INTRODUCTION

- Skeletal dysplasias (SD) are a heterogeneous group of heritable disorders (n=450) that affect the development of bone and connective tissue.¹
  - Determining a specific diagnosis when an SD is suspected by ultrasound is challenging due to the wide phenotypic spectrum.²
- Non-invasive prenatal testing (NIPT) employs next generation sequencing technology to analyze circulating cell-free DNA from maternal plasma.
- NIPT for single gene disorders (NIPT-SGD) is currently capable of screening for DNA sequence variants in 30 single genes associated with clinically serious conditions and is offered to patients with singleton pregnancies at gestational age 26 weeks.
- NIPT-SGD allows for population-based screening for conditions with relatively high prevalence.³ In the general population, the combined incidence of the conditions being screened is approximately 0.17% (1,600).³
  - Analytical validation studies have shown sensitivity and specificity of >99% (Figure 1).¹³

OBJECTIVE

- To demonstrate the utility of NIPT-SGD test in suspected SD cases and to narrow the differential diagnosis of ultrasound.

STUDY DESIGN

- Results obtained from NIPT-SGD in 2 case studies were compared with the clinical (differential) diagnosis based on ultrasound findings.

RESULTS: CASE STUDY 1

26-year old G3P2, referred at 19 weeks for an anatomy ultrasound (Figure 2).
  - Long bone lengths below the 5th percentile and appeared bowed.
  - Lack of calcification/mineralization and limited ossification of the central vertebral elements.
  - Small chin and a bell-shaped chest.

Suspected Diagnosis: Achondroplasia type II

NIPT-SGD Test Results: Identified a novel, likely pathogenic variant, c.2656G>A (p.G886S) in the COL1A2 gene, suggesting an increased risk of OI.
  - A different missense variant at the same amino acid position c.2503G>A (p.G835S) has been reported as a likely pathogenic variant.
  - Confirmatory DNA testing via amniocentesis on the COL1A2 gene was consistent with the NIPT-SGD results.

Pregnancy Outcome:
  - Preterm premature rupture of the membranes at 34 weeks with stillborn fetus.
  - Clinical findings at birth included a large head, multiple dysmorphisms, hypoplastic male genitalia and extremely short extremities.
  - Autopsy was not performed.

REFERENCES


CASE STUDY 2

22-year old G1, referred at 29 weeks for an anatomy ultrasound (Figure 3).
  - Long bone lengths below the 3rd percentile.
  - Bilateral bowing of the femurs and a small fetal thorax.

Suspected Diagnosis: Achondroplasia with “no findings to suggest a lethal form of dwarfish”

NIPT-SGD Test Results: Identified pathogenic variant, c.2503G>A (p.G835S) in the COL1A2 gene, suggesting an increased risk of OI.
  - The c.2503G>A variant has been classified as OI type III per the Silence classification with clinical features including fractures at birth, progressively short stature and severe deformity.⁴

Pregnancy Outcome:
  - Cesarean section delivery at 23 weeks 6 days, weighing 1610 g.
  - Documentation around the time of delivery did not include results of NIPT-SGD.
  - Skeletal survey performed on birth suggested a differential diagnosis of thanatophoric dysplasia vs. camptomelic dysplasia with achondroplasia thought less likely.
  - Although no evidence of fractures were reported to support OI at birth, X-ray of the femurs on the first day of life showed a fracture of the right femoral shaft.

CONCLUSIONS

- NIPT-SGD test results in the two illustrated cases suggested a different diagnosis than suspected based upon ultrasound findings.
- The COL1A2 variants identified in these 2 cases are associated with autosomal dominant OI.
- Establishment of diagnosis of OI and the differentiation between lethal versus non-lethal SD can provide valuable information on prognosis, management, and counseling for patients.

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DISCLOSURES

- Dr. Parmar, JS, KL, and AM are employees and equity holders at Natera, Inc. KAM is a consultant and equity holder at Natera, Inc.

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