Advances in Obesity, Endocrinology, and Diabetes

Volume 3 Issue 2 (July-Dec 2026) | **ISSN**: 3049-0715

CASE REPORT

Genotype phenotype correlation of a homozygous DDX11 variant of uncertain significance in a 21-year-old Sudanese woman with a Warsaw Breakage Syndrome phenotype

Mustafa Alqaysi, MD[1] Bashar Sahar, MRes[2] Malak AlMukhtar[3]

[1] Department of Pediatrics, CMC Hospital, Dubai, United Arab Emirates
[2] Department of Adult Endocrinology, CMC Hospital, Dubai, United Arab Emirates
[3] School of Medicine, Queen's University Belfast, Belfast, United Kingdom

Correspondence
Dr Mustafa Alqaysi, MD, Department of Pediatrics,
CMC Hospital, Dubai, United Arab Emirates
Mustafa.alqaysi@cmcdubai.ae

Abstract

Warsaw Breakage Syndrome (WABS) is a rare autosomal recessive chromosome instability disorder caused by biallelic pathogenic variants in DDX11 [1]. It is characterised by growth restriction, microcephaly, intellectual disability and sensorineural hearing loss [1,4,5]. We report a 21-year-old Sudanese woman with severe proportionate short stature, microcephaly, intellectual disability, hearing loss and pigmentary skin changes. Genetic testing identified a homozygous DDX11 missense variant (c.707A>G; p.His236Arg), classified as a variant of uncertain significance (VUS). Despite uncertain classification, the phenotype is highly suggestive of WABS. This case highlights the importance of clinical correlation in interpreting VUS findings in rare cohesinopathies [5,8].

Background

Warsaw Breakage Syndrome (WABS; OMIM #613398) is a rare autosomal recessive chromosome instability disorder first described in 2010 [1]. It is caused by biallelic pathogenic variants in DDX11, which encodes a DNA helicase involved in sister chromatid cohesion, DNA replication and genomic stability [1–3].

Clinically, WABS is characterised by prenatal and postnatal growth restriction, microcephaly, developmental delay, intellectual disability and sensorineural hearing loss [1,4,5]. Additional findings may include craniofacial dysmorphism, skeletal anomalies and pigmentary skin changes [4,5].

Volume 3 Issue 2 (July-Dec 2026) | **ISSN**: 3049-0715

Because of overlap with other chromosome instability syndromes such as Fanconi anaemia, Bloom syndrome and Roberts syndrome, molecular testing is essential for diagnosis [5,8]. However, interpretation of rare DDX11 variants remains challenging when classified as variants of uncertain significance [5,8].

Case Presentation

A 21-year-old Sudanese woman was referred for genetic evaluation due to severe short stature and global developmental delay.

Developmental history revealed delayed motor and language milestones from infancy. She required long-term assistance for daily activities due to intellectual disability.

On examination, she had:

- Severe proportionate short stature (below 3rd percentile)
- Marked microcephaly
- Craniofacial dysmorphism (non-specific)
- Bilateral hearing impairment
- Abnormal skin pigmentation

There was no history of bone marrow failure, recurrent infections or malignancy.

Investigations

- Routine haematological and biochemical investigations were normal.
- Audiological evaluation confirmed bilateral sensorineural hearing loss, a characteristic feature of WABS [4,5].
- Genetic testing was performed due to suspicion of a chromosome instability disorder.

Genetic testing

- **Gene: DDX11 (NM_030653.4)**
- **Variant: c.707A>G (p.His236Arg)**
- **Zygosity: Homozygous**
- **Classification: Variant of uncertain significance (VUS)**
- **No additional pathogenic or likely pathogenic variants detected**

Differential Diagnosis

The differential diagnosis included:

- Warsaw Breakage Syndrome (DDX11-related disorder) [1,5]
- Fanconi anaemia (excluded due to lack of bone marrow failure) [5,8]
- Bloom syndrome [5]
- Roberts syndrome [5]
- Cornelia de Lange syndrome spectrum [8]
- The clinical phenotype together with the DDX11 finding supported a cohesinopathy most consistent with WABS.

Volume 3 Issue 2 (July-Dec 2026) | **ISSN**: 3049-0715

Treatment and Management

There is no disease-modifying therapy for WABS [5,8]. Management is supportive and multidisciplinary:

- Audiological rehabilitation
- Developmental and educational support
- Nutritional and growth monitoring
- Neurological follow-up
- Genetic counselling regarding autosomal recessive inheritance and recurrence risk [5,8]

Outcome and Follow-Up

The patient remains clinically stable under multidisciplinary follow-up, with focus on improving communication and functional independence.

Discussion

Warsaw Breakage Syndrome is a rare cohesinopathy caused by biallelic DDX11 variants leading to defects in sister chromatid cohesion and genomic instability [2,3,6]. The phenotype includes growth restriction, microcephaly, intellectual disability and hearing loss [1,4,5].

In this case, a homozygous DDX11 variant (c.707A>G; p.His236Arg) was identified and classified as a VUS. Although not previously established as pathogenic, the phenotype is highly consistent with WABS.

This case highlights several important issues:

First, phenotype-driven diagnosis remains essential in rare disorders [5,8]. Second, VUS findings should not be used in isolation for diagnosis. Third, strong genotype–phenotype correlation may suggest pathogenicity in rare disease genes. Finally, adult presentation of WABS is rarely reported and expands the known phenotypic spectrum [5,7].

This case likely represents a DDX11-related cohesinopathy within the WABS spectrum, pending future variant reclassification.

Learning Points

- Warsaw Breakage Syndrome is a rare autosomal recessive disorder caused by DDX11 variants [1].
- Clinical features include short stature, microcephaly, intellectual disability and hearing loss [1,4,5].
- Variants of uncertain significance require cautious interpretation and clinical correlation [5,8].
- Homozygous rare variants in strong phenotype–gene matches may still be clinically meaningful.
- Adult presentations of WABS are rare and expand the phenotypic spectrum [5,7].

Volume 3 Issue 2 (July-Dec 2026) | **ISSN**: 3049-0715

References

1-van der Lelij P, Chrzanowska KH, Godthelp BC, et al. Warsaw breakage syndrome, a cohesinopathy associated with mutations in the DNA helicase DDX11. Am J Hum Genet. 2010;86:262–266.

2-Capo-Chichi JM, Bharti SK, Sommers JA, et al. Identification and biochemical characterization of a novel mutation in DDX11 causing Warsaw breakage syndrome. Hum Mutat. 2013;34:103–107.

3-Bharti SK, Khan I, Banerjee T, et al. Molecular functions and cellular roles of the ChlR1/DDX11 DNA helicase defective in Warsaw breakage syndrome. Cell Mol Life Sci. 2014;71:2625–2639.

4-Eppley HE, Mendelsohn BA, Slavotinek AM. Warsaw breakage syndrome associated with novel DDX11 mutations and cochlear anomalies. Am J Med Genet A. 2017;173:238–245.

5-Alkhunaizi E, Shaheen R, Bharti SK, et al. Warsaw breakage syndrome: further clinical and genetic delineation. Am J Med Genet A. 2018;176:2404–2418.

6-Pisani FM, Napolitano E, Napolitano LMR, Onesti S. Molecular and cellular functions of the Warsaw breakage syndrome DNA helicase DDX11. Genes (Basel). 2018;9:564.

7-Bailey C, Fryer A, Greenslade M. Two further patients with Warsaw breakage syndrome: is a mild phenotype possible? Clin Genet. 2019;95:315–317.

8-Chrzanowska KH, Gregorek H, Dembowska-Bagińska B, et al. Warsaw breakage syndrome. In: Adam MP, Mirzaa GM, Pagon RA, eds. GeneReviews®. Seattle: University of Washington; updated periodically.