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Scientific Abstract or Case Study?

Case Study Abstract

Title:

Prenatal Diagnosis of a Novel Biallelic *ARFGEF1*-Related Disorder Due to Uniparental Isodisomy: a Case Report

Abstract Format:

Poster Presentation Only

Background:

ARFGEF1-related neurodevelopmental disorder is caused by heterozygous loss-of-function variants in the *ARFGEF1* gene and leads to a variable degree of developmental delay, impaired speech, intellectual disability, and epilepsy. There are no reported cases of biallelic *ARFGEF1* loss-of-function in humans. Here, we present such a case, indicating that this is a novel genetic syndrome with a severe fetal presentation.

Case presentation:

A 37-year-old G4P2012 was evaluated by Maternal Fetal Medicine at 11w4d due to her abnormal ultrasound findings. The ultrasound was significant for reduced fetal movement, nuchal and scalp edema, and spinal curvature. Given these findings, the patient was referred for genetic counseling. The family history was significant for the couple's other child, diagnosed with a mild intellectual disability, speech delay, history of developmental regression, and autism spectrum disorder. The father of the fetus also has a reported history of unspecified learning disabilities. There were no reported pregnancy complications or teratogen exposures.

Chorionic villus sampling (CVS) for karyotype and chromosomal microarray analysis was performed at 12w6d, revealing a normal chromosome complement (46,XX) with complete uniparental isodisomy of chromosome 8. The patient elected to proceed with amniocentesis to evaluate for mosaicism for numerical abnormalities of chromosome 8, as well as duo exome sequencing (ES) through Ambry Genetics on extracted fetal

DNA from the CVS and maternal blood to evaluate for autosomal recessive conditions unmasked by the uniparental isodisomy.

The ultrasound findings evolved over the course of the pregnancy to include arthrogryposis multiplex congenita, severe hydrocephalus/hydranencephaly, polyhydramnios, and fetal growth restriction. Fetal MRI at 31w6d demonstrated severe hydrocephalus or hydranencephaly with a present falx but no cerebral mantle, severely hypoplastic brainstem, severe thoracolumbar kyphoscoliosis, small lungs, and bilateral clubfoot and club hand. The patient was seen by pediatric neurology and counseled that both volitional movement and autonomic function were likely to be affected by the brain abnormalities and that the fetus may only survive minutes to hours after delivery.

Results from the duo ES were available at 29w3d and revealed that the fetus was homozygous for a non-maternally inherited pathogenic variant in the *ARFGEF1* gene (c.3814C>T (p.R1272*)). This gene is located on chromosome 8, and the homozygosity was presumed to be due to the uniparental isodisomy previously reported. This alteration is expected to result in loss of function (LOF) by premature protein truncation and nonsense-mediated mRNA decay. Human genetic tolerance to LOF via gnomAD shows low predicted tolerance to LOF (LOEUF=0.143). Subsequent familial testing showed the brother of the fetus is heterozygous for this variant, further suggesting paternal inheritance. Additional familial testing is underway, including for the father and extended family members.

A multidisciplinary care conference was arranged with the family who elected neonatal comfort care at delivery, which occurred in the 37th week via repeat cesarean section. Postnatal physical examination was consistent with the reported fetal ultrasound abnormalities. In alignment with the family's perinatal palliative care plan, she was held by the family with minimal intervention from medical staff. She was pronounced dead less than an hour after her birth. An autopsy was declined.

Conclusion:

This is the first reported case of biallelic *ARFGEF1*-related disorder, which resulted in a severe fetal phenotype (arthrogryposis multiplex congenita, growth restriction, and severe abnormalities of the central nervous system) and perinatal lethality. ES is a useful tool for the evaluation of anomalous fetuses and helps identify underlying variants within areas of uniparental isodisomy of non-imprinted chromosomes. As prenatal ES gains broader clinical use, there is an increased potential to reveal ultrarare, novel genetic syndromes with severe presentations.

Topic Focus:

Prenatal Genetics

Primary Category:

Prenatal Genetics

Keywords:

Brain/Nervous System;Congenital Anomaly;Exome sequencing;Fetal Pathology;Malformation;Phenotype;Phenotypic delineation of disorders;Prenatal Diagnosis;Ultrasound;Uniparental Disomy

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