745

Lessons From the Placental Trophoblast: NIPT Detection of Pallister-Killian Mosaic Syndrome

Samantha Caldwell[1], Theresa Boomer[1], Jenna Wardrop[1], Sidra Boshes[1], Phillip Cacheris[1], Ron McCullough[1]
1. Sequenom Laboratories® 3595 John Hopkins Court, San Diego, CA 92121

Integrated GENETICS
LabCorp Specialty Testing Group
sequenom

I. Introduction

Traditional noninvasive prenatal testing (NIPT) is a valuable screening tool for common aneuploidies. With MaterniT® GENOME, noninvasive detection of additional cytogenetic abnormalities is possible. Pallister-Killian mosaic syndrome is uniquely characterized by the presence of supernumerary isochromosome 12p, i(12p). The tissue specificity and clinical variability of Pallister-Killian mosaic syndrome can make diagnosis challenging. Herein we describe three cases of i(12p) and their NIPT results.

II. Methods

Maternal blood samples submitted to Sequenom Laboratories® for MaterniT® GENOME 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 and sub chromosomal events, and genome wide events 7 MB and larger, as described by Lefkowitz et al.[2]

III. Cases

Case 1:

Indication: congenital diaphragmatic hernia. MaterniT® GENOME result: 34.3Mb gain 12(p11.1-p13.33), as displayed in the ideogram below. Suggestive of 40% mosaicism for 12p (20% i(12p)), established by comparing fetal fraction to the fraction of the observed event. Amniocentesis karyotype confirmed 80% mosaic i(12p) consistent with Pallister-Killian mosaic syndrome.

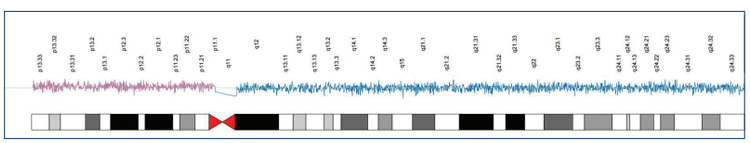
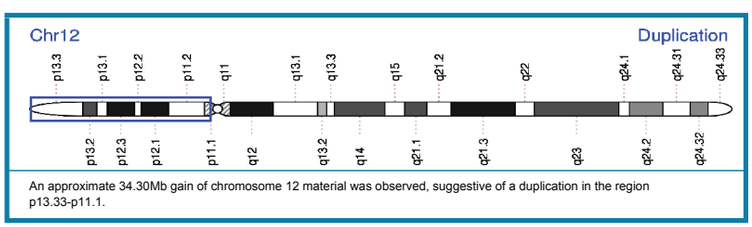


Image 1: Case 1, Chromosome 12 Ideogram

Test Result	Positive **Gain of chromosome 12(p13.33-p11.1) material**

Lab Director's Comments

A gain of chromosome 12 material was observed. It is estimated to be 34.30Mb in size and is suggestive of a duplication in the region p13.33-p11.1. This region has been reported to be involved in Pallister-Killian mosaic syndrome. 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 34.30Mb gain of chromosome 12 material was observed, suggestive of a duplication in the region p13.33-p11.1.

Image 2: Above image represents a MaterniT® GENOME report including detailed comments and ideogram of predicted event.

Case 2:

Indication: AMA; 6mm NT. MaterniT® GENOME result: 33.9Mb gain 12(p11.1-p13.33), as displayed in the ideogram below. Suggestive of 65% mosaicism for 12p (32.5% i(12p)), established by comparing fetal fraction to the fraction of the observed event. Amniocentesis karyotype and microarray confirmed 75% mosaic i(12p) consistent with Pallister-Killian mosaic syndrome.

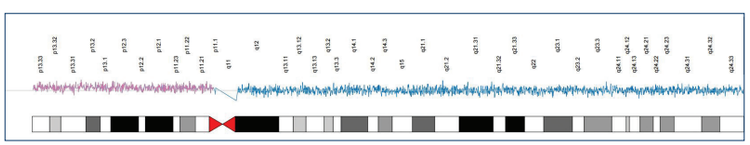


Image 3: Case 2, Chromosome 12 Ideogram

Case 3:

Indication: congenital diaphragmatic hernia, club foot, increased nuchal fold. MaterniT® GENOME result: 34.3Mb gain 12(p11.1-p13.33), as displayed in the ideograms below. Suggestive of 64% mosaicism for 12p (32% i(12p)), established by comparing fetal fraction to the fraction of the observed event. Amniocentesis karyotype and microarray confirmed 80% mosaic i(12p) consistent with Pallister-Killian mosaic syndrome.

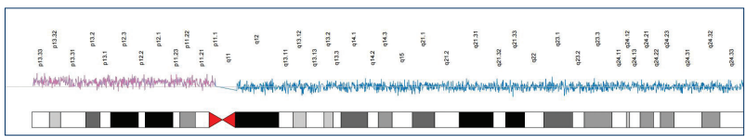


Image 4: Case 3, Chromosome 12 Ideogram

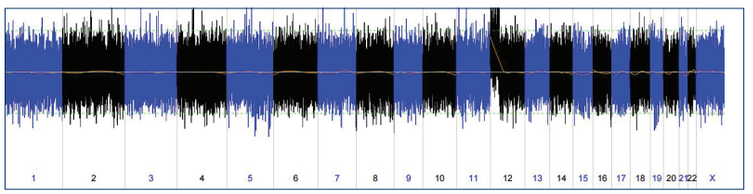


Image 5: Case 3, Full genome profile view of 12p duplication, suggestive of iso(12p)

IV. Conclusion

MaterniT® GENOME is uniquely positioned to report esoteric abnormalities ≥7Mb, including gains of 12p, which may suggest i(12p). This *de novo* isochromosome is more commonly observed in advanced maternal age pregnancies, resulting from maternal meiotic errors with subsequent i(12p) retention or loss. The mosaic nature of the syndrome poses a challenge for both screening and diagnostic testing, as the mosaicism can be highly variable and tissue dependent. The ability of NIPT to view the placental (trophoblast) genome may capture the early formation of a *de novo* i(12p) abnormality.

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. Leftkowitz 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.2016.02.030

LabCorp