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Complex Chromosomal rearrangements t(2;9;18) and duplication 4(q28.1q28.1): Prenatal Findings with Uncertain Phenotypic Significance

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Abstract

Complex chromosome rearrangements(CCR)are rare structural abnormalities involving multiple chromosomal breakpoints. Phenotypic outcomes in carriers are highly variable, and the risk of spontaneous miscarriage in CCR carriers may reach as high as 50–100%.We describe a female fetus with a complex chromosomal translocation accompanied by a copy number variant: 46,XN,t(2;9;18)(q31.3;p22;p11.2), along with a 1.11 Mb duplication at 4q28.1(copy number:3).The chromosomal analysis of her mother showed the same complex translocation, confirming the diagnosis. This case represents a rare familial CCR involving three chromosomes and three breakpoints. This case highlights the importance of integrating clinical phenotypes, cytogenetics, CNV-sequencing, and parental studies to clearly guide cases of chromosomal structural abnormalities accompanied by variations of unknown significance.

Key points

What's already known about this topic?

Currently, genetic counseling for complex chromosomal rearrangements (CCRs) remains challenging due to the uniqueness and complexity inherent to different CCRs; the application of sequencing technologies can facilitate prenatal genetic counseling and interpretation of CCRs.

What does this study add?

A favorable neonatal outcome provides a reference for the detected CCRs t(2;9;18) and duplication 4q28.1q28.1, and enriches the genetic phenotypic spectrum in this region.

1. Fetal Phenotype

A 29-year-old G2P0A1 patient was referred at 18 weeks of gestation for futher evaluation following high risk(1:154) for Trisomy 18 of the Second Trimester maternal serum screening.Her obstetric history included one prior spontaneous miscarriage at approximately 4 weeks' gestation. First trimester screening,including serological tests and nuchal translucency,was normal. Amniocentesis was performed under ultrasound guidance, and chromosome culture identification, low-depth whole genome sequencing(CNV-seq)were conducted.Amniocentesis revealed the chromosomal analysis of the fetus as 46,XN,t(2;9;18)(q31.3;p22;p11.2)(Fig. 1a)and the result of CNV-seq revealed a 1.11 Mb duplication in the 4q28.1q28.1 region,shown as seq[GRCh37]4q28.1q28.1(124324748_125438688)x3,classified as a variant of uncertain significance (VUS)(Fig. 1c,Fig. 1d). Parents genetic counseling and provided peripheral blood samples for chromosomal analysis. Chromosome analysis of the mother was 46,XX,t(2;9;18)(q31.3;p22;p11.2), confirming maternal inheritance of the complex translocation(Fig. 1b).

2. Diagnostic Method

Fetal amniotic fluid cells and parental peripheral blood lymphocytes were cultured for cytogenetic analysis. The fetal DNA extracted from amniocytes underwent low-coverage whole-genome sequencing (CNV-seq).Chromosomal analysis of the patient was performed from amniotic fluid cells and peripheral blood lymphocytes using conventional G-banding techniques, using GTG banded metaphases at 400–500 band resolution.

Using the MGISEQ-200 platform (BGI,Wuhan,China), low-depth whole-genome sequencing was performed on fetal genomic DNA extracted from cultured amniotic fluid cells. The sequencing library was prepared using DNA nanoball (DNB) technology with combinatorial probe-anchor synthesis chemistry. Single-end sequencing was conducted with SE35 + 10bp read configuration. Raw FASTQ files were aligned to the GRCh37 (hg19) reference genome using BWA, and variants were filtered through a validated bioinformatics pipeline.

3. Diagnostic Results and Interpretation

Parental cytogenetic analysis demonstrated that the mother carried the identical chromosomal translocation, 46,XX,t(2;9;18)(q31.3;p22;p11.2), whereas the father's chromosomal analysis was normal. CNVseq of fetal DNA identified a 1.11 Mb duplication at 4q28.1: seq[GRCh37]4q28.1q28.1(124324748_125438688)x3. According to the GRCh37 gene maps, the only OMIM gene in this region is *SPRY1* (chr4:124,317,950–124,324,915); no other known disease-associated genes lie fully within the duplicated segment. Review of population CNV databases (DGV, gnomAD) revealed no common variants overlapping this segment, and no correlation with specific fetal ultrasound anomalies has been reported. Consequently, this duplication remains classified as a variant of uncertain significance.

4. Pregnancy Outcome and Neonatal Findings

Multidisciplinary counseling was provided by maternal–fetal medicine specialists, pediatricians, and clinical geneticists. The parents were counseled regarding the identified complex chromosomal rearrangement and the 4q28.1 duplication, both of which were explained as having uncertain clinical significance. It was noted that the mother carried the same structural chromosomal rearrangement and had a prior history of early miscarriage. Given the variable phenotypic expressivity observed in CCR carriers, the parents were informed of the uncertain implications of the CNV and the potential reproductive risks associated with the chromosomal translocation. After weighing the available information, the parents elected to continue the pregnancy.

At 35 + 2 weeks' gestation, the patient was admitted for non-reassuring fetal status and underwent cesarean delivery. A liveborn female infant was delivered with a birth weight of 2.55 kg and Apgar scores of 9–10 at 1 and 5 minutes, respectively. No dysmorphic features or structural anomalies were noted at birth. Postnatal follow-up to date has demonstrated normal growth and developmental milestones.

5. Disscusion

Complex chromosomal rearrangements(CCRs)are structural chromosomal aberrations involving breakage of two or more chromosomes with subsequent exchange of chromosomal segments(Yang and Hao 2022). As rare events, CCRs may be familial or de novo, and their identification is often clinically significant. The phenotypic consequences in CCR carriers are variable: female carriers frequently exhibit an increased risk of spontaneous miscarriage, whereas male carriers more commonly present with infertility(Cheng et al. 2024; Liu et al. 2024). Current research suggests that the mechanisms underlying CCR formation remain poorly understood. Genetic counseling for CCR carriers is challenging given the unique and complex nature of each rearrangement; however, the application of sequencing technologies in the prenatal setting has greatly facilitated counseling and interpretation of CCRs(Ou et al. 2020; Wang et al. 2025). Additionally, parental chromosomal analysis is important for determining the origin of fetal structural variants. Therefore, accurate assessment of whether patients with adverse pregnancy histories are CCR carriers and evaluation of their associated reproductive risks is essential(Lou et al. 2020). These considerations also underscore the value of genetic counseling in guiding parental decision-making in the context of uncertain genomic information. In this setting, a favorable neonatal outcome provides a reference for the interpretation of the detected variant of uncertain significance(VUS), although continued developmental monitoring remains warranted. In the present case, the infant was confirmed to be healthy at birth, with no observable phenotypic abnormalities.

This case contributes to a better understanding of CCRs and aids in the interpretation of the genomic and phenotypic spectrum within this region.Overall, this report reinforce the necessity of comprehensive cytogenetic evaluation and long-term surveillance in pregnancies involving complex chromosomal variants.

Declarations

Conflicts of Interest

There are no conflicts of interest declared by the authors.

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Not applicable

Ethics Statement

Approval for the study was obtained from the local ethics committee of the Shenshan Medical Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University(No.2025-SSKY-082-01). The study was a retrospective study. The institutional ethics committee exempted the authors from obtaining individual informed consent.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

HYY and PW determined the topic, YHZ and YXL wrote the manuscript, PW,HYY and SF revised the manuscript, YHZ,LTZ and JW collected date and drew pictures. All authors contributed to the article and approved the submitted version.

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Consent

Patient consent statement is not needed for this study.

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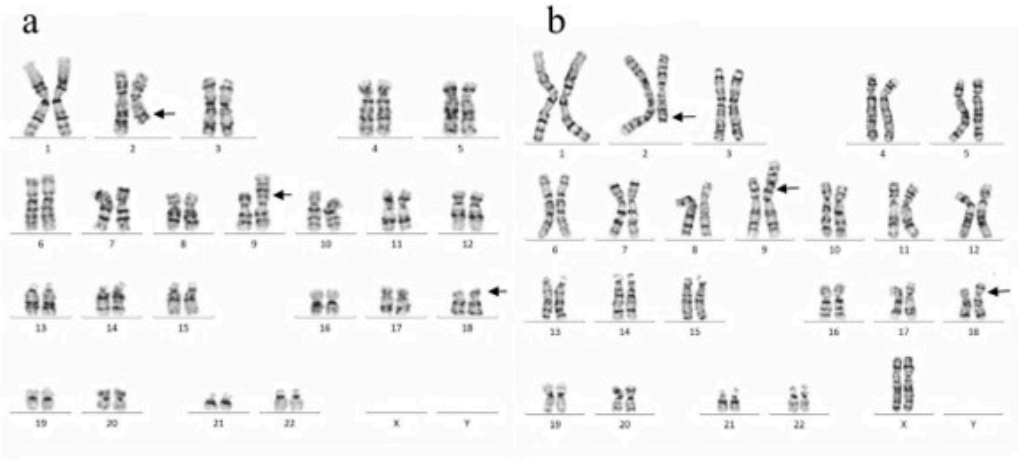
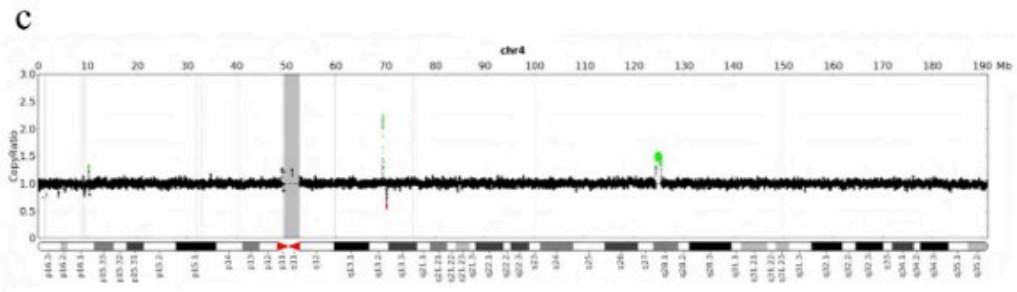
Figures





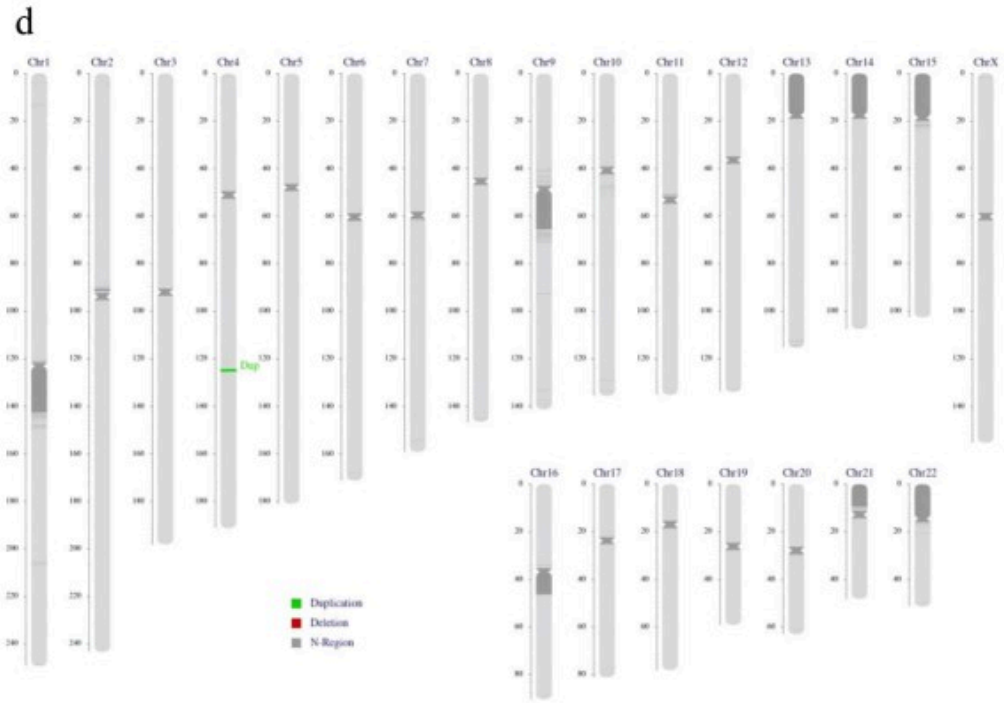


Figure 1

Cytogenetic and molecular findings in the fetus and mother.(a) G-banded metaphase spread from cultured fetal amniocytes demonstrating a complex translocation: 46,XN,t(2;9;18)(q31.3;p22;p11.2). (b) G-banded metaphase spread of maternal peripheral blood lymphocytes confirming the identical balanced translocation: 46,XX,t(2;9;18)(q31.3;p22;p11.2). (c,d) Low-depth whole-genome sequencing (CNV-seq) of fetal DNA (from amniocytes) showing a 1.11 Mb duplication at 4q28.1 (seq[GRCh37]4q28.1q28.1(124324748_125438688)x3).