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The many faces of monosomy X: Unexpected outcomes of monosomy X NIPT results

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I. Introduction

Since the introduction of NIPT, use of circulating cell free DNA (cfDNA) testing has become an important resource to evaluate pregnancies for common autosomal and sex chromosome aneuploidies (SCAs). Mosaicism and/or sex chromosome structural abnormalities can complicate counseling of positive SCA results, particularly when clinical or diagnostic findings contradict the NIPT result. Here we describe ten cases of monosomy X NIPT results and their unexpected, yet biologically reasoned, outcomes.

II. Methods

Maternal blood samples submitted to Sequenom® Laboratories for MaterniT21® PLUS or MaterniT® GENOME testing were subjected to DNA extraction, library preparation, and whole genome massively parallel sequencing as described by Jensen et al and Lefkowitz et al. [1-2] Outcome information was elicited from or supplied by the clinical provider(s) via phone or email.

III. Results

Table 1: Unexpected Outcomes of Monosomy X NIPT Results

Case	NIPT Result	Fetal sex by ultrasound	Diagnostic Testing	Diagnostic Testing Result	Proposed Biologic Mechanism
1	Initial result: Monosomy X Redraw result: Monosomy X	Male	Amniocentesis	50% 45,X/50% 46,XY	Fetal mosaicism with co-segregating XY cell line
2	Monosomy X	Female	CVS	72% 47,XXX/27% 45,X	Placental mosaicism with co segregating aneuploid cell line
3	Monosomy X	Female	Amniocentesis	45,X/47,XXX	Fetal mosaicism with co segregating aneuploid cell line
4	Monosomy X	Female	Postnatal	45,X[10]/46,XX[5]/46,X,r(X)[5]	Fetal mosaicism secondary to ring chromosome
5	Monosomy X (Image 1)	Female	CVS & Amniocentesis	47,XXX	Skewed mosaicism with co-segregating aneuploid cell line
6	Monosomy X (suspected maternal; unable to discern fetal SCA)	Female	Maternal	45,X[8]/46,XX[42]	Maternal mosaicism
7	Monosomy X (suspected maternal; unable to discern fetal SCA) (Image 2)	Female	Maternal & Postnatal	Maternal Karyotype: 45,X[9]/46,XX[11] Postnatal FISH: 45,X[20/400] Postnatal karyotype: 46,XX.nuc ish(DXZ1x1)[20/400]	Maternal and fetal mosaicism
8	Monosomy X	Female	Amniocentesis	46,X,del(X)(p22.2) [30]; FISH probe showed absence of Xp	Fetal mosaicism secondary to structural X abnormality
9	Monosomy X	Female	CVS & Amniocentesis	CVS FISH: 45,X[67]/46,XX[33] Amnio FISH: 46,XX[50] Amnio SNP array: 46,XX female with uniparental isodisomy X	Monosomy rescue resulting in isodisomy X
10	Monosomy X (Image 3)	Male	Amniocentesis	46,X,i(Yp)[9]/45,X[6]	Fetal mosaicism secondary to structural Y abnormality

Images 1-3. In the sex chromosome aneuploidy (SCA) plots below, the X and Y axis represent the X and Y chromosome Z-scores, respectively.

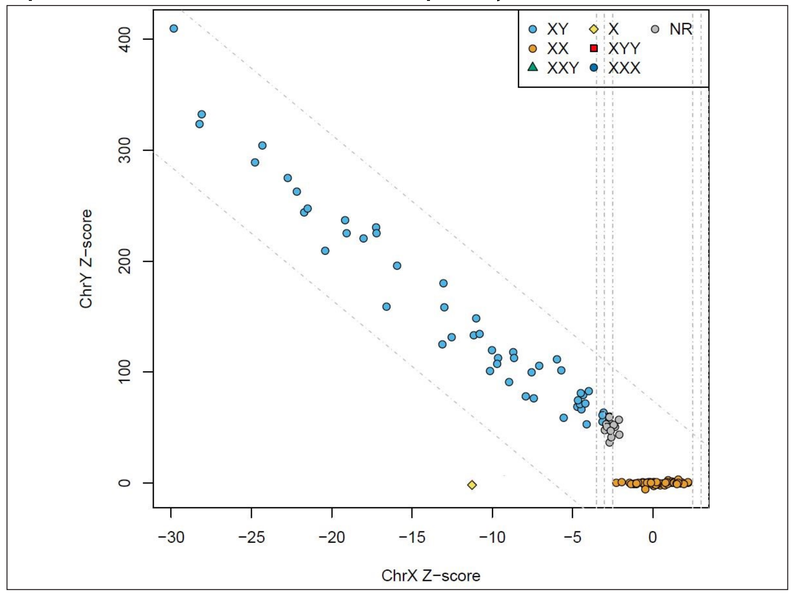

Image 1: SCA Plot - Case 5.

NIPT Result: Monosomy X

CVS & Amniocentesis Result: 47,XXX

Yellow diamond in SCA plot (left) represents this sample's X and Y chromosome data. The negative X chromosome Z-score signifies the underrepresentation of chromosome X, suggestive of monosomy X, namely in the placental trophoblast.

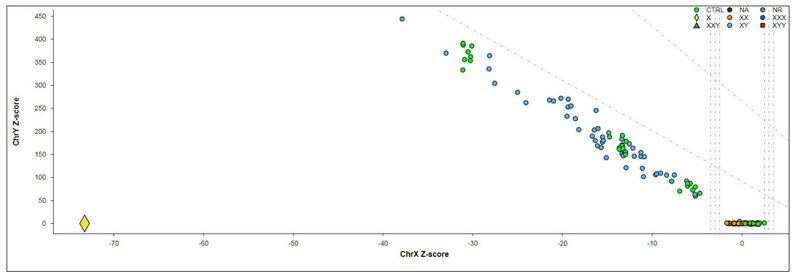

Image 2: SCA Plot – Case 7.

NIPT Result: Monosomy X (suspected maternal; unable to discern fetal SCA)

Maternal & postnatal testing: Maternal and fetal XO/XX mosaicism

Yellow diamond in the far left corner of SCA plot (left) represents this sample's X and Y chromosome data. Note the dramatic underrepresentation of chromosome X, suggestive of maternal involvement.

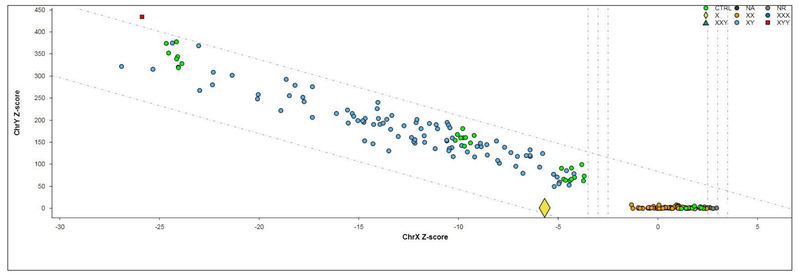

Image 3: SCA Plot – Case 10.

NIPT Result: Monosomy X

Amniocentesis Result: 46,X,i(Yp)[9]/45,X[6]

Yellow diamond in SCA plot (left) represents this sample's X and Y chromosome data. The negative X chromosome Z-score signifies the underrepresentation of chromosome X, suggestive of monosomy X. The sample's position relative to the Y axis illustrates the lack of Y chromosome signal, presumably due to skewed XO/i(Yp) mosaicism in the placental trophoblast.

IV. Conclusion

Monosomy X can be accompanied by a variety of co-segregating cell lines. This cytogenetic complexity coupled with placental tolerance of XO cell lines may lead to unexpected outcomes following a monosomy X NIPT result. As illustrated in the above cases, co-segregating euploid or aneuploid cell lines, placental, fetal, and/or maternal mosaicism, isodisomy X, and structural X and/or Y abnormalities such as isochromosomes, rings or segmental deletions, are all unique but possible outcomes following a monosomy X result. These unexpected outcomes underscore the importance of clinical correlation, diagnostic testing, and consideration of a broader clinical differential.

V. References

1. Jensen TJ1, 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.2016.02.030

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