CASE REPORT

Clinical and Genetic Study of Three Inherited Microdeletions of Chromosome 16p11.2

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ABSTRACT

Copy number variations (CNVs) in chromosome 16p11.2 are not rare. 16p11.2 microdeletion is among the most commonly known genetic etiologies of overweightness, autism spectrum disorder (ASD), and related neurodevelopmental disorders. We report the prenatal diagnosis and genetic counseling of three cases with inherited 16p11.2 microdeletions. In these families, mother/father and fetus have the same microdeletion. Following the use of molecular genetic techniques including array-based methods, the number of reported cases has rapidly increased. A combination of prenatal three-dimensional ultrasound, karyotype analysis, chromosomal microarray analysis (CMA), copy number variation sequencing (CNV-seq), whole-exome sequencing (WES), and genetic counseling is helpful for the prenatal diagnosis of chromosomal microdeletions/microduplications. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Copy number variations (CNVs) in 16p11.2 between break points 4 and 5 (BP4–BP5) (600 kb, chr16; 29.6–30.2 mb-HG19) occur at a frequency of ~3 in 10 000.[1] 71% of the 16p11.2 deletions occur *de novo* and the recurrent ~600 kb 16p11.2 microdeletion is among the most commonly known genetic etiologies of overweightness, autism spectrum disorder (ASD), and related neurodevelopmental disorders.[2]

METHODS

Patients and samples

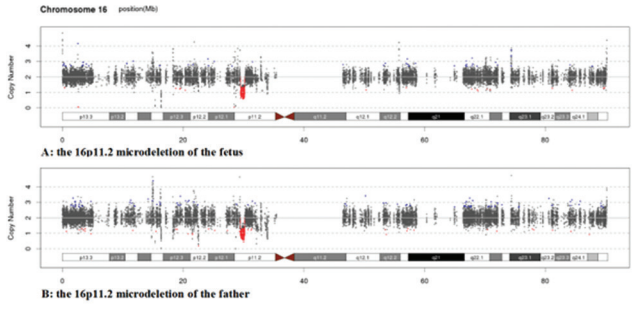
Case 1. In 2018, a 35-year-old, gravida 1, para 0 woman (weight 76 kg and height 159 cm) underwent amniocentesis at 18 weeks of gestation because of advanced age. Cytogenetic analysis of the cultured amniocytes revealed a normal karyotype of 46,XY. Chromosomal microarray analysis (CMA) on uncultured amniocytes was performed using the Affymetrix CytoScan 750K chip, which includes 550k non-polymorphic markers and 200k SNP markers. CMA detected a 599-Kb chromosomal microdeletion in the region of 16p11.2,[3] arr[GRCh37] 16p11.2(29,587,325_30,190,012)x1 (Figure 1). Then we performed both CMA and conventional karyotyping using the samples from the parents' peripheral blood. Their karyotypes were normal. The CMA results showed that the mother had the same microdeletion as the fetus. SNP markers in the Affymetrix CytoScan 750K chip confirmed a maternal origin of the 16p11.2 microdeletion. Three-dimensional ultrasound examination showed no dysmorphisms or intrauterine growth restriction (IUGR) in the fetus. After genetic counseling, the parents decided to continue the pregnancy.

At 38 weeks of gestation, the expectant mother gave birth vaginally to a male baby. The baby's growth parameters at birth were in the normal ranges (weight 3.4 kg and length 49 cm). Apgar scores were 7/8/9. The baby received a complete physical examination and the results were normal. At the 36-month checkup, the baby was developing normally (Intelligence Quotient (IQ) = 102, weight 17.3 kg, and height 96 cm).

Case 2. In 2019, a 22-year-old, gravida 1, para 0 woman underwent amniocentesis at 18 weeks of gestation because she thought her husband's intelligence was slightly below average. Cytogenetic analysis of the cultured amniocytes

Figure 1. CMA Detected a 599 Kb Chromosomal Microdeletion in the Region of 16p11.2 (arr[GRCh37] 16p11.2(29,587,325_30,190,012)x1)

Figure 2. Trio-WES Showed a 650 Kb Paternal Chromosomal Microdeletion in the Region of 16p11.2 (arr[GRCh38] 16p11.2(29,537,127_30,188,737)x1) of the Fetus



revealed a normal karyotype of 46,XX. CNV-seq on uncultured amniocytes was performed using the technology of next generation sequencing (NGS).[4-5] Trio-whole-exome sequencing (Trio-WES) was performed on this family. The Novaseq6000 platform (with the mode of 150-bp pair-end sequencing, Illumina, San Diego, USA), was used for sequencing the genomic DNA from this family. We aligned the sequencing reads to the human reference genome (hg38/GRCh38) using the tool of Burrows-Wheeler Aligner.

CNV-seq detected a 650-Kb chromosomal microdeletion in the region of 16p11.2, arr[GRCh37] 16p11.2 (29,537,127_30,188,737)x1 of the fetus. Trio-WES confirmed a paternal origin of the 16p11.2 microdeletion (Figure 2). Three-dimensional ultrasound examination showed no dysmorphisms or intrauterine growth restriction (IUGR) in the fetus. After genetic counseling, the parents decided to continue the pregnancy.

Now the baby is three years old with normal development (IQ = 96, weight 17.1 kg, and height 95 cm).

Case 3. In 2023, a 24-year-old, gravida 1, para 0 woman came to our hospital for genetic counseling because CNV tests revealed that she had the same chromosomal 16p11.2 microdeletion as the aborted embryos.

We suggested that she can undergo amniocentesis at 18 weeks' gestation or get pregnant through embryo selection with preimplantation genetic testing of *in vitro* fertilization (IVF).

DISCUSSION

CNVs of the human 16p11.2 genetic locus are associated with a range of neurodevelopmental disorders, including autism spectrum disorder, intellectual disability, and epilepsy. In this study, the chromosomal deletion is associated with 16p11.2 microdeletion syndrome, the deleted region of 16p11.2 contained a lot of genes, just as *PRRT2* (614386), *KCTD13* (608947), *TBX6* (602427), and so on.

At synapses, *PRRT2* is involved in regulating presynaptic transmitter release. *KCTD13* is an adaptor of the E3 ligase Cul3, controlling the degradation of RhoA and other protein substrates. *TBX6* is an important gene for congenital vertebral malformations (CVM). The absence of this region (16p11.2) has incomplete penetrance, and some patients may have mild clinical manifestations (see http://cs-tl.de/DB/CA/HCM/0-Start.html).[6-8]

The phenotypic spectrum associated with the 16p11.2 microdeletion varies widely but includes ASD, intellectual disability/developmental delay, epilepsy/seizures, macrocephaly, dysmorphic feature/congenital anomaly, and possibly other primary psychiatric disorders. The microdeletions are more likely to be penetrant and associated with nonspecific major or minor dysmorphism. There are probands with deletion-positive ASD with a less severe phenotype than siblings with deletion-negative ASD, underscoring the significant phenotypic heterogeneity.[9-14]

In case 1, the mother carries the same microdeletion and has a normal phenotype (IQ = 96, she has been working in a supermarket after high school graduation), except mild obesity (before pregnancy: weight 68 kg and height 159 cm).

In case 2, the father carries the same microdeletion and has a normal phenotype (height 163 cm, IQ = 95, he has been a driver after junior high school graduation).

In case 3, the female carrier has a normal phenotype (height 154 cm, IQ = 98, after graduating from junior high school, she worked at home as a farmer).

In cases 1 and 2, prenatal three-dimensional ultrasound didn't reveal any abnormalities in the fetuses. After genetic counseling, the parents decided to continue the pregnancy, and now, their babies are developing normally. Despite this, we have provided a statement to the parents that some corresponding phenotypes may appear later, including autism spectrum disorder, intellectual disability, and epilepsy.

From these three cases, we can see that the three carriers have highly similar phenotypes-short stature, IQ at the lower limit of normal people, basic normal social skills, be able to support themselves through simple work. The microdeletions of chromosome 16p11.2 are listed in the University of California Santa Cruz (UCSC) genomic browser as pathogenetic – thus, in this paper the three carriers of the deletion are lucky, possibly due to complicated reasons such as genetic penetrance. These cases can provide useful information for future genetic counseling.

CONCLUSION

To summarize, we present three families with inherited microdeletion of chromosome 16p11.2. Our cases can be

helpful for prenatal diagnosis and genetic counseling. Chromosomal microdeletions and microduplications are difficult to detect by conventional cytogenetics. Combination of prenatal three-dimensional ultrasound, karyotype analysis, CMA, CNV-seq, and genetic counseling is helpful for the prenatal diagnosis of chromosomal microdeletions/microduplications.[15]

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research was approved by the Ethics Committee of Renmin Hospital of Shiyan. The guardians of patients gave informed consent to participate in the study.

CONSENT FOR PUBLICATION

The guardians of patients gave informed consent for the publication of this study.

DATA AVAILABILITY

Please contact the corresponding author for data requests.

AUTHOR DISCLOSURE STATEMENT

The authors have no conflicts of interest relevant to this article.

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