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Expanding the clinical spectrum of Cernunnos/XLF deficiency: a literature review of a rare cause of severe combined immunodeficiency including a novel case

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Abstract

Background Severe combined immunodeficiency (SCID) is a congenital immunodeficiency characterized by significant numerical or functional defects in T lymphocytes and is often accompanied by B lymphocyte dysfunction. It presents early in life with severe, recurrent opportunistic infections. Early diagnosis and hematopoietic stem cell transplantation (HSCT) are vital for patient survival. Cernunnos/XLF deficiency is an autosomal recessive form of SCID caused by mutations in the *NHEJ1* gene, which plays a critical role in repairing DNA double-strand breaks. First described in 2006, this condition remains exceedingly rare, with only about 55 cases reported to date. This study aimed to describe a novel infant with Cernunnos/XLF deficiency and to review previously reported patients carrying the same variant, thereby expanding the clinical spectrum of this rare disease.

Methods With written informed consent, we retrospectively evaluated a pediatric patient with Cernunnos/XLF deficiency followed at our clinic. Demographic, clinical, laboratory, and radiological findings were reviewed. The diagnosis was based on clinical and immunological features and confirmed via clinical exome sequencing. A literature review was conducted to compare the genotype–phenotype correlations of previously reported patients carrying the same *NHEJ1* variant.

Results We report an infant who was hospitalized at 6.5 months of age with a preliminary diagnosis of meningitis and was subsequently diagnosed with Cernunnos/XLF deficiency. The patient exhibited microcephaly, growth retardation, recurrent infections, prolonged SARS-CoV-2 PCR positivity, and localized BCGitis following live Bacillus Calmette–Guérin (BCG) vaccination. Immunological evaluation revealed T- and B-cell lymphopenia and hypogammaglobulinemia. Genetic testing confirmed a homozygous nonsense mutation in *NHEJ1*. HSCT from a matched sibling donor was performed.

Conclusion This study describes a rare case of Cernunnos/XLF deficiency diagnosed in early infancy, underscoring the value of early recognition and the critical role of genetic testing and HSCT. It also expands the clinical spectrum

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of the disease and provides a comparative perspective with previously reported patients carrying the same mutation. In infants presenting with unexplained infections or complications related to live vaccines, inborn errors of immunity should be considered. Our findings emphasize the importance of timely diagnosis and comprehensive, multidisciplinary follow-up, particularly in patients with additional complications.

Keywords BCG vaccine, Cernunnos/XLFdeficiency, NHEJ1 protein, Inborn errors of immunity (IEIs), Severe combined immunodeficiency

Background

Severe combined immunodeficiency (SCID) is a genetically heterogeneous disorder within the group of inborn errors of immunity (IEIs), formerly referred to as primary immunodeficiencies (PIDs). SCID typically presents as severe opportunistic infections and growth retardation in early infancy. It is characterized by severe impairment of both cellular and humoral immune responses resulting from molecular defects in T and B lymphocyte differentiation or function [1–3].

Among the genetic defects implicated in the etiopathogenesis of SCID are mutations in the nonhomologous end joining (NHEJ) pathway, which is responsible for repairing DNA double-strand breaks (DSBs). Two main pathways are involved in DSB repair: homologous recombination and NHEJ. The NHEJ pathway is the primary DSB repair mechanism in mammalian cells. It is active throughout the cell cycle. Additionally, it facilitates the rejoining of programmed DSBs generated during Variable (V), Diversity (D), and Joining (J) [V(D)J] recombination during immune system development [4–6].

Several genes regulate this pathway, including *DCLRE1C*, *PRKDC*, *LIG4*, *XRCC4*, and *NHEJ1* (encoding Cernunnos, also known as XRCC4-like factor, XLF) [4, 6]. Cernunnos/XLF is a critical component of the NHEJ pathway that interacts with XRCC4 (X-ray repair cross-complementing 4) to increase the stability and activity of the DNA ligase IV complex, thereby facilitating the alignment and ligation of broken DNA ends [7, 8]. Deficiencies in this critical function lead to impaired V(D)J recombination, failure of immune system maturation, and the development of SCID. Cernunnos/XLF deficiency (OMIM#611291) is a rare autosomal recessive genetic disorder characterized, in addition to the SCID phenotype, by microcephaly, growth retardation, bird-like facial appearance, radiosensitivity, premature senescence of hematopoietic stem cells, occasional autoimmune manifestations, and rarely myeloproliferative disease [6, 7, 9, 10]. The disease can be fatal unless hematopoietic stem cell transplantation (HSCT) is performed.

In this study, we report an infant case with Cernunnos/XLF deficiency, confirmed by genetic analysis, who exhibited a T (–) B (–) NK (+) SCID phenotype, microcephaly, growth retardation, recurrent infections, and localized BCGitis. Given the rarity of this condition and the limited number of reported patients with this variant, documenting additional cases is essential to better delineate the clinical spectrum and explore potential genotype–phenotype correlations. Therefore, we reviewed previously reported patients with the same variant to enhance the current understanding of this IEI. Our objective is to expand the clinical spectrum of Cernunnos/XLF deficiency, to highlight the diagnostic and therapeutic challenges associated with this rare condition, and emphasize the life-saving role of early HSCT, particularly drawing attention to donor selection issues when only carrier relatives are available.

Methods

Clinical, laboratory, and radiological data from a pediatric patient who was diagnosed with Cernunnos/XLF deficiency and followed in our pediatric immunology clinic were retrospectively analyzed. The evaluation included medical history, physical examination, and immunological assessments. The laboratory tests included complete blood count (CBC), serum immunoglobulin levels, vaccine responses, peripheral lymphocyte subset analysis, and adenosine deaminase (ADA) genetic analysis (buccal swabs).

Imaging studies—including chest X-ray, abdominal ultrasonography, transfontanel ultrasonography, and superficial soft tissue ultrasonography—were reviewed for evidence of pulmonary, infectious, neurological, and oncological involvement. Additionally, bone marrow aspiration was performed.

Clinical and laboratory findings were compared with those of previously reported patients carrying the *NHEJ1* c.532C > T (p.R178X) variant. To identify such cases, a focused literature review was conducted across PubMed, ClinVar, Embase, Scopus, and Web of Science, covering the period from 2006 (when Cernunnos/XLF deficiency was first described) to August 2025. Keywords included *"NHEJ1,"* "Cernunnos deficiency," "XRCC4-like factor," "nonhomologous end-joining factor 1," as well as variant-specific terms ("c.532C > T," "p.R178X"). Only patients harboring the identical variant were included for comparison. Clinical, immunological, and genetic features were analyzed descriptively and summarized in tabular form; no statistical analyses were performed given the limited number of cases.

Genetic analysis

Peripheral blood samples were collected from the proband, his parents, and his sibling after written informed consent was obtained. Genomic DNA was extracted from leukocytes via the QIAamp DNA Mini Kit (Qiagen, 51304, Düsseldorf, Germany) according to the manufacturer's instructions. Library preparation and clinical exome sequencing (CES) were performed for the proband via the Celemics G-Mendeliome CES Panel Kit (Celemics, Inc., Seoul, Republic of Korea) and the samples were sequenced on the MiniSeq platform (Illumina Inc., USA). Over 99.14% of the targeted regions (exonic regions of all nuclear genes plus ± 10 bp of intron boundaries) were sequenced > 50 times, with an average coverage depth of ~ 100 ×. Sequence reads were aligned to the human reference genome (hg19, GRCh37) via the Burrows–Wheeler Aligner (version 16.7.9). Next-generation sequencing (NGS) data were analyzed via Genomize SEQ software (Genomize, Istanbul, Turkey). The Integrative Genome Viewer (IGV) (http://software.broadinstitute.org/software/igv/) was used for visualizin g the status of each read alignment. Non-synonymous (nonsense, missense, frameshift, in-frame) variants with minor allele frequency less than 1.0% in population studies (Exome Aggregation Consortium database-ExAC, 1000 Genomes-1000G, and Genome Aggregation Database-gnomAD) were filtered. American College of Medical Genetics and Genomics (ACMG) criteria were also applied. Retained variants were searched for in ClinVar (Clinical Variants Database) and the Human Genome Mutation Database (HGMD).

Sanger sequencing of genomic DNA from the patient, his parents, and his sibling was performed via specific primers for exon 5 of the *NHEJ1* gene to confirm the variant detected via next-generation sequencing (NGS) and to assess its presence in the parents and the sibling (Fig. 1a, b).

The variant was analyzed and classified according to the guidelines of ACMG [11] and cross-referenced with the ClinVar database.

Results

Our patient

The patient is a 1-year-old boy who, at 6.5 months of age, presented to our emergency department with a 3-day history of fever, rhinorrhea, lethargy, opisthotonus, and diarrhea. He was admitted with a preliminary diagnosis of meningitis and was referred to the immunology clinic because cytopenia was detected during initial laboratory testing.

His perinatal history was notable for spontaneous vaginal delivery at 35 weeks gestation with a birth weight of 2450 g. The patient required a 15-day neonatal intensive care unit stay for transient tachypnea of the newborn and early-onset sepsis. At 2 months of age, he was again hospitalized for sepsis and subsequently experienced two episodes of bronchiolitis and recurrent diarrhea. His immunizations, including BCG, were administered on schedule according to the national program (hepatitis B at birth and at 1 month; BCG, pentavalent vaccine (DTaP–IPV–Hib), and pneumococcal conjugate vaccine (PCV) at 2 months; and booster doses of pentavalent and PCV at 4 months).

His family history revealed second-degree consanguinity; his sister was healthy. Two of the father's uncles had a history of cerebral palsy.

On examination, the patient appeared moderately to severely ill. He was febrile and tachypneic. Body weight was 4700 g (< 5th percentile, – 3.4 standard deviation score [SDS]), length was 56 cm (< 5th percentile, – 4 SDS), and head circumference was 37 cm (< 5th percentile, – 4.6 SDS). The patient appeared lethargic, could not hold his head unsupported, and exhibited opisthotonus, microcephaly, and bird-likefacies (Fig. 2a). The anterior fontanel measured 0.3 × 0.3 cm and was open with mild bulging; the oropharynx was erythematous. Chest auscultation revealed rhonchi and wheezing. On abdominal examination, the liver was palpable 2 cm below the costal margin.

Laboratory tests revealed bicytopenia (anemia and lymphopenia) and elevated levels of acute-phase reactants (CRP: 397 mg/L, procalcitonin > 75 ng/mL). A review of his records confirmed persistent lymphopenia since the neonatal period. Lumbar puncture revealed 20 leukocytes/μL via direct microscopy. Empirical therapy with ceftriaxone, vancomycin, and acyclovir was initiated for presumed meningoencephalitis. During follow-up, discharge from the left ear was observed, and the cultured sample was positive for *Pseudomonas aeruginosa*. With suspected external otitis, ceftriaxone therapy was changed to cefepime, topical ciprofloxacin was initiated, and the discharge was frequently aspirated. Cerebrospinal fluid culture revealed no growth, and the viral meningitis panel was negative. *Staphylococcus hominis* was isolated from blood cultures, and treatment was adjusted according to the identified pathogens. Despite the hemolytic features, the direct coombs (DC) test result was negative. The patient received an irradiated red blood cell transfusion. Granulocyte colony-stimulating factor (G-CSF) treatment was initiatedfor agranulocytosis during follow-up. Rhinovirus and SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) were detected in the respiratory viral panel. Other viral screening tests (EBV, CMV, HIV, TORCH panel) were negative.

Immunological assessment revealed hypogammaglobulinemia and inadequate vaccine responses. Peripheral lymphocyte subset analysis revealed that T lymphocytes were decreased both proportionally and numerically, B

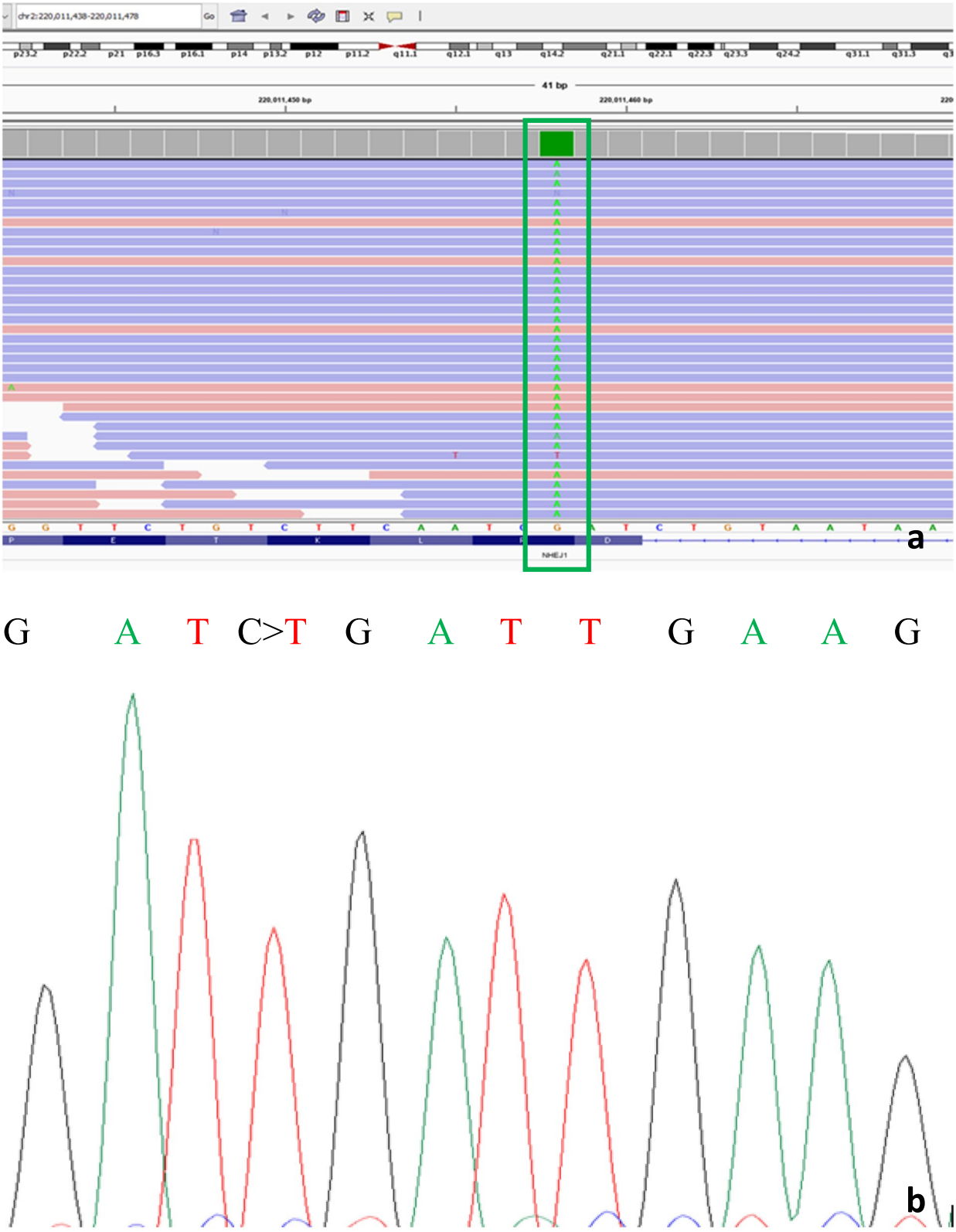


Fig. 1 **a** An Integrative Genomics Viewer (IGV) image showing the homozygous c.532C > T (p.Arg178Ter) pathogenic variant in the *NHEJ1* gene. **b** DNA sequencing chromatogram of this homozygous variant in the proband

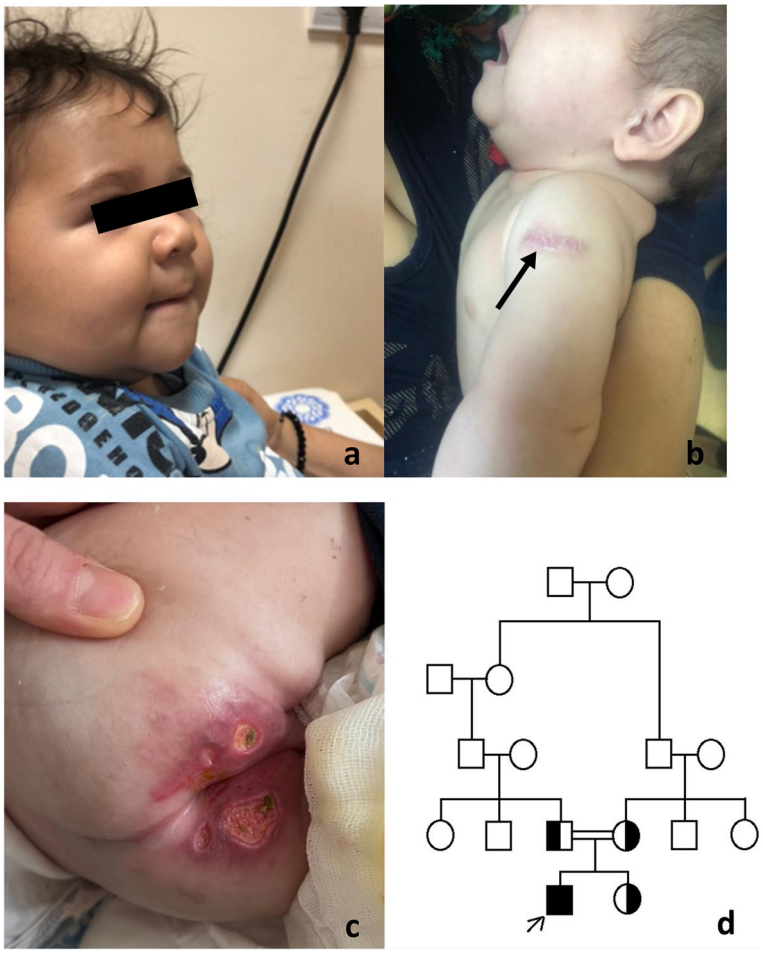


Fig. 2 **a** Microcephaly (below the 5th percentile) and bird-like facies in the proband. **b** Localized changes at the site of BCG vaccination. **c** Ulcerated, infected lesion in the gluteal region. **d** Pedigree diagram of the proband

lymphocytes were proportionally normal but numerically decreased, and NK cells were proportionally increased but numerically normal (Table 1). Autoantibody screenings were negative for DC, anti-thyroid peroxidase, and anti-thyroglobulin antibodies. The tuberculin skin test (PPD) was anergic. Chest and neck ultrasound failed to visualize the thymus; transfontanel ultrasonography was normal. Abdominal ultrasound was unremarkable except for horseshoe kidney anomaly. Routine urinalysis was unremarkable. Trivial mitral regurgitation was observed via echocardiography. The ADA enzyme level was normal. A targeted IEI gene panel and human leukocyte antigen (HLA) typing were initiated under the presumed diagnosis of SCID.

With the suspicion of T (–) B (–) NK (+) SCID, the patient was started on cotrimoxazole and fluconazole prophylaxis along with intravenous immunoglobulin replacement therapy (IGRT).

On the 10th day of hospitalization, the patient developed localized erythema and swelling at the BCG vaccination site and was referred to the Department of Pediatric Infectious Diseases. Mycobacterial screening was unremarkable, and isoniazid and rifampicin prophylaxis was initiated for presumed local BCGitis (Fig. 2b). Antibiotic treatment for the causative agent was completed and the patient was discharged on cotrimoxazole, fluconazole, isoniazid, rifampicin prophylaxis, G-CSF, and IGRT every 3 weeks (800 mg/kg, replacement dose).

One month after discharge, the patient presented with a wound in the gluteal region. Ulcerative lesions developed during follow-up (Fig. 2c). Imaging excluded abscesses. A working diagnosis of ecthyma prompted treatment with meropenem, vancomycin, and fluconazole. Wound care was applied with local mupirocin, *Triticum vulgare*, and hypochlorous acid. Epithelialization was achieved at approximately week 3. During this period, neutropenia worsened (ANC:100/μL) and the patient was referred to the Pediatric Hematology Clinic. Bone marrow examination revealed dysplasia and ineffective hematopoiesis, and the bone marrow was cellular and heterogeneous. Malignancy was ruled out and G-CSF was restarted.

Table 1 Hematological and immunological findings in our patient with Cernunnos/XLF deficiency

Parameter	At diagnosis (6.5 months)	At 9 months	At 13 months (final pre-HSCT evaluation)
Complete blood count (CBC)			
Hb (g/dL)	7.5	10.8	11.9
Platelets (/μL)	218,000	294,000	171,000
WBC (/μL)	2800	1700	2100
Neutrophils (%)	23.9%	14%	42.2%
ANC (/μL)	700	200	900
Lymphocytes (%)	33.2%	18.9%	12.9%
ALC (/μL)	900	300	300
Peripheral lymphocyte subsets			
CD3%	27.5% (50%–77%)	38.5% (50%–77%)	35% (54%–76%)
CD3 absolute count (/μL)	247.5 (2400–6900)	115.5 (2400–6900)	105 (1600–6700)
CD4%	20.5% (33%–58%)	26% (33%–58%)	19.5% (31%–54%)
CD4 absolute count (/μL)	184.5 (1400–5100)	78 (1400–5100)	58.5 (1000–4600)
CD8%	2% (13%–26%)	4% (13%–26%)	7.5% (12%–28%)
CD8 absolute count (/μL)	18 (600–2200)	12 (600–2200)	22.5 (400–2100)
CD19%	35% (13%–35%)	13% (13%–35%)	11.5% (15%–39%)
CD19 absolute count (/μL)	315 (700–2500)	39 (700–2500)	34.5 (600–2700)
CD56%	34.6% (2%–13%)	46.5% (2%–13%)	46% (3%–17%)
CD56 absolute count (/μL)	311 (100–1000)	139.5(100–1000)	138 (200–1200)
Serum immunoglobulins			
IgG (mg/mL)	< 0.75 (1.66–5.82)	7.95[a] (3.3–10.54)	8.09[a] (3.75–11.74)
IgA (mg/mL)	1.69 (− 0.28–0.74)	0.26 (− 0.2–1.26)	0.25 (0.08–0.81)
IgM (mg/mL)	0.37 (− 0.09–1.47)	< 0.2 (0.06–1.67)	0.66 (0.18–1.79)
Total IgE (IU/mL)	< 1	< 1	-
Vaccine antibodies			
Anti-HBs (mIU/mL)	0	-	-
ADA genetic analysis (buccal swab)	Negative	-	-

Abbreviations: *Hb* hemoglobin, *WBC* white blood cell count, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count, *CD* cluster of differentiation, *Ig* immunoglobulin, *Anti-HBs* hepatitis B surface antibody, *ADA* adenosine deaminase

[a]Indicates immunoglobulin levels measured during IGRT

*Numbers in parentheses indicate the values of age-matched healthy controls

During follow-up, the patient experienced two bronchiolitis episodes at 7.5 and 11 months of age, and specific IgE tests for aeroallergens and foods revealed no sensitization. During the bronchiolitis episode at 11 months, *respiratory syncytial virus* was detected. Following treatment, regular inhaled corticosteroid (ICS) therapy was initiated. SARS-CoV-2 PCR results remained positive for approximately 5 months. Despite medium-dose ICS prophylaxis, wheezing recurred, prompting pulmonary and infectious disease consultations. Chest radiographs revealed no infiltrates and his clinical status remained stable; no further diagnostic interventions or special therapies were pursued, and ICS was continued for symptomatic control.

The patient was evaluated by pediatric neurology and developmental pediatrics. Denver II testing was applied to assess neurodevelopmental milestones and they were found to be age-appropriate (head control at 2 months, supported sitting at 6 months, walking at 13 months). At 14 months, the patient sustained a post-traumatic left knee fracture due to a fall, which resolved within one month without sequelae.

Genetic analysis identified a homozygous nonsense variant, c.532C > T (p.Arg178Ter), in exon 5 of the *NHEJ1* gene (ENST00000356853.5).). Sanger sequencing demonstrated that the parents and the sibling had heterozygous c.532C > T variant (Fig. 2d). This variant, associated with Cernunnos/XLF deficiency and listed as severe combined immunodeficiency 124 in OMIM (#611291), was detected through CES analysis (Fig. 1a). It has been classified as pathogenic according to the ACMG criteria and has also been previously reported as pathogenic in the ClinVar database [11]. The family underwent genetic and HLA typing, which revealed that the healthy sister was a full match. Despite being a carrier of the same NHEJ1 variant, she had normal clinical and immunological findings. As no other suitable donor was available, a matched sibling HSCT was performed, and the patient is currently under post-transplant follow-up (Fig. 3, clinical timeline).

Discussion

In our patient, a homozygous c.532C > T nonsense mutation in exon 5 of the *NHEJ1* gene was detected. This mutation introduced a stop codon at amino acid 178 (p.R178X), resulting in the loss of approximately one third of the C-terminal region. The *NHEJ1* gene is located on chromosome 2q35 and encodes the Cernunnos/XLF protein [7]. This protein comprises 299 amino acids. It interacts with DNA ligase IV to mediate the repair of DSBs. *NHEJ1* gene mutation causes loss of function of the Cernunnos/XLF protein, leading to disruption of the NHEJ pathway [12]. The most common mutations reported in this gene are missense and nonsense mutations and certain splicing region defects. Deletions, insertions, and duplications account for 10.2% of the reported cases. Although various mutations have been identified, no definitive genotype–phenotype correlation has yet been established for Cernunnos/XLF deficiency [13]. The

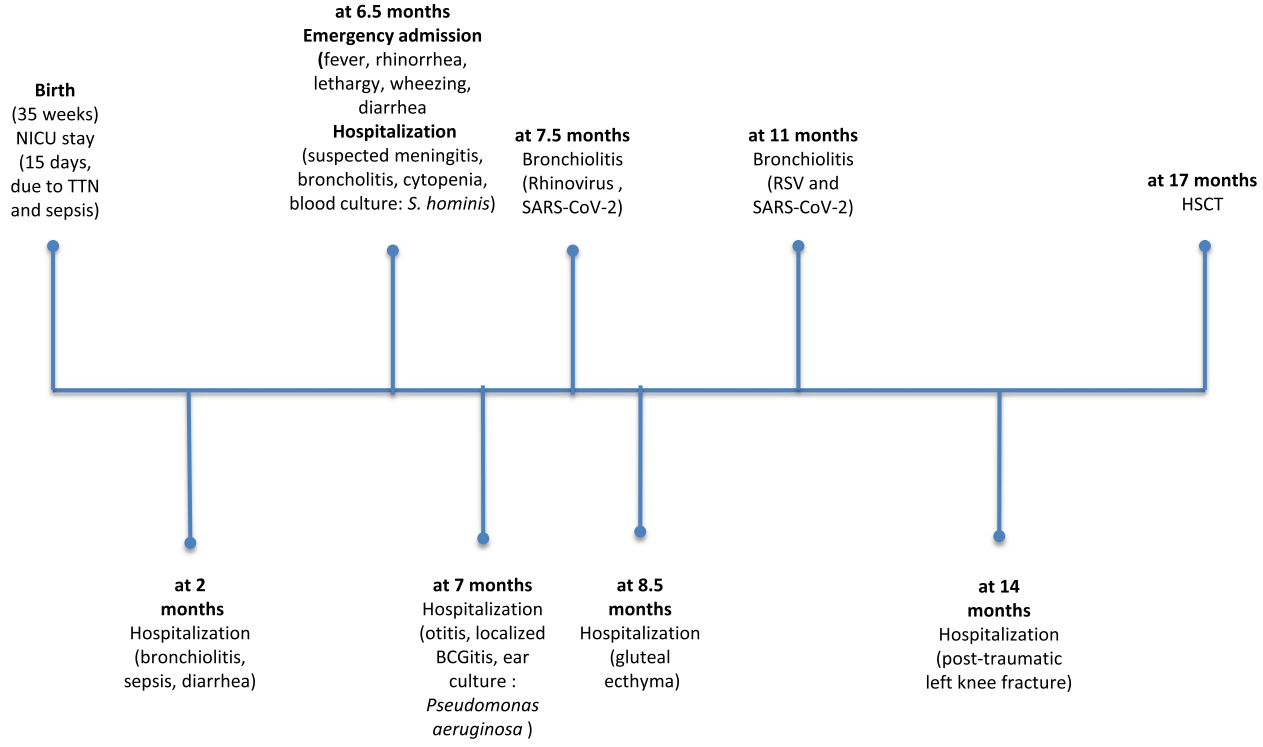


Fig. 3 Timeline of the proband's clinical course

clinical phenotype may vary according to genetic variants. With this perspective, we conducted a comparative review of all published cases harboring this exact variant, summarizing their demographic, clinical, immunological features (Tables 2 and 3).

DSB repair–associated mutations in the NHEJ pathway play critical roles in the development of adaptive immunity [3]. Somatic DNA reorganization of the V(D)J gene segments encoding T-lymphocyte and B-lymphocyte antigen receptors—that is, V(D)J recombination—is essential for adaptive immune maturation. Loss of function of any NHEJ pathway component results in failed V(D)J recombination and, consequently, impaired maturation of T and B lymphocytes. The number of NK cells remains within normal limits, as these cells do not undergo V(D)J recombination [3, 13]. Accordingly, defects in the NHEJ pathway typically present with a T(−) B(−) NK(+) immunophenotype [1]. As observed in the present case, this phenotype has been frequently reported in the literature; however, Jamee et al. [21] described an unusual T (−) B (+) NK (+) immunophenotype in a patient with Cernunnos/XLF deficiency.

To the best of our knowledge, approximately 55 cases of Cernunnos/XLF deficiency have been documented in the literature. Although the age at diagnosis varies, the number of cases diagnosed during infancy remains very limited [2, 7, 9, 16, 18]. The present patient represents one of the rare instances in which the genetic variant was identified and the diagnosis was established within the first year of life. Given the clinical course of the disease and pronounced lymphopenia, we believe that these patients can be diagnosed even earlier.

Evaluation of 17 previously reported patients carrying the same variant revealed that the most common clinical manifestations were growth retardation ($n = 17$, 100%), microcephaly ($n = 15$, 88.2%), and infectious disorders ($n = 12$, 70.6%). Less frequently observed findings included cytopenia ($n = 6$, 35.3%), facial dysmorphism ($n = 5$, 29.4%), developmental delay ($n = 3$, 17.6%), and malignancy ($n = 1$, 5.9%). In addition to growth retardation, microcephaly, bird-like facies, severe cytopenias, an SCID phenotype and recurrent severe viral and bacterial infections since the neonatal period, the present case also exhibited localized BCGitis and prolonged SARS-CoV-2 PCR positivity.

The NHEJ pathway is implicated not only in immune development but also in cerebral cortical formation; deficiencies in this pathway may lead to neuronal migration defects and thinning of the cortical mantle [5]. Furthermore, microcephaly is a shared phenotypic feature of DNA-PKcs, DNA ligase IV, and Cernunnos/XLF deficiencies, whereas it is generally absent in DCLRE1C (Artemis) deficiency, another NHEJ pathway defect [3]. This distinction can aid in differential diagnosis. Our patient presented with microcephaly but no additional neurological abnormalities, and the transient

Table 2 Demographic and clinical characteristics, treatments, and outcomes of patients with the *NHEJ1* c.532C > T (p.R178X) mutation

N	Country of origin	AOO/AOD (mo)	Sex/Cons	Zygosity	Clinical manifestations	Treatments	Life status at the time of study	Ref
Our patient	Turkey	≤ 1/6.5	M/Yes	Homozygous	Microcephaly, growth retardation, bird-like face, meningitis and sepsis, wheezing attacks, recurrent respiratory tract infections, BCGitis, bacterial otitis, perianal abscesses, chronic diarrhea, anemia, neutropenia,lymphopenia	IGRT, AB and AF prophylaxis, HSCT	Alive	-
P1	Turkey	1/24	NR/Yes	Homozygous	Microcephaly, growth retardation, recurrent respiratory and digestive tract infections	IGRT	Deceased (4 y,septic shock)	[7]
P2	Turkey	36/36	F/Yes	Homozygous	Microcephaly, growth retardation, polydactyly, bird-like face, spontaneous chromosomal breakages, pancytopenia, recurrent perianal abscesses	IGRT, HSCT (candidate)	Alive	[14]
P3	Turkey	6/20	F/Yes	Homozygous	Microcephaly, growth retardation, wheezing attacks, clubbing, recurrent respiratory tract infections and bronchiolitis obliterans and pulmonary HTN mucocutaneous candidiasis, purulent otitis, diffuse molluscum contagiosum	IGRT, AB prophylaxis	Deceased (4.5 y, Unknown)	[15]
P4	Turkey	NR/1	F/Yes	Homozygous	Microcephaly, bird-like face, growth retardation	HSCT	Alive	[2]
P5	Turkey	2/9	F/Yes	Homozygous	Microcephaly, bird-like face, growth retardation, autoimmune anemia, neutropenia, recurrent respiratory tract infections, urinary tract infection, otitis media, CMV pneumonia,	RBC transfusions, IGRT, IS, AB prophylaxis, HSCT	Alive	[2]
P6	Netherlands	NR/1,5	NR/NR	Homozygous	Microcephaly, growth retardation, recurrent (opportunistic) infections, diarrhea	HSCT At 1.5 mo	Alive	[16]
P7	Netherlands	NR/120	NR/NR	Homozygous	Microcephaly, growth retardation, respiratory tract infections	HSCT at10y	Alive	[16]
P8	Netherlands	NR/11	NR/NR	Homozygous	Microcephaly, growth retardation, recurrent respiratory fungal infections	HSCT (candidate)	Alive	[16]
P9	Netherlands	NR/96	NR/NR	Homozygous	Microcephaly, growth retardation, recurrent respiratory tract infections	HSCT (candidate)	Alive	[16]
P10	Netherlands	NR/108	NR/NR	Homozygous	Microcephaly, growth retardation, respiratory tract infections, diarrhea	HSCT at9y	Alive	[16]
P11	Netherlands	NR/12	NR/NR	Homozygous	Microcephaly, growth retardation, BCGitis, bacterial otitis and autoimmunity	HSCT at12mo	Alive	[16]
P12	Turkey	NR/12	NR/Yes	Homozygous	Microcephaly, growth retardation, dystrophy and mouth lesions and AIHA	RBC transfusions, HSCT	Deceased (1,5 y, septic shock)	[17]
P13	Turkey	3/7	M/Yes	Homozygous	Microcephaly, growth retardation, bird-like face, oral thrush, recurrent respiratory tract infections, chronic diarrhea, fungal abscess, pancytopenia, neutropenia, Non-Hodgkin lymphoma	IGRT, AB and AF prophylaxis Anti-epileptic, Chemotherapy (RTX and MTX) HSCT (candidate)	Alive	[18]
P14	Turkey	10/42	F/Yes	Homozygous	Microcephaly, growth retardation, bird-like face, respiratory and urinary tract infections, diarrhea, pancytopenia	IGRT, AB prophylaxis	Alive	[19]
P15	Iran	First months of life/42	F/Yes	Homozygous	Microcephaly, growth retardation, developmental delay, axillary lymphadenitisfollowing BCG, AIHA	IS	Alive	[5]

Table 2 (continued)

N	Country of origin	AOO/AOD (mo)	Sex/Cons	Zygosity	Clinical manifestations	Treatments	Life status at the time of study	Ref
P16	Turkey	NR/18	F/Yes	Homozygous	Growth retardation, developmental delay	HSCT	Alive	[20]
P17	Turkey	NR/66	F/Yes	Homozygous	Growth retardation, developmental delay	HSCT	Alive	[20]

AB antibiotic, *AF* antifungal, *AIHA* autoimmune hemolytic anemia, *AOO* age of onset, *AOD* age of diagnosis, *Cons* consanguinity, *HSCT* hematopoietic stem cell transplantation, *HTN* hypertension (used here as pulmonary hypertension), *IGRT* immunoglobulin replacement therapy, *IS* immunosuppressive therapy, *MTX* Methotrexate, *RBC* red blood cell, *RTX* Rituximab, *NR* not reported

Table 3 Immunological findings of patients with the *NHEJ1* c.532C > T (p.R178X) mutation

N	Lymphocyte (/μL)	T cells (/μL)	CD4 (/μL)	CD8 (/μL)	B cell (/μL)	IgG (mg/mL)	IgA (mg/mL)	IgM (mg/mL)	Ref
Our patient	900↓	247↓	184↓	18↓	315↓	< 0.75↓–10.78[a]	0.12–1.69	< 0.2–0.66	-
P1	1220↓	730↓	150↓	559	75↓	< 0.33↓	< 0.06↓	1.39	[7]
P2	NR	83%	42%	47%	0↓	1.4↓	0.22↓	0.84↓	[14]
P3	700–1120↓	132–750↓	99–380↓	316–436↓	67–56↓	0.17–5.6[a]↓	0.4–1.17↓	0.33–0.42	[15]
P4	4836	725↓	546↓	1740↑	372↓	5.6↓	4.6↓	0.42	[2]
P5	990	534↓	148↓	366↓	59↓	1.4↑	0.7↑	6.7↑	[2]
P6	NR	NR	NR	NR	NR	NR	NR	NR	[16]
P7	NR	NR	NR	NR	NR	NR	NR	NR	[16]
P8	1500↓	200↓	0↓	100↓	40↓	NR	NR	NR	[16]
P9	900↓	900	300	400↓	10↓	NR	NR	NR	[16]
P10	NR	NR	NR	NR	NR	NR	NR	NR	[16]
P11	NR	NR	NR	NR	NR	NR	NR	NR	[16]
P12	NR	NR	NR	NR	NR	NR	NR	NR	[17]
P13	850↓	540↓	420↓	130↓	60↓	7.84	0.6	1.9	[18]
P14	1070	300	NR	NR	253	1.34	0.06	1.38	[19]
P15	765↓	306	214	61↓	38↓	4.31	1.23	0.96	[5]
P16	2410	NR	NR	NR	NR	NR	NR	NR	[20]
P17	400↓	NR	NR	NR	NR	NR	NR	NR	[20]

[a]Indicates monitoring of immunoglobulin levels from the date of diagnosis until after treatment. NR, not reported; ↓ below reference range; ↑ above reference range

opisthotonus observed during meningitis resolved after treatment.

Consistent with the literature, our patient also exhibited recurrent wheezing attacks, otitis, and anal ulcers [13, 15, 21]. In another case report with the same genetic variant diagnosed at 20 months of age and experienced recurrent bronchiolitis episodes, bronchiolitis obliterans and pulmonary hypertension developed at 3.5 years of age and the patient was lost at 4.5 years [15]. Given our patient's young age, early diagnosis, and the opportunity for HSCT, we hope that such complications can be prevented.

Consistent with the literature, our patient demonstrated marked lymphopenia from the neonatal period; lymphopenia levels can vary among cases [6, 9]. This variability is explained by the presence of alternative DNA repair proteins that operate exclusively to repair DSBs during lymphocyte development [22]. While most reported cases, such as our patient, exhibit a T (–) B (–) phenotype, some cases have been found to have normal B-cell counts [1, 13].

In our patient, who presented with bicytopenia, bone marrow examination revealed no findings consistent with malignancy. Supportive treatments such as G-CSF were required, particularly due to worsening neutropenia. Although anemia, neutropenia, and thrombocytopenia have frequently been reported in the literature, thrombocytopenia was not observed in our patient [2, 9, 13]. Neutropenia unresponsive to G-CSF therapy has rarely been documented [21]. In our patient, neutropenia was initially refractory to G-CSF treatment, but a partial response was obtained during follow-up.

Autoimmune cytopenia has been reported in approximately 23% of patients with Cernunnos/XLF deficiency, occurring more frequently in those with the "leaky" form of the disease [1]. This phenomenon has been attributed to an imbalanced T-cell repertoire or impaired peripheral tolerance [7]. In patients with anemia, autoimmune hemolytic anemia (AIHA) and DC positivity are often reported [2]. However, our patient was DC negative. While he presented with severe anemia and required a single erythrocyte transfusion, follow-up evaluations indicated a more moderate course.

The absence of findings supporting autoimmunity in our patient, in conjunction with severe lymphopenia, neutropenia, hypogammaglobulinemia, and recurrent severe infections, suggests that this is not a "leaky" form. At presentation, our patient's IgG level was markedly low, IgA was elevated, and IgM remained within the normal range. During follow-up, IgA levels gradually declined, whereas IgM levels fluctuated (Table 1). In severe forms such as the present case, high IgM levels and low IgG and IgA levels—indicative of class-switch recombination deficiency—have been frequently reported [7, 9, 10]. Nevertheless, patients with normal immunoglobulin levels have also been documented [5, 9].

Although our patient had received all age-appropriate vaccinations, dual antituberculosis prophylaxis was initiated following the development of local BCGitis and was continued until HSCT. Importantly, live vaccines are contraindicated in SCID patients because of the risk of life-threatening complications, and therefore subsequent live vaccinations were withheld in our patient. In the literature, BCG vaccine-related complications have been reported in five patients with Cernunnos/XLF deficiency in addition to the present case [1, 5, 16, 21, 23]. Two of these patients shared the same variant as our patient; one developed BCGitis [5, 16] (Tables 2 and 3). Conversely, another patient experienced only axillary lymphadenitis following BCG vaccination, while other live vaccines were administered without complications; no immunodeficiency findings were noted beyond microcephaly, growth retardation, and AIHA, and the patient reportedly led a normal life without special precautions [5]. Nevertheless, because BCG vaccination remains part of routine immunization schedules in developing countries such as Türkiye, it is advisable that, before the administration of live vaccines—particularly Measles, Mumps, and Rubella and BCG—a CBC be performed to screen for lymphopenia, and that children found to have lymphopenia (especially low T-cell counts) undergo pediatric immunology evaluation. In patients presenting with BCG vaccine-related complications, Cernunnos/XLF deficiency—as with other forms of SCID—should be considered in the diagnostic workup.

Previous studies have demonstrated that HSCT from both HLA-matched sibling donors and matched unrelated donors can be a successful therapeutic option for patients with Cernunnos/XLF deficiency [2, 24]. One report described a patient who survived without HSCT until 16 years of age but succumbed to severe varicella infection and cytomegalovirus reactivation [9]. Another patient was diagnosed at 20 years of age and remained stable on IGRT without HSCT [13]. Missense or splice-site variants are commonly reported in patients who survive beyond 8 years of age without HSCT; these variants may permit the production of partially functional protein products [22]. One of the longest-surviving reported patients carried the c.390 + 1G > C splice-site mutation in *NHEJ1* and lived for 30 years without HSCT [22]. Another patient, harboring two distinct missense mutations, died at 18 years of age from septic shoc [7]. Long-term survival without HSCT is rare.

In our patient, the use of a heterozygous sibling donor was necessary due to the absence of alternative HLA-matched donors. This approach has both advantages and limitations. On one hand, the availability of an HLA-identical sibling provides timely access to transplantation, which can be life-saving in critically ill patients. While HSCT from HLA-matched sibling donors generally achieves high long-term survival rates in SCID patients, specific data on the use of carrier sibling donors remain limited [25, 26]. On the other hand, the long-term safety and functional competence of carrier donors remain uncertain, and outcome data are scarce. Therefore, further studies evaluating the outcomes of HSCT using carrier sibling donors are needed. Such data will contribute to a better understanding of transplant outcomes from genetically related carrier donors and provide a basis for optimizing HSCT strategies in the future.Because Cernunnos/XLF deficiency is a DNA-repair/radiosensitivity disorder, special consideration must be given to the intensity of conditioning regimens prior to HSCT. In our patient, to minimize the risks associated with alkylating agents, a reduced-intensity conditioning protocol was applied, consisting of busulfan 9.6 mg/kg, fludarabine 150 mg/m^2, and ATG 10 mg/kg.

Limitations

Importantly, the immunological evaluation in this study included serum immunoglobulin levels, vaccine responses, peripheral lymphocyte subsets, and ADA genetic analysis together with an IEI gene panel. However, TRECs (T-cell receptor excision circles)/KRECs (K-deleting recombination excision circles) levels could not be assessed due to laboratory limitations, the patient's severe clinical course, and the urgent need for HSCT. These assays provide clinically relevant and standardized quantitative measurements of thymic (T-cell) and bone marrow (B-cell) output, and are widely used both in the diagnosis of SCID and in monitoring immune reconstitution following HSCT. Although the combination of early infantile onset, severe infectious burden, profound lymphopenia from the neonatal period, hypogammaglobulinemia, absence of autoimmunity, and rapid clinical deterioration strongly support the classification of our case as a severe SCID phenotype, we acknowledge that incorporating TRECs/KRECs analysis in future studies would further strengthen immunological characterization and help distinguish "leaky" from severe SCID phenotypes.

Several functional assays would have further strengthened the immunological characterization of our patient. Radiosensitivity testing (e.g., γH2AX assay) and detailed TCR (T-cell Receptor) repertoire analysis (PROMIDISα or TCR Vα7.2 flow cytometry) have been reported as valuable tools in DNA repair disorders [27–29]. Performing these tests in both our patient and the heterozygous HLA-matched sibling donor could have provided additional insights into the genotype–functional phenotype relationship and donor safety. These tests could not be performed due to laboratory limitations and the patient's clinical status. Nonetheless, they should be considered in future evaluations, particularly prior to HSCT, to optimize conditioning regimens and donor choice.

Due to laboratory limitations, we were unable to perform naïve vs memory T-cell subset analysis (CD45RA/RO, CD31 on CD4) and mitogen proliferation assays (PHA), V(D)J recombination functional assays or in vitro NHEJ reporter assays, and telomere length/telomerase expression. Had these evaluations been available, they would have provided more robust documentation of the patient's residual T-cell function, functional immunologic phenotype, and bone marrow phenotype.

Moreover, our patient presented with microcephaly but no additional neurological abnormalities. Developmental milestones were age-appropriate according to Denver II testing, and transfontanel ultrasonography was normal. Nevertheless, given the established role of NHEJ1/Cernunnos in neural progenitor division and brain development [30], brain Magnetic Resonance Imaging (MRI) has been planned. Since the patient is currently under post-HSCT follow-up, MRI will be scheduled in the post-transplant period. These aspects represent an additional limitation of our current report, and longitudinal neurodevelopmental evaluation remains warranted.

Conclusion

Cernunnos/XLF deficiency has a broad clinical spectrum. In patients presenting with microcephaly, growth retardation, lymphopenia, and hypogammaglobulinemia accompanied by recurrent and/or severe infections, Cernunnos/XLF deficiency should be strongly suspected. Prompt comprehensive immunological evaluation and genetic analyses are critical for early diagnosis and for planning curative HSCT. In patients with an SCID phenotype, avoidance of live vaccines until definitive diagnosis is essential to prevent potentially life-threatening complications. Comprehensive reports of newly identified patients and novel pathogenic variants will refine our understanding of the disease's clinical manifestations, facilitate earlier diagnosis, and positively influence patient management. Further studies and data on this patient group are needed to elucidate the efficacy of HSCT and improve optimal donor selection.

Abbreviations

AB	Antibiotic
ACMG	American College of Medical Genetics and Genomics
ADA	Adenosinedeaminase
AIHA	Autoimmunehemolyticanemia
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
AOD	Age of diagnosis
AOO	Age of onset
BCG	Bacillus Calmette–Guérin
CBC	Complete blood count
CES	Clinical Exome Sequencing
ClinVar	Clinical Variants Database
Cons	Consanguinity
DC	Direct Coombs
DSB	Double-strand break
G-CSF	Granulocyte colony-stimulating factor
HGMD	Human Genome Mutation Database
HLA	Human leukocyte antigen
HR	Homologous recombination
HSCT	Hematopoietic stem cell transplantation
ICS	Inhaled corticosteroid
IEI	Inborn error of immunity
IGV	Integrative Genome Viewer
IGRT	Immunoglobulin replacement therapy
KRECs	K-deleting recombination excision circles
MRI	Magnetic Resonance Imaging
NGS	Next-generation sequencing
NHEJ	Nonhomologous end joining
PCV	Pneumococcal conjugate vaccine
PID	Primary immunodeficiency
PPD	Purified Protein Derivative
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCID	Severe combined immunodeficiency
SDS	Standard deviation score
TORCH	Toxoplasma, Other, Rubella, Cytomegalovirus, Herpes
TCR	T-cell Receptor
TRECs	T-cell receptor excision circles
V(D)J	Variable (V), Diversity (D), andJoining (J)
XLF	XRCC4-like factor
XRCC4	X-ray repair cross-complementing 4

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Clinical trial number

Not applicable.

Authors' contributions

ÖA and NU contributed to the conceptual framework and study design. GK conducted the literature review, wrote the main manuscript, and prepared the tables and figures. FH contributed to the description of the genetic methodology and the preparation of genetic illustrations. ÖA, SG, SOA, DBB, HY, ETKM, and ŞÖY contributed to the revision and improvement of the manuscript. All the authors reviewed and approved the final version.

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Data availability

The datasets generated and/or analysed during the current study are available in ClinVar repository under the accession number SCV006308847. The dataset includes variant-level information derived from clinical exome sequencing performed for diagnostic purposes.

Declarations

Ethics approval and consent to participate

Approval for this case report was not required under the institutional policy of Dokuz Eylül University for single case reports. The case description has

been reported in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. Written informed consent was obtained from the patient's family for the sharing and publication of clinical data and photographs.

Consent for publication
Written informed consent was obtained from the patient's parent for the use of anonymized medical data and clinical photographs in this publication.

Competing interests
The authors declare no competing interests.

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