A Rare Case of Microduplication on Chromosome 13 Detected as High Risk for Trisomy 13 on NIPT Screening

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J Fetal Med 2023;10:49–51.

Abstract

Noninvasive prenatal testing (NIPT) has revolutionized the screening methods for fetal chromosomal aneuploidies with high utility for aneuploidies for common chromosomes 13,18, 21, X and Y. Trisomy 13 is often associated with major and minor fetal malformations and can be screened by antenatal fetal scan and first- and second-trimester biochemical screening. We describe a case with high risk for trisomy 13 on NIPT, but without any fetal abnormalities on fetal scan. As recommended, follow-up invasive testing of amniotic fluid by chromosomal microarray detected a microduplication on chromosome 13, which has been associated with congenital microcoria. This case demonstrates the high sensitivity and clinical utility of NIPT in detecting rare copy number variations, which can assist families in making informed reproductive decisions. This also emphasizes that all screen positive NIPT cases should be confirmed with an appropriate diagnostic test by an invasive method.

Keywords
- NIPT
- trisomy 13
- chromosomal microarray
- microduplication
- copy number variation
- microcoria

Introduction

Noninvasive prenatal testing (NIPT) was introduced as a screening test for high-risk pregnancies, but has gained popularity and is being introduced in routine prenatal care to screen for fetal aneuploidies as well as microdeletions and duplications. The conventional maternal serum screen (MSS) tests (dual/triple/quadruple markers) along with the fetal ultrasound have an overall aneuploidy detection rate of 65 to 95% depending on the methods used. The detection rate with a combination of markers is high in a high-risk population (50 to 75%), but false-positive rates are also high.[1] Based on the combination of MSS and ultrasound findings, trisomy 13 is often picked up by the end of the second trimester.

Massively parallel sequencing and selective analysis of cell free fetal DNA in maternal plasma has created a huge impact on screening for common aneuploidies with high sensitivity and specificity.[1] NIPT screens for common chromosomal aneuploidies like trisomy 21 (T21), trisomy 18 (T18), trisomy 13 (T13), and sex aneuploidies and can be expanded for other chromosomal aneuploidies and common microdeletion–microduplication syndromes. The NIPT performance showed 100% sensitivity and 99.9% specificity for the detection of T21, 92.9% sensitivity and 100% specificity for T18, and 100% sensitivity and 99.9% specificity for T13. The positive predictive values for T21, T18 and T13 were 98.3, 100, and 90.0%, respectively.[2]

article published online
May 16, 2023

DOI https://doi.org/10.1055/s-0043-57251.
ISSN 2348-1153.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

As per the recommendations of American College of Obstetrics & Gynaecolgy, NIPT is considered a screening test and any high-risk result needs to be validated by a diagnostic test on a prenatal sample obtained by invasive testing.[3]

We present a case that was found to be at high risk for T13 on NIPT, despite the absence of any major or minor fetal findings. Trisomy 13 occurs due to an extra copy of chromosome 13 due to nondisjunction during meiosis. The incidence of T13 is approximately 1 in 5,000 births with a 50% possibility of fetal death before 20 weeks of gestation and 6 to 13% still births.[4] Live-borns with T13 have a poor prognosis and 90% live less than 1 year of age. The typical clinical features include intrauterine growth restriction, microcephaly, facial dysmorphism, cardiac and central nervous system anomalies, and limb defects. Patients surviving past infancy have a severe psychomotor disorder, failure to thrive, intellectual disability, and seizures.[5]

Case Report

A 41-year-old female (G2P1L1) opted for NIPT in view of an advanced maternal age. Her ultrasound reports showed a single intrauterine fetus of 23 weeks of gestation with no abnormal findings. She underwent pretest genetic counseling. Maternal whole blood was collected in a laboratory validated Streck tube. The plasma sample was further processed as per standard laboratory protocol. Low-pass ($\times$0.1 genome coverage) massively parallel sequencing was performed on the NovaSeq platform (5200 Illumina Way [formerly 5200 Research Pl] San Diego, CA, United States). Her NIPT results were indicative of high risk for T13 with a *Z*-score of 5.09 on a fetal fraction 22.91%, and showed low risk for all other 22 chromosomal aneuploidies. In the post-test genetic counseling session, she was informed about the result and was recommended further diagnostic testing. Post an informed consent, invasive prenatal diagnosis (amniocentesis) was opted for. Maternal cell contamination (MCC) was ruled out by quantitative fluorescent polymerase chain reaction technique (3500 ABI Genetic Analyser-8 Capillary). A total of 16 STR markers for chromosome 13, 18, and 21 were used to test for MCC and it also ruled out aneuploidy of chromosome 13. Chromosomal microarray (CMA) was performed on the amniotic fluid (AF-DNA) as per standard protocols on the Affymetrix CytoScan Optima platform that consists of a total of 315,608 probes covering control, copy number (CN), and single-nucleotide polymorphism. The CMA optima analysis using Chromosome Analysis Suite ver.3.0 (ChAs) software detected a duplication of approximately 2.014374Mb on chromosome 13 [ISCN: arr [GRCh37] 13q31.3q32.1 (93798371_95812745) $\times$ 3]. The duplicated region contained 6 OMIM genes [*GPC6* (*604404); *DCT* (*191275); *TGDS* (*616146); *GPR180* (*607787); *SOX21* (*604974); *ABCC4* (*605250)]. This copy number variation (CNV) was reported as a variant of uncertain significance (VOUS) due to lack of adequate literature evidence and lack of phenotype confirmation of the fetus. As per literature, only one case with duplication in this region has been reported with clinical features of isolated microcoria.[6] A post-test genetic counseling session was conducted in conjunction with the referring fetal medicine specialist. The parents decided to continue the pregnancy due to the lack evidence of a severe phenotype. Following-up the pregnancy, a full-term male baby was delivered by lower segment cesarean section with no obvious dysmorphic clinical features. The couple was recommended to undergo a CMA to ascertain if the CNV in the baby is de novo or inherited. The mother was also detected to have the same duplicated region of 13q31.3q32.1 and she had no phenotypic features associated with the condition, indicating that the variant could be benign. However, the couple was counseled to have the baby evaluated by an ophthalmologist at regular intervals for evolution of the phenotype.

Discussion

NIPT has paved the way for prenatal screening with the advantage of being highly sensitive and specific for detecting common chromosomal aneuploidies. Though it can also detect microdeletions and microduplications, it is at a lesser resolution in comparison to CMA.[7] Moreover, like any other screening method, false-negative and false-positive results make it mandatory to do further confirmatory testing by invasive methods and testing fetal samples directly by more validated methods. G-band karyotyping was the standard approach for genetic evaluation of fetus with abnormal ultrasound findings or high-risk biochemical screen. CMA is now recommended as a test of choice to detect aneuploidies or any other significant unbalanced submicroscopic aberrations that cannot be picked by routine karyotyping.

In the current case, NIPT was offered for advanced maternal age, without any fetal abnormalities on ultrasound. A high risk for T13 was reported on NIPT and led to high anxiety and difficult decision making for the fetal medicine specialist as well as the couple. An invasive procedure, followed by a validated diagnostic test confirmed the presence of a CNV in the fetal sample and ruled out any major aneuploidy of T13.

The 13q31.3q32.1 region is associated with an extremely rare autosomal dominant disorder, congenital microcoria (MCOR #OMIM 156600), which causes malformation of irises. The clinical features of the disorder include absence or underdeveloped dilator muscle fibers, pinpoint pupils, iris hypopigmentation, light hypersensitivity and hemeralopia. Juvenile onset glaucoma, astigmatism, and axial myopia are complications associated with MCOR resulting in visual impairment or blindness.[8] Previous literature has majorly reported "microdeletions" in the 13q32 region causing congenital microcoria.[9] Multiple families of this rare disease were reported, with submicroscopic chromosomal rearrangements mapped on the locus at 13q32. It was concluded that the *GPR180* gene, located within the deleted region, encodes a G protein-coupled receptor involved in smooth muscle cells growth and it was concluded that deletions of this gene are the cause of MCOR.[10] There is only one case report, where an 18-month-old girl with nonsyndromic

congenital microcoria was found to have a 289 kb region "microduplication" on chr13q32.1, encompassing 11 genes including GPR180.[6] This patient displayed only microcoria in contrast to the previously reported patients with the microdeletion who presented with MCOR and iridocorneal angle dysgenesis. In the present case, we have reported approximately 2 Mb microduplication on chromosome 13q31.3q32.1 region, encompassing 6 OMIM genes including *GPR180.* It was classified as a VOUS, due to lack of literature evidence (only one case reported) and no confirmatory phenotype (being a fetus). The parents decided to continue the pregnancy after proper counseling about the condition. The case will be followed up to look for any development of the phenotype after birth.

Based on this case, we would like to emphasize the importance of confirming any high-risk NIPT with a diagnostic test before making any irreversible reproductive decision. It is important to receive genetic counseling about the limitations of the test and the significance of performing the invasive confirmatory test to understand the fetus's prognosis in postnatal life.[11] Any VOUS detected in CMA or next-generation sequencing-based testing is an area that still requires a considerable amount of clarification, and parental testing to determine its significance and its clinical correlation with the unborn fetus is crucial before we accept or reject it any significance.

Conclusion

Reproductive decisions based on VOUS should be approached with appropriate nondirective genetic consultation, and parents should be offered the choice of making an informed decision.

Implications for Clinical Practice

Due to lack of guidelines for screening tests for aneuploidy, especially based on newer genomic tests,[12] many times irreversible reproductive decisions are taken by couples. Every high-risk screening test has to be validated by a diagnostic test to confirm the test result. The diagnostic yield of each validation test is also different and an appropriate test has to be chosen. CMA is still recommended as the better testing option for a high-risk NIPT result, but sometimes fluorescence in situ hybridization or conventional karyotyping need to be offered, especially if there is a high positive predictive value shown in NIPT result or fetus has a soft marker or major anomaly on scan. Pre-test and post-test genetic counseling is an important step to help the couple cope with unexpected results especially when the ultrasound scan is normal

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
We acknowledge the family for the patience and support during the entire process of pretest and posttest counseling and providing us a postnatal follow-up.

References

1 Bianchi DW, Parker RL, Wentworth J, et al;CARE Study Group. DNA sequencing versus standard prenatal aneuploidy screening. N Engl J Med 2014;370(09):799–808
2 Lee DE, Kim H, Park J, et al. Clinical validation of non-invasive prenatal testing for fetal common aneuploidies in 1,055 Korean pregnant women: a single center experience. J Korean Med Sci 2019;34(24):e172
3 Screening for Fetal Chromosomal Abnormalities. ACOG Practice Bulletin, Number 226 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics. Society for Maternal-Fetal Medicine Obstet Gynecol. 2020;136(04):e48–e69
4 Goel N, Morris JK, Tucker D, et al. Trisomy 13 and 18-Prevalence and mortality-a multi-registry population based analysis. Am J Med Genet A 2019;179(12):2382–2392
5 Springett A, Wellesley D, Greenlees R, et al. Congenital anomalies associated with trisomy 18 or trisomy 13: a registry-based study in 16 European countries, 2000-2011. Am J Med Genet A 2015; 167A(12):3062–3069
6 Pozza E, Verdin H, Deconinck H, et al. Microcoria due to first duplication of 13q32.1 including the GPR180 gene and maternal mosaicism. Eur J Med Genet 2020;63(05):103918
7 Srinivasan A, Bianchi DW, Huang H, Sehnert AJ, Rava RP. Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. Am J Hum Genet 2013;92(02): 167–176
8 Toulemont PJ, Urvoy M, Coscas G, Lecallonnec A, Cuvilliers AF. Association of congenital microcoria with myopia and glaucoma. A study of 23 patients with congenital microcoria. Ophthalmology 1995;102(02):193–198
9 Angée C, Nedelec B, Erjavec E, Rozet JM, Fares Taie L. Congenital microcoria: clinical features and molecular genetics. Genes (Basel) 2021;12(05):624
10 Fares-Taie L, Gerber S, Tawara A, et al. Submicroscopic deletions at 13q32.1 cause congenital microcoria. Am J Hum Genet 2015;96 (04):631–639
11 Devers PL, Cronister A, Ormond KE, Facio F, Brasington CK, Flodman P. Noninvasive prenatal testing/noninvasive prenatal diagnosis: the position of the National Society of Genetic Counselors. J Genet Couns 2013;22(03):291–295
12 Badeau M, Lindsay C, Blais J, et al. Genomics-based non-invasive prenatal testing for detection of fetal chromosomal aneuploidy in pregnant women. Cochrane Database Syst Rev 2017;11(11): CD011767

