Detection of structural abnormalities of the Y chromosome by noninvasive prenatal testing

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INTRODUCTION

Noninvasive prenatal testing (NIPT) has rapidly evolved from initially offering trisomy 21 to now covering trisomy 18, trisomy 13 and sex chromosome abnormalities.

Our published clinical validation studies show very high sensitivity and specificity for detecting such conditions. Here we report accurate detection of structural abnormalities of the Y chromosome in patients mosaic for Turner variants by noninvasive prenatal testing.

METHODS

Maternal plasma samples were subjected to DNA extraction and library preparation followed by massively parallel sequencing as described by Jensen et al.

Sequenom Laboratories has processed over 150,000 samples since the inception of the MaterniT21™ PLUS test.

CONCLUSIONS

Analysis of cell-free fetal DNA in maternal plasma has successfully evolved into an important analytical tool with high sensitivity and specificity for fetal aneuploidy testing. In addition to detecting full trisomies, our whole genome sequencing approach provides vital details about sub-chromosomal structural abnormalities.

In this study we demonstrate that although chromosome Y is inherently very challenging to sequence due to the presence of a large region of heterochromatin, we were able to detect structural Y changes in mosaic Turner variant cases by noninvasive prenatal testing.

With the advance of sequencing technology and optimized bioinformatics algorithms, NIPT is rapidly approaching the functional capabilities of chromosomal microarray analysis, with the added benefit of being noninvasive.

RESULTS

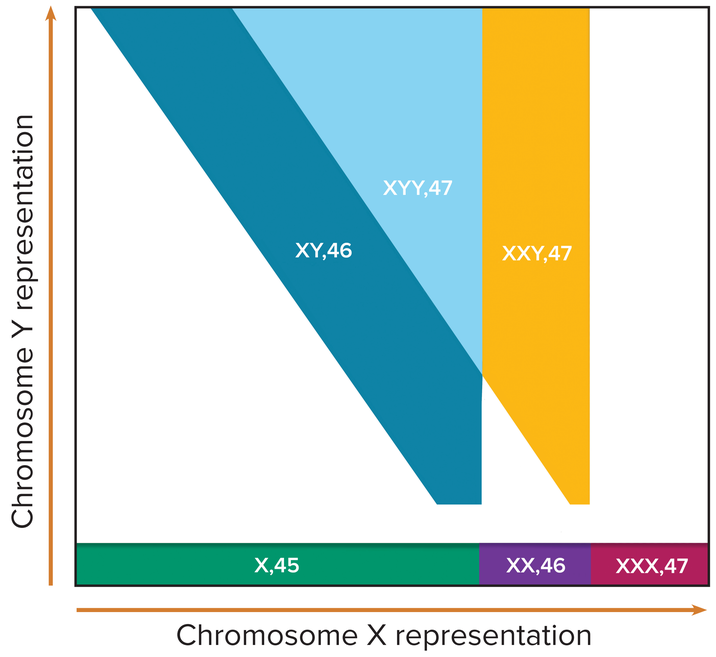


Figure 1

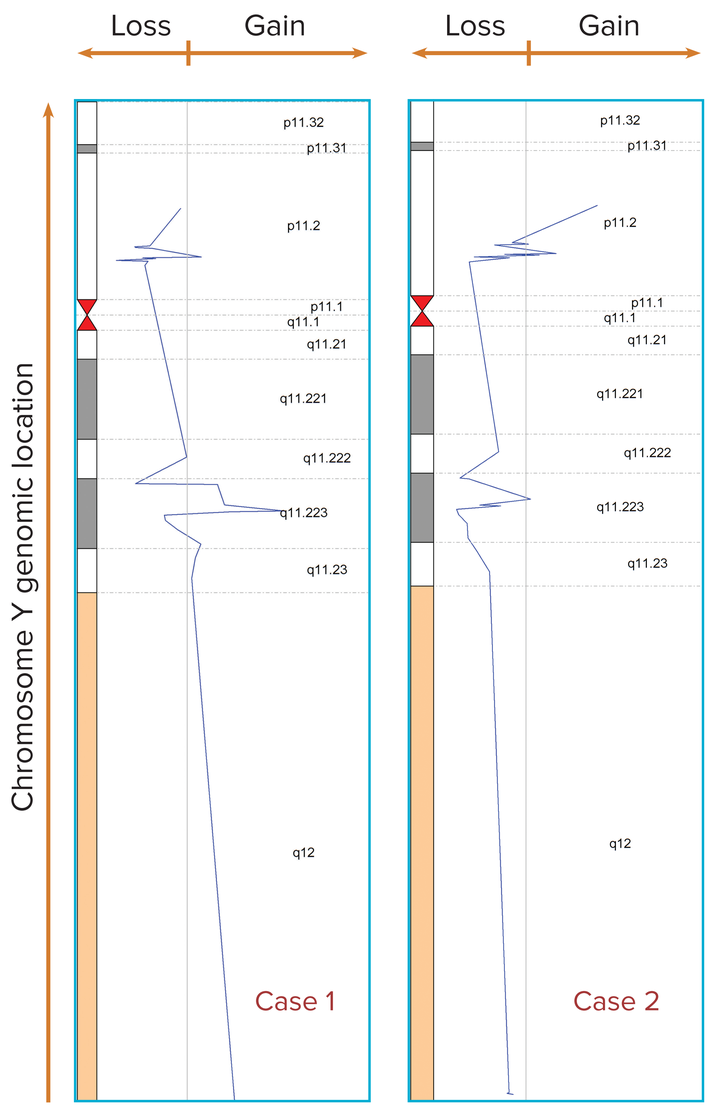
Distribution of sex chromosome X and Y representations:

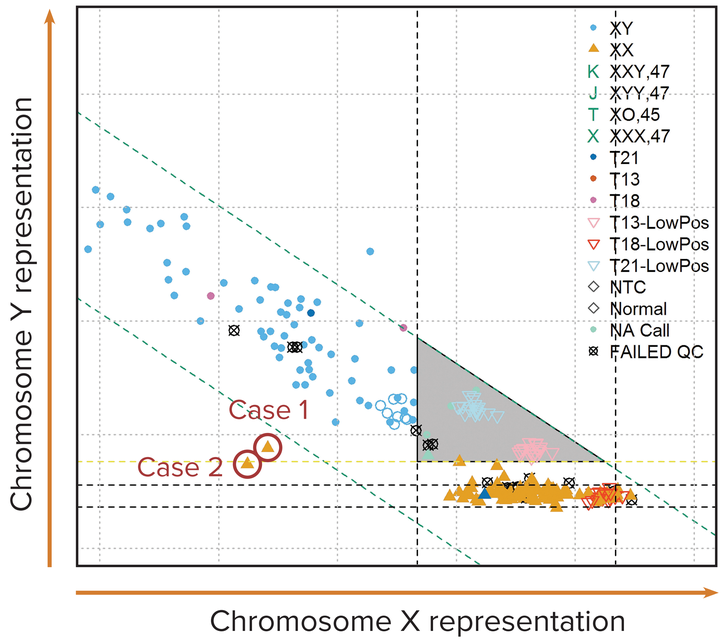
The colored zones demarcate different representation levels.

*The **green and magenta** regions have very low or no Y chromosome representation and an under or over representation of chromosome X respectively.*

***Purple and turquoise** regions represent normal female and male respectively.*

***Blue and yellow** regions show male and females with overrepresentation of chromosome Y respectively.*





Case 1

45,X,-Y[8]/46,X,r(Y)[7]: Karyotype and FISH analysis on amniotic fluid demonstrated a mosaic pattern including a ring Y, with presence of heterochromatin material (Yq12) and absence of the SRY gene region (Yp11.3). Clinically, ultrasound imaging was consistent with a female fetus, in concordance with our result.

Case 2

46,X,idic(Y)(p10)dn[4]/45,X[11]: Karyotype analysis on amniotic fluid demonstrated a mosaic pattern including a de novo isodicentric Yp, with duplication of the SRY gene region (Yp11.3) and absence of Yq material. Clinically, ultrasound imaging was consistent with a male fetus.

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