Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(7) 1–6

DOI: 10.1177/03000605221109400
journals.sagepub.com/home/imr
SAGE

Prenatal diagnosis and molecular cytogenetic characterization of an inherited microdeletion of chromosome 16p11.2

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Abstract

Copy number variations (CNVs) in chromosome 16p11.2 (deletions and duplications) are not rare. 16p11.2 microdeletion is among the most commonly known genetic etiologies of autism spectrum disorder, overweightness, and related neurodevelopmental disorders. Here, we report the prenatal diagnosis and genetic counseling of a maternally inherited 16p11.2 microdeletion. In this family, the mother and fetus both have a normal phenotype and the same microdeletion. Following the use of molecular genetic techniques, including array-based methods, the number of reported cases has rapidly increased. The combination of prenatal ultrasound, karyotype analysis, chromosomal microarray analysis (CMA), and genetic counseling is helpful for the prenatal diagnosis of chromosomal microdeletions/microduplications.

Keywords

Chromosomal microarray analysis, chromosomal microdeletion, chromosomal microduplication, 16p11.2 microdeletion, prenatal diagnosis, molecular cytogenetics, genetics

Date received: 1 March 2022; accepted: 6 June 2022

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Introduction

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

Case report

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 (Figure 1). Chromosomal microarray analysis (CMA) on uncultured amniocytes was performed using the Affymetrix CytoScan 750K chip (Waltham, MA, USA), which includes 550,000 non-polymorphic markers and 200,000 single nucleotide polymorphism (SNP) markers. CMA detected a 599-kb chromosomal microdeletion in the region of 16p11.2,[3] arr[GRCh37] 16p11.2(29,591,327_30,190,029)x1 (Figure 2). We then performed both CMA and conventional karyotyping using the samples from the parents' peripheral blood. Their karyotypes were both 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. Ultrasound examination showed no dysmorphisms or intrauterine growth restriction (IUGR) in the fetus (Samsung Medison WS80A Color

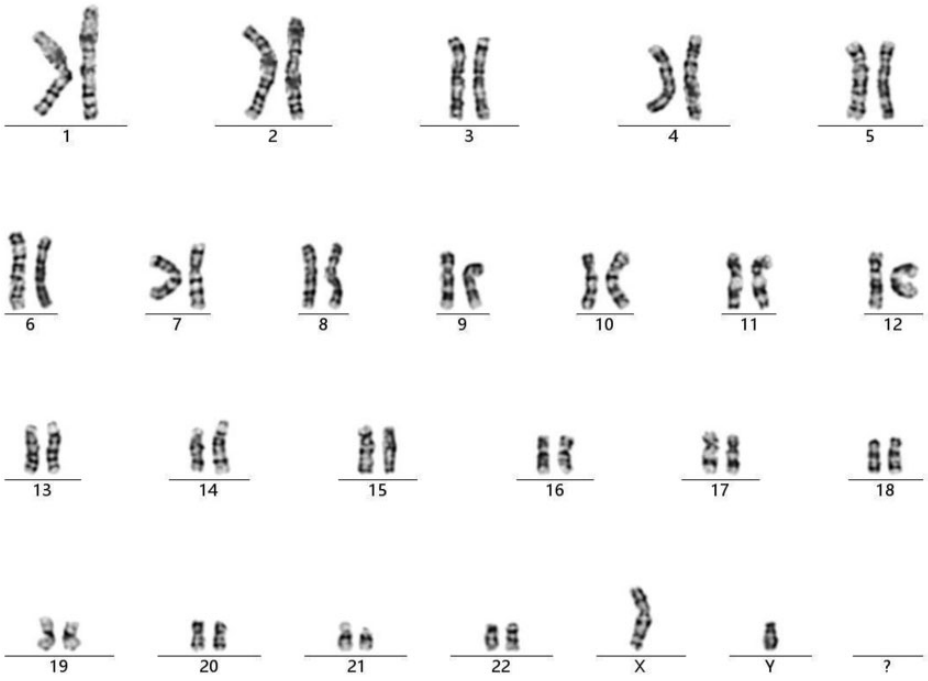

Figure 1. The karyotype of 46, XY.

Figure 2. Chromosomal microarray analysis (CMA) detection of a 599-kb chromosomal microdeletion in the region of 16p11.2 arr[GRCh37] 16p11.2(29,591,327_30,190,029)x1.

Doppler ultrasound diagnostic instrument; 3D imaging mode). 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) of 102, weight of 17.3 kg, and height of 96 cm).

Discussion

The majority of unbalanced chromosome abnormalities (UBCA) families have a degree of phenotypic effects. Thus, at the cytogenetic level, a lack of phenotypic consequences is the exception rather than the rule.[4] Some resources, such as the Database of Chromosomal Imbalance and Phenotype in Humans using Ensemble Resources (DECIPHER) (http://www.sanger.ac.uk/PostGenomics/decipher/) and Chromos Omics Database (cases with heteromorphisms) (http://cs-tl.de/DB/CA/HCM/0-Start.html), can facilitate the process of distinguishing pathogenic alterations from phenotypically neutral variations in the immediate future.

CNVs of the human 16p11.2 genetic locus are associated with a range of neurodevelopmental disorders, including ASD, intellectual disability, and epilepsy. The 16p11.2 microdeletion has been found in nearly 1 in 100 people with autism, in nearly 1 in 1000 people with a language or psychiatric disorder, and in nearly 3 in 10,000 people in the general population.[5]

The chromosomal deletion is associated with 16p11.2 microdeletion syndrome, where the deleted region of 16p11.2 contains the following Online Mendelian Inheritance in Man (OMIM) genes: ALDOA, CDIPT, DOC2A, FAM57B, GDPD3, HIRIP3, KCTD13, KIF22,

MAPK3, MAZ, MVP, PAGR1, PPP4C, PRRT2, QPRT, SEZ6L2, SPN, TAOK2, TBX6, YPEL3, and ZG16.

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 (CVMs). The absence of this region (16p11.2) has incomplete penetrance, and some patients 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 (see Table 1).[9–15]

The case described here enriches the phenotypical spectrum linked to the 16p11.2 microdeletion. In this case, 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, she weighed 68 kg and is 159 cm tall. The prenatal ultrasound did not reveal any abnormalities in the fetus. After genetic counseling, the parents decided to continue the pregnancy, and the baby is now developing normally. However, although the baby is currently developing normally, we have notified the parents that some corresponding phenotypes may appear later, including ASD, intellectual disability, and epilepsy.

For these reasons, if a genetic pathology is suspected, it is fundamental to study the proband from the clinical point of view, extend the clinical examination to her parents, and provide a good family anamnesis. It is also essential that a multidisciplinary team carefully evaluates the patient.

Table 1. Penetrance of neurodevelopmental disorders and physical abnormalities among chromosome 16p11.2 deletion carriers.

Number of 16p11.2 deletion carriers					
ASD	ID	E/S	Mac.	DF/CA	Refs
41/217	61/217	–	–	–	10
3/62	–	–	–	–	11
4/25	5/25	–	6/25	–	12
3/16	–	5/16	11/16	5/16	13
51/317	–	69/317	–	67/317	14
28/78	8/78	–	–	–	15

ASD, autism spectrum disorder; ID, intellectual disability; E/S, epilepsy/seizures; Mac, macrocephaly; DF/CA, dysmorphic feature/congenital anomaly.

Conclusion

To summarize, we present a family 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. The combination of prenatal ultrasound, karyotype analysis, CMA, and genetic counseling is helpful for the prenatal diagnosis of chromosomal microdeletions/microduplications.[16]

Acknowledgements

We thank all the participants and families in this study for their cooperation.

Author contributions

ML, JG, and YW performed the clinical diagnosis and treatment. LL performed the pathological examination. ML conducted the genetic testing and wrote the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

This research was approved by the Ethics Committee of Maternal and Child Health Hospital of Xiaogan (Approval No. 2021-132). All patient guardians provided written informed consent to participate in the study.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Web resources

Chromosome Anomaly Collection: http://www.ngrl.org.uk/Wessex/collection/

Database (Cases with heteromorphisms): http://cs-tl.de/DB/CA/HCM/0-Start.html

DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources): http://www.sanger.ac.uk/PostGenomics/decipher/

DGV (Database of Genomic Variants): http://projects.tcag.ca/variation/

ISCA (International Standard Cytogenomic Array consortium): https://www.iscaconsortium.org/

OMIM (Online Mendelian Inheritance in Man): http://www.omim.org/

Small supernumerary marker chromosomes: http://ssmc-tl.com/Start.html

UCSC (University of California Santa Clara) Web browser: http://genome.ucsc.edu/

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