Disorders of sex development (DSD): Inconsistencies between clinical features and peripheral blood cultured karyotypes

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Objectives:

- Sex differentiation and development are complex processes requiring precise spatiotemporal expression and interactions of specific genes and gene products.
- In some patients with disorders of sex development (DSD), the peripheral blood karyotype diverges from anticipated findings based on phenotypic features and confounds diagnosis and medical management (1,2).
- To test our hypothesis that sex chromosome mosaicism occurs in different tissues, we ascertained for sex chromosome mosaicism in 13 patients by using fluorescence in-situ hybridization (FISH) on different cell types.

Methods:

- We identified 13 patients with DSDs; 12 of 13 patients had female phenotype and one patient had male phenotype.
- In addition to cultured peripheral blood karyotypes, we performed additional genetic studies using FISH on different tissues: Cells from urine samples (n=5); Cells from cord blood (n=1); Cells from gonadal tissue (n=2); and Uncultured peripheral blood (n=13).
- We compared patient phenotypes with cultured peripheral blood karyotypes and results of FISH studies.

Cell line representations among various tissues

Patient	**P1**		**P2**			**P3**		**P4**		**P5**			**P6**		**P7**		**P8**		**P9**			**P10**		**P11**		**P12**		**P13**	
Age, years	0.3		10.8			1.5		10.1		4.8			21.5		0.9		1.5		1.1			11.5		2		3		14.9	
Gender	F		F			F		F		F			F		F		F		M			F		F		F		F	
Cell lines	46,XY	45,X	46,XY	i(Y) (p10)	45,X	46,XX	45,X	46,XX	45,X	46,XX	45,X	47,XXX	46,X,r(X)	45,X	46,X,i(X)(q10) /46,X,r(X)	45,X	45,X	46,XY	45,X	46,XY	der(Y) x2~4	46,XX	45,X	46,XX	45,X	46,XX	45,X	46,XY	45,X
cultured PB	85%	15%	35%	0%	65%	3%	97%	90%	10%				70%	30%	100%	0%	75%	25%	40%	0%	60%	100%	0%	100%	0%	100%	0%	90%	10%
uncultured PB	98%	2%	0%	35%	65%	10%	90%	70%	30%	28%	48%	24%	40%	60%	95.40%	4.6%	55%	45%	56%	24%	20%	73%	27%	91%	9%	87%	13%	77%	23%
cord blood																			56%	16%	27%								
buccal cells																												70%	30%
urine	36%	64%	0%	11%	89%								62%	38%					95%	5%	0%							56%	44%
gonadal tissue			0%	100%	0%																							30%	70%
Phenotype	HLH, MCA, Uterus present		Short stature, Uterus present, Streak gonads			Micro-opthalmia, Linear skin defects		Short stature		FTT			DD		Infantile hepatic hemangioma		Gonadoblastoma, Uterus present, Left streak; Right dysgenetic		Bilateral palpable testes in scrotum			FTT, short stature, microcephaly		FTT, IUGR, GH deficiency, ectopic poster pituitary		FTT		Crohn's disease, gonadoblastoma	

DD- Developmental delay; HLH -Hypoplastic left heart; MCA-Multiple congenital anomalies; FTT -failure to thrive; IUGR - intrauterine growth retardation; GH -growth hormone

Results:

- Twelve of thirteen patients had female phenotype.
- In 8 patients (P4, P6, P7, P8, P10, P11, P12, and P13), the percentage of mosaicism was higher from the FISH analysis on uncultured cells than cultured peripheral blood cells. The results of the FISH analysis were crucial to confirm the diagnosis of mosaic Turner Syndrome in 3 patients, (P10, P11, and P12).
- One phenotypically female patient (P1) with 46,XY cell line on cultured peripheral blood cells had absence of *SRY* in 64.2% of uncultured urine cells indicating loss of Y chromosome or deletion of *SRY* gene among urine cells.
- One phenotypically male patient with 45,X karyotype on NIPT was found to have three other cell lines with the derivative Y chromosome markers in uncultured cord blood and urine cells.

Conclusions:

- FISH analysis using urinary epithelial cells is a noninvasive method that is helpful in management of DSD due to the common embryonic origins of gonads and kidneys.
- Ascertaining for chromosomal mosaicism aids management recommendations and shared decision-making discussions with families and other health care providers.
- Mosaicism is not always uniform throughout the body; somatic mutations can result in tissue specific mosaicism.
- These variations may contribute to the disparity in phenotype-genotype correlations among children with DSD and may impact clinical management especially if Y chromosomal material is identified in a 45,X patient (P3).

Speculation:

We speculate that urine samples may better represent the percentage of mosaicism within gonadal tissues.

References:

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3. Bisat T, et al., Y chromosome mosaicism in the gonads, but not in the blood, of a girl with the Turner phenotype and virilized external genitalia. Clin Genet. 1993;44:142-5.

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