1934

Prenatal diagnosis of mosaic 45,X/46,X,idic(Y) after discordant findings from cell free DNA and prenatal ultrasound: A case series

Lauren Petrarca, Karyn Schmeidler, Samantha Caldwell
Integrated Genetics, Laboratory Corporation of America®, Philadelphia, PA

I. Introduction

The mosaic karyotype of 46,X,idic(Y)/45,X is associated with a highly variable phenotype. This can range from a Turner syndrome-like female appearance, to ambiguous genitalia, to an infertile male phenotype.[1] This case series illustrates the variability with three examples of this karyotype identified through prenatal diagnosis following apparently discordant or abnormal cell free DNA (cfDNA) results.

Table 1: Summary of Cases

CASE	INDICATION	NIPT	CVS	AMNIO	KARYOTYPE	MICROARRAY	ULTRASOUND
1	NIPT positive Turner syndrome	45,X	Yes	Yes	46,X,idic(Y)/45,X: CVS and amnio	Not performed	Female
2	NIPT positive Turner syndrome	45,X	Yes	Yes	45, X: CVS 46,X,idic(Y): amnio	46,X,idic(Y)/45,X: amnio only	Female
3	Discordant NIPT/ultrasound	Normal female	No	Yes	46,X, idic(Y)/45,X	Concordant with karyotype	Male

II. Methods and Results

Cases 1 and 2 (Table 1) both involve 41-year-old patients who were referred for prenatal genetic counseling following cfDNA results screen positive for 45,X. Both patients elected CVS procedures with fluorescent *in situ* hybridization (FISH) for chromosomes 13,18, 21, X,Y and karyotype analysis. Both patients had uninformative FISH results reportedly due to suspected fetal mosaicism. The karyotype for the first patient (P1) was: 46,X,idic(Y)(q11.21)[17]/45,X[3]. The karyotype for the second patient (P2) was: 45,X. Given the possibility of confined placental mosaicism, both patients elected to have amniocentesis with karyotype and P2 also elected fetal microarray analysis. Fetal sonograms at the time of amniocentesis revealed normal female genitalia (P1) and normal male genitalia (P2). The karyotype for P1 revealed: 46,X,idic(Y)[3]/45,X[34]. For P2, the karyotype revealed 46,X,idic(Y)(q11.21) in all cells while subsequent microarray analysis revealed 46,X,idic(Y)/45,X mosaicism (estimated 80% idic Y and 20% 45, X).

Case 3 (Table 1) involved a 33-year-old patient (P3), who presented with discordant sex results between cfDNA and fetal sonogram. The patient's cfDNA result was consistent with a normal female while an anatomy ultrasound at 16 weeks revealed normal male genitalia. P3 elected amniocentesis with karyotype and microarray analysis. Karyotype revealed: 46,X,idic(Y)(q11.21)[9]/45,X[6] and microarray analysis also showed mosaicism (estimated 80% idic Y and 20% 45,X).

III. Discussion

These three cases confirm the value of prenatal diagnosis following abnormal sex chromosome cfDNA results and in situations in which there is discordance between the expected sex based on the cfDNA result versus the fetal ultrasound genitalia phenotype. **Case 1** showed normal female genitalia on ultrasound and this case showed a majority of cells (~92% by amniotic fluid karyotype analysis) were 45,X cells.

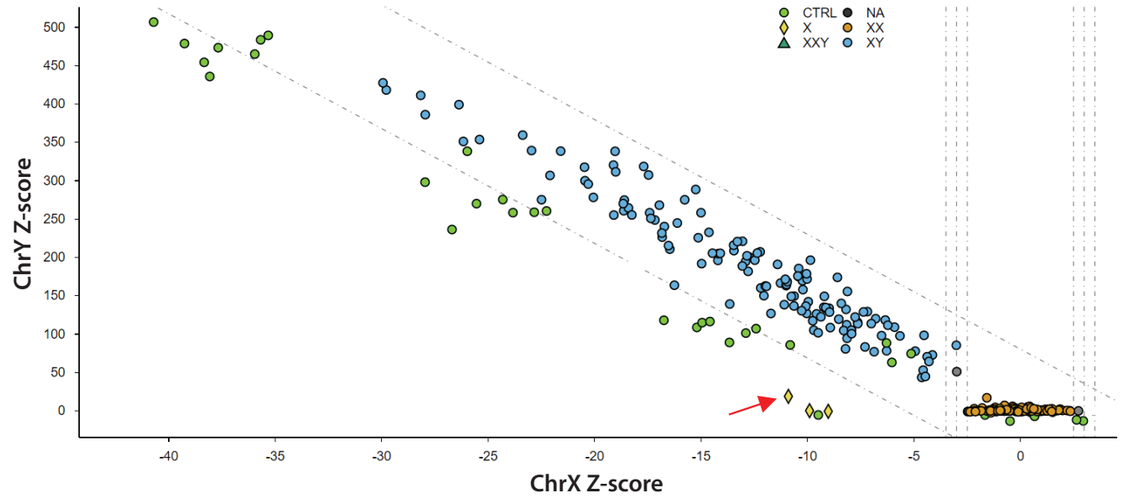
Cases 2 and 3 showed normal male genitalia on ultrasound and in these cases a majority of cells (80% by amniotic fluid microarray analysis) were idic Y. These three cases show a correlation between mosaic cell ratio and sexual phenotype. This information may be helpful for genetic counselors when counseling patients with complex sex chromosome abnormalities.

IV. Conclusions

The difficulty with prenatal prediction of phenotype presented a significant genetic counseling challenge given the wide range of outcomes associated with the isodicentric Y karyotype. After multiple discussions with the genetic counselor, pediatric geneticists, and maternal fetal medicine specialists; all three patients in this series elected pregnancy termination. Although this karyotype is not novel, these cases may be identified more frequently in the future due to increased cfDNA testing. Patients face difficult decisions due to the limited resources and data regarding outcomes from prenatally diagnosed individuals with this karyotype.

Figure 1. cfDNA Data for Case 2

P2's cfDNA data is denoted by the arrow, with the negative X chromosome Z-score (–11) signifying underrepresentation of chromosome X, suggestive of monosomy X. Additionally, P2's sample is slightly elevated up the Y axis indicating the presence of slight Y chromosome signal, not meeting the threshold for male sex reporting.



V. References

1. Kelly TE, Franko JB, Rogol A, Golden WL. Discordant phenotypes and 45,X/46,X,idic(Y). *J Med Genet.* 1998; 35(10):862-864.

Integrated Genetics is a brand used by Esoterix Genetic Laboratories, LLC, a wholly owned subsidiary of Laboratory Corporation of America® Holdings.
Poster presented at the 39th NSGC Virtual Annual Conference, 2020 November 18-22.