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False negative genome wide NIPT of large terminal 4q deletion due to placenta mosaicism confirmed on CVS/fetal SNP array, karyotype, WES

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Introduction

NIPT for common autosomal trisomy (13,18,21) is known to have a small false negative rate; these false neg cases are most commonly due to placenta mosaicism in the cytotrophoblast even when the fetus is fully affected both genotypically and phenotypically. The frequency of false negative genome NIPT for copy number variants (CNV) such as deletions, duplications and unbalanced rearrangements is currently unknown.

A healthy multigravida > US/genome wide NIPT at 18 wks.

US > bilateral renal agenesis, anterior abdom wall skin defect, nonvisualized bladder, 2vc, non-visualized genitalia, situs solitus, dextrocardia, right lung hypoplasia and anhydramnios.

Genome nipt > normal

Transabdom CVS direct snp microarray > 50% mosaicism for a pathogenic 24 MB terminal denovo 4q deletion

CVS mesenchymal cell culture karyotype/fetal WES > nonmosaic 24 MB 4q terminal denovo deletion (same chromosome breakpoints).

Misoprostol termination/autopsy confirmed US > cloacal exstrophy and absent kidneys/genitalia/anus (OEIS syndrome) ; parental blood karyotypes > normal



Conclusion

Genome wide nipt for CNVs (deletions/duplications) may result in a false negative cell free dna screen when placenta mosaicism is present even in setting of fully affected fetus via the same biological mechanism that occurs in common trisomy (13/18/21).

Large population level genome NIPT prospective studies will need to be performed to determine the frequency of these events in the general population.