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

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Background

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

Case Presentation

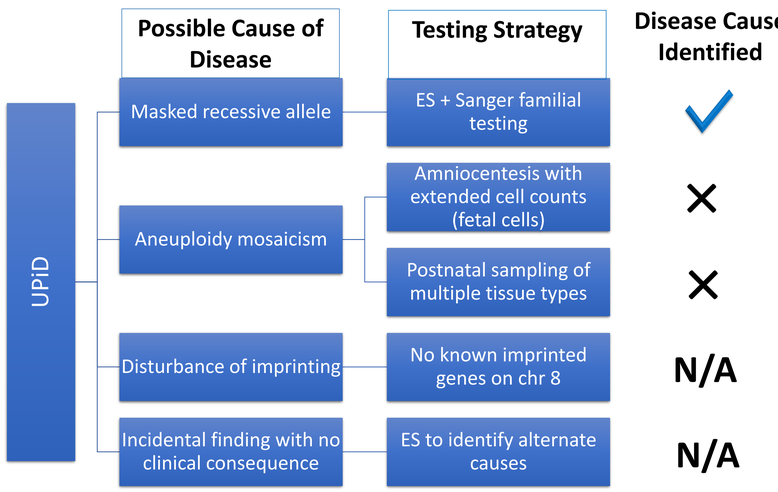
A 37-year-old G4P2012 was evaluated by Maternal Fetal Medicine at 11w4d due to her abnormal ultrasound (US) findings. The US was significant for reduced fetal movement, nuchal and scalp edema, and spinal curvature. Given these findings, the patient was referred for genetic counseling.

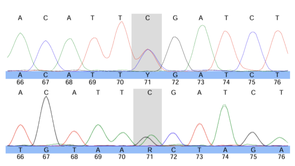
Genetic Testing

Test	Gestational Age	Result
Karyotype*	12w6d	46,XX
SNP Microarray*	12w6d	arr[hg19] (8)x2 hmz Consistent with complete uniparental isodisomy (UPiD) of chromosome 8
Exome Sequencing (ES) Duo mother/fetus	29w3d	Homozygous, pathogenic, non-maternal *ARFGEF1* variant c.3814C>T (p.R1272*), located on 8q13.2

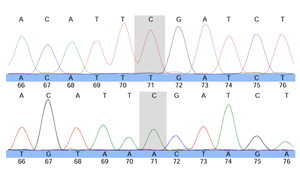
*Performed on samples from chorionic villus sampling (CVS) and repeated on amniocentesis

Testing Strategy after Discovery of UPiD

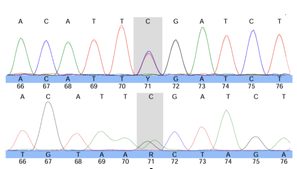




Father

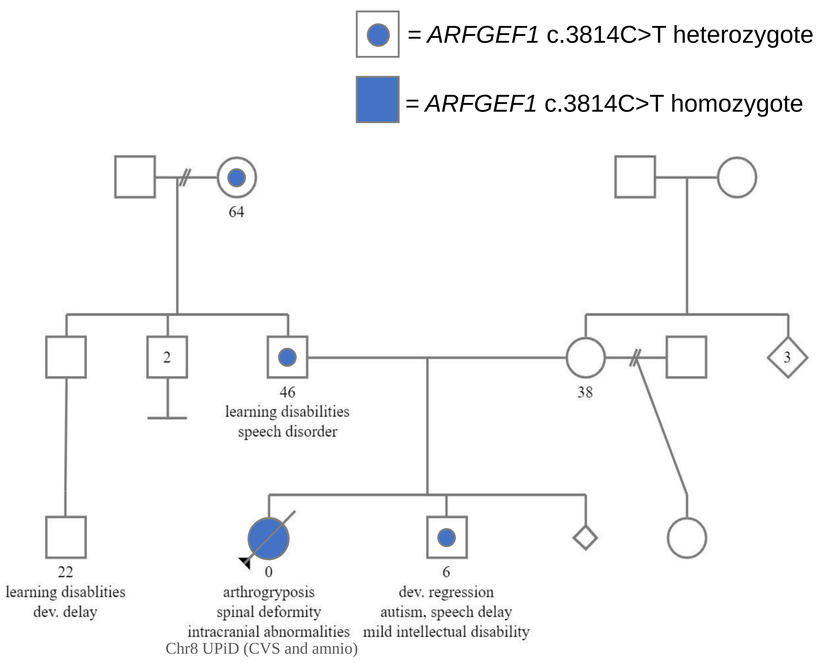


Proband

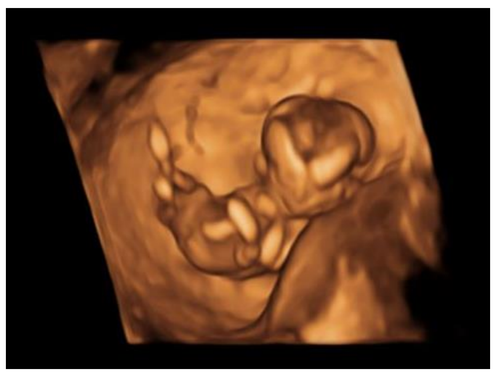


Brother

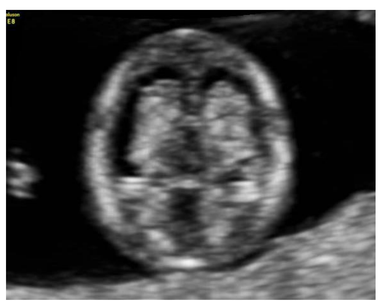
Pedigree



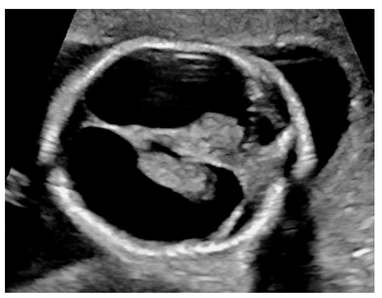
Familial variant testing revealed that the proband's brother, father, and paternal grandmother are heterozygous for the ARFGEF1 c.3814C>T variant.



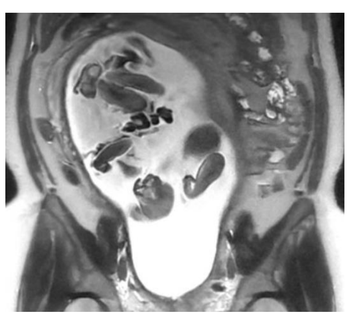
US at 12w4d showing abnormal spinal curvature and abnormal limb posturing



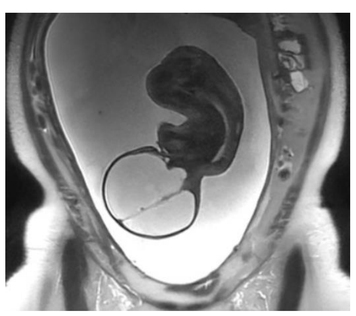
US at 12w4d showing the intracranial anatomy



US at 20w6d showing severe bilateral ventriculomegaly



Fetal MRI at 31w6d showing clubbed hands and feet



Fetal MRI at 31w6d showing abnormal spinal curvature and severe hydrocephalus/ hydranencephaly

Prenatal Imaging

Ultrasound findings throughout the pregnancy

- Arthrogryposis multiplex congenita
- Severe hydrocephalus/hydranencephaly
- Polyhydramnios
- Fetal growth restriction
- Severe kyphoscoliosis

Fetal echocardiogram results at 26w6d

- Normal cardiac structure and function

Fetal MRI findings at 31w6d

- Severe hydrocephalus or hydranencephaly
- Present falx but no identifiable cerebral mantle
- Severely hypoplastic brainstem
- Severe thoracolumbar kyphoscoliosis
- Small lungs
- Bilateral clubfoot and club hand

Case Management

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. 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.

Conclusions

- **This is the first reported case of biallelic *ARFGEF1*-related disorder**
  - 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**
  - Helps identify underlying variants within areas of uniparental isodisomy of non-imprinted chromosomes
- **Prenatal ES increases potential to reveal ultrarare, novel genetic syndromes with severe presentations**

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