

60例16p11.2微缺失胎儿的产前超声及遗传学特征分析

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[摘要] 目的: 临床上16p11.2微缺失胎儿出生后的表型主要包括孤独症、精神分裂症和智力障碍, 并伴有肥胖和先天性畸形等表现, 但有关16p11.2微缺失胎儿的产前表型研究有限, 本研究旨在通过分析16p11.2微缺失胎儿的产前超声与遗传学特征的相关性, 为临床遗传咨询提供参考。方法: 收集2016年10月至2024年12月多中心产前诊断为16p11.2微缺失的60例胎儿临床资料, 包括孕妇年龄、羊水穿刺的指征及孕周、胎儿超声检查及全基因组拷贝数变异测序(copy number variation sequencing, CNV-seq)检测结果, 对胎儿父母同时进行CNV-seq检测, 以明确变异来源, 并对所有病例进行妊娠结局随访。结合产前超声表现、遗传学检测结果及妊娠结局, 对16p11.2微缺失胎儿的产前超声表型及基因组变异特征进行系统分析。结果: 在43 721例行CNV-seq检测的胎儿中共发现60例16p11.2微缺失(60/43 721, 0.14%), 其中49例为近端缺失(BP4-BP5)、9例为远端缺失(BP2-BP3)、2例为大片段缺失(BP2-BP5)。49例16p11.2近端缺失(BP4-BP5)胎儿中18例存在结构异常(6例为半椎体并脊柱侧弯、4例为肾发育异常、2例为主动脉缩窄、6例为其他)、26例为超声软指标[11例为NT增厚(其中1例合并单脐动脉)、6例为轻度脑室扩张(其中1例合并羊水过多)、9例为其他]和5例为超声检查无异常。9例16p11.2远端缺失(BP2-BP3)胎儿中2例存在宫内生长受限、4例为超声软指标(2例为鼻骨缺如、1例为单脐动脉、1例为NT增厚)及3例为超声检查无异常。2例16p11.2大片段缺失(BP2-BP5)胎儿中1例表现为膈疝, 1例为NT增厚。72%的病例为新发变异(36/50), 28%遗传自父母(14/50), 67%的病例选择终止妊娠(35/52)。结论: 16p11.2微缺失胎儿的产前超声表型具有高度异质性, 其中16p11.2近端缺失(BP4-BP5)产前主要表现为半椎体并脊柱侧弯、肾发育异常及NT增厚。而16p11.2远端缺失(BP2-BP3)则可能与宫内生长受限和超声软指标相关。

[关键词] 半椎体; 肾发育异常; 超声软指标; 16p11.2微缺失; 拷贝数变异; 超声

Prenatal ultrasound and genetic characteristics of 60 fetuses with 16p11.2 microdeletion

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ABSTRACT

Objective: The postnatal phenotypes of fetuses with 16p11.2 microdeletion mainly include

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autism spectrum disorder, schizophrenia, and intellectual disability, often accompanied by obesity and congenital malformations. However, studies on the prenatal phenotypes of fetuses with 16p11.2 microdeletion remain limited. This study aims to investigate the correlation between prenatal ultrasound findings and genetic characteristics of fetuses with 16p11.2 microdeletion, thereby providing evidence for clinical genetic counseling.

Methods: Clinical data of 60 fetuses prenatally diagnosed with 16p11.2 microdeletion at multiple centers between October 2016 and December 2024 were collected. Data included maternal age, indications for amniocentesis and gestational age at testing, fetal ultrasound findings, and copy number variation sequencing (CNV-seq) results. CNV-seq was also performed in both parents to determine the origin of the variants. Pregnancy outcomes were followed up for all cases. Based on prenatal ultrasound findings, genetic test results, and pregnancy outcomes, the prenatal phenotypes and genomic characteristics of fetuses with 16p11.2 microdeletion were systematically analyzed.

Results: Among 43 721 fetuses who underwent CNV-seq testing, 60 cases of 16p11.2 microdeletion were identified (60/43721, 0.14%). Of these, 49 cases had proximal deletions (BP4-BP5), 9 had distal deletions (BP2-BP3), and 2 had large deletions (BP2-BP5). Among the 49 fetuses with proximal 16p11.2 deletions (BP4-BP5), 18 had structural abnormalities, including 6 cases of hemivertebra with scoliosis, 4 cases of renal developmental abnormalities, 2 cases of coarctation of the aorta, and 6 cases of other abnormalities. Twenty-six fetuses presented with ultrasound soft markers, including 11 cases of increased nuchal translucency (NT) thickness (1 accompanied by a single umbilical artery), 6 cases of mild ventriculomegaly (1 accompanied by polyhydramnios), and 9 cases of other soft markers. Five fetuses showed no ultrasound abnormalities. Among the 9 fetuses with distal 16p11.2 deletions (BP2-BP3), 2 had intrauterine growth restriction, 4 presented with ultrasound soft markers (2 with absent nasal bone, 1 with a single umbilical artery, and 1 with increased NT thickness), and 3 had no ultrasound abnormalities. Among the 2 fetuses with large 16p11.2 deletions (BP2-BP5), 1 presented with congenital diaphragmatic hernia and the other with increased NT thickness. Of the 50 cases, 72% (36/50) were de novo variants and 28% (14/50) were inherited from a parent. Regarding pregnancy outcomes, 67% (35/52) of pregnancies were terminated.

Conclusion: Prenatal ultrasound phenotypes of fetuses with 16p11.2 microdeletion are highly heterogeneous. Proximal 16p11.2 deletions (BP4-BP5) are primarily associated with hemivertebra accompanied by scoliosis, renal developmental abnormalities, and increased NT thickness. In contrast, distal 16p11.2 deletions (BP2-BP3) may be associated with intrauterine growth restriction and ultrasound soft markers.

KEY WORDS

hemivertebra; renal developmental abnormality; ultrasound soft markers; 16p11.2 microdeletion; copy number variations; ultrasonography

16p11.2 微缺失是导致胎儿神经发育障碍和孤独症谱系障碍最常见的已知遗传病因之一, 发病率约为 1/2 000^[1-2]。临床上有关 16p11.2 微缺失胎儿出生后

的表型主要包括孤独症谱系障碍、精神分裂症和智力障碍, 并伴随肥胖、结构畸形和头围异常等表现^[3-5], 但由于 16p11.2 微缺失胎儿具有罕见性及产前

表型记录的不完整等, 目前有关16p11.2微缺失胎儿基因型与产前表型关联的研究仍非常有限^[6-7]。为了更好地阐述16p11.2微缺失胎儿的产前表型, 本研究对60例产前诊断为16p11.2微缺失胎儿的超声表型进行细化, 并结合相关位点覆盖的疾病基因, 对16p11.2微缺失胎儿的产前基因型和表型进行更深入的分析和探讨, 以便为临床遗传咨询提供更有价值的信息。

1 对象与方法

1.1 伦理声明

本研究已获得中南大学湘雅医院伦理委员会批准[审批号: 伦审科快第(科202211714)]。研究对象均签署了侵入性产前诊断的书面知情同意书。

1.2 对象

收集2016年10月至2024年12月来自多中心的43 721例产前样本, 每例孕妇均接受超声检查和全基因组拷贝数变异测序(copy number variation sequencing, CNV-seq)检测, 共纳入13 312例超声异常、17 679例超声软指标和12 730例超声正常且孕妇高龄样本。孕妇在行CNV-seq检测前均接受详细的遗传咨询, 包括遗传检测的适用性、局限性和风险。

1.3 方法

1.3.1 样本采集、检测方法和结果分析

从羊水、脐带血中提取DNA进行全基因组CNV-seq检测。采用DNeasy血液和组织试剂盒(德国Qiagen公司产品)提取基因组DNA。采用Qubit 2.0荧光计测定基因组DNA的浓度和纯度。采用HiSeq2000平台(美国illumina公司)进行CNV-Seq检测, 36 bp单端测序, 测序深度为0.1x, 共获得500万条原始测序读长, 其检测拷贝数变异(copy number variation, CNV)的分辨率约为100 kb。

根据2019年美国医学遗传学与基因组学学会(American College of Medical Genetics and Genomics, ACMG)发布的标准化判读指南^[8]对CNV的临床意义进行评估, 依照证据总得分将CNV的致病性分成5类, 包括致病(pathogenic, P)、可能致病(likely pathogenic, LP)、临床意义不明(variants of uncertain significance, VUS)、可能良性(likely benign, LB)和良性(benign, B)。

1.3.2 随访

通过医院信息系统查询病历资料并结合电话随访, 对产前诊断为16p11.2微缺失的病例进行妊娠及

出生后结局追踪。收集内容包括家系验证结果、产前超声检测发现及妊娠结局。对于继续妊娠的病例, 记录孕期超声动态变化、产检情况及分娩结局, 对活产儿进行定期随访并记录其生长发育情况。

2 结果

2.1 基本特征

在43 721例行CNV-seq检测的胎儿样本中共检测到16p11.2微缺失60例, 检出率为0.14%(60/43 721)。60例16p11.2微缺失的范围为0.22~1.72 Mb, 根据断裂点位置分为3类: 其中49例为近端缺失(BP4-BP5), 9例为远端缺失(BP2-BP3), 2例为大片缺失(BP2-BP5)。此外, 6例合并其他染色体片段缺失/重复变异, 具体包括胎儿Y2008140002合并4q35.2重复1.36 Mb、胎儿Y2003120077合并Xp21.1重复0.42 Mb、胎儿Y2009220222合并18p11.31-p11.23重复0.52 Mb、胎儿Y2009250094合并4q22.3重复1.56 Mb、胎儿FDLV01E1合并Xp22.31重复1.66 Mb、胎儿Y1801090070合并Xp22.31缺失1.66 Mb, 上述合并的拷贝数变异除了Xp22.31缺失1.66 Mb为致病性变异, 其余均为临床意义未明变异。在50例经父母验证后的病例中, 36例为新发变异, 14例为遗传自父母(其中母源性遗传10例, 父源性遗传4例)。经遗传咨询后, 有35例(包括新发变异24例、遗传变异6例、来源不明5例)选择终止妊娠, 17例活产, 8例失访。

2.2 超声征象

与16p11.2微缺失相关的产前超声特征详见表1。49例16p11.2近端缺失(BP4-BP5)胎儿中, 18例为结构异常[包括半椎体并脊柱侧弯6例, 肾发育异常4例(其中肾实质回声增强2例、右肾缺如1例、左肾发育不良1例), 主动脉缩窄2例, 肠管扩张、腹水、肺囊腺瘤、脑积水、心包积液及胼胝体缺如合并透明隔腔缺如各1例]; 26例为超声软指标[包括NT增厚(其中1例合并单脐动脉)11例、轻度脑室扩张6例(其中1例合并羊水过多)、单脐动脉2例、右锁骨下动脉迷走2例、永存左上腔静脉2例、心室强光点2例、轻度肾盂分离合并羊水过多1例]; 5例为高龄且超声检查无异常。

在9例16p11.2远端缺失(BP2-BP3)的胎儿中, 4例为超声软指标[包括鼻骨缺如2例、NT增厚和单脐动脉各1例]; 2例为宫内生长受限[为16p11.2大片缺失(BP2-BP5)的胎儿, 膈疝和NT增厚各1例]; 3例为高龄且超声检查无异常。

表1 60例16p11.2微缺失胎儿的产前超声特征

Table 1 Prenatal ultrasonic features of 60 fetuses with 16p11.2 microdeletion

Characteristics	BP2- BP3/ No.	BP4- BP5/ No.	BP2- BP5/ No.
Number of ultrasound anomalies	2	18	1
Skeleton anomalies	0	6	0
Hemivertebra and Scoliosis	0	6	0
Urinary anomalies	0	4	0
Renal hypoplasia	0	1	0
Renal agenesis	0	1	0
Hyperechogenic kidney	0	2	0
Brain anomalies	0	2	0
Hydrocephalus	0	1	0
Agenesis of the corpus callosum	0	1	0
Chest/heart anomalies	0	4	1
Coarctation of the aorta	0	2	0
Cystic adenomatoid malformation	0	1	0
Pericardial effusion	0	1	0
Congenital diaphragmatic hernia	0	0	1
Abdominal anomalies	0	2	0
Bowel dilatation	0	1	0
Ascites	0	1	0
Fetal growth restriction	2	0	0
Number of ultrasound soft markers	4	26	1
Increased nuchal translucency	1	11	1
Mild ventriculomegaly	0	6	0
Single umbilical artery	1	2	0
Other ultrasound soft markers	2	7	0
Number of normal ultrasound	3	5	0

The BP2-BP3 represents a distal deletion ($n=9$); the BP4-BP5 represents a proximal deletion ($n=49$); the BP2-BP5 represents a large fragment deletion ($n=2$).

2.3 超声表型与相关基因

49例16p11.2近端缺失(BP4-BP5)胎儿中6例出现半椎体并脊柱侧弯, 缺失范围为0.49~0.59 Mb, 其中胎儿Y1904120016缺失的范围最小, 为0.49 Mb, 在孕27周超声发现胎儿第8和9胸椎半椎体并脊柱侧弯(图1), 最小共同区间覆盖的在线人类孟德尔遗传数据库(Online Mendelian Inheritance in Man, OMIM)基因有 *KIF22*、*PRRT2*、*TLCD3B*、*ALDOA*、*TBX6* 和

CORO1A, 其中 *TBX6* 基因变异会导致脊椎肋骨发育不全(OMIM: 122600; 图2)。此外, 有4例16p11.2近端缺失(BP4-BP5)胎儿出现肾发育异常, 包括右肾缺如1例、左肾发育不良1例、肾实质回声增强2例; 缺失范围为0.48~0.60 Mb, 缺失范围最小的2例表型有差异, 右肾缺如1例, 肾实质回声增强合并NT增厚及脉络丛囊肿1例。最小共同区间覆盖的OMIM基因有 *KIF22*、*PRRT2*、*TLCD3B*、*ALDOA*、*TBX6* 和 *CORO1A*(图3)。

9例16p11.2远端缺失(BP2-BP3)的胎儿中2例表现为宫内生长受限, 缺失范围为0.22~0.84 Mb, 最小共同区间覆盖的OMIM基因有 *ATP2A1*、*CD19*、*LAT*、*SH2B1* 和 *TUFM*。本研究中16p11.2微缺失片段最大的2个病例(缺失大小分别为1.70 Mb和1.72 Mb), 产前超声表型差异显著, 1例提示为膈疝, 另1例仅表现为NT增厚, 缺失区域共同包含的致病基因有10个, 分别是 *ALDOA*、*ATP2A1*、*CD19*、*CLN3*、*KIF22*、*LAT*、*PRRT2*、*SH2B1*、*TBX6* 和 *TLCD3B*。



图1 胎儿Y1904120016的产前超声表现(半椎体及脊柱侧弯)

Figure 1 Ultrasonography (hemivertebra and scoliosis) of fetus Y1904120016

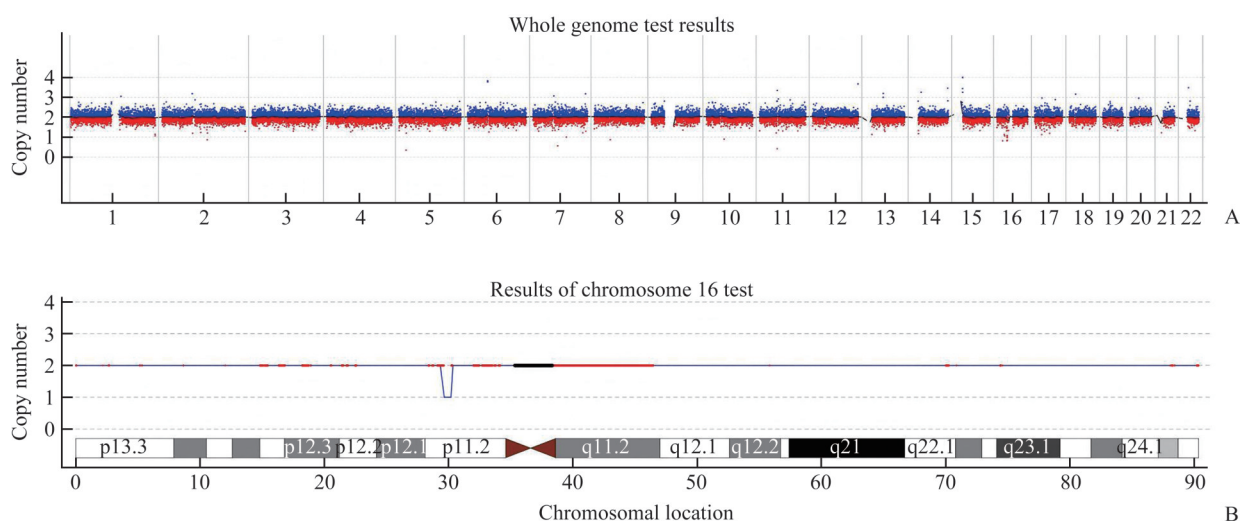


图2 胎儿Y1904120016的CNV结果

Figure 2 CNV findings of fetus Y1904120016

A: CNV-seq genome-wide copy number variation analysis revealed a copy number abnormality involving chromosome 16. B: A high-resolution view of chromosome 16 demonstrates a 0.49 Mb deletion in the 16p11.2 region. CNV: Copy number variation.

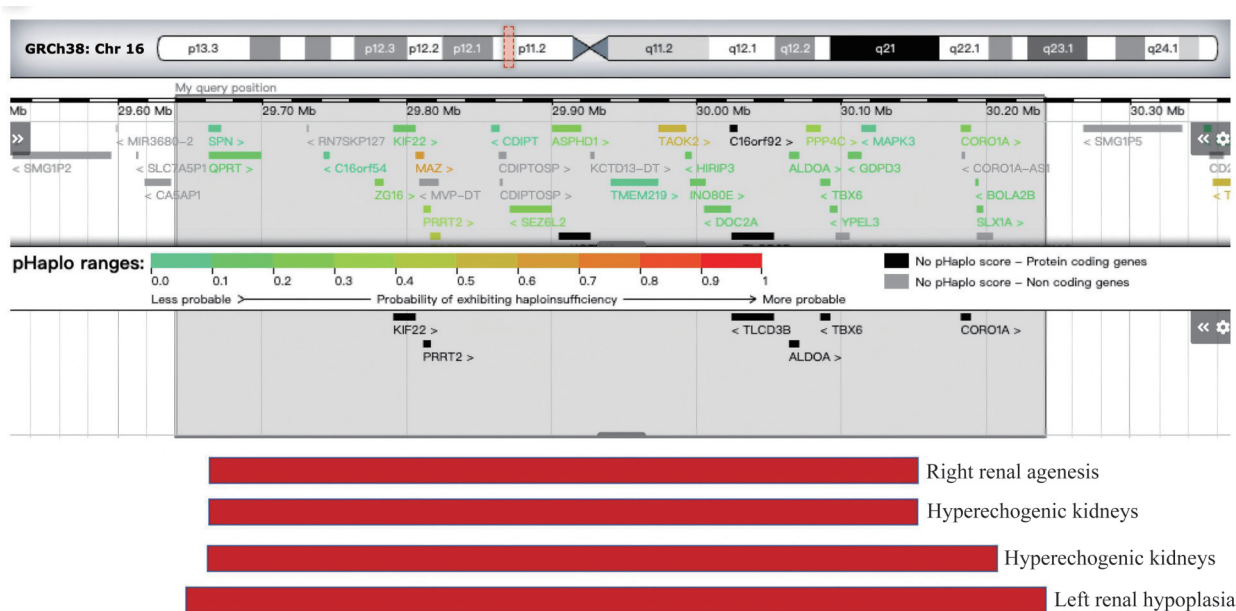


图3 4例有肾发育异常表型的16p11.2微缺失位点示意图

Figure 3 Schematic diagram of the 16p11.2 microdeletion in 4 cases of renal abnormality

Red bars indicate the deletion regions associated with 4 cases of renal developmental abnormalities.

3 讨论

本研究回顾性分析60例16p11.2微缺失胎儿的产前超声特征及遗传学特点,是目前已知的最大样本阐述16p11.2微缺失产前表型的研究之一。本研究发现16p11.2微缺失的总体产前检出率为0.14%。这与之前的研究^[9]结果一致。16p11.2微缺失的产前表型

谱跨度较大,可从无明显异常到严重结构畸形,16p11.2近端缺失(BP4-BP5)的主要产前表型为半椎体并脊柱侧弯、肾发育异常及轻度脑室扩张,而16p11.2远端缺失(BP2-BP3)则主要表现为宫内生长受限和超声软指标异常。

进一步细化表型后发现,半椎体并脊柱侧弯是16p11.2近端缺失(BP4-BP5)产前最常见的超声特征。

一项纳入12例16p11.2近端缺失胎儿表型的研究^[10]显示,5例胎儿存在骨骼系统异常,其中3例为半椎体,1例为蝴蝶椎,1例为椎体小。本研究中49例16p11.2近端缺失胎儿有6例出现半椎体并脊柱侧弯,为16p11.2微缺失和椎体发育异常的相关性提供支撑和依据。16p11.2近端缺失(BP4-BP5)包含的*TBX6*基因变异可通过影响蛋白转录活性从而导致脊椎肋骨发育不全(OMIM: 122600),特别是同时携带亚效等位基因时,其先天性脊柱侧弯的发病率可达11%^[11]。Lin等^[10]研究发现半椎体/蝴蝶椎是*TBX6*基因相关先天性脊柱侧弯最显著的特征,因此*TBX6*可能是导致16p11.2微缺失胎儿半椎体并脊柱侧弯表型的关键基因^[11]。近年研究^[12-13]发现*TBX6*还是参与先天性肾与泌尿道畸形的新基因,其单倍剂量不足可能是16p11.2微缺失肾发育缺陷的潜在驱动因素。在*TBX6*基因突变小鼠模型中,*TBX6*杂合缺失可导致13%的单侧肾发生^[13]。本研究中4例16p11.2近端缺失胎儿表现出多样的肾发育异常表型,涵盖肾缺如、肾发育不良和肾实质回声增强。综上,*TBX6*基因单倍剂量不足可能是16p11.2微缺失骨骼与泌尿系统相关表型的共同核心驱动因素^[14]。

除了结构畸形外,本研究还发现16p11.2近端缺失(BP4-BP5)与超声软指标密切相关,其中NT增厚是最常见的超声软指标(11/49),其次是轻度脑室扩张(5/49),这2项超声软指标在16p11.2微缺失胎儿中既往已有报道^[9,15-16]。值得关注的是,在本研究病例中观察到的永存左上腔静脉和右锁骨下动脉迷走在以往报道^[10,17]的16p11.2微缺失胎儿中仅有极少数的散发病例记录。16p11.2微缺失是导致精神发育障碍的复发性致病性拷贝数变异,部分病例产前可能并没有典型的结构异常,而仅仅表现为超声软指标或正常超声。

与16p11.2近端缺失(BP4-BP5)表型特征不同,16p11.2远端缺失(BP2-BP3)产前则主要表现为宫内生长受限,重叠区域共包含5个致病基因,其中*CD19*和*LAT*基因与免疫缺陷相关。*TUFM*基因的纯合或复合杂合突变会导致联合氧化磷酸化缺陷4型,表现为严重早发性乳酸中毒和进行性致死性婴儿脑病。而*ATP2A1*基因突变则主要导致肌肉发育异常。*SH2B1*基因是瘦素和胰岛素信号的中介因子,该基因的缺失可以导致肥胖和糖尿病^[18],也有研究^[19]认为包含*SH2B1*基因的16p11.2微缺失是引发胎儿宫内生长受限的危险因素,然而目前ClinGen数据库中关于*SH2B1*基因单倍剂量不足的证据较少。16p11.2远端缺失与宫内生长受限这一表型相关的基因还有待进一步研究。16p11.2远端缺失(BP2-BP3)产前还可以表

现为单脐动脉、鼻骨缺如或超声无异常。总体上,16p11.2远端缺失(BP2-BP3)产前更常见的是宫内生长受限和超声软指标,而非结构畸形。

膈疝是16p11.2微缺失病例中比较罕见的表型特征,研究^[20]发现*TBX6*的剂量失衡(重复或缺失)与先天性膈疝的发生相关,并推测16p11.2近端缺失(BP4-BP5)可能与膈疝相关。但另有研究^[21]报告了1例合并膈疝的16p11.2远端缺失(BP2-BP3)胎儿,并提出*ATP2A1*可能是16p11.2微缺失胎儿膈疝发生的候选基因,同时推测该表型的发生可能还需要与其他参与膈肌发育的基因发生等位变异后的联合作用。Pan等^[22]的研究亦证实*ATP2A1*基因的靶向破坏会影响新生小鼠的膈肌发育。本研究同样发现1例合并膈疝的16p11.2微缺失胎儿,其缺失范围更大,覆盖BP2-BP5区域,*ATP2A1*基因和*TBX6*基因均包含在内。因此,与16p11.2微缺失膈疝表型相关的基因还有待进一步探究。

本研究通过分析60例16p11.2微缺失胎儿的产前超声和遗传学特征,明确了不同断裂点类型的16p11.2微缺失胎儿的主要产前特征。16p11.2微缺失胎儿的产前表型具有高度异质性,可涵盖从超声无异常到多种结构畸形的广泛表现,其中16p11.2近端缺失(BP4-BP5)最主要的结构异常为半椎体并脊柱侧弯及肾发育异常,而最常见的超声软指标为NT增厚及轻度脑室扩张。而16p11.2远端缺失(BP2-BP3)则可能与宫内生长受限和超声软指标相关。

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