Leveraging whole genome sequencing in noninvasive prenatal screening: a case of Prader-Willi syndrome due to uniparental disomy

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Introduction

Noninvasive prenatal screening (NIPS) has been rapidly incorporated into clinical care since 2011. Initially replacing traditional aneuploidy screening in high-risk populations, NIPS is becoming a first-line screening approach in the general obstetric population for the common aneuploidies of chromosomes 21, 18, and 13. With a whole genome sequencing (WGS) approach to NIPS, detection of uniparental disomy of all autosomes is possible, providing potential additional clinical benefit. Here we describe a case of Prader-Willi syndrome (PWS) with trisomy of chromosome 15 (T15) clearly identified by analysis with a WGS-based NIPS.

Background

Prader-Willi syndrome is a genetic disorder characterized by intellectual disability, dysmorphic features, and behavioral disorders, including hyperphagia often leading to obesity. Prader-Willi syndrome can result from a number of genetic mechanisms that disable the paternal copy of a series of genes on chromosome 15. While most cases of PWS are caused by a deletion of the paternally inherited genes in the PWS critical region, 25% to 50% of diagnoses are due to maternal uniparental disomy (matUPD) of chromosome 15, in which both copies of the chromosome are inherited from the mother². NIPS microdeletion analysis for the PWS region is available; however, the microdeletion analysis is unable to provide insight into the risk for PWS due to matUPD 15 in a pregnancy. NIPS analyzes cell-free DNA of the mother and her pregnancy, which originates primarily from the placenta. When diagnostic testing of the placenta via CVS identifies T15, additional analysis via amniocentesis is recommended to screen for T15 as well as specialized testing to identify UPD. Trisomy 15 present in early embryonic development can result in UPD15 after trisomy rescue in which the only paternal (or only maternal) copy of 15 is lost and cells are again chromosomally balanced but have an imprinting defect (see Figure 1).

Case Report

PRENATAL

A 26-year-old patient with a singleton pregnancy and no identified risk factors underwent WGS-based NIPS using the Prequel Prenatal Screen at 10 weeks 6 days gestation. The NIPS analysis pipeline calculates z-scores for all autosomes, allosomes, and five microdeletions, including the 15q PWS critical region. Results were issued for the requested chromosomes: 21, 18, 13, X and Y.

NIPS results for the requested chromosomes were negative for the common trisomies (21, 18, 13) and positive for an increased risk for monosomy X. The patient reportedly did not pursue prenatal diagnosis.

POSTNATAL

The clinician reported the newborn was diagnosed with PWS due to maternal uniparental disomy of chromosome 15 (without indication of monosomy X). A comprehensive review of the NIPS WGS data including assessment of all autosomes showed a clear signal for trisomy 15 (Fig. 2). Trisomy 15 is expected to have been present in the placenta.

Discussion

The clear signal for trisomy 15 on NIPS indicates the likely presence of T15 in the placenta. Trisomy rescue resulting in maternal UPD 15 in the fetus is the expected mechanism that resulted in the PWS diagnosis in the newborn. This case illustrates the potential benefit of NIPS screening and reporting on aneuploidies beyond 13, 18, 21. Such screening could provide the family with advance knowledge of the risk for a UPD syndrome. Because a standard karyotype is normal in cases of UPD, the additional information is important to both the families and medical care providers because it indicates that specialized testing for UPD is required beyond standard karyotype in such a scenario. Though expanded aneuploidy screening is not currently commonly offered, the WGS-based NIPS algorithm already has the capacity to detect rare aneuploidies and provide advance knowledge to more families seeking prenatal information about the health of their pregnancy.

Conclusions

NIPS is well accepted as a superior screening method for identifying common trisomies; however, the benefit of reporting aneuploidy for other autosomes is not yet well-defined. This case presents the potential benefit of reporting autosomal aneuploidies beyond 21, 18, and 13. Such a result alerts the clinician and patient to the possibility of a non-aneuploidic genetic disorder and prompts discussion of the condition and specialized testing. As UPD is not detectable via standard amniocentesis karyotype, an aneuploid NIPS result for an imprinted chromosome signals the need for additional testing to capture UPD. WGS-based NIPS expanded to report on any aneuploidy can identify more pregnancies with genetic syndromes by identifying those pregnancies at risk for UPD disorders.