Isodicentric Y chromosome karyotypes identified following positive prenatal noninvasive cell-free DNA screening results: A case series

Kailey Owens, MS, CGC; Tessa Niemchak, MS, CGC; Nicole Truitt, MS, CGC; Thomas Monroe, PhD

Progenity, Inc. Ann Arbor, Michigan, United States

progenity®
Prepare for life.

Introduction

Genetic counseling for monosomy X (MX) results from prenatal noninvasive cell-free DNA screening can be challenging due to the possibility of placental, fetal, or maternal mosaicism. Around 5% of individuals with MX are mosaic for a cell line with a Y chromosome, most often isodicentric Y (idic(Y)).[1,2] The phenotype of MX/idic(Y) is highly variable. Here we review the literature on MX/idic(Y) and present 3 cases with NIPT results indicative of MX and diagnostic testing results of idic(Y) with or without mosaicism for a MX cell line.

Between 40-60% of MX cases have identifiable mosaicism for another cell line, with 5% of all cases having mosaicism for a cell line with a Y chromosome.[1] Idic(Y) is the most common structural abnormality of the Y chromosome.[2] Since dicentric chromosomes are unstable, >95% of idic(Y) cases have mosaicism for a MX cell line.[3]

The genotype and phenotype of MX/idic(Y) cases is highly variable (Table 1). In particular, genital and gonadal development is on a spectrum and does not strongly correlate with the level of idic(Y) mosaicism in blood, although it may correlate with the level of mosaicism in gonadal tissue.[2,4] Cases of MX/idic(Y) are at increased risk for hypospadias and gonadoblastoma.[1,3,5-6] It is recommended that MX cases with mosaicism for any Y chromosome material undergo gonadectomy.[5-6]

TABLE 1: LITERATURE REVIEW OF ISODICENTRIC Y CHROMOSOME CASES

Publication	Number of people studied with genotype	Identifiable 45,X cell line	Phenotypic sex			Gonadoblastoma	Other Features
			Male	Female	Ambiguous Genitalia		
Hsu 1994[3]	74 people with idic(Yp)	73/74	20	37	17	4/74 (1 male, 3 females)	Features of Turner syndrome (in 3 males, 14 females, and 4 with ambiguous genitalia)
	44 people with idic(Yq)	42/44	14	18	12	4/44 (2 females, 2 with ambiguous genitalia)	Features of Turner syndrome (in 3 males, 3 females, and 1 with ambiguous genitalia)
DesGroseilliers 2006[2]	9 people with idic(Y)	6/9	3 (the 3 w/o 45,X line)	5	1	4/6 (only those with 45,X cell line evaluated)	Features of Turner syndrome (in 4/5 females and 1 with ambiguous genitalia)
Bruyere 2006[7]	12 people with idic(Yp)	12/12	11	0	1	Not reported	Short stature

Case Series

Progenity performs noninvasive cell-free DNA screening for chromosomal aneuploidy, and attempts to collect clinical outcome data, consistent with good quality assurance practices. Clinical outcome data is collected for cases classified as “Aneuploidy Detected” and “Aneuploidy Suspected” through a follow-up form sent to the ordering provider eight weeks after sample submission. Information regarding ultrasound findings, diagnostic testing, and pregnancy outcome is requested.

The case series presented here includes three cases of “Aneuploidy Detected” MX for which outcome data was received indicating that follow up diagnostic testing was pursued and revealed an idic(Y) cell line.

TABLE 2: CLINICAL CHARACTERISTICS OF THIS CASE SERIES

Case	Indication	GA	NIPT result	Diagnostic test	Diagnostic result	Genitalia on Ultrasound
1	Advanced maternal age	12w3d	MX	Karyotype	46,X,idic(Y)	Normal male
2	Routine screening	12w4d	MX	FISH and Karyotype	FISH: 72 cells XY, 28 cells X0 Karyo: 45,X[73]/ 46,X,idic(Y)(p10)[27]	Normal male
3	Routine screening	12w3d	MX	Karyotype	46,X,idic(Y)(p10) [20]/45,X[3]	Ambiguous

Discussion

The above cases, along with the literature review, illustrate the phenotypic variability that is present among individuals with MX/idic(Y) genotypes. The variability in appearance of external genitalia cautions against relying on ultrasound examination or physical examination at birth to confirm or rule out a diagnosis of MX. Genetic testing should be recommended to all patients with a finding of MX on noninvasive cell-free DNA screening, whether this is pursued prenatally or after the child is born. Specific attention should be focused on whether there is mosaicism for a cell line with a Y chromosome, as the presence of Y chromosomal material necessitates evaluation for gonadoblastoma, even at an early age. Individuals with MX/idic(Y) genotypes should be evaluated for other features commonly seen in MX as well, as they are potentially at risk of developing these features.

The above cases highlight the importance of appropriate pre- and post-test counseling for noninvasive cell-free DNA screening. In considering sex chromosome aneuploidies, it is especially important that patients are aware of the variability of features, the lower positive predictive value (PPV), and the possibility that the result may suggest an underlying chromosome aneuploidy that is not specifically targeted by the test.[8] Given the uptake of non-invasive cell-free DNA screening by non-genetics professionals, genetic counselors in both clinical and industry positions are in a unique position to help these professionals provide their patients with appropriate test result counseling and follow-up both pre- and postnatally.

REFERENCES

1. Oliveira RM et al. “Y chromosome in Turner syndrome: review of the literature.” Sao Paulo Med J. 2009; 127(6):373-8.
2. DesGroseilliers M et al. “Phenotypic variability in isodicentric Y patients: study of nine cases.” Clin Genet. 2006; 70:145-50.
3. Hsu, LYF. “Phenotype/karyotype correlations of Y chromosome aneuploidy with emphasis on structural aberrations in postnatally diagnosed cases.” Am J Med Genet. 1994; 53:108-40.
4. Guedes AD et al. “Determination of the sexual phenotype in a child with 45,X/46,X,idic(Yp) mosaicism: importance of the relative proportion of the 45,X line in gonadal tissue.” Am J Med Genet. 2006; 140A:1871-75.
5. Zelaya G et al. “Gonadoblastoma in patients with Ullrich-Turner syndrome.” Pediatr Devel Pathol. 2015; 18:117-21.
6. Gravholt CH et al. “Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting.” Eur J Endocrinol. 2017 Sep; 177(3):G1-G70.
7. Bruyère H et al. “Isodicentric Yp: prenatal diagnosis and outcome in 12 cases.” Prenat Diagn. 2006; 26:324-9.
8. Sachs A et al. “Recommended pre-test counseling points for noninvasive prenatal testing using cell-free DNA: a 2015 perspective.” Prenatal Diag. 2015; 35:968-71.