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CASE REPORT

A Case of a Fetus with a Chimeric Duplication of 9p21.1p13.1 and a Normal Pregnancy Outcome

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ABSTRACT

Background: **The clinical characteristics of 9p trisomy or 9p partial trisomy syndrome are growth retardation and intellectual disability, auricular deformity, eye distance too wide, sunken eyeballs, bulbous nose, low corners of the mouth, abnormal development of hands and toes and so on.**
Methods: **Fetal amniotic fluid cells were detected through CNV-seq, and the results were analyzed and compared. Conventional G-banding karyotyping was used to detect fetal amniotic fluid cells and parental peripheral blood.**
Results: **The CNV-seq result of amniotic fluid cells showed that about 8.60 Mb chimeric duplication in 9p21.1p 13.1, with a chimeric proportion of 26%, and the variant was classified as likely pathogenic. The karyotype result of amniotic fluid cells was 47,XN,+mar[24]/46,XN[76]. The peripheral blood karyotypes of both parents showed no apparent abnormalities. The pregnancy outcome of the fetus was normal.**
Conclusions: **The phenotype and pathogenicity of CNV mosaicism are difficult to determine. During genetic counseling, a comprehensive risk assessment should be conducted by integrating test results and literature evidence. The decision on the pregnancy outcome must be based on the principle of informed consent and respect the wishes of both parents.**
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KEYWORDS

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INTRODUCTION

Trisomy 9 is a relatively rare chromosome number abnormality that is seriously teratogenic and lethal. The more common clinical phenotypes are varying degrees of mental retardation, congenital heart system diseases, and developmental abnormalities of the skeletal system. Most embryos with trisomy 9 undergo spontaneous miscarriage in the first trimester, while the minority who survive to birth are predominantly mosaic cases [1]. Chimera refers to the presence of two or more cell lines in an individual. Trisomy 9 mainly includes complete trisomy, partial long-arm trisomy and partial short-arm trisomy. Trisomy 9p syndrome is one of the more common chromosomal abnormalities in live-born infants, following only trisomies 21, 18, and 13 in frequency.

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One possible explanation is that these chromosomes, like 9p, are relatively gene-poor [2,3]. As early as 1970, Rethore [4] first identified and reported the karyotype of trisomy 9p, subsequently describing the clinical characteristics of this trisomy syndrome. In 1975, Centerwall [5] identified the anomaly types of trisomy 9p, which are usually caused by a balanced translocation between chromosome 9 and other chromosomes in the parents, leading to partial trisomy of chromosome 9 in the offspring. Rare cases may also occur due to de novo mutations of unknown etiology during gametogenesis. This study conducted cytogenetic and molecular genetic analyses on a fetus with a partial 9p mosaic duplication, and followed up on the pregnancy outcome, enriching the theoretical basis for genetic counseling of patients with chromosome 9 mosaic duplications.

CASE PRESENTATION

Clinical case

The patient was a 37-year-old pregnant woman with a last menstrual period (LMP) of November 4, 2024 and a history of regular 26-day menstrual cycles. The patient has a history of one induced abortion. Due to advanced maternal age and in accordance with the principle of informed consent, amniocentesis was performed for CNV-seq and karyotype analysis of the fetus. Peripheral blood samples were also collected from both parents for conventional G-banding karyotype analysis. The patient has a history of animal contact and denies any family history of genetic disorders.

Research methods

Under strict aseptic technique and guided by ultrasound probe, transabdominal amniocentesis was performed on the pregnant woman. Three tubes of amniotic fluid were collected: one 10 mL and two 8 mL, all stored in disposable sterile centrifuge tubes. One 10 mL aliquot of amniotic fluid was processed using magnetic bead-based DNA extraction, with the final DNA concentration reaching ≥ 2.5 ng/μL. The extracted DNA was used as a template for library construction with a CNV-seq detection kit, followed by molecular genetic analysis performed on the MGISEQ-2000 sequencing platform. The sequencing data were analyzed using PSCC, with the GRCh37/hg19 serving as the reference genome. Copy number variations are classified into five categories based on their clinical significance: pathogenic (total score ≥ 0.99), likely pathogenic (0.90 ≤ total score ≤ 0.98), variant of uncertain significance (-0.89 ≤ total score ≤ 0.89), likely benign (-0.98 ≤ total score ≤ -0.90), and benign (total score ≤ -0.99). The primary findings of the report present chromosomal triploidy, aneuploidy variants, as well as known and clearly pathogenic or likely pathogenic microdeletions/microduplications exceeding 100 Kb. The secondary findings disclose microdeletions/microduplications over 100 Kb that are of uncertain clinical significance. As a general principle, benign and likely benign copy number variants are not reported. Two 8 mL aliquots of amniotic fluid were allocated for cell culture using a dual-line processing approach. The cultures were maintained in a 37℃ CO_2 incubator for one week, followed by medium replacement. Cells were harvested on the following day for slide preparation and G-banding. Chromosomal karyotype analysis of metaphase cells was performed using the MetaSight® and AutoVision® of DIAGENS, with results described according to the International System for Human Cytogenomic Nomenclature (ISCN 2024). For routine specimens, 50 metaphases were counted and 10 karyotypes were analyzed per case. For specimens suspected of mosaicism, the number of karyotypes counted and analyzed was increased. Using heparin anticoagulant tubes, 2 mL of peripheral blood was collected from both parents via venipuncture. Under aseptic conditions, the peripheral blood samples were inoculated into lymphocyte culture medium and incubated at 37℃ for 3 days. Two drops of colchicine were then added, followed by an additional 2 hours of incubation before cell harvest. Following slide preparation and microscopic analysis, the chromosomal karyotypes were described in accordance with the International System for Human Cytogenomic Nomenclature (ISCN 2024).

RESULTS

The CNV-seq analysis of fetal amniotic fluid cells revealed the finding: seq[GRCh37] dup(9)(p21.1p13.1) [0.26]. The size of the duplicated segment is 8.60 Mb. According to the ClinGen CNV Scoring System, the variant scored between 0.9 and 0.98, classifying it as likely pathogenic (Figure 1). The fetal karyotype result was 47,XN,+mar[24]/46,XN[76]. Peripheral blood chromosome analyses of both parents revealed no significant abnormalities. Following genetic counseling and family discussion, the couple decided to continue the pregnancy. The newborn subsequently delivered showed no apparent abnormalities.

DISCUSSION

Chromosome 9 is one of the 23 pairs of human chromosomes, classified as a medium-sized submetacentric chromosome in the C group. Under normal circumstances, one copy is inherited from each parent. The vast majority of fetuses with trisomy 9 die in the first trimester of pregnancy, but a small number survive through pregnancy and are even born. Feingold and Atkins [6] reported the first case of a living child with trisomy 9 in 1973, who survived for 28 days. In 1981, Mantagos [7] also reported two cases of trisomy 9 in neonates who died shortly after birth. In 2009, Kannan [1] described a case of trisomy 9 in an infant who survived for 20 days. The above reports show that children with trisomy 9 have a short survival period and have

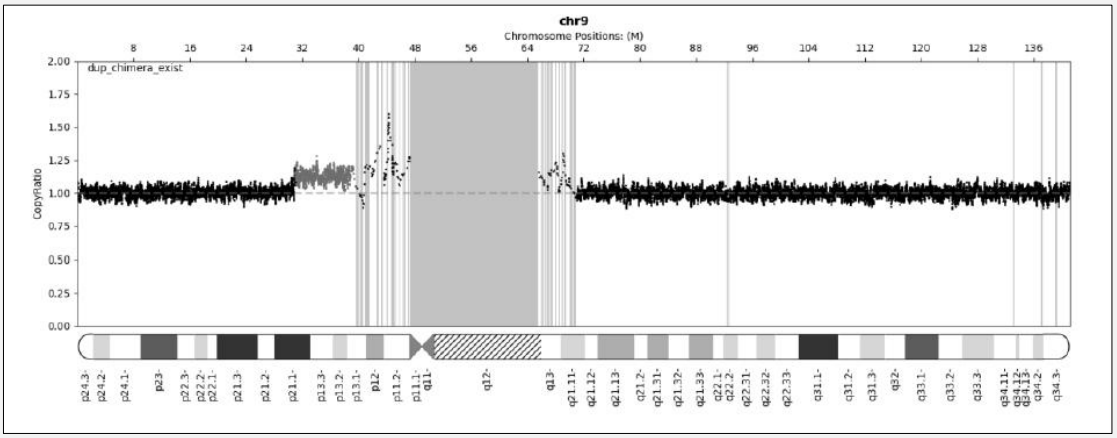

Figure 1. The primary finding from CNV-seq analysis of fetal amniotic fluid cells revealed an approximately 8.60 Mb mosaic duplication in the 9p21.1p13.1 region, with a mosaicism level of 26%, which was classified as a likely pathogenic variant.

unique craniofacial malformations: low ears, microjaw, bulbous nose, small eyes or eyelid clefts, cleft palate, and severe congenital multiple malformations.

The first reported case of a child with mosaic trisomy 9 was described by Haslam [8] in 1973. The patient was a 9-year-old boy who presented with severe intellectual disability, distinctive facial features, short stature, hypotonia, a ventricular septal defect, patent ductus arteriosus, and significant brain abnormalities. Pejcic [9] monitored a male infant with a 10% mosaicism level for trisomy 9 until 6 months of age, documenting manifestations that included facial and skeletal anomalies, various visceral malformations, and suspected psychomotor impairment. Chen [10] identified a case of about 10% trisomy 9 mosaicism with concomitant maternal uniparental disomy, in which intrauterine growth retardation was noted, yet postnatal development up to 6 months was normal. Trisomy 9 chimerism syndrome has a diverse phenotype, similar to complete trisomy 9, but is usually less abnormal than complete trisomy 9 and has a longer lifespan.

Trisomy 9p syndrome is characterized by growth retardation, severe intellectual disability, distinctive craniofacial abnormalities (including hypertelorism, down slanting palpebral fissures, downturned corners of the mouth, and cup-shaped ears) [11], as well as congenital heart defects, central nervous system anomalies, and abnormalities of the renal, skeletal, and genitourinary systems [12,13]. It has been suggested that duplication of 9p22.1p22.3 segment causes typical craniofacial abnormalities. Other scholars believe that the duplication of 9p21.2p21.3 segment is related to language retardation. In this study, both parents of the fetus had normal karyotypes, and the 9p variant identified in the amniotic fluid cells was a de novo mutation. However, the duplicated region (9p21.1p13.1) does not fall within the critical intervals previously described, and this case is chimera, which may be the reason why there are no obvious abnormalities in the fetus at birth. Hu [14] (2023) reported two cases with similar duplications who were born healthy and showed no observed clinical phenotypes at follow-ups until 2 and 3.5 years of age.

In summary, genetic counseling for a fetus with a chromosome 9 duplication should be integrated with other prenatal examinations and literature to conduct a comprehensive risk assessment. Although the pregnancy outcome in this case was uneventful, it is recommended that the child undergo long-term follow-up and detailed physical examinations.

Declaration of Generative AI in Scientific Writing:

DeepSeek was used during the preparation of this work in order to improve language. After using this tool, it was reviewed and the content edited as needed. The authors take full responsibility for the content of the publication.

Declaration of Interest:

All authors declare that they have no competing interests.

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