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RESEARCH

OTUD5-related rare X-linked multiple congenital anomalies and neurodevelopmental syndrome: clinical findings and review of the literature

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Abstract

The *OTUD5* gene (OMIM #300713), located on Xp11.23, encodes the ovarian tumor deubiquitinase 5, a deubiquitinase enzyme with critical functions in chromatin remodeling, transcriptional regulation, neuroectodermal differentiation, and innate immune signaling. Hemizygous pathogenic variants in *OTUD5* are associated with X-linked multiple congenital anomalies–neurodevelopmental syndrome (MCAND, OMIM #301056), a rare multisystem disorder characterized by developmental delay, intellectual disability, craniofacial dysmorphism, and variable involvement of the cardiac, skeletal, and genitourinary systems. Although fewer than 30 cases have been reported worldwide, the clinical spectrum appears to be highly heterogeneous, ranging from early infantile lethality to survival into adulthood.We report a male patient, born prematurely at 32 weeks, who presented with global developmental delay, neonatal seizures, truncal hypotonia, and multiple dysmorphic features. Facial dysmorphism, microcephaly, overlapping fingers, hypospadias, bilateral cryptorchidism, congenital heart defects, bilateral sensorineural hearing loss, and structural brain abnormalities were observed. Despite supportive management, the patient died at 1.5 years of age due to pneumonia complicated by sepsis.Genetic testing through whole-exome sequencing identified a hemizygous missense variant in OTUD5, NM_001136157.2:c.1195 C>T (NP_001129629.1:p.Arg399Trp). Segregation analysis confirmed maternal carrier status and heterozygosity in one female sibling. Our findings indicate that bilateral sensorineural hearing loss and cranial anomalies may constitute variable or previously underrecognized features of MCAND; however, validation in additional, systematically evaluated cases is necessary before these manifestations can be regarded as part of the established phenotypic spectrum. Furthermore, the patient's fatal course due to infectious complications underscores the role of OTUD5 in innate immunity and suggests a possible predisposition to immune deficiency. This case emphasizes the importance of early genetic testing in patients with complex congenital anomalies and supports close monitoring for infections as part of comprehensive clinical management.

Keywords Newborn · Genetic counseling · Developmental delay · Dysmorphic features · Rare disease

Introduction

The *OTUD5* gene (OMIM #300713), located on Xp11.23, encodes the ovarian tumor deubiquitinase 5 (*OTUD5*) protein, a deubiquitinase enzyme belonging to the OTU family [1]. This enzyme primarily cleaves K48-linked ubiquitin chains and plays a role in chromatin remodeling and transcriptional regulation. By targeting chromatin-associated proteins, it exerts critical regulatory effects on neuroectodermal differentiation and cell fate determination [2].

In addition, *OTUD5* has been shown to play a role in α-synuclein (α-Syn) degradation independent of its deubiquitinase activity. Conditional knockout of *Otud5* in

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dopaminergic neurons results in more severe α-Syn pathology and dyskinesia following α-Syn fibril injection. These findings suggest a protective role of *OTUD5* against α-Syn accumulation in dopaminergic neurons in a Parkinson's disease model [3].

Clinically, pathogenic hemizygous variants in *OTUD5* cause X-linked multiple congenital anomalies–neurodevelopmental syndrome (MCAND, OMIM #301056). Although Beck et al. [2] referred to this syndrome as "LINKED" (LINKage-specific deubiquitylation deficiency-induced embryonic defects), in this study we will use the term MCAND, as designated in OMIM.

MCAND is an X-linked recessive multisystem congenital disorder characterized by a broad and variable clinical phenotype. Affected individuals commonly present with growth retardation, intellectual disability, global developmental delay, hypotonia, and craniofacial dysmorphism, along with variable involvement of the cardiac, skeletal, and genitourinary systems. The severity of the phenotype ranges widely, from early infantile lethality to survival into the second or third decades of life. Frequently reported dysmorphic and structural features include hydrocephalus-associated macrocephaly, craniosynostosis, deep-set eyes, hypertelorism, broad forehead, flat nasal bridge, low-set ears, strabismus, hypospadias, cryptorchidism, limb contractures, foot deformities, and short stature [4]. The marked clinical heterogeneity observed among individuals with MCAND underscores the complexity of *OTUD5*-related disease and suggests variability in the functional consequences of different pathogenic variants. Further clinical and molecular characterization of affected individuals is essential to refine genotype–phenotype correlations and to expand the current understanding of the clinical spectrum associated with *OTUD5* dysfunction.

This study aims to present the clinical data of a patient diagnosed with MCAND (OMIM #301056), a condition rarely reported in the literature. By addressing the phenotypic manifestations of pathogenic *OTUD5* variants, the study seeks to contribute to a better understanding of the genetic and clinical spectrum of the disease.

Materials and methods

Patient

Written informed consent was obtained from the patient's legal guardians. Ethical approval for this study was granted by the Balıkesir Atatürk City Hospital Ethics Committee on October 23, 2025, with approval number 2025/10/20.

A three-month-old male infant was referred to the genetics clinic for investigation of a possible genetic etiology, following follow-up in the pediatric neurology clinic due to facial dysmorphism, global developmental delay, and a history of neonatal seizures. The patient's medical records, clinical findings, physical examination results, and pedigree were reviewed in detail. The evaluation was performed jointly by a clinical geneticist and a pediatric neurologist.

Genetic testing

Genomic DNA was extracted from leukocytes obtained from peripheral blood samples of the patient and his parents. Initial genetic investigations included karyotype analysis and chromosomal microarray analysis (CMA), followed by whole-exome sequencing (WES). Detected variants were subsequently validated, and segregation analysis within the family was performed using Sanger sequencing.

DNA isolation was performed automatically using the HiPurA® prefilled clinical multipurpose nucleic acid purification kit in conjunction with the HIMEDIA InstaN Mag-96 system. DNA concentration was quantified using a Qubit® fluorometer (Thermo Fisher Scientific, USA).

Array-based comparative genomic hybridization (array-CGH) was conducted using the Agilent GenetiSure Cyto 8 × 60 K CGH microarray chip, following the manufacturer's protocol. The employed chip enables genome-wide analysis with a practical resolution of approximately 100 kb, covering the entire genome with 60,000 probes. The median spacing between Agilent microarray probes is ~ 7.1 kb. Data obtained from this analysis were mapped to the NCBI reference genome.

For WES, libraries were prepared using the Roche® KAPA HyperExome 96 rxn kit and sequenced on the MGI DNBSEQ-G400 platform. Bioinformatic analysis of the generated FastQ files was performed using the Genomize SEQ platform (v8.7.0).

Variant analysis and classification

Microarray data were analyzed by comparing them to the NCBI Human Genome Build 38 reference genome using CytoGenomics v5.2.1.4 (Agilent) software.

Raw sequencing data were processed using the Genomize® data analysis platform (https://seq.genomize.com). Sequence reads were aligned to the NCBI Human Genome Build 38 (GRCh38) reference genome. Variant calling was performed following standard quality control procedures, including the exclusion of low-quality reads, variants with insufficient read depth, low genotype quality scores, or strand bias.

A multistep filtering strategy was applied to prioritize potentially disease-causing variants. First, variants were filtered based on their genomic location and functional

consequence, retaining variants located in coding regions and canonical splice sites. Nonsense, missense, frameshift, splice-site, indel, in-frame, and synonymous variants were considered; Second, common variants were excluded by applying a minor allele frequency (MAF) threshold of < 1% across multiple population databases, including the 1000 Genomes Project (1000G), the Exome Sequencing Project (ESP), the Exome Aggregation Consortium (ExAC), and the Genome Aggregation Database (gnomAD).

Sequencing data were visualized using the Integrative Genomics Viewer (IGV). Newly identified variants were queried in the HGMD® and ClinVar databases for confirmation, and their pathogenicity was assessed using in silico prediction tools, including AlphaMissense, REVEL, and Combined Annotation Dependent Depletion (CADD). Variant classification was performed in accordance with the American College of Medical Genetics and Genomics (ACMG) and Association for Clinical Genomic Science (ACGS) guidelines ([5]; ACGS Best Practice Guidelines for Variant Classification in Rare Disease). Finally, segregation analysis was conducted using DNA samples obtained from available family members.

Results

A three-month-old male patient was evaluated in the pediatric neurology clinic due to prominent facial dysmorphism and global developmental delay. He was born prematurely at 32 weeks of gestation to a gravida 2, para 2 mother, following premature rupture of membranes, with a birth weight of 1500 g (−1.04 SD) and a head circumference of 30 cm (−0.07 SD). In the neonatal period, his clinical course was critical due to prematurity and low birth weight. Following neonatal seizures, antiepileptic therapy was initiated, and he required neonatal intensive care support for 3.5 months.

Feeding difficulties developed due to swallowing dysfunction, and nutritional support was provided via a nasogastric tube. At the corrected age of 12 months, physical examination revealed significant growth retardation, with a body weight of 5.3 kg (−4.85 SD), head circumference of 41.5 cm (−3.84 SD), and length of 62 cm (−4.61 SD). Facial dysmorphism was characterized by a triangular facial shape, followed by frontal bossing and a broad forehead; thick eyebrows and long eyelashes; hypertelorism, epicanthus inversus, and upslanting palpebral fissures; a flat and low nasal bridge with anteverted nares; and a thick upper lip vermilion with a prominent Cupid's bow and high-positioned oral commissures. Additional findings included microcephaly, strabismus, overlapping fingers, hypospadias, and bilateral cryptorchidism. bilateral sensorineural hearing loss, and structural brain abnormalities (Fig. 1). Echocardiographic evaluation revealed patent ductus arteriosus (PDA) and secundum-type atrial septal defect (ASD).

Brain MRI demonstrated a thin corpus callosum, cavum septum pellucidum et vergae, and mild ventriculomegaly (Fig. 1). Neurological examination showed marked truncal hypotonia and severe delay in motor milestones. The patient was unable to sit unsupported, roll over, or walk; he did not establish verbal communication or follow commands, but he did exhibit a social smile.

Audiological evaluation confirmed bilateral sensorineural hearing loss, and hearing aids were provided at

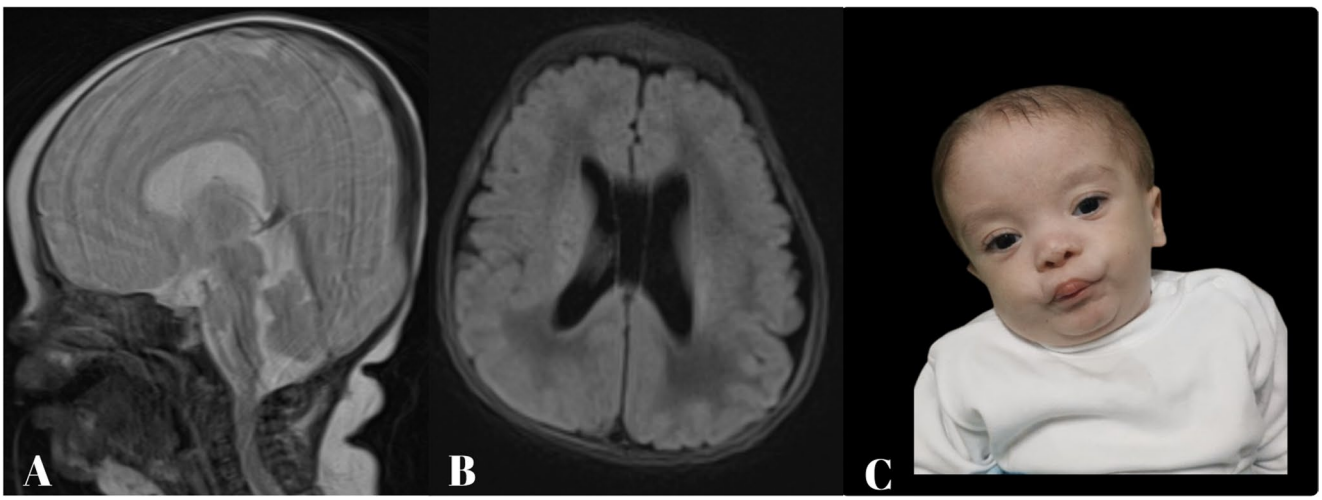

Fig. 1 Clinical and radiological features of the patient carrying a likely pathogenic *OTUD5* variant. T2-weighted midsagittal MR image (**A**) and axial FLAIR sequence (**B**) demonstrate a diffusely thin corpus callosum and cavum septum pellucidum et vergae with enlarged ventricles. Facial dysmorphic features, including flat nasal bridge, frontal bossing, broad forehead, retrognathia, premaxillary protrusion, hypertelorism, strabismus, telecanthus, epicanthus inversus, triangular facial configuration, thick upper lip, and high-positioned oral commissures (**C**)

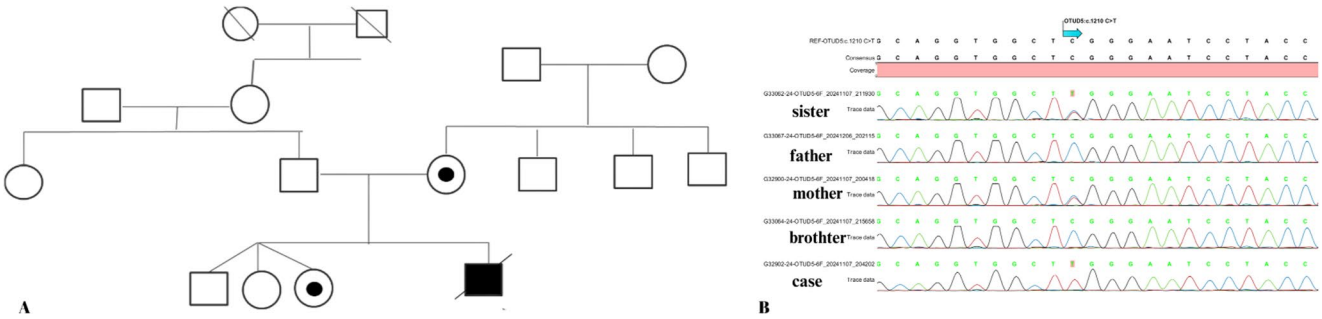

Fig. 2 Pedigree and genetic findings in the patient with an *OTUD5* variant. (**A**) Family pedigree; (**B**) Sanger sequencing traces showing segregation analysis of the *OTUD5* variant (c.1195 C>T, p.Arg399Trp [NM_001136157.2]) among all family members available for genetic testing

9 months of age. There was no family history of hearing loss, and audiological examinations of both parents were normal. Seizures did not recur, and antiepileptic therapy was discontinued. However, hypotonia and global developmental delay persisted. The patient experienced recurrent infections and died at 1.5 years of age due to pneumonia complicated by sepsis. Laboratory evaluation revealed reduced serum immunoglobulin levels, including IgG (614 mg/dL) and IgA (62 mg/dL). However, due to the patient's early death, comprehensive immunological assessments, such as lymphocyte subset analysis or evaluation of specific antibody responses, could not be performed.

Genetic findings

Chromosomal analysis revealed a 46,XY karyotype, while chromosomal microarray analysis was unremarkable. Whole-exome sequencing (WES) identified a hemizygous missense variant in the *OTUD5* gene, NM_001136157.2:c.1195 C > T (NP_001129629.1:p.Arg399Trp). According to current ACMG/ACGS guidelines [5], this variant was evaluated with respect to the PM2, PP1, PP2, and PP3 criteria. In silico predictive tools, including CADD, AlphaMissense, and REVEL, supported pathogenicity at a supporting level. Additionally, the variant has been reported as pathogenic in the ClinVar database.

Evolutionary conservation analysis demonstrated a highly conserved region at the variant site (phyloP100way: 2.308; PhastCons100way: 1.0). According to the Human Gene Mutation Database Professional 2024.4, a total of 15 different variants in *OTUD5* have been reported to date, including 13 missense/nonsense, 1 splice-site, and 1 small deletion.

Segregation analysis within the family demonstrated that the variant was inherited from the heterozygous carrier mother, and one sister was also identified as a heterozygous carrier; both individuals were clinically asymptomatic (Fig. 2).

Table 1 Clinical features of the present case compared with previously reported individuals carrying the same variant and those with other variants in the same gene

		Literature review			
		Same variant			Other variants
	Our Case	F6-P8 [2]	F6-P9 [2]	Case 3 [7]	26 cases from 10 families*
Gender	M	M	M	M	M
Alive time	1.5 y	2 y	8 y	19 m	Youngest: deceased in utero Oldest: 49 y
GDD/ID	+	+	+	+	22/22
Epilepsy	+	-	-	-	6/15
Hypotonia	+	+	+	+	6/9
Abnormal CNS imaging findings	+	+	+	-	8/10
Cardiac Anomalies	+	-	+	+	11/21
Genitourinary Anomalies	+	+	+	+	23/24
Skeletal system	-	-	-	-	8/24
Craniofacial	+	+	+	+	13/16
Others	Hearing loss	-	-	GERD	Hirsutism

F family, *M* male, *m* months, *y* years, *GDD* global developmental delay, *ID* IntellectualDisability, *NA* not assessed, *GERD* gastro-esophageal reflux disease,*CNS* central nervous system

* Data summarized from Beck et al. [2], Saida et al. [7], Tripolszki et al. [4], Tian et al. [8], and Giovenino et al. [6]

Discussion

To date, a limited number of MCAND cases have been reported in the literature and we presented 29 previously reported cases and our case with the diagnosis of MCAND in Table 1; Fig. 3 [2, 4, 6–8].

In this study, a hemizygous missense variant, NM_001136157.2:c.1195 C > T (NP_001129629.1:p.Arg399Trp), in the *OTUD5* gene that was detected using WES analysis was reported. According to the ACMG criteria [9], this variant meets the PM2, PP2, and PP3 criteria

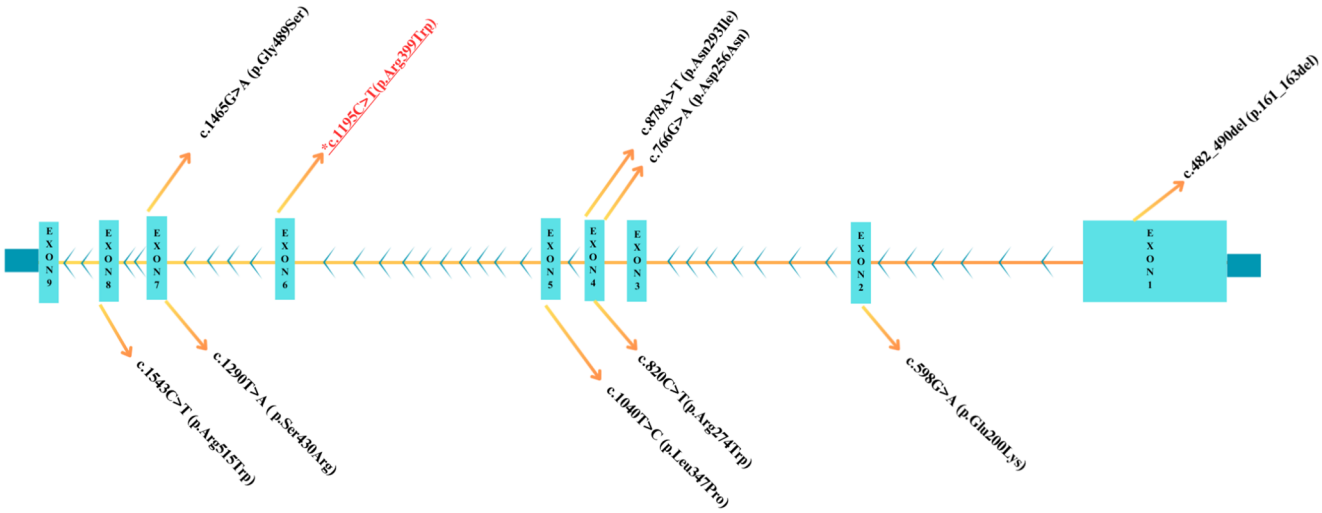

Fig. 3 Exon locations of *OTUD5* gene variants identified in the present case and in previously reported patients are shown. Variant mapping was performed according to the NM_001136157.2 transcript. The codon corresponding to the variant identified in our patient is highlighted in red

and is therefore categorized as a variant of uncertain significance (VUS). However, the same variant has previously been reported as pathogenic by Beck et al., and as likely pathogenic by Saida et al., highlighting variability in variant interpretation across studies [2, 7]. When reassessed in accordance with the ACMG/ACGS guidelines [5], the accumulated evidence supports classification of this variant as likely pathogenic, based on PM2_M (rarity in population databases), PP2 (predisposition of missense variants to pathogenicity), PP3 (supporting in silico predictions), and PP1_M (segregation demonstrated by [2]).

The clinical findings of the present case are largely consistent with those reported in individuals carrying *OTUD5* variants. Global developmental delay/intellectual disability (GDD/ID) represents a consistent feature across all reported cases. Frequently described neurological manifestations, including hypotonia, epilepsy, and abnormal central nervous system (CNS) imaging findings, were also observed in our patient, in line with previous reports. In addition, extracerebral features such as genitourinary and craniofacial anomalies further support the multisystem involvement associated with *OTUD5*-related disorders (Table 1). However, given the limited number of reported cases and the scarcity of available data, any conclusions regarding genotype–phenotype correlations remain speculative, highlighting the need for larger patient cohorts.

The presence of global developmental delay, craniofacial dysmorphism (including triangular face, epicanthus inversus, hypertelorism, flat nasal bridge, thick eyebrows, thick upper lip, long eyelashes, and frontal bossing), and truncal hypotonia in this patient suggests that the phenotypic spectrum associated with pathogenic *OTUD5* variants may be more heterogeneous than currently appreciated; however, given the limited number of reported cases, this observation should be interpreted with caution and warrants confirmation in additional individuals.

In contrast to many previously reported cases, our patient did not present with the cardiac anomalies such as ventricular septal defects or Tetralogy of Fallot described by Saida et al., nor with the limb contractures, hirsutism, polydactyly, pulmonary atresia or stenosis, and renal anomalies reported in the literature, but instead exhibited only overlapping fingers and laryngomalacia, thereby underscoring the marked phenotypic variability associated with OTUD5-related disorders [2, 4, 7].

Beck et al., emphasized that *OTUD5* plays a critical role during embryogenesis and that loss-of-function variants may lead to a broader clinical spectrum than initially anticipated [2]. In the current literature, hearing loss has been rarely reported in *OTUD5*-related MCAND, and it remains unclear whether this finding represents a core component of the syndrome or a secondary, coincidental feature. In our patient, audiological evaluation revealed bilateral sensorineural hearing loss, and hearing aids were provided at 9 months of age; however, no significant language development was observed despite amplification. There was no family history of hearing loss, and proband-only whole-exome sequencing (including CNV analysis) did not identify any additional pathogenic variants that could account for the auditory phenotype. Nevertheless, given the marked genetic and etiological heterogeneity of hearing loss, the possibility of an additional genetic diagnosis cannot be completely excluded.

In this context, the hearing loss observed in our patient may represent a rare manifestation within the *OTUD5*-associated phenotypic spectrum, or alternatively, a secondary finding related to prematurity or perinatal factors. Further clarification of this association will require broader genetic

approaches, such as trio-based whole-genome sequencing (WGS), along with longitudinal clinical follow-up and periodic data reanalysis. Similarly, the cranial findings in our patient were carefully evaluated: while microcephaly was considered reflective of underlying neurodevelopmental involvement, posterior plagiocephaly was determined to be positional rather than craniosynostotic, as cranial MRI demonstrated preserved cranial sutures with asymmetric flattening of the occipital region. Notably, clinical examination of both parents revealed no cranial anomalies. Taken together, these findings highlight the clinical variability observed in *OTUD5*-related MCAND and underscore the need for systematic evaluation in larger patient cohorts to determine whether hearing loss constitutes a consistent feature of the disorder.

At the molecular level, *OTUD5* is a cysteine protease belonging to the deubiquitinase family containing an ovarian tumor (OTU) domain, playing critical roles in DNA repair, chromatin remodeling, and regulation of innate immunity [10, 11]. Functional impairment has been shown to weaken type I interferon responses [11]. Moreover, Li et al., reported that *OTUD5* stabilizes TRIM25 and suppresses PML expression, which may have important implications for antiviral responses and apoptosis [12].

Our patient's clinical course, marked by recurrent respiratory tract infections, persistent stridor, and death at 1.5 years of age from pneumonia complicated by sepsis, suggests a potential predisposition to infectious disease. This concern is substantiated by laboratory findings demonstrating decreased serum immunoglobulin concentrations, specifically IgG (614 mg/dL) and IgA (62 mg/dL). This clinical trajectory closely parallels the severe phenotype described by Tripolszki et al., in which early infantile death was a prominent feature frequently associated with multisystem involvement and increased susceptibility to infections [4]. In contrast, the presentation reported by Tian et al., was characterized by a more variable clinical course without uniformly early lethal outcomes [8]. Additionally, genetic testing (conventional karyotyping, chromosomal microarray analysis, and whole-exome sequencing) did not identify any pathogenic or likely pathogenic variants that would account for a primary immunodeficiency.

Given the established role of *OTUD5* in chromatin remodeling and transcriptional regulation, both of which are integral to immune cell development and differentiation, it is biologically plausible that pathogenic variants in this gene may contribute to immune dysregulation [2, 13]. However, to date, no primary immunodeficiency disorder has been conclusively associated with *OTUD5* variants, and a direct causal relationship cannot be inferred from the present observations. Accordingly, this finding should be interpreted as a biologically plausible yet unproven hypothesis that warrants systematic investigation in larger patient cohorts and through dedicated functional immunological studies.

The marked clinical variability observed among individuals harboring pathogenic *OTUD5* variants is likely multifactorial. First, differences in variant type and location may result in variable residual protein function, leading to a spectrum of disease severity. Second, skewed X-chromosome inactivation in females and mosaic expression patterns may further modify phenotypic outcomes. Third, the contribution of genetic modifiers and background variation, including variants in genes involved in ubiquitin signaling, chromatin remodeling, or immune regulation, may influence disease expressivity. Finally, environmental factors such as recurrent infections, nutritional status, and access to early medical care may additionally modulate the clinical course. Collectively, these factors provide plausible explanations for the heterogeneous genotype–phenotype correlations reported to date.

In conclusion, this case adds further clinical detail to the phenotypic variability associated with *OTUD5* variants and suggests less commonly reported features, such as hearing loss and immune dysfunction, may be part of the clinical spectrum. Early implementation of genetic testing in patients presenting with complex congenital anomalies is critical for accurate diagnosis and appropriate clinical management. Furthermore, early identification and close monitoring of patients at risk for immune deficiency may be valuable in preventing infections and prolonging survival. Future large-scale studies will contribute to a better understanding of genotype–phenotype correlations associated with *OTUD5* variants and provide a foundation for the development of individualized, precision-based therapeutic strategies.

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Author contributions All authors contributed to the study conception and design. Neurological Evaluation: AE; Genetic Evaluation: HB, DGA; Psychiatric Evaluation: GÜB; Radiological Evaluation and Reassessment of the Brain MRI: AT; Material, Methods, and Data Collection: HB, DGA; Data Analysis and Interpretation: HB, DGA; Writing and Revisions: AE, HB, DGA.

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Data availability All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate Ethics approval for this study was obtained from the Balıkesir Atatürk City Hospital Ethics Committee on October 23, 2025 (Decision No: 2025/10/20). Written informed consent was obtained from the patient's legal guardians.

Competing interests The authors declare no competing interests.

Disclosure/Conflict of Interest The authors declare that they have no conflicts of interest to disclose.

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