The journey of two mosaic trisomy 22 NIPT results

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1. Introduction
Premal genetic counseling frequently involves non-invasive prenatal testing (NIPT) for trisomies 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 this technology has evolved, some laboratories offer NIPT which includes additional chromosomes and/or microsatellite and microsatellite replication studies, and there is limited information regarding positive, negative predictive values and outcomes for these less common results. Other laboratories may only offer chromosomes other than 21, 18, and 12, 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 abnormalities 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 the genetic counseling process throughout the pregnancy.

2. Background
Many laboratories now offer NIPT for less common trisomies, including trisomy 22. Trisomy 22 is often considered the placenta and trisomic rescue the explanation for the differences between NIPT results and fetal karyotype (Gane, 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 SMC, from rescue event can form by chromosomal fragmentation during meiosis or mosaicism. Figure 2 displays a schematic of an SMC connected to UPD. Based on Yune et al. (2014) concludes that every SMC may be principally connected with UPD.

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

4. Results
Case 1: The patient’s NIPT report stated as “increased representation of chromosome 22,” suggestive of mosaic trisomy 22. Diagnosis testing via amniocentesis with karyotype analysis revealed a small supernumerary marker chromosome (sSMC) in all cells analyzed. Microarray analysis showed a 0.9Mb terminal region of homozygosity (ROH) on 22q with normal copy number, indicating the SMC 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, live full-term baby.

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 75% mosaicism. Due to potential for confined placental mosaicism, follow-up amniocentesis was performed. Karyotype identified an sSMC in all karyocytes (Figure 4), while microarray, using original copy number with a 0.55Mb contiguous region of homozygosity on chromosome 22q. Follow up testing confirmed maternal origin. The normal copy number indicated the SMC, unrelated and only heterochromatic and not expected to cause phenotype. The screening and diagnostic results indicate that the segmental ROH of 22q (34 millions) of chromosome 22 occurred from crossing over of homologous chromosomes followed by independent segregation, resulting in an initial trisomic 22 embryo that was rescued into a mosaic event, ultimately resulting in an UPD and an SMC. Due to the ROH identified, expanded carrier screening was performed for both cases, which did not reveal an abnormal carrier status. In the two cases, the pregnant patients were delivered a healthy baby.

5. Conclusions
The initial unexpected NIPT result and the continued additional testing recommendations generated an extended period of microchromatid analysis and a continuous buildup of anxiety for both couples (Figure 5). The pregnant patients frequently mentioned the difficulty to bond with and accept the pregnancy due to the forthcoming considerations of termination. As genetic counselors, 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 peripheral cytogeneticists and patients turned to the genetic counselors in the genetic counseling process to understand and interpret the complex underlying molecular mechanisms behind the NIPT and diagnostic results. Additionally, the professional expertise that genetic counselors provide is 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 non-automated microarray identified on NIPT. With the ability of NIPT to identify potential placental mosaics, providers that receive abnormal NIPT results should understand the potential for and implications of marker chromosomes, trisomic rescue, and UPD, as well as the ability of a genetic counselor in these situations. With limited data on less common NIPT findings, informed consent and comprehensive disclosure of results of genetic counseling are imperative.

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