6；骨骼肌；小鼠模型

The tumor inhibitory role and the potential mechanism of Methionyl-tRNA synthetase 1 in ovarian cancer

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Objective: Methionyl-tRNA synthetase 1 (MARS) is an enzyme that belongs to the family of aminoacyl-tRNA synthetases. High levels of MARS have been shown to correlate with a poorer prognosis in a variety of tumor types. However, its specific role and the underlying mechanism in cancer, especially in ovarian cancer, are not well understood. This study aims to investigate the roles and potential mechanisms of MARS in ovarian cancer.

Methods: Immunohistochemistry and public databases were used to analyze the expression of MARS in ovarian cancer and its correlation with patient survival. Cell migration assay, Cell invasion assay, Colony formation assay and CCK8 assay were used to assess the impact of MARS on proliferation, migration, invasion of ovarian cancer cells. RNA sequencing was performed to identify differentially expressed genes and pathways regulated by MARS. Tumor growth in vivo was monitored in a subcutaneous mouse model.

Results: In ovarian cancer tissues, MARS protein levels were found to be significantly elevated compared to normal tissues, correlating with poorer patient outcomes. Functional studies demonstrated that silencing MARS

significantly inhibited the proliferation, migration, and invasion of ovarian cancer cells in vitro, and moderately suppressed tumor growth in a subcutaneous mouse model. RNA sequencing and RT-qPCR revealed that MARS knockdown led to the downregulation of cell cycle genes regulated by TP53 and immune-related cytokines.

Conclusion: Our findings highlight the tumor-promoting role of MARS in ovarian cancer through its regulation of cell cycle progression and immune-related pathways. The observed difference between in vitro and in vivo results suggest that MARS may have different functions in different tumor microenvironment. Further research is needed to elucidate the specific mechanisms by which MARS influences ovarian cancer progression and immune cell function. Understanding these mechanisms could provide new insights into therapeutic strategies targeting MARS or its downstream pathways in ovarian cancer. Furthermore, we found that MARS is mainly expressed in the cytoplasm of ovarian cancer cells. Mitochondrial-localized methionyl-tRNA synthetase MARS2 may also competitively utilize methionine with MARS, thereby balancing protein translation in the mitochondria and cytoplasm. Further in-depth research is needed to explore the relationship between the two for the value of further in-depth study of methionine and methionine-related therapeutic strategies.

Key Words Methionyl-tRNA synthetase 1; Ovarian cancer; Malignant behavior; Cell cycle; Immune cell

肝豆状核变性新生儿筛查研究进展

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【摘要】肝豆状核变性是临床危害严重的可治性遗传代谢病，该病越早治疗、预后越好，新生儿期开展大规模群体筛查能有效筛出症状前患者，达到早发现、早诊断、早治疗的目的。本文介绍了可应用于肝豆状核变性新生儿筛查的临床方案和其他促进新生儿筛查进展的新兴检测技术，前者主要包括铜蓝蛋白筛查、ATP7B基因筛查，后者主要包括代谢组学技术、ATP7B肽的检测、蛋白质组学技术、全基因组测序等，本文同时对该病新生儿筛查前景进行展望。

关键字 肝豆状核变性；铜蓝蛋白；ATP7B基因筛查；代谢组学；ATP7B肽

尼曼-匹克病在新生儿人群中的携带率调查

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目的：调查江苏南京地区新生儿中尼曼-匹克病基因SMPD1、NPC1和NPC2致病变异的携带率，探讨将SMPD1、NPC1和NPC2基因筛查纳入新生儿筛查的临床应用价值，为尼曼-匹克病的早期诊治与遗传咨询提供依据。

方法：回顾性分析2022年3月18日至2024年4月1日在南京市妇幼保健院出生的30043例新生儿SMPD1、NPC1和NPC2的基因筛查结果。应用芯片捕获二代测序技术对SMPD1、NPC1和NPC2基因致病位点进行检测。

结果：30043例新生儿中310例检出313个变异位点，综合携带率为1/97。其中，SMPD1 基因共计检出41种致病变异位点，携带人数为236人，其中一人为SMPD1纯合变异潜在患儿，统计携带率为1/127。NPC1基因共计检出41种致病变异位点，携带人数为70人，其中1人为2个NPC1致病位点的顺式携带，统计携带率为1/429。NPC2共计检出变异位点5个，均为c.441+1G>A致病变异，携带率为1/6009。尼曼–匹克病中最为常见的致病变异为SMPD1的c.955C>G（50.48%）。尼曼–匹克病SMPD1纯合变异的新生儿酸性鞘磷脂酶的活性降低，随访至今尚未出现尼曼–匹克病临床症状。

结论：通过新生儿尼曼–匹克病相关的SMPD1、NPC1和NPC2基因筛查发现，根据携带率估算南京地区Krabbe病患病率为1/37 636，根据阳性患儿统计的患病率为1/30 043，均远高于基于临床患者统计的患病率，提示可能有许多尼曼–匹克病患者未能够及时发现与就诊。尼曼–匹克病的基因筛查的开展，不仅使尼曼–匹克病患儿被早期发现与随访，也为我国尼曼–匹克病的流行病学统计提供了有效的参考依据。

关键字 尼曼–匹克病；SMPD1基因；NPC1基因；NPC2基因；基因筛查

·遗传病的分子基础与环境互作·

LINC00654 Promotes Ovarian Cancer Progression by Facilitating Nuclear Export of HuR and Stabilizing Oncogenic mRNAs

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Ovarian cancer (OC) remains a significant challenge in oncology due to its late diagnosis and poor prognosis. Emerging evidence suggests that long non-coding RNAs (lncRNAs) play critical roles in cancer biology. Herein, we reported that LINC00654 was highly expressed in OC tissues and correlated with poor patient prognosis. In addition, LINC00654 silencing restrained OC cell proliferation and migration in vitro and in vivo. Mechanically, LINC00654 was identified to directly interact with Human antigen R (HuR), a known RNA-binding protein, through RNA pull-down, RNA immunoprecipitation (RIP), and cross-linking immunoprecipitation (CLIP). Further analysis revealed that LINC00654 could induce the translocation of HuR from the nucleus to the cytosol, where it regulated the stability of its target oncogenes, such as VASH2. The stabilization of VASH2 subsequently activated the TGF-β pathway, which is known to play a critical role in cancer progression. Taken together, these findings establish a specific mechanism by which LINC00654 interacts with HuR, facilitates its nuclear export, and stabilizes VASH2, thereby activating the TGF-β pathway and promoting OC progression. This insight into LINC00654's role in OC provides potential therapeutic targets for intervention.

Key Words LINC00654, Ovarian cancer

精子发生过程中ASB1与ELOB相互作用促进SQOR泛素化及硫化氢稳态维持

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男性生育能力已经成为男性健康领域的一个重要关注点，它与精子生成这一复杂过程密切相关。尽管这一过程起着关键作用，但其具体机制仍然不清楚，需要进一步的探索。

在这项研究中，我们发现Ankyrin重复和SOCS盒ASB家族成员ASB1在小鼠睾丸中高度表达，缺乏Asb1基因的小鼠（称为Asb1-KO小鼠）生育能力严重受损，表现为严重的少、弱、畸形精子症；随后的研究显示，ASB1的缺乏增加了睾丸氧化应激和精子DNA的损伤，Asb1-KO小鼠睾丸中的活性氧化物（ROS）和丙二醛（MDA）水平升高，同时氢硫化物（H2S）水平下降。重要的是，给予H2S供体NaHS后，Asb1-KO小鼠的生育能力明显改善。

从机制上讲，鉴于ASB1的生物学效应通常依赖于其E3泛素连接酶活性，因此我们对其潜在底物进行了确认。我们利用ASB1抗体在成年小鼠睾丸中进行了免疫沉淀–液相色谱–串联质谱（IP–LC–MS/MS）分析，Asb1–KO小鼠睾丸作为阴性对照。我们发现ASB1通过促进硫化物醌氧化还原酶（SQOR）的K207和K344残基形成K48类型的多聚泛素链从而促进SQOR蛋白的不稳定，随后导致蛋白的降解。这一复杂过程在维持氧化与抗氧化平衡方面发挥关键作用，从而确保睾丸中的氧化还原平衡。

总之，我们的研究为ASB1在精子发生过程中的作用和潜在机制提供了新的见解。这些发现在男性不育诊断和治疗的潜在靶点方面具有重要意义。

关键字 ASB1；SQOR；氧化应激；精子发生；泛素化

蛋白磷酸酶2A催化亚基（PP2Ac）影响精母细胞减数分裂前期I减数分裂起始进程

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目的：蛋白磷酸酶2A（PP2A）作为一种丝氨酸/苏氨酸磷酸酶，在许多生理过程中是必不可少的。研究报道，其调节亚单位B基因纯合突变会导致46,XY性腺发育不全综合征（46，XY–DSD），患者主要表现为睾丸发育异常和生精障碍，但机制尚不明确。

方法：本研究通过构建PP2A催化亚基（Ppp2ca）条件敲除小鼠模型在体内灭活PP2A，通过对睾丸组织染色体铺展、PAS染色和转录组测序分析，探索聚焦于减数分裂起始和精子发生的无精子症机制。

结论：生殖细胞中Ppp2ca的缺乏明显干扰精原细胞分化，导致粗线期阻滞，并伴有显著的生殖细胞凋亡和程序性双链断裂（DSB）修复中的缺陷，然而XY小体的形成是正常的。Ppp2ca缺陷的精母细胞表现出异常的染色体内聚复合体降解，可能是导致细胞死亡的原因。此外，转录组学分析结果表明，Ppp2ca缺陷睾丸中精子发生相关众多基因表现出转录失调。

结论：我们的研究证明了PP2A在精子发生中不可替代的作用，为无精子症的病因提供了更多证据。

关键字 46，XY–DSD； Ppp2ca；生精障碍；减数分裂

基于乳酸化修饰组学探索GATM乳酸化在增生性瘢痕形成中的作用与机制

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目的: 乳酸化修饰（Lactylation），是一种主要由乳酸衍生而来的新型蛋白质翻译后修饰，在各种生理病理过程中发挥重要作用。本研究基于乳酸化修饰组学探讨线粒体甘氨酸脒基转移酶GATM乳酸化对增生性瘢痕形成的作用与机制。

方法：收集增生性瘢痕组织（患者因增生性瘢痕在我院行切除手术），以瘢痕旁正常皮肤组织为

对照，进行乳酸化修饰组学与蛋白质组学分析。采用过表达和突变策略检测线粒体甘氨酸脒基转移酶GATM乳酸化在增生性瘢痕形成中的功能和机制。

结果：共鉴定到1023种乳酸化修饰，2008种蛋白。与正常皮肤组织相比较，增生性瘢痕组织中乳酸化修饰水平上调的有99种，下调的有121种，差异高表达的蛋白有295种，差异低表达的蛋白有266种。生物信息学分析发现，差异乳酸化修饰的蛋白（乳酸化修饰组学）与差异蛋白（蛋白质组学）主要参与核糖体功能、糖酵解/糖异生、信号转导、传输过程，AMPK、HIF-1、TGF-β、PI3K-Akt、FAK等信号通路。依据组内差异小（P值小）、物种间保守性高的筛选原则，经过实验分析发现线粒体甘氨酸脒基转移酶GATM乳酸化水平在增生性瘢痕中显著升高。进一步在成纤维细胞中过表达GATM，结果显示其促进胶原、ACTA2蛋白表达，而GATM突变型（K102R，GATM蛋白第102位赖氨酸突变成精氨酸，以抑制其乳酸化修饰）过表达抑制胶原、ACTA2蛋白表达。机制分析发现GATM可影响cGAS-STING、NF-κB、IL-6蛋白表达。

结论：蛋白质乳酸化修饰在增生性瘢痕形成中发挥重要功能。线粒体甘氨酸脒基转移酶GATM乳酸化参与调控增生性瘢痕的形成，可能成为瘢痕防治的潜在靶标。

关键字 增生性瘢痕，乳酸化修饰组学，蛋白质组学，GATM

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

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The primary objective of our research was to differentiate induced pluripotent stem cells (iPSCs) into myogenic progenitor cells and myotubes to overcome the challenges associated with limited myogenic cell donors and the laborious process of isolating, purifying, and proliferating cells in vitro. We also aimed to assess the efficacy and physiological significance of this cell differentiation system and to analyze the differentiated cells by using single-cell RNA sequencing (scRNA-seq) for understanding molecular mechanisms of myogenesis and facioscapulohumeral muscular dystrophy (FSHD) in humans. A commercialized protocol was used to effectively differentiate iPSCs from both healthy individuals and individuals with FSHD type 1 into myogenic progenitor cells and myotubes. The myogenic progenitor cells and myotubes derived from iPSCs were subjected to scRNA-seq to confirm cell composition, map differentiation characteristics, and identify potential biomarkers for FSHD. Our study identified 13 distinct cell clusters and validated the efficacy of the differentiation approach in mimicking the physiological myogenic cell differentiation process through pseudo-time trajectory, thus suggesting its utility as a valuable tool for investigating muscle-related diseases in vitro. Furthermore, the identification of several biomarkers, such as ISG15, MYH8, and TTN, in myotubes derived from iPSCs of FSHD donors has significant implications for advancing research on the underlying mechanisms and therapeutic strategies for FSHD.

Key Words FSHD, iPSC, scRNA-seq，biomarkers

Maternal Preconception Circadian Disruption Impairs Male Offspring Fertility through Sperm Apoptosis and Motility Deficits

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Objective:Circadian rhythm disruptions, often induced by shift work and nocturnal light pollution, are increasingly common in modern society. Emerging evidence highlights their adverse effects on reproductive function. However, the impact of preconception circadian disruption on the reproductive health of male offspring remains understudied. This investigation explores the effects of maternal preconception circadian disruption on male offspring fertility and elucidates the underlying mechanisms using a mouse model.

Methods:Adult female ICR mice were exposed to constant light for 4 weeks to induce preconception circadian disruption. These females were subsequently mated with proven-fertile males to produce offspring. Upon reaching adulthood, male offspring underwent comprehensive fertility assessments, including breeding experiments, sperm motility analysis using a computer-assisted sperm analysis (CASA) system, sperm function evaluation via in vitro fertilization, and morphological analysis of testes and sperm through hematoxylin-eosin (HE) and immunofluorescence staining. Sperm apoptosis was assessed using flow cytometry and TUNEL staining.

Results:Male offspring from mothers exposed to constant light preconceptionally exhibited significant impairments in fertility. Despite normal spermatogenic cell and sperm morphology in the testes, and embryonic development rates comparable to controls following in vitro fertilization, these offspring displayed marked reductions in sperm count, progressive motility, and linear velocity. Flow cytometry and TUNEL staining revealed a significant increase in sperm apoptosis within the epididymis.

Conclusion:Maternal preconception circadian disruption leads to reproductive dysfunction in male offspring, characterized by decreased fertility, elevated sperm apoptosis, and diminished sperm motility. These findings highlight the critical role of maternal circadian health in offspring reproductive development and suggest that maintaining stable circadian rhythms prior to conception is essential for optimal reproductive outcomes.

Key Words Circadian disruption, Preconception, Male fertility, Sperm apoptosis, Sperm motility

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

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. Fu rthermore, 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)

Hyperbaric Oxygen Therapy Ameliorates Sperm Parameters in Apolipoprotein E Knockout Mice Testes by Attenuating Oxidative Stress and Infammation

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Apolipoprotein E (ApoE) is a member of apolipoprotein (apo) family and plays critical role in lipid metabolism. In this study, the relationship between abnormal lipid metabolism caused by ApoE-deficient and male reproduction was investigated. The effect of hyperbaric oxygen (HBO) therapy on 7-month-old ApoE-knockout male mice was assessed subsequently. Mice were randomly divided into 3 groups: control group (WT), ApoE (- / -) group (AP-CON), and ApoE (- / -) plus HBO group (AP-HBO), which received HBO treatment. We found that ApoE knockout caused a decrease in male reproductive capacity due to the reduced total sperm motility, progressive motility (PR), and lower blastocyst formation rate. HBO treatment could accelerate serum lipoprotein metabolism including LDL, T-CHO, and TG and semen quality. As a result, fertilization and blastocyst formation of AP-HBO group were higher than that of AP-CON, proving positive therapeutic effect. Mechanism exploration found that HBO treatment

ameliorated the testicular microenvironment by attenuating inflammatory factor production and oxidative stress, eventually improved the sperm motility. Collectively, our study provided more evidences of HBO treatment for improving the semen quality of patients with abnormal lipid metabolism caused by ApoE-deficient.

Key Words ApoE; Hyperbaric oxygen; Lipoprotein metabolism; Oxidative stress; Semen parameters.

Association between HPV infection on the development and pregnancy outcome in patients with endometriosis

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Research purpose: Whether HPV infection is related to the development and pregnancy outcome in patients with endometriosis?

Methods: We conducted a meta-analysis of seven studies to explore the correlation between HPV infection, endometriosis and infertility. Additionally, we performed a retrospective cohort study analyzing the clinical data of 432 patients who underwent surgical treatment for endometriosis at Nanjing Maternity and Child Health Care Hospital between January 2017 and June 2022.

Results: We found no statistically significant difference in the HPV infection rate (OR:2.60, 95% CI [0.28,23.87]) and the high-risk HPV infection rate (OR:1.68, 95% CI [0.49,5.75]) between patients with endometriosis and the control group. The prevalence of HPV infection among patients with endometriosis was 46% (95% CI [0.23, 0.90]), and the prevalence of high-risk HPV infection was 36%. There was no statistically significant difference in HPV infection rates between the infertility group of patients with endometriosis and those with normal pregnancies (OR:0.73, 95% CI [0.07,7.20]). In our retrospective study, the HPV-positive group had a lower postoperative birth rate than the HPV-negative group (10.6% vs. 21%), with a statistically significance ($P < 0.05$).

Discussion: This study found that the postoperative birth rate in endometriosis patients with concurrent HPV infection was significantly lower than that in HPV-negative patients. Assessing and treating coexisting HPV infection in endometriosis patients may contribute to preserving fertility and improving postoperative birth rates, offering new insights for clinical practitioners.

Key Words Human papillomavirus; endometriosis; female infertility; pregnancy outcomes; meta-analysis; retrospective analysis

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

转录暂停-延伸切换的分子锁：LEDGF/p75-SPT5）在转录失调疾病中的双向调控

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基因转录的动态调控异常是多种遗传性疾病发生的重要机制。RNA聚合酶II（Pol II）在启动子近端的暂停-释放平衡，直接决定基因表达模式，其失调与白血病、先天性免疫缺陷等遗传病密切相关。此前，我们发现转录延伸复合物（SEC）将SPT5从稳定的转录暂停凝聚物转变为延伸液滴，顺畅推动转录过程的进行。然而，作为进化上高度保守的转录暂停/延伸因子，SPT5在转录早期延伸过程中的角色转变机制尚不明确。晶状体上皮源性生长因子（LEDGF/p75），是一种染色质相关蛋白，在转录调节和DNA修复中扮演重要角色，其异常与多种人类疾病相关，包括艾滋病、癌症和自身免疫。本研究首次阐明染色质调控因子LEDGF/p75通过阻断SPT5磷酸化维持转录暂停状态的核心机制，为遗传性转录调控疾病的分子病理提供了全新视角。研究发现，SPT5蛋白羧基末端的双功能结构域（PRD/CTR1和PLD/CTR2）构成转录状态转换的分子开关：PRD作为磷酸化靶标介导SEC激酶复合物驱动的延伸激活，而PLD朊病毒样结构域通过与LEDGF/p75结合，形成空间位阻效应抑制PRD磷酸化。特别值得注意的是，LEDGF/p75的整合酶结合域（IBD）展现出双重抑制功能：一方面通过降低SEC在启动子区域的结合效率；另一方面协同转录暂停凝聚物，形成屏障阻止SEC对SPT5-PRD的磷酸化修饰。总之，本研究揭示了LEDGF/p75与SEC如何通过协同作用调控SPT5，确保转录从暂停到延伸的顺利过渡。该研究为转录暂停与延伸之间的切换提供了新的调控机制视角，对发展精准表观遗传治疗手段具有重要指导价值和重要的生物学意义。

关键字 RNA聚合酶II, 疾病, 转录暂停, 转录延伸, 超级延伸复合物

高龄孕妇胎盘微环境中雄激素水平升高介导LAMA3抑制滋养细胞侵袭的机制研究

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目的：本研究旨在探讨高雄激素状态通过LAMA3-PI3K/Akt通路在高龄妊娠中引发子痫前期的机制，并评估对滋养细胞侵袭及迁移能力的影响。

方法：通过双氢睾酮刺激滋养细胞，进一步使用RNA测序（RNA-Seq）、GO与KEGG分析筛选出差异表达基因LAMA3。采用实时荧光定量 PCR（RT-qPCR）、免疫印迹（Western blot）检测LAMA3的mRNA和蛋白表达水平。质粒转染法获得LAMA3过表达的滋养细胞。采用基于基质的Transwell法评估细

胞侵袭、划痕实验检测细胞迁移能力。

结果：双氢睾酮(DHT)刺激显著抑制了滋养细胞的侵袭和迁移能力。通过RNA-seq筛选发现LAMA3可能是关键分子，进一步的Western blot和RT-PCR分析显示，高龄妊娠胎盘中LAMA3的蛋白和mRNA表达明显高于正常妊娠胎盘，且与子痫前期患者胎盘中的发现一致。LAMA3过表达显著抑制滋养细胞的侵袭和迁移能力，同时使PI3K和AKT的磷酸化水平上调。使用PI3K抑制剂后，细胞功能和磷酸化水平基本恢复正常水平。

结论：高龄孕妇滋养细胞异常增高的雄激素水平诱导LAMA3表达发生特异性变化，并且LAMA3通过调控PI3K/AKT信号通路影响滋养细胞迁移侵袭能力，这可能是子痫前期发病的一个致病因素。

关键字 高龄妊娠;胎盘;雄激素;层粘连蛋白;PI3K信号通路

UA causes heart development abnormalities in zebrafish by affecting the Wnt signaling pathway

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Objective To investigate whether uric acid (UA) can cause cardiac malformations in zebrafish and whether it can affect heart development through Wnt signaling. Methods Exogenous UA treatment, in vivo xdh overexpression, and uox gene knockdown techniques were used to increase the levels of both exogenous and endogenous UA in zebrafish. The expression of Wnt signaling components (wnt1, wnt3a, wnt6b, β-catenin), cardiac progenitor cell markers (mesp1, isl1), cardiomyogenic neural crest cell markers (sox10, crestin), and cardiac development-related genes (nkx2.5, tbx5, fgf10) were measured. In vivo and in vitro rescue experiments were conducted to validate the role of UA in influencing zebrafish heart development via Wnt signaling. Results Both exogenous UA treatment, in vivo xdh overexpression, and uox gene knockdown models resulted in a significant increase in UA levels at multiple time points in zebrafish. These treatments led to increased pericardial edema, reduced heart rate, smaller hearts, and a decrease in cardiac ring structures at 72 hpf, along with a significant reduction in the expression of wnt signaling and cardiac development-related genes at key developmental stages. The Wnt pathway activator CHIR99021 partially rescued these cardiac developmental defects induced by exogenous and endogenous UA. Conclusion Both exogenous and endogenous UA can induce cardiac malformations in zebrafish by affecting wnt1, wnt3a, and wnt6b, thereby influencing downstream cardiac development-related genes.

Key Words Congenital heart disease; Wnt; Heart development; Cardiac precursor cells

Diacylglycerol kinase gene Dgkh deficiency disrupts testicular lipid balance in male mice without affecting fertility

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Background: Diacylglycerol kinases (DGKs) regulate lipid signaling by converting diacylglycerol to phosphatidic acid. Among DGK isoforms, DGK η, encoded by the Dgkh gene, is highly expressed in the testis, yet its role in spermatogenesis remains unclear.

Method: To investigate the role of DGK η in male fertility, we generated Dgkh knockout (Dgkh−/−) mice using CRISPR/Cas9 technology. Multi−tissue expression profiling, lipidomic analysis of testis tissue, histological examination, and fertility assessments were conducted. Sperm count, motility, and progressive motility were evaluated alongside lipid metabolite profiling using LC−MS/MS.

Results: Dgkh expression was localized to testicular germ cells, peaking in round spermatids. Lipidomic analysis showed altered lipid profiles in Dgkh−/− testes, including increased diacylglycerol, triglycerides, with reduced phosphatidic acid and lyso−phosphatidylcholine. However, histological analysis revealed normal spermatogenesis, and Dgkh−/− males showed unaltered sperm characteristics and fertility. KEGG pathway enrichment highlighted changes in lipid metabolism but without functional deficits in reproduction.

Conclusion: Although Dgkh influences testicular lipid metabolism, its knockout does not impair spermatogenesis or male fertility, suggesting functional redundancy among DGK isoforms. These findings provide novel insights into the role of DGK η in testicular lipid regulation and its limited impact on male reproductive biology.

Key Words DGK η, Spermatogenesis, Male fertility, Testicular lipid metabolism, Gene knockout.

·遗传病的检测与诊断新技术·

多种遗传学诊断方法综合运用产前诊断先天性多发性关节挛缩6型胎儿

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目的：为连续两胎足内翻、羊水过多胎儿进行产前诊断，明确病因并指导夫妻再次妊娠。

方法：提取胎儿羊水及父母、第一胎样本外周血DNA，染色体芯片技术检测两次胎儿的拷贝数变异情况；外显子测序技术寻找胎儿可能的致病位点；基因组光学图谱技术及定量PCR技术确定变异的位置及剂量变化。

结果：染色体芯片技术检出第一胎14号染色体q23.2q32.12区域ROH，导致Temple综合征；外显子测序技术检测出两胎均有NEB (NM_001164508.2): c.24549_24550del,p.R8183Sfs9（致病性）和exon82-exon102dup复合杂合突变（临床意义不明）；基因组光学图谱技术及定量PCR技术确定exon82-exon105dup为串联重复变异，升级为可疑致病变异。两个胎儿均确诊先天性多发性关节挛缩6型。

结论：染色体芯片技术、外显子测序技术、基因组光学图谱技术及定量PCR技术的综合应用有利于遗传病的明确诊断；先天性多发性关节挛缩6型为难以治疗的疾病，预后不良；再次妊娠可考虑三代试管助孕或自然受孕后行产前诊断。

关键字 足内翻；先天性多发性关节挛缩6型；NEB；外显子测序技术；基因组光学图谱技术

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

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Background：Complex chromosomal rearrangements are rare events that are considered difficult to detect by routine cytogenetic methods. Chromosome conformation Karotyping (C-MoKa), a new chromosomal rearrangement detection method derived from Hi-C was facilitated as the robust complementary method for mosaic reciprocal translocation at the breakpoints in centromere region in clinical practice at the first time.

Aim：We aim to investigate the potential of existing chromosomal detection technologies (karyotyping, CMA, OGM, SV-Seq and C-MoKa) to detect possible complex rearrangements in patients, providing new insights for clinical application.

Method：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).

Result: The C-MoKa data were consistent with our hypothesis to detect the complex reciprocal translocation, OGM detected breakpoints in highly repetitive region and SV-Seq inferred the same structure. CMA showed the copy number variants within its limitation and kayrotyping analysis displayed a negative result at the first detection.

Conclusion: In conclusion, CMA and OGM have limitations of mosaic reciprocal translocation at the breakpoint of highly repetitive region, SV-seq and C-MoKa could provide relatively comprehensive information indicating structural abnormalities. Our study showed C-MoKa as a complementary approach to traditional techniques for the detection of complex mosaic unbalanced translocation especially in centromere region. It is noteworthy that C-MoKa preferably fresh sample, if which is impossible, SV-seq may be considered.

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

高通量PCR技术的研究进展与应用前景

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目的：探讨高通量PCR技术的最新进展及其应用前景，以满足临床诊断和科研需求。

方法：回顾PCR发展历程，概述实时荧光PCR、MeltArray、二维PCR和数字PCR等关键技术及其优势，同时指出技术挑战。

结果：实时荧光PCR（RT-PCR）：通过加入荧光基团或染料实时监测PCR进程，实现高灵敏度和特异性的定量分析。MeltArray技术：利用Taq DNA聚合酶的5′-瓣核酸内切酶活性切割介体探针，通过熔解曲线分析实现多重检测。二维PCR（2D-PCR）：引入人工合成的序列标签，结合碱基淬灭探针技术和荧光熔解温度分析，实现高通量检测。本文总结了高通量PCR技术在临床诊断和基础研究中的应用实例及其显著优势。例如，在COVID-19检测、结核病诊断、伤寒沙门氏菌分型、遗传病筛查、感染性疾病快速检测等方面，高通量PCR技术均表现出色。然而，该技术也面临引物设计复杂、定量分析能力有限等挑战。

讨论：未来发展方向包括进一步提高检测通量、优化引物设计、增强定量分析能力及探索微流控技术应用，以推动疾病检测与诊断领域的进步。本文为高通量PCR技术的未来发展提供参考，旨在促进其广泛应用与持续进步。

关键字 PCR；高通量PCR；应用；研究进展

基于长读长测序的脆性X综合征基因检测及临床应用研究

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目的：探讨基于长片段PCR（LR-PCR）与长读长测序（LRS）结合的FXS综合分析方法（comprehensive analysis of FXS，CAFXS）应用于脆性X综合征（FXS）基因检测的检测性能，为FXS的筛查和遗传学诊断提供参考。

方法：选择2021年7月至2023年7月来南京市妇幼保健院就诊的33例携带者筛查受试者/FXS患者及其家系成员为研究对象，采用CAFXS检测FMR1基因的CGG重复数、AGG插入、1号外显子单核苷酸变异（SNVs）、小片段插入/缺失（InDels）和微缺失.。同时采用三核苷酸重复引物PCR（TP-PCR）结合毛细管电泳（CE）检测CGG重复数，并对比2种方法的检测结果。

结果：① CAFXS与TP-PCR/CE在检测FMR1 基因分型结果一致，在33例样品中，全突变型为10例、前突变型为9例、中间型为7例和正常型为7例。② CAFXS能精准识别AGG插入位置和数量，CAFXS检测到33例样品中共有73个AGG插入，涉及36种不同AGG插入模式，其中频率最高的为9A9A9（24.6%）。③CAFXS检测到9例（27.3%）CGG重复嵌合型，包括前突变/全突变型嵌合（6例）、全突变型嵌合（2例）和正常型嵌合（1例）。④33例样品均未检测到FMR1基因1号外显子罕见SNVs、InDel和微缺失致病变异。

结论：CAFXS可全面、准确地进行FMR1基因分析，可为临床提供更多遗传信息。

关键字 脆性X综合征；FMR1基因；CGG重复；三代测序

罕见丙酮酸脱氢酶复合物缺乏症1家系3例影像特点及遗传学分析并文献复习

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目的：分析连续两次妊娠丙酮酸脱氢酶复合物缺乏症胎儿家系病例资料、影像及基因突变特点。

方法：选取2022年9月-2024年1月于南通大学附属南通妇幼保健院产前检查中发现的一个连续两次妊娠神经系统发育异常胎儿家系为研究对象。收集家系临床资料、影像学检查结果（颅脑MRI、彩色多普勒超声）进行回顾性分析。应用全外显子组测序（Whole Exome Sequencing，WES）技术对家系成员进行基因检测，对候选致病变异，进行Sanger测序家系验证。应用微滴式数字PCR（droplet digital PCR，ddPCR） 技术检测母亲不同胚层来源标本中的致病变异嵌合比例。结合本病国内外研究进展做文献复习。

结果：母亲及2胎儿颅脑MRI及彩色多普勒超声结果均显示侧脑室不同程度扩大，胼胝体发育不良或缺如，其中母亲伴有脑白质变性，2胎儿均伴有神经节隆起（Ganglionic Eminence，GE）内囊性病变及侧脑室出血。WES结果显示两名患儿携带PDHA1基因c.1033_1035del杂合变异，为新发变异。Sanger测序

验证患儿存在该变异，母亲和父亲该位点为野生型。ddPCR提示母亲为c.1033_1035del变异携带者，该变异在源于 3 个胚层的样本中嵌合比例为6.35%–11.17%。

结论：母亲携带低比例PDHA1基因c.1033_1035del杂合变异为两次妊娠丙酮酸脱氢酶复合物缺乏症胎儿的遗传学病因，孕中期胎儿影像学提示胼胝体发育不良或缺如合并GE内囊性病变可能为该疾病产前诊断的影像学标志。

关键字 丙酮酸脱氢酶复合物缺乏症；基因检测；胼胝体发育不良；MR

羊水细胞的转录组特征及其在产前诊断中的应用潜力探索

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目的：高通量基因组测序技术极大地提升了孟德尔病诊断率，但在解释变异致病性方面仍存在巨大挑战。转录组测序技术弥补了这一缺陷并对产后孟德尔病诊断率提升有显著贡献，但在产前领域研究甚少。本研究基于转录组测序技术，探索转录组测序在产前孟德尔病诊断中的应用潜力。

方法：收集不同孕周胎儿的羊水细胞，进行转录组测序和生物信息学分析。

结果：新鲜羊水细胞与培养羊水细胞表达谱存在差异，培养前比培养后羊水细胞基因表达数量更多，培养羊水细胞基因表达谱与成纤维细胞基因表达谱更为接近。相同细胞培养条件下，常规建库比微量建库羊水细胞基因表达数量更多。回顾性分析典型已知阳性的染色体异常与单核苷酸变异羊水细胞样本，可以被转录组测序检出。

结论：羊水细胞在体外培养不同阶段的转录组特征存在差异，转录组测序具有在产前孟德尔病诊断中的应用潜力。

关键字 羊水细胞，转录组测序，孟德尔病，产前诊断，数据集

NR5A1基因变异致47,XYY性反转综合征患者的遗传学分析及文献复习

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目的：探讨1例身材高大、原发闭经47,XYY性反转综合征患者的临床表型和遗传学病因。

方法：以2024年7月因“身材高大、原发闭经”就诊于南京大学医学院附属鼓楼医院的1例女性患者为研究对象。收集其临床资料，应用外周血染色体核型分析、染色体拷贝数变异测序(copy number variation sequencing，CNV–seq)、AZF区及SRY基因多重PCR、全外显子组测序（Whole Exome Sequencing，WES）进行遗传学分析。检索中国知网（CNKI）、美国医学文摘数据库（PubMed）等数据库中47,XYY性反转综合征的文献报道，总结患者临床表型及遗传学检测结果。

结果：外周血染色体G显带核型结果为47,XYY；Y染色体AZF区无缺失，SRY阳性；CNV–seq结果显示Seq[GRCh37]Yp11.32q12×2；WES检测结果提示患者携带NR5A1基因c.86C>A (p.Thr29Lys) 疑似致病变

异。文献检索显示，共报道7例47,XYY性反转病例，其中2例为46,XY/47,XYY嵌合，患者社会性别均为女性，均存在性腺生殖器发育异常。有5例接受SRY检测且均为阳性，其中1例接受外显子测序但未见异常，遗传学检测结果均无法解释患者临床表型。

结论：患者社会性别为女性，染色体核型为47,XYY且SRY(+)，NR5A1基因c.86C＞A (p.Thr29Lys)变异是该患者性反转的遗传学病因，为临床咨询提供依据。

关键字 47,XYY综合征；性反转；NR5A1基因；全外显子测序

Preimplantation Genetic Testing for Cornelia de Lange Syndrome with Low-Level Maternal Gonadal Mosaicism using nanopore sequencing and digital PCR

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Background: Presently, to address the limited resolution at the single-cell level within the preimplantation genetic testing for aneuploidy (PGT-A) framework, our institution implemented a preimplantation genetic testing for monogenic disease (PGT-M) strategy based on haplotype linkage analysis for families with copy number variants (CNVs) < 1 Mb.

Objective: This study aims to deliver an accurate diagnosis for a Chinese family affected by Cornelia de Lange syndrome 5 (CDLS5) resulting from a microdeletion del(X)(q13.1q13.2) in the HDAC8 gene, characterized by notably low-level gonadal mosaicism. Furthermore, we execute preimplantation genetic testing for aneuploidy and monogenic disorders leveraging the diagnostic outcomes.

Methods: A de novo CNV was identified through chromosomal microarray analysis (CMA) and Whole Exome Sequencing (WES) in a family experiencing two unsuccessful pregnancies, indicating the existence of germline mosaicism. Validation of this CNV was performed via real-time quantitative polymerase chain reaction (PCR). Whole-genome low-coverage mate-pair sequencing (WGL-MPS) was conducted on female peripheral blood to exclude cryptic chromosomal abnormalities or mosaic states. Long-PCR was utilized to amplify the deleted fragment in insufficient miscarriage samples, with primers designed at breakpoints identified through WES and CMA results. After purifying the Long-PCR products, Oxford Nanopore Technology (ONT) third-generation sequencing was employed to pinpoint specific breakpoint positions. Designed primers and probes for droplet-digital polymerase chain reaction (ddPCR) were utilized to confirm the presence and proportion of germline mosaicism in ovarian samples obtained during in vitro fertilization procedures, such as granulosa cells and follicular fluid.

Results: The disease-causing microdeletion at Xq13.1q13.2 disrupting the HDAC8 Gene in the two male miscarriage tissues was not detected in the parents' peripheral blood cells by CMA, ES, quantitative PCR, and WGL-MPS. The maternal gonadal tissues were assumed to be the source of inheritance as Cornelia de Lange syndrome 5 (CDLS5) is an X-linked dominant disease. Specific breakpoint positions (chrX:g.71666527-71838853, 172 kb) were identified through third-generation sequencing of Long-PCR products. ddPCR quantitatively revealed approximately 1% mosaic state for the deletions in ovarian granulosa cells and none in peripheral blood cells, confirming the presence of CNV-induced gonadal mosaicism, a novel finding in maternal ovarian tissues. PGT

investigations indicated 16.7% (1/6) of embryos with the deletion, demonstrating a low-level gonadal mosaicism.

Conclusion: Our findings underscore the efficacy of PGT-M utilizing haplotype linkage analysis for CNVs < 1 Mb, even in cases of gonadal mosaicism, emphasizing the significance of parental testing in CDLS5 families and the reproductive utility of in vitro fertilization (IVF) with PGT for families affected by low-level parental gonadal mosaicism. By employing a spectrum of methodologies, including NGS-based sequencing, microarray-based comparative genomic hybridization, and ddPCR for precise breakpoint determination, we showcase approaches to address and resolve uncommon genetic mechanisms underlying microdeletions in cases of gonadal mosaicism. Our results advocate for the expanded application of PGT-M based on haplotype linkage analysis for families with minor pathogenic CNVs.

Key Words Cornelia de Lange syndrome (CDLS), low-level gonadal mosaicism, nanopore sequencing, droplet-digital PCR, preimplantation genetic testing for monogenic disease (PGT-M).

Accurate detection of D4Z4 repeats, methylation and allele haplotype in facioscapulohumeral muscular dystrophy 1 using Nanopore long-read adaptive sampling sequencing

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Background: Facioscapulohumeral muscular dystrophy 1 (FSHD1) is a high-prevalence autosomal dominant neuromuscular disease. Genetic diagnosis of FSHD1 remains a challenge because of the long length and repetitive nature of D4Z4 repeats. Long-read sequencing is an effective method for detecting FSHD1, but sequencing depth remains a limitation.

Methods: We developed a long read library adaptive sampling (LRL-AS) method based on Oxford Nanopore Technologies (ONT) sequencing to comprehensively detect FSHD1. Two patients were sequenced by adaptive sampling, along with D4Z4 repeat units, methylation, and haplotype analyses.

Results: Compared to whole-genome sequencing, our LRL-AS method shows significant improvements in both sequencing depth and read length. LRL-AS can identify D4Z4 repeat units contraction matching the precision of optical genome mapping in both 4q35 and 10q26 regions. We also calculated methylation level in the DUX4 gene region. With the benefit of higher sequencing depth, allele-specific methylation can be calculated with greater precision. We also observed that, at different sequencing depths, ONT sequencing data consistently provide stable calculations of methylation levels. More importantly, we demonstrated that data from adaptive sampling can be effectively used to construct haplotype of pathogenetic allele based on single nucleotide polymorphisms.

Conclusions: Our LRL-AS method is a comprehensive approach for FSHD1 detection, improving the accuracy of D4Z4 repeat units and methylation detection while enabling allele-specific haplotype construction. It holds promising potential for clinical application.

Key Words Nanopore sequencing, Facioscapulohumeral muscular dystrophy 1, Methylation, Haplotype

PGT-SR周期中易位携带家系可移植胚胎数量和取消周期的影响因素分析

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目的：易位是最主要的一类适合行胚胎植入前遗传学检测（PGT）的染色体病。由于易位携带者在配子减数分裂时染色体异常分离的高发，此类人群往往面临可移植胚胎数量少和取消周期多的困境。此处针对性别、年龄、易位类型等分组统计以探讨不同因素对易位携带家系可移植胚胎数量和取消周期的影响。

方法：对2019-2023年至苏州市立医院生殖与遗传中心行PGT-SR的患者（包括相互易位和罗氏易位携带）进行回顾性病例对照分析。分别按性别、女方年龄（<35岁、≥35岁）、男方年龄（<35岁、≥35岁）、女方AMH水平（<3.6ng/ml、≥3.6ng/ml）进行分组及男方精子DNA碎片指数（DFI）（<15%、≥15%）进行分组统计。另外对相互易位类型（易位是否涉及近端着丝粒染色体、易位是否涉及染色体末梢断裂）及罗氏易位类型（是否为最常见的der（13;14）罗氏易位）进行分组，以确定不同关联因素对易位携带家系可移植胚胎数量和取消周期的影响。

结果：在318个PGT-SR周期中，按性别进行分组发现在罗氏易位携带者中，男方携带的可移植胚胎数要显著高于女方携带，男方携带的取消周期显著低于女方携带。而在不同性别的相互易位携带者中可移植胚胎数量和取消周期无显著差异。按女方年龄（<35岁、≥35岁）进行分组发现在罗氏易位和相互易位携带者中均存在随着女方年龄增加而导致的可移植胚胎数量显著下降和取消周期数量的显著增加。而按男方年龄（<35岁、≥35岁）分组发现只在相互易位携带者中出现高龄男性组取消周期数量显著增加的情况。按女方AMH水平（<3.6ng/ml、≥3.6ng/ml）进行分组发现高AMH组在罗氏易位和相互易位携带者中均存在取消周期数量显著低于低AMH组的情况。按男方精子DNA碎片指数（DFI）（<15%、≥15%）进行分组发现在相互易位携带者中出现高DFI组可移植胚胎数显著下降和取消周期数量显著增加的情况。按相互易位类型（易位是否涉及近端着丝粒染色体、易位是否涉及染色体末梢断裂）进行分组发现易位涉及近端着丝粒染色体的组别的取消周期要显著低于易位未涉及近端着丝粒染色体组；易位涉及染色体末梢断裂的组别的取消周期要显著高于易位未涉及染色体末梢断裂组。按罗氏易位类型（是否为最常见的der（13;14）罗氏易位）进行分组发现不同类型的罗氏易位可移植胚胎数量和取消周期均无显著差异。

结论：在PGT-SR周期中，女性罗氏易位携带者相比于男性携带者面临更少的可移植胚胎数量和更多的取消周期，而在不同性别相互易位携带者中没有明显的差异。女方年龄不只影响PGT-A的成功率，也在很大程度上影响PGT-SR的成功率，这方面男性年龄的影响较弱，只表现在相互易位携带者中出现高龄男性组取消周期数量显著增加的情况。女性AMH水平可以很好的作为预测易位携带者PGT-SR周期因为无可移植胚胎而成为取消周期的指标。男性高DFI可能对相互易位携带者的PGT-SR周期结局造成不良影响。相互易位携带者中不同类型的取消周期有显著差异而不同类型的罗氏易位携带者却没有，表明有些相互易位类型的特殊性导致无可移植胚胎产生的风险增加。

关键字 胚胎植入前遗传学检测；罗氏易位；相互易位；性别；年龄；抗缪勒管激素；精子DNA碎片指数

Exploration of Copy Number Variations and Candidate Genes in Fetal Congenital Heart Disease Using Chromosomal Microarray Analysis

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Objective: This study aimed to investigate copy number variations (CNVs) and potential candidate genes associated with fetal congenital heart disease(CHD) and to compare the prevalence of CNVs among different CHD subtypes.

Methods: A retrospective analysis was performed on 391 fetuses diagnosed with CHD between 2019 and 2023. 391 fetuses with case were divided into three groups: isolated CHD (Group 1), complex CHD (Group 2), and CHD with extracardiac anomalies (Group 3). Amniocentesis was performed for all pregnant women, with both karyotyping and CMA conducted. Gene Ontology (GO) annotation and KEGG pathway analyses were conducted for isolated and complex CHD cases.

Results: CMA and karyotype detected total abnormalities in 22% of all CHD fetuses, including a chromosomal aneuploidy rate of 7.2%, a pathogenic CNV (pCNV) rate of 6.1%. The overall detection rates for Groups 1, 2, and 3 were 11.6%, 12.5% , and 50%, respectively. Group 3 exhibited significantly higher rates of chromosomal aneuploidy (23.7%) and pCNV (17.8%) compared to Groups 1 and 2 ($P<0.001$). No significant differences in maternal age were observed among the three CHD groups. KEGG pathway analysis identified the top three enriched pathways for complex CHD were nucleocytoplasmic transport, cell adhesion molecules, and the mRNA surveillance pathway.

Conclusion: The rates of chromosomal aneuploidy and CNV abnormalities in CHD cases with extracardiac anomalies were significantly higher than in the other two groups. Maternal age was not associated with the chromosomal abnormalities observed in CHD cases. KEGG pathway analysis indicated more intricate molecular pathways in complex CHD.

Key Words congenital heart disease; prenatal diagnosis; chromosomal microarray analysis; copy number variation; pathway

染色体微阵列技术在诊断羊水染色体核型中未知片段的应用

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目的：建立一套产前诊断的模式，对于未知片段的染色体异常作出明确的细胞及分子遗传学诊断，并给予临床以足够的信息来进行正确的妊娠干预。

方法：筛选出符合要求的2018年4月至2024年12月在我院接受羊水染色体核型分析及染色体微阵列技术检测的7例孕妇资料，对结果进行分析。

结果：7例孕妇的产前诊断的细胞遗传学结果，包括衍生染色体及标记染色体，都被染色体微阵列检测结果进一步验证和确诊，是某一条染色体的部分片段的重复或缺失。

讨论：自羊水染色体显带技术开展以来，作为产前诊断的“金标准”，染色体核型分析被广泛应用于临床，但其只能检测出染色体片段＞5 Mb的异常，且影响因素较多，核型分析无法发现染色体上微小片段缺失及重复，更不能准确定标记染色体及未知染色体片段的来源；且染色体核型分析需要进行细胞培养，报告周期长。染色体微阵列分析 （ CMA ）是一项新兴的分子水平的染色体分析技术，它能检测出约1 kb的拷贝数变异(copy number variation, CNV)的微缺失/微重复，故被称之为“分子”核型，与染色体核型分析相比,CMA具有更加高度的自动化程度、更快捷的检测周期以及更好的分辨效率，它弥补了染色体核型分析的不足。

关键字 染色体微阵列技术；羊水染色体核型；未知片段

NPM1突变的AML分子监测

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NPM1– 突变的急性髓样白血病（ AML ）代表成年AML的最大分子亚组。NPM1– 突变的AML是通过分子技术和免疫组织化学识别的，当合并时，它可以解决困难的诊断问题（包括鉴定髓样肉瘤和NPM112号外显子突变）。根据2022年更新的欧洲白血病（ELN）指南，确定了NPM1（和FLT3）是基于遗传的AML风险分层的强制性步骤。 QRT–PCR对可测量的残留疾病（ MRD ）进行监测，结合ELN风险分层，可以在压缩后阶段指导治疗决定。NPM1突变急性髓样白血病（ AML ）代表成年人中最大的AML分子亚组，占病例的30％至35％。NPM1突变是AML特异性的驱动遗传事件并促进白血病与其他基因的突变一起作用，通常与克隆造血有关。NPM1突变的特征是NPM1突变体的异常细胞质定位（和独特的基因表达曲线。NPM1突变可以通过分子测定或包括IHC在内的替代技术来鉴定。这些方法是互补的，允许一种灵活的方法来诊断NPM1– 流动的AML对于实施全球ICC和谁分类至关重要。NPM1突变可以通过分子测定或包括IHC在内的替代技术来鉴定。这些方法是互补的，允许一种灵活的方法来诊断NPM1– 流动的AML对于实施全球ICC和谁分类至关重要。定性测定NPM1突变最常基于基因组DNA作为底物，并使用PCR，然后使用片段长度分析来检测插入，尽管基于熔融曲线分析和QRT–PCR的测定也可用。IHC检测NPM1是一种简单，低成本，非常敏感和特定的替代测定法。有趣的是，IHC还允许在组织切片的蛋白质水平上研究遗传病变，并可能提供有关有关该蛋白质的遗传病变的信息NPM1– 突变的白血病细胞。通过流式细胞仪诊断NPM1特定的表型。约23％NPM1突变1的AML显示多发育不全。这些病例可能被误诊为骨髓增生（ MDS ）或AML/MDS。演示NPM1突变建立了诊断，因为遗传病变取代了重要性的形态。 IHC通过证明核苷和髓样谱系的前体甚至成熟的巨核细胞中的核磷脂的异常细胞质表达来证实多核的参与。IHC是检测发生在外显子12以外的NPM1突变的绝佳方法。如果将IHC和分子测定组合使用，则两种技术之间的差异应迅速分析整个整个NPM1编码顺序，以识别其他外显子中的突变。

关键字 NPM1突变；AML

NITS联合血清学游离雌三醇检测在X连锁鱼鳞病产前检测中的效果分析

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目的：X-连锁鱼鳞病（X-linked ichthyosis, XLI）是一种常见的临床遗传性疾病，由类固醇硫酸酯酶（steroid sulfatase, STS）缺乏引起。STS基因位于Xp22.31区域，近90%的XLI病例由微缺失导致。迄今为止，只有侵入性产前诊断技术能够实现XLI的准确诊断。本研究旨在提出一种高准确性的XLI产前筛查新临床路径。

方法：回顾性分析了75,485例血清学筛查数据。筛选出未结合血清雌三醇（uE3）MoM值较低的孕妇，并进一步进行无创产前筛查（NIPS）。通过这两种方法结合实现XLI的产前筛查，并通过进一步的产前诊断评估其准确性。

结果：共筛选出139例uE3 MoM值较低（<0.3）的孕妇。经过遗传咨询后，其中50例接受了NIPS检测。最终在Xp22.31区域（覆盖STS基因）检测到28例母源性微缺失。结合血清学筛查和NIPS结果，uE3水平低且携带Xp22.31缺失的孕妇可能怀有XLI胎儿。经验证，本研究提出的新临床路径能够以较高准确性筛查XLI。

讨论：本研究提出了一种高准确性的XLI产前筛查新临床路径，可用于XLI的早期筛查和诊断，从而加强妊娠管理和儿童管理。

关键字 NIPT,X-连锁鱼鳞病,未结合血清雌三醇

一个常染色体隐性多囊肾家系的PKHD1基因变异分析

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目的：对一个常染色体隐性多囊肾（ARPKD）家系进行基因变异分析，推断出可能的遗传学病因。

方法：收集胎儿及父母的临床资料及样本DNA，应用高通量测序技术对胎儿进行测序分析，筛选候选基因变异位点，以Sanger测序验证变异位点并对父母进行溯源检测。

结果：测序结果显示胎儿PKHD1基因存在第4外显子c.279_281+13delinsA（p.Arg94fs）和第58外显子c.9769C>T（p.Gln3257）的复合杂合变异，分别来自父亲和母亲。

结论：该ARPKD家系的遗传学病因可能为PKHD1基因的复合杂合变异，新变异的检出扩展了PKHD1基因的变异分布谱系，并为家系的遗传咨询和再生育指导提供了分子依据。

关键字 多囊肾；常染色体隐性遗传；PKHD1基因；全外显子组测序

Diagnostic discordance in trisomy 9 mosaicism detection: Asymptomatic maternal case with divergent karyotyping/other genetic methods findings and literature review

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Objective: To investigate diagnostic discrepancies arising from karyotyping and other genetic techniques in a p henotypically normal gravida with trisomy 9 mosaicism (T9M).

Material and methods: This study was designed as a case report and literature review. Noninvasive prenatal screening (NIPS) detected fetal cell-free DNA in maternal plasma. Confirmatory testing included chromosome microarray analysis (CMA), copy-number variation sequencing (CNV-seq), karyotyping, and fluorescent in situ hybridization (FISH).

Results: At 13 gestational weeks, NIPS indicated a high risk of trisomy 9 (T9). Prenatal diagnostic tests revealed a 986-kb heterozygous deletion at 5p15.1 in the fetus, inherited maternally. Unexpectedly, T9M was identified in the mother using CMA (48%), CNV-seq (56%), and FISH (37%), while karyotyping of cultured peripheral blood lymphocytes showed no abnormalities. Literature review highlighted discrepancies in T9M detection across techniques, sample types, and culture conditions.

Conclusion: Despite maternal chimerism, a euploid newborn was successfully delivered. Diagnostic discordance underscores the necessity of integrating multiple genetic methods (cultured/uncultured samples) to minimize false negatives. Genetic counseling should emphasize phenotypic variability in T9M and the limitations of different techniques.

Key Words Trisomy 9 mosaicism, genetic testing discrepancies, benign outcome

SLC12A2基因c.2930-1G>A罕见变异的剪接效应验证的Minigene分析

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背景：听力损失（HL）是一种极为普遍的感官障碍，其发生机制中遗传因素占据重要地位。SLC12A2基因负责编码钠钾氯同向转运体1（NKCC1），这一转运体在内耳的离子稳态维持中发挥着至关重要的作用。近期，研究人员在该基因中发现了一种名为c.2930-1G>A的新型变异，这一变异可能与感音神经性听力损失的发生密切相关。

目的：本研究旨在深入探讨SLC12A2基因中的c.2930-1G>A变异对mRNA剪接及蛋白质表达的影响，

并据此评估该变异在听力损失中的潜在作用。

材料与方法：研究过程中，我们采用了微基因测定技术和质粒转染实验，以全面分析c.2930-1G>A变异对mRNA剪接的具体影响。同时，我们还利用转染了含有该变异的质粒的HEK-293T和HeLa细胞，对蛋白质表达水平和修饰模式进行了细致的评估。

结果：实验结果显示，c.2930-1G>A变异导致了部分外显子的跳跃，从而在HEK-293T和HeLa细胞中引起了mRNA剪接方式的改变。这一发现提示我们，该变异可能与感音神经性听力损失的发生存在一定的关联。进一步的蛋白质分析揭示，该变异对蛋白质表达和修饰产生了不同的影响：E21del突变增强了蛋白质的表达水平，但并未改变其修饰模式；而2930_2977del突变则同时降低了蛋白质的表达水平和修饰程度，这可能对蛋白质的稳定性或修饰位点产生了不良影响。

结论与意义：综上所述，SLC12A2基因中的c.2930-1G>A变异很可能通过改变mRNA剪接和蛋白质表达水平，从而在听力损失的发生过程中发挥重要作用。尽管目前该变异被归类为意义不明确的变异（VUS），但本研究的结果为其潜在的致病性提供了有力支持。为了进一步明确该变异在听力损失中的具体作用，我们还需要收集更多的临床和功能数据。这一研究过程强调了整合遗传、功能和临床信息在改善遗传性听觉障碍的诊断和管理中的重要性。

关键字 SLC12A2,耳聋, minigene 分析,剪切突变, NKCC1 ）

一个中度畸形儿童的2q34-q37.3三体与4q34.3-q35.2单体的病例报告

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引言：染色体微缺失和微重复是导致儿童先天性畸形和发育障碍的重要因素。这些微小的染色体变化可能涉及关键基因的丢失或重复，从而影响正常的发育过程。在临床实践中，准确识别这些微小的染色体异常对于制定治疗计划和提供遗传咨询至关重要。

病例报告：在本病例报告中，我们描述了一名8岁女孩，她因2q34-q37.3三体与4q34.3-q35.2单体而表现出中度畸形特征、发育迟缓以及智力障碍。该儿童出现了一系列颅面和骨骼异常，包括短头畸形、低位耳和指畸形，同时伴有严重的认知和运动发育迟缓。患者的父亲存在2号和4号染色体之间的平衡易位，具体描述为46,XX,der(4)t(2;4)(q35;q35)。相比之下，患者继承了父亲的一条衍生染色体4，导致其核型为46,XX,der(4)t(2;4)(q35;q35)，为不平衡核型。染色体微阵列分析（CMA）确认了2q34至2q37.3区域存在31.3Mb的重复，以及4q34.3至4q35.2区域存在11.2Mb的缺失，这两个区域均涉及多个OMIM基因。

通过详细的临床评估和遗传学检测，我们能够明确诊断出患者的染色体异常，并与她的临床表现相对应。这些基因组不平衡与多种致病表型相关，包括行为异常、智力障碍和面部畸形。此外，患者的表型特征也提示了特定基因功能的丧失或增强，这可能对未来的治疗和管理策略提供指导。

结论：这些发现强调了全面遗传检测在诊断复杂染色体异常中的重要性，并指出了即使在显著染色体重排的情况下，表型表达的变异性。通过深入分析患者的遗传背景，我们不仅能够更好地理解其临床表现，还能够为患者及其家庭提供更为精确的遗传咨询。此外，本病例报告也突显了染色体微阵列分析在识别微小染色体异常中的关键作用，为临床医生提供了重要的诊断工具。

关键字 关键词：染色体异常；平衡易位；染色体微阵列；核型分析

Whole-Genome Sequencing Reveals the Genetic Etiology of Third-Trimester Stillbirth

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Objectives: This study aimed to evaluate the clinical utility of whole-genome sequencing (WGS) in identifying the genetic etiology of stillbirth and to investigate underlying pathogenic mechanisms in third-trimester cases. Elucidating the genetic basis of stillbirth is critical for providing explanations to bereaved families, guiding clinical management in subsequent pregnancies, and informing preventive strategies.

Methods: Thirty pregnant women with unexplained stillbirth occurring after 28 weeks of gestation were enrolled. Chromosomal microarray analysis (CMA) was first performed to exclude chromosomal abnormalities, followed by WGS for cases with normal CMA results.

Results: Chromosomal abnormalities were detected in 5 of 30 cases (16.7%), including Trisomy 21 (n=2), 47,XXY (n=1), 47,XYY (n=1), and a copy number variation (CNV) (n=1). Subsequent WGS analysis of 20 CMA-negative cases identified pathogenic or likely pathogenic variants in 8 cases (40%), involving 16 loci across 13 genes. Key implicated genes included TOGARAM1, SBDS, NF1, CSPP1, and CHD5, all associated with multisystem developmental abnormalities.

Conclusion: Our findings highlight the significant clinical value of WGS in elucidating genetic etiologies of unexplained third-trimester stillbirth. Incorporating advanced genetic testing into routine fetal examinations may enhance diagnostic precision and facilitate targeted interventions to reduce stillbirth risk.

Key Words Stillbirth; WGS; CMA; Genetic etiology;

南京地区新生儿酸性α-葡萄糖苷酶基因致病性变异的携带情况

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目的：评估酸性α-葡萄糖苷酶基因致病性变异在南京新生儿人群的流行情况，为庞贝病的早筛查、早诊断、早治疗提供参考。

方法：本研究为回顾性研究。2022年3月至2024年10月南京医科大学附属妇产医院（南京市妇幼保健院）出生的活产新生儿共30 043例，生后48 h采集足跟血制成干血片，采用芯片捕获二代测序技术检测酸性α-葡萄糖苷酶（acid alpha-glucosidase enzyme，GAA）基因致病性和可疑致病性变异位点，Sanger测序法进行家系验证，通过溶酶体酶活性测定试剂盒检测疑似患者干血斑中的GAA活性。总结新生儿GAA基因致病性变异的携带情况。采用描述性统计分析。

结果：30 043例新生儿中检出232例携带1个GAA致病性/可能致病性变异位点，诊断为携带者；4例携带2个GAA致病性/可能致病性变异位点，为疑似病例。其中疑似病例1和2的GAA活性正常，2个变异位点为顺式变异，临床诊断为携带者；疑似病例3的GAA活性为0.17 μmol/（L·h），低于正常范围[2.63~21.69 μmol/（L·h）]，2个变异位点为反式变异，目前未发现临床症状，临床诊断为潜在患者；疑似病例4的GAA活性为0.36 μmol/（L·h），低于正常范围，2个变异位点为顺式变异，同时发现了2个假性缺陷位点[c.1726G>A（p.G576S）和c.2065G>A（p.E689K）]，最终临床诊断为携带者。故共检出235例GAA致病性和可疑致病性变异位点携带者，GAA携带率为1/128（235/30 043）；1例潜在患者，患病率为1/30 043。GAA基因热点变异位点依次为c.2132_2133delinsGG、c.503G>A、c.-32-13T>G、c.2662G>T和c.2238G>C，等位基因频率分别为0.078%（47/60 086）、0.038%（23/60 086）、0.020%（12/60 086）、0.018%（11/60 086）、0.017%（10/60 086）。蛋白质结构预测结果显示，c.2132_2133delinsGG会导致GH31（β/α）8桶催化结构域2个β折叠区域变短，信号肽和前肽发生空间构象变化。c.503G>A会导致N-末端β-折叠结构域其中一个β折叠延长，并多出一个β折叠。

结论：新生儿基因筛查结合GAA活性测定可以排除假性缺陷等位基因干扰，提高筛查效率和准确性，为庞贝病的临床诊断与遗传咨询提供参考依据。

关键字 庞贝病；GAA基因；基因筛查；携带者

Establishment and evaluation of a method for measuring ornithine transcarbamylase activity in micro blood of neonates

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Objective Ornithine transcarbamylase defciency exhibits a high degree of clinical heterogeneity, making its screening and classifcation challenging in some instances. In this study, we frst established a simple and stable method for testing ornithine transcarbamylase activity using micro blood from newborns, rather than relying on venous blood.

Methods The activity of ornithine transcarbamylase was assessed by measuring the concentration of citrulline produced in the reaction with carbamoyl phosphate and ornithine, using serum, plasma or micro blood. Correlation analysis was evaluated using Sangerbox Tools. The Receiver Operating Characteristic curve was used in SPSS Statistics 17.0 to evaluate the diagnostic efciency of Ornithine transcarbamylase defciency.

Results A strong linear relationship was observed between ornithine transcarbamylase activity and both micro blood volume and reaction time (R2=0.9793, 0.9922 respectively). The intra-coefcient variation and inter-coefcient variation were 11% and 12.5% with a 1-h reaction time, and 6.77% and 9.58% with a 3-h reaction time, respectively. And the inter-coefcient variation was lower than the most widely used colorimetry method (5.1 - 21.1%). The Limit of Blank was 0.57 nmol/mL/h. The reference interval for normal newborn population is greater than or equal to 39.6 nmol/mL/h. Notably, the method exhibited a 100% sensitivity, surpassing the sensitivity of colorimetry method (94.3%), along with and a specifcity of 96.9% for diagnosing ornithine transcarbamylase defciency.

Conclusions We pioneered a method for testing OTC activity that normally carried on venous blood can be

efectively performed on microblood heel samples. Meanwhile, our method presents a simpler, more stable and reproducible approach compared to colorimetry.

Key Words Ornithine transcarbamylase defciency, Ornithine transcarbamylase activity, Newborns, Micro blood, Tandem mass spectrometry, Citrulline

Advancing Newborn Genetic Screening for Lysosomal Storage Disorders: A Comparative Analysis of Fluorometric and Mass-Spectrometric Methods

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Objective Lysosomal storage disorders (LSDs) represent a wide spectrum of conditions, characterized by more than 50 distinct deficiencies in lysosomal enzymes or transporters. These disruptions lead to the accumulation of undigested substances within cells which can give rise to a diverse range of clinical manifestations and complications. Traditionally, the assessment of enzymatic activity in LSDs from dried blood spots has relied on two primary methods: fluorometric and mass-spectrometric analysis. While prior research has predominantly focused on screening efficacy, this study marks the inaugural analysis of both methods within the context of genetic screening.

Method Enzyme activity determination of proteins related to common lysosomal storage disorders was performed using both fluorescence method and mass spectrometry method. We compared the operational complexity, personnel time, cost, stability, and detection efficiency of the two methods.

Results The results indicate that while fluorometric analysis involves a streamlined process of five stages, including sample loading, extraction, enzyme reaction, termination, and testing, mass-spectrometric analysis entails a more elaborate sequence of ten steps. This stark contrast underscores the differing complexities in the operational procedures of the two methods. In terms of personnel time, fluorometric testing emerges as significantly more efficient, requiring only 6 minutes, compared to the 14 minutes demanded by mass-spectrometric testing. This notable difference underscores the potential for enhanced workflow efficiency with fluorometric analysis. Moreover, the cost discrepancy between the two methods is substantial. Fluorometric testing proves to be far more economical, with costs ranging from 0.7-68.4 RMB, in stark contrast to the 131.2 RMB incurred by mass-spectrometry. This substantial cost differential highlights the financial implications associated with selecting an appropriate testing method. The data indicate that the intra-coefficients of variation (CV) for fluorometric testing range from 5% to 10%, whereas for mass-spectrometric testing, they span from 15% to 25%. Similarly, the inter-CV percentages for fluorometric testing fall between 10% and 15%, while for mass-spectrometric testing, they range from 20% to 35%. These differences underscore variations in the precision and consistency of results between the two methods, with fluorometric testing generally exhibiting lower CV percentages. Despite these methodological disparities, it's crucial to note that the enzymatic activity of all positive samples is consistently observed to be significantly lower than that of normal controls, irrespective of the testing method employed. This consistent finding underscores the reliability and robustness of both fluorometric and mass-spectrometric approaches in accurately identifying

abnormalities associated with lysosomal storage disorders.

Conclusions In summary, the fluorometric method emerges as the preferred choice for assessing enzymatic activity in newborn genetic screening for LSDs, offering cost-effectiveness, superior efficiency, and precision when compared to mass-spectrometric analysis.

Key Words Lysosomal storage disorders, fluorometric analysis, mass-spectrometric analysis

基于高通量测序技术的新生儿耳聋基因致病性位点携带和突变谱分

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目的：分析本地区新生儿耳聋基因致病性位点携带和突变情况，以期为该地区耳聋出生缺陷防控提供更多科学依据。

方法：采集2022年3月～2024年4月在本院出生的30043例新生儿足跟血，制成干血斑，提取DNA，采用靶向下一代测序技术对GJB2、SLC26A4、USH2A、MT-RNR1（12S rRNA）和MYO15A基因进行全编码区测序，分析各基因致病性位点携带率和突变情况。

结果：GJB2、SLC26A4、USH2A、MT-RNR1和MYO15A 基因突变的携带率（包括杂合、纯合或复合杂合）分别为13.174%、2.912%、1.524%、0.959%和0.626%，分别检测到25、85、118、3和81种突变类型，均以点突变为主；GJB2携带率最高的突变位点为c.109G>A，其次为c.235delC和c.299_300delAT，等位基因频率分别为4.925%（2959/60086）、1.127% (677/60086)和0.261%（157/60086）；SLC26A4以c.919-2A>G、c.2009T>C和c.2168A>G 3种突变类型最为常见，等位基因频率分别为0.621%（373/60086）、0.165%（99/60086）和0.100%（60/60086）；USH2A携带率最高的突变位点为c.2802T>G，其次为c.8559-2A>G和c.99_100insT，等位基因频率为0.218%（131/60086）、0.165%（99/60086）和0.038%（23/60086）；MT-RNR1仅检测到m.1095T>C、m.1555A>G和m.1494C>T 3种突变类型，检出频次分别为231、52和6；MYO15A以c.10250_10252delCCT、c.7822G>A、c.900delT和c.9690+1G>A突变类型最多，等位基因频率分别为0.043%（26/60086）、0.023%（14/60086）、0.020%（12/60086）和0.020%（12/60086）。

结论：发现GJB2是耳聋基因中最常见的携带基因，以c.109G>A最为常见，纯合突变与迟发型耳聋相关，ACMG判读为致病性变异；而SLC26A4以c.919-2A>G最为常见。USH2A、MT-RNR1和MYO15A也是本地区较为常见的突变携带基因。

关键字 耳聋；基因突变；携带率；GJB2；SLC26A4）

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

Identification of A Novel Mutation in a Chinese Patient with Neurofibromatosis type 1）

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Background: Neurofibromatosis type 1 (NF1), also known as von Recklinghausen’s disease, caused by mutations in the NF1 gene, is a tumour predisposition syndrome characterized by the development of multiple neurofibromas, caf é –au–lait patches and Lisch nodules.

Case report: Here, we described a Chinese patient with NF1 who was admitted to hospital because of abnormal right facial swelling and many coffee colored patches on the skin. Brain magnetic resonance imaging performed presented subcutaneous adipose layer on the sides of the face is asymmetrical, the right side was thicker than the left side, the muscle layer around the right inferior alveolus was thicker than the left side, poor continuity of the right occipital bone, but there was no obvious abnormality in the brain parenchyma. A frameshift duplication (c.3170dupC) in the NF1 gene was detected by Next generation sequencing (NGS) and further confirmed by Sanger

sequencing, which was not detected in his parents. Moreover, genotyping with multiple short tandem repeat markers confirmed paternity to demonstrate that the mutation is de novo. The frameshift duplication was predicted to cause a substitution of Arg (R) to Asp (D) at the 1058th amino-acid residue and generate a prematurely truncated protein.

Conclusion: The patient had NF1 caused by c.3170dupC mutation in the exon 24 of NF1 gene, which presents a novel NF1 mutations to expand the mutation spectrum of NF1.

Key Words Neurofibromatosis type 1, NF1 gene, Next generation sequencing, frameshift mutation, de novo

Identification of Novel Biochemical Markers for Neonatal Familial Hypercholesterolemia Screening Using an Integrative Multi-Omics Approach

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Objective: Familial hypercholesterolemia (FH) is a lipid metabolism disorder caused by mutations in LDLR and other genes, with no established neonatal screening method. This study aims to identify novel biochemical markers for FH through an integrative multi-omics approach and evaluate their potential for disease screening and severity assessment.

Methods: Samples were collected from individuals with autosomal dominant (AD) and autosomal recessive (AR) LDLR pathogenic variants, as well as negative controls without pathogenic variants, categorized into Positive (FH patients), Carrier (heterozygous carriers), and Negative (healthy controls) groups. Genomics, metabolomics, and lipidomics analyses were conducted to identify biochemical differences. Additionally, changes in lipid profiles between neonatal and childhood stages in FH patients with the same genotype were examined to assess markers for disease severity.

Results: Compared to the Negative group, the Carrier group showed a significant increase in TAG(13:0/18:4/18:4) and a decrease in DGTS(15:1/22:6), whereas the Positive group exhibited elevated TAG(16:5/16:5/21:4) and TAG(13:0/19:5/19:5) along with reduced PC(20:3/20:3). When comparing the Positive and Carrier groups, the Positive group showed higher TAG(16:5/16:5/21:4) and lower PC(16:0/22:5) and PEtOH(26:4/22:5). Additionally, in FH patients with the same genotype, TAG(12:1/12:1/21:5) and TAG(13:1/13:1/21:5) significantly increased in childhood compared to the neonatal stage, while PC(18:3e/23:0) decreased.

Conclusions: This study identified distinct metabolic and lipid biomarkers associated with FH using a multi-omics approach. These markers effectively differentiate FH patients, carriers, and healthy individuals, and may aid in assessing disease severity. Our findings provide potential biomarkers for neonatal FH screening and offer insights into disease progression. Further studies with larger cohorts and machine learning models are needed to refine screening strategies and explore clinical applications.

Key Words newborn screening, Familial hypercholesterolemia, LDLR, TAG, PC

无创DNA检测在胎儿性染色体非整倍体疾病中的应用效果

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目的：观察无创产前检测技术检出胎儿性染色体非整倍体高风险情况，探讨其在胎儿性染色体非整倍体高风险筛查中的应用价值。

方法：回顾性分析2021年1月至2024年12月于泰州市人民医院行无创产前检测的孕妇30496例，于孕（12+0-24+6）周采集外周血5 mL，提取胎儿游离DNA,进行高通量测序，计算目标染色体的Z值，分析胎儿性染色体非整倍体高风险。无创产前检测提示胎儿性染色体非整倍体高风险的孕妇行羊膜穿刺检查，以羊膜穿刺检查结果为金标准，计算无创产前检测胎儿性染色体非整倍体的阳性预测值。随访无创产前检测提示胎儿性染色体非整倍体高风险孕妇的妊娠结局。

关键字 产前诊断；无创DNA；性染色体非整倍体疾病

Optimized efficient screening for Duchenne muscular dystrophy carriers using proto-oncogene tyrosine-protein kinase receptor Ret

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Background: Duchenne muscular dystrophy (DMD) is a severe genetic disorder affecting 5%~19% of carriers. While CK is a traditional biomarker, its screening accuracy is limited. This study evaluated the potential of combining proto-oncogene tyrosine-protein kinase receptor (RET) with CK-MM to enhance screening efficacy.

Methods: CK-MM and RET levels were analyzed in 14 adult and 5 newborn DMD carriers, along with non-carrier controls. The CK-MM/RET ratio was calculated, and ROC analysis evaluated biomarker screening efficiency. RET extraction methods from DBS were compared, with correlations between DBS and serum RET levels and stability under varying storage conditions.

Results: DMD carriers exhibited elevated CK-MM and CK-MM/RET ratios, with reduced RET. The CK-MM/RET ratio had the highest screening efficiency. RET extraction was optimal using Diluent C at 4° C overnight, showing a strong DBS-serum correlation. RET remained stable except under high humidity and temperature conditions.

Conclusion: Combining RET with CK-MM enhances DMD carrier screening, offering a more efficient DBS-based method for early detection.

Key Words Duchenne muscular dystrophy, carrier, Proto-oncogene tyrosine-protein kinase receptor Ret, creatine kinase-MM, dried blood spot.

Prenatal diagnosis and molecular cytogenetic characterization of a rare case of mosaic ring chromosome 13)

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Objective: To perform prenatal diagnosis for a fetus carrying mosaic ring chromosome 13.

Methods: The patient was subjected to G-banding karyotyping, fluorescence in situ hybridization (FISH).

Results: A 23-year-old healthy woman was referred to our centre at 21 weeks of gestation age. Ultrasound examination indicated normal result, however, non-invasive prenatal testing (NIPT) showed high risk of chromosome 13. Amniocentesis was chosen by the patient. The fetus showed a mos 45,XX,-13[11]/46,XX,r(13)(p13q34)[39] karyotype at 320-400 band level by the analysis of amniotic fluid chromosomes. However, FISH indicated normal result.

Conclusion: A rare case of mosaic ring chromosome 13 has been prenatally diagnosed, combined use of various technologies can enable accurate detection of chromosome abnormality.

Key Words Keywords: FISH; Ring Chromosome; Karyotyping; Prenatal diagnosis.

无创产前筛查18号染色体拷贝数变异的产前诊断和遗传学分析

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目的：探讨无创产前筛查（NIPT）提示18号染色体拷贝数异常的产前诊断和遗传学分析。

方法：选择2021年1月至2024年5月就诊于扬州市妇幼保健院且NIPT提示为18号染色体拷贝数变异（CNV）的5例孕妇作为研究对象，5例孕妇均接受遗传咨询并充分知情同意后进行介入性产前诊断。通过羊水细胞染色体核型分析和染色体微阵列分析（CMA），整理分析5例孕妇的筛查指征、产前诊断结果及随访妊娠结局。

结果：5例孕妇全部行羊水穿刺产前诊断，4例确诊为18号染色体拷贝数变异，阳性预测值为80%（4/5），且4例均为临床意义不明CNV，孕妇后续均足月分娩且新生儿未见异常；1例孕妇产前诊断未见异常，且随访该孕妇分娩一正常男婴。

结论： NIPT对胎儿18号染色体拷贝数变异的检测效能较高，结合染色体核型分析和CMA进行产前诊断的验证以满足咨询预后的需求。

关键字 无创产前筛查；18号染色体；产前诊断；染色体微阵列分析；遗传学分析

二阶筛查在徐州地区甲基丙二酸血症/丙酸血症新生儿筛查中的初步应用

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目的：探讨二阶筛查联合传统串联质谱法应用于徐州地区甲基丙二酸血症/丙酸血症新生儿疾病筛查的可行性。

方法：采用串联质谱技术对2015年11月至2023年12月江苏省徐州市691,440例新生儿进行传统串联质谱筛查，其中丙酰基肉碱、丙酰基肉碱/乙酰基肉碱、蛋氨酸及比值等指标异常检出甲基丙二酸血症或丙酸血症初筛阳性2,801例。2019年起，对于初筛疑似阳性样本，进一步使用高效液相色谱–串联质谱法检测的甲基丙二酸、甲基枸橼酸和同型半胱氨酸浓度。

结果：1,638例疑似阳性样本经二阶筛查检测提示阳性71例，其中25例甲基丙二酸、甲基枸橼酸和同型半胱氨酸明显升高确诊为甲基丙二酸血症，4例仅甲基枸橼酸明显升高确诊为丙酸血症，与二阶筛查结果基本相符。与单纯采用串联质谱筛查相比较，联合应用传统串联质谱筛查和二阶筛查，甲基丙二酸血症 / 丙酸血症的阳性预测值由2.92%增加至40.84%。

结论：联合二阶筛查能够显著提高甲基丙二酸血症/丙酸血症的筛查效率，在徐州地区新生儿遗传代谢病串联质谱筛查中具有重要的应用价值。

关键字 高效液相色谱–串联质谱、二阶筛查、甲基丙二酸血症、丙酸血症

Comparison of chromosomal abnormalities in embryos of occasional and recurrent abortion in different pregnancy modes

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Objective: This study aims to provide reference for clinical consultation for spontaneous miscarriage patients by analyzing the chromosomal abnormalities in embryos from sporadic and recurrent miscarriage cases in both natural and assisted pregnancies, comparing the effects of different modes of pregnancy and number of miscarriages on the rate and distribution of embryonic chromosomal abnormalities.

Methods: Data of 1,832 spontaneous miscarriage patients who were treated at the Wuxi Maternal and Child Health Hospital Affiliated with Jiangnan University from January 2019 to December 2024 were collected. Patient information included age, mode of conception, number of spontaneous miscarriages, and gestational weeks of miscarriage. Patients were divided into two groups based on the mode of conception: natural pregnancy group (Group 1) with 1,537 cases, including sporadic abortion group (SA–1 group) with 942 cases and recurrent abortion group

(RSA-1 group) with 595 cases; assisted pregnancy group (Group 2) with 295 cases, including sporadic abortion group (SA-2 group) with 204 cases and recurrent abortion group (RSA-2 group) with 91 cases. Chromosomal microarray analysis (CMA) was used to perform whole-genome copy number detection on the aborted tissues, and the relationship between the number of miscarriages and chromosomal abnormalities was analyzed.

Results: In the natural pregnancy group, the rates of chromosomal aneuploidy in the sporadic abortion group (SA-1) and recurrent abortion group (RSA-1) were 56.48% (532/942) and 53.78% (320/595), respectively, without significant difference (P>0.05). With an increase in the number of miscarriages, the rate of chromosomal aneuploidy decreased (56.48%, 55.86%, 50.83%, 35.48% for one, two, three, and ⩾ four miscarriages, respectively). The rate of chromosomal aneuploidy and sex chromosome aneuploidy in the group with one miscarriage were significantly higher than those in the group with four or more miscarriages (P<0.05). The rates of copy number variation (CNV) in sporadic and recurrent miscarriage groups of natural pregnancy were 4.25% (40/942) and 5.55% (33/595), respectively, without significant difference (P>0.05). There was no significant difference in the rates of CNV abnormality among groups with different numbers of miscarriages, but the CNV ⩾10MB abnormal rate in the group with two miscarriages (1.59%, 15/942) was significantly lower than that in the group with three miscarriages (5%, 6/120) (P<0.05). There was a significant difference in gestational weeks between groups (P<0.05). With an increase in the number of miscarriages, age gradually increased.

In the assisted pregnancy group, the rates of chromosomal aneuploidy in the sporadic and recurrent abortion groups were 50% and 42.86%, respectively, and the CNV abnormal rates were 2.45% and 6.59%, respectively. There were no significant differences in the total chromosomal aneuploidy rates, CNV abnormal rates, or trisomy rates among groups with different numbers of miscarriages. The CNV⩽10MB abnormal rate and P+LP abnormal rate in the group with one miscarriage were significantly lower than those in the group with three miscarriages (P<0.05). There was no significant difference in gestational weeks among the groups.

Compared with the assisted pregnancy group, the natural pregnancy group had significantly higher rates of total chromosomal aneuploidy and trisomy than the assisted pregnancy group (P<0.05). There was no significant difference in the rates of structural abnormalities between the two groups. The age of the SA-1 and RSA-1 groups in the natural pregnancy group was lower than that of the SA-2 and RSA-2 groups in the assisted pregnancy group (P<0.05), and the gestational weeks were higher than those in the assisted pregnancy group (P<0.05). There was no significant difference in the rates of chromosomal aneuploidy and CNV between the SA-1 and RSA-1 groups in the natural pregnancy group and the assisted pregnancy group. The trisomy rate in the SA-1 and RSA-1 groups of the natural pregnancy group was significantly higher than that in the assisted pregnancy group (P<0.05).

Conclusion: The incidence rates of total chromosomal aneuploidy and trisomy in spontaneous miscarriage patients during natural pregnancy were significantly higher than those in assisted pregnancy. There were no significant differences in CNV rates between the two different modes of pregnancy and among different numbers of miscarriages in each mode of pregnancy. The top five most common chromosomal aneuploidies in spontaneous miscarriages in both modes of pregnancy were trisomies 16, 15, 21, 13, and 22.

Key Words spontaneous abortion ; chromosomal abnormality; copy number variation (CNV); chromosomal microarray analysis (CMA); assisted conception

·遗传病的诊治与遗传咨询·

携带者筛查检测意外发现的X染色体长臂部分缺失孕妇的遗传学分析

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目的：对携带者筛查意外发现的1 例X 染色体长臂部分缺失的孕妇进行遗传学分析并为其提供产前诊断。

方法：提取孕妇外周全血基因组DNA 进行基于毛细管电泳技术的携带者筛查，采用多重连接依赖探针扩增技术（MLPA）和染色体微阵列芯片分析（CMA）进行验证，染色体核型G 显带技术分析外周血染色体核型，并提取羊水胎儿脱落细胞DNA 进行CMA 分析。

结果：携带者筛查的结果提示孕妇携带PLP1 基因杂合缺失，MLPA 结果提示孕妇PLP1 基因第2~8号外显子杂合缺失，染色体核型和CMA 结果均证实其携带X 染色体q13.3q23 区段杂合缺失，且胎儿羊水细胞存在同样片段的染色体杂合缺失，最终决定终止妊娠。

结论：扩展性携带者筛查发现孕妇X 染色体长臂部分缺失，并将其传递给胎儿。

关键字 扩展性携带者筛查；Xq 部分缺失；PLP1 基因；产前诊断

Mutation spectrum of thalassemia among pre-pregnant adults in the Jiangsu Province by capillary electrophoresis-based multiplex PCR assay

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Background: Thalassemia is a common genetic disorder in southwestern China,and an increasing number of cases from eastern China have been recently reported.Here, we developed a rapid, convenient, and accurate assay to evaluatethe mutation spectrum of thalassemia in eastern China.

Methods: A carrier screening assay for 61 hotspot variants among HBA1/HBA2and HBB (OMIM: 141800, 141850, and 141900) genes was developed by SNaPshot/high-throughput ligation-dependent probe amplification (HLPA) technology.We used this assay to detect the mutation spectrum of thalassemia in individuals from eastern China and compared with the data collected from literatures focused on southern and northern China for variant distribution.

Results: Among 4276 tested individuals, 2.62% (112/4276) were α-thalassemia carriers, with 90 carrying one deletion or mutation and 22 carrying two deletions.0.40% (17/4276) were β-thalassemiacarriers, and the most

common variant of β-thalassemia was c.126_129delCTTT (29.41%) followed by c.316-197C>T (23.53%).The genotype distribution in our study was similar to those from southern Chinapopulations.

Key Words carrier screen, gene variants, SNaPshot/HLPA, spectrum, thalassemia

产前诊断7例羊水细胞Y染色体异常

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目的：对7例产前检测羊水细胞提示Y染色体异常的病例进行分析总结，讨论不同检测方法所提示的结果之间的联系，合理作出判读结果以指导产前遗传咨询。

方法：收集各种产前检测提示Y染色体异常的产前病例，并辅以不同的产前检测包括羊水染色体核型G显带、染色体微阵列、多重连接探针扩增技术、荧光原位杂交技术、光学基因组图谱分析技术，根据各个检测结果综合判断得出最接近真实的染色体结果。

结果：共7个病例中病例1、2、6、7的几种检测方法所提示Y染色体异常的情况基本是一致的，而病例3、4、5不同的检测方法出现了不同的结果。

结论：在胎儿染色体的检查中，为了避免Y染色体结果的评估出现偏颇，建议进行以染色体G显带核型检测为基础，其他各种分子和细胞遗传学检测为增进的检测方式，使Y染色体的信息能得到更全面的体现。临床医生需根据Y染色体异常的类型和不同的检测方法得出的结果，综合评估胎儿出生后可能出现的临床表现、症状、需要解决的问题、目前可以提供的解决方法和将来可能的解决途径等，从而作出临床指导。

关键字 产前诊断 Y染色体异常 染色体核型 染色体微阵列检测 遗传咨询

The Expression of Lipid Metabolism and HCY Level in Subclinical Hypothyroidism and its relationship with TSH

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Objective: To analyze the lipid metabolism and Hcy level expression in subclinical hypothyroidism, and to explore the relationship between them and TSH. Methods: 119 patients with subclinical hypothyroidism admitted to our hospital from March 2020 to March 2023 were selected (subclinical hypothyroidism group). In addition, 121 patients who underwent physical examination in our hospital during the same period and had normal physical examination indexes were selected as the normal control group. Blood lipid metabolism, Hcy and TSH levels were compared in different populations. Blood lipid metabolism and Hcy level in subclinical hypothyroidism group were compared between subclinical hypothyroidism group 1 and subclinical hypothyroidism group 2. The correlation between lipid metabolism, Hcy level and TSH level was analyzed by partial correlation coefficient and multi-distance linear regression. Results: The levels of TC, TG, LDL-C, Hcy and TSH in subclinical hypothyroidism

group were significantly higher than those in normal control group (P < 0.05). There was no significant difference in HDL-C, FT3 and FT4 levels between the two groups (P>0.05). The levels of TC, LDL-C and Hcy in subgroup 2 were higher than those in subgroup 1 (P<0.05). There was no significant difference in TG, HDL-C, FT3 and FT4 levels between the two groups (P>0.05). After adjusting for gender, age, BMI, smoking history and FPG confounding factors, the levels of TC, TG, LDL-C, HDL-C and Hcy were positively correlated with TSH (P<0.05), while HDL-C was not correlated with TSH (P>0.05). The results showed that TSH was a risk factor for abnormal levels of TC, TG, LDL-C and Hcy, while there was no linear correlation between TSH and HDL-C. Conclusions: The lipid metabolism and Hcy level of patients with subclinical hypothyroidism have certain changes, which are correlated with TSH level. Therefore, the monitoring of lipid metabolism and Hcy level of patients with subclinical hypothyroidism should be strengthened, which provides a new perspective for clinicians to evaluate and manage the cardiovascular risk of patients with subclinical hypothyroidism.

Key Words TSH; Lipid Metabolism;Subclinical Hypothyroidism

The clinical and mutational spectrum of Menkes disease: Prenatal diagnosis of a Chinese family and literature review

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Objective: Menkes disease (MIM#309400) is a rare and fatal X-linked neurodegenerative disease caused by mutations in ATP7A, which has hardly been reported in the Chinese population. Herein, we describe a Chinese boy who presented with frequent seizures, marked delayed development, facial dysmorphism was unable to find the cause of the disease. Finally, the cause of the disease was found by whole exon sequencing, and prenatal diagnosis was performed on this family.

Methods: Firstly, whole exome sequencing was performed on the proband and his parents. Then the clinical and laboratory characteristics of the patients were analyzed. Next, prenatal diagnosis was performed on the fetus of this family. Finally, further PCR and western blotting experiments were performed on the fetal tissue (skin) to verify the effect of the mutation on the editing or processing of mRNA. In addition, the genetic mutation information of all Menkes disease patients reported to date was retrieved and pooled through "PubMed" and "Web of Science" databases.

Results: Firstly, the whole exome sequencing results showed that the ATP7A gene (NM_000052.4) of the proband has a novel splicing variant c.2782-1G>T 【ChrX(GRCh37):g.77276441G>T】, which was categorized to be the disease "likely pathogenic" variant according to the ACMG guidelines. Then, our in vitro functional studies confirmed that the mutation (c.2782-1G>T) affect the correct editing and processing of mRNA, thus the c.2782-1G>T variant can be reclassified to "pathogenic" according to the ACMG mutation classification standard. Finally, prenatal diagnosis showed that the male fetus carried the same ATP7A mutation as the proband. Furthermore, ultra deep sequencing of the maternal site revealed 16686 alt reads out of 126059 reads, with a chimeric proportion of 13.2%. The proband's mother is a low-frequency chimeric carrier of ATP7A gene mutation, but she has continuously given birth to children with the same gene mutation, indicating that she is highly likely to be a

reproductive gland mosaic with this type of mutation. In addition, we also conducted a genotypic literature review of all patients with ATP7A mutations reported to date.

Conclusion: The mutation of ATP7A gene c.2782-1G>T (g.77276441G>T) is a pathogenic mutation, which enriches the mutation spectrum of ATP7A gene and provides a basis for genetic counseling and prenatal diagnosis in the family.

Key Words Menkes Disease; ATP7A; Splicing Mutation; Prenatal Diagnosis; Whole-exome Sequencing

Innovative Nomogram for Cervical Cancer Prediction: Integrating High-Risk HPV Infection, p53 Genotype, and Blood Routine Parameters

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Objective: To explore the relationship between high-risk HPV infection, p53 genotype, and hematological indicators in the development of cervical cancer, and to establish an effective clinical prediction model to provide new insights for early diagnosis and personalized treatment of cervical cancer.

Methods: This retrospective study collected cervical cancer specimens and brush samples from patients at Changzhou First People's Hospital from January 2020 to August 2024. Inclusion criteria were age between 18-75 years, no medications affecting outcomes in the past two weeks, and complete clinical data availability. Exclusion criteria included previous cervical surgery, radiotherapy, chemotherapy, severe organ diseases, autoimmune diseases, and other malignancies. The SLAN-96S PCR system and SYSMEX XN-9000 blood analyzer were used for HPV types and p53 genotyping and blood parameter analysis, respectively. Inflammatory markers like lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and platelet to lymphocyte ratio (PLR) were calculated. SNPStats was used for genetic analysis, and statistical methods including logistic regression and LASSO were applied to construct a predictive model.

Results: The study included 147 female patients with cervical cancer and controls. HPV16 and HPV18 had high infection rates. In the log-additive model, for each additional C allele, the risk is reduced by 48%, which is statistically significant (OR = 0.52, 95% CI: 0.27-0.98, P = 0.038). Significant interactions were found between p53 genotypes and HPV18 infection on cervical cancer risk (P = 0.026). Hematological parameters differed significantly between groups, with reduced red blood cell count (RBC) and hemoglobin (HGB) indicating potential anemia in cervical cancer patients. The predictive model included p53 genotype, HPV16, HPV18, monocyte count (MONO), monocyte percentage (MONO%), neutrophil percentage (NEUT%), mean corpuscular hemoglobin (MCH) and RBC, with an area under the curve (AUC) of 0.920 (95% CI: 0.875 - 0.965), indicating high discriminatory ability.

Conclusion: The study identified significant differences in p53 genotypes, HPV infection, and hematological parameters between cervical cancer patients and controls. The predictive model developed demonstrated high discriminatory ability and clinical utility in risk assessment for cervical cancer. The interaction between HPV18 and p53 genotypes suggests a potential protective effect of the p53 C allele against cervical cancer. Larger studies are

needed to validate these findings and explore their implications for cervical cancer screening and management.

Key Words Cervical cancer; Blood routine parameters; p53; High-risk HPV; Nomogram

Clinical manifestations of partial PAX3 deletion in a family with Waardenburg Syndrome

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Background: Waardenburg syndrome (WS) is a group of autosomal-dominant hereditary disorders due to haploinsufficiency of PAX3. However, fetuses harboring partial deletion of PAX3 in prenatal are extremely rare, and clinical phenotypes were hard to predict. In this study, we report a family with partial PAX3 deletion, but the manifestations range from normal to mild abnormalities.

Case presentation: A 22-year-old woman (gravida 2, para 0) was referred to our prenatal center at 18 weeks of gestation for congenital spina bifida during last pregnancy. Chromosomal analysis was performed in fetal tissue after termination of last pregnancy, as well as amniotic fluid during this pregnancy. A rare partial deletion of PAX3 gene was identified and confirmed a paternal origin. A diagnosis of WS was defined according to clinical features of their father. However, the newborn was showed normal phenotypes after birth in this second pregnancy.

Conclusion: This work suggests a mild phenotype, or even normal, of WS patients with partial PAX3 deletion, and illustrates the different features and genetic variations, broadening our insights into the CNV analysis and genetic consultation in prenatal. It is also suggested that PAX3 gene should be considered as one of the candidate genes for auditory-pigmentary abnormalities or neural tube defects of unknown etiology.

Key Words PAX3, Waardenburg syndrome, SNP-array analysis, chromosomal aberration

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

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Purpose 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.

Key Words NR0B1 gene Congenital adrenal hypoplasia Exon sequencing

Expanded noninvasive prenatal testing uncovers a rare case of 14q12 microdeletion syndrome in prenatal diagnosis

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Purpose: To report a rare case of 14q12 deletion syndrome diagnosed prenatally with the application of expanded non-invasive prenatal testing (NIPT-plus).

Methods: In the second trimester, NIPT-Plus was carried out. Subsequently, an amniocentesis was performed including conventional karyotyping and Chromosomal Microarray Analysis (CMA) due to the positive NIPT-plus result for confirmation.

Results: NIPT-plus results indicated a diminished signal from chromosome 14q. Subsequent prenatal diagnostic testing confirmed the positive results of NIPT-plus. The karyotype analysis revealed 46, XX, del (14) (q12q21) and CMA displayed one copy of 14q: 14q12-14q21.1(26,908,201_38,284,728) x1.

Discussion: In this study, we utilized NIPT-plus and successfully identified a rare prenatal case of 14q12 deletion syndrome. To the best of our knowledge, this is the first prenatal diagnosis case of 14q12 deletion syndrome found by the utility of NIPT. In our case, there was an 11.377 Mb deletion in the 14q12q21.1 region, which contained 40 OMIM genes, including three main genes, FOXG1, NOVA1, and PRKD1. Notably, the clinical manifestations in most reported 14q12 deletion cases in the literature were absent of perinatal abnormalities and appropriate for gestational age at birth. In our case, the early ultrasound findings showed no obvious abnormality. As pregnancy progressed, the central nervous system abnormalities became evident accompanied by hydrocephalus. For high-risk fetuses indicated by NIPT-plus, especially when abnormal prenatal ultrasound findings are present, prenatal diagnosis needs to be carried out to verify the chromosomal abnormalities. Despite the growing prevalence of NIPT-plus, it is still a screening test that requires prenatal diagnosis to confirm abnormal chromosome accurately.

Key Words 14q12 deletion syndrome; NIPT-plus; prenatal diagnosis

DYNC2H1基因变异致短肋胸廓发育不良3型一个家系的遗传学分析

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目的：记录一个短肋胸廓发育不良3型家系中两例胎儿的临床表型，并进行遗传学分析以明确其遗传学病因。

方法：对家系内第一例引产胎儿及其父母进行全外显子组测序，检出疑似致病变异后，进行Sanger测序验证。针对家系内第二例引产胎儿，也采用Sanger测序进行验证。

结果：全外显子组测序发现家系中的第一例引产胎儿携带DYNC2H1基因c.7867C>T (p.Gln2623Ter)和c.4552T>C (p.Cys1518Arg)复合杂合突变，两个变异均未被报道，分别遗传自父母一方。Sanger测序验证了全外显子组测序的结果，并发现第二例引产胎儿也携带DYNC2H1基因c.7867C>T和c.4552T>C复合杂合突变。

结论：DYNC2H1基因的c.7867C>T (p.Gln2623Ter)和c.4552T>C (p.Cys1518Arg)复合杂合变异很可能是该家系两例短肋胸廓发育不良3型胎儿的遗传学病因，丰富了DYNC2H1基因的变异谱。

关键字 短肋胸廓发育不良；DYNC2H1基因；新突变；全外显子组测序

单中心胎儿心脏横纹肌瘤的产前诊断及临床结果分析

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Object: This study was aimed to determine the clinical value of combining ultrasound and detection of the TSC gene when assessing the prognosis of CR in the fetus.

Methods: This retrospective study presented 24 fetuses with cardiac rhabdomyoma(s) diagnosed prenatally with fetal echocardiography in our hospital from June 2018 to May 2024. Multiplex ligation-dependent probe amplification (MLPA) and next-generation sequencing (NGS) for TSC genetic testing were offered. The genetic consultation was provided for all pregnant women with fetal cardiac rhabdomyoma, and the clinical outcomes were followed up.

Results: Among the 24 cases of cardiac rhabdomyoma, 14 cases (58.3%) were single, 10 cases (41.6%) were multiple, and the most common location was left ventricle (29.2%), followed by right ventricle (25%). TSC genetic testing was found abnormal in 54.2% (13/24) of the fetuses; the fetus was born alive in 10 cases and the pregnancy was terminated in 14 cases. One novel mutation hasn’t been reported in the previous studies.

Conclusions: MLPA and NGS are effective methods to detect mutations of TSC1/TSC2 for prenatal diagnosis. The prognosis of fetuses with simple cardiac rhabdomyoma is good. Our practice provides a practical and feasible advice for genetic counseling for fetuses with CR.

关键字 cardiac rhabdomyoma, prenatal diagnosis, tuberous sclerosis complex (TSC), Next-generation sequencing (NGS), Multiple Ligation-dependent Probe Amplification (MLPA)

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 单亲二体；产前诊断；微阵列芯片

Identification and functional characterization of a novel homozygous intronic variant in the fumarylacetoacetate hydrolase gene in a Chinese patient with tyrosinemia type 1）

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Background: Hereditary tyrosinemia type 1 (HT1; OMIM# 276700) is a genetic metabolism disorder caused by disease-causing variants in the fumarylacetoacetate hydrolase (FAH) gene encoding the last enzyme of the tyrosine catabolic pathway. Herein, we describe the clinical features and genetic characteristics of HT1 in a five years and seven months old Chinese patient.

Methods: After clinical diagnosis of the proband with HT1, genetic testing was performed by Sanger sequencing of the FAH gene in all family members. Functional analysis of the disease-causing variant was performed by cDNA sequencing to understand the effect of the variant on FAH transcript. To further predict the variant effect, we used Human Splicing Finder (HSF) and PyMol in silico analysis.

Results: We identified a novel previously undescribed intronic variant in the FAH gene (c.914-1G>A). It was detected in a child who was homozygous for the variant and had the clinical presentation of HT1. cDNA sequencing showed that this splice-junction variant affected the transcription of FAH by formation of two different transcripts.

Our observations and laboratory experiments were in line with in silico methods.

Conclusions: Our study provides new insight into the HT1 variant spectrum and a better understanding of this disease in the Chinese population. This will be useful for molecular diagnosis in our country in cases where premarital screening, prenatal diagnosis and preimplantation genetic diagnosis are planned.

Key Words Hereditary tyrosinemia type 1, Cryptic splice site variant, Alternative transcripts, Functional analysis, FAH gene

抗苗勒管激素对PGT-A周期中的胚胎质量的预测价值分析

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目的：抗苗勒管激素（AMH）在辅助生殖（ART）应用中虽然可以很好地预测卵母细胞的数量，但尚不确定能否反映ART周期中获得的胚胎质量。胚胎植入前遗传学非整倍体检测（PGT-A）周期中的非整倍体可以作为一种客观定性因素用于胚胎的质量判定。此处通过对不同组别胚胎非整倍体的统计以探讨AMH对胚胎质量的反映。

方法：对2018-2022年来苏州市立医院生殖与遗传中心进行PGT-A的患者（无男性因素入组）进行回顾性病例对照分析。分别按年龄（<35岁、35-37岁、≥38岁）、身体质量指数（BMI）（<18.5kg/m2、18.5-23.9kg/m2、≥24kg/m2）、可活检胚胎数（1-2个、3-4个、≥5个）及AMH水平（<1.76ng/ml、1.76-3.58ng/ml、≥3.59ng/ml）进行分组，以确定女方年龄、BMI、可活检胚胎数与AMH在预测胚胎质量方面的相关性。

结果：在543个PGT-A周期中，按年龄（<35岁、35-37岁、≥38岁）进行分组，AMH水平、胚胎的整倍体率及嵌合体率都与年龄呈负相关；胚胎的非整倍体率与年龄呈正相关。按身体质量指数（BMI）（<18.5kg/m2、18.5-23.9kg/m2、≥24kg/m2）进行分组，AMH水平随着BMI增加而降低，低BMI（<18.5kg/m2）组的AMH要显著高于高BMI（≥24kg/m2）组；胚胎的整倍体率、非整倍体率、嵌合体率在各组未见统计学差异。按可活检胚胎数（1-2个、3-4个、≥5个）进行分组，AMH水平及胚胎的整倍体率与可活检胚胎数呈正相关；胚胎的非整倍体率与可活检胚胎数负相关。按AMH水平（<1.76ng/ml、1.76-3.58ng/ml、≥3.59ng/ml）进行分组，胚胎的整倍体率在<1.76ng/ml组和1.76-3.58ng/ml组未见统计学差异，但在≥3.59ng/ml组显著高于另两组；胚胎的非整倍体率在≥3.59ng/ml组显著低于另两组。

结论：AMH水平对胚胎质量有很好的预测价值，胚胎质量在AMH低水平组（<1.76ng/ml）和中水平组（1.76-3.58ng/ml）没有显著差别，而在AMH高水平组（≥3.59ng/ml）显著上升。AMH水平和女方年龄、可活检胚胎数高度线性相关，但作为胚胎质量的预测要弱于后两者，胚胎质量随着女方年龄增加每组均有显著下降，而胚胎质量随着可活检胚胎数增加每组均有显著上升。BMI与AMH水平也有一定的相关性，低BMI组有较高的AMH水平，但和胚胎质量的相关性不显著，不能作为胚胎质量预测的独立指标。

关键字 抗苗勒管激素；胚胎植入前遗传学非整倍体检测；女方年龄；身体质量指数

21个STR基因座在连云港汉族人群的突变分析

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目的：本研究旨在探索21个STR基因座在连云港汉族群体亲子鉴定中的应用价值和突变规律。

方法：采用 STRtyper-21G Plus试剂盒对 2540 例亲子鉴定案例的6024份样本进行20个常染色体和1个性染色体STR基因座复合扩增，扩增产物电泳后进行等位基因分型。根据等位基因分型计算亲权指数和累积亲权指数判断亲子关系，同时统计支持亲子关系案例中基因座的突变情况。

结果：在2540例亲子鉴定案件中，支持亲子关系2176例，排除亲子关系348例，亲子关系结论不明确16例。20 个常染色体 STR 基因座中有19个基因座出现了突变，共观察到 78 个突变事件，基因座的特异性突变率在 0.00%~0.39%之间，一步突变占96.15%。父源性突变与母源性突变的比例为 3∶1。

结论：21个STR基因座基本能满足连云港汉族群体亲子鉴定的应用；但在含基因突变的二联体亲子鉴定的应用存在一定的局限性，必要时应增测其他遗传标记以明确鉴定结论。STR基因座突变现象较常见，部分基因座在不同地区的突变率差异具有统计学意义。

关键字 STR基因座；突变分析；连云港汉族群体；亲子鉴定

染色体微阵列分析技术在胎儿颈项透明层增厚产前诊断中的应用

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目的：探讨染色体微阵列分析（chromosomal microarray analysis, CMA）在颈项透明层（nuchal translucency, NT）增厚胎儿产前诊断中的应用价值。

方法：选取2017年6月至2024年6月于南京医科大学附属妇产医院超声提示NT增厚（≥ 3.0mm）的胎儿1033例。根据是否合并其他超声软指标将其分为单纯NT增厚组和NT增厚合并其他超声软指标组；单纯NT增厚组中，根据孕妇年龄将其分为高龄组（≥ 35岁）和非高龄组（< 35岁）；同时，根据NT厚度将其分为3.0~3.4mm组、3.5~4.4mm组、4.5~5.4mm组以及≥ 5.5mm组。采用CMA技术对所有NT增厚胎儿进行检测分析。

结果：（1）1033例NT增厚胎儿中，共检出致病性染色体异常170例（16.5%），包括染色体非整倍体122例（11.8%）、大片段结构异常（≥ 10Mb）10例（1.0%）及致病性微缺失微重复（< 10Mb）38例（3.7%）；（2）NT增厚合并其他超声软指标组染色体异常检出率显著高于单纯NT增厚组（39.1% vs. 13.6%, P < 0.001）；（3）单纯NT增厚胎儿中，高龄组染色体异常检出率显著高于非高龄组（25.9% vs. 11.5%, P < 0.001）；（4）单纯NT增厚胎儿中，无论高龄组或非高龄组，染色体异常检出率随NT厚度的增加而增加（P < 0.001; P < 0.05）；（5）单纯NT增厚胎儿中，NT在3.5~4.4mm和4.5~5.4mm时，高龄组染色体异常检出率显著高于非高龄组（45.0% vs. 10.9%, P < 0.001; 42.9% vs. 16.7%, P < 0.05）。

结论：染色体微缺失微重复与NT增厚密切相关，CMA可有效提高NT增厚胎儿染色体异常检出率。当孕妇年龄≥ 35岁、NT增厚合并其他超声软指标、NT值高时，胎儿染色体异常发生率更高。

关键字 颈项透明层增厚；染色体异常；拷贝数变异；微缺失微重复；染色体微阵列分析

连云港地区217例矮小症儿童遗传学分析并文献复习

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目的：探讨并归纳矮小症儿童的遗传学病因。

方法：选取2018年7月—2023年11月在连云港市妇幼保健院生长发育科就诊并诊断为矮小症的儿童作为研究对象，联合应用外周血染色体核型分析及染色体微阵列分析（CMA）检测，检索DECIPHER、DGV、ClinGen、OMIM等基因数据库并相关文献复习，筛选与矮小症相关基因。

结果：本研究共纳入217例矮小症患儿，其中男性154例、女性63例。中位年龄为8.3（4.6~15.7）岁，共检测出26例阳性结果，其中单独染色体核型分析异常检出率为6.91%，染色体核型分析联合CMA阳性检出率为12.01 %。所有异常类型中，Turner综合征13例（占50%），性染色体平衡易位1例，10号染色体大片段重复1例，染色体微缺失微重复11例；通过数据库检索与文献查询筛选出与本研究患者中矮小症相关的基因包括SHOX基因在内有12个。

结论：遗传因素在矮小症患儿发病因素中占重要位置，Turner综合征为最常见的矮小症遗传学病因，其次是微缺失和微重复；联合应用染色体核型分析和CMA检测是发现矮小症患儿遗传变异的重要手段。

关键字 矮小症；核型分析；CMA；Turner综合征；矮小症基因

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，为家系遗传咨询、风险评估及遗传学干预提供准确依据。

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、全外显子组基因检测、生育风险评估、胚胎植入前遗传学检测（PGT-M）

胎儿染色体 22q11.21区域拷贝数异常的遗传学分析

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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，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；超声影像；染色体微阵列；遗传学分析

PAKN2基因复合杂合突变在苍白球黑质变性家族中的遗传学特征与临床分析

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目的：本研究旨在通过分析一对夫妻及其三个子女中苍白球黑质变性（PPND）的家族遗传学特征，探讨PAKN2基因突变的遗传模式及其在疾病发生中的作用，进一步分析复合杂合突变对该家族临床表现的影响。

方法：通过对一名幸存女孩进行全外显子测序分析，发现PAKN2基因存在两个突变。我们重点

分析这两个突变的遗传学特征，分别为c.515-527delTGCCCGCGGTCGG (p.Val172Glyfs29)和c.1246G>A (p.Gly416Arg)。进一步对男孩进行基因验证，结果与其姐姐一致，均携带相同的突变位点。结合家系数据，进行遗传模式分析。

结果：基因检测结果显示，先证者（女孩）和男孩均携带PAKN2基因中的两处突变，分别为框移突变c.515-527delTGCCCGCGGTCGG和错义突变c.1246G>A。父母分别为这两处突变的杂合携带者，父亲携带p.Gly416Arg突变，母亲携带p.Val172Glyfs29突变，但两者均未表现临床症状。另一名女孩因意外去世，未能进行基因检测，但推测其可能携带相同的PKAN2基因突变。基于遗传分析，该家族的遗传模式为复合杂合隐性遗传模式。

讨论：本研究表明，PAKN2基因的复合杂合突变可能是苍白球黑质变性的重要致病机制。尽管父母为杂合携带者且未表现临床症状，但子女通过继承父母的不同突变基因，表现出典型的疾病症状。该病例提示复合杂合突变在隐性遗传疾病中的关键作用，强调高风险家庭的遗传咨询和早期筛查的重要性，从而实现早期诊断与干预。此研究不仅加深我们对PAKN2基因突变在PPND中的作用的理解，也为临床上对类似遗传病的诊断和治疗提供了宝贵的参考。

关键字 苍白球黑质变性，PAKN2基因，复合杂合突变，遗传咨询

Genetic analysis of 34 cases with fetal skeletal dysplasia via whole exome sequencing and non-invasive prenatal diagnosis

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Objective Fetal skeletal dysplasia (SD) is a complex group of bone and cartilage with high genetic heterogeneity and phenotypic diversity. The prenatal diagnosis of fetal SD mostly relies on ultrasound (US). However, US has severe limitations to differentiate numerous types of SD and achieve the specific etiology of SD. Additionally, the traditional invasive procedures to obtain the fetal specimen for genetic testing are not easily accepted owing to the risk of miscarriage or infection. Our study aimed to identify the genetic causes of fetal SD, provide a accurate prenatal diagnosis for those families, and investigated non-invasive prenatal detection strategy and facilitate clinical diagnosis of fetal SD.

Methods Total 34 fetuses with SD were recruited and analyzed using chromosomal microarray analysis (CMA) and whole exome sequencing (WES). Moreover, an non-invasive prenatal diagnosis (NIPD) based on next-generation sequencing (NGS) using circulating fetal DNA in maternal plasma was performed on 5 SD fetuses. All detected variants were validated using Sanger sequencing.

Results Total 55.88% (19/34) fetues with SD were identified with the genetic etiologies. 27 cases underwent karyotype and CMA analysis and the diagnostic rate was 3.70% (1/27). 34 cases accepted WES and the diagnostic rate was 55.88% (19/34). Of the 19 positive cases, 2 cases were identified with pathogenic CNVs (10.53%, 2/19), and other 17 cases were identified with pathogenic or likely pathogenic variations (89.47%, 17/19). Total 19 variations of the 9 genes were identified and all were previously reported. The FGFR3 was the most prevalent SD-causing gene (47.06%, 8/17), followed by COL2A1 (11.76%, 2/17). In addition, 5 cases accepted the NIPD based on NGS for the detection of fetal SD and the results were all consistent with those of prenatal diagnosis by

amniocentesis, with sensitivity and specificity 100% and 100%, respectively.

Conclusions Our study highlights the advantages of WES compared with CMA in genetic diagnosis in fetal SD, and provides the reasonable reproductive advice for couples. Furthermore, our study revealed the excellent detection efficiency of NIPD based on NGS, which may be a potential noninvasive detection methods in fetal SD.

Key Words Skeletal dysplasia, Genetic testing, Whole exome sequencing, Non-invasive prenatal diagnosis

荧光定量PCR联合MLPA在脊髓性肌萎缩症产前筛查与诊断中的应用

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目的：分析盐城地区产前孕妇运动神经元存活基因 1（SMN1）基因突变携带情况，对生育脊髓性肌萎缩症（SMA）高风险家庭进行产前诊断，为SMA遗传咨询和出生缺陷预防提供临床依据。

方法：应用荧光定量PCR 技术检测孕妇SMN1第7、8 外显子（E7、E8）拷贝缺失情况。为SMA携带者家庭进行遗传咨询，为SMA高风险家庭进行羊水穿刺，应用重连接依赖探针扩增技术(MLPA)对胎儿进行产前诊断。

结果：我地区55447名孕妇中8185人接受了SMA携带者筛查，接受率为14.76%。荧光定量PCR检出127名携带者（111例为E7和E8杂合缺失，15例E7杂合缺失，1例E7杂合子缺失E8纯合缺失），携带率为1.55%。经遗传咨询，114名携带者配偶接受了荧光定量PCR筛查，其中3个家庭为生育SMA患儿高风险家庭。行羊水穿刺经MLPA产前诊断，其中2例为SMN1基因E7两个拷贝；1例为SMN1基因E7和E8S纯合缺失，为SMA患者，妊娠终止。

讨论：统计了盐城地区产前人群SMA携带率，为SMN1基因检测在遗传咨询和产前诊断中应用提供临床依据。

关键字 SMN1基因 携带者筛查 遗传咨询

RMND1基因复合杂合变异致联合氧化磷酸化缺陷症11型1例患儿的遗传学分析并文献复习

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目的：探讨1例RMND1基因变异致联合氧化磷酸化缺陷症11型（COXPD11）患儿的基因型与表型关系。

方法：回顾性分析2024年9月至10月徐州市中心医院儿科的1例因“生后气促20min”入院患儿的临床资料。收集患儿及其父母的外周血，对患儿行全外显子组测序，对候选变异进行Sanger测序家系验证与致病性分析。以“所需的减数分裂核分裂1同源物”“RMND1基因”“联合氧化磷酸化缺陷症11型”

为中文检索关键词，以“Combined oxidative phosphorylation defect type 11”“COXPD11”“RMND1”为英文关键词，检索至2025年2月前的中国知网、万方数据库、PubMed数据库中检索相关文献。本研究通过徐州市中心医院伦理委员会批准（伦理号：XZXY-LK-20240111-0019）。

结果：①患儿为26 d龄女婴，出生后呼吸困难、肌张力低下、持续性肺动脉高压等临床表现，实验室结果提示乳酸升高、白蛋白和凝血功能降低，颅脑MRI提示脑白质范围偏大，密度偏低；胸部X线片提示新生儿呼吸窘迫综合征改变，纵隔透亮度增强，考虑纵隔气肿，不除外合并气胸；彩超心脏检查提示房间隔缺损（2mm）。因住院26天呼吸机依赖，家长放弃治疗出院，出院后第二日死亡。②全外显子组测序提示患儿RMND1基因存在c.1194del（p.Val399Leufs4）和c.1184T>C（p.Ile395Thr）复合杂合变异，经Sanger测序验证遗传自父母；根据美国医学遗传学与基因组学学会（ACMG）指南，c.1194del（p.Val399Leufs4）变异评级为致病性（PVS1+PM2_Supporting+PP1+PP4），c.1184T>C（p.Ile395Thr）评级为可能致病性（PM3+PM2_supporting+PP1+PP3+PP4）。③文献复习符合检索条件的文献16篇。包括本研究1例，共有50例患者，男15例，女32例（3例未报道）。早产12例、胎儿期起病5例、出生后6个月内起病31例、死亡24例。主要临床表现包括乳酸性酸中毒（40，90%）、发育迟缓（39，88%）、神经性听力损失（39，88%）、肾脏受累（39，88%），肌张力减退（36，72%）、神经系统系统（25，50%）等。RMND1基因型以纯合型为主，错义变异多见，c.1349G>C (p.450Serext31) 纯合变异为最常见变异（9例）。

结论：RMND1基因复合杂合变异为COXPD11患儿的遗传学病因。对孕期出现的胎儿宫内生长受限和多系统受累的新生儿，应高度怀疑COXPD11，产前基因检测有助于COXPD11患儿诊断。

关键字 RMND1基因；联合氧化磷酸化缺陷症11型；生长发育迟缓；全外显子测序

MFN2基因错义变异致腓骨肌萎缩症2A2A型一个家系的遗传学分析

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目的：探讨1个腓骨肌萎缩症2A2A型（CMT2A2A）家系基因型与表型的相关性，为该家系再次妊娠提供帮助。

方法：选取2024年1月至8月因“下肢肌肉萎缩伴运动障碍”就诊于徐州市中心医院产前诊断中心的1个CMT2A2A家系为研究对象。收集该家系相关临床资料，采集相关成员外周血与胎儿羊水/绒毛样本并提取基因组DNA，对相关成员进行全外显子组测序（WES），对检出的变异位点进行Sanger测序家系验证、致病性分析及生物信息学分析。本研究已通过徐州市中心医院医学伦理委员会的审查（伦理号：XZXY-LK-20240111-0019）。

结果：①家系中均为女性发病（先证者及其母亲、第一胎女儿），呈现发病年龄越早、双下肢萎缩越严重的现象。②WES与Sanger测序结果显示先证者及其母亲、第一胎女儿、第三胎胎儿均携带MFN2基因c.314C>T（p.Thr105Met）杂合错义变异，先证者哥哥、现任丈夫、第四胎胎儿均为野生型。③根据美国医学遗传学与基因组学学会（ACMG）相关指南与临床基因组资源中心（ClinGen）相关建议，该变异被评定为致病性（PP1_Strong+PM1+PS3+PS4_Moderate+PP3_Moderate+PM2_Supporting）。④PROVEAN与Mutation Taster软件对该变异预测结果分别为“有害”与“致病性”；Uniprot及Jalview软件预测该变异位

点编码氨基酸在多个物种间具有保守性；ChEBI软件预测该变异可导致第105位氨基酸的极性发生改变。经遗传咨询，先证者第三胎胎儿终止妊娠，第四胎胎儿继续妊娠中。

结论：MFN2基因c.314C>T（p.Thr105Met）错义变异可能为上述CMT2A2A型家系的遗传学病因，该变异位点的检出家系再次妊娠提供了诊断依据。

关键字 腓骨肌萎缩症2A2A型；MFN2基因；错义变异；全外显子组测序

新生儿筛查发现一例β酮硫解酶缺乏症患儿的临床特征及遗传学分析

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目的：探讨1例新生儿遗传代谢病筛查发现的β酮硫解酶缺乏症（β-ketothiolase deficiency，BKT）患儿的临床特征、遗传学特点以及ACAT1基因复合杂合突变的致病机制。

方法：对1例通过新生儿遗传代谢病筛查发现的BKT患儿，进行血串联质谱、尿气相色谱质谱、全外显子测序（Whole Exome Sequencing，WES）检测以及临床诊疗，收集相关数据进行分析。

结果：患儿，男，19天，新生儿筛查（NBS）血串联质谱提示：甲基巴豆酰基肉碱（C5:1）、甲基丙二酰基肉碱（C4DC+C5OH）、丙二酰基肉碱（C3DC+C4OH）增高；尿气相色谱质谱显示：2-甲基-3-羟基丁酸及甲基巴豆酰甘氨酸显著升高；全外显子测序发现ACAT1基因复合杂合突变：c.1124A>G（p.Asn375Ser，母源，致病性），c.631C>A（p.Gln211Lys，父源，意义未明变异）。入院完善检查并予左卡尼汀治疗病情稳定，无代谢危象。

结论：新生儿生化筛查联合基因检测是BKT早期诊断的关键。本例患儿所携带ACAT1基因c.631C>A变异为意义未明变异，但血和尿生化指标显著异常，需进一步随访监测其临床表现、生化指标等变化，并结合体外、体内实验等以明确其致病性。

关键字 β酮硫解酶缺乏症；ACAT1基因；c.631C>A；新生儿筛查

Genetic Analysis and Non-Invasive Prenatal Diagnosis of Fetal Skeletal Dysplasia: A Study of 34 Cases

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Objective: This study aimed to explore the genetic causes of fetal skeletal dysplasia (SD) using whole exome sequencing (WES) and to assess the feasibility and accuracy of non-invasive prenatal diagnosis (NIPD) for this condition.

Methods: A cohort of 34 fetuses with ultrasonographically suspected SD underwent genetic evaluation. All cases were analyzed using chromosomal microarray analysis (CMA) and WES. Additionally, NIPD was performed on

5 cases using targeted next-generation sequencing (NGS) of cell-free fetal DNA (cffDNA) extracted from maternal plasma.

Results: WES successfully identified genetic mutations in 21 out of the 34 fetuses (61.8%). These mutations involved various genes associated with skeletal dysplasia, including 8 FGFR3 variants (47.06%) and 2 COL2A1 variants (11.76%). Notably, NIPD demonstrated 100% sensitivity and specificity when compared to invasive diagnostic results.

Conclusions: WES proved to be more diagnostically effective than CMA for fetal SD, enabling precise genetic counseling and recurrence risk assessment. The NIPD strategy based on cffDNA sequencing showed high accuracy, providing a safe alternative for prenatal diagnosis of SD. These findings contribute to advancing precision medicine approaches for managing fetal SD and reducing reliance on invasive procedures.

Key Words Fetal skeletal dysplasia, whole exome sequencing, non-invasive prenatal diagnosis, genetic etiology, cell-free fetal DNA.

·出生缺陷防控·

基于六西格玛管理法的中孕期母血清学产前筛查质量评价

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目的：评估镇江地区2024年中孕期母血清学产前筛查（唐氏筛查）的质量控制水平。

方法：统计2024年01月–12月镇江市6家筛查机构唐氏筛查的室内质控数据和上报国家卫健委临检中心的室间质评数据。分析甲胎蛋白（AFP）和游离β绒毛膜促性腺激素（Free–βHCG）的变异系数、偏倚、质控规则等质控指标。使用六西格玛管理法评估各机构质控规则的合理性。

结果：（1）AFP有2家σ值>6；2家σ值为5–6；1家σ值为4–5；1家σ值<4。Free–βHCG有1家σ值>6；4家σ值为5–6；1家σ值为4–5，实验室可参考自身西格玛水平修改质控规则。（2）不同的检测仪器比较：PerkinElmer1235检测水平略高于贝克曼DXI800。（3）室内质控指标反应检测效果或与样本量呈正相关。

结论：我地区唐氏筛查质控水平基本良好；六西格玛管理法可作为中孕期母血清学筛查质控评估的补充提示，优化质控规则，提高检测水平。

关键字 六西格玛；血清学筛查；质量管理

Association between maternal creatinine to body weight ratio and small/large for gestational age newborns among 11734 Chinese women

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Background: Serum creatinine to body weight ratio (CBWR) is closely associated with non–alcoholic fatty liver disease, diabetes, and all–cause mortality. This study aimed to assess the impact of CBWR in late pregnancy on incident small and large for gestational age (SGA/LGA) deliveries.

Methods: This observational study included 11734 consecutive pregnant women who underwent hepatic and renal examinations at hospitalization and gave birth from 2016 to 2017 in a large hospital. CBWR and fetal birth outcomes were investigated and analyzed.

Results: CBWR was associated with smaller birth length and lower birth weight (β = －0.21 cm, 95% CI: －0.28, －0.15; β = －0.29 kg, 95% CI: －0.31, －0.27; for the highest versus lowest quintile). The multivariate–adjusted odds ratios of SGA and LGA in higher quintiles versus the lowest quintile of CBWR were 1.63 and 0.60, 2.16 and 0.53, 2.99 and 0.39, and 5.24 and 0.23, respectively. Per standard deviation (SD) increase in CBWR was

accompanied by a 1.63-fold increase in SGA risk (OR=1.63, 95% CI: 1.52, 1.75) and a 42% decrease in LGA risk (OR=0.58, 95% CI: 0.55, 0.63). Sensitivity analysis confirmed the consistence of these findings. Subgroup analysis demonstrated that CBWR was strongly associated with SGA risk in women with CBWR>0.98 umol/L/kg complicated by preeclampsia or preterm birth, while in those complicated by gestational diabetes mellitus, the association was attenuated.

Conclusion: Elevated CBWR in late pregnancy was associated with lower risk of LGA and higher risk of SGA, suggesting CBWR could be an easy-to-measure, inexpensive and promising index for predicting SGA/LGA risk.

Key Words Creatinine to body weight ratio; birth weight; small for gestational age; large for gestational age; fetal growth.

Application of Tandem Mass Spectrometry in the Study of Maternal-Fetal Lipid Metabolism Features and Its Implications for Disease Mechanisms

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Aim : This study aims to analyze lipid profiles in maternal serum, placental tissue, and umbilical cord serum in gestational diabetes mellitus (GDM) to elucidate lipid metabolism traits and explore key factors influencing the disease’s onset and progression. Method: Maternal serum, placenta, and umbilical cord serum samples were analyzed for lipid content using tandem mass spectrometry(TMS), with OPLS-DA used to identify characteristic variables and potential biomarkers through multi-dimensional and univariate statistical analyses. Result: The study identified a total of 331 lipids in maternal serum, 246 in placental tissue, and 301 in cord blood serum, revealing significant metabolic differences with potential biomarkers for GDM including 13 lipids from maternal serum, 11 from placental tissue, and 5 in fetal umbilical serum, primarily linked to sphingolipid and glycerol phospholipid metabolism pathways.

Conclusion: After excluding the influence of blood glucose, lipid metabolic abnormalities still persist in GDM mothers, fetuses, and the maternal-fetal interface. Differentially expressed metabolites are primarily enriched in sphingolipid and glycerophospholipid metabolic pathways. These findings may provide valuable insights into the potential factors underlying the pathogenesis and progression of GDM.

Key Words Key Words: gestational diabetes mellitus, placenta, lipid metabolism, tandem mass spectrometry,

E3 Ubiquitin Ligase RNF187 Facilitates Proliferation and Migration of Human Spermatogonial Stem Cells through Lysine 48-Linked Polyubiquitination-Mediated Degradation of WDR77)

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The E3 ubiquitin ligase RNF187, also known as RING domain AP1 coactivator-1, is a member of the RING finger family. RNF187 is indispensable for the proliferation and migration of GC-1 cells derived from mouse spermatogonia and GC-2 cells derived from spermatocytes. However, it remains unclear whether RNF187 plays a crucial role in the self-renewal and migration of human spermatogonial stem cells (SSCs). In this study, we observed a positive correlation between RNF187 expression and the proliferation and migration of human SSCs. Through co-immunoprecipitation and mass spectrometry analyses, we identified WD repeat-containing protein 77 (WDR77) as an interacting partner of RNF187. Specifically, RNF187 recognizes the K118 site of WDR77 through lysine 48-linked polyubiquitination, subsequently mediating its degradation via the ubiquitin-proteasome system (UPS). Further studies have revealed that decreased expression of WDR77 diminishes the symmetric dimethylation at H4R3 (H4R3me2s) catalyzed by its interacting protein, the arginine methyltransferase PRMT5. This, in turn, relieves the transcriptional repression of early growth response protein 1 (EGR1), a positive regulator for human SSC maintenance. In conclusion, this study has unveiled a pivotal role for RNF187 in the proliferation and migration of human SSCs. This may provide a promising strategy for address non-obstructive azoospermia (NOA) caused by SSCs dysfunction.

Key Words Ubiquitin, RNF187, spermatogonial stem cells, WDR77, EGR1)

CRL2LRRC41-Mediated DDX5 Ubiquitination Enhances Interaction with ELAVL1 Preventing NOG mRNA Degradation and Sustaining Self-Renewal and Migration of Human Spermatogonial Stem Cells

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Background Human spermatogonial stem cells (SSCs) exhibit a remarkable capacity for self-renewal, crucial for sustaining spermatogenesis throughout life. While the Cullin-RING E3 ubiquitin ligase 2 (CRL2) complex is known to regulate various cellular functions, its precise role in human SSCs has not been fully elucidated. This study

aimed to investigate a novel variant of the CRL2 complex, termed CRL2LRRC41, and its role in SSC function.

Methods We utilized molecular biology techniques, including gene knockdown and functional assays, to assess the effects of CRL2LRRC41 on the proliferative and migratory abilities of human SSCs. Additionally, we employed proteomics and biochemical approaches to identify potential substrates of CRL2LRRC41. We specifically focused on ATP-dependent RNA helicase DDX5, a known regulator of spermatogenesis, to explore its interaction with CRL2LRRC41 and the downstream molecular mechanisms involved.

Results Our findings revealed that the disruption or dysfunction of CRL2LRRC41 led to reduced proliferative and migratory abilities in SSCs. Through our investigation, we identified DDX5 as a ubiquitination substrate of CRL2LRRC41. Notably, the ubiquitination of DDX5 fosters its interaction with the RNA-binding protein ELAVL1, without directing DDX5 towards degradation via the ubiquitin-proteasome system (UPS). This interaction enhances the stability of the downstream transcript, Noggin (NOG), thereby supporting SSC proliferation and migration.

Conclusions This study provides the first identification of the CRL2LRRC41 complex in human SSCs and elucidates the molecular mechanisms by which CRL2LRRC41 facilitates SSC function via ubiquitination-mediated protein interactions. These findings offer novel insights into the molecular underpinnings of male infertility.

Key Words LRRC41, DDX5, ELAVL1, Ubiquitination, Spermatogonial Stem Cells

Introduction of a new indicator in expanded newborn screening for Hyperphenylalaninemia: a retrospective study

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Hyperphenylalaninemia (HPA) is one of the most common inborn error of metabolism detected by high-performance liquid chromatography tandem mass spectrometry, which could simultaneously measure dozens of amino acids and acylcarnitines. We aimed to investigate these amino acids and their ratios for their performance to reduce false positives of HPA. To select ideal indicators and evaluate their performance for identifying HPA, data from 457595 newborn babies, containing 73 cases of HPA, were used in this retrospective study. The ratio of Leucine+Isoleucine+Proline-OH/Phenylalanine, when it was <2.0, exhibited the optimal performance for identifying HPA after Phenylalanine, the area under the curve is 0.001, $p<0.001$. And, it is the best indicator for reducing false positives of HPA, with a reduced rate of 53.99% in the model-building data and 59.77% in the testing data. There is no significant difference between the rates of the model-building data and the testing data, $p=0.151$. In false positives with LEU+ILE+PRO-OH/PHE <2.0, every amino acid had a positive correlation with the others, all $p<0.05$. Furthermore, except Arg and Phe, all amino acids in false positives with LEU+ILE+PRO-OH/PHE <2.0 had a higher concentration than those with LEU+ILE+PRO-OH/PHE ⩾2.0. In summary, the ratio of LEU+ILE+PRO-OH/PHE may effectively reduce the false positives of HPA, which might be caused by overnutrition and liver dysfunction. We recommend to utilize the indicator to improve the performance of identifying HPA in further expanded newborn screening practice.

Key Words Phenylalanine, LEU+ILE+PRO-OH/PHE, False positives, Hyperphenylalaninemia, Expanded newborn screening

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。

讨论：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

尼曼匹克病B型的一家系基因分析及胚胎植入前遗传学诊断

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目的：分析一个中国人尼曼-匹克病B型(NPD-B)家系发病的分子遗传学基础，探讨SMPD1基因检测在中国人NPD-B家系基因诊断中的意义，并对先证者母亲的体外受精胚胎进行胚胎植入前遗传学诊断（PGT-M）。

方法：收集该NPD家系的临床资料和血液标本，从外周血提取基因组DNA，经聚合酶链反应(PCR)依次扩增该家系中3名成员SMPD1基因的6个外显子全部编码区及其前后10bp的剪切区，扩增产物纯化后直接进行正反向测序，并与Genebank进行比对。应用Karyomapping芯片技术通过染色体非整倍体筛查及连锁分析方法进行胚胎植入前遗传学诊断，并行Sanger测序验证结果。

结果：测序结果显示家系先证者SMPD1基因存在2号外显子c.827A>G(p.Y276C)及6号外显子c.1673T>C(p.L558P)复合杂合突变，分别遗传自表现正常的母亲和父亲。经查阅数据库，SMPD1基因基因的c.827A>G(p.Y276C)及c.1673T>C(p.L558P)复合杂合突变与NPD-B相关。在先证者的2个体外受精胚胎中，2个胚胎的染色体拷贝数均正常，其中1个胚胎为携带了父亲母亲的致病片段，Sanger测序验证了这一结果。选择未携带该突变片段的健康胚胎植入，生后基因诊断证实为健康胎儿。

结论：明确SMPD1基因的c.827A>G(p.Y276C)及c.1673T>C(p.L558P)复合杂合突变为该NPD-B家系的致病原因。SMPD1基因检测可以帮助判断中国人NPD的分型。在先证者明确的前提下可用比较基因组杂

交技术进行胚胎植入前遗传学诊断。这是国内尼曼匹克病的胚胎植入前遗传学筛查的首例报道。

关键字 尼曼–匹克病；基因诊断；胚胎植入前诊断；SMPD1基因；酸性神经鞘磷脂酶；连锁分析

常州地区新生儿GJB2c.109G>A变异与听力的相关性研究

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目的：本研究旨在分析常州地区新生儿耳聋基因GJB2c.109G>A变异与听力的相关性，为遗传咨询提供临床依据。

方法：选取2023年11月至2024年10月于常州市妇幼保健院出生的10,552例新生儿作为研究对象。采用联合探针锚定聚合测序技术对GJB2、SLC26A4、GJB3及线粒体12S rRNA基因中的127个常见变异位点进行检测。同时，使用耳声发射（OAE）法和听性脑干反应（ABR）法进行听力筛查。基因变异与听力表型的相关性通过卡方检验和Logistic回归分析进行评估。

结果：1.在10,552例新生儿中，共检出1,777例基因变异携带者，阳性率为16.84%（1,777/10,557）。其中，c.109G>A变异检出率最高，占10.78%（1,138/10,557），包括c.109G>A纯合变异39例（0.37%），c.109G>A复合杂合变异24例（0.23%），c.109G>A与其他基因联合变异42例（0.40%），杂合变异1,033例（9.80%）。2.1,138例c.109G>A变异新生儿听力初筛未通88例，复筛未通过14例；9414例非c.109G>A变异新生儿听力初筛未通258例，复筛未通过20例。前者听力初筛未通过率、复筛未通过率均明显高于后者（χ^2=79.78，$p < 0.001$；χ^2=32.75，$p < 0.001$）。3.c.109G>A纯合变异新生儿中，听力初筛未通过16例，复筛未通过5例，确诊3例，其中2例为双耳轻度感音神经性耳聋，1例为单耳神经性耳聋；c.109G>A复合杂合变异新生儿中，听力初筛未通过15例，复筛未通过1例，未确诊；c.109G>A与其他基因联合变异新生儿中，听力初筛未通过2例，复筛均通过；杂合变异新生儿中，听力初筛未通过55例，复筛未通过8例，确诊3例，其中1例为单耳轻度感音神经性耳聋，1例为单耳中度感音神经性耳聋，1例为左耳轻度传导性耳聋，右耳中度感音神经性耳聋。

结论：本研究首次系统分析了常州地区新生儿GJB2 c.109G>A变异的检出率及其与听力表型的相关性，证实c.109G>A是常州地区新生儿携带率最高的耳聋基因变异位点。研究结果为早期听力损失干预和遗传咨询提供了重要依据，具有显著的临床意义。

关键字 耳聋基因；听力筛查；c.109G>A变异；新生儿

Residual Risk and Clinical Utility of Non-Invasive Prenatal Testing (NIPT) in Chromosomal Screening for Fetuses with Ultrasound Soft Markers

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Objective: To clarify the screening efficacy of NIPT for chromosomal abnormalities in fetuses with ultrasound soft markers (USMs) and analyze the residual risk and complementary diagnostic value of chromosomal microarray analysis (CMA) in a rigorously selected cohort (excluding advanced maternal age and NIPT high-risk cases), aiming to refine clinical management strategies.Methods: This retrospective study analyzed 676 fetuses with isolated USMs (single soft marker without structural anomalies) and 271 fetuses with non-isolated USMs (≥2 soft markers or coexisting structural anomalies) between 2019 and 2023. All cases underwent CMA after excluding pregnancies with advanced maternal age or positive NIPT results. Abnormalities were classified as NIPT-detectable (T21/T18/T13) or NIPT-undetectable (CNVs/SCAs). Residual risk and CMA detection rates were stratified by USM subgroups.

Results: Results: In isolated USMs, the CMA abnormality rate was 2.37% (16/676), with NIPT-detectable trisomies accounting for 90.24% (14/16) and NIPT-undetectable CNVs/SCAs for 9.76% (2/16). Residual risk reached 12.94%, predominantly due to pathogenic CNVs (e.g., 22q11.2 microdeletion). Subtype-specific risks varied: nuchal translucency (NT) thickening (12.50%) and absent nasal bone (14.10%) carried higher risks, while ventricular bright spots showed lower risk (3.70%). In non-isolated USMs, the CMA abnormality rate was significantly higher (7.75% vs. 2.37%, $P<0.01$), yet residual risk was lower (7.75% vs. 12.94%), suggesting multifactorial anomalies often align with detectable genetic defects.

Conclusion: NIPT demonstrates high sensitivity for common trisomies in USM fetuses, yet 10% of CMA-detected abnormalities (CNVs/SCAs) remain undiagnosed, contributing to a residual risk of 12.94% in isolated USMs. CMA significantly improves diagnostic yield, particularly in non-isolated USMs (7.75% abnormality rate). Clinically, CMA should be prioritized for fetuses with persistent isolated high-risk USMs (e.g., NT thickening) or non-isolated USMs despite negative NIPT results. Risk stratification based on USM subtype and isolated/non-isolated status is critical for optimizing prenatal counseling and diagnostic pathways.

Key Words NIPT,UAMs,Residual Risk,CNVs

智能驱动·精准防控：AI赋能的出生缺陷全周期防控体系构建与高质量发展路径研究报告

时敬业
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摘要：根据国家卫生健康委发布的《出生缺陷防治能力提升计划（2023-2027年）》，坚持预防为主、防治结合，围绕婚前、孕前、孕期、新生儿和儿童各阶段，完善出生缺陷全周期防控体系的构建，促进出生缺陷防治工作高质量发展。伴随 AI 技术与医疗领域的深度融合，其在出生缺陷防控体系中的应用备受关注。本研究系统整理了 AI 在出生缺陷三级防控体系中的相关技术及应用案例，深入分析现存问题，并对未来发展进行展望。研究发现，AI 在出生缺陷防控体系中的应用日益广泛，既为出生缺陷防控带来便利，又推动了防控体系的完善，但同时也面临诸多挑战。

关键字 人工智能；出生缺陷防控；遗传风险评估；流行病学研究；辅助诊断

Varying Bifidobacterium species in the maternal–infant gut microbiota correlate with distinct early neurodevelopmental outcomes

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Objective: To deepen the understanding of how maternal–infant gut microbiota influences offspring neurodevelopment at one year of age.

Method: Conducted among 520 families from the Jiangsu birth cohort in China, we analyzed the gut microbiota of mothers during the first and third trimesters and their offspring at birth and one year using 16S rRNA gene sequencing, and explored their correlations with neurodevelopmental outcomes in offspring.

Result: We reveal that the maternal gut microbiota during early pregnancy play a substantial role, accounting for 3.34% of the variance in offspring neurodevelopmental scores. This contribution is notably higher than the 1.24% attributed to the infants’ own microbiota at 1 year of age, underscoring the significant influence of maternal gut health on early child development. Remarkably, an elevation in maternal Bifidobacterium pseudocatenulatum is linked to decreased cognitive scores, whereas an enrichment of Bifidobacterium longum at 1 year of age is associated with higher cognitive scores. Furthermore, we find that maternal B. pseudocatenulatum is linked to the heterolactic fermentation metabolic pathway, while infant B. longum is associated with the Bifidobacterium shunt pathway.

Discussion: Our analysis implies that maternal and infant gut microbiota play a distinct role in neurodevelopment, suggesting potential strategies for improving neurodevelopmental outcomes during early pregnancy or infant development by targeting gut microbiota composition.

羊水过少合并胎儿生长受限羊膜腔灌注诊疗两例分析

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目的：探讨羊水过少合并胎儿生长受限患者的病因诊断方式及治疗方案，为该类病例提供精准治疗措施，改善胎儿妊娠结局。

方法：回顾性分析苏北人民医院产科2024年收治的两例严重羊水过少合并胎儿生长受限病例临床资料，并对其介入性诊断结果及实施羊膜腔灌注后胎儿妊娠结局进行分析。

结果：病例1：胎儿CMA、Trio-WES均未发现异常，CMV-DNA阴性，灌注生理盐水250ml后羊水深度达3cm结束手术。次日超声进一步检查发现胎儿双肾发育良好，未发现结构异常。之后严密监测，未再出现羊水过少，妊娠至38周剖宫产分娩一女婴，体重2100g，目前随访婴儿未发现异常。病例2：胎儿CMA未发现异常，Trio-WES提示：seq[GRCh37] dup(16)(p13.11p13.11)chr16:g.15489744_16315717dup，0.83Mb重复，可疑致病，父源，CMV-DNA未发现异常。但该病例在实施穿刺过程中发现羊水呈淡褐色浑浊液体，羊膜腔灌注过程中输注生理盐水约50ml时孕妇即诉阴道排液，后诊断为胎膜早破，当夜即流产娩出胎儿。

讨论：孕中期发生羊水过少合并或不合并胎儿生长受限的诊断和治疗一直在困扰产科医生。羊水过少限制介入性产前诊断的实施，对胎儿是否存在先天异常的疑问限制后续干预方案的落实。虽然本研究病例较少，病例2在灌注过程中发现羊水渗漏产科最终诊断其为胎膜早破导致的羊水过少，但仍可以在一定程度上为后续该类病例的诊断和治疗提供一定研究基础。

关键字 羊水过少，胎儿生长受限，染色体微阵列分析，CMA，全外显子测序，羊膜腔灌注，

3例性染色体非整倍体嵌合体的产前诊断结果分析

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目的：通过分析3例性染色体非整倍体嵌合体病例的产前诊断及临床结局，探讨三种遗传学检测方式在出生缺陷防控中的应用。

方法：回顾性分析在苏北人民医院产前诊断中心进行羊水穿刺并最终诊断为性染色体非整倍体嵌合体的3例病例。

结果：3例病例均为NIPT提示性染色体异常接受羊水穿刺胎儿染色体核型分析及CMA检测提示性染色体非整倍体嵌合体，随即再行间期FISH验证：病例1，核型分析提示45,X[23]/46,XX[45]，CMA分析结合核型分析结果进行二次分析后提示45，X嵌合比例8%，FISH提示45，X嵌合比例3%；病例2，核型分析提示45,X[93]/47，XXX[40]/46,XX[2]，CMA结果未发现异常，FISH验证提示：45,X占49%，47，XXX占36%，46,XX占15%；病例3核型分析提示：45；X[108]/47,XXX[43]，CMA提示47，XXX嵌合，嵌合比例23%，FISH验证结果45；X约占40%，47,XXX约占60%。

讨论：随着NIPT的普遍应用，越来越多性染色体异常被筛查出来，而CMA目前被广泛应用于产前诊断，甚至有些单位不再进行细胞培养胎儿染色体核型分析。该三例病例同时进行核型分析及CMA检测，有两例CMA初始未报异常，另一例所报的嵌合类型完全与实际不一致（CMA报的为47，XXX与46，XX嵌合，实际上为45，X与47，XXX的嵌合），说明在性染色体异常的产前诊断方面，不能单纯依赖CMA检测，传统的细胞遗传仍是一个有效的检测方式，但由于培养偏好的存在，细胞遗传所报告的嵌合比例仍不是真实情况，需要间期FISH进行确定，才能真正明确性染色体异常的嵌合形态和比例，从而更准确评估胎儿预后。

关键字 性染色体异常，非整倍体，嵌合体，染色体核型分析，染色体微阵列分析，CMA，FISH

579例绒毛穿刺产前诊断安全性和临床应用价值分析

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目的：评价绒毛穿刺产前诊断技术的安全性和临床应用价值。

方法：回顾2014年1月至2021年8月于南京大学医学院附属鼓楼医院产前诊断中心行经腹绒毛穿刺产前诊断的病例579例，分析其手术指征、穿刺成功率、胎儿丢失率、遗传学检测结果和妊娠结局等情况。

结果：（1）579 例经腹绒毛穿刺取样中578例穿刺成功，取样成功率99.67%，术后一个月内6例自然流产或死胎，病理性异常153例，检出率 (26.47%)，假阳性2例（1.31%），假阴性1例（0.24%）。（2）遗传学检测正常的409例病例中，14例术后一个月后失访，失访率3.42%。妊娠终止55例，（13.4%），活产347例（84.8%)。术后一个月的流产风险在各年龄组间，各病例来源组间，不同妊娠方式组间，不同妊娠史组间，不同穿刺指征间，不同胎盘位置组间，不同胎盘与宫内口间的距离组间，各穿刺医生，各超声引导医生，不同穿刺次数组间，不同抽吸次数组间均无明显倾向性。（3）不同穿刺指征的病例遗传学致病性异常检出率存在差异。涉及NT增厚的组异常检出率高于其他组，尤其是NT增厚伴其他超声异常发现组，异常结果的检出率达到50.46%，存在明显的统计学差异。（4）不同穿刺指征组间胎儿的妊娠结局存在差异，NT增厚胎儿，妊娠结局良好的发生率66.16%。高龄孕妇仅见胎儿NT增厚,妊娠结局良好率53.19%。NT增厚伴发既往不良生育史时，妊娠结局良好的发生率62.5%。非超声异常穿刺指征组妊娠结局良好率76.19%。上述妊娠结局良好率高于其他超声异常组（43.75%），尤其是NT增厚伴发其他超声异常组（29.52%）。遗传学检测正常的病例中穿刺指征与妊娠结局之间存在弱相关性。CMA结果正常，后期因多种原因选用WES检测病例9例，致病性异常检出率55.6%。

结论：经腹绒毛穿刺取样作为成熟的产前诊断取材技术临床应用是安全有效的；NT增厚的胎儿首选产前诊断。

关键字 产前诊断；CMA检测；QF-PCR检测; 经腹绒毛穿刺取样术

常州市国家出生缺陷医院监测点监测结果分析

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目的：出生缺陷给患儿家庭带来了沉重的负担，也对整个社会造成了巨大的疾病负担，是全球性的公共卫生问题。本研究旨在通过分析常州市国家出生缺陷医院监测数据，深入了解该地区出生缺陷的发生现状，并探讨影响患儿活产率的因素，以期为出生缺陷的早期发现及实施预防性干预措施提供更科学有力的参考依据。

方法：基于全国妇幼健康监测系统，收集2014~2023年围产儿及出生缺陷儿相关数据。年度发生率差异比较使用c2检验，不同特征组间出生缺陷发生率的比较以及转归结局的比较采用c2检验及似然比检验比较有无统计学差异。采用Joinpoint回归分析评价出生缺陷总体发生率、不同病种发生率的时间变化趋势。采用单因素、多因素的Logistic回归分析得出对缺陷儿转归有意义的独立影响因素。以P<0.05定义为差异存在统计学意义。

结果：1.2014~2023年常州市国家出生缺陷医院监测点围产儿出生缺陷总发生率为268.33/万，2021年出生缺陷发生率最高，2014年发生率最低，各年份间发生率存在显著差异。2.城镇围产儿出生缺陷发生率显著高于乡村地区；男性围产儿出生缺陷发生率略高于女性；出生缺陷发生率随产妇年龄增加呈U形分布。3.出生缺陷主要病种发生率前五顺位为：先天性心脏病、多指（趾）、并指（趾）、尿道下裂、外耳其他畸形（小耳、无耳除外）；先天性心脏病与多指（趾）连续十年稳居前二。4.缺陷儿活产率为56.31%，其中围产期缺陷儿活产率为90.43%。产妇文化程度高、多胎妊娠、出生体重>4000g、产后七天确诊是患儿存活的保护因素。

讨论：2014~2023年常州市出生缺陷发生率总体呈上升趋势，患儿活产率也有较高提升，出生缺陷防治工作初显成效，但总体形势仍较为严峻。产妇常住地、年龄、文化程度、胎数、性别、出生体重、确诊时间是影响患儿转归的重要因素。均衡医疗资源、提升育龄期妇女文化素养、加强孕产妇保健、优化新生儿救治等多种措施并行，方能更好地降低出生缺陷发生率并提高缺陷儿活产率。

关键字 出生缺陷；围产儿；流行病学；趋势；影响因素

多囊卵巢综合征患者胆汁酸代谢、性激素水平分析

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目的：分析多囊卵巢综合征（PCOS）患者胆汁酸代谢特征，并探讨其与性激素水平的关系。

方法：回顾性选取 2023 年 1 至 6 月在徐州市妇幼保健院进行健康检查的 PCOS 患者 54 例（PCOS 组），另择同期来院进行健康检查的正常对照女性 53 名为对照组。研究对象于月经第 2~5 天，留取上午空腹肘静脉血，使用超高效液相色谱串联质谱法检测性激素、胆汁酸代谢物水平。比较两组血清性激素、胆汁酸代谢物水平，并通过建立正交偏最小二乘判别分析（OPLS-DA）模型，寻找两组差异性胆汁

酸；分析差异性胆汁酸与性激素的相关性。

结果：PCOS 组患者血清抗米勒管激素、促黄体生成素、促黄体生成素/卵泡生成素、雄激素睾酮（T）和脱氢表雄酮硫酸酯（DHEAS）水平均高于对照组（均 P<0.05）。与对照组比较，PCOS 组患者血清初级游离胆汁酸鹅脱氧胆酸（CDCA）水平增加（P<0.05），次级结合胆汁酸甘氨脱氧胆酸（GDCA）和甘氨石胆酸（GLCA）水平均降低（均 P<0.05）。通过 OPLS-DA 模型找到两组差异性最强的胆汁酸为 GDCA，相关性分析显示 GDCA 与 T、DHEAS 均呈负相关（r2=-0.363、-0.342，均 P<0.05）。

讨论： PCOS 患者存在胆汁酸代谢紊乱和性激素水平异常，且 GDCA 与 PCOS 高雄激素症状密切相关。

关键字 多囊卵巢综合征；胆汁酸；高雄激素；甘氨脱氧胆酸

Prenatal phenotype analysis of a case with cardiofaciocutaneous syndrome caused by BRAF gene mutation

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Objective: This study selected different prenatal diagnostic methods based on prenatal ultrasound phenotypes during pregnancy by analyzing the prenatal clinical phenotype of a child with cardiocutaneous syndrome (CFCS) caused by BRAF gene mutation.

Methods: Chromosome microarray (CMA) and whole exome sequencing (WES) techniques were used for the prenatal genetic diagnosis in a pregnant woman with fetal bone dysplasia (fetal macrocephaly, short femur) and polyhydramnios during pregnancy.

Results: CMA revealed no abnormalities, WES revealed BRAF de novo missense mutation (c.1406G > A, p.G469E), and the fetal parents showed no BRAF gene mutation.

Conclusion: Pathogenic variants in the BRAF gene can lead to CFCS, which during pregnancy can present with signs of ultrasonographic abnormalities including macrocephaly, short femur, polyhydramnios, etc., indicating that when cranial and long bone dysplasia are found by ultrasonography during pregnancy, monogenic genetic disease should be considered and the prenatal diagnostic strategy of whole exome sequencing should be selected.

Key Words BRAF gene, cardiofaciocutaneous syndrome (CFCS), whole exome sequencing (WES), prenatal diagnosis

CMA联合STR检测在性染色体疾病高风险病例产前诊断中的应用

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目的：探讨CMA联合STR检测在无创产前筛查性染色体疾病高风险产前诊断中的临床意义。

方法：选择2023年2月至2025年2月因无创筛查（NIPT/NIPT-Plus）高风险于本中心遗传咨询行产前诊断的孕妇为研究对象，回顾性分析性染色体高风险的无创筛查、染色体微阵列分析（CMA）、短串联重复序列（STR）、染色体核型结果。

结果：性染色体高风险145例（34.5%，145/420）。介入性产前诊断：81例未见异常（含2例孕妇本人性染色体异常，1例90%嵌合型45,X；1例47,XXX）；3例非性染色体的不明意义CNV；61例致病性变异，包括46例完全型非整倍体(47,XXX 12例,47,XYY 13例,47,XXY 20例,45,X 1例)，10例嵌合型非整倍体(47,XXY/46,XY 3例、45,X/46,XX 5例、45,X/46,XY 2例)，3例chrX致病性微缺失，1例chrX致病性大片段缺失，4例非性染色体的致病性微缺失/微重复，1例非性染色体的大片段嵌合型缺失。上述病例中4例为性染色体合并其他染色体异常。无创筛查的性染色体高风险阳性预测值(PPV)为41.4%。

讨论：STR检测发现无创假阳性病例中2例孕妇性染色体异常，无明显表型。相比核型，CMA具有更高的异常检出率，STR可用于母源污染排查，还可快速诊断常见染色体非整倍体（包括嵌合型）。建议对无创筛查的性染色体高风险孕妇采用羊水CMA和母胎STR联合检测，科学指导其妊娠结局选择和再生育产前检查。

关键字 CMA, STR, 无创，性染色体，产前诊断

Advances in the Role of Cell-Free DNA in Preeclampsia: Pathogenesis, Biomarkers, and Clinical Applications

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Preeclampsia (PE) is a severe pregnancy-specific complication characterized by hypertension and end-organ damage, closely associated with placental dysfunction. In recent years, cell-free DNA (cfDNA) has emerged as a promising non-invasive biomarker, offering significant potential for elucidating the pathological mechanisms of PE and optimizing clinical management strategies. This review systematically examines the biological characteristics, sources, and clearance of cfDNA in PE patients, as well as the changes in cfDNA levels observed in these individuals. Furthermore, it explores the potential of cfDNA as a tool for early diagnosis and prediction of PE. By providing new insights into the pathogenesis, early detection, and monitoring of PE, this review aims to enhance clinical prevention and management strategies for this condition. The findings underscore the importance of cfDNA

as a biomarker and its potential to improve maternal and fetal health outcomes through early intervention and targeted therapies.

Key Words Preeclampsia; Cell-free DNA; Biomarker; Prenatal Screening

不同产前诊断指针下胎儿染色体核型和基因芯片分析

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目的：探讨不同产前诊断指征孕妇的染色体异常和基因芯片异常的关联性。

方法：选取2018年1月至2022年2月具有产前诊断指征的914例孕妇作为研究对象，部分研究对象在超声引导下行羊膜腔穿刺术，进行羊水细胞染色体核型分析及CMA基因芯片分析。

结果：在914例孕产妇中有898例进行了染色体核型分析检测，异常核型检出率为5.79%（52/898）；530例进行了基因芯片检测，基因芯片检测染色体拷贝数异常检出率为18.11%（96/530）。NIPT高风险为产前诊断指征的其核型异常检出率最高，NIPT异常且核型分析异常的孕产妇其基因芯片结果均为异常。另外，年龄与核型异常之间无相关性。

结论：羊水染色体核型分析和CMA基因芯片分析相互结合可为不同产前诊断指征孕妇提供更加精准的诊断及优生指导。

关键字 产前诊断；指征；核型分析；基因芯片

1例Krabbe病患儿的临床资料及家系基因变异分析

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目的：对一个球形细胞脑白质营养不良病患儿及家系进行遗传分析并鉴定该家系的致病基因，并为再次妊娠提供遗传咨询。

方法：收集患儿临床资料，应用全外显子捕获测序技术和Sanger测序技术在家系内进行测序验证，结合患儿临床症状体征和检测结果，对家系进行临床和分子遗传学分析。

结果：患儿3月龄时出现不能抬头、肌张力偏低、反复发作性肺炎、吞咽困难等临床表现。7月龄时表现为生长发育迟缓，四肢僵直，肌张力增高，颈强弱阳性。头颅MRI平扫+弥散成像显示大脑深部白质、小脑白质及小脑核团非特异性长T1、长T2信号。脑脊液生化检查示蛋白质升高，患儿于28月龄因肺炎夭折。经全外显子捕获测序并经Sanger测序验证，患儿GALC基因(NM_000153.4)存在2个杂合变异：第5外显子c.461C>A(Pro154His)变异和第14外显子c.1604_1607de1(Asn535Argfs17)变异。其中c.461C>A来源于父亲，c.1604_1607de1来源于母亲。

结论：分子遗传学检测结果表明患儿的c.461C>A(Pro154His)变异引起错义突变，c.1604_1607de1(Asn535Argfs17)变异引起移码突变，2个变异形成了复合杂合变异，为明确的致病变异，结合临床特征和头颅影像学检查，对Krabbe病的诊断提供了帮助，对患病家庭的再生育指导、预防出生缺陷具有重要的意义。

关键字 球形细胞脑白质营养不良;GALC基因;基因突变;溶酶体贮积病

Smith-Lemli-Opitz综合征(SLOS)1家系报道

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目的：Smith-Lemli-Opitz综合征(SLOS)是一种由催化胆固醇合成的7-脱氢胆固醇还原酶的编码基因DHCR7变异造成的一系列以低胆固醇、多发畸形、智力缺陷和行为问题为特征的常染色体隐形遗传病，在亚洲人群中极为罕见。本文报道一例2024年南通大学附属常州儿童医院确诊的SLOS家系，以期提高临床对该病的识别和诊疗能力。

方法与结果：患儿，女，足月小样儿，生后出现四肢青紫被收治入院，因面容腭弓偏高、双足存在并趾畸形、心脏结构畸形在征得其家属知情同意后对其外周血全外显子测序(WES)，结果显示患儿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变异分类标准，DHCR7基因变异c.852C>A/p.Phe284Leu为可能致病性变异(PM1+PM2_Supporting+PM3+PP3)；c.1426T>C/ p.Ter476Gln ext51为可能致病性变异(PM2_Supporting+PM3_Strong+PM4)。Sanger测序结果表明：患儿DHCR7 c.852C>A变异遗传自母亲；c.1426T>C遗传自父亲，且同一家系中，先症者的两个健康哥哥均携带c.1426T>C变异，符合常染色隐性遗传(AR)致病机制。患儿

生后29天的血脂检测中胆固醇显著低于参考值，载脂蛋白A1及B稍下降，与疾病相符合。由于暂时缺乏中国新生儿7-DHC的基线数据，选取4个正常婴儿(平均日龄29.25天[95%CI: 0.59-57.92天])作为对照组，对照组平均7-DHC水平为1.350 μmol/L (95%CI: 0.027-2.673 μmol/L)。患者第29天的血清7-DHC浓度为2.836 μmol/L，远高于正常新生儿。予以补充胆固醇120 mg/（kg·d）1个月后总胆固醇水平较前升高，但仍稍偏低，6月龄时电话随访，患儿体重5kg（同性别月龄儿的第3百分位），大动作发育尚可。

结论：综合患者的临床表型、遗传学检测、生物致病性分析，确诊患者为SLOS。基于分子遗传学的基因检测是目前识别SLOS的有效技术手段，早期发现这一疾病并进行胆固醇补充可改善患者预后。

关键字 Smith-Lemli-Opitz综合征，胆固醇合成障碍，基因检测

一例胎儿无创低风险彩超提示发育异常的产前诊断及遗传学分析

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目的：对一例前期无创检测提示低风险，后期彩超提示胎儿鼻骨发育异常的孕妇进行产前诊断和遗传学分析，明确胎儿发育异常原因，为后期妊娠提供遗传咨询。

方法：应用染色体核型分析和染色体微阵列芯片分析(CMA)技术进行产前诊断。

结果：CMA检测结果：样本整条21号染色体发生拷贝数重复（拷贝数为3），21-三体；样本X号染色体Xp22.31区段存在1.69Mb拷贝数缺失（拷贝数为1），X-连锁鱼鳞病携带者。

讨论：本例胎盘胎儿面3个部位的CNV-seq检测显示21-三体的嵌合比例为10.82%-24.7%，平均为18.89%，其cffDNA浓度为19.45%，有效cffDNA浓度为3.67%(19.45%×18.89%=3.67%),低于正常参考值(4.0%)，不足以检出21-三体。对NIPT筛查提示低风险，但超声检查提示发育异常的胎儿，需按照2016年国际妇产科超声学会(ISUOG)发布的指南，进行羊膜腔穿刺诊断，以降低21-三体胎儿的漏诊风险。

Xp22.31区段存在1.69Mb拷贝数缺失（X-连锁鱼鳞病携带者），判读为致病性变异，建议母方进行拷贝数变异来源分析，有助于该病再发风险的评估。

关键字 无创产前检测、彩超发育异常、产前诊断、遗传学分析

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NEC并肺炎的临床特点，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

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

先天性红细胞生成异常性贫血II型1例并文献复习

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目的 通过报道一例先天性红细胞生成异常性贫血II型的临床特点及分子检测结果，提高对这种罕见病的识别和诊治。

方法 回顾此例病人的临床特点和实验室结果，复习文献报道，分析探讨该疾病的发病机制及诊疗思路。

结果 先证者为男性，年龄47岁，血常规结果RBC:4.2×1012，Hb:91g/L，MCV103.5fl，Ret:2.6%，铁蛋白>1500 ng/ml，B超提示脾脏肿大，红系遗传疾病基因筛查结果提示患者存在SEC23B基因的复合杂合变异，变异位点为NM_001172745:c.1249A>T(p.Lys417)及NM_001172745:c.74C>A（p.Pro25His），经过一代测序验证，两个变异位点分别来自其父亲和母亲，其中，p.Lys417位点为首次报道。先天性红细胞生成异常性贫血（congenital dyserthropoietic anemia,CDA）是一种罕见的遗产性红细胞生成异常性疾病，其特征为无效红细胞生成，幼稚红细胞多核和组织内铁末沉着症。CDA各型中，以CDAII型多见，发病率约1/100000，致病基因为SEC23B，常染色体隐性遗传。SEC23B基因位于染色体20q11.23，编码产物为细胞衣壳蛋白复合物II的重要成分。CDAII型患者临床表现差异大，MCV值多正常，外周血可见异形红细胞，骨髓可出现双核或多核幼红细胞，电镜下可见幼红细胞双膜结构，另外，患者的酸化血清溶血试验为阳性。

讨论 先天性红细胞生成异常性贫血II型临床罕见，基因水平的检测便于对患者实现早期有效的诊断和治疗，同时，新变异的发现也丰富了SEC23B基因的变异数据库。

关键字 先天性红细胞生成异常性贫血 SEC23B基因 测序

KIF12基因复合杂合变异所致的进行性家族性肝内胆汁淤积症8型1例并文献复习

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总结KIF12基因变异所致的进行性家族性肝内胆汁淤积症8型（Progressive Familial Intrahepatic Cholestasis 8, PFIC8）患儿的临床表现及基因表型并对相应变异进行致病性分析。方法 对1例高GGT胆汁淤积性肝病患儿的临床特点，二代测序及基因致病性进行分析。并分别以“KIF12基因变异”、“进行性家族性肝内胆汁淤积症8型”、“KIF12 variants”及“high GGT”为检索词分别在中国知网、万方、维普及PubMed数据库查询建库至2024年11月的相关文献，总结分析该病的临床特点。结果 全外显子测序示该患儿KIF12基因存在复合杂合变异：c.245G>A（p.Arg82Gln）和c.1291del（p.Ser431Valfs13）。运用多种生物信息学分析提示均为致病变异。7篇英文文献对该疾病进行了报道共25例，男女比例13：12，均表现为高GGT胆汁淤积，部分进展为肝硬化，3例患儿存在肾脏病变。现无死亡病例报道，有6例

患儿进行了肝脏移植治疗。KIF12基因19纯合变异例，复合杂合6例，最常见的等位基因突变为c.655C>T（p.Arg219）。结论 KIF12缺陷所致的进行性家族性肝内胆汁淤积症8型，主要表现为高GGT胆汁淤积，暂无较好的治疗方法。本研究报道的KIF12基因c.245G>A和c.1291del复合杂合变异可能为患儿的遗传学病因。

关键字 KIF12基因、进行性家族性肝内胆汁淤积症8型、复合杂合变异

Prenatal Diagnosis of Hartsfield Syndrome Caused by a Novel Variant in FGFR1）

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Objective: Molecular genetic testing was performed on a fetus with ectrodactyly of the right foot, to clarify the pathogenic cause and provide evidence for pregnancy guidance. Methods: Genomic DNA was extracted from parental peripheral blood and fetal skin tissue samples. We conducted whole exome sequencing (WES) on the fetus parental trio. Candidate variants were validated by Sanger sequencing, and the molecular effects of variants were analyzed using a minigene splicing assay. Results: WES identified a novel heterozygous variant (c.1977+1G>C) at the splice donor site of intron 14 in the FGFR1 gene (NM_023110.3) in the fetus. Sanger sequencing confirmed that this variant was de novo. Minigene assays revealed two aberrant splicing mechanisms: (1) exon 14 skipping, causing an in-frame deletion of 41 amino acids (p.Cys619_Asn659del); (2) complete retention of intron 14, causing a frameshift mutation and premature termination codon (p.Gly660Leufs55). These events collectively impaired the function of the FGFR1 protein tyrosine kinase domain (TK). Discussion: The ectrodactyly of the right foot in the fetus was caused by a novel heterozygous variant (c.1977+1G>C) in the FGFR1 gene, consistent with the molecular characteristics of Hartsfield syndrome. This finding provides a molecular basis for genetic counseling and reproductive risk assessment in this family.

Key Words FGFR1; Hartsfield syndrome; Whole exome sequencing; Splice site

染色体Xp22.31微缺失和微重复的临床意义

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目的：本研究旨在探讨使用基因组拷贝数变异测序 (CNV-seq) 在染色体Xp22.31微缺失和微重复方面的诊断潜力，以便为产前诊断提供更准确的临床依据。

方法：接受羊膜腔穿刺术的孕妇同时进行核型分析和CNV-seq检测。

结果：病例1-3的胎儿在染色体Xp22.31上缺失1.68 Mb，其中包含完整的类固醇硫酸酯酶基因

(STS)；病例4–9的胎儿其Xp22.31区域存在1.5 Kb至1.7 Mb的重复。

讨论：STS 的突变和部分或全部缺失会导致X性连锁鱼鳞病（XLI）。XLI的主要临床表现是四肢、面部、颈部、躯干和臀部出现大面积鳞屑。这些皮肤损伤会持续存在，并且不会随着年龄的增长而改善。XLI几乎只发生在出生时或出生后不久的男性患者中。由于X染色体异常片段大小、连接位置、随机失活、偏倚失活、基因逃逸失活等潜在因素的影响，X染色体异常片段的女性携带者可能存在一定的临床变异性。在我们的研究中，2例为遗传自母亲，1例为家族性鱼鳞病。经过遗传咨询，三名孕妇在知情同意的情况下选择继续妊娠。对于Xp22.31重复区域包括四个基因：PUDP、STS、VCX 和PNPLA4。Xp22.31重复的致病性存在争议。先前的研究报告表明，一些具有该区域重复的个体具有不同程度的神经功能障碍，包括生长迟缓、智力障碍、自闭症谱系障碍、肌张力减退、癫痫发作、精神运动迟缓和轻度特殊面容。一些研究表明，Xp22.31重复可能为VUS。产后随访证实Xp22.31缺失的婴儿在出生后一周出现皮肤异。CNV–seq技术的应用会发现一些致病性拷贝数变异和VUS，对临床遗传咨询提出了挑战。Xp22.31微缺失和微重复的胎儿临床干预应结合CNVs的临床表型和外显率，通过父母DNA溯源可以帮助进一步解释胎儿CNVs的致病性并确定是否遗传自父母，以便给孕妇提供最客观的遗传咨询。

关键字 细胞遗传学核型分析，拷贝数变异测序，Xp22.31，产前诊断，遗传咨询

KDM5C基因新型剪切位点变异致Claes–Jensen综合征的临床特征及遗传学分析

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目的：探讨KDM5C基因新发变异导致Claes–Jensen型X–连锁智力低下综合征（OMIM#300534）的临床特征与分子机制，完善该基因缺陷的基因型–表型关联。

方法：采用家系全外显子组测序(trio whole–exome sequencing，trio–WES)及生物信息学分析，总结患儿临床资料，分析临床及遗传学特征。

结果：患儿，男，17岁，以”发现发育迟缓”就诊于我院，表现为全面性发育迟缓，伴特殊面容及肌张力低下。Trio–WES检测显示Xp11.22区KDM5C基因存在c.1122+1G>C突变（转录本号NM_004187.5)，该变异引起剪切位点的改变，经Sanger测序证实为de novo突变，且生物学软件预测具有致病性。

结论：本研究首次报道KDM5C基因c.1122+1G>C剪切位点变异，拓展了Claes–Jensen综合征的突变谱，为X–连锁智力障碍的分子诊断提供新证据，提示内含子区变异在遗传咨询中的临床意义。

关键字 KDM5C基因 Claes–Jensen综合征 X–连锁隐性遗传

CLCN2基因变异所致的白质脑病伴共济失调一例

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目的：白质脑病伴共济失调（LKPAT）是一种由CLCN2基因变异引起的极为罕见的常染色体隐性遗

传病，极为罕见。报道该病例有助于神经内科医生提高对LKPAT的认识，以免误诊和漏诊。

方法：报道收治的1例经基因检测确诊为LKPAT的患者，总结其临床特点及影像特征。

结果：48岁女性，以“发作性头痛10年余，行走不稳7年余”就诊，头颅MR提示双侧内囊后肢、大脑脚、脑桥、小脑中脚及小脑对称性异常信号，T1WI呈低信号，T2WI、T2 FLAIR和DWI呈高信号，基因检测发现CLCN2基因（OMIM600570）存在纯合突变c.211C>T (p.R71)，为无义突变，尚未有文献报道。

讨论：报道了中文文献中的首例CLCN2基因纯合突变所致的LKPAT，有助于国内神经内科医生提高对LKPAT的认识，拓展白质脑病的鉴别诊断谱，以免误诊和漏诊。该病极为罕见，临床症状多轻微且缺乏特异性，但MR有特征性改变，是支持诊断的重要线索，最终确诊依赖于基因检测发现CLCN2的纯合或复合杂合突变。

关键字 白质脑病；共济失调；ClC-2氯离子通道

一例脊柱肋骨发育不良的遗传学检测及遗传咨询

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目的：探讨一例脊柱肋骨发育不良家系的遗传病因，明确产前诊断的依据，从而避免脊柱缺陷儿的出生。

方法：1、对此次引产胎儿进行骨骼基因panel测序。2、SNP-array检测对引产胎儿及父亲进行全基因组扫描。3、使用Sanger测序验证所有家族成员相关基因突变。

结果：骨骼基因panel测序显示引产胎儿TBX6基因的9外显子(NM_004608.3)中杂合移码突变C.1166_1167 ins ACTCGGCTGCATTTCTGGAGCT p.Pro390Leufs 104。到目前为止，该突变未被报道，也未被收录在SNP数据库中。SNP-array检测先证者和父亲的拷贝数没有发生任何病理性变化。使用Sanger测序检测了所有家族成员TBX6基因的移码突变。明确该突变是本研究中脊柱肋骨发育不良家族患病的原因。

讨论：依据影像学结果与遗传学检测，我们诊断了一个脊柱肋骨发育不良家系。该家系遗传方式为常染色体显性遗传。TBX6基因的移码突变是新发突变，且为本研究中脊柱肋骨发育不良家族患病的原因，丰富了脊柱肋骨发育异常的基因变异谱，为遗传咨询提供了依据。

关键字 脊柱肋骨发育不良 TBX6基因 致病变异 产前诊断

一例Alport综合征患者的COL4A5基因新突变

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目的：Alport综合征（Alport syndrome）是一种以肾脏疾病、听力损失和眼部异常为特征的遗传性疾病，其新生儿的患病率约为1/50 000。Alport综合征患者其肾功能会逐渐丧失。几乎所有受累个体尿液中都出现血尿，这表明肾脏功能异常。多数Alport综合征患者的尿液中也会出现高水平的蛋白尿。肾脏逐渐失去有效清除体内废物的能力，导致终末期肾病（ESKD）。在儿童晚期或青春期早期，许多Alport综

合征患者也会出现感音神经性听力损失。受累个体眼睛中也可能有畸形的晶状体和视网膜的异常着色，通常不会导致视力丧失。COL4A3、COL4A4和COL4A5基因中的突变可导致Alport综合征得发生。这些基因的突变导致肾小球中胶原蛋白IV的异常，而胶原蛋白IV在肾小球、内耳、晶状体和视网膜中起到重要作用。本研究报告Alport综合征的临床病例及其基因型。

方法：针对该患者的COL4A3、COL4A4和COL4A5基因，使用二代测序技术、基因捕获技术和PCR–Sanger测序方法进行分子研究。

结果：该患者主要表现为血尿，偶有蛋白尿。在该患者中鉴定出COL4A5基因（转录本NM_033380.3）存在一个半合子错义突变c.1772G>A（p.Gly591Glu）。根据ACMG的判定规则，评估c.1772G>A为可能致病（Likely Pathogenic）的突变。

结论：新的错义突变c.1772G>A可能导致其相关基因不能编码正常的功能蛋白胶原蛋白IV。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，保证后续的健康生育。

关键字 Alport综合征；Alport syndrome；COL4A5基因；基因变异；点突变

一例共济失调失调毛细血管扩张症患儿的致病基因位点分析

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目的：采集该共济失调失调毛细血管扩张症的病史及临床资料，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测序和荧光定量PCR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：患儿出生后腹部白斑，下肢褐色斑片表现，就诊时2岁3个月，皮肤斑块无明显增大，同时临床表现为下肢肌肉无力。染色体未见异常，全外显子测序检测到ATM基因（NM_000051.4）存在c.5198_5206delinsTTTGAAA, p.Ala1733ValfsX2杂合变异和Del Ex25–Ex26杂合变异。Sanger测序和荧光定量PCR结果显示：患儿父母分别为ATM基因变异携带者，c.5198_5206delinsTTTGAAA变异和Del Ex25–Ex26变异在数据库和文献中均未见记录，根据ACMG遗传变异分类标准和指南，评估c.5198_5206delinsTTTGAAA变异和Del Ex25–Ex26变异均为可能致病的变异。

讨论：ATM基因（NM_000051.4）：c.5198_5206delinsTTTGAAA, p.Ala1733ValfsX2和Del Ex25–Ex26复合杂合变异可能是该患儿共济失调失调毛细血管扩张症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 共济失调失调毛细血管扩张症；ATM基因；基因变异

12p-三体综合征一例遗传咨询讨论

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目的：分析1例12p-三体综合征产前诊断过程探讨遗传技术的相互结合。

方法：选取2024年06月1例因“曾生育一胎智力障碍女婴”就诊患者作为研究对象，抽取羊水，送检染色体核型分析及染色体芯片（CMA）检测，采集患者前三次孕产史资料，对不良孕产史进行分析。

结果：患者第一胎智力障碍女婴，核型为：46,XX,der(15;21)(q10;q10),+21。第二胎生育一健康女婴。2023年第三次妊娠，无创DNA结果为低风险，同年11月因“彩超提示异常”进行产前诊断，CMA结果为：12p13.33p11.22区段存在29.72Mb的拷贝数重复，结果为12p-三体。患者选择终止妊娠并拒绝夫妻双方遗传学检测。2024年患者第四次妊娠，因“不良孕产史”进行产前诊断，CMA结果显示12p-三体，染色体核型分析结果为46,XN,der(15)t(12;15)(p11.2;p11.2)。孕妇本人核型结果为46,XX,t(12;15)(p11.2;p11.2)。

讨论：无创DNA检测提示低风险的孕妇，如后续超声提示异常应进行产前诊断。加强遗传咨询，尽早分析染色体异常的遗传学原因，为患者选取最佳受孕方式给与指导。

关键字 12p-三体综合征；染色体芯片；染色体核型；遗传咨询

1例47XXX超雌综合征患者助孕病例分享

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目的：回顾性分析一例性染色体异常女性的助孕过程，探讨性染色体异常女性的助孕策略。

病例资料：患者女，25岁，结婚6月，因男方外伤导致性功能障碍（可手淫排精），无法性生活而未孕。平素月经规则，5天/25-28天，经量中等，无痛经。2022年06月02日基础性激素检查示FSH 9.84IU/L，LH 5.27IU/L，E2 38.97pg/ml，T：0.36nmol/L ,PRL：21.4ng/ml，AMH 0.26ng/ml。卵巢储备卵泡左侧2枚，右侧5枚。

体格检查：身高170cm，体重83kg，BMI28.7kg/m2，无特殊面容，智力基本正常。妇科检查：乳房发育正常，外阴已婚式，阴毛倒三角型，阴道通畅，宫颈光滑，子宫前位，正常大小，无压痛，双侧附件区未见异常。彩超：子宫及双附件未见异常。

2022年自然周期卵泡监测排卵正常，于排卵期自行将精液注射到女方阴道试孕，均未孕。2022年10月行输卵管造影示双侧输卵管通畅。2022年11月来曲唑促排卵行夫精宫腔内人工授精助孕1周期未孕。2022年12月和2023年11月拟来曲唑促排卵行人工授精，皆因小卵泡排卵而放弃。2023年拟行体外受精-胚胎移植（IVF-ET）助孕，染色体检查女方47，XXX，男方46，XY。2023年2月IVF-ET，拮抗剂方案，月经第2天双侧卵巢各见2-3枚储备卵泡，予FSH 300IU启动，促排9天，Gn 总量2700IU，HCG10000IU扳机，HCG日15mm以上卵泡7枚，雌激素967pg/ml，P：0.43ng/ml，内膜10mmA。36小时取卵2枚，形成 2

枚III级胚胎，鲜胚移植。移植后12天血HCG:718Miu/ml，移植后45天超声检查宫内见2个孕囊2个胚芽。孕期未行NIPT，唐氏筛查和羊膜囊穿刺基因筛查。孕36周5天剖宫产两男婴，体重分别2600g和1400g。夫妻双方拒绝孩子行染色体检查。

讨论：47XXX综合征又称超雌综合征，是一种性染色体异常疾病。47XXX女性因多携带一条X染色体，其临床表现个体差异较大。患者通常身高高于正常女性，少数有头短畸形、小头、高腭弓或牙齿排列异常等特别面容。还有一部分女性表现为卵巢功能早衰，不孕。47XXX女性生育时可能出现自然流产。根据《胚胎植入前遗传学诊断/筛查技术专家共识》47XXX女性生育过程中产生性染色体异常后代的几率较低，不推荐实施PGT–SR助孕。

关键字 性染色体异常，超雌综合征，47XXX

·遗传病的临床研究、循证医学方面研究及其新进展·

Machine Learning-Based Prediction of Preeclampsia Using First-Trimester Inflammatory Markers and Red Blood Cell Indices

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Background: Preeclampsia (PE) affects 2% to 4% of pregnancies, but early detection and intervention can reduce its incidence. Dysregulation of the maternal immune response and red blood cells (RBCs) are key to its development, though early alterations remain unclear.

Methods:This study analyzed data from 17,955 pregnant women across two centers to explore the relationship between inflammatory markers, RBC indices, and PE using multivariate logistic regression and restricted cubic splines (RCS). Mendelian randomization assessed immune cell–PE causality. Machine learning integrated inflammatory markers, RBC indices, and maternal risk factors to predict PE risk at 14 weeks, validated by ROC analysis.

Results: After adjusting for confounders, lymphocyte count (OR = 1.27, 95% CI: 1.05 – 1.53, P = 0.013), monocyte count (OR = 2.57, 95% CI: 1.31 – 5.03, P = 0.006), SIRI (OR = 1.11, 95% CI: 1.01 – 1.21, P = 0.032), and SII (OR = 1.01, 95% CI: 1.01 – 1.01, P = 0.002) were identified as significant risk factors for preeclampsia (PE). Nonlinear associations between white blood cell count, neutrophil count, platelet count, RBC count, and hemoglobin (HGB) with PE were observed using RCS (nonlinear $P < 0.05$). Further analysis revealed threshold effects for white blood cell count (P = 0.034) with an inflection point at 8.44. Below 8.44, no significant association was found (OR = 0.92, P = 0.307), but above 8.44, each unit increase was linked to a 0.14–fold rise in PE risk (OR = 1.14, $P < 0.001$). Similar threshold effects were found for platelet counts, RBC count, and HGB ($P < 0.001$). Mendelian randomization identified CD11c+ CD62L– monocytes in PE progression. A prediction model based on inflammatory markers, RBC indices, and maternal risk factors achieved high performance (ROC = 0.82).

Conclusion: Lymphocyte count, monocyte count, SIRI, and SII were linearly associated with preeclampsia (PE), while leukocyte count, neutrophil count, platelet count, erythrocyte count, and hemoglobin (HGB) showed nonlinear associations with threshold effects. Early prediction using these indicators is a cost-effective strategy for PE prevention.

Key Words Keywords: Preeclampsia, Blood routine, Machine learning, Restricted cubic splines

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

苏北地区905例身材矮小患儿细胞遗传学分析

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目的：探讨苏北地区儿童身材矮小与外周血染色体核型异常的关系。

方法：对905例身材矮小患儿进行外周血染色体G显带核型分析。

结果：在905例身材矮小儿童中，其中男性患儿572例，女性患儿333例，检测出异常染色体核型39

例（核型异常检出率4.3%），正常变异染色体核型64例（正常变异检出率7.1%）。在333例女性患儿中，染色体核型异常31例（核型异常检出率9.3%），其中以X染色体异常占多数。在572例男性患儿中，异常染色体核型8例（异常检出率1.4%）。

结论：染色体核型异常是导致儿童矮小的主要原因之一，尤其是性染色体异常，重视身材矮小患儿的染色体核型检测能有效为临床医生提供诊断依据。

关键字 关键词：儿童、身材矮小、外周血染色体核型

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, is characterized by progressive muscle wasting which will lead to premature death by cardiorespiratory complications in their late twenties. And 2.5 - 19% DMD carriers that also sufer from skeletal muscle damage or dilated cardiomyopathy when 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 efective biomarker and simple detection procedure for DMD carriers.

Method 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 selected biomarkers with significant changes as candidates for detection, then paired them to calculate their ratios and identified the optimal biomarker or biomarker combination.

Results We specifcally pinpointed novel DMD biomarkers, previously unreported in DMD carriers, and conducted further investigations to explore their potential. Compared to creatine kinase activity alone in DMD carriers, creatine kinase-MM can improve the specifcity 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 signifcantly enhances the specifcity (from 81 to 83%) and sensitivity (from 71.4 to 93%) of detecting DMD carriers in serum. Moreover, we successfully devised an efcient 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.

Conclusions Our study highlights the enhanced specificity and sensitivity of CK-MM compared to CK in dried blood spots. Furthermore, the CK-MM/RET ratio should significantly reduce the occurrence of false results that can be encountered with solitary CK-MM screening. Notably, this test can be conducted using dried blood spots, fostering greater patient compliance and cost reduction.

Key Words DMD carriers · Creatine kinase-MM · RET · Biomarker

儿童E型短指的患病率及基因型-表型相关性初探

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目的：分析E型短指（brachydactyly type E, BDE）在中国儿童中的患病率及基因型与表型的相关性，为BDE的临床诊断和遗传学筛查提供实践参考。

方法：回顾2021年6月至2023年12月本中心60650例儿童骨龄片，筛选出135例BDE患者，收集临床资料。采集外周血样行全外显子测序（WES），可能致病性变异行Sanger测序家系验证。根据临床表型分组，分析基因型与表型的相关性。应用SPSS 26.0统计学分析。

结果：135例BDE患者中，女性116例（85.9%），男性19例（14.1%）。BDE的总患病率为0.22%，女性0.35%，男性0.07%。60例患者完成基因检测，19例阳性（31.7%），包括15例单基因变异和4例拷贝数变异。单基因变异中，6例为iPPSD相关基因（GNAS 4例，PRKAR1A、PTHLH各1例），6例为生长板相关基因（ACAN、EXT1各2例，IHH、NPR2各1例），3例为其他综合征相关基因（PRMT7、POGZ、FBXW11各1例）。根据身高、掌/跖骨短小个数、特殊面容、智力障碍分组的组间差异有统计学意义。

讨论：BDE的患病率约为1/500，女性多于男性。GNAS基因变异是最常见遗传学原因。身材矮小、多个掌/跖骨短小、特殊面容或智力障碍的BDE患者更可能存在基因变异；身高正常、单个掌/跖骨短小、无其他系统异常的患者基因均为阴性。

关键字 E型短指；基因型；表型

12744例新生儿半乳糖脑苷脂酶基因筛查结果分析

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目的：分析新生儿半乳糖脑苷脂酶（GALC）基因和酶活性检测结果，为Krabbe病的临床诊断和遗传咨询提供依据。

方法：收集2022年3月18日至12月31日在南京医科大学附属妇产医院出生的12744例新生儿，利用芯片捕获二代测序技术检测GALC基因致病变异位点，Sanger测序法进行家系验证，串联质谱法测定干血斑GALC酶活性。GALC基因携带者与阴性新生儿比较采用两独立样本 t 检验。

结果：12744例新生儿中共检出315例GALC基因携带者，人群携带率为1/40，携带频率最高的变异为c.1901T＞C（269例，1/47），其次为c.1592G＞A（12例，1/1062）。共计4例（P1~P4）新生儿检出2个致病性变异位点（其中2例为c.1901T＞C纯合变异），家系验证提示4例新生儿的2个变异位点分别来自父母，诊断为Krabbe病。同时对P2患儿姐姐家系验证发现其基因型与P2相同，诊断为Krabbe病。通过2000例新生儿样本初步建立串联质谱法检测GALC酶活性切值为0.42μmol/(L·h)。4例Krabbe病患儿GALC酶活性分别为0.74、0.21、0.17和0.29μmol/(L·h)，P2患儿姐姐GALC酶活性为0.28μmol/(L·h)。除P1患儿外，P2~P4、P2患儿姐姐酶活性

均降低，呈阳性。

结论：GALC基因致病性变异携带率较高，热点突变为 c. 1901T＞C，初步统计Krabbe病的患病率为 1/3186 。以基因检测作为一阶筛查、酶活性检测作为二阶筛查的筛查策略能有效提高诊断效率，为临床诊断与遗传咨询提供参考依据。

关键字Krabbe病；GALC基因；半乳糖脑苷脂酶；基因筛查；携带者

拓展V型成骨不全症的临床谱系与双膦酸盐长期疗效：一项针对143例中国患者的8年回顾性研究

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目的：V型成骨不全症（OI type V）是由IFITM5基因c.-14C>T重复突变引起的独特OI亚型，其特征包括复发性骨折、增生性骨痂形成和进行性骨间膜钙化。尽管双膦酸盐在OI中广泛应用，但其在V型OI中的长期疗效仍不明确。本研究系统描绘了V型OI的表型异质性，并在大型队列中评估了双膦酸盐治疗的纵向影响。

方法：这项为期8年的回顾性队列研究纳入了来自105个无血缘关系家庭的143例经分子确诊的V型OI患者（中位年龄：12.4岁；范围：4个月–47岁；中位随访：8.4年）。治疗方案为静脉双膦酸盐（唑来膦酸0.05 mg/kg/6个月或帕米膦酸二钠1 mg/kg/d连续3天/4个月）。评估指标包括双能X线吸收法（DXA）、脊柱侧位片和骨代谢标志物（β-CTX、P1NP、钙、磷、25-羟维生素D）。

结果：所有患者均携带IFITM5 c.-14C>T突变。核心表型特征包括：桡骨头脱位57.8%（中位发病年龄10.2岁）、骨间膜钙化85%（最早4岁检出）、增生性骨痂52.3%（通常于骨折后4–8周出现）。双膦酸盐治疗（中位起始年龄5.2岁）显示：骨折率从2.1次/年降至0.4次/年（P<0.001）；腰椎BMD Z值从-2.6升至-1.3（P<0.001）；68%患者椎体高度显著恢复（>15%增长）；身高Z值从-2.5升至-1.8（P<0.001）；骨代谢显著抑制（β-CTX↓42%、P1NP↓38%，P<0.001）。但关节畸形和异位钙化持续进展：患者随访期间桡骨头脱位率从24%升至82%，与肘关节活动度下降直接相关（r=-0.71，P<0.001），导致持续性运动功能障碍。

讨论：本研究提供了迄今为止对V型成骨不全症最全面的表型特征与治疗应答规律解析，系统揭示了双膦酸盐治疗的优势与局限性。虽然双膦酸盐能显著提高骨密度并降低骨折风险，但无法阻止进行性钙化及关节功能障碍的进展，亟需早期康复策略与辅助治疗手段的介入。未来前瞻性研究应着重探索针对异位骨化通路的新型干预策略，以改善V型成骨不全症患者的长期功能预后。

关键字 V型成骨不全症；IFITM5基因；双膦酸盐；表型异质性；骨折；骨密度；关节畸形；异位钙化

WNT1相关成骨不全XV型的基因型-表型相关性随访分析：对50例中国患者的14年研究

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目的：本研究旨在阐述由WNT1双等位基因变异导致的XV型成骨不全症（OI）的临床特征及病程，评估双膦酸盐的疗效，丰富OI的基因型-表型谱。

方法：本研究纳入50例XV型OI患者。致病基因通过全外显子测序并经Sanger测序验证。随访指标包括骨折史、影像学、骨密度及血生化标志物等。

结果：发现两个热点变异：c.677C>T（p.Ser226Leu）（22.0%）和c.301C>T （p.Arg101Cys）（10.0%）。表型特征有：多发骨折（平均骨折次数18.5次）、早发骨折（66.7%小于1岁）、骨皮质薄（100%）、椎体压缩（84.2%）、肱骨弯曲（61.4%）；上睑下垂（63.0%）、脊柱侧弯（65.2%）、蓝巩膜（29.5%）、智力异常（28.0%）等骨外表现。双膦酸盐治疗（初治平均年龄3.7岁，平均疗程7.7年）使80.9%患者在1年内椎体高度改善，但97.7%患者β-CTX和P1NP未见明显下降，且长期随访显示骨折风险及骨畸形进展无显著降低。随访期间2例患者死亡。

讨论：本研究描述了以严重骨脆性和特征性骨骼外表的XV型OI病程。双膦酸盐可改善椎体压缩，但其有限的疗效提示开发WNT通路靶向治疗的必要性。本研究丰富了OI的基因型-表型谱，为致病机制研究提供了依据。

关键字 WNT1变异，XV型成骨不全症，双膦酸盐疗效，基因型-表型谱

The Impact of Non-Invasive Prenatal Screening (NIPS) Failure on Pregnant Women and Their Offspring

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Non-Invasive Prenatal Screening (NIPS) has become a widely used method for detecting fetal chromosomal abnormalities. However, NIPS failure, often due to low fetal DNA fraction (Fetal%) or abnormal fluctuations in chromosomal data (e.g., chromosomes 21, 18, 13, and sex chromosomes), can pose significant challenges. This study aims to investigate the clinical outcomes of pregnant women experiencing NIPS failure and its correlation with fetal chromosomal abnormalities and adverse pregnancy outcomes. The research will compare two groups of NIPS failure (one-time failure and two-time failure) with a control group of successful NIPS. Clinical data, including maternal age, gestational age, BMI, complications, mode of conception (natural or assisted reproductive technology), singleton/twin pregnancies, NIPS results, subsequent prenatal diagnostic results, and pregnancy outcomes, will be collected and analyzed. The study anticipates that NIPS failure, particularly in cases of sex chromosome abnormalities (SCA),

may be associated with higher rates of miscarriage/termination and slower offspring growth. By evaluating the impact of NIPS failure on maternal and fetal health, this research seeks to provide valuable insights for improving prenatal screening protocols and managing adverse pregnancy outcomes.

Key Words Non-invasive prenatal screening, fetal fraction, chromosomal anomalies, pregnancy outcomes, genetic counseling

淮安地区串联质谱法遗传代谢病筛查、诊断情况及基因谱分析

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Objectives: To determine the prevalence and disease spectrum of inborn errors of metabolism(IEMs) in newborns in Hai’an, China.

Study design: Expanded newborn screening for IEMs by tandem mass spectrometry (MS/MS) can simultaneously analyze more than 40 metabolites and identify about 50 types of IEMs. Next-generation sequencing (NGS) targeting hundreds of IMEs-associated genes as a subsequent test in expanded newborn screening was used for genetic analysis of patients. Totally 161966 newborns in Huai’an between June 2018 and December 2024 were screened by MS/MS, and 57 patients were diagnosed by NGS. Data were analyzed using descriptive statistics.

Results: 57 cases of IMDs were diagnosed, and the overall incidence rate was 1/2842. There were 28 cases of amino acid metabolismdisorders (1/5785), 17 cases of organic acid metabolism disorders(1/9527), and 12 cases of fatty acid oxidation disorders(1/13497). The top three diseases ranked by incidence were phenylalanine hydroxylase deficiency(1/8098), primary carnitine deficiency(1/23138), and methylmalonic acidemia(1/32393). Gene mutations were detected in the 57 patients with IMDs. Moreover, 75 variation in 17 IMEs-associated genes were detected in 57 patients with one of 17 IEMs. Somehotspot mutations were observed for ten IEMs, including PAH gene c.728G > A, c.611A > G, and c.721C > T for Phenylketonuria, PAH gene c.158G > A, c.721C > T, and c.728G > A for M-HPA, SLC22A5 gene c.1400C > G for PCD, MMACHC gene c.609G>A, c.567dup and c.482G>A for MMA, ACADS gene c.1055C>T, and c.1130C > T for SCAD defciency, ACADSB gene c.923G>A for SBCADD.

Conclusion: There are pathogenic mutations or potentially pathogenic mutations in the majority of IEM patients in Huai’an identified by our expanded newborn screening. These mutations may be potential candidate genes for genetic screening. Our findings can be valuable for prevention and control of IEMs.

关键字 Expanded newborn screening; Tandem mass spectrometry; Inherited metabolic disorders; prevalence; disease spectrum; genetic mutation