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Where there's a Y there's a way: Monosomy X by NIPS but male by ultrasound

Jordan D Willbur[1], Samantha Caldwell[2], Sharon Molinari[1], Laura Kline[1], Deanna Hutchinson[1], Michelle Garcia[1]
[1]Labcorp Genetics and Women's Health, Laboratory Corporation of America®, Morrisville, NC; [2]Labcorp Genetics and Women's Health, Laboratory Corporation of America®, La Jolla, CA

I. Introduction

IMPORTANCE: Non-invasive prenatal screening (NIPS) analyzes placental cytotrophoblast DNA fragments which serve as a proxy for fetal status. Consequently, there can be discrepancies between NIPS results and true fetal involvement, particularly when mosaicism is present. Given the placental tolerance for monosomy X (XO) cell lines and XO's proclivity for co-segregating cell lines, this is especially poignant for monosomy X results by NIPS. As this testing is offered more frequently, it becomes increasingly necessary to understand some of the limitations of testing and possible fetal outcomes.

OBJECTIVE: In this case series we describe fetal outcomes and genetic counseling implications when fetal sex via ultrasound is male but NIPS resulted positive for monosomy X.

II. Methods

Maternal blood samples submitted to Sequenom Laboratories® for MaterniT® 21 PLUS or MaterniT® GENOME testing were subjected to DNA extraction, library preparation, and whole genome massively parallel sequencing as described by Jensen et al. (2013) and Lefkowitz et al. (2016). For the purposes of this study, internal databases were searched for samples with monosomy X data by NIPS and with reported fetal sex discrepancies and/or Y chromosome detection upon confirmatory testing. Only those samples with internal diagnostic cytogenetic testing were selected for further characterization.

III. Results

Table 1. Fetal diagnostic testing result and Y chromosome categorization after monosomy X NIPS and unknown or male fetal sex

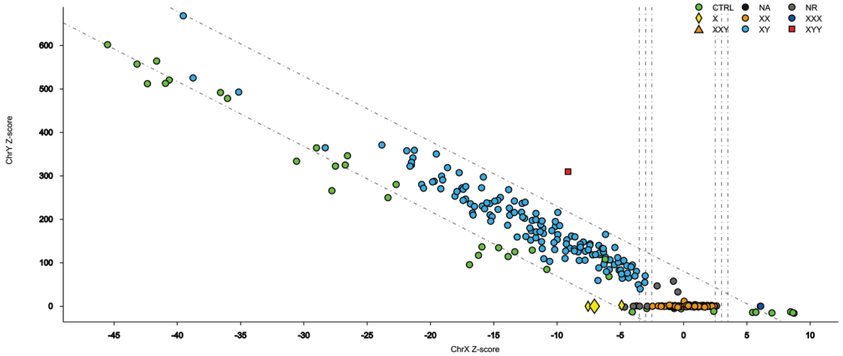
Fifteen samples were identified that were reported as monosomy X on NIPS but were identified to be consistent with male fetal sex by ultrasound and/or had a Y cell line upon diagnostic testing at Labcorp/Integrated Genetics. Five categories of fetal outcomes were established based on this case series: mosaicism for monosomy X and isodicentric Y (n=7, 47%); an isodicentric Y (n=2, 13%); mosaicism for monosomy X and isoY (n=2, 13%); mosaicism for monosomy X and XY (n=2, 13%); or normal male results (n=2, 13%).

Case #	NIPS Result	Fetal Sex by Ultrasound	Specimen Type	Cytogenetic Testing	Diagnostic Result	Y Categorization
1	Neg female*	Male	Amnio	Chromosomes	46,X,idic(Y)(q11.22)[10]/45,X[6]	Mosaic Idic(Y) and XO
2	Neg female*	Male	Blood Blood	Chromosomes Array	45,X[8]/46,X,idic(Y)(q11.23) Yp11.32q11.223(168,547-24,985,261)x1.5, Yq11.223q12(24,985,261-40,257,388)x0	Mosaic Idic(Y) and XO
3	XO	Male	Amnio	Chromosomes	46,X,idic(Y)(p10)dn[4]/45,X[11]	Mosaic Idic(Y) and XO
4	XO	Male/ambiguous	Amnio Amnio	Chromosomes Array	45,X[11]/46,X,idic(Y)(q11.2)[4] Yp11.33q11.222(168,546-22,046,161)x0~2, Yq11.222q12(22,046,161-59,373,565)x0	Mosaic Idic(Y) and XO
5	XO	Male	Amnio	Chromosomes	45,X[8]/46,X,idic(Y)(q11.21)[16]	Mosaic Idic(Y) and XO
6	XO	Male	Amnio Amnio	Chromosomes Array	45,X[24]/46,X,idic(Y)(q11.21)[3] Yp11.31q11.221(2650140-17789297)x0~2, Yq11.221q12(17789610-59373566)x0	Mosaic Idic(Y) and XO
7	XO	Male	CVS Amnio Amnio	Chromosomes Chromosomes/FISH Array	45,X[37]/46,X,+mar[3] 46,X,idic(Y)(q11.22).ish idic(Y)(SRY++,DYZ3++,DYZ1-) Yp11.31q11.222(0-20,608,555)x1~2, Yq11.222q11.23(20,609,789-59,373,565)x0	Mosaic Idic(Y) and XO
8	XO	Male	Amnio Amnio	Chromosomes Array	46,X,?idic(Y)(q11.2),inv(9)(p12q13) Yp11.31q11.21(2,650,140-14,353,576)x2, Yq11.21q12(14,353,576-57,772,954)x0	Idic(Y)
9	XO	Male	Amnio Amnio cult	Chromosomes/FISH Array	46,X, idic(Y)(q11.21).ish idic(Y)(q11.21)(SRY++,DYZ3++,DYZ1-) Yp11.32q11.221(1-18,263,893)x2, Yq11.221q12(18,263,894-59,373,566)x0	Idic(Y)
10	XO	Unknown	Amnio	Chromosomes	45,X[10]/46,X,isoYq10 [5]	Mosaic isoY and XO
11	XO	Male	Amnio Amnio	Chromosomes Array	46,X,i(Y)(p10)[9]/45,X[6] Yp11.32q11.221(238,479-19,567,237)x0~2, Yq11.221q11.222(19,567,237-20,609,709)x0~1, Yq11.222q12(20,609,709-59,373,937)x0	Mosaic isoY and XO
12	XO	Unknown	Amnio Amnio	Chromosomes Array	45,X arr (1-22)x2,(X)x1,(Y)x0~1	Mosaic XY and XO
13	XO	Male	Amnio Amnio cult	Chromosomes Array	45,X[7]/46,XY[9] arr (1-22)x2,(X)x1,(Y)x0~1	Mosaic XY and XO
14	XO	Male	Amnio Amnio	Chromosomes Array	46,XY arr(1-22)x2,(XY)x1	Normal male
15	XO	Male	Amnio Amnio	Chromosomes Array	46,XY arr(1-22)x2,(XY)x1	Normal male

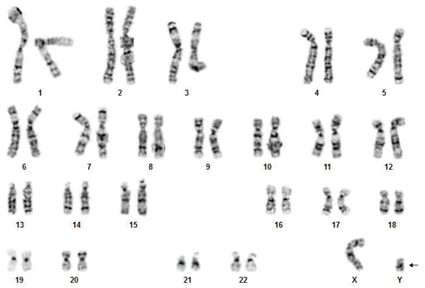
* sample was reported prior to the laboratory reporting SCA

Figure 1. Case 7 NIPS and cytogenetic images

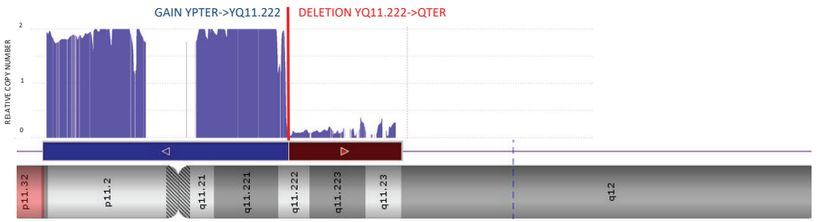
A. NIPS sex chromosome aneuploidy plot. The X and Y axis represent the X and Y chromosome Z-scores, respectively. The enlarged yellow diamond represents X and Y data specific to this sample. The negative X chromosome Z-score indicates underrepresentation of the X chromosome, suggestive of monosomy X.



B. Karyotype. Cytogenetic analysis of cultured amniocytes shows an isodicentric Y chromosome in 22 metaphase cells from seven colonies in one primary and one trypsinized culture.



C. Microarray data and ideogram. SNP microarray analysis was performed using the Affymetrix Cytoscan™ HD platform and detected a non-mosaic terminal Yq deletion and a mosaic terminal gain of Yp and proximal Yq, consistent with an isodicentric Y chromosome. Copy number is indicated on the left side of the figure, with the purple regions showing the amount of chromosome material present. The blue bar on the corresponding Y-chromosome ideogram indicates a gain of chromosome material while the red bar indicates a loss of material. The microarray analysis does not have markers on distal Yq. The idic(Y) is consistent with the chromosome structure in the G-banded chromosome study.



IV. Conclusions

The cases described here display the importance of clinical correlation and confirmatory diagnostic testing following a positive monosomy X NIPS result, as monosomy X can be accompanied by a variety of co-segregating cell lines and placental cytotrophoblast representation of those cells lines may be skewed. In 73% (11/15) of the cases diagnostic testing confirmed mosaicism for the NIPS-reported sex chromosome aneuploidy (SCA). Similarly, 11/15 cases had a structurally abnormal Y cell line, which are inherently unstable and prone to mosaicism. The NIPS result, phenotypic fetal sex, and diagnostic testing results will be dependent on mosaic load, tissue distribution, and genes present in the abnormal Y chromosome. Explaining possible discrepancies between NIPS and fetal sex on ultrasound is a point that should be discussed in a genetic counseling session.

V. References

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