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I. Introduction

Noninvasive prenatal testing (NIPT) for fetal aneuploidies by massively parallel sequencing has emerged as a powerful tool in the management of high-risk pregnancies. It is vital that patients receive pre-test counseling about the limitations of the test. Fetal sex discrepancies between NIPT and ultrasound can be due to a number of well documented reasons. Here we discuss six select examples of various complicated fetal sex discrepancies between ultrasound and NIPT, which diagnostic testing revealed to be due to rare complex chromosomal rearrangements.

II. Methods

Maternal blood samples submitted to Sequenom Laboratories® for MaterniT®21PLUS testing were subjected to DNA extraction, library preparation, and whole genome massively parallel sequencing as described by Jensen et al.¹

III. Results

Table 1. Diagnostic testing results compared with NIPT results in gender discrepancies

Case	NIPT Result	Ultrasound	Diagnostic Test	Diagnostic Test Result
1	45, X	Male	Amnio Karyo	Majority 45,X; 20/120 cells 46,X, idic(y)
2	Male	Female	Postnatal Karyo	47,XX,+mar[15]/46,XX[5]. ish der(Y)(SRY-,DYZ3+,DYZ1-). Confirmed maternal.
3	45, X (x3)	Male	Amnio Karyo	45,X[12]/46,X, idic(Y)(q12), der(21)t(Y;21)(p11.23;p13)[2]/47,s12,+r(?Y)(p11.3q12)[3] . ish idic(Y)(SRY++), r (?Y)(SRY-), der(21) t (Y;21) (SRY+). Normal parental karyotypes.
4	Male	Female	Amnio Karyo	46,X,i(Yq12)[33]/45,X[17]
5	Male	Female	Amnio Karyo and Array	46,XY,der(9)t(9;X)(p24.3;p21.1); arr[hg19] Xp22.33p21.1(60701-33146672)x2 (dup 33mb)
6	Female (x2)	Male	Postnatal Karyo	SRY-positive 46,XX

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 overrepresentation of chromosome X respectively. Purple and turquoise regions represent normal female and male respectively. Blue and yellow regions show male and females with over representation of chromosome Y respectively.

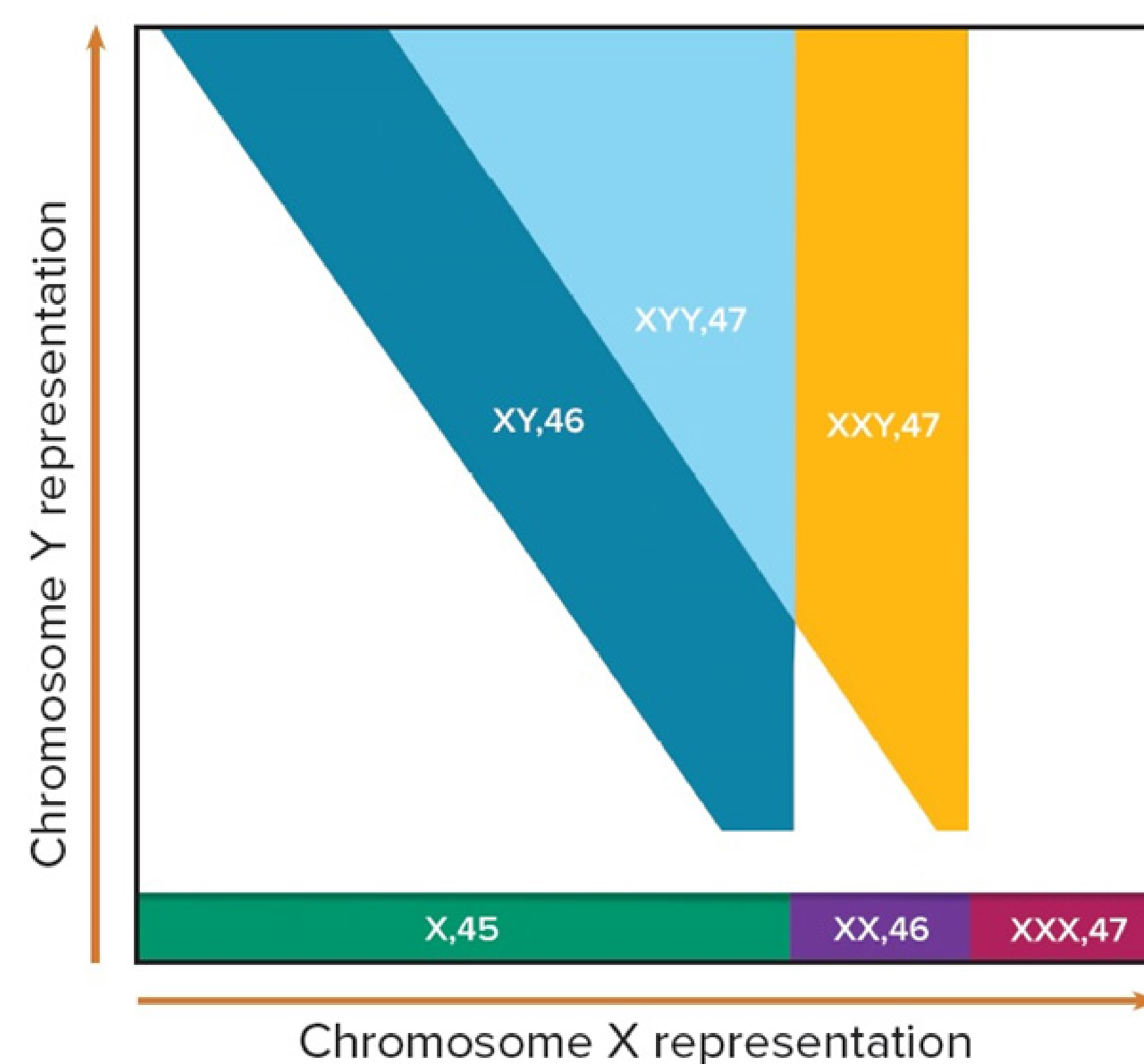


Figure 2. Standard Y trace

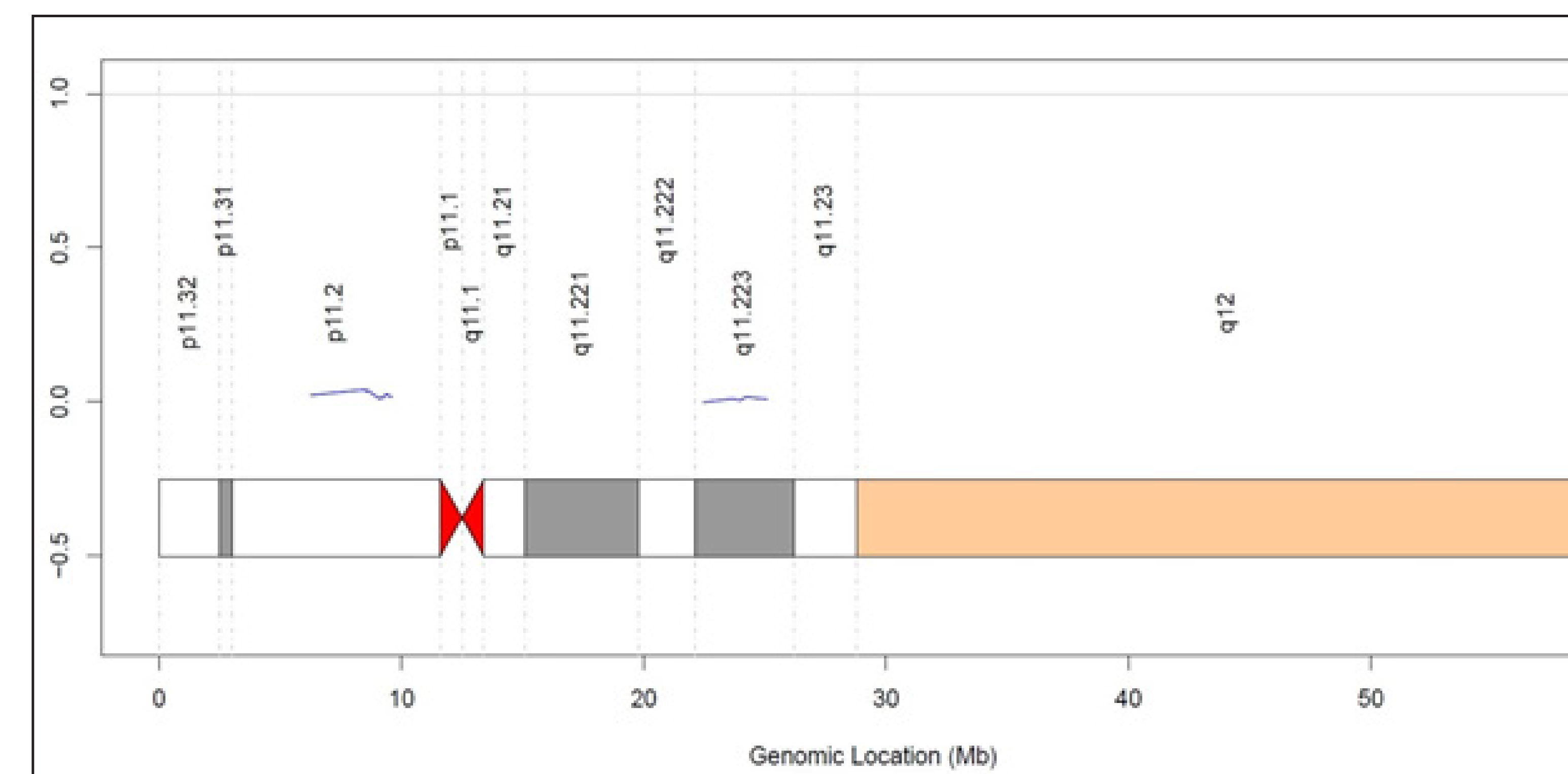
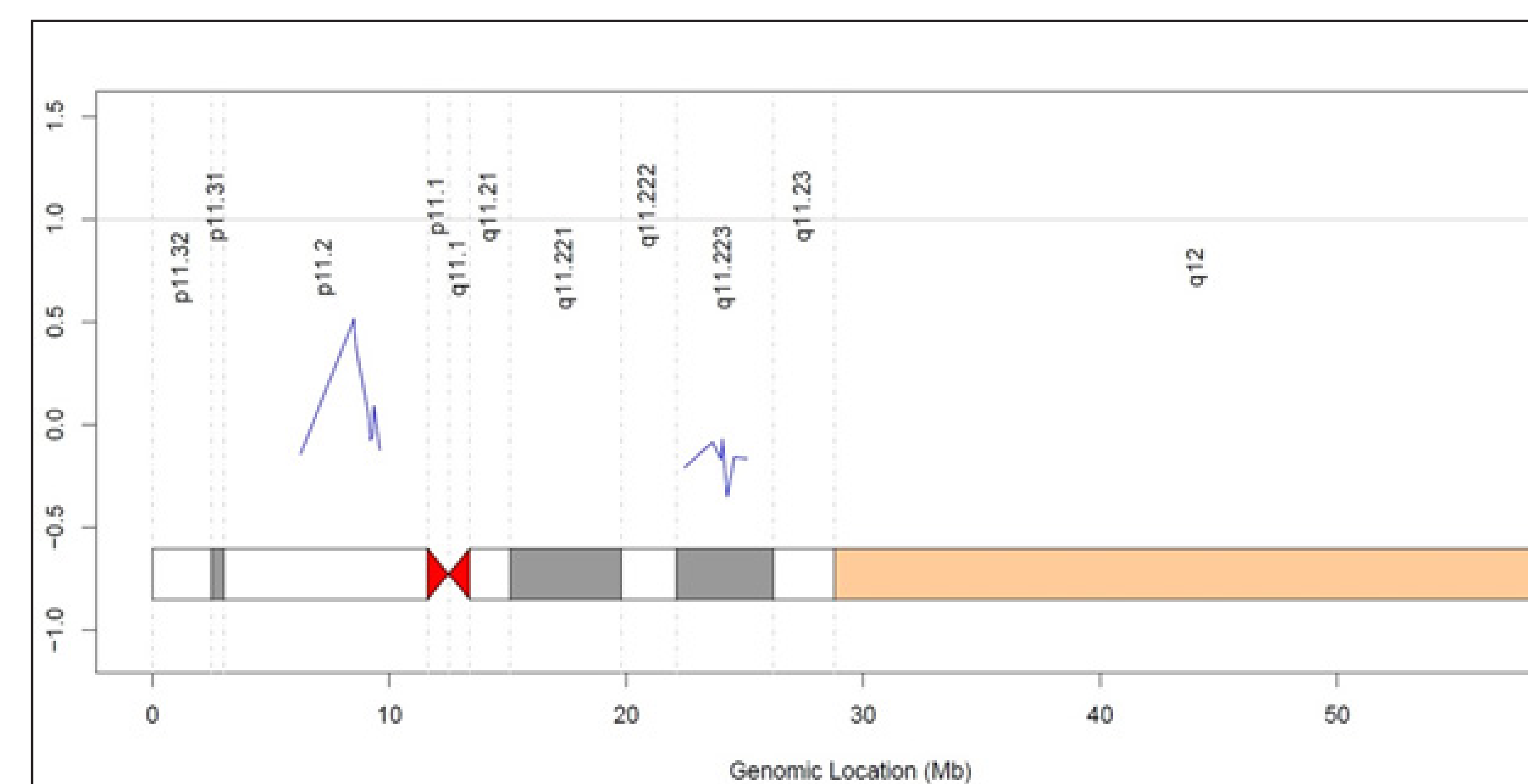


Figure 3. Y trace from case 2- XY by NIPT, Female by Ultrasound, Karyotype 47,XX,+mar[15]/46,XX[5]. ish der(Y)(SRY-,DYZ3+,DYZ1-).



IV. Conclusion

Fetal sex discrepancies between ultrasound and NIPT are a rare but known limitation. These discrepancies can be explained by a co-twin loss (or vanishing twin/second sac), history of transplant, fetal sex reversal syndromes/chromosome abnormalities, as well as maternal chromosome abnormalities. The cases discussed illustrate the complexity of the NIPT fetal sex algorithm. Fetal sex discordance may not always prompt fetal or neonatal karyotyping, but it should be considered in certain circumstances. Prenatal screening requires a multifaceted approach to uncover the whole story.

V. References

- Jensen TJ1, Zwiefelhofer T, Tim RC, et al. High-throughput massively parallel sequencing for fetal aneuploidy detection from maternal plasma. PLoS One. 2013;8(3):e57381. doi: 10.1371/journal.pone.0057381. Epub 2013 Mar 6.