CASE REPORT

Prenatal Diagnosis and Molecular Cytogenetic Analyses of a *de novo* Deletion on Chromosome 4p16.3p15.33

Huili Luo, MD; Ruijie Chang, MD; Fangfang Liu, MD; Xia Gao, MD

ABSTRACT

Wolf-Hirschhorn syndrome (WHS) (OMIM 194190) is a contiguous gene syndrome with an estimated prevalence of around 1 in 50 000 births. The syndrome is caused by the deletion of a critical region (Wolf-Hirschhorn Syndrome Critical region-WHSCR) on chromosome 4p16.3. Its core features are typical facial gestalt, growth retardation, intellectual disability, developmental delay, and seizures. Prenatal diagnosis of WHS helps clinicians and parents make informed decisions about pregnancy management. In this research, a 31-year-old woman (gravida 1, para 0) underwent amniocentesis at 18 weeks gestation because of the short nasal bone of the fetus on prenatal ultrasound. Chromosomal microarray analysis (CMA) on uncultured amniocytes revealed a *de novo* 11.36-Mb deletion on chromosome 4p16.3p15.33, spanning from position 40 000 to 11 400 000 (hg19). After genetic counselling and being informed of the unfavorable prognosis, the parents decided to terminate the pregnancy. We provide a detailed description of a *de novo* 11.36-Mb deletion on chromosome 4p16.3p15.33 (Wolf-Hirschhorn syndrome). CMA has more advantages than karyotype analysis in detecting chromosomal microdeletions/microduplications. A combination of karyotype analysis, CMA, prenatal ultrasound, and genetic counseling is helpful for the prenatal diagnosis of chromosomal deletions/duplications. (*Altern Ther Health Med.* 2023;29(8):907-909).

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INTRODUCTION

The Wolf–Hirschhorn syndrome (WHS) (OMIM 194190) is a multiple congenital anomalies/intellectual disability syndrome, which affects 1 in 50,000 live births with a 2:1 female-to-male ratio.[1] It was first described by Cooper and Hirschhorn (1961).

WHS is caused by a partial loss of genetic material from the distal portion of the short (p) arm of chromosome 4p16.3 (Wolf-Hirschhorn Syndrome Critical region-WHSCR), which has a variable size that reflects the spectrum and severity of the disease. WHS is associated with a wide range of clinical features. The core phenotype includes a typical facial appearance called Greek warrior helmet facies (hypertelorism, short and broad nose, short philtrum, downturned mouth, and low set dysplastic ears), intellectual disability ranging from mild to severe, growth delay, hypotonia, seizures, and microcephaly.[2] Other manifestations include congenital heart defect, cleft palate, hearing loss, kidney and genito-urinary tract malformations such as hypospadias. Ophthalmological and dental abnormalities and skeletal abnormalities like talipes, mesomelia, radioulnar synostosis, fused vertebrae and ribs, and hip dislocation can also be features of the syndrome. Here, we describe a *de novo* 11.36-Mb deletion on chromosome 4p16.3p15.33 (WHS).

CASE PRESENTATION

A 31-year-old woman (gravida 1, para 0) underwent amniocentesis at 18 weeks gestation because of the short nasal bone of the fetus on prenatal ultrasound (Figure 1). She and her 34-year-old husband were normal, healthy, and non-consanguineous. There was no family history of birth defects or genetic diseases.

G-banding karyotype analysis was performed on cultured amniocytes. CMA on uncultured amniocytes was

Figure 1. Short nasal bone of the fetus on prenatal ultrasound

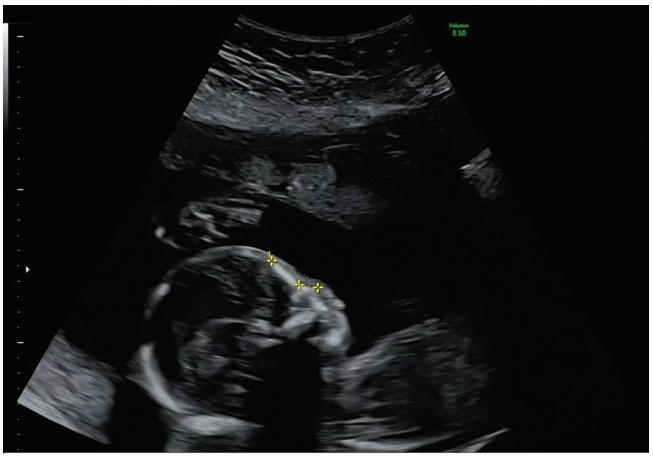


Figure 2. The karyotype of 46,XX,del(4)(p16.3p15.3)

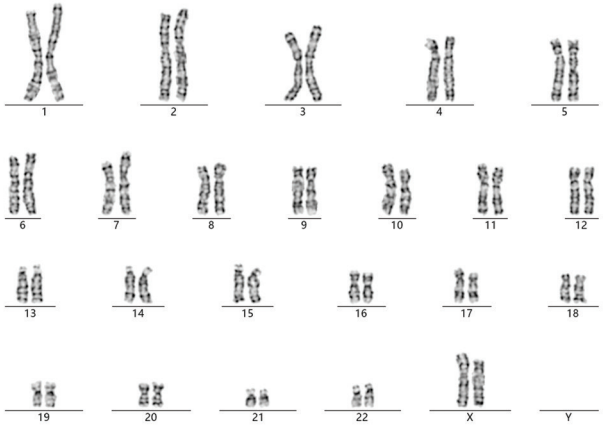
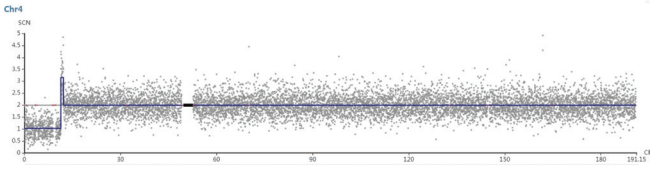


Figure 3. CMA detected a 11.36-Mb chromosomal deletion in the region of 4p16.3p15.33 (arr[GRCh37]4p16.3p15.33 (40 000_11 400 000) × 1)



performed using the Affymetrix CytoScan 750K chip, which includes 550k non-polymorphic markers and 200k SNP markers. G-banding karyotype analysis mainly examines chromosome number and structural abnormalities. CMA mainly detects chromosomal microdeletions/microduplications. Chromosomal GTG-banding on cultured amniocytes revealed a karyotype of 46, XX, del (4)(p16.3p15.3) (Figure 2). CMA on uncultured amniocytes detected an 11.36-Mb chromosomal deletion in the region of 4p16.3p15.33, which is to be reported according to the International System of Cytogenomic Nomenclature 2020 (ISCN 2020)[3] as arr[GRCh37] 4p16.3p15.33 (40 000_11 400 000) × 1 (Figure 3). Then we performed CMA and chromosomal GTG-banding using the parents' peripheral blood samples. Their karyotypes and CMA results were normal.

We performed a comprehensive physical examination of the parents and failed to identify anything abnormal. Ultrasound examination showed the fetus's short nasal bone, small mandible, and wide eye distance. After genetic counselling and being informed of the unfavourable prognosis, the parents decided to terminate the pregnancy. Pathological examination revealed a small mandible, short philtrum, wide eye distance (Intraocular distance: 1.9 cm, extraocular distance: 4.5 cm), no bony structure in the nasal bone, without heart or kidney malformation.

DISCUSSION

The Wolf–Hirschhorn syndrome (WHS) (OMIM 194190) is one of the most common deletion syndromes and is caused by deletion (complete or partial) of the short arm of chromosome 4. The frequency of WHS was more prevalent in females (70%).[4] Patients exhibited the characteristic clinical features of WHS, including growth delay (IUGR or postnatal growth delay), distinctive facial features (Greek warrior helmet facial appearance), and intellectual disability.[5] Hypotonia was detected in 80%, while epilepsy or EEG anomalies occurred in 80%–90% of patients, Postnatal short stature and microcephaly, intellectual disability, and hypotonia were reported in many studies with a frequency approaching 100 percent.[4-5]

In most patients with WHS, the phenotype results from de novo chromosomal terminal deletions involving chromosome region 4p16.3. The severity of the clinical presentation has been correlated to the size of the deleted region and the breakpoint site.[4,6] Three major phenotypic groups were defined as mild, moderate, and severe. The first comprises a small deletion of 3.5 Mb or less and is more likely underdiagnosed. The moderate second type is the more frequent category with deletions between 5 and 18 Mb and usually has the typical WHS features. The third severe category results from very large deletions of 22–25 Mb or more and is characterized by additional severe complex features, including typical facial appearance, severe intellectual disability, severe growth delay, severe seizures, neurological abnormalities, ophthalmic abnormalities, congenital heart malformations, skeletal, renal anomalies and cleft palate and hypospadias.[7] Nonetheless, the cardinal phenotypic features of WHS are thought to result from contiguous gene regions, of which deletion is sufficient to result in WHS characteristic features. Many of these genes are yet to be identified.

Overlapping regions of multiple cases diagnosed with WHS has helped to decide the critical region of WHS, namely WHSCR1, and WHSCR2, which has been narrowed down to a 200 kb region on 4p16.3.[8-9] Typical WHS, even in the mild form of its clinical phenotype, is largely assumed to be a multigenic disorder. Thus, neither WHSCR1 nor WHSCR2 was established as a definite genetic cause of WHS,

but they allowed further exploration of possible candidate genes.[10-12]

In this case, the female fetus belongs to the second type with deletions from 4p16.3 to p15.33(11.36-Mb); she has the typical WHS features, just as small mandible, short philtrum, wide eye distance, absence of nasal bone, but without heart or kidney malformation.

Some further considerations are appropriate. Severe growth retardation and seizures are the major problems in the clinical management of WHS. The characterization of the pathogenic genes for these features may allow the development of gene therapy for WHS. Since haploinsufficiency is the basic pathogenetic mechanism in WHS, the unaltered copies of each deleted gene on the homologous chromosome are the ideal target for attempts to increase their expression by reactivating drugs.[7] We will continue to analyse this disease's genetic mechanism and clinical manifestations in future studies.

CONCLUSION

WHS is a contiguous gene syndrome resulting from hemizygosity of the 4p16.3 region. We provide a detailed description of a de novo 11.36-Mb deletion on chromosome 4p16.3p15.33 with WHS. A combination of karyotype analysis, CMA, prenatal ultrasound, and genetic counseling is helpful for the prenatal diagnosis of chromosomal deletions/duplications, helping for parents to make informed decisions regarding pregnancy management.

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AUTHOR'S CONTRIBUTIONS

Huili Luo and Ruijie Chang are responsible for clinical diagnosis and treatment. Xia Gao and Fangfang Liu are responsible for genetic testing and thesis writing. Huili Luo, Ruijie Chang, and Fangfang Liu contributed equally to this work.

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AVAILABILITY OF DATA AND MATERIALS

Please contact the corresponding author for data requests.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research was approved by the Ethics Committee of Renmin Hospital of Shiyan. All patient guardians gave informed consent to the study.

CONSENT FOR PUBLICATION

All patient guardians gave informed consent to the publication of this study

COMPETING INTERESTS

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

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