HHS Public Access

Author manuscript

Prenat Diagn. Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

Prenat Diagn. 2023 October ; 43(11): 1463–1466. doi:10.1002/pd.6439.

Two unrelated fetuses with *ITPR1* missense variants and fetal hydrops

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Abstract

We describe two fetuses from unrelated families with likely pathogenic variants in *ITPR1* that presented with nonimmune fetal hydrops. Trio exome sequencing revealed a de novo heterozygous likely pathogenic missense variant c.7636G>A (p.Val2531Met) in *ITPR1* (NM_001378452.1) in proband 1 and a de novo heterozygous likely pathogenic missense variant c.34G>A [p.Gly12Arg] in proband 2. Variants in *ITPR1* have been associated with several genetic conditions, including spinocerebellar ataxia 15, spinocerebellar ataxia 29, and Gillespie syndrome. Our report on two patients details a previously undescribed severe fetal presentation of nonimmune hydrops fetalis associated with missense variants in the *ITPR1* gene.

Keywords

ITPR1 ; spinocerebellar ataxia; Gillespie syndrome; nonimmune hydrops fetalis

1. Fetal phenotype

Proband 1 was identified on ultrasound at 22 5/7 weeks with hydrops fetalis, urinary tract dilation, ventriculomegaly, and enlarged cisterna magna (Figure 1). Maternal blood type was O negative, antibody screen negative. Amniotic fluid toxoplasmosis, parvovirus B19, and cytomegalovirus (CMV) PCR were negative.

Proband 2 was identified at 22 1/7 weeks gestation with cardiomegaly, pericardial effusion, ascites (Figure 1), elevated middle cerebellar artery (MCA) dopplers (2.86 MoM). Maternal blood type was B positive with negative antibody screen. Amniotic fluid parvovirus B19 and CMV PCR were negative.

Author contributions: All authors contributed to manuscript development and editing.

2. Diagnostic Method

Amniocentesis was completed at 22 6/7 weeks gestation for Proband 1 and at 23 0/6 weeks for Proband 2. Genomic capture was completed using the Aligent SureSelectXT exome capture kit and Illumina NovaSeq 6000 sequencer and Sanger sequencing was used for confirmatory testing in both cases.

3. Diagnostic results and interpretation

Both probands had cytogenetic testing with normal fluorescence in situ hybridization (FISH) for common aneuploidies and normal prenatal chromosome single nucleotide polymorphism (SNP) microarray.

For Proband 1, trio exome analysis revealed a heterozygous likely pathogenic *ITPR1* variant c.7636G>A [p.Val2546Met], as previously reported in Vora et al.[1] For Proband 2, trio exome analysis revealed a heterozygous likely pathogenic *ITPR1* variant c.34G>A [p.Gly12Arg]. Both variants are de novo in a trio exome (PS2), absent from gnomAD (PM2), in silico models predicted damaging with a CADD score of 29.6 for Proband 1 and CADD score of 32 for Proband 2, Polyphen probably damaging, SIFT deleterious, REVEL 0.702 for proband 1 and REVEL 0.99 for Proband2 (PP3), and missense variants have been a mechanism of disease with a low rate of benign missense variation (PP2) (Table 1B). The variant identified for Proband 1 has been reported in ClinVar as likely pathogenic in one additional individual.

4. Pregnancy outcomes and neonatal findings

Proband 1 was delivered by cesarean at 36 6/7 weeks for persistent fetal hydrops. Birthweight was 4280 grams and Apgar scores were 6 and 8 at 1 and 5 minutes, respectively. The hydrops resolved postnatally, but the neonate had severe and persistent hypotonia and difficulty with extubation. Postnatal diagnoses include bronchomalacia, subglottic stenosis, bicuspid aortic valve, atrial septal defect, grade 5 vesicoureteral reflux, persistent gastroesophageal reflux requiring gastrostomy-jejunostomy tube, stage 3a chronic kidney disease, secondary hyperparathyroidism, hypothyroidism, and Eagle-Barret syndrome. At age 5, he has developmental delays and central and peripheral hypotonia (Table 1A).

For proband 2, the pregnancy was terminated at 24 weeks gestation. Pathological evaluation of the product of conception showed mildly edematous fetus, hydropic placental tissue, liver with extensive extramedullary hematopoiesis with shifts toward erythroid precursors, and adrenal glands with nuclear cytomegaly (Table 1A).

5. Discussion

We present two unrelated fetuses with prenatal diagnosis of fetal hydrops with variants identified in *ITPR1*, expanding the phenotype associated with *ITPR1*-related spinocerebellar ataxias.

Inositol 1,4,5-triphosphate receptor, type 1 (*ITPR1)* encodes the inositol 1,4,5-triphosphate (IP_3) receptor, which is an IP_3-gated calcium channel. These channels are found in the endoplasmic reticulum, involved in calcium homeostasis, and expressed widely in human tissues.[2]

Variants in *ITPR1* have been implicated in several genetic syndromes including spinocerebellar ataxia 15 (SCA15), spinocerebellar ataxia 29 (SCA29), and Gillespie syndrome.[3] Missense variants have been associated with sporadic infantile onset, nonprogressive cerebellar ataxia and hypotonia.[4] An *ITPR1* variant has been reported in a child diagnosed with an increased nuchal translucency (4.8 mm) on first trimester ultrasound who was subsequently diagnosed with hypotonia, developmental delay and pontocerebellar hypoplasia.[5]

To our knowledge, these are the first cases of *ITPR1* variants associated with hydrops fetalis. The phenotype reported for Proband 1 was felt to be consistent with those reported with *ITPR1* variants given the diagnosis of severe hypotonia postnatally. However, given the paucity of prenatal phenotypic data, some uncertainty remains. Although hydrops has not been previously reported, it is plausible that this severe prenatal phenotype may result in early pregnancy loss. These cases highlight the importance of using prenatal sequencing combined with ultrasound imaging to further refine our knowledge of the prenatal presentation of single gene disorders.

Funding:

This work was funded by US National Institutes of Health grants R21TR002770 (NV) and R01HD105868 (NV).

Funding source: K23HD088742 (NICHD; PI: Vora); R01HD105868 (NICHD; PI: Vora)

Ethical approval and publication consent:

Written parental consent was obtained as part of prenatal exome sequencing study for Proband 1. For proband 2, University of Colorado IRB deemed this exempt from IRB approval due to it being a single deidentified case.

Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Vora NL, Gilmore K, Brandt A, Gustafson C, Strande N, Ramkissoon L, Hardisty E, Foreman AKM, Wilhelmsen K, Owen P, Weck KE, Berg JS, Powell CM, Powell BC. An approach to integrating exome sequencing for fetal structural anomalies into clinical practice. Genet Med. 2020 May;22(5):954–961. doi: 10.1038/s41436-020-0750-4. Epub 2020 Jan 24. Erratum in: Genet Med. 2020 Aug;22(8):1426. [PubMed: 31974414]
2. Yule DI, Betzenhause MJ, Joseph SK. Linking structure to function: Recent lessons from inositol 1,4,5-triphosphate receptor mutagenesis. Cell Calcium. 2010 Jun 47(6):469–79. [PubMed: 20510450]
3. Gerber S, Alzayady KJ, Burglen L, Brémond-Gignac D, Marchesin V, Roche O, Rio M, Funalot B, Calmon R, Durr A, Gil-da-Silva-Lopes VL, Ribeiro Bittar MF, Orssaud C, Héron B, Ayoub E, Berquin P, Bahi-Buisson N, Bole C, Masson C, Munnich A, Simons M, Delous M, Dollfus

H, Boddaert N, Lyonnet S, Kaplan J, Calvas P, Yule DI, Rozet JM, Fares Taie L. Recessive and Dominant De Novo ITPR1 Mutations Cause Gillespie Syndrome. Am J Hum Genet. 2016 May 5;98(5):971–980. [PubMed: 27108797]

4. Sasaki M, Ohba C, Iai M, Hirabayashi S, Osaka H, Hiraide T, Saitsu H, Matsumoto N. Sporadic infantile-onset spinocerebellar ataxia caused by missense mutations of the inositol 1,4,5-triphosphate receptor type 1 gene. J Neurol. 2015 May;262(5):1278–84. [PubMed: 25794864]
5. van Dijk T, Barth P, Reneman L, Appelhof B, Baas F, Poll-The, BT. A de novo missense mutation in the inositol 1,4,5-triphosphate receptor type 1 gene causing severe pontine and cerebellar hypoplasia: Expanding the phenotype of ITPR1-related spinocerebellar ataxia's. Am J Med Genet A. 2017; 173(1): 207–212. [PubMed: 27862915]

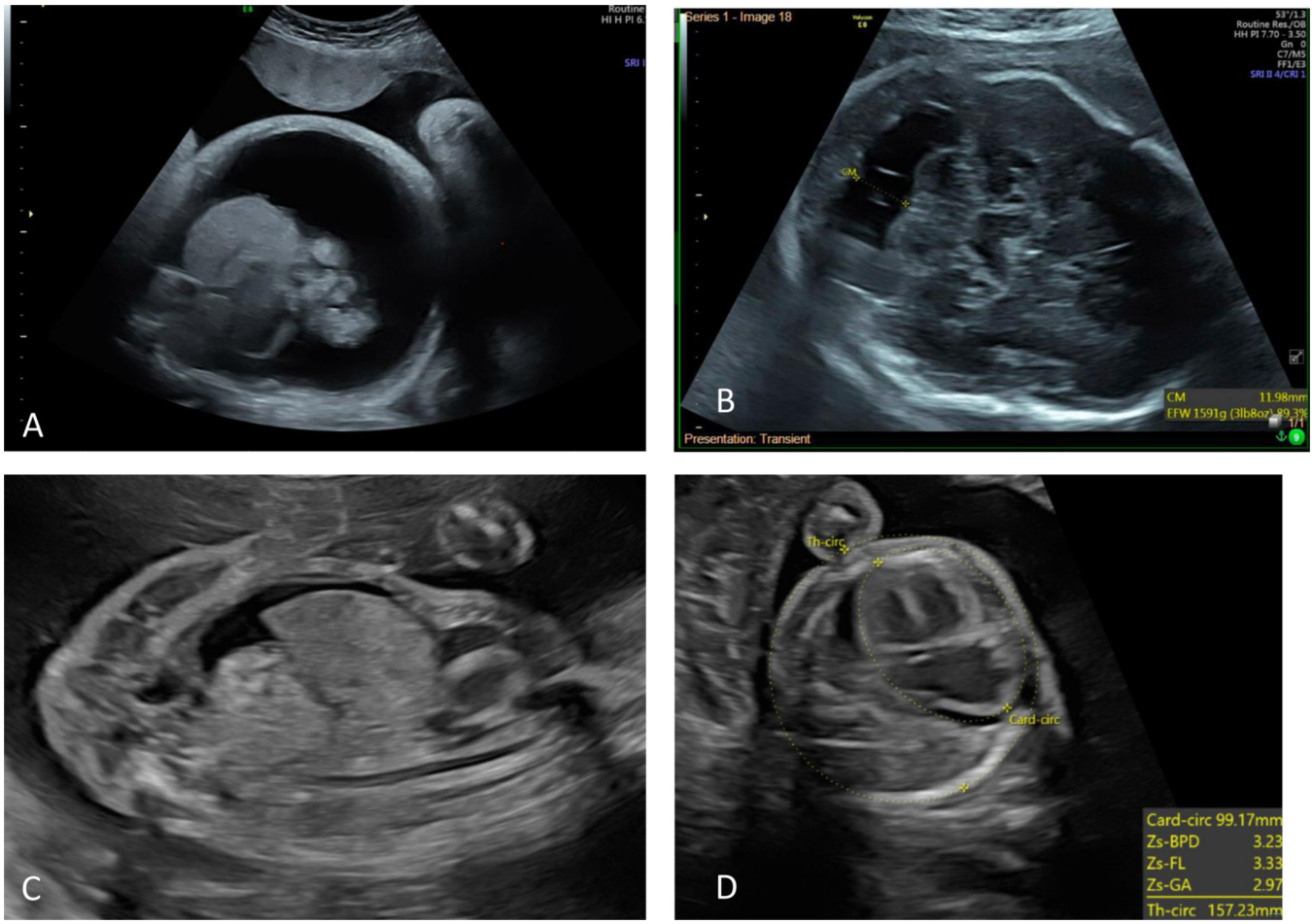

Figure 1:
Ultrasound images of fetal hydrops. Panel A demonstrating ascites in Proband 1. Panel B demonstrates the enlarged cysterna magna. Panel C demonstarting ascities and pleural effusions in proband 2. Panel D demonstrating cardiomegaly in proband 2.

Table 1 A:

Clinical data

Proband	Parental details			Gestation at diagnosis	Phenotypes (HPO terms)	Obstetric History	Family history	Outcome
1	Maternal	Age	34	22w6d	Nonimmune hydrops fetalis (HP:0001790), Pyelectasis (HP:0010945), Ventriculomegaly (HP:0010952) Enlarged cisterna magna (HP:0011427)	G3P2012	Paternal family history of renal reflux requiring surgical correction. (patient's father and paternal aunt)	Delivered at 36w6d, cesarean delivery due to hydrops. Apgar's 6 and 8. Weight: 4280 gm (>99 percentile), length: 95 percentile, head circumference >99 percentile. Postnatal resolution of hydrops, severe and persistent hypotonia, bronchomalacia with subglottic stenosis, persistent gastroesophageal reflux requiring gastrotomy-jejunostomy tube, intestinal malrotation requiring surgery, grade 5 vesicoureteral reflux, stage 3a chronic kidney disease, hyperparathyroidism, hypothyroidism, and Eagle-Barret syndrome. Bicuspid aortic valve, atrial septal defect. Developmental delays
		Ethnicity	White					
	Paternal	Age	Unknown					
		Ethnicity	White					
2	Maternal	Age	35	22w1d	Nonimmune hydrops fetalis (HP:0001790), Cardiomegaly (HP:0001640)	G3P1021	Prior pregnancy with multiple anomalies on anatomy US, large cleft lip and palate, FGR, abnormal skull shape, small cerebellum, low set ears, abnormal interventricular septum and outflows. Extracted DNA negative for *ITPR1* variant.	Elective pregnancy termination at 24w4d Pathological evaluation of the product of conception showed mildly edematous fetus, hydropic placental tissue, liver with extensive extramedullary hematopoiesis with shifts toward erythroid precursors, and adrenal glands with nuclear cytomegaly.
		Ethnicity	Asian					
	Paternal	Age	36					
		Ethnicity	Asian					

Table 1 B:

Genetic findings

Proband	Procedure (Gest Age)	Direct/ culture?	Performed test	Secondary confirmatory test	Gene (name; REFSEQ)	Known disease (OMIM)	Variant	ACMG classification	Criteria applied	Inheritance & zygosity	Interpretation
1	Amniocentesis (22w6d)	Direct	Exome sequencing	Sanger sequencing	*ITPR1* (NM_001378452.1:c.7636G>A)	Spinocerebellar ataxia, Gillepsie syndrome	c.7636G>A [p.Val2531Met]	Likely pathogenic	PS2, PM2, PP3, PP2	De novo, heterozygous	Likely pathogenic
	Amniocentesis (23w0d)	Cultured	Exome sequencing	Sanger sequencing	*ITPR1*(NM_001378452.1:c.34G>A)	Spinocerebellar ataxia, Gillepsie syndrome	c.34G>A [p.Gly12Arg]	Likely pathogenic	PS2, PM2, PP3, PP2	De novo, heterozygous	Likely pathogenic