I. Objective

Esoteric aneuploidy (non-trisomy 13/18/21) detection via non-invasive prenatal DNA (cfDNA) screening presents several unique challenges; they are relatively common, often confined to the placenta, and have variable clinical impact.3,4 Herein we describe one of very few clinical reports of mosaic trisomy 2, in addition to the first and only cfDNA-identified case of a true fetal mosaic trisomy 2 in the medical genetic literature.

II. Study Design

The maternal blood sample was subjected to DNA extraction, library preparation, and genome-wide massively parallel sequencing.5 Sequencing data were analyzed using a novel algorithm to detect trisomies and subchromosomal, genome-wide copy number variants 7Mb and larger.

III. Results

The patient presented to Maternal Fetal Medicine clinic at 10.7 weeks’ gestation for genetic counseling and routine ultrasound. Advanced maternal age and a prior trisomy 2 pregnancy prompted expanded cfDNA screening, ultimately yielding a trisomy 2 result (~65% mosaicism, 6% fetal fraction) and residual risk for uniparental disomy (UPD, see Image 1).6,7 Amniocentesis inclusions of single nucleotide polymorphism (SNP) microarray testing was recommended to assess both trisomy and UPD risk.

Trisomy 2 is a relatively common finding per placental literature, usually confined to the placemence, and carries an exceedingly low risk for true fetal mosaicism.8,9 A limited number of published confirmed trisomy 2 case studies was a substantial counseling limitation, noted for highly variable outcome data (see Table 2).8,9

Chronic villus sampling (CVS) was declined and fetal ultrasound showed normal growth and nuchal translucency measurement at 10.7 weeks. However, a subsequent scan at 16 weeks showed a 2 vessel cord and a 1 week leg in femur/length, increasing to a 2 week leg by 10 weeks. Fetal echocardiogram showed hypoplastic left ventricular output (LVOT) and possible coarctation of the aorta. Amniocentesis at 20 weeks with SNP microarray revealed 23% mosaicism for Trisomy 2 and normal biallelic inheritance, ruling out UPD. The pregnancy continued with growth lag measuring 5 weeks behind at 33 weeks. Palliative care was discussed, as prognosis was guarded.

Premature rupture of membranes (PROM) at 34.4 weeks prompted delivery of a 3 lbs, 8oz (650g) neonate with Apgars of 2 and 8. An extended NICU stay ensued, with clinical outcome exceeding expectations. No confirmatory postnatal genetic testing was found on record and presumably was felt of limited utility given the concordant cfDNA and amniocentesis results, multiple congenital anomalies, and the limitation mosaic 2 pose with variable tissue specificity. Head ultrasound and MRI shortly after birth were essentially normal, consistent with prematurity. A large atrial septal defect (ASD) was repaired at 5 months of age, resolving post-right ventricular hypertrophy and right ventricular systolic dysfunction. Now approaching age three, the child is reportedly doing well overall. Her last clinic measurements showed improvement in growth and size, measuring 111th height, 20ths weight, and 30ths head circumference. Endocrinology consultation was favorable, finding no pathology and normal growth velocity. Mild axial hypotonia persists, while once delayed motor skills are now deemed on target. A persistent heart murmur is noted. Ophthalmology continues to follow the child for high hyperopia, that is improving.

IV. Conclusion

While many esoteric trisomies remain confined to the placenta and are of variable clinical consequence, the risk for true and occult fetal mosaicism cannot be dismissed. This case report illustrates the first known case, amniocen confirmed true fetal mosaic trisomy 2.

Key Findings

- Whole-genome cfDNA screening can detect esoteric autosomal trisomies (e.g. Trisomy 2) that have variable clinical impact on placental function and risk for true fetal mosaicism, necessitating a high risk obstetrical approach to pregnancy management. (see Table 1)
- Trisomy 2 is a common mosaic phenotype-presenting case, is typically confined to the placenta and associated with IUFD, but carries a small risk for true fetal mosaicism and UPD.
- Although CVS testing offers important placental insight in cases such as these, amniocentesis is ultimately necessary to clarify fetal risk.

V. References