ACOG
Annual Clinical and Scientific Meeting
Seattle, Washington
April 24–27, 2020

Multiple Aneuploidy Pattern Detected by Non-Invasive Prenatal Screening in Successive Pregnancies

Authors: E JARVIS[1], C FELS[1], S PLONKA[2], F LIAO[3], R KLEIN[1], and J WEISBERGER[4]

[1]MyGeneTeam, Miami, Florida, USA; [2]Rosh Maternal Fetal Medicine, New York, New York, USA; [3]Illumina, San Diego, California, USA; [4]BioReference Laboratories, Elmwood Park, New Jersey, USA

WOMEN'S HEALTH genpath an OPKO Health Company

Introduction

In 2011, aneuploidy screening using cell-free DNA (cfDNA) present in maternal blood became clinically available. Non-invasive prenatal screening (NIPS) is now commonly used to screen for trisomies 13, 18, and 21, sex chromosome aneuploidies, and certain microdeletions during pregnancy. Though much research has been done regarding NIPS since its inception, occasionally unexpected results are returned, such as the detection of multiple aneuploidies, which can be difficult to interpret. We present a case where NIPS detected a similar pattern of multiple aneuploidies in sequential pregnancies and review the subsequent work-up that followed.

Case Presentation

A 25 year-old G3P2 patient had NIPS, by massively parallel sequencing (MPS), in her second and third pregnancies that revealed a pattern of multiple aneuploidies. During her second pregnancy, her NIPS result was positive for trisomies 18 and 21. Further bioinformatics review revealed possible partial trisomy 13 and complete trisomies 14 and 20, in addition to the previously reported trisomies. NIPS by MPS repeated at another lab was non-reportable. Verbal explanation from the other lab indicated they were seeing similar data, but there was a lot of noise in addition to soft elevations and depressions. Amniocentesis revealed normal karyotype, microarray, FISH for chromosomes 13, 14q, 18, 20p, 20q, and 21, and chromosome 14 uniparental disomy test results. Maternal karyotype and microarray were normal. The patient had a negative oncology evaluation which included chest, abdominal and pelvic MRIs, breast ultrasound, and maternal chromosomal breakage studies. The patient had an insignificant medical and medication history. The patient delivered a healthy 6 lbs 1 oz female baby by normal spontaneous vaginal delivery (NSVD). The placenta was small for gestational age, but the placental karyotype was normal, 46,XX.

During the patient's third pregnancy (most recent pregnancy), she had blood drawn for NIPS, by MPS, at 12 weeks gestation. The laboratory reported that a similar NIPS pattern to her previous pregnancy was detected, therefore precluding evaluation of fetal aneuploidy screening using this platform. The patient declined the amniocentesis and further fetal aneuploidy screening. The second trimester ultrasound at 15w4d detected fetal hyperechoic bowel, and a subsequent detailed ultrasound at 21w2d gestation was within normal limits and the hyperechoic bowel had resolved. Maternal chromosomal breakage studies were repeated and were normal. The patient also declined additional follow-up with the oncologist.

Since the submission of our abstract, the patient reportedly had a NSVD of a healthy, 7.7 lbs male baby. No postnatal genetic testing was performed on the baby or the placenta.

Pregnancy History

1ST PREGNANCY

Uncomplicated pregnancy, healthy male, currently 6 y.o.

2013

2ND PREGNANCY

Nov – NIPS detects multiple aneuploidy pattern

2017

Nov – Amniocentesis reveals all normal results

2017

Dec – Maternal karyotype, microarray, and oncology evaluation are negative

2017

March – NSVD of 6lb 1oz healthy female with normal placental karyotype

2018

3RD PREGNANCY

May – NIPS reveals pattern similar to previous preganancy

2019

June – Patient declines fetal testing, repeat maternal chromosome breakage studies are normal

2019

July – 21w2d ultrasound is normal and patient declines further testing and evaluation

2019

Dec – NSVD of 7.7lb healthy male with no postnatal genetic testing performed

2019

NIPS Results

CLARITEST NON-INVASIVE PRENATAL TEST W/MICRODELETIONS

CLINICAL INFORMATION

Pregnancy Type: Singleton	Maternal Weight: 111	Gestational Age in Weeks: 18

RESULTS

ANEUPLOIDY DETECTED - see below

Fetal Fraction: 7%	Sex of Fetus: Consistent with Female

CHROMOSOMES	RESULT	INTERPRETATION	PPV
Chromosome 21	ANEUPLOIDY DETECTED	Results consistent with trisomy for chromosome 21	31.9%
Chromosome 18	ANEUPLOIDY DETECTED	Results consistent with trisomy for chromosome 18	5.3%
Chromosome 13	No aneuploidy detected	Results consistent with two copies of chromosome 13	
Sex Chromosomes	No aneuploidy detected	Results consistent with two sex chromosomes	

MICRODELETIONS	RESULT	INTERPRETATION
22q11.2 deletion	No microdeletions detected	Results consistent with no microdeletion detected in the region of interest
15q11.2 deletion	No microdeletions detected	Results consistent with no microdeletion detected in the region of interest
1p36 deletion	No microdeletions detected	Results consistent with no microdeletion detected in the region of interest
4p-/Wolf-Hirschhorn	No microdeletions detected	Results consistent with no microdeletion detected in the region of interest
5p-/Cri du Chat	No microdeletions detected	Results consistent with no microdeletion detected in the region of interest

Comments: Trisomy 18 and trisomy 21 were both detected. This type of double aneuploidies is rare, but may occur. This is a screening test; therefore false positive and false negative results can occur. Results may be reflective of fetal, placental, or maternal conditions. No irreversible clinical decision should be made based on these screening results alone. Clinical correlation is indicated. If definitive diagnosis is desired, chorionic villus sampling or amniocentesis would be necessary, with consideration of prenatal microarray or region specific DNA probes. Genetic counseling is recommended. The fetal fraction (FF) is estimated to be 7%. FF estimation is one component of this algorithm and is combined with other quality metrics to determine the confidence in the results. The FF estimate is not used in isolation to exclude samples. Positive predictive value (PPV) is calculated based on stated performance, maternal and gestational age as provided on the Test Requisition Form (TRF). Other factors may impact the patient specific PPV.

2017 ClariTest NIPS result

2017 Bioinformatic review of data

Findings	Comment
Single trisomy of a test or non-test chromosome	
Full or segmental monosomy of a single chromosome	
Multiple chromosomal aberrations	Possible trisomy of chromosomes 13 (partial), 14, and 20 in addition to the previously reported trisomy of chromosomes 18 and 21.
Other	

CLARITEST NON-INVASIVE PRENATAL SCREEN W/MICRODELETIONS

CLINICAL INFORMATION

Pregnancy Type: Singleton	Maternal Weight: 109	Gestational Age in Weeks: 12

RESULTS

Unable to Report - see below

Fetal Fraction: NA	Sex of Fetus: Not Reported

CHROMOSOMES	RESULT	INTERPRETATION

Comments: The pattern detected in this sample is similar to the one identified in a previous pregnancy from this same patient (105595068) [11/09/17, 09:04 AM], therefore precluding the evaluation of fetal status using this screening platform. Results should be interpreted in the context of available clinical information, and with appropriate follow up, before making any pregnancy management decisions.

2019 ClariTest NIPS result

Conclusion/Implications

NIPS analyzes cfDNA in maternal blood originating from maternal and cytotrophoblast cells. The similar NIPS pattern observed in both of this patient's pregnancies indicates a likely maternal etiology. When multiple aneuploidies are observed by NIPS, possible etiologies include maternal benign tumor or malignancy and fetal, placental or maternal chromosome abnormalities. However, for this patient, subsequent fetal and maternal evaluations were normal. This case highlights that NIPS may yield unexpected results that are not representative of the fetal or maternal karyotypes and an extensive multi-specialty work-up may be recommended in these scenarios.

