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Case Report

Detection of fetal trisomy 9 mosaicism by noninvasive prenatal testing through maternal plasma DNA sequencing

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ABSTRACT

Objective: Noninvasive prenatal testing (NIPT) is widely used as a powerful screening tool to detect common aneuploidies. However, its application for detection of rare chromosomal abnormalities remains inconclusive.

Case report: A 38-year-old woman (gravida 2, para 0) requested NIPT as a primary screening test for fetal aneuploidies at 13 weeks and 1 day of gestation. An unexpected Trisomy 9 (T9) abnormality was highly suspected. Amniocentesis was arranged for further diagnosis at 18 weeks of gestation. Final karyotyping reported 47,XX,+9 [18]/46,XX [12], indicating 60% T9 mosaicism.

Conclusion: This case shows strong evidence that NIPT can be a powerful screening tool to detect rare fetal trisomies at very early gestation.

Background

Most pregnant women without indication for chorionic villous sampling or amniocentesis receiving prenatal screening for fetal aneuploidies rely on measurement of multiple biochemical markers in maternal serum as well as ultrasound examination of fetal nuchal translucency or biparietal diameter in the first and second trimesters. If fetal chromosomal abnormalities are suspected, chorionic villous sampling or amniocentesis remain the gold standard for prenatal diagnosis and carry little critical risks, such as miscarriage, abortion, and intrauterine infection [1]. Recently, noninvasive prenatal testing (NIPT) by massively parallel sequencing of cell-free DNA in maternal circulation, which contains an average of 10%–20% fetal DNA during the second trimester, has been applied for prenatal aneuploidy screening [2]. The benefit of NIPT is the safe and accurate detection of fetal aneuploidies at early gestation. Based on several large prospective trials [3–6], the general detection rate of trisomy (T) 21, T18, and T13 is >99%, while the false positive and negative rates are 0.1%–0.2%, if the maternal plasma–free fetal DNA fraction is adequate.

According to positive NIPT results, it is strongly suggested to confirm the results by invasive prenatal diagnosis methods, because the fetal DNA tested originated from placental trophoblasts [7]. Nonetheless, NIPT can detect common fetal autosomal aneuploidies, such as T21, T18, and T13, and sex chromosomal aneuploidies, while several other studies have reported the technical potential of NIPT for detecting other chromosomal aneuploidies, mosaicism, and small copy number variations [4–6,8,9]. In addition to identification of these rare genetic conditions, NIPT may also have clinical utility for detection of rare fetal trisomies. Here, we present a rare case of fetal T9 mosaicism that was originally detected by NIPT and confirmed by traditional invasive prenatal diagnosis methods. We also compare this case with other reported cases of T9 mosaicism.

Case report

The patient was a 38-year-old woman (gravida 2, para 0). She had no family history of chromosomal abnormalities or congenital

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Fig. 1. Karyotyping analysis of amniotic fluid cells. Final karyotyping reported 47,XX,+9 [18]/46,XX [12], indicating 60% trisomy 9 mosaicism (red circle).

fetal malformations. There was no sign of spontaneous abortion during early pregnancy. All prenatal laboratory data were within normal range. Because of her advanced maternal age and hesitation for the unavoidable risks of invasive prenatal diagnosis methods, she selected NIPT as a primary screening test for fetal autosomal aneuploidies at 13 weeks and 1 day of gestation after counseling.

Sample preparation, maternal plasma DNA sequencing, and bioinformatics analysis were performed as previously described [10]. Briefly, 5 mL of maternal blood was collected in a Streck tube for sample preparation within 72 h. Cell-free DNA extraction, library construction, and massively parallel sequencing were performed at ISO17025-certified clinical laboratories using BGISEQ-500 platforms (BGI, China). Bioinformatics analysis was carried out using the proprietary algorithm previously reported [10], which uses the binary hypothesis T-score to classify a high-risk sample (T-score > 3 or < −3) or low-risk sample (T-score > −3 or <3). Assessment of all 23 pairs of chromosomes was included in the experimental protocol.

Under the qualification of 7.87% cell-free fetal DNA fraction (3.5% is the least reliable cell-free fetal DNA level), NIPT results showed low risk of T21 (T-score = −1.35), T18 (T-score = −0.59), T13 (T-score = −0.51), T6 (T-score = −1.89), and T22 (T-score = 1.19). Sex chromosomes, including monosomy X (X0), XXY, XXX, and XYY, were also within normal limits. Other deletion syndromes, such as Cri du chat syndrome (5p15deletion), 1p36 deletion syndrome, 2q33.1 deletion syndrome, 16p12.2-p11.2 deletion syndrome, type II DiGeorge syndrome (10p14-p13 deletion), Jacobsen syndrome (11q23 deletion), Prader–Willi/Angelman syndrome (15q11.2 deletion), and Van der Woude syndrome (1q32.2 deletion), were also considered low risk. Aneuploidy of other chromosomes or chromosomal deletions/duplications were not detected. An unexpected T9 abnormality (T-score = 7.16) was highly suspected.

After counseling for the NIPT results, the patient agreed to undergo amniocentesis for further analysis at 18 weeks of gestation. Final karyotyping reported 47,XX,+9 [18]/46,XX [12], indicating 60% T9 mosaicism (Fig. 1). Subsequent confirmation fetal ultrasound showed bilateral low-set ears, micrognathia, clitoromegaly, and partial depletion of the corpus callosum (Fig. 2).

After a complete prenatal survey, a final consultation was given and the couple decided to terminate the pregnancy. Medical termination was performed at 20 weeks and 2 days of gestation. Gross examination of the abortus showed female sex, bilateral low-set ears, micrognathia, and clitoromegaly, compatible with the previous ultrasound (Fig. 3).

Discussion

In 1973, Haslam and colleagues reported the first case of T9 mosaicism, while Feingold and colleagues reported the first example of a child with full T9 using blood lymphocytes in the same

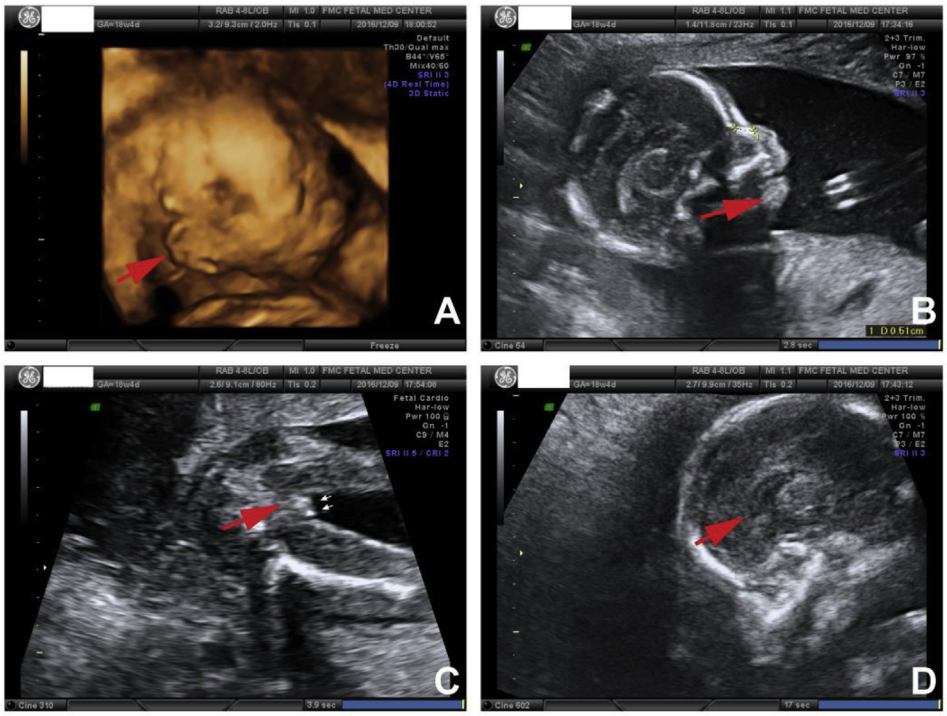

Fig. 2. The *arrow* denotes the site of fetal ultrasound showing bilateral low-set ears (A), micrognathia (B), clitoromegaly (C), and partial depletion of the corpus callosum (D).