Prenatal Diagnosis

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Prenatal Diagnosis of Warsaw Breakage Syndrome: Fetal Compound Heterozygous Variants in the *DDX11* Gene Associated With Growth Restriction, Cerebral, and Extra-Cerebral Malformations

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ABSTRACT

Warsaw Breakage Syndrome (WABS) is a rare autosomal recessive cohesinopathy characterized by growth retardation and congenital anomalies. This report aims to highlight the prenatal diagnosis of WABS through ultrasound findings and genetic testing. We report a case of prenatal diagnosis of WABS in a 24-week gestation fetus exhibiting microcephaly, delayed sulcation, short corpus callosum, cerebellar vermis hypoplasia and intrahepatic portal-systemic shunts. The couple had a history of a prior pregnancy termination due to severe intrauterine growth restriction and cerebral malformations. Whole exome sequencing revealed compound heterozygous pathogenic variants [NM_030653.4:c.1403dupT, p.(Ser469Valfs*32) and c.1672C>T, p.(Arg558*)] in the *DDX11* gene, consistent with WABS. The same pathogenic variants were identified in the prior terminated fetus upon subsequent analysis. Postmortem examination of the proband confirmed the prenatal ultrasound findings. This case expands the understanding of the prenatal phenotypic spectrum of WABS by identifying specific cerebral and extracerebral anomalies associated with pathogenic variants in the *DDX11* gene. Incorporating advanced genetic diagnostics like whole exome sequencing into prenatal care provides valuable information for genetic counseling and management of rare genetic disorders.

1 | Fetal Phenotype

A 25-year-old woman gravida 4, para 2 was referred at 24 + 3 weeks of gestation. Sonographic assessment (Figure 1B,C,D) of the proband (II,4) detected microcephaly (HP:0000252) with a head circumference of 199.2 mm (-3DS) [3], delayed sulcation (HP:0002536), short corpus callosum (HP:0200012) [1], cerebellar vermis hypoplasia (HP:0006817) [2], an intrahepatic arterio-venous (HP:0012022) as well venous-venous shunt (HP:0012022) (Figure 1B–D). Fetal weight was estimated at the 11th percentile [4]. The parents were nonconsanguineous, and the familial history was noncontributory (Figure 1A). Patient's

Summary

- What's already known about this topic?
  - Warsaw Breakage Syndrome is a rare cohesinopathy due to biallelic variants in the *DDX11* gene, primarily characterized by growth restriction and developmental delay.
  - To date, Warsaw Breakage Syndrome has been predominantly diagnosed postnatally, with limited available data regarding both phenotype and genotype.
- What does this study add?
  - We report a new case of antenatal diagnosis of Warsaw Breakage Syndrome and highlight associated cerebral and extra-cerebral anomalies identified via ultrasound.
  - Provides new insights into the prenatal phenotype of Warsaw Breakage Syndrome.
  - Highlights the importance of exome sequencing in fetal malformations of cortical development.

obstetrical history was significant for two prior term healthy pregnancies and termination of pregnancy at 25 weeks (II,2) for intrauterine growth restriction (HP:0001511), brachycephal (HP:0000248), corpus callosum hypoplasia (HP:0002079), cerebellar vermis hypoplasia (HP:0006817) and hyperechogenic bowel (HP:0010943). Clinical findings are reported in Table 1A.

2 | Diagnostic Method

Genetic analysis of the proband (II,4) was performed by array-CGH and whole-exome sequencing on DNA extracted from amniotic fluid. The findings were validated through Sanger sequencing. Familial segregation analysis was performed by Sanger sequencing on parental blood samples and DNA extracted from cultured amniotic cells of the fetus from the first terminated pregnancy (II,2).

3 | Diagnostic Results and Interpretation

Two compound heterozygous pathogenic variants [NM_03-0653.4: c.1403dupT, p.(Ser469Val*fs**32) and c.1672C>T, p.(Arg558*)] in the *DDX11* gene (OMIM*601150) were detected in the proband (II,4), whereas no pathogenic copy number variants were identified. The same compound heterozygous variants in

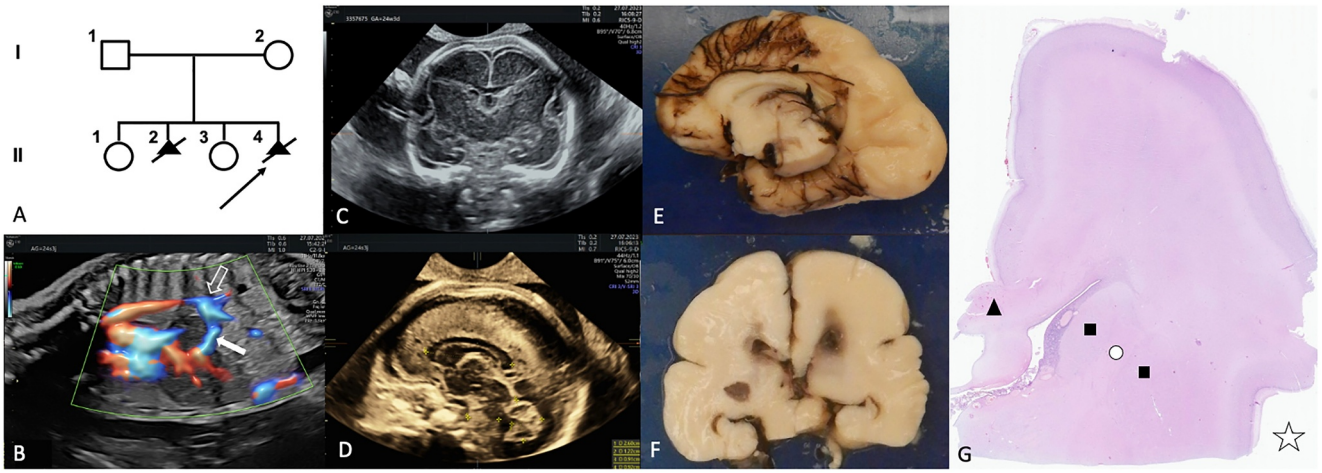

FIGURE 1 | (A) Family tree including the proband (II,4) with compound heterozygous variants. Prenatal ultrasound imaging at 24 + 3 weeks: (B) 2D-color Doppler view illustrating a shunt between the hepatic artery (outlined arrow) and left portal vein (solid white arrow). (C) Coronal plane demonstrating delayed sulcation of the sylvian fissures. (D) 3D multiplanar sagittal plane illustrating measurement of the length of the corpus callosum (26 mm, 5th–10th percentile) [1], the antero-posterior diameter of the vermis (9.1 mm, 5th–10th percentile) [2] and the cranio-caudal diameter of the vermis (12.2 mm, < 5th percentile) [2] at 24 weeks. At 27 weeks, the length of the corpus callosum remained at 26 mm (< 5th percentile) [1], the antero-posterior diameter of the vermis (9.3 mm, 5th percentile) [2] and the cranio-caudal diameter of the vermis (14.0 mm, < 5th percentile) [2]. Postmortem findings at 28 weeks of gestation: (E) Sagittal view showing similar findings to ultrasound imaging with a short appearing corpus callosum and a well-developed calcarine sulcus. (F) Coronal view of the fronto-parietal-temporal lobes showing the third ventricle and thalami. The cortical surface displays few gyri with a poorly developed lateral sulcus for the gestational age. (G) Hematoxylin and eosin-stained slide: coronal view of the right fronto-parietal lobes at the level of the lateral fissure, highlighting an abnormally wide lateral fissure (star) with normal cortical architecture. The caudate and putamen, internal capsule, and corpus callosum are also visible (indicated by the symbols: square, circle, and triangle, respectively). [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1A | Clinical data.

Case	Parental details			Gestation at diagnosis	Phenotypes (HPO terms)	Obstetric history	Family history	Outcome
II,4a (proband)	Maternal	Age	25	24 weeks	Microcephaly (HP:0000252)	G4P2TA1	Unremarkable	Termination of pregnancy at 28 weeks
		Ethnicity	Caucasian		Delayed gyration (HP:0002536)			
	Paternal	Age	34		Short corpus callosum (HP:0200012)			
		Ethnicity	Caucasian		Cerebellar vermis hypoplasia (HP:0006817)			
					Intrahepatic portal-systemic shunt (HP:0012022)			
II,2 (sibling)				25 weeks	IUGR (HP:0001511) Brachycephaly (HP:0000248)			Termination of pregnancy at 26 weeks
					Corpus callosum hypoplasia (HP:0002079)			
					Cerebellar vermis hypoplasia (HP:0006817)			
					Hyperechogenic bowel (HP:0010943)			

DDX11 were detected in the DNA of the terminated fetus (II,2). The duplication c.1403dupT inherited from the mother caused a premature stop codon in exon 13, whereas the substitution c.1672C>Tof paternal origin created a premature stop codon in exon 15. Both variants were present in the Genome Aggregation Database (gnomAD; v.4.0.0) and reported as pathogenic in ClinVar. The pathogenic variants in *DDX11* and ultrasound findings were consistent with the diagnosis of Warsaw Breakage Syndrome (WABS). Genetic findings are illustrated in Table 1B.

4 | Pregnancy Outcomes and Postmortem Findings

Postmortem examination of the fetus (II,4) (Figure 1E–G) confirmed microcephaly, diffuse delayed sulcation, hypoplastic vermis and corpus callosum (Figure 1E–G). Furthermore, an intrahepatic portal-systemic shunt was suggested by mixing two different colorants. However, the confirmation of the presence of this shunt is limited by potential technical artifacts due to the small vessel caliber during injection.

5 | Discussion

To date, a limited number of WABS cases have been reported in the literature since the first diagnosis in 2010, with one of these identified prenatally [5]. WABS is a rare recessive hereditary disease caused by bi-allelic variants in the gene *DDX11*, which encodes a DEAD box protein [6]. This protein functions as an ATP-dependent DNA helicase with 5′ to 3′ directionality, and is part of the superfamily 2 of DNA helicases [7]. *DDX11* maintains chromosome transmission fidelity, genome stability, DNA repair and sister chromatid cohesion. Clinical features thus far observed in WABS patients include pre- and postnatal growth retardation, severe microcephaly, facial dysmorphia, hearing loss due to cochlear malformations, cardiac malformations and skin pigmentation anomalies [8]. Both fetuses (II,2/II,4) had major malformations detected at ultrasound in the second trimester of pregnancy and genetic analysis detected the same compound heterozygous pathogenic variants of the *DDX11* gene: a frameshift variant in the maternal allele (c.1403dupT) and a nonsense variant in the paternal allele (c.1672C>T), leading to truncated proteins. One fetus also exhibited a feature newly identified as part of the WABS spectrum: intrahepatic

TABLE 1B | Genetic findings.

Case	Procedure (gest age)	Direct/ culture?	Performed test	Secondary confirmatory test	Gene (name; REFSEQ)	Known disease (OMIM)	Variant	ACMG classification	Criteria applied	Inheritance and zygosity	Interpretation
II,4 (proband)	Amniocentesis (24)	Direct	Whole exome sequencing	Sanger sequencing	DDX11 (NG_023352.1)	Warsaw Breakage Syndrome (613398)	Allele 1: c.1403dupT (p.Ser469Valfs*32)	Pathogenic	PVS1, PM2, PM3	Autosomal recessive heterozygous	Pathogenic
							Allele 2: c.1672C>T (p.Arg558*)	Pathogenic	PVS1, PM2, PM3	Autosomal recessive heterozygous	Pathogenic
II,2 (sibling)	Postmortem (25)	Culture	Sanger sequencing		DDX11 (NG_023352.1)	Warsaw Breakage Syndrome (613398)	Allele 1: c.1403dupT (p.Ser469Valfs*32)	Pathogenic	PVS1, PM2, PM3	Autosomal recessive heterozygous	Pathogenic
							Allele 2: c.1672C>T (p.Arg558*)	Pathogenic	PVS1, PM2, PM3	Autosomal recessive heterozygous	Pathogenic

portal-systemic anomalies (II,4). Currently, the limited number of identified variants and insufficient clinical descriptions hinder the establishment of a phenotype-genotype correlation for *DDX11* mutations. Our findings aim to improve the detailed characterization of WABS's antenatal phenotypic spectrum.

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Ethics Statement

The authors have nothing to report.

Consent

Consent has been obtained from the patient for this publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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