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Telomere capture: An underlying mechanism of copy number variant (CNV) confined placental mosaicism (CPM)

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I. Introduction

Confined placental mosaicism (CPM) is a known and familiar biological limitation of cfDNA screening. With the advent of genome-wide cfDNA screening, there is potential to detect copy number variants (CNVs) that may be confined to the placenta. Complex biological mechanisms, such as telomere capture, may help explain discrepancies between cfDNA findings and diagnostic testing results. Here we describe a case of a fetal concordant 1p36 deletion with apparent CPM of a chromosome 4 duplication, where both findings were detected on cfDNA screening.

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 trisomies, select microdeletions, and genome wide events 7Mb and larger, as described by Lefkowitz et al.[2] Postnatal placental testing was facilitated by the ordering provider and completed by Integrated Genetics.

III. Case Details

A 22yo patient elected to pursue genome-wide cfDNA screening after abnormal serum biochemical screening. MaterniT® GENOME was positive for a 35.04Mb duplication of terminal 4p and a 2.0Mb deletion of terminal 1p, which is associated with 1p36 deletion syndrome. The patient elected to pursue amniocentesis which yielded a 46,XY karyotype and concurrent microarray revealed a 3.40Mb terminal 1p deletion. No chromosome 4 abnormalities were detected. Postnatal placental microarray revealed a 2.93Mb 1p deletion and a mosaic (~51%) 34.90Mb 4p duplication, consistent with the NIPT results.

Table 1. Results summary

	MaterniT®GENOME positive for 35.04Mb gain at 4p16.3-p15.1 and 2.0Mb loss at 1p36.33, associated with 1p36 microdeletion syndrome
Indication	Abnormal serum screening: high AFP with 1:9 ONTD risk
Ultrasound findings	Cerebellar hypoplasia and hypoplastic nasal bone
Amniocentesis	Direct prenatal SNP array revealed a 3.40Mb terminal deletion of 1pter-1p36.32
Postnatal placental testing	Direct SNP array revealed a 2.93Mb terminal deletion of 1pter-1p36.22 and a mosaic (~51%) 34.90Mb terminal duplication of 4pter-p15.1
Maternal studies	46,XX and negative FISH for 1p36

Figure 1. MaterniT® GENOME ideograms of chromosome 1 (*upper*) and chromosome 4 NIPT data (*lower*)

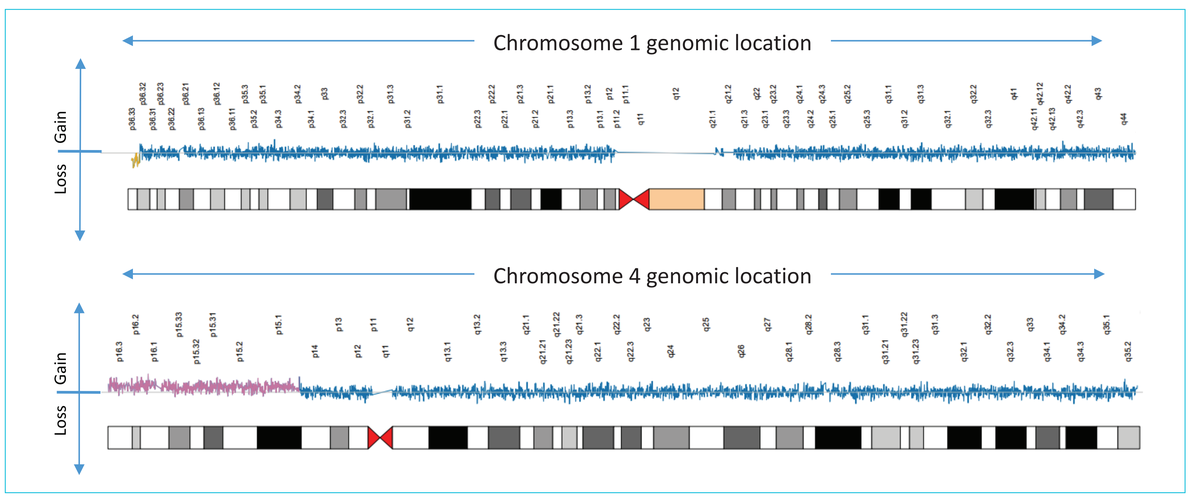
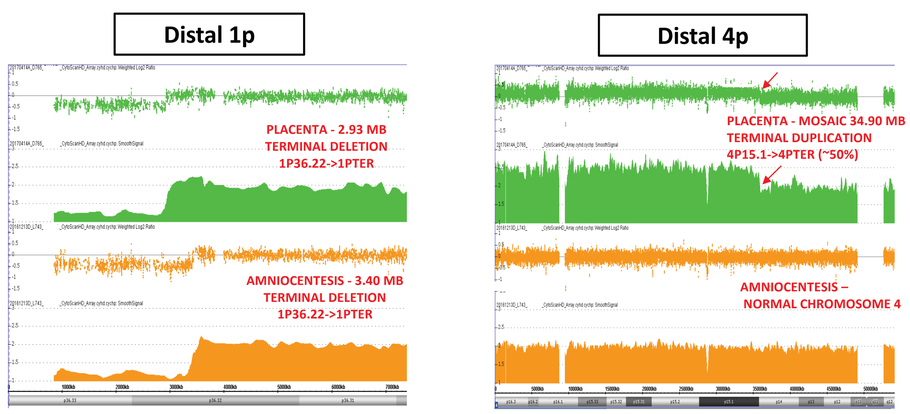


Figure 2. Reveal® SNP Microarray analysis from placental tissue & amniocytes

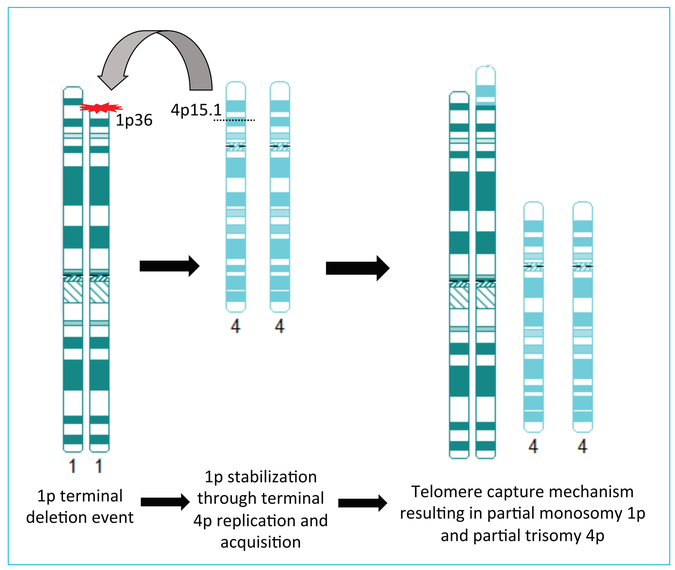
Upper graph in each shows the log2 levels and lower graph shows the real dosage. X axis reflects the distance from the short arm telemeres while the Y axis indicates the copy number target results (set to a range of 1-3 copies).



IV. Discussion

After fetal amniocyte confirmation of the 1p microdeletion but not the larger 4p duplication, placental testing at delivery was performed to evaluate for CPM. The placental studies confirmed the 1p deletion and a 4p mosaic duplication. The likely biological explanation is the molecular phenomenon of telomere capture. Telomere capture is a known mechanism that acts to stabilize an 'open' terminal deletion.[3] We propose that in order to stabilize this 1p deletion, a somatically derived telomere sequence was acquired from another chromosome (in this case, 4p). Base pair erosion likely accounts for the advancing 1p deletion size in amniocytes vs. placenta (3.4Mb vs. 2.93Mb). This erosion can be attributed to instability before the apparent delayed telomere capture (51% mosaicism) and instability following the subsequent loss of the 4p captured segment. The loss of the large 4p segment in amniocytes may have been driven by fetal developmental selection. The somatic nature of this stabilization effort, including intermediate structure formation, suggests mosaicism is likely part of this molecular cascade.

Figure 3. Telomere capture mechanism



V. Conclusion

While CPM is often associated with aneuploidy, CPM of CNVs is possible and may be due to complex mechanisms like telomere capture. Potential for CNV placental mosaicism underscores the need for diagnostic testing and is an important piece of genome-wide cfDNA counseling, especially since the often tissue-specific mosaicism may not be completely confined to the placenta and/or transient developmental effects may already have occurred before follow up testing. In more complicated cases, it is important that detailed cfDNA screening data be made available to diagnostic laboratories to ensure a more complete analysis of clinical results.

VI. 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-ivasive prenatal test for genome-wide detection of fetal copy number variants. *Am J Obstet Gynecol*. doi:http://dx.doi.org/10.1016/j.ajog.2016.02.030.

3. Yu S, Graf WD. Telomere Capture as a Frequent Mechanism for Stabilization of the Terminal Chromosomal Deletion Associated with Inverted Duplication. *Cytogenet Genome Res* 2010; 129:265-274.

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