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Mosaicism in Clinical Genetics

Unexpected discrepancy between NIPT, ultrasound, and phenotype: Ambiguous Genitalia in a Fetus with 45,X/46,XY Mosaicism

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Objective:

Non-invasive prenatal testing (NIPT) has emerged as a widely adopted screening tool for detecting fetal chromosomal abnormalities. Despite its high sensitivity and specificity, NIPT relies on analysis of cell-free placental DNA, which may not always reflect the true fetal karyotype. Discordant results between NIPT and ultrasonography, particularly in cases of sex chromosome mosaicism, present significant diagnostic challenges. We report a rare case of fetal sex discordance identified during prenatal screening, ultimately confirmed as 45,X/46,XY mosaicism, highlighting the limitations of NIPT and the importance of confirmatory testing and genetic counseling.

Methods:

We report the case of a 32-year-old pregnant woman who underwent non-invasive prenatal testing (NIPT) detecting fetal DNA in maternal plasma based on paired-end MPSS platform assay (Illumina inc, USA) at 14 weeks of gestation. The first screening result indicated a normal XY constitution with low-level Y chromosome signals. Subsequently, ultrasound examination suggested female-appearing genitalia. Due to the inconclusive sex result, NIPT was repeated at 17 weeks and detected the presence of a Y chromosome. Amniocentesis was subsequently performed at 20 weeks, and karyotype analysis confirmed 45,X[45]/46,XY[5] mosaicism in the fetus.

Results:

The chromosomal constitution is associated with a broad phenotypic spectrum, ranging from Turner syndrome-like females to ambiguous genitalia or males with mild genital abnormalities. Ultimately, the infant was delivered with ambiguous genitalia, representing a rare cause of disorders of sex development (DSD).

Conclusions:

The discordance observed in this case illustrates the biological complexity of mosaicism where placental DNA analyzed by NIPT has limitations in accurately representing the true fetal karyotype particularly in mosaic conditions. Nevertheless, both NIPT and ultrasound serve as essential complementary screening tools, offering only partial perspectives on the prenatal genetic landscape. Confirmatory testing through amniocentesis is crucial for resolving genotype–phenotype discrepancies. Clinically, this case emphasizes the importance of comprehensive genetic counseling and multidisciplinary care in managing disorders of sex development, ensuring families receive accurate information and appropriate support.

Hosts: Baylor College of Medicine | The Chinese University of Hong Kong | CU Medicine Faculty of Medicine

Supporting Organizations: 香港遺傳諮詢學會 Hong Kong Society of Genetic Counselling

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Discordant Prenatal Findings: A Case of 45,X/46,XY Mosaicism Presenting with Ambiguous Genitalia

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BACKGROUND

Non-invasive prenatal testing (NIPT) analyzes cell-free DNA in maternal plasma, primarily of placental origin. NIPT relies on analysis of cell-free placental DNA, which may not always reflect the true fetal karyotype. Discordance with ultrasound or phenotype may occur in cases of confined placental mosaicism or fetal mosaicism.

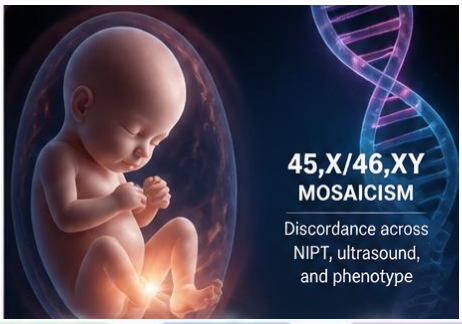
OBJECTIVE

To report a case of 45,X/46,XY mosaicism presenting with ambiguous genitalia and highlight the importance of integrating genetic, imaging, and clinical findings.

Table1. NIPT raw data result shown a normal XY constitution with low-level Y chromosome signals.

frag_size_dist	0.004344917
fetal fraction	0.108339082
NCV_X	-11.4300354
NCV_Y	25.47673553
number_of_cnv_events	0
non_excluded_sites	9748228
region_classification	NO ANOMALY DETECTED - XY
chromosome	chrX
start_base	1
end_base	155270560
start_cytoband	p22.33
end_cytoband	q28
region_size_mb	155.3
region_llr_trisomy	-46.30976522
region_llr_monosomy	173.2863807
region_t_stat_long_reads	-34.53428662
region_mosaic_ratio	0.916214911
region_mosaic_llr_trisomy	-20.99636188
region_mosaic_llr_monosomy	172.6807383

METHODS





A rare case of fetal sex confirmed as 45,X/46,XY mosaicism. The chromosomal constitution is associated with a broad phenotypic spectrum, ranging from Turner syndrome-like females to ambiguous genitalia or males with mild genital abnormalities. Ultimately, the infant was delivered with ambiguous genitalia, representing a rare cause of disorders of sex development (DSD).

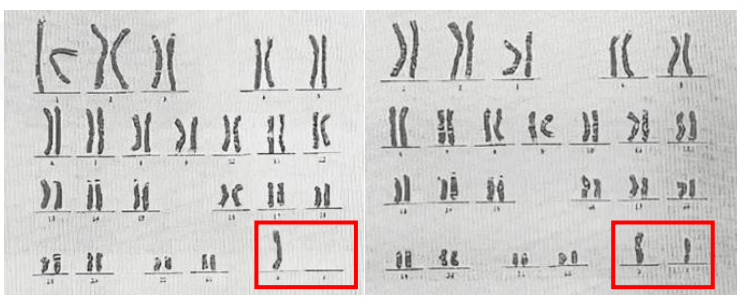


Figure.1 Amniotic fluid chromosome analysis by G-banding revealed 45,X[45]/46,XY[5] mosaicism in the fetus.

CONCLUSION

- Placental mosaicism can limit NIPT accuracy; amniocentesis is required to resolve genotype-phenotype discrepancies.
- Confirmatory testing and genetic counseling are essential.
- Multidisciplinary genetic counseling is critical for management and family support.

KEY TAKE-HOME MESSAGE

Discordance among NIPT, ultrasound, and phenotype should prompt comprehensive genetic evaluation to guide clinical decision-making.

NGG SAFE