

Expanded Aneuploidy Analysis Reveals Trisomy 2: Evidence of Rare Aneuploidy via NIPS Provides Opportunity for Focused Care

Susan Hancock, MS, CGC; Albert Lee, PhD; Kevin Haas, PhD; Carrie Haverty, MS, CGC
All authors are current or former employees of Myriad Genetics and/or Myriad Women's Health

INTRODUCTION

- Noninvasive prenatal screening (NIPS) is currently widely used to screen for common aneuploidies (Trisomy 21, 18, 13).
- A whole genome sequencing (WGS) approach to NIPS allows for expanded aneuploidy analysis (EAA) with detection of aneuploidy in any autosome. This includes the so-called “rare” autosomal aneuploidies (involving any autosome other than the common aneuploidies).
- Such other autosomal aneuploidies have long been associated with placental insufficiency and fetal syndromes when identified by chorionic villus sampling (CVS).^{1,2}
- Recent literature has revealed an association between NIPS identification of such aneuploidies and similar adverse perinatal outcomes.^{3,4}
- Here we describe a case of Trisomy 2 identified by WGS-based NIPS resulting in actionable information for pregnancy management.

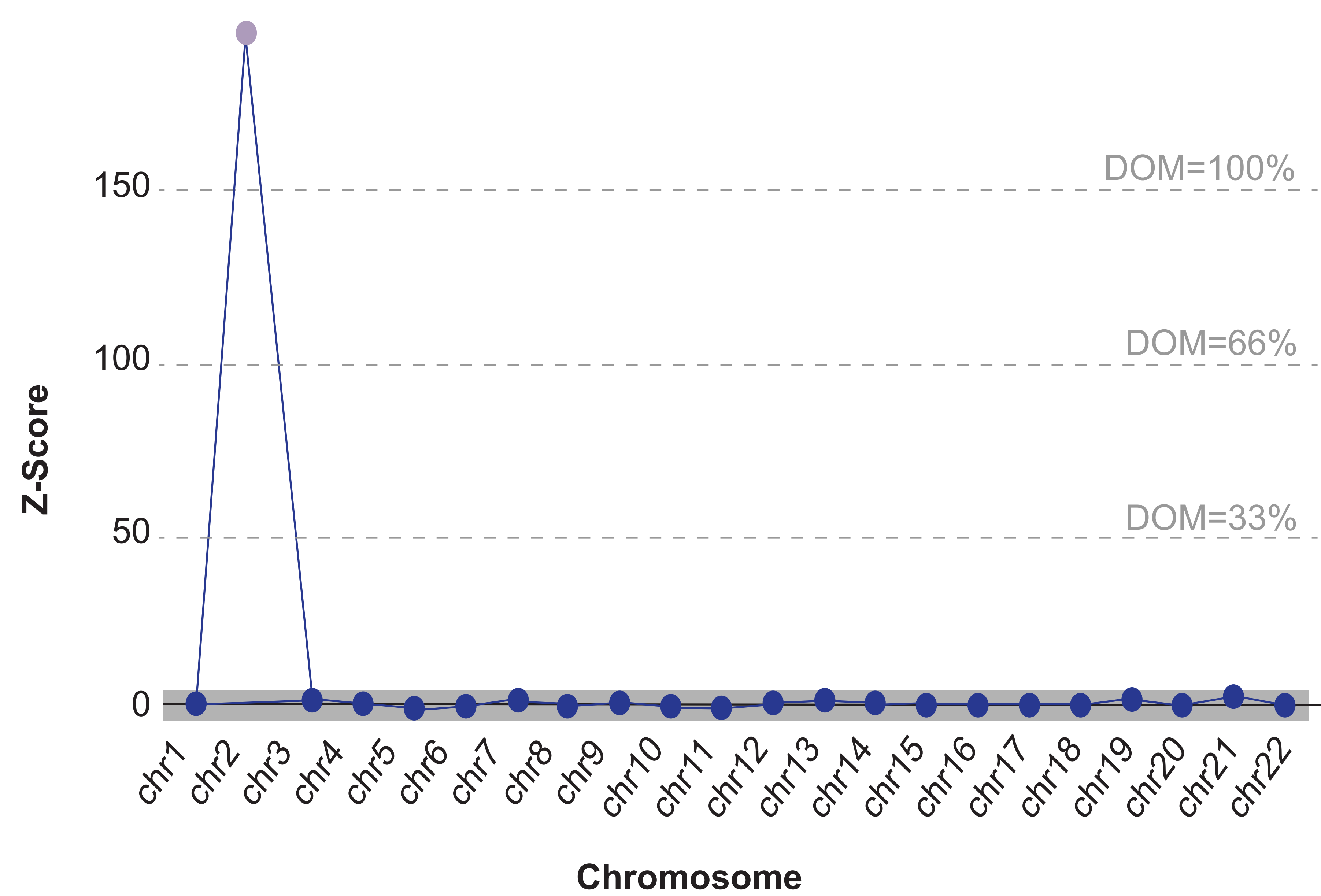
METHODS

- A 32-year-old patient with a singleton pregnancy and asymmetric growth restriction, with particularly short long bones identified on ultrasound, underwent WGS-based NIPS using Prequel™ (Myriad Women's Health) at 32 weeks, 3 days gestation.
- The Prequel analysis pipeline detects aneuploidies by computing the significance of enrichment or depletion in WGS read density for autosomes, allosomes, and microdeletions. Analysis was requested and reported for all of these regions.
- Degree of mosaicism (DOM) represents the estimated percentage of the placental cell-free DNA that is affected with a detected aneuploidy.
- DOM can be calculated by comparing the fetal fraction estimates from the positive chromosome to the inferred fetal fraction for the entire sample. If the ratio is greater than 100%, it is rounded down to 100%.
- DOM was calculated for this sample.

RESULTS

- The sample screened positive for Trisomy 2 on Prequel™. DOM calculation was 100%, indicating that the cell-free DNA originating from the placenta was likely uniformly impacted by Trisomy 2 (non-mosaic Trisomy 2 in the placenta). Results were negative for all other regions (Figure 1).
- The provider was informed of the results and risk for placental and fetal complications.
- The provider indicated that prior to receiving the patient's NIPS results, a skeletal dysplasia was a primary consideration as the cause of poor growth among the differentials, based on the pattern of asymmetrical growth restriction and the particularly short long bones.
- Trisomy 2 finding on NIPS prompted the provider to deprioritize the concern for skeletal dysplasia and a molecular genetic workup for this indication. A similar clinical presentation of extremely short long bones had previously been documented with Trisomy 2 confined to the placenta.⁵
- Based on the significant potential for placental insufficiency as the cause of growth abnormality, the provider focused follow-up on this etiology, instituting close surveillance for additional signs of placental insufficiency.
- Because of the potential for true fetal mosaicism for Trisomy 2, amniocentesis was offered to the patient. Amniocentesis revealed a 46,XY karyotype.
- Delivery of the infant was recommended at 37 weeks gestation. The neonate was small for gestational age, weighing 4lbs 9oz.
- The neonate was normal on newborn exam, with no concern for skeletal dysplasia. The newborn was reported to do well after delivery and was discharged home with his mother. One-month follow-up reported a normal, thriving infant.

Figure 1. Z-score profile of normalized depth from whole genome sequencing of cell-free DNA



CONCLUSIONS

- NIPS is a well accepted screening method for identifying common trisomies; however, the benefit of reporting aneuploidy for other autosomes is not yet well-established.
- This case demonstrates that detection of such aneuploidies can alert the clinician to the possibility of placental dysfunction, allowing for interventions that may reduce the risk for serious complications such as stillbirth, and may avoid costly and unnecessary genetic testing.
- In addition to detecting fetal syndromes, NIPS with expanded aneuploidy analysis may provide the opportunity to detect serious placental complications and improve pregnancy outcomes.
- Correlation of clinical outcome with DOM appreciated via NIPS may provide additional insight into magnitude of risk for adverse outcome. More research is needed to better define if and how this information can impact patient counseling.

References: 1. Malvestiti, F. et al., *Prenat Diagn.*, 2015, 35(11). 2. Toutain, J. et al., *PLoS One.*, 2018, 13(4). 3. Pertile, M.D. et al., *Sci Transl Med.*, 2017, 9(405). 4. Van Opstal, D. et al., *Genet Med.*, 2017, 20(5). 5. Pertile, M., “An Update on Rare Autosomal Aneuploidies” presentation at SMFM 2019.