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Email : editorijhess@gmail.com

Prenatal Exome Sequencing Identifies Two PIEZO1 Variants In Recurrent Nonimmune Hydrops Fetalis: A Case Report

Tedy Teguh Satriadi[1)], Dheafitri Riezka Fahmi[2)], Ketut Rama Wijaya[3)], Rachmad Nugroho[4)], Rudianto Halim Putera[5)]
[1)] Department of Obstetrics and Gynecology, RSUD Kanujoso Djatiwibowo, Indonesia
[2)] Department of Obstetrics and Gynecology, Universitas Indonesia, Indonesia
[3,4,5)] Department of Obstetrics and Gynecology, Universitas Gadjah Mada, Indonesia

*Corresponding Author
Email: tedysatriadi@gmail.com

Abstract

Nonimmune hydrops fetalis (NIHF) is a heterogeneous fetal condition characterized by abnormal fluid accumulation in two or more fetal compartments. Prenatal exome sequencing has increasingly identified monogenic causes of otherwise unexplained NIHF, with PIEZO1 among the most frequently implicated genes. Biallelic loss-of-function PIEZO1 variants are associated with autosomal recessive generalized lymphatic dysplasia with NIHF. A 26-year-old woman, gravida 3 para 1 abortus 1, had one prior pregnancy complicated by hydrops fetalis that ended in pregnancy loss. In the current pregnancy, cell-free DNA screening at 16 weeks 4 days showed low risk for common aneuploidies and selected microdeletion syndromes, with a female fetus and fetal fraction of 9.1%. Maternal serology for cytomegalovirus, toxoplasmosis, syphilis, and parvovirus B19 was non-reactive or negative. Ultrasound demonstrated ascites, bilateral pleural effusions, generalized edema, increased nuchal translucency, tricuspid regurgitation, a cavum velum interpositum cyst, and increased abdominal circumference, fulfilling criteria for NIHF. Prenatal chromosomal microarray showed no phenotype-related copy-number variant and a normal chromosomal constitution. Prenatal exome sequencing of amniotic fluid identified a heterozygous likely pathogenic PIEZO1 nonsense variant, NM_001142864.2:c.1857C>A p.(Tyr619), and a second heterozygous PIEZO1 missense variant of uncertain significance, NM_001142864.2:c.6338C>T p.(Pro2113Leu). A heterozygous EPHB4 variant of uncertain significance was also reported as potentially relevant. Parental segregation was recommended to determine whether the two PIEZO1 variants were in trans. At 20 weeks' gestation, cordocentesis and intraperitoneal intrauterine transfusion were performed for suspected fetal anemia/hemolytic hydrops. Maternal irregular red-cell antibody screening and direct antiglobulin testing were negative, supporting a nonimmune mechanism. This case highlights recurrent NIHF in a family in whom prenatal exome sequencing identified two PIEZO1 variants after chromosomal, infectious, and alloimmune evaluations were unrevealing. The PIEZO1 findings represent the leading molecular explanation, but a definitive autosomal recessive diagnosis requires parental segregation and further evidence regarding the VUS. Early genomic testing can refine etiologic assessment, recurrence counseling, and reproductive planning in unexplained or recurrent NIHF.*

Keywords: PIEZO1; Nonimmune Hydrops Fetalis; Recurrent Fetal Hydrops; Generalized Lymphatic Dysplasia; Prenatal Exome Sequencing; Intrauterine Transfusion; Ephb4.

INTRODUCTION

Hydrops fetalis is defined by abnormal fluid accumulation in at least two fetal compartments, including ascites, pleural effusion, pericardial effusion, and generalized skin edema (Bellini et al., 2015; Khairudin et al., 2023). When red-cell alloimmunization is not responsible, the condition is classified as nonimmune hydrops fetalis (NIHF), which now represents the large majority of hydrops cases and carries substantial perinatal morbidity and mortality (Bellini et al., 2015; Khairudin et al., 2023; Norton et al., 2015). The differential diagnosis is broad and includes cardiovascular, chromosomal, hematologic, infectious, thoracic, lymphatic, metabolic, and syndromic disorders. Because prognosis and recurrence risk depend strongly on etiology, contemporary evaluation is stepwise and typically includes assessment for alloimmunization, structural anomalies, fetal anemia, congenital infection, and chromosomal disease before a monogenic diagnosis is considered (Khairudin et al., 2023; Norton et al., 2015).

Genomic testing has changed the diagnostic approach to unexplained NIHF. Prenatal exome sequencing can identify a molecular diagnosis in a meaningful proportion of fetuses that remain unexplained after standard cytogenetic and infectious evaluation. In a systematic review of prenatal exome studies, PIEZO1 variants accounted for approximately 10% of NIHF cases with a molecular diagnosis, making PIEZO1 the most frequently reported single gene in that setting (Brewer et al., 2023).

PIEZO1 encodes a mechanically activated cation channel with established roles in erythrocyte volume regulation, vascular mechanotransduction, and lymphatic development (Coste et al., 2010; Saotome et al., 2018). Biallelic loss-of-function variants cause autosomal recessive PIEZO1-related generalized lymphatic dysplasia with NIHF, whereas gain-of-function variants cause dehydrated hereditary stomatocytosis (Albuisson et al., 2013; Andolfo et al., 2013; Fotiou et al., 2015; Lukacs et al., 2015). PIEZO1 is also functionally expressed in human endometrium and myometrium (Barnett et al., 2022; Hennes et al., 2019), and recent experimental work demonstrates an essential role in trophoblast fusion and placental development (Zhang et al., 2025). These findings provide biologic plausibility for an important role of PIEZO1 in fetal and placental development, although variant-level interpretation remains critical in prenatal diagnosis.

We report a fetus with severe second-trimester NIHF and a previous sibling pregnancy affected by hydrops, in whom chromosomal microarray was negative and prenatal exome sequencing identified one likely pathogenic PIEZO1 variant and one PIEZO1 variant of uncertain significance. The report emphasizes the diagnostic value of genomic testing while also illustrating the limitations of assigning causality when variant phase and VUS pathogenicity remain unresolved. The report was prepared in accordance with CARE case-report principles (Gagnier et al., 2014; Riley et al., 2017).

RESEARCH METHODS

Patient information and obstetric history

A 26-year-old woman, gravida 3 para 1 abortus 1 (G3P1A1), presented during her third pregnancy. Her obstetric history included one previous term live birth and one prior pregnancy complicated by hydrops fetalis that ended in pregnancy loss. The recurrence of the hydrops phenotype in the current pregnancy raised concern for an inherited fetal disorder.

Preconception laboratory testing approximately 20 months before the index pregnancy had shown detectable HbH inclusion bodies (<1%), interpreted as suggestive of alpha-thalassemia trait. Iron, transferrin saturation, HbA2, and HbF were not suggestive of iron deficiency or beta-thalassemia. Because paternal alpha-globin genotype testing was not available in the records, an alpha-thalassemia-related fetal disorder could not be completely excluded from historical laboratory data alone.

Fetal findings

Ultrasonography in the second trimester demonstrated fetal ascites, bilateral pleural effusions, generalized skin edema, increased nuchal translucency, tricuspid regurgitation, an intracranial cavum velum interpositum cyst, and increased abdominal circumference. These findings fulfilled the clinical definition of NIHF because abnormal fluid accumulation involved more than one fetal compartment (Khairudin et al., 2023; Norton et al., 2015). The laboratory genetic referral additionally documented abnormal fetal cardiovascular physiology, central nervous system morphology, gastrointestinal and pulmonary morphology, scalp morphology, and heart-valve physiology.

Timeline

Time point	Gestational age	Event
Preconception (~20 months before index pregnancy)	—	Maternal hemoglobin study showed HbH inclusion bodies <1%, suggestive of alpha-thalassemia trait.
Prior pregnancy	—	Pregnancy complicated by hydrops fetalis and pregnancy loss.
Early diagnostic workup	16 weeks 4 days	Cell-free DNA screening: low risk for trisomy 21, 18, 13, monosomy X, triploidy, and tested microdeletion syndromes; female fetus; fetal fraction 9.1%.
Same diagnostic period	~16–17 weeks	Maternal CMV IgM, Toxoplasma IgM, and syphilis TP antibody non-reactive; parvovirus B19 IgM and IgG negative.
Amniotic-fluid testing	~16–17 weeks	Amniocentesis performed for prenatal chromosomal microarray and exome sequencing. No significant maternal-cell contamination detected.
Genetic report	~20 weeks	CentoArray prenatal: no phenotype-related CNV; normal chromosomal constitution. CentoXome: PIEZO1 likely pathogenic variant + PIEZO1 VUS; EPHB4 VUS reported as potentially relevant. Parental segregation recommended.
Fetal intervention	20 weeks 0 days	Cordocentesis followed by intraperitoneal intrauterine red-cell transfusion for suspected fetal anemia/hemolytic hydrops.
Blood-bank evaluation	20 weeks 0 days	Mother O Rh-positive; father B Rh-positive; no evidence of irregular maternal red-cell sensitization; direct Coombs and auto-control negative; major maternal-paternal crossmatch incompatible in keeping with ABO heterospecificity.

Etiologic assessment

A structured evaluation for NIHF was undertaken. Cell-free DNA screening was low risk for the common aneuploidies tested. Importantly, a concurrent prenatal chromosomal microarray (CentoArray® Prenatal) performed on amniotic-fluid DNA showed no phenotype-related copy-number variant and a normal chromosomal constitution, reported as arr(1-22)x2 with a normal gonosomal complement. No copy-number-neutral regions of absence of heterozygosity greater than 10 Mb were detected, and significant maternal-cell contamination was not identified.

Maternal infectious testing was unrevealing: CMV IgM, Toxoplasma IgM, and syphilis TP antibody were non-reactive, while parvovirus B19 IgM and IgG were negative. The available results therefore did not support these common infectious causes of fetal hydrops.

Blood-bank testing showed maternal blood group O Rh-positive and paternal blood group B Rh-positive. Maternal red-cell testing showed no in-vivo sensitization or unexpected antibody, with negative direct antiglobulin testing and negative auto-control. The major crossmatch between maternal serum and paternal B-positive red cells was

incompatible, which is expected in the setting of naturally occurring maternal anti-B and does not by itself demonstrate pathologic alloimmunization. Overall, the blood-bank workup did not identify an irregular red-cell alloantibody to explain the hydrops.

Etiologic category	Assessment	Result / interpretation
Common aneuploidy / microdeletion screening	cfDNA/NIPT	Low risk for trisomy 21, 18, 13, monosomy X, triploidy and tested microdeletions; fetal fraction 9.1%.
Chromosomal copy-number abnormalities	Prenatal SNP microarray	Negative; normal chromosomal constitution; no phenotype-related CNV.
Maternal cell contamination	STR analysis	Not significant.
CMV	Maternal CMV IgM	Non-reactive.
Toxoplasmosis	Maternal Toxoplasma IgM	Non-reactive.
Syphilis	Treponemal antibody	Non-reactive.
Parvovirus B19	IgM and IgG	Negative.
Red-cell alloimmunization	Antibody screen / direct Coombs / auto-control	No irregular antibody or in-vivo sensitization identified; direct Coombs and auto-control negative.
Hemoglobinopathy	Maternal Hb study	HbH inclusion bodies <1%, suggestive of alpha-thalassemia trait; paternal alpha-globin status not available.

Prenatal exome sequencing

Prenatal exome sequencing (CentoXome® Prenatal Solo) was performed on DNA extracted directly from amniotic fluid. The assay reported 99.69% of targeted nucleotides covered at ≥20× and no significant maternal-cell contamination. Two heterozygous PIEZO1 variants were identified. The first, NM_001142864.2:c.1857C>A p.(Tyr619*), is a nonsense variant creating a premature stop codon and was classified as likely pathogenic. The second, NM_001142864.2:c.6338C>T p.(Pro2113Leu), is a missense variant classified as a variant of uncertain significance (VUS).

Because PIEZO1-related generalized lymphatic dysplasia with NIHF is typically inherited in an autosomal recessive manner, the reporting laboratory recommended targeted parental testing to establish whether the two variants were in trans. Without segregation data, the fetal result cannot be considered a definitive biallelic molecular diagnosis. A heterozygous EPHB4 VUS, NM_004444.4:c.1310_1314delTGTCTinsGGTCC p.(Val437Gly), was also reported as a potentially relevant finding because EPHB4 is associated with autosomal dominant lymphatic malformation. The reporting laboratory did not consider this finding diagnostic in isolation.

Gene	Variant	Protein	Zygosity	Classification	Comment
PIEZO1	NM_001142864.2:c.1857C>A	p.(Tyr619*)	Heterozygous	Likely pathogenic (class 2)	Nonsense; premature stop codon; novel according to

					laboratory report.
PIEZO1	NM_001142864.2:c.6338C>T	p.(Pro2113Leu)	Heterozygous	VUS (class 3)	Missense; in-silico predictions supportive but insufficient for pathogenic classification.
EPHB4	NM_004444.4:c.1310_1314delTGTCTinsGGTCC	p.(Val437Gly)	Heterozygous	VUS (class 3)	Reported as potentially relevant; associated gene has an autosomal dominant lymphatic phenotype.

Fetal intervention and follow-up

At 20 weeks 0 days' gestation, cordocentesis was performed because of concern for a hematologic contribution to the severe hydrops, followed by intraperitoneal intrauterine red-cell transfusion. The available records document the procedure and blood-bank compatibility workup but do not provide a complete fetal hematology panel sufficient to independently quantify the degree or mechanism of fetal anemia.

Detailed subsequent perinatal outcome, results of parental segregation testing, and functional validation of the PIEZO1 VUS were not available in the records reviewed for this manuscript. These missing data are therefore not inferred or reconstructed.

RESULTS AND DISCUSSION

This case is clinically notable for severe second-trimester NIHF recurring in a family with a prior hydrops-affected pregnancy, together with two fetal PIEZO1 variants identified by prenatal exome sequencing after major chromosomal, infectious, and alloimmune evaluations were unrevealing. The findings make PIEZO1 the leading molecular candidate while simultaneously illustrating why prenatal genomic results must be interpreted conservatively when one allele remains a VUS and phase is unknown.

The diagnostic pathway is consistent with the principle that NIHF is a phenotype rather than a single disease. Standard evaluation aims to identify potentially treatable or prognostically important causes, including alloimmune disease, fetal anemia, structural abnormalities, congenital infection, and chromosomal abnormalities (Bellini et al., 2015; Khairudin et al., 2023; Norton et al., 2015). In this case, a low-risk cfDNA screen was followed by a negative prenatal SNP microarray, which is diagnostically more informative for clinically significant copy-number abnormalities than screening alone. Infectious serology was unrevealing, and no irregular maternal red-cell alloantibody was identified. These results increased the relative likelihood of a monogenic disorder and provided a strong rationale for prenatal exome sequencing.

The PIEZO1 result is biologically and clinically plausible. PIEZO1 is a mechanosensitive cation channel that participates in cellular responses to mechanical force (Coste et al., 2010; Saotome et al., 2018). Biallelic loss-of-function variants have been linked to generalized lymphatic dysplasia with NIHF (Fotiou et al., 2015; Lukacs et al., 2015), and a systematic review of prenatal exome data found PIEZO1 to be the most commonly reported single gene among molecularly diagnosed NIHF cases (Brewer et al., 2023). The fetus in this report showed a phenotype compatible with severe lymphatic dysfunction, including generalized edema, ascites, and bilateral pleural effusions. In addition, emerging experimental evidence has shown that PIEZO1 is expressed in placental trophoblasts and is required for trophoblast fusion and placental development (Zhang et al., 2025), further expanding the mechanistic context in which PIEZO1 dysfunction may affect pregnancy.

Nevertheless, causality cannot be considered established. The c.1857C>A p.(Tyr619*) variant was classified as likely pathogenic, whereas c.6338C>T p.(Pro2113Leu) remained a VUS. Under ACMG/AMP principles, a VUS should not be used as a stand-alone basis for clinical diagnosis or irreversible management decisions (Richards et al., 2015). In an autosomal recessive disorder, parental segregation is particularly important because demonstration that the two variants are in trans would support a biallelic genotype, whereas a cis configuration would substantially weaken the proposed mechanism. Functional data or additional affected-family segregation could further clarify the missense variant.

The additional EPHB4 VUS is also of interest but should remain secondary in interpretation. Pathogenic EPHB4 variants are an established cause of autosomal dominant lymphatic-related hydrops fetalis (Martin-Almedina et al., 2016). However, the fetal EPHB4 finding was a VUS, and the available data do not establish that it contributed independently or synergistically to the phenotype. It is therefore best regarded as a hypothesis-generating finding rather than evidence of oligogenic disease.

Maternal alpha-thalassemia trait warrants separate consideration because severe alpha-thalassemia can cause fetal hydrops. Detectable HbH inclusion bodies suggested maternal alpha-globin carrier status, but the paternal alpha-globin genotype was not available. Standard exome sequencing may not reliably detect all large deletions or complex rearrangements within the alpha-globin locus. Accordingly, if clinically relevant to retrospective etiologic clarification or future reproductive planning, targeted parental HBA1/HBA2 deletion testing would be the appropriate method to more definitively assess this differential.

The fetal transfusion highlights a practical management challenge in severe NIHF. Intrauterine transfusion is established therapy when fetal anemia is confirmed or strongly suspected (Lindenburg et al., 2014). In the present case, intervention was performed in the setting of suspected hemolytic hydrops, but maternal alloimmune testing was negative and the available records do not include sufficient fetal hematologic values to determine the exact contribution of anemia to the hydrops. The transfusion should therefore be reported as a

therapeutic intervention for suspected fetal anemia rather than evidence that immune hemolysis was proven.

This case also has implications for future reproductive counseling. If parental segregation demonstrates that the two PIEZO1 variants are in trans and the missense VUS is subsequently upgraded to pathogenic or likely pathogenic, the recurrence risk would be consistent with autosomal recessive inheritance, including a 25% risk for an affected conceptus in each pregnancy. Until those criteria are met, counseling should explicitly communicate uncertainty. Once a disease-causing familial genotype is established, options can include targeted prenatal diagnosis and preimplantation genetic testing for monogenic disease (PGT-M) in accordance with established practice recommendations (ESHRE PGT-M Working Group et al., 2020).

Strengths and limitations

A major strength of this report is the breadth of the etiologic evaluation, which included cfDNA screening, prenatal chromosomal microarray, infectious serology, blood-bank investigation, and prenatal exome sequencing from amniotic fluid. The recurrence of a similar fetal phenotype in a previous pregnancy further increases suspicion of an inherited cause.

The principal limitation is the absence of parental segregation results, which prevents confirmation that the two PIEZO1 variants are in trans. Functional validation of the missense VUS was also unavailable. Detailed fetal hematology at the time of transfusion and complete pregnancy/neonatal outcome data were not available. Finally, paternal alpha-globin molecular testing was not documented, so an alpha-thalassemia-related contribution cannot be fully excluded.

CONCLUSION

Prenatal exome sequencing identified one likely pathogenic PIEZO1 variant and one PIEZO1 VUS in a fetus with severe recurrent NIHF after chromosomal microarray, infectious testing, and maternal alloimmune evaluation were unrevealing. The phenotype and gene-disease relationship make PIEZO1 the leading candidate etiology; however, the result should not be labeled a definitive biallelic diagnosis until variant phase and the clinical significance of the VUS are clarified. This case supports early genomic evaluation in unexplained or recurrent NIHF and underscores the importance of segregation analysis for accurate recurrence counseling and precision reproductive planning.

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