Discordant result from non-invasive prenatal testing (NIPT) in a phenotypical male fetus with abnormal Y chromosome in 45,X/46,XY mosaicism

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Objective
The sensitivity and specificity of noninvasive prenatal testing (NIPT) for detection of sex chromosome aneuploidies compared to common autosomal trisomies are significantly lower and the performance of NIPT regarding mosaicism is not well described. We present a case with mismatch between NIPT and the prenatal test with amniocentesis.

Methods
NIPT by targeted next-generation sequencing, rapid aneuploidy test (QF-PCR), and high resolution aCGH applying Agilent 180K oligo array.

Results
A 27-year-old multiparous in a consanguineous marriage was referred to our hospital for first-trimester screening. The gestation age (GA) was, however, 16+1 weeks based on the head circumference (HC), and the screening was done only by combined maternal age and maternal serum biochemistry (GA 12+0). The estimated risk for trisomy 21 was high (1/83). The patient opted for NIPT, that subsequently indicated a > 99% risk for monosomy X. The pregnancy was continued without invasive diagnostics. The routine fetal anomaly scan at GA 20+6 showed a male fetus with suspected penoscrotal hypospadias. No other major malformation especially none related to monosomy X (cardiac and kidney abnormalities) were diagnosed. QF-PCR analysis showed a normal male karyotype, whereas arrayCGH analysis of uncultured amniotic cells revealed a mosaic karyotype of 45X/46XY with absence of most of the q-arm of chromosome Y (Yq11.221q12). The abnormal Y chromosome was present in 80-90% of DNA from amniotic fluid. The pregnancy was continued after genetic counseling about risk of pseudohermaphroditism, infertility and reduced height. Mental development was expected to be in the normal range. Throughout pregnancy we regularly monitored by ultrasound. By the end of pregnancy there was signs of fetal growth retardation. In GA 38+2 the patient gave birth to a phenotypical boy weighing 2610g with penoscrotal hypospadias and no other malformations. The postnatal chromosome analysis on the newborn confirmed the prenatal diagnose.

Conclusion
The false negative result for presence of Y-chromosome on NIPT could be caused by mosaicism only being present in the fetus and very low levels of Y chromosome material in maternal blood. Mosaic pregnancies, in which differences occur in the distribution and proportion of euploid and aneuploid cells, are important biological factors that decrease the effective DNA fraction to yield a false-negative aneuploidy. Positive results of NIPT should be carefully evaluated and an invasive diagnostic procedure should be considered, especially for sex chromosome abnormalities.