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Case Report

Detection of 22q11.2 deletion syndrome by single-nucleotide polymorphism based non-invasive prenatal test

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ABSTRACT

Non-invasive prenatal test (NIPT) has become a popular screening test worldwide for screening common trisomies. In addition, the test can also sex chromosomal aneuploidies (SCAs) with similar sensitivity. In recent years, the scope of NIPT has extended to screen pregnancies for clinically significant microdeletions (MDs), rare autosomal aneuploidies, and subchromosomal abnormalities. The clinical utility of NIPT screening beyond trisomies 21,18,13 and SCAs are still being evaluated because of low positive predictive value which in turn leads to an increase in invasive procedures. Here, we present a case where SNP - NIPT correctly identified a microdeletion syndrome, i.e., 22q11.2DS in a pregnant woman with normal ultrasound findings. This NIPT finding was further confirmed in the chromosomal microarray study and FISH.

1. Introduction

The introduction of non-invasive prenatal testing (NIPT) in 2011 has transformed the prenatal screening scenario. The test utilizes cell-free DNA obtained from maternal plasma to screen for common whole chromosomal abnormalities such as Trisomy 21, Trisomy 18 and Trisomy 13 in addition to sex chromosomal aneuploidies (SCAs) such as Turner syndrome (MX), Klinefelter syndrome (XXY), Triple X syndrome (XXX) and Jacobs syndrome (XYY) in the fetus. This superior screening test is the most sensitive for screening these conditions compared to conventional maternal serum screening. Furthermore, international committees such as American College of Medical Genetics and Genomics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) agree that the cell-free DNA based test is the most sensitive and specific screening test that can be offered to pregnant women.[1,2]

Different NIPT methodologies are being used in clinical practice, these include whole genome-based approach or targeted based approach. With further developments, the clinical utility of NIPT is being expanded to screen for other chromosomal conditions such as rare autosomal aneuploidies, microdeletions/microduplications and monogenic disorders. Single nucleotide polymorphisms-based (SNP-based) NIPT is one such targeted NIPT that can screen for clinically significant common microdeletions such as 22q11.2 deletion syndrome, 1p36 deletion syndrome, cri-du-chat, Prader-Willi, and Angelman microdeletion syndromes along with whole chromosomal aneuploidies i.e. common trisomies and SCAs.

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Here, we present a case where SNP based NIPT helped an expectant couple in prenatal diagnosis of 22q11.2 microdeletion syndrome which was then confirmed on FISH and CMA. Further, this case report highlights the importance of the need for an efficient screening technology to screen for such clinically significant common microdeletions.

2. Case Presentation

A 39- year- old expectant mother and her 40- year-old husband, in a non-consanguineous marriage, who previously had one healthy child and a history of two miscarriages (including one for Trisomy 21) was pregnant for the fourth time. Ultrasound reports were indicative of a single, live fetus, with no clinically significant abnormalities. However, through the first-trimester screening (FTS), an estimated risk of 1:67 for Trisomy 13/ 18 was calculated. Due to the high risk, advanced maternal age, and previous history of miscarriages, they were offered NIPT for fetal aneuploidies and select chromosomal microdeletions.

The maternal blood sample was collected at 11 weeks 5 days gestational age and Panorama® SNP based NIPT, of Natera was performed at MedGenome Laboratory Ltd. Panorama® NIPT uses the Next- Generation Aneuploidy Test Using SNPs (NATUS) algorithm to deduce the fetal fraction and provide a personalised risk score.

The first sample did not yield a result due to borderline low fetal fraction. Two weeks later, a redrawn sample of the maternal blood was tested. The risks estimated for the individual whole chromosomal aneuploidies were low. However, a high risk of 1:5 was predicted for DiGeorge syndrome with a fetal fraction of 3.6% (Figure 1). Following this NIPT report, the couple were counselled to undergo confirmatory diagnosis to confirm the NIPT result.

The couple then underwent amniocentesis. Chromosomal karyotyping, Fluorescent in situ hybridization (FISH) and Chromosomal Microarray (CMA) were carried out on the amniotic fluid sample. Chromosomal karyotype revealed a normal karyotype of 44 autosomes and 2 sex chromosomes (Figure 2 A). FISH probes for common aneuploidies and 22q11.2 region were used and an interstitial deletion at 22q11.2 was established with no aneuploidies in chromosomes 13,18,21 and sex chromosomes (Figure 2 B). Additionally, the chromosomal microarray confirmed a 3.1 Mb deletion involving chromosome 22 within 22q11.21 region indicating monosomy of this region (Figure 3). Based on the confirmatory diagnostic results and following appropriate genetic counselling sessions, the woman had requested the clinician for the termination of pregnancy.

3. Discussion

The most common fetal chromosomal abnormalities include whole chromosomal aneuploidies and subchromosomal aneuploidies such as copy number variations (CNVs) less than 10Mb also known as microdeletions/microduplications (Martin K., et al. 2018). Such CNVs may be associated with clinically significant phenotype and can be found in approximately 1% of pregnancies undergoing invasive procedures such as chorionic villus sampling or amniocentesis.[3] Although chromosomal microdeletions/microduplications are rare, combined, they are more prevalent than common trisomies.[4] In addition, their incidence is not associated with advanced maternal age and is more common than Trisomy 21 in women younger than 30 years of age.[4] Among CNVs, the most common microdeletion is 22q11.2 deletion syndrome (22q11.2DS) with a population prevalence of 1 in 3000 to 1 in 6000 live births and several reports suggest a higher prevalence of approximately 1 in 1000.[5] It is also the most common pathogenic CNV to be identified prenatally with an estimated prevalence of 1 in 990 to 1 in 2148.[6]

22q11.2DS is also known as DiGeorge or velocardiofacial syndrome. It is a group of microdeletions located in 22q11.2 region.[7] It is a contiguous gene disorder with autosomal dominant inheritance pattern and mostly occurs de novo.[4,7] About 10% of cases are inherited from a parent who might be mildly affected and can go unrecognized. Despite having complete penetrance, this disorder has high variable expressivity[7] and can remain undiagnosed in about one-third of affected children.[5] 22q11.2DS is characterized by a spectrum of clinical phenotype including congenital heart defects, hypocalcemia, immune deficiency, autism, palate abnormalities, intellectual disabilities, and increased risk of mental disorders in adulthood.[4,5,8]

In prenatal scenarios, ultrasound (USG) abnormalities are quite common in fetuses with 22q11.2DS with cardiac defect being the most common abnormality. Other USG anomalies can also be detected given that 22q11.2DS is a multisystem syndrome. However, the detection rate of 22q11.2DS through USG scans remains low[8] and the USG abnormalities are detected on second trimester scan leading to delayed prenatal diagnosis of the fetus.[7] Given the prevalence, low detection rate and delayed prenatal diagnosis necessitate an efficient screening test that can help the expectant couple make an informed reproductive decision or aid in management at the time of delivery if the couple decides to continue the pregnancy. The current gold standard for detecting 22q11.2DS is chromosomal microarray (CMA), performed on chorionic villus samples or amniotic fluid.[7] Both samples are obtained through invasive procedures which are associated with a small but significant risk of miscarriage.

REPORT SUMMARY

Result	*Fetal Fraction*
High Risk for 22q11.2 deletion syndrome	3.6%

Follow up genetic cosunseling and confirmatory diagnostic testing with microaaray is recommended to further evaluate the findings.

Result Details: Aneuploidies

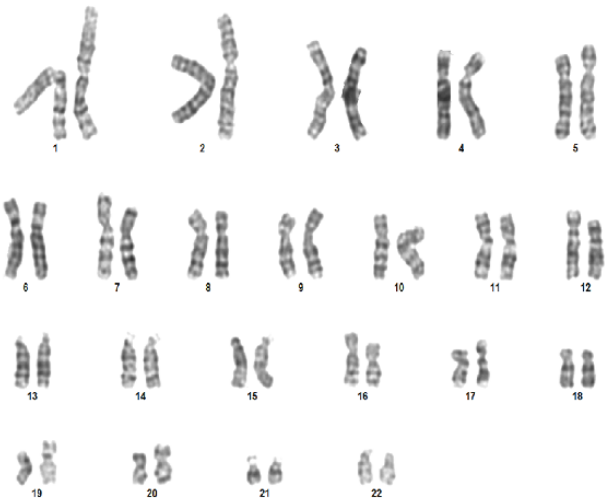
Condition Tested[1]	RESULT	RISK BEFORE TEST[2]	PANORAMA RISK SCORE[3]
TRISOMY 21	Low Risk	1/100	<1/10,000
TRISOMY 18	Low Risk	1/300	<1/10,000
TRISOMY 13	Low Risk	1/922	<1/10,000
MONOSOMY X	Low Risk	1/568	<1/10,000
TRIPLOIDY/VANISHING TWIN	Low Risk		

Result Details: Microdeletions

Condition Tested[1]	RESULT	RISK BEFORE TEST[2]	RISK AFTER TEST
22q11.2 deletion syndrome	High Risk	1/2,000	1/5
1p36 deletion syndrome	Low Risk	1/5,000	1/6,300
Angelman syndrome	Risk unchanged	1/12,000	1/12,000
Cri-du-chat syndrome	Low Risk	1/20,000	1/27,000
Prader-Willi syndrome	Low Risk	1/10,000	1/13,800

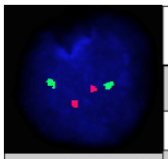
Fig. 1: SNP– based NIPT result was screened as Low risk for common aneuploidies, Monosomy X, Triploidy/Vanishing twin and high risk for 22q11.2DS

A)

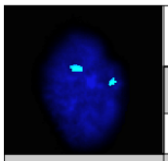


Sex chromosomes not shown as per Pre-conception and Prenatal diagnostic techniques act 2003.

B)

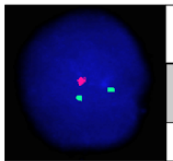


	LSI probe Hydridization		Cells No.	Result
	Green	Orange		
	Chr. 13	Chr. 21	50	Normal
Signals Per cell	Two	Two	50	Normal



	CEP probe Hydridization		Cells No.	Result
	Aqua	Green/Orange		
	Chr. 18	Sex Chr.	50	Normal
Signals Per cell	Two	Two	50	Normal

Sex chromosome signals not shown as per Pre-conception and Prenatal diagnostic techniques act 2003.



	Probe Hydridization		Cells No.	Result
	Green (22q13.3)	Orange (22q11.2)		Interstitial deletion of 22q11.2 region
	22	22	50	
Signals Per cell	2	1	50	

Fig. 2: **A**): Karyotype revealed a normal set of whole chromosomes consistent with NIPT finding; **B**): FISH result revealed interstitial deletion of 22q11.2 region confirming the NIPT result

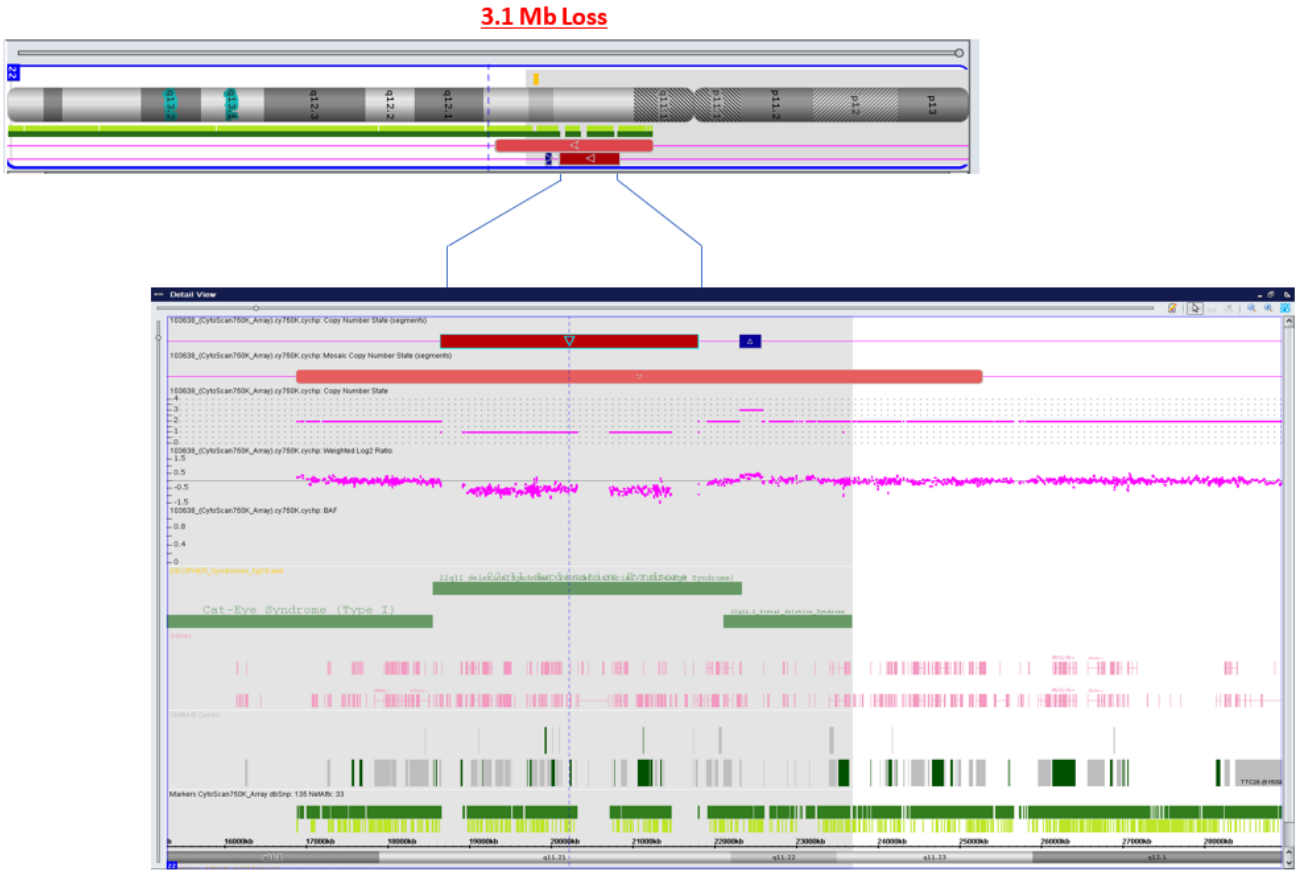


Fig. 3: Chromosomal microarray performed on the amniotic fluid sample detected 3.1Mb loss in the 22q11.2 region and therefore, confirming 22q11.2DS which is consistent with the NIPT result

The superior performance of NIPT has revolutionized the prenatal screening scenario. Due to its high sensitivity and non-invasive nature of the test, NIPT has become a widely adopted screening test to screen for common chromosomal aneuploidies in the fetus. The study by Shi P., et al, 2021 illustrated the utility of expanded NIPT for screening microdeletions/microduplications syndrome. The study reported 27 true positive cases of microdeletion/microduplication syndromes in pregnant women with normal USG scans performed between 11 – 14 weeks of gestation and reported a PPV of 50% in this population.[9] The SNP based NIPT demonstrated a sensitivity of 97.8% and a false positive rate of 0.76% to screen for 22q11.2DS[8] with an updated algorithm positive predictive value of 52.6% was reported.[4] It is critical to offer appropriate pretest and posttest genetic counseling while offering NIPT for screening common microdeletions (MDs). High risk for any of the deletion syndrome should be followed up, investigated further and a thorough evaluation of the pregnancy should be carried out. The counseling sessions should also cover the performance and limitations of the test. The ACOG 2020 guidelines do not recommend using NIPT to screen common microdeletions until further data on clinical validation studies in the average risk population is obtained.[2] However, the latest ACMG 2022 guidelines conditionally recommend that NIPT for screening 22q11.2 deletion syndrome can be offered to all pregnant women.[6]

As seen in the case report, the couple was offered NIPT at an early gestation age (11w 5d) due to the previous history and they could make an informed decision regarding their pregnancy with the help of appropriate guidance in the form of genetic counselling sessions. Thus, this report demonstrates that NIPT can help in the early detection of 22q11.2DS and proper pregnancy management can be offered to the couple in case they decide to further continue the pregnancy.

4. Source of Funding

None.

5. Conflict of Interest

None.

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