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Prenatal diagnosis and molecular cytogenetic characterization of an inherited microdeletion of 18q12.3 encompassing SETBP1

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Abstract

The 18q12.3 region contains the SET binding protein 1 (SETBP1) gene. SETBP1 mutations or deletions are associated with Schinzel–Giedion syndrome or intellectual developmental disorder, autosomal dominant 29. We report the prenatal diagnosis and genetic counseling of a patient with a maternally inherited 18q12.3 microdeletion. In this family, the mother and son carried the same microdeletion. Chromosomal microdeletions and microduplications are difficult to detect using conventional cytogenetics, whereas the combination of prenatal ultrasound, karyotype analysis, chromosomal microarray analysis, and genetic counseling is helpful for the prenatal diagnosis of chromosomal microdeletions/microduplications.

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Introduction

Schinzel–Giedion syndrome (SGS) is a multiple malformation syndrome mainly characterized by severe intellectual disability, distinctive facial features, and multiple congenital anomalies, including skeletal abnormalities, genitourinary and renal malformations, cardiac defects, and an increased pediatric cancer risk.[1,2] Patients with intellectual developmental disorder, autosomal dominant 29 (MRD29) always have mild intellectual disability and speech delay. Recently, SGS and MRD29 have been linked to *de novo* heterozygous deleterious variants in the SET binding protein 1 (SETBP1) gene. SETBP1 is located on chromosome 18q12.3. To date, nine different variants clustering in exon 4 of SETBP1 have been identified.[2]

Case report

In 2017, a 28-year-old, gravida 1, para 0 woman underwent amniocentesis at 17 weeks of gestation because of intellectual disability and language disorder. Cytogenetic analysis of the cultured amniocytes was performed. Chromosomal microarray analysis (CMA) of uncultured amniocytes was performed using the Affymetrix CytoScan 750K chip (Affymetrix, Santa Clara, CA, USA), which includes 550k nonpolymorphic markers and 200k SNP markers. CMA detected a 93-kb chromosomal microdeletion in the region of 18q12.3 (Figure 1), whereas the GTG-banding of the fetus was normal. The karyotype of the fetus according to the International System of Cytogenomic Nomenclature 2020[3] was 46,XY.arr[GRCh37] 18q12.3 (42,524,597_42,617,993)x1.

Then, we performed both CMA and conventional karyotyping using samples from the parents' peripheral blood and their karyotypes were normal. The CMA results illustrated that the mother carried the same microdeletion as the fetus. SNP markers in the Affymetrix CytoScan 750K chip confirmed the maternal origin of the 18q12.3 deletion. Ultrasound revealed no dysmorphisms or intrauterine growth restriction in the fetus. After genetic counseling, the parents decided to continue the pregnancy. At 39 weeks of gestation, the expectant mother gave birth vaginally to a male baby weighing 2950 g. The baby received a complete physical examination, and the results were normal. At 2 years of age, the child underwent the Gessell examination, which indicated intellectual disability (intelligence quotient = 76) and language disorder (development quotient = 67).

Discussion

SGS and MRD29 are extremely rare autosomal dominant inheritance disorders. The precise prevalence of SGS and MRD29 is unknown. Mutations or deletions of SETBP1 are associated with MRD29 and SGS.[4] The classic clinical features of SGS are multiple developmental anomalies

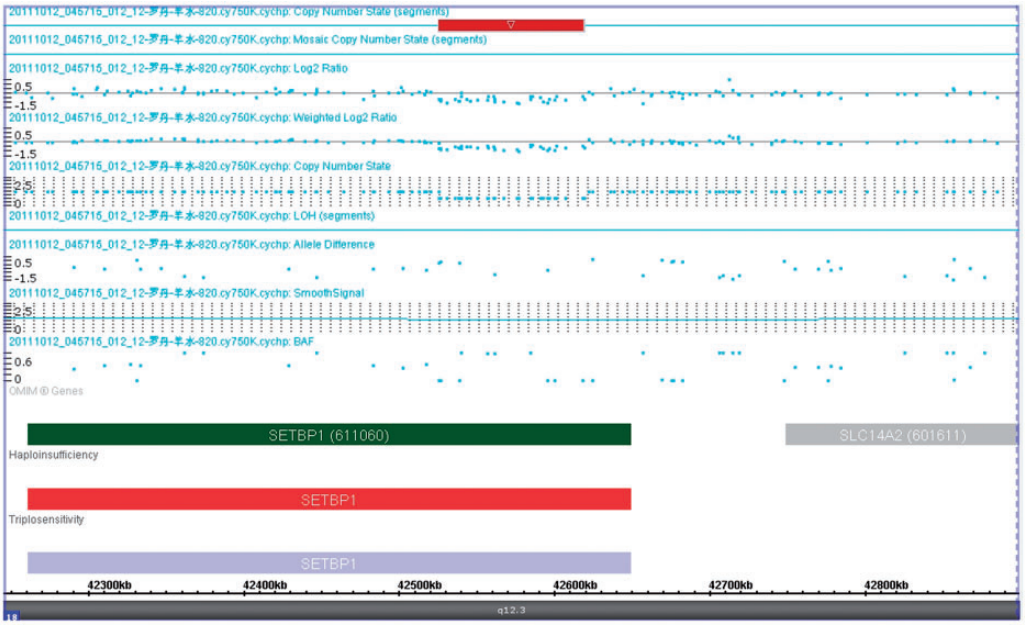

Figure 1. Chromosomal microarray analysis detected a 93-kb chromosomal microdeletion in the region of 18q12.3 (arr[GRCh37] 18q12.3(42,524,597_42,617,993)x1).

including psychomotor retardation with progressive neurodegeneration; seizures; craniofacial, skeletal, and urogenital malformations, and a higher prevalence of malignant neoplasms.[5] Patients with MRD29 always have mild intellectual disability and speech delay. In 2010, heterozygous mutations or deletions in the SETBP1 gene were identified as the genetic causes of SGS and MRD29. Gene Ontology analysis of deregulated SETBP1 target genes indicated that they were the key controllers of visceral organ development and brain morphogenesis.

With the introduction of molecular genetics in the diagnosis of SGS, it is possible that atypical patients could be diagnosed. Some prenatal abnormalities in patients with SGS can be identified on ultrasonography, and the early molecular diagnosis of SGS could also be confirmed by amniocentesis.[6]

SGS has been characterized by profound neurodevelopmental delay, characteristic facial gestalt, epilepsy, hydronephrosis, and multiple congenital anomalies. Most reported patients with SGS died before the age of 2 years.

Deletions or mutations of SETBP1 have been reported in only 16 individuals with a distinct MRD29 phenotype characterized by subtle dimorphisms, expressive speech impairment with intact receptive language abilities, decreased fine motor skills, and hyperactivity or autistic traits.[4,7,8]

In this family, we successfully diagnosed two cases of MRD29. Two cases without facial abnormality were associated with mild intellectual disability and language disorder because of the inherited chromosomal microdeletion of 18q12.3.

Deficits in expressive language have been reported in individuals carrying chromosomal microdeletions in 18q12.3, exclusively

including SETBP1, as well as larger 18q chromosomal deletions, and in patients with SETBP1 point mutations causing haploinsufficiency.[9]

The two novel cases further support the hypothesis that SETBP1 haploinsufficiency is the main molecular mechanism implicated in the developmental speech deficits in MRD29.

Conclusion

Our case report demonstrated the utility of CMA at the time of amniocentesis for identifying deleted genes and the parental origin of the microdeletion, and the acquired information is helpful for genetic counseling.[10]

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Availability of data and materials

Please contact the corresponding author for data requests.

Author contributions

Yaqing Zhou and Yijun Wu were responsible for clinical diagnosis and treatment.
Yan Quan was responsible for the pathological examination.
Yinxing Zhang was responsible for genetic testing and manuscript writing.

Consent for publication

The patient provided written informed consent for the publication of this study.

Declaration of conflicting interest

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

Ethics approval and consent to participate

The research was approved by the Ethics Committee of Huangshi Central Hospital (approval number: 2021-0197). Written informed consent was obtained from the mother for participation in the study.

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