Key Summary of Conference Abstract

Suspected Gonadal Mosaicism Identified by Abnormal Prenatal Cell-free DNA Screening in 2 Consecutive Pregnancies

Background

- Prenatal cell-free DNA (cfDNA) screening can identify chromosomal abnormalities, such as Klinefelter syndrome, in both the fetus and the mother.[1] Abnormalities that are present in only the mother can be reported as incidental findings instead of positive results.
- These abnormalities may occur in all cells (constitutional), some somatic cells (somatic mosaicism),[1,2] or only germline cells (gonadal mosaicism).
- Parental gonadal mosaicism can explain why parents who do not have a causative somatic mutation have multiple offspring with the mutation.[3]
- **Objective:** The investigators report a case in which Klinefelter syndrome in 2 consecutive pregnancies was suspected to be due to maternal gonadal mosaicism.

Case Description

- A 32-year-old woman, who already had a son with Klinefelter syndrome (47,XXY), underwent prenatal cfDNA screening at 11 weeks' gestation.
  - Prenatal cfDNA screening was performed using fully-automated, massively parallel shotgun sequencing.
  - The prenatal cfDNA screening result indicated the fetus was male and had an increased risk for 47,XXY. However, invasive confirmation testing was declined.
- Both parents underwent routine karyotype analysis.
  - The maternal and paternal karyotypes were normal (46,XX and 46,XY, respectively), and fluorescence in situ hybridization (FISH) analysis confirmed the results.
- Maternal microarray analysis (Affymetrix CytoScan® HD array platform) was consistent with a 46,XX chromosome complement.

Discussion and Conclusions

- Prenatal cfDNA screening of the woman's 2 pregnancies indicated an increased risk of Klinefelter syndrome; however, chromosomal abnormalities were not identified in either parent's somatic cells.
- Other potential causes of the abnormality (recurrent meiotic nondisjunction involving the same trisomy and consecutive pregnancies affected by Klinefelter syndrome) were considered rare and thus unlikely to be the cause.
- Therefore, the chromosomal abnormality was likely present in the germline of one of the parents. Since males with Klinefelter syndrome are typically infertile, 47,XXX was most likely present in the maternal germline.
- Thus, an abnormal prenatal cfDNA screening result that was identified in multiple pregnancies led investigators to suspect maternal gonadal mosaicism.

Poster Presented at the American College of Medical Genetics Annual Clinical Genetics Meeting

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American College of Medical Genetics Annual Clinical Genetics Meeting
Phoenix, AZ
March 24, 2017
Time: 10:30 AM-12:00 PM

Webpage
https://acmg.expoplanner.com/index.cfm?do=expomap.sess&event_id=8&session_id=3090

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