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CASE REPORT

A Normal Phenotype Case of a Small Supernumerary Marker Chromosome Chimeric Carrier with 12p11.21p11.21 Duplication

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ABSTRACT

Background: **sSMC refers to an additional chromosome added to the karyotype of normal human chromosomes, which can be identified by cytogenetic techniques, but its source and structure cannot be determined, and its size is generally ≤ chromosome 20 during metaphase. The clinical phenotype of patients with sSMC can be normal, or they can show severe clinical manifestations such as growth retardation, intellectual disability, and organic diseases.**
Methods: **Draw 3 mL of peripheral blood using a heparin anticoagulant tube. Peripheral blood lymphocytes were cultured for 72 hours and then used to prepare sample slides, perform G-banding, and conduct chromosomal karyotype counting and analysis. Draw 2 mL of peripheral blood using an EDTA anticoagulant tube. DNA was extracted by magnetic bead method, and chromosome copy number variation sequencing (CNV-seq) was performed by MGISEQ-2000 sequencer to analyze chromosomal aneuploidy and chromosome copy number variations above 100 kb.**
Results: **The karyotype result of peripheral blood chromosomes in the case was 47,XX,+mar[38]/46,XX[17]. CNV-seq detected approximately 1.47 Mb duplications in 12p11.21p11.21 regions with a copy number of 3.**
Conclusions: **CNV-seq can accurately locate sSMC whose sources and characteristics cannot be identified by traditional chromosomal G-banding technology, which is helpful in determining whether the sSMC of carriers have clinical phenotypic correlation.**
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KEYWORDS

sSMC, duplication, carrier

INTRODUCTION

Small supernumerary marker chromosome (sSMC) refers to chromosomes with abnormal structures other than normal human chromosomes, which can be derived from any fragment on any of the 46 human chromosomes, and was first reported by Ilberry in 1961. The incidence of sSMC varies in different populations, with an incidence of 0.4 - 1.5/1,000 in prenatal diagnosis, 0.66/1,000 in newborns, and a higher incidence of 3.27/1,000 in people with mental retardation [1]. The clinical phenotype of sSMC carriers varies according to the

source, size, presence of euchromatin and chimeric ratio of sSMC. The phenotype can vary significantly from normal to severe diseases, including brain dysfunction, craniofacial abnormalities, growth retardation and so on. Currently, there are approximately 3.3 million sSMC carriers worldwide, and 30% of them have an abnormal clinical phenotype [2,3]. The diversity of sSMC carrier phenotypes has caused great trouble for clinical genetic counseling. Therefore, precise localization of sSMC is particularly important. The case in this study compensates for the shortcomings of traditional chromosomal karyotyping techniques that cannot identify sSMC sources and characteristics by applying CNV-seq.

CASE PRESENTATION

Clinical case

The patient was a female, 28 years old, height 165 cm, weight 53.7 kg, regular menstruation, pulse 76 beats/minute, respiration 20 breaths/minute, blood pressure 115/62 mmHg, with a bachelor's degree, normal phenotype, and no family history of genetic diseases. She had a missed abortion in July 2025, and the tissue showed 12p11.21p11.21 duplication and the fragment size was 1.49 Mb, which is a mutation of undetermined clinical significance. The patient requested to test her peripheral blood chromosome karyotype and chromosome copy number variation sequencing analysis.

Research methods

Peripheral blood was collected from the patient with a heparin anticoagulant tube and an EDTA anticoagulant tube. Under sterile conditions, peripheral blood from the heparin anticoagulant tube was inoculated into lymphocyte culture medium and cultured in an incubator at 37°C for 72 hours. Three drops of colchicine were added, and the cells were harvested after an additional 2 hours of culture. After hypotonicity, fixation, sample slide preparation and G-banding, the ZEISS automatic chromosome karyotype scanning and analysis system was used to analyze the chromosome karyotype of metaphase cells. The chromosome karyotype was described with reference to the International System for Human Cytogenomic Nomenclature (ISCN2024). The DNA of the peripheral blood in the EDTA anticoagulant tube was extracted by magnetic bead method, and the library was constructed with a CNV-seq detection kit. Sequencing was performed using the MGISEQ-2000 sequencer. Sequencing data was analyzed using PSCC, and the reference genome was GRCh37/hg19. The copy number variations were divided into five categories. They were pathogenic (total score ≥ 0.99), likely pathogenic ($0.90 \leq$ total score ≤ 0.98), variant of uncertain significance ($-0.89 \leq$ total score ≤ 0.89), likely benign ($-0.98 \leq$ total score ≤ -0.90), and benign (total score ≤ -0.99). The primary test results showed chromosomal triploid and aneuploidy variants and more than 100 kb microdeletions/microduplications that were known, clearly pathogenic or suspected to be pathogenic, and the secondary test results showed more than 100 kb microdeletions/microduplications of unclear clinical significance. In principle, benign and likely benign copy number variations are not reported.

RESULTS

The result of the patient's peripheral blood chromosome karyotype is: 47,XX,+mar[38]/46,XX [17]. The karyotype is chimera, in which one cell line has one more marker chromosome than normal. The main CNV-seq result was no chromosomal aneuploidy variants or more than 100 kb microdeletions/microduplications that were known, clearly pathogenic or suspected to be pathogenic. The secondary result indicated seq[GRCh37] dup(12)(p11.21p11.21), and the duplication segment size was 1.47 Mb, which is a mutation of unclear clinical significance (Figure 1).

DISCUSSION

sSMC refers to additional chromosomal fragments, which are small and cannot be clearly identified by traditional cytogenetic banding techniques, so molecular genetic methods are required for identification. Most sSMCs originate from proximal centromere chromosomes, with sSMCs from chromosome 15 accounting for 22.9% of all cases and other proximal centromere chromosome sSMCs accounting for 23.8%. sSMC derives from non-proximal centromere chromosomes accounting for 35.9%, most commonly isobrachial chromosomes 12p and 18p, and about 11.2% of sSMCs originate from sex chromosomes X or Y [4].

Most sSMCs are de novo mutations, accounting for about 70%, while about 30% come from familial inheritance, of which 20% is inherited from mother and 10% from father [5]. The CNV of the patient's missed abortion tissue in this study was derived from the patient herself, the fetal mother. Because the duplicate fragment of 12p11.21p11.21 region detected by CNV-seq scored 0 points according to ClinGen CNV scoring system, it was a mutation of unknown clinical significance. And the mother's clinical phenotype is normal, so why the fetus stopped developing is still a mystery.

Trisomy/monomer self-rescue, post-fertilization division error, and gamete complementarity are the three main speculations about sSMC production mechanism [6]. At present, there are three main manifestations of known sSMC: inverted duplication, circular chromosomes, and small chromosomal fragments with centromeres. This case belongs to the third type. The presence of a clinical phenotype in sSMC carriers and the severity of the clinical phenotype mainly depend on factors such as the source, size, chimeric ratio, and uniparental disomy of the sSMC [7]. The size and copy number of

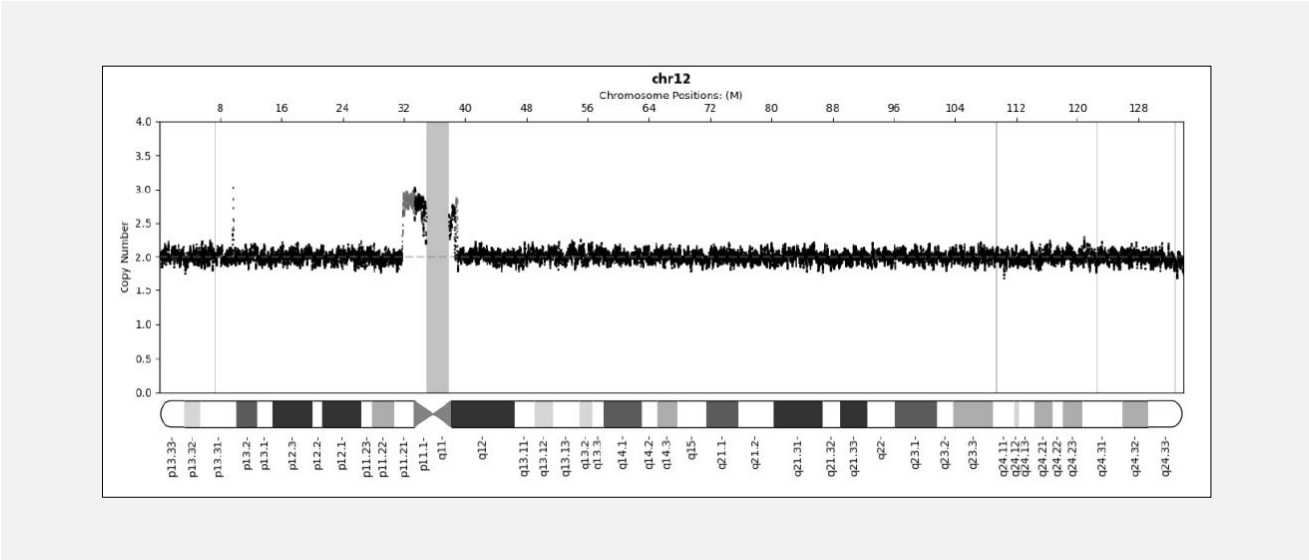

Figure 1. The patient's peripheral blood CNV-seq result indicates seq[GRCh37] dup(12)(p11.21p11.21).

The duplication segment size is 1.47 Mb.

the duplicate segment in this study show significant differences from the 12p tetrasomy [Pallister-Killian syndrome (PKS)]. PKS is a multisystem sporadic genetic disorder, in which patients carry an additional isochromosome composed of two 12p, in addition to a normal pair of chromosome 12. The clinical manifestations of this syndrome are mainly facial roughness, hypotonia, developmental delay, intellectual disability, pigmented skin differences, hearing loss, seizures, diaphragmatic hernia congenital heart defects, and other systemic abnormalities. The small duplication fragment on 12p in this case involves fewer pathogenic genes and does not constitute tetrasomy, which may explain the normal clinical phenotype observed in this patient.

The genotype-phenotype correlation of sSMC is complex and unclear, and it is generally believed that sSMC derived from family inheritance does not affect the clinical phenotype or has little effect on the clinical phenotype. Based on chromosomal karyotyping, this case was further investigated with CNV-seq testing. This approach not only allowed direct visualization of the sSMC morphology through karyotyping but also compensated for the limitation of karyotype analysis in precise localization via CNV-seq. Additionally, it confirmed that the chromosomal copy number variation in the missed abortion tissue was inherited from the mother. Although the current clinical phenotype of this case suggests that the carried sSMC may have limited correlation with the phenotype, the diagnosis and counseling regarding sSMC require comprehensive evaluation and interpretation by professional genetic experts or physicians. It is recommended that the carrier seek genetic counseling based on her personal and family history and undergo comprehensive maternal and fetal examinations during future pregnancies.

Declaration of Interest:
All authors declare that they have no competing interests.

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