The Journal of Obstetrics and Gynecology of India (March–April 2023) 73(2):180–182
https://doi.org/10.1007/s13224-022-01730-y

CASE REPORT

True Fetal Trisomy 22 Detected Using Genome-Wide Noninvasive Prenatal Testing

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Received: 21 March 2022 / Accepted: 30 October 2022 / Published online: 13 January 2023

Introduction

Autosomal aneuploidies occurring in chromosomes other than 13, 18, and 21 and sex chromosomal aneuploidies are referred to as 'Rare autosomal aneuploidies' (RAAs). A prenatal incidence of 0.41% is noted for RAAs on chorionic villus sampling (CVS) procedures. Aneuploidies in autosomes other than 13, 18, and 21 and sex chromosomal aneuploidies may result in increased fetal-placental diseases such as non-viable pregnancy, early miscarriage, intrauterine fetal growth restriction, uniparental disomy, multiple congenital anomalies, fetal demise, or normal live birth [1]. The screen-positive rate of RAAs on NIPT is 0.04% to 0.83%. However, the PPV of RAAs on NIPT is found to be 6–29%. The increased false positives for RAAs on NIPT are most commonly due to confined placental mosaicism (CPM) [2] but may also arise due to vanishing twin or maternal malignancies. Clinically relevant abnormalities can be detected in 30–75% of the high-risk cases of RAAs in NIPT [1].

Trisomy 22 is the second most common aneuploidy found in the product of conceptus samples, after Trisomy 16. Sonographic findings in the first trimester for Trisomy 22 may be insignificant. Most surviving cases of Trisomy 22 will show multiple ultrasound markers only in the second or third trimester. Abnormal prenatal findings of Trisomy 22 may include IUGR, increased nuchal translucency, congenital heart defects, hydrocephaly, hydrothorax, and even cleft lip and palate [1]. Thus, NIPT may be useful in picking such cases early in pregnancy. Here, we describe a case of Trisomy 22 picked up by genome-wide NIPT which was recommended for screening due to high risk in maternal serum screening and abnormal ultrasound findings.

Case Report

A 26-year-old primi gravida, on her antenatal scan at 16 weeks 3 days of gestation, showed unossified nasal bone, mild left axis deviation of the heart, fetal growth, and amniotic fluid was normal, and no other obvious structural defects or soft markers for chromosomal aneuploidies were found. The risk for Trisomy 21 was increased from 1 in 977 to 1 in 149 in the second-trimester screening. NIPT or confirmatory testing by invasive testing (amniocentesis) was suggested and explained to the parents. Following this, the patient opted for NIPT. Ten ml of maternal blood was sent for NIPT to screen for common chromosomal aneuploidies.

A next-generation whole genome sequencing technique NIPT was used for screening common chromosomal aneuploidies. The test revealed a low risk for common chromosomal aneuploidies, i.e., Trisomy 13, 18, 21, and sex chromosomal aneuploidies (XO, XXY, XXX, and XYY), and had a fetal fraction of 17.6% (Table 1). However, the whole genome data revealed a high risk for Trisomy 22. This was conveyed to the clinician. An invasive procedure followed by confirmatory testing was suggested. The patient opted for

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Table 1 Log Likelihood Ratio Scores obtained on fetal cell-free DNA analysis

Condition	Risk status	LLR score (Observed)	LLR score cutoff
Trisomy 21	Low risk	− 87.6199	> 2.5
Trisomy 18	Low risk	− 129.033	> 3
Trisomy 13	Low risk	− 163.626	> 3
Sex chromosomal aneuploidies	Low risk	NA	NA
Trisomy 22	High risk	310.36	> 13.5

Log Likelihood Ratio (LLR) is computed for each sample by considering coverage-based scores and the estimated fetal fraction. The assay assesses the LLR for each target chromosome and each sample to provide a determination of aneuploidy. The values above the cut-off with respective LoD (Fetal fraction cutoff) are considered 'High Risk' and others are categorized as 'Low Risk'

medical termination of pregnancy after the follow-up scan revealed Tetralogy of Fallot along with the unossified nasal bone. The products of conception were analyzed by SNP-based 315 K microarray analysis. Chromosomal microarray analysis revealed ~ 30% mosaic gain of chromosome 22 (34.3 Mb) from 22q11.1 to qter, indicating mosaic trisomy 22 (Fig. 1). The chromosomal microarray result was concordant with the NIPT findings.

Discussion

The prevalence of rare autosomal aneuploidies and structural chromosomal abnormalities across live-born, demised, and terminated pregnancies with fetal abnormalities can be ~ 17%. Thus, it is significant enough to be relevant in prenatal testing. The sensitivity of NIPT to detect mosaic trisomies can be more than CVS because CVS provides a localized sample of the placenta, unlike NIPT consisting of more cells from all over the placenta. Even though in most cases the finding of an RAA in NIPT might be confined to the placenta, such findings may not be harmless to the pregnancy. Benn et al. describe a study in 4,50,000 pregnancies, and it was found that 60% of all RAT findings on NIPT were either confirmed in the fetus, showed abnormal fetal phenotype, or had an adverse pregnancy outcome. Trisomies more commonly associated with a fetal pathology include Trisomy 8, 9, 12, 14, 15, 16, and 22. [1]

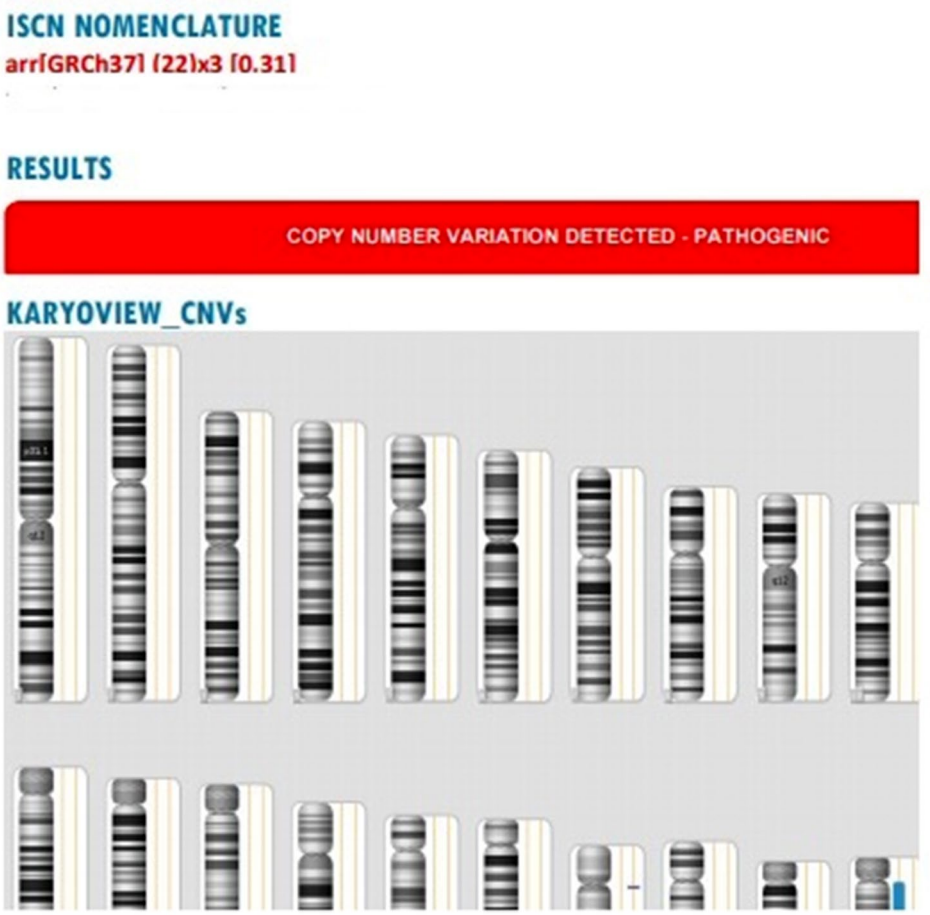

Fig. 1 Microarray analysis on the product of conception revealed 30% mosaic Trisomy 22

The utility of expanded NIPT to predict abnormal pregnancy outcome is more compared to traditional screening methods such as maternal serum screening or ultrasound. Structural abnormalities in the fetus can be detected prenatally in 15–85% of the cases. Fifty percent of the major structural abnormalities can be detected in the first-trimester scan. Some specific structural defects in the fetus are strongly associated with chromosomal aneuploidies.

Multiple abnormalities in second- and third-trimester ultrasound are more prevalent in the case of Trisomy 22. Published case studies of abnormal prenatal ultrasound findings for Trisomy 22 in the first trimester are very few. Though, one reported case describes the presence of cystic hygroma at 10 weeks of gestation and the development of other abnormalities such as cleft lip and ventricular septal defect at 16 weeks of gestation [3]. Also, it is found that pregnancies with a prior higher risk on maternal serum screening tend to show a higher PPV (theoretical PPV of 11–64%) for RAA in NIPT [4]. However, the overall PPV for RAA is still lower than that of other common aneuploidies because of higher chances of CPM, low incidence, and non-viability of true fetal aneuploidies. In our current case, the patient presented with both abnormal findings in ultrasound since the first-trimester scan and increased risk in maternal serum screening.

Despite the low PPV of RAAs on NIPT, more than 60% of Trisomy 22 on NIPT can have an abnormal outcome when confirmed by invasive testing [1]. Postnatal mosaic trisomy 22 has been reported with clinical presentations of dysmorphic features, growth retardation, developmental delay, mental retardation, cardiac abnormalities, ear, and gastrointestinal abnormalities. Though Trisomy 22 is one of the common rare autosomal aneuploidies, due to variable phenotypic expression of mosaic and non-mosaic trisomy 22, genetic counseling for prenatal detection of Trisomy 22 is challenging. Genetic counseling for RAAs in prenatal screening must also include awareness about growth restriction, mosaicism (fetal and confined), and UPD.

Genome-wide NIPT detects a greater number of clinically relevant aneuploidies compared with targeted NIPT which detects only common chromosomal aneuploidies. It was found that 16.3% of pregnancies with abnormal cytogenetic results were missed in targeted NIPT [2]. Non-mosaic rare autosomal aneuploidies may more often end in early miscarriages. However, if an RAA is found in NIPT, it warrants further confirmatory testing such as Karyotype or Chromosomal Microarray that can establish the true status of the fetus. It is also important that appropriate pre and post-test counseling explains the expanded screening, its findings, and its probable outcomes. It can help in the management of the pregnancy outcome as well planning further pregnancies.

Trisomy 22 is one of the common autosomal aneuploidies after Trisomy 13, 18, and 21. This case represents a true positive prenatal detection of trisomy 22 using genome-wide NIPT which suggests that genome-wide NIPT has increased clinical utility by helping in early detection and pregnancy management.

Declarations

Conflict of interest Authors Shweta Mahalingam, Angela Devanboo, Avinash Pradhan, Aswini Suravarapu, Venkataswamy E, Ramprasad V. L., and Priya Kadam are employed with MedGenome Laboratories Private Limited during the course of the project.

Informed consent Informed consent to publish was obtained from the patient included in the study.

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