·临床研究·

81例产前超声诊断胎儿异常的基因检测分析及临床价值

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［摘　要］ **目的：**探讨在产前超声诊断胎儿异常（含结构畸形及软指标）但染色体微阵列分析（chromosome microarray analysis，CMA）未明确病因的情况下，行全外显子组测序（ whole exome sequencing，WES）分析的价值。 **方法：**收集2022年1月—2024年1月在南京医科大学附属妇产医院超声科检查发现胎儿异常，经遗传咨询后选择侵入性产前诊断，抽取绒毛或羊水行CMA检测，结果均为阴性的81例胎儿，对这些样本再行WES检测。基因变异位点的判定参照美国医学遗传学和基因组学学会遗传变异分类标准与指南进行分类。将致病性和可能致病性变异列为阳性结果，将临床意义未明、良性、可能良性列为阴性结果。 **结果：**81例超声异常者包含47例单系统异常（58.02%）和34例多系统异常（41.98%）。WES共检出14例（17.28%）阳性，其中单系统异常和多系统异常各7例，其余67例阴性（82.72%）。阳性胎儿最多见的超声异常为心血管系统异常和骨骼系统异常，均为5例（35.71%），其次为泌尿系统异常4例（28.57%），此外2例胎儿在早期合并颈项透明层（nuchal translucency，NT）增厚（14.29%），中孕期超声发现多系统异常。 **结论：**超声异常胎儿尤其是合并心血管、骨骼、泌尿系统异常或多系统异常时，如CMA检测未能明确病因，建议行WES检测，有可能发现遗传学病因。

［关键词］ 产前超声；产前诊断；染色体微阵列分析；全外显子测序

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Genetic testing analysis and clinical value of 81 cases of prenatal ultrasound diagnosis of fetal abnormalities

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［**Abstract**］ **Objective：** To investigate the value of whole exome sequencing（WES） in cases of fetal abnormalities diagnosed by prenatal ultrasound（including structural malformations and soft markers） where chromosome microarray analysis（CMA） failed to clarify the cause. **Methods：** A total of 81 fetuses were selected from the Department of Ultrasound at the Affiliated Obstetrics and Gynaecology Hospital of Nanjing Medical University，who were diagnosed with fetal abnormalities between January 2022 and January 2024. Following genetic counseling，invasive prenatal diagnoses were chosen，and chorionic villus sampling or amniocentesis was performed for CMA testing，which yielded negative results. WES analysis was then conducted on these samples. The determination of genetic variants was classified according to the guidelines of the American Society for Medical Genetics and Genomics（ACMG）. Pathogenic and possibly pathogenic variants were categorized as positive results，while clinical significance unknown，benign，and possibly benign were categorized as negative results. **Results：** The 81 ultrasound anomalies consisted of 47（58.02%） monosystemic and 34（41.98% ） multisystemic anomalies. WES detected a total of 14（17.28% ） positive cases，including 7 cases each of monosystemic and multisystemic anomalies，while the remaining 67 cases（82.72% ） were negative. The most common ultrasound abnormalities in positive fetuses were cardiovascular system abnormalities and skeletal system abnormalities，each occurring in 5 cases（35.71%），followed by urinary system abnormalities in 4 cases（28.57%）. In addition，2 fetuses had combined nuchal translucency（NT） thickening at early stage（14.29%），and multiple abnormalities were found by ultrasound at mid-trimester. **Conclusion：** Fetuses with ultrasound anomalies，especially when combined with cardiovascular，skeletal，urinary anomalies or multisystem anomalies，are

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recommended to undergo WES testing if CMA testing fails to clarify the etiology, which may identify new potential causative genes.
[**Key words**] prenatal ultrasound; prenatal diagnosis; chromosome microarray analysis; whole exome sequencing
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产前超声检查发现胎儿异常时往往伴有染色体异常、基因变异或某些遗传综合征的部分表型，因此寻找胎儿超声异常与遗传学的关系，对于评估胎儿预后以及临床决策具有重要意义[1]。当产前超声提示胎儿异常时，染色体微阵列分析（chromosome microarray analysis，CMA）可作为侵入性产前诊断的一线遗传学检测技术，但部分病例仍无法找到明确的遗传学病因。全外显子组测序（whole exome sequencing，WES）作为新的产前诊断检测手段，可在单个碱基层面上对基因变异相关遗传病进行检测，是CMA检测未明确病因的超声异常胎儿补充检测方法[2]。本研究将产前超声提示胎儿异常（含结构畸形及软指标）但CMA未确诊的81例患者行WES检测并将结果对照分析，以期为产前遗传诊断及咨询提供有力依据。

1 对象和方法

1.1 对象

选取2022年1月—2024年1月在南京医科大学附属妇产医院超声科检查发现超声异常（含超声软指标或结构异常）的81例孕妇，其中单胎妊娠77例，双胎妊娠4例。孕妇年龄22~41岁，孕周11~36^{+6}周。所有孕妇均至产前诊断门诊咨询并选择侵入性产前诊断（抽取绒毛或羊水）进行遗传学检测，这些样本经CMA检测为阴性，进一步再行WES检测。后续分娩信息通过查阅病例、电话随访等方式获得。本研究经南京医科大学附属妇产医院伦理委员会审批通过（批准号2024KY-125），研究遵循赫尔辛基宣言，所有孕妇均签署知情同意书，全部患者的隐私和权利受到严格保护。

1.2 方法

1.2.1 产前超声检查

选用GE E10、Philips iU22、Philips EPIQ7、三星WS80A等彩色多普勒超声诊断仪，探头频率为3.0~5.0 MHz，按规范行早孕期超声筛查、中孕期结构筛查、超声心动图检查及中晚孕期的常规超声检查，并记录超声异常情况。

1.2.2 遗传学

基因变异位点的判定参照美国医学遗传学和基因组学学会（American College of Medical Genetics and Genomics，ACMG）遗传变异分类标准与指南[3]，分为致病性、可能致病性、临床意义未明、良性、可能良性。本研究将致病性（P）和可能致病性（LP）变异列为阳性结果，将临床意义未明、良性、可能良性列为阴性结果[4]。

1.3 统计学方法

采用SPSS25.0软件，计数资料用例数（百分率）[n（%）]表示，组间比较采用卡方检验，$P < 0.05$为差异有统计学意义。

2 结 果

2.1 超声结果

81例超声异常胎儿有47例（58.02%）为单系统异常，其中心血管系统异常11例，主要包括室间隔缺损、法洛氏四联征、心脏横纹肌瘤等；泌尿系统异常11例，主要表现为多囊性发育不良肾、双肾实质回声增强、肾盂增宽等；骨骼系统异常6例，主要表现为四肢长骨短、脊柱发育异常、足内翻等；颜面部及颈部异常13例，主要表现为唇腭裂、小下颌、颈项透明层（nuchal translucency，NT）增厚等；其他异常6例，主要表现为胼胝体发育不全、脐膨出、腹腔囊性包块等。多系统异常34例（41.98%）。

2.2 遗传学分析

对CMA阴性的81例胎儿样本行WES分析，成功率100%。WES共检出14例（17.28%）阳性，67例（82.72%）阴性。14例阳性胎儿有7例为单系统异常中检出（7/47，14.89%），7例为多系统异常中检出（7/34，20.59%），多系统异常阳性检出率高于单系统异常。

14例WES阳性胎儿的超声结果、基因变异及妊娠结局见表1，分别为PKD1基因杂合变异1例，FGFR3杂合变异1例，MYH3基因杂合变异1例，PTPN11基因杂合变异2例，TNNT3基因杂合变异1例，TBX6基因杂合变异1例，TRPV基因纯合变异1例，L1CAM半合变异1例，TSC2基因杂合变异1例，COLA1基因杂合变异1例，ANKRD11基因杂合变异1例，CPT2基因杂合变异1例，HNF1B基因杂合变异1例。

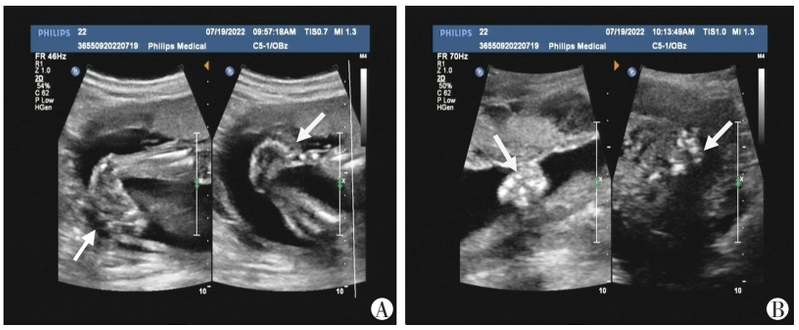
阳性胎儿最多见的超声异常为心血管系统异常5例（5/14，35.71%），如心脏横纹肌瘤、房间隔缺

表1 14例WES检测阳性胎儿的超声结果、基因变异及妊娠结局

Table 1 Ultrasound finding，gene variants，and pregnancy outcomes in 14 fetuses with positive WES test results

Number	Ultrasound results	Gene	Mutation site	Whether newly issued	Pathogenicity	Source of variation	Related diseases	Pregnancy outcome
1	Increased echogenicity of both kidneys；bilateral polycystic kidneys	PKD1	c.10993_10994del	No	LP	Maternal	Autosomal dominant polycystic kidney disease	Be born
2	Abnormal development of the skeletal system：irregular cranial ring，narrow thoracic cage；the spine is straight and the echo is reduced；all four limbs are significantly short.	FGFR3	c.724C>T	Yes	P	-	Lethal osteodysplasia；chondrodysplasia	Induce labour
3	Bilateral hook hands，foot eversion，polydactyly，gastrointestinal malformation	MYH3	c.1385A>G	Yes	LP	-	Distal joint contracture	Induce labour
4	NT thickening（5.7 mm），lymphatic cyst，absent ductus venosus，ventricular septal defect	PTPN11	c.1507G>A	Yes	P	-	Noonan syndrome type 1；LEOPARD syndrome type 1	Induce labour
5	Bilateral foot inversion，interlocking fingers of both hands	TNNT3	c.188G>A	Yes	P	-	Distal arthrogryposis type 2B	Be born
6	Spinal dysplasia，multiple vertebrae disordered	TBX6	c.994del	No	LP	Paternal	Type 5 vertebral rib dysplasia	Be born
7	Short femur，increased echogenicity of both kidneys，large cardiothoracic ratio	TRPV 6	c.1447C>T	No	LP	Paternal，maternal	Neonatal transient hyperparathyroidism	Induce labour
8	Agenesis of the corpus callosum	L1CAM	c.925G>A	No	LP	Maternal	X - linked hydrocephalus with stenosis of the aqueduct of Sylvius，MASA syndrome，X-linked agenesis of the corpus callosum	Induce labour
9	Cardiac rhabdomyoma（multiple），ventricular septal defect	TSC2	c.5140 C>T	Yes	P	-	Tuberous sclerosis type 2	Induce labour
10	The long bones of the limbs of twin fetuses are shorter than those of the corresponding gestational age，and the shape of the femurs is abnormal.	A fetus COL1A1	c.341del	No	P	Paternal	Osteogenesis imperfecta	Induce labour
11	NT thickening（3.9 mm），poor development of the nasal bone on one side of the fetus，a small amount of fluid in the abdominal cavity，and a ventricular septal defect	ANKRD11	c.2175_2178del	Yes	P	-	KBG syndrome	Induce labour
12	Unilateral lateral ventricle enlargement，posterior fossa enlargement，bilateral infantile polycystic kidney	CPT2	c.852del	No	LP	Paternal	Neonatal lethal carnitine palmitoyltransferase 2 deficiency	Induce labour
13	Increased echogenicity of both kidneys，left and right renal pelvis are 0.45 cm and 0.66 cm wide respectively	HNF1B	c.494G>A	No	LP	Paternal	Renal cyst - diabetes syndrome and non-insulin-dependent diabetes mellitus	Be born
14	Unilateral lateral ventricle enlargement，persistent left superior vena cava，atrioventricular septal defect，small fetus	PTPN11	c.1391G>C	No	P	Maternal	Noonan syndrome type 1；LEOPARD syndrome type 1	Induce labour

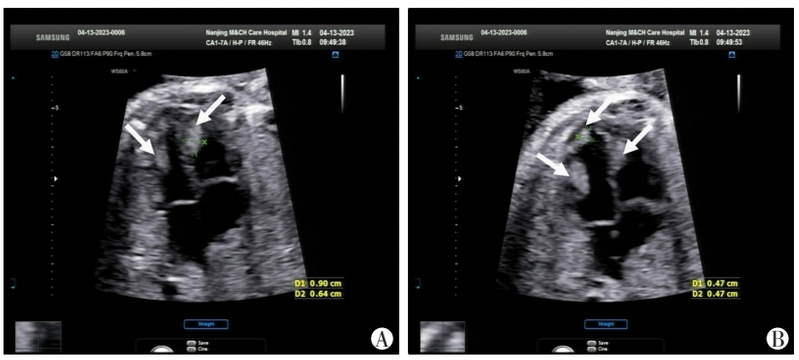
损、室间隔缺损等；骨骼系统异常5例（5/14，35.71%），如脊柱发育异常、股骨形态异常、足内翻等；其次为泌尿系统异常4例（4/14，28.57%），如多囊肾，双肾实质回声增强等。还有2例胎儿早期合并NT增厚（2/14，14.29%），中孕期超声发现多系统异常。部分阳性胎儿超声异常图像见图1~3。



A：Bilateral foot inversion（arrow）. B：Clasp hands together（arrow）.

图1　胎儿双侧足内翻，双手交叠指（病例5）

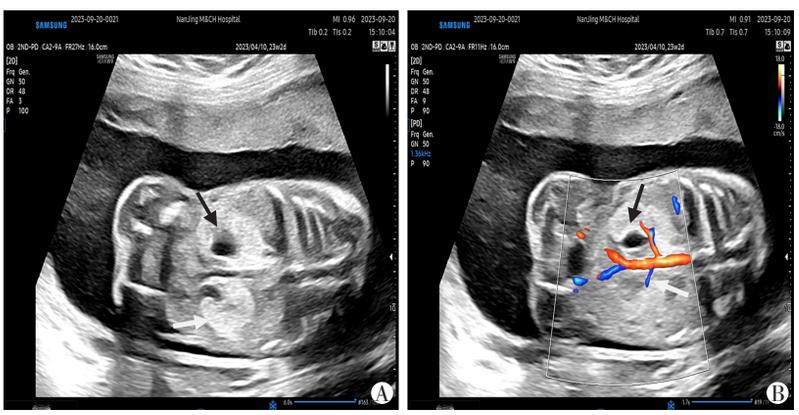
Figure 1　Bilateral talipes equinovarus in fetus，overlapping fingers on both hands（case 5）



A，B：Multiple strong echo nodules in the ventricle（arrow）.

图2　胎儿心脏多发横纹肌瘤（病例9）

Figure 2　Multiple rhabdomyomas of the fetal heart（case 9）



A：Increased echogenicity of both kidneys（arrow）. B：Bilateral renal artery blood flow（arrow）.

图3　胎儿双肾实质回声增强（病例13）

Figure 3　Increased echogenicity of both fetal kidneys（case 13）

2.3　妊娠结局

81例孕妇中21例因胎儿严重畸形或遗传学异常而终止妊娠，1例出生后2 h死亡，1例失访，58例正常分娩出生。14例WES阳性者有10例终止妊娠，有4例孕妇经遗传咨询及慎重考虑后，选择继续妊娠至新生儿出生。

3 讨 论

胎儿超声异常目前已经成为产前诊断的主要指征，虽然应用染色体核型分析及CMA检测，约20%的超声异常胎儿可以明确遗传学病因，但仍有近80%的超声异常胎儿未能明确病因[5-6]。因此探寻提高胎儿超声异常病例遗传学检出率的方法，找到新的遗传学检测工具显得尤为迫切。ACMG产前WES应用指南提出，对于超声异常、核型及CMA正常的胎儿建议行WES检测[7]。在核型/CMA阴性的胎儿，WES可提高8%~10%的致病变异检出率[8-9]。本研究81例超声异常胎儿，CMA均为阴性，WES额外检出了14例（17.28%）致病性变异，基因结果均可解释当前表型，提示WES在产前诊断与咨询中的价值。

本研究结果表明胎儿心血管异常及骨骼系统异常在致病性变异中最多见，与既往研究结果基本一致[10-11]。其中病例9为心脏的多发性横纹肌瘤，WES检测为TSC2基因杂合变异，与结节性硬化症2型有关。因此，WES能提高先心病胎儿致病性变异检出率，是CMA的有力补充。已有证据表明对骨骼发育异常胎儿行WES检测阳性率较高[12-13]，涉及的基因包括FGFR3、COL1A1等，其中FGFR3突变与骨骼发育异常关系最密切。本研究中病例2为多发性骨骼发育异常，WES检测为FGFR3基因杂合变异，与致死性骨发育不良、软骨发育不良等有关；病例10为股骨形态异常合并四肢长骨短，WES检测为COLA1基因杂合变异，与成骨发育不全有关。因此WES可作为骨骼系统异常致病基因检测的重要方式，对明确其产前遗传学诊断有重要意义。

本研究泌尿系统异常检出率位列第2，共计4例（28.57%）。病例1为双肾体积增大，实质回声增强，诊断为胎儿双侧多囊肾，孕妇本人也为双侧多囊肾，WES检测致病基因为PKD1基因杂合变异，母源，其超声征象与遗传学检测结果与董敏等[14]、Shuster等[15]的研究结果相似。本研究还有2例伴有双肾实质回声增强的胎儿WES检测为阳性，病例13为HNF1B基因杂合变异，与肾囊肿-糖尿病综合征有关；病例7为TRPV6基因纯合变异，与新生儿暂时性甲状旁腺功能亢进有关。因此对于CMA阴性的双肾实质回声增强胎儿，需后期动态观察肾脏发育情况，必要时行WES检测以排除基因异常。

本研究还包含2例胎儿早期合并NT增厚，中孕期筛查均为多系统异常，WES检测发现1例为PTPN11基因杂合变异，与Noonan综合征有关；1例为ANKRD11基因杂合变异，与KBG综合征有关。Emms等[16]认为许多遗传综合征如Noonan综合征与NT增厚密切相关，因此早孕期NT增厚有可能为基因异常的线索。

综上所述，WES为产前诊断胎儿遗传病的重要手段，能发现CMA无法检测的基因异常，弥补了传统产前诊断技术的不足。对于CMA检测阴性的超声异常胎儿，特别是合并心血管系统、骨骼系统及泌尿系统异常或多系统异常时，WES有助于提高遗传学的诊断率[17-19]，为产前遗传咨询、医疗决策及胎儿预后评判提供理论依据。

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所有作者声明无利益冲突。

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Author's Contributions：

WANG Yongmei was responsible for project research and development, experimental design, ultrasound diagnosis and image acquisition; WU Yun was responsible for organize and implement technical guidance; ZHOU Ting and YANG Ling were responsible for ultrasound diagnosis and image acquisition; ZHANG Qinxin was responsible for genetic data analysis.

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