751

Uncovering the Complexities of the Placenta: A Case of Trophoblast Mosaicism

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I. Introduction

Noninvasive prenatal testing (NIPT) analyzes cell-free DNA (cfDNA) in maternal blood. DNA fragments contributed by a pregnancy are believed to originate predominantly from placental trophoblasts, the primary source of cells analyzed during a direct preparation from chorionic villus sampling (CVS). The common biological origin of this DNA may reveal differences between the placental and fetal genomes, as well as mosaicism within the placenta itself.

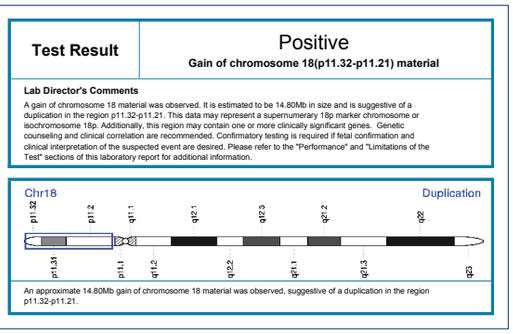
II. Methods

Maternal blood samples submitted to Sequenom Laboratories® for MaterniT® GENOME testing were subjected to DNA extraction, library preparation, and whole-genome massively parallel sequencing as described by Jensen et al.[1] Sequencing data were analyzed using a novel algorithm to detect aneuploidies and other subchromosomal events as described by Lefkowitz et al.[2]

III. Results

A 37 year old patient elected to pursue genome-wide cfDNA testing. Screening was positive for a 14.80Mb gain of material from chromosome 18p, suggestive of a supernumerary 18p marker chromosome or isochromosome 18p. The patient elected to pursue CVS which yielded a positive result for trisomy 18 from FISH analysis, and an abnormal SNP microarray on direct villi showing extra material from 18p, predicted to be present at 39% mosaicism. However, the fetal karyotype, which is obtained from long-term culture of mesenchymal cells, was consistent with a normal male. Amniocentesis returned normal FISH and microarray results.

Figure 1. MaterniT® GENOME report including detailed laboratory director comments and ideogram of event



Test Result	Positive Gain of chromosome 18(p11.32-p11.21) material

Lab Director's Comments

A gain of chromosome 18 material was observed. It is estimated to be 14.80Mb in size and is suggestive of a duplication in the region p11.32-p11.21. This data may represent a supernumerary 18p marker chromosome or isochromosome 18p. Additionally, this region may contain one or more clinically significant genes. Genetic counseling and clinical correlation are recommended. Confirmatory testing is required if fetal confirmation and clinical interpretation of the suspected event are desired. Please refer to the "Performance" and "Limitations of the Test" sections of this laboratory report for additional information.

An approximate 14.80Mb gain of chromosome 18 material was observed, suggestive of a duplication in the region p11.32-p11.21.

Figure 2. Ideogram of chromosome 18 demonstrating overrepresentation of 18p11.32-p11.21

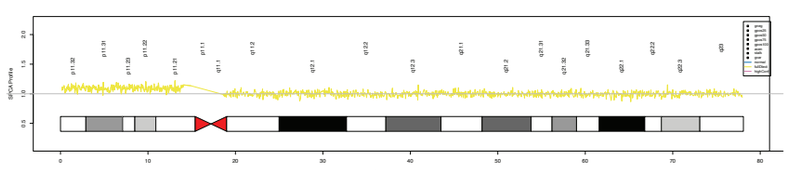


Figure 3. Genome-wide profile from cfDNA sequencing showing overrepresentation of 18p

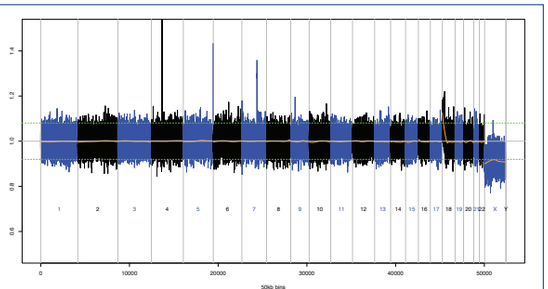


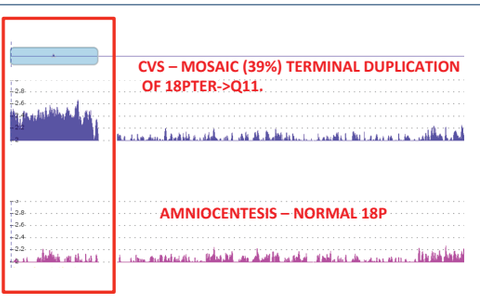
Table 1. Summary of results

	MaterniT® GENOME positive for 14.80Mb gain of 18p
High risk indication	Advanced maternal age
CVS FISH results	Positive for trisomy 18
CVS Microarray results (from direct villi)	Mosaic terminal duplication of 18pter->q11.1
CVS karyotype results (from long-term culture)	46,XY
Amniocentesis FISH & microarray results	Normal male
Ultrasound findings	No major fetal anomalies noted except questionable location of cord insertion
Delivery	41 weeks
Postnatal follow-up	Baby alive and well, no further studies performed
Likely CPM Classification	CPM Type I

Table 2.[3] Summary of different types of mosaicism (confined placental mosaicism and true fetal mosaicism)

Type	Nature	Trophoblast (direct)	Mesenchyme (culture)	Amniocytes
I	CPM	Abnormal	Normal	Normal
II	CPM	Normal	Abnormal	Normal
III	CPM	Abnormal	Abnormal	Normal
IV	TFM	Abnormal	Normal	Abnormal
V	TFM	Normal	Abnormal	Abnormal
VI	TFM	Abnormal	Abnormal	Abnormal

Figure 4. (Upper) Reveal® SNP Microarray results from analysis of direct chorionic villi; (Lower) Reveal® SNP Microarray results from amniocentesis



IV. Conclusions/Implications

This case illustrates how cfDNA testing prompted a diagnostic evaluation that subsequently identified type I confined placental mosaicism (CPM), in which an abnormal cell line is found in the trophoblastic cell layer of the placenta, and presumably absent from the mesenchyme and fetus. This case report adds to a growing body of literature that is redefining the concept of "false positive" or "discordant positive" results from NIPT.

V. References

1. Jensen TJ, Zwiefelhofer T, Tim RC, et al. High-throughput massively parallel sequencing for fetal aneuploidy detection from maternal plasma. *PLoS One* 2013; 8(3):e57381. doi:10.1371/journal.pone.0057381. Epub 2013 Mar 6.
2. Lefkowitz RB, Tynan J, Liu T, et al. Clinical validation of a non-invasive prenatal test for genome-wide detection of fetal copy number variants. *American Journal of Obstetrics & Gynecology*. doi:http://dx.doi.org/10.1016/j. ajog.2016.02.03
3. Adapted from: Grati FR. Chromosomal Mosaicism in Human Feto-Placental Development: Implications for Prenatal Diagnosis. *J. Clin. Med* 2014, 3, 809-837; doi:10.3390/jcm3030809

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