CASE REPORT

First Iraqi case of OTUD6B-related disorder: A novel splice-site variant and review of the literature

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ABSTRACT

OTUD6B-related disorder is a rare autosomal recessive syndrome characterized by intellectual disability, developmental delay, seizures, and dysmorphic features. Since its first description in 2017, fewer than 25 cases have been reported globally. Here, we describe the first genetically confirmed case from Iraq with a novel homozygous splice-site variant in the *OTUD6B* gene.

Whole-exome sequencing (WES) was performed on a 2.5-year-old male presenting with global developmental delay, infantile spasms, microcephaly, dysmorphic facial features, and a ventricular septal defect. Both parents were first cousins. WES identified a novel homozygous splice-site variant in *OTUD6B*: c.235-3C>G. This variant was absent in gnomAD and 1000 Genomes databases and is predicted to disrupt normal mRNA splicing. The same variant was found in a heterozygous state in both parents. Clinically, the patient shares many hallmark features of OTUD6B-related disorder, including hypotonia, feeding difficulties, ear anomalies, and abnormal dentition. Additional findings in this case include a prominent cartilaginous coccyx, metopic suture craniosynostosis, and reduced visual and auditory acuity, expanding the known phenotypic spectrum. This case confirms the pathogenicity of a novel splice-site variant in *OTUD6B* and further illustrates the phenotypic variability of *OTUD6B*-related disorder. It emphasizes the diagnostic value of WES in consanguineous populations and contributes new data to the global understanding of this rare condition. (www.actabiomedica.it)

Key words: *OTUD6B*-related disorder, splice-site variant, intellectual disability, consanguinity, rare disease, whole-exome sequencing

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Introduction

OTUD6B-related disorder is a rare, multisystemic, autosomal-recessive syndrome caused by biallelic pathogenic variants in the *OTUD6B* gene. It is clinically characterized by intellectual disability, developmental delay, seizures, microcephaly, dysmorphic facial features, and, in some cases, cardiac and skeletal abnormalities. The clinical spectrum varies in severity and may include hypotonia, feeding difficulties, congenital heart defects, and global developmental delay (GDD). The disorder is inherited in an autosomal recessive manner, requiring pathogenic alleles from both parents for disease manifestation. Consequently, the likelihood of homozygous pathogenic variants is increased in consanguineous families. In populations with a high rate of consanguinity, such as in parts of the Middle East, identifying rare inherited disorders like this is of increasing clinical relevance. The association between *OTUD6B* variants and syndromic intellectual disability was first described by Santiago-Sim *et al*. (1), who identified 12 individuals from six families (two non-consanguineous and four consanguineous) sharing hallmark clinical features including seizures, developmental delay, and craniofacial dysmorphisms. Since then, several case reports have contributed to expanding the known phenotypic spectrum and supporting the pathogenicity of novel variants. The first Mexican case, for instance, revealed systemic involvement with hypothyroidism and immune dysfunction (2), indicating that *OTUD6B*-related phenotypes may involve broader organ systems. In contrast, a report by Abdel-Salam *et al*. (3) refined the clinical definition by excluding retinal degeneration as a core feature, highlighting the importance of precise genotype–phenotype correlation. Subsequent replication studies have confirmed the role of splice-site and non-coding variants in disease causation (4). *Alkuraya* emphasized the disorder's phenotypic heterogeneity and the challenge of recognizing it in the absence of pathognomonic features, particularly in populations with high consanguinity (5). The first Spanish case further reinforced key manifestations of the disorder, including dysmorphic facies, seizures, and limb anomalies, supporting its global prevalence and underdiagnosis (6) (Figure 1). The *OTUD6B* gene, located on chromosome 8q21.3, encodes a deubiquitinating enzyme (DUB) that recycles ubiquitin and regulates protein degradation via the 26S proteasome (7). Variations in genes encoding enzymes that regulate ubiquitination are implicated in intellectual disability and related syndromes (8). *OTUD6B* also plays crucial roles in DNA repair, apoptosis, oncogenic pathways, and cell cycle checkpoints (7,9). *OTUD6B* is widely expressed in multiple tissues, including the brain, gastrointestinal tract, liver, lungs, endocrine organs, and immune cells (10), consistent with the disorder's multisystemic nature. Furthermore, *OTUD6B* is a known downstream regulator of mTORC1, a master controller of protein synthesis, neural differentiation, and cellular growth (11,12). Despite the growing recognition of *OTUD6B*-related disorder, diagnosis remains challenging due to its rarity, variable expressivity, and overlap with other neurodevelopmental syndromes. Whole-exome sequencing (WES) has become indispensable in identifying pathogenic variants, especially in genetically heterogeneous disorders and consanguineous populations. In this report, we present the first confirmed case of *OTUD6B*-related disorder in Iraq, identified through WES in a child born to consanguineous parents. We describe the patient's clinical features, a novel homozygous splice-site variant, and compare the findings to previously reported cases, thereby expanding the global understanding of this rare condition.

Case report

The proband is a 2.5-year-old male, born at term via Caesarean section after an uneventful pregnancy to first-cousin parents from the Kurdistan region of Iraq. He was the first live-born child following two prior spontaneous abortions. His birth weight was 6.6 kg, and his height was 76.5 cm. Postnatally, the patient was admitted to the neonatal intensive care unit (NICU). The patient has exhibited global developmental delay (GDD) since infancy. He achieved head control at 4 months and a social smile at 2 months. At 2.5 years of age, he remains unable to sit without support. His developmental age is approximately 5 months for motor skills and 7 months for babbling. He also demonstrates generalized hypotonia, feeding

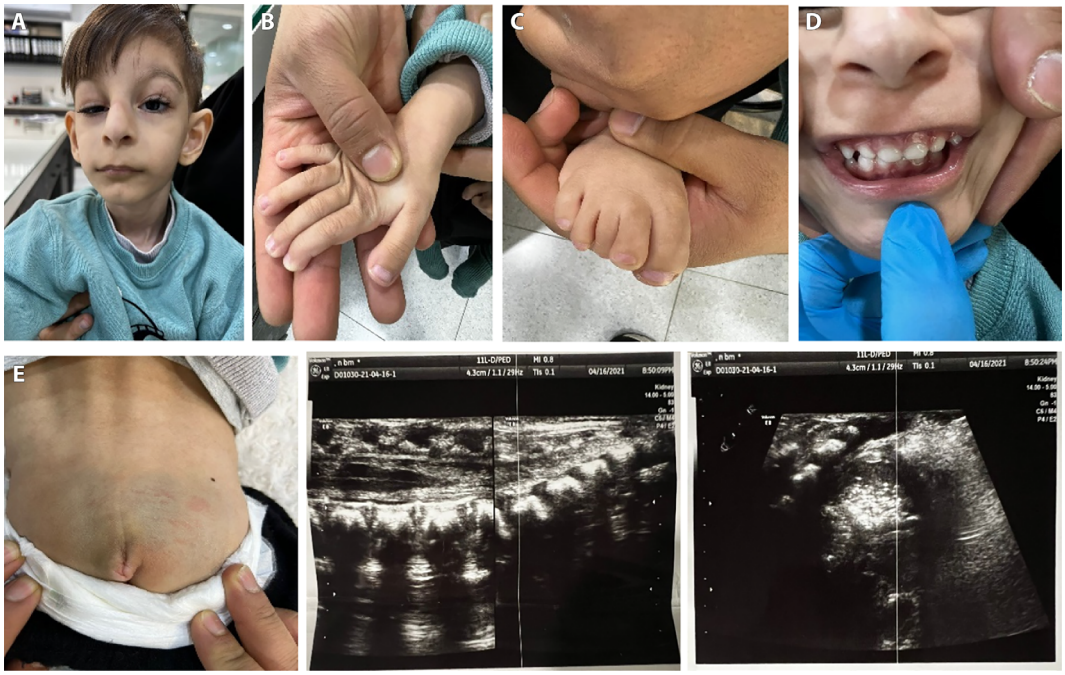

Figure 1. Clinical and radiological features of the index patient. A) Frontal view of the index patient showing dysmorphic facial features. (B-C) Hands and feet showing large thumbs, broad distal phalanges, and fetal pads. (D) Abnormally shaped teeth. (E) Musculoskeletal ultrasound revealed a prominent cartilaginous coccyx, with no evidence of meningocele or sacrococcygeal mass. The spinal cord appeared normal in echogenicity, terminating at L2. (consent obtained for image publication).

difficulties, inappropriate crying, and seizures, which have become more frequent over time. Gastroesophageal reflux disease (GERD) is present, though he has no history of constipation and maintains a normal sleep pattern. Physical examination revealed multiple dysmorphic features, including right eye congenital ptosis, metopic suture craniosynostosis, protruding and elongated ears, and prominent distal phalanges (Figure 1 A-D). Notably, he has microcephaly with a head circumference below the 3rd percentile for age. Additional findings include cryptorchidism (bilateral undescended testes), a prominent cartilaginous coccyx without signs of meningocele or sacrococcygeal mass, and failure to thrive. Spinal ultrasound showed normal spinal cord echogenicity terminating at the L2 level (Figure 1E). Cardiovascular examination and imaging revealed acyanotic congenital heart disease with a large perimembranous (PM)-type ventricular septal defect (VSD), a peak gradient of 25 mmHg, non-obstructive systolic anterior motion (SAM), doming of the pulmonary valve with an annulus diameter of 13 mm and peak velocity of 40 mmHg, and dilation of the left atrium and left ventricle. Mild pulmonary hypertension was also noted. In March 2022, the patient underwent paediatric open-heart surgery, including transatrial Dacron patch closure of the VSD, resection of a subaortic membrane, and pulmonary valvotomy. Following surgery, he developed a postoperative fever, and seizure episodes began shortly thereafter. Echocardiography following the procedure confirmed an intact VSD closure with no residual shunt, corrected mitral valve function, mild right ventricular outflow tract (RVOT) gradient, dilated main pulmonary artery, and normal biventricular function without pericardial or pleural effusion. Neurologically, he was diagnosed with West syndrome, characterized by infantile spasms and hypsarrhythmia. Electroencephalography (EEG) revealed bursts of generalized high-amplitude sharp-spike waves and slow-wave discharges, consistent with this diagnosis. Brain MRI demonstrated microcephaly and patchy fluid in the bilateral mastoid air cells, more prominent on the left, suggestive of mastoiditis.

A non-contrast CT scan of the brain revealed no significant structural abnormalities. The patient also suffers from recurrent bronchopneumonia due to *Pseudomonas aeruginosa*, accompanied by copious bronchorrhea, persistent respiratory distress, and gross failure to thrive. Visual and auditory responsiveness is diminished. Genetic testing was initiated due to the complexity of the clinical presentation. Chromosomal microarray analysis was unremarkable. Further genetic evaluation was conducted using WES, which identified a novel homozygous splice-site variant in *OTUD6B* (c.235-3C>G), located in intron 2. This variant is absent from major population databases, including gnomAD and the 1000 Genomes Project. According to the American College of Medical Genetics and Genomics (ACMG) criteria, the variant was classified as likely pathogenic, based on its predicted impact on splicing, absence in population controls, and compatibility with the patient's phenotype (13). Segregation analysis revealed that both parents are heterozygous carriers of the variant (Table 1). These findings support a diagnosis of an *OTUD6B*-related neurodevelopmental disorder.

Discussion

This case report presents the first confirmed diagnosis of *OTUD6B*-related disorder in Iraq, thereby contributing to the growing global understanding of this rare neurodevelopmental syndrome. The proband, a 2.5-year-old male born to consanguineous parents, exhibited hallmark features of the disorder, including GDD, intellectual disability, seizures, microcephaly, dysmorphic facial features, and congenital heart defects. WES identified a novel homozygous splice-site variant (c.235-3C>G) in the *OTUD6B* gene, classified as likely pathogenic. Comparison with previously reported cases (Table 2 and Figure 2) reveals significant phenotypic overlap. Intellectual disability and developmental delay were universal across nearly all published cases, consistent with our patient. Seizures were observed in 16 out of 20 cases (80%), aligning with the patient's diagnosis of West syndrome. Microcephaly was present in 60% of cases and was similarly observed in our proband. Facial dysmorphism, including a long philtrum, prominent nasal bridge, and large ears, was a common feature that our patient shared. Cardiovascular anomalies, although variable, occurred in ~47% of cases (Figure 2); our case included a complex congenital heart defect (VSD with SAM and pulmonary valvular abnormalities), which required surgical intervention. Additional findings in our case, such as cryptorchidism, align with less commonly reported features, four cases to date, but are increasingly recognized as part of the broader *OTUD6B*-related phenotype. The presence of a prominent coccyx and metopic suture craniosynostosis and reduced visual and auditory acuity have not been reported in previous literature, suggesting potential novel features or underreported traits of the disorder. Furthermore, the patient's visual and auditory impairments and the persistence of bronchorrhea point to multisystemic involvement consistent with the gene's widespread expression profile. The variant in this case report has not been reported in major population databases, highlighting its novelty and making it the third intronic variant associated with OTUD6B-related disorder. Its location at a splice site—a region essential for accurate splicing and transcript processing—further supports the growing body of evidence that non-coding and splice-site variants in *OTUD6B* are critical contributors to disease. Segregation analysis confirmed an autosomal recessive inheritance pattern,

Table 1. Segregation Analysis of the OTUD6B Splice-Site Variant (c.235-3C>G) in the Patient and Parents.

Subject	Gene (Transcript)	Variant	Location	Zygosity	Clinical Phenotype
Patient	OTUD6B (NM_016023.5)	c.235-3C>G	Intron 2	Homozygous	OTUD6B-related disorder
Father	OTUD6B (NM_016023.5)	c.235-3C>G	Intron 2	Heterozygous	Not affected
Mother	OTUD6B (NM_016023.5)	c.235-3C>G	Intron 2	Heterozygous	Not affected

Table 2. Comparison of Clinical and Molecular Characteristics Present in Patients with Pathogenic Variants Within *OTUD6B*.

Feature	Index patient	Fam1	Fam2	Fam3	Fam4	Fam5	Fam6	Fam7	Fam8	Fam9	Fam10
Genetic Variant	c.235-3C>G	c.433 C>T	c.433 C>T	c.433 C>T	c.469_473 delTTAAC	c.173-2A>G	c.647 A>G	c.324 +1G>C c.405 +1G>A	c.433 C>T	c.631 G>T	c.433 C>T
Protein Change	Splice-site	p.Arg 145*	p.Arg 145*	p.Arg 145*	p.Leu157 Argfs*8	Splice-site	p.Tyr216 Cys	Splice-site	p.Arg 145*	p.Glu 211*	p.Arg 145*
Gender	M	F	M	M (3)	M (3)	F (2)	M(2), F(1)	F	F	F	M
Ethnicity	Iraqi Kurd	Hispanic	Hispanic/ Italy	Egypt	Syria	Palestine	Turkey	Italy	Spain	Saudi Arabia	Mexico
Intellectual Disability	Severe	Severe	Severe	Severe +(3)	Severe +(2)	Severe +(2)	Moderate (2), Mild (1)	Mild	+	NA	Severe
Seizures	+	+	+	+(3)	+(2)	+(2)	+(3)	+	+	–	+
Speech Delay	+	+	+	+(3)	+(2)	+(2)	–(3)	+	+	NA	+
Hypotonia	+	+	+	+(3)	+(2)	+(2)	–(3)	+	+	NA	+
Gross Motor Delay	+	+	+	+(3)	+(2)	+(2)	–(3)	+	NA	+	+
Microcephaly	+	+	+	–(2), +(1)	-(2)	–(2)	–(3)	+	+	+	+
Long Philtrum	+	+	+	+(3)	–(2)	–(2)	–(3)	+	+	+	+
Prominent Nasal Bridge	+	+	+	+(3)	–(2)	–(2)	–(3)	–	+	+	+
Large Ears	+	–	–	–(3)	–(2)	–(2)	–(3)	+	+	+	+
Congenital Heart Defect	VSD, SAM, PS	NA	–	PS, ASD	PS, ASD, VSD	–	VSD	TOF/ ASD	NA	TOF	PDA
Feeding Difficulties	+	+	+	+(3)	+(2)	+(2)	–(3)	+	+	+	+
Respiratory Infections	+	+	–	+(3)	–(2)	–(2)	–(3)	NA	NA	+	+
Craniosynostosis	Metopic	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Prominent Coccyx	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cryptorchidism	+	NA	+	–(2)	+	–	–	NA	NA	NA	NA

Abbreviations: NA: Not Assessed or Not Available; +: Present; –: Absent; (n): Number of family members; VSD: Ventricular Septal Defect; SAM: Systolic Anterior Motion; ASD: Atrial Septal Defect; PS: Pulmonary Stenosis; TOF: Tetralogy of Fallot; PDA: Patent Ductus Arteriosus

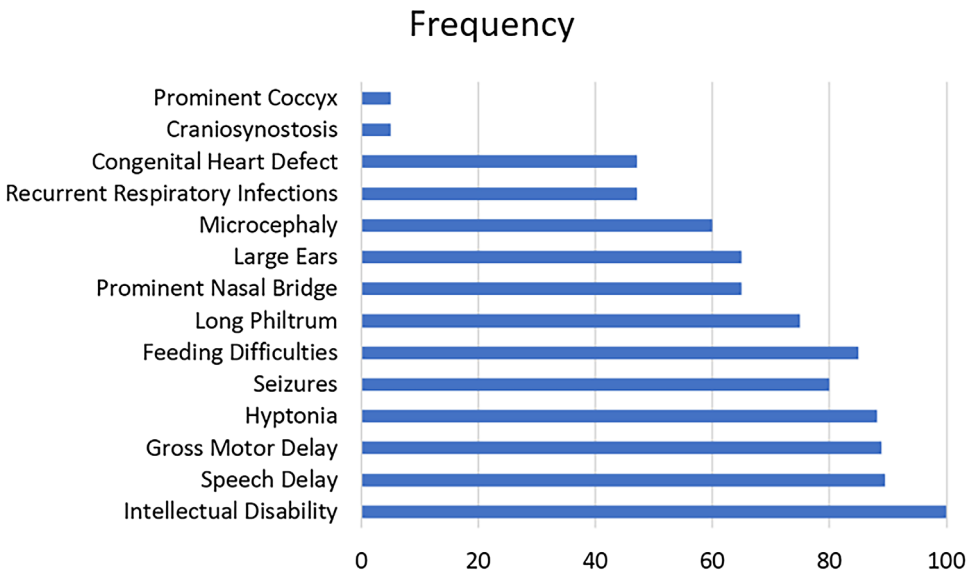

Figure 2. Frequency of Clinical Features in OTUD6B-Related Disorder in all studies to date.

with both parents identified as heterozygous carriers of the variant (Table 1). The clinical variability noted in *OTUD6B*-related disorder is further demonstrated by contrasting reports: Some individuals with milder manifestations lack seizures or hypotonia, while others exhibit systemic involvement such as hypothyroidism or immune dysfunction. Such heterogeneity complicates clinical recognition, emphasizing the need for molecular diagnostics to achieve accurate diagnosis and management. In summary, our case supports and expands the clinical spectrum of OTUD6B-related disorder. The identification of a novel pathogenic variant reinforces the role of comprehensive genomic testing in unexplained neurodevelopmental disorders, especially within consanguineous populations. Further studies are warranted to elucidate genotype-phenotype correlations and to determine whether features such as craniosynostosis and a prominent coccyx are part of the disorder's core phenotype or incidental findings.

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Authors' Contribution: Data collection, DS; data curation, DS and MO; writing- original draft, DS; validation, DS and MO; writing -review & editing: MO.

Declaration on the Use of AI: The authors declare that Grammarly was used to enhance readability and language. The authors thoroughly reviewed and edited the manuscript as necessary, taking full responsibility for its accuracy and content.

Consent for Publication: The patient's parents gave written informed consent to publish this case report, including clinical data and images.

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