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# The journey of two mosaic trisomy 22 NIPT results

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## 1. Introduction

Prenatal genetic counseling frequently involves non-invasive prenatal testing (NIPT) to screen patients for chromosomal disorders, most commonly trisomy 21, 13 and 18. NIPT relies on genetic material from the placenta to screen for these genetic disorders. As the technology has evolved, some laboratories offer NIPT which includes additional chromosomes and/or microdeletion and microduplication syndromes and there is limited information regarding positive/negative predictive values and outcomes for these less common results. Other laboratories may use chromosomes other than 21, 18, and 13, for quality control metrics, and although they may not be clinically validated to report abnormalities in these other regions, additional information may be provided regarding anomalies detected. We report on two cases that presented to genetic counseling due to reported abnormalities of chromosome 22 detected by NIPT (**Figure 1**). This case report details the diagnostic odyssey for both patients and the role genetic counseling plays throughout the process.

## 2. Background

Many laboratories now offer NIPT for less common trisomies, including trisomy 22. Trisomy 22 is often confined to the placenta and trisomic rescue explains the differences between NIPT results and true fetal involvement (Grati, 2014). Evidence of trisomic rescue can appear in follow up diagnostic testing such as chorionic villus sampling (CVS) or amniocentesis in the form of a small supernumerary marker chromosome (sSMC) and/or uniparental disomy (UPD). An sSMC from a rescue event can form by chromosomal fragmentation during meiosis or mitosis. **Figure 2** displays a schematic of an sSMC connected to UPD. Research by Liehr et al. concludes that every sSMC may be principally connected with UPD.

## 3. Methods

For both cases, the methodology utilized for results included: NIPT via massively parallel sequencing, single nucleotide polymorphism (SNP) microarray analysis, and G banding karyotype.

## 4. Results

**Case 1:** The patient's NIPT report stated an "increased representation of chromosome 22, suggestive of mosaic trisomy 22." Diagnostic testing via amniocentesis with karyotype analysis revealed a small supernumerary marker chromosome (sSMC) in all cells analyzed. Microarray analysis showed a 13.6Mb terminal region of homozygosity (ROH) on 22q with normal copy number, indicating the sSMC detected on karyotype contained inactive heterochromatin. Although follow up studies were not performed, maternal UPD is suspected. The pregnancy resulted in the birth of a reportedly healthy 6 lb 9 oz baby girl.

**Case 2:** The patient presented due to an "overrepresentation of chromosome 22" detected on NIPT. Diagnostic testing via chorionic villus sampling (CVS) revealed mosaic trisomy 22 and a small supernumerary marker chromosome (sSMC) on karyotype (**Figure 3**). Chromosomal microarray (CMA) testing reported 70% mosaic trisomy 22. Due to potential for confined placental mosaicism, follow up amniocentesis was performed. Karyotype identified an sSMC in all karyotypes (**Figure 4**) while microarray noted normal copy number with a 6.55Mb contiguous region of homozygosity on chromosome 22q. Follow up UPD testing confirmed maternal origin. The normal copy number indicated the sSMC contained only heterochromatin and not expected to cause a phenotype.

The screening and diagnostic results indicate that the segmental ROH of 22q likely occurred from crossing over of homologous chromosomes followed by nondisjunction in meiosis I, resulting in an initial trisomic 22 embryo that was corrected via a rescue event, ultimately resulting in UPD and an sSMC. Due to the ROH identified, expanded carrier screening was performed for both cases, which did not reveal any autosomal recessive conditions located in the regions of concern.

## 5. Conclusions

The initial unexpected NIPT result and the continued additional testing recommendations generated an extended period of inconclusiveness and a continuous buildup of anxiety for both couples (**Figure 5**). The pregnant patients frequently mentioned the inability to bond with and accept the pregnancy due to the lingering considerations of termination. As a genetic counselor, we aim to provide couples with more conclusive results. Despite frustration with the inability to do so with the initial diagnostic results, these cases expanded the genetic counselors' understanding of molecular mechanisms and how evidence of these mechanisms can be visualized in fetal screening and diagnostic testing.

In both cases, the perinatologists and patients turned to the genetic counselors in order to understand and interpret the complex underlying molecular mechanisms behind the NIPT and diagnostic results. Additionally, the professional expertise that genetic counselors provide aided in the crucial recognition for follow up testing including expanded carrier screening and UPD studies.

These cases highlight that information from both microarray and karyotype aid in interpretation of prenatal results, especially in the setting of rare autosomal trisomies identified on NIPT. With the ability of NIPT to identify potential placental mosaicism, providers that receive abnormal NIPT results should understand the potential for and implications of marker chromosomes, trisomic rescue, and UPD, as well as the utility of a genetic counselor in these situations. With limited outcome data on less common NIPT findings, informed consent and comprehensive disclosure of results via genetic counseling are imperative.

## Tables + Figures

**Figure 1. Raw data from the NIPT of Case 1; note the increase in chromosome 22 visible on the graph**

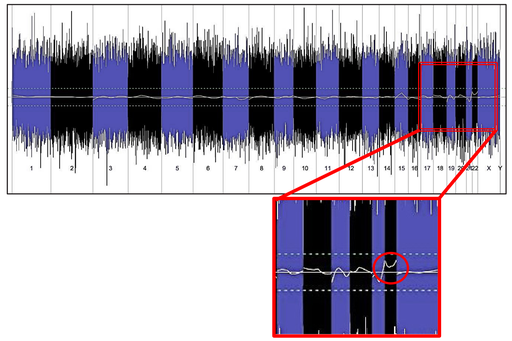


**Figure 2. Schematic of an sSMC associated with UPD (Liehr et al, 2011)**

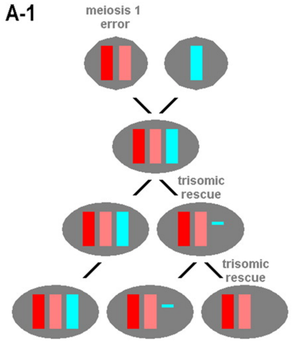



**Figure 3. Three karyotypes produced from CVS on case 2: 3A depicts the sSMC, 3B a full trisomy 22 and 3C a normal karyotype. Karyotypes were present in a mosaic 22/1/11 ratio, respectively**

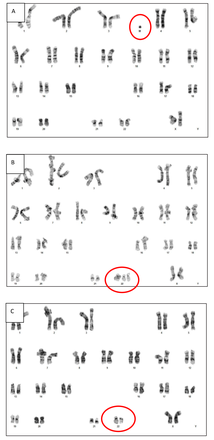


**Figure 4. Case 2 karyotype from amniocentesis; all cells showed an sSMC with no mosaicism**

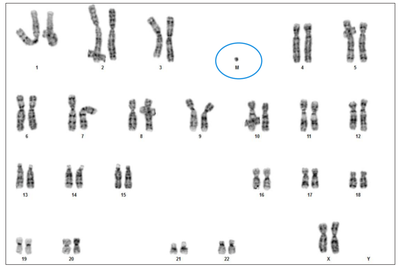
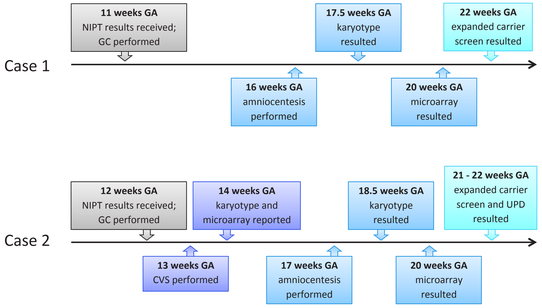


**Figure 5. Timelines of results**




GA: Gestational Age
GC: Genetic Counseling

## References

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