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CASE REPORT

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Novel pathological genetic variant associated with DOCK8 deficiency: case report with successful hematopoietic stem cell transplantation

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Abstract
Deficiency of dedicator of cytokinesis 8 (DOCK8) is a combined immunodeficiency characterized by severe atopic dermatitis, recurrent infections, and elevated serum immunoglobulin E (IgE) levels. Following genetic confirmation, early hematopoietic stem cell transplantation (HSCT) is the treatment of choice. We report a 7-year-old girl who presented with refractory atopic dermatitis and recurrent sinopulmonary infections. Laboratory evaluation revealed markedly elevated total IgE, lymphopenia, decreased memory B cells, and poor vaccine responses. Whole exome sequencing identified a previously unreported homozygous nonsense mutation in the *DOCK8* gene (c.5382C>A; p.Tyr1794*). Functional validation was achieved through flow cytometry, which demonstrated significantly reduced DOCK8 protein expression. The patient underwent successful HSCT from a fully matched (10/10) HLA-compatible donor following conditioning with fludarabine and treosulfan. At 1 year follow-up, full donor chimerism was achieved, and the patient remained in remission. This case highlights a novel pathogenic variant in DOCK8 deficiency and demonstrates curative success following definitive diagnosis and timely HSCT.

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Introduction

Deficiency of dedicator of cytokinesis 8 (DOCK8) is a rare autosomal recessive form of combined immunodeficiency. According to the International Union of Immunological Societies (IUIS) classification, deficiency of DOCK8 is categorized among inborn errors of immunity (IEI) as a combined immunodeficiency with associated or syndromic features, representing a less severe phenotype compared to severe combined immunodeficiency (SCID).[1] Clinical manifestations include severe atopic dermatitis, recurrent sinopulmonary infections, mucocutaneous candidiasis, viral skin infections, elevated serum IgE levels, eosinophilia, and increased risk of malignancy. Diagnosis may be delayed due to similarities with common atopic conditions.[2]

DOCK8 is a large gene located on chromosome 9 that comprises 48 exons. The encoded protein is of approximately 190 kDa and expression is high in hematopoietic tissues. The DOCK8 protein contributes to cytoskeletal remodeling, cell migration, immune signaling, and cytokine production.[2,3] All reported DOCK8 mutations, regardless of their type, are shown to result in a combined immunodeficiency phenotype requiring hematopoietic stem cell transplantation (HSCT) for definitive treatment.[4] Most DOCK8 mutations are large deletions that completely remove protein function.

Here, we present a pediatric case of *DOCK8* deficiency harboring a novel homozygous nonsense mutation, confirmed through immunological and functional analyses, and successfully treated with HSCT.

Case Report

A 7-year-old girl, the second child of consanguineous parents, was referred to our clinic for immunodeficiency evaluation because of severe treatment-resistant atopic dermatitis and recurrent infections. The dermatologic manifestations had first appeared in the neonatal period, accompanied by oral candidiasis. Over the years, she underwent four to five hospitalizations annually for sinopulmonary and cutaneous infections. She also had a history of allergic reactions to cow milk and eggs during infancy.

The patient was followed by single center, with her complaints being managed as acute episodes by various physicians without systematic immunologic evaluation or coordinated care. Her clinical history was attributed to allergic and infectious conditions, which led to a delay in investigating an underlying immune deficiency.

On physical examination, both her height and weight were below 3rd percentile. She exhibited coarse facial features, generalized xerosis, severe eczema on the extremities, yellowish crusted lesions on the upper right lip, pustules in the nasal region, dark and thickened desiccated plaques in the axillary area, and fissures in the intergluteal region (Figure 1). Auscultation of the lungs revealed diffused rales. Chest X-ray showed bilateral widespread pneumonic infiltrates, and intravenous (i.v.) antibiotic therapy was initiated.

Laboratory findings included anemia (Hb: 8.2 g/dL), lymphopenia (1090/mm^3), decreased IgA (10 mg/dL), markedly elevated IgE (2562 kU/L), and poor antibody response to vaccines (anti-hepatitis B surface antibody (HBs): 2 IU/L; tetanus antibody: 0.04 IU/mL; and anti-A: 1/4). Initial eosinophil count was 380/mm^3, with a gradual increase noted on follow-up. Lymphocyte subset analysis revealed age-inappropriate reductions in cluster of differentiation 3$^+$ (CD3$^+$), cluster of differentiation 4$^+$ (CD4$^+$), and CD16$^+$56$^+$ (a subset of Natural Killer cells [NK]) cell counts. Although CD19$^+$ B cells were within the normal range, class-switched memory B cells were markedly decreased. Detailed immunological and hematological parameters are presented in Table 1. The patient was started on regular intravenous immunoglobulin replacement besides antibiotic and antifungal prophylaxis. Following the initiation of immunoglobulin replacement and antimicrobial prophylaxis, a partial reduction in infection frequency was observed, although complete resolution of cutaneous manifestations was not achieved prior to transplantation. The extended T cell subset analysis, including naïve and memory CD4+ populations, was not performed as part of the routine immunological workup.

Combined immunodeficiency was suspected based on recurrent sinopulmonary and cutaneous infections, growth retardation, severe atopic dermatitis, elevated IgE, and lymphopenia. Secondary immunodeficiencies were excluded. Among hyper-IgE syndromes, loss of function of STAT3 (a transcription factor and intracellular signalling protein) was considered doubtful, given the autosomal dominant inheritance pattern and absence of skeletal and pulmonary complications. Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX [*FOXP3* mutation]) syndrome and Wiskott–Aldrich syndrome (WAS) were excluded on clinical and inheritance grounds. Deficiency of PGM3 and ZNF341 was also deemed inconsistent with the overall presentation. Whole exome sequencing was therefore performed, which identified the *DOCK8* mutation described below.

Whole exome sequencing was performed in collaboration with the Medical Genetics Department. A novel homozygous nonsense mutation was identified in the *DOCK8* gene (NM_203447: c.5382C>A, p.Tyr1794*). This variant was not reported in public databases, such as 1000 Genomes, gnomAD, or ExAC. According to the American College of Medical Genetics and Genomics (ACMG) criteria, it was classified as potentially pathogenic based on PVS1 and PM2 evidence codes. *In silico* analysis further supported its pathogenicity: the variant had a combined annotation dependent depletion score of 43 and was predicted to be disease-causing by the following prediction tools: MutationTaster (1-deleterious, range: 0–1), DANN (1-deleterious, range: 0–1), BayesDel (0.66-deleterious [strong]), range: −1.29334 to 0.75731).

DOCK8 protein expression was assessed by flow cytometry (BD FACSCanto II; BD Biosciences, NJ, USA) on peripheral blood mononuclear cells. Intracellular staining of CD3$^+$ and CD20$^+$ cells demonstrated reduced mean fluorescence intensity, compared to healthy controls (Figure 2). The analysis was performed using a DOCK8-specific monoclonal antibody (clone G-2, Cat# sc-376911; Santa Cruz Biotechnology, Dallas, TX, USA) and a secondary antibody (clone RMG1, Cat# 406606; BioLegend, San Diego, CA, USA). Data were analyzed with the Kaluza software.Segregation analysis by targeted next-generation sequencing confirmed

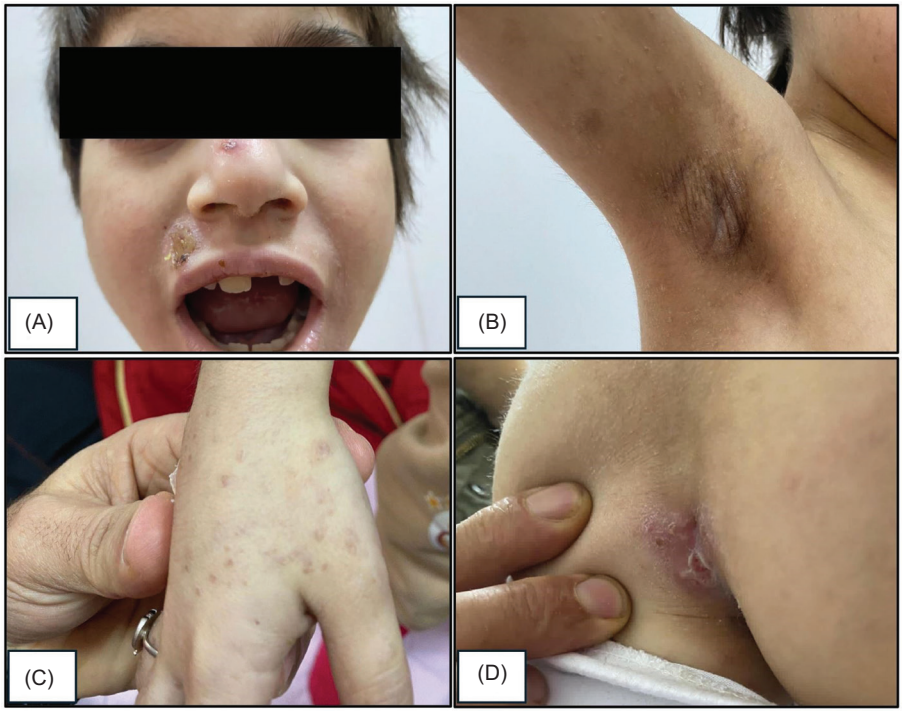

Figure 1 Cutaneous findings of the patient on physical examination. (A) Coarse facial features with a yellowish-crusted lesion on the right upper lip and pustular lesions in the nasal area; (B) hyperpigmented, thickened, and desiccated plaques in the axillary folds; (C) severe eczema on the extremities, and (D) fissures in the intergluteal region.

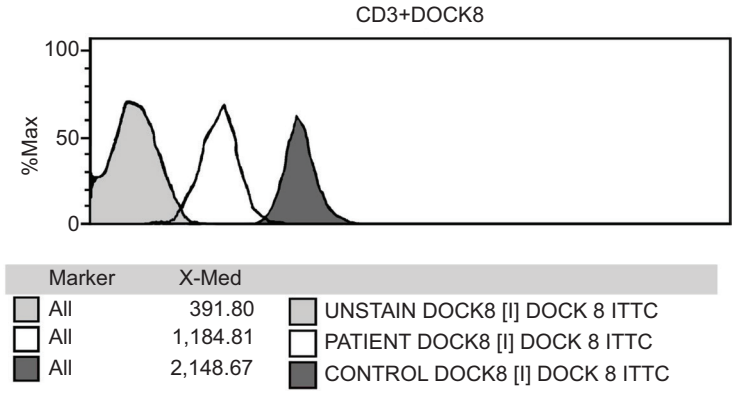

Figure 2 Flow cytometric evaluation of intracellular DOCK8 protein expression in $CD20^+$ B cells (left panel) and $CD3^+$ T cells (right panel). Histograms display the distribution of DOCK8 fluorescence intensity, with the *y*-axis representing the percentage of maximum cell count (%Max). Three populations are shown: unstained control (blue), patient (green), and healthy control (red). Median fluorescence intensity (X-Med) values are indicated below each histogram. The patient demonstrated markedly reduced DOCK8 expression, compared to the healthy control in both $CD20^+$ B cells (X-Med: 1470.84 vs. 2345.70) and $CD3^+$ T cells (X-Med: 1184.81 vs. 2148.67), consistent with DOCK8 protein deficiency.

heterozygous carrier status in both parents and the unaffected sibling, consistent with an autosomal recessive inheritance pattern.

Approximately 7 months elapsed between definitive diagnosis and HSCT. During this period, the patient received supportive care, including intravenous immunoglobulin replacement and antimicrobial prophylaxis, which resulted in partial clinical stabilization with reduced frequency of infection, although skin manifestations persisted. Given the progressive nature of DOCK8 deficiency and the risk of infectious complications and malignancy without definitive intervention, HSCT was planned. The patient received anti-thymocyte globulin as part of serotherapy. A reduced-intensity conditioning regimen containing fludarabine and treosulfan was administered, followed by matched 10/10 HLA-compatible HSCT. Graft-versus-host disease (GvHD) prophylaxis included cyclosporine and mycophenolate mofetil.

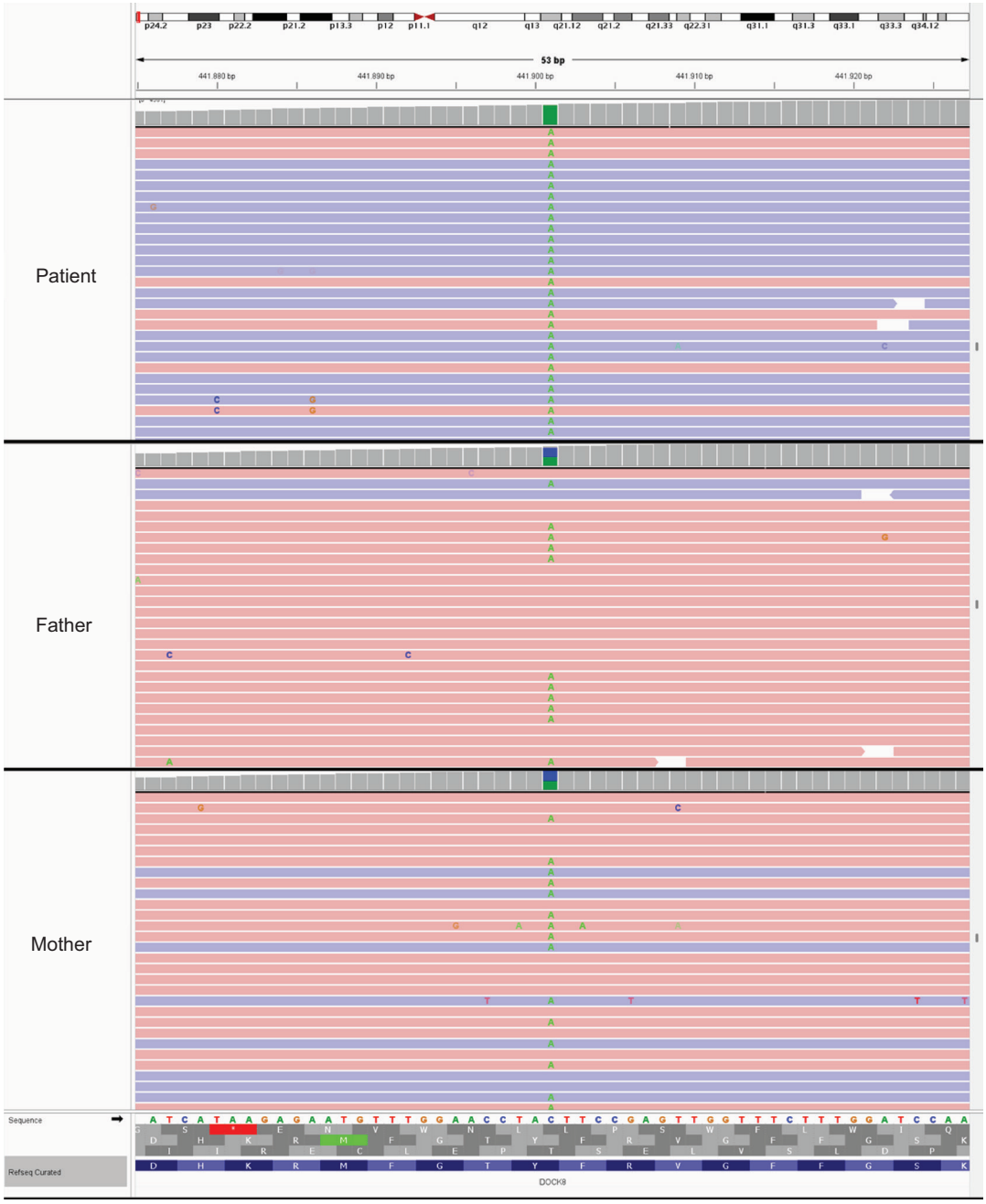

Figure 3 Next-generation sequencing (NGS) analysis of the DOCK8 variant (c.5382C>A, p.Tyr1794*) in the patient and parents. Integrative Genomics Viewer (IGV) visualization demonstrates homozygous variant in the patient (top panel) and heterozygous carrier status in the father (middle panel) and mother (bottom panel). The variant position is indicated by the green nucleotide change (C>A). Initial Sanger sequencing in the parents yielded suboptimal quality; therefore, targeted NGS was performed for segregation analysis.

Neutrophil and platelet engraftments were achieved on days 12 and 11, respectively. At 2- and 3-month follow-up, full donor chimerism (99%) was confirmed. No signs of GvHD were observed; mycophenolate mofetil was discontinued after 1 month and cyclosporine was tapered off by 6th month. At 1 year follow-up, full donor chimerism was determined to be sustained, and necessary vaccinations were initiated. The patient's immunological and hematological parameters before and after HSCT are summarized in Table 1.

Discussion

The presented case displays clinical and immunological features consistent with the classical phenotype of DOCK8 deficiency.[5] However, in this patient, the clinical presentation was interpreted for an extended period as atopic dermatitis and food allergy, which contributed to delayed diagnosis. This is a common limitation in hyper-IgE syndromes, as it is erroneous to rely solely on phenotypic

Table 1 Pre-HSCT and post-HSCT immunological and hematological profile of the case.

Parameter (unit)	Normal range	Pre-HSCT (2023)	Post-HSCT (2025)
Hemogram			
Hemoglobin (g/dL)	11.5-15.5	11	10.8
Hematocrit (%)	35-45	35	33.3
Platelets (/mm³)	150,000-400,000	996,000	217,000
Neutrophils (/mm³)	1500-8000	3910	2160
Eosinophils (/mm³)	<500	850	60
Immunoglobulins			
IgG (mg/dL)	600-1500	1252	888
IgA (mg/dL)	50-250	<10	65
IgM (mg/dL)	40-230	49	128
IgE (IU/mL)	<100	2562	363
Lymphocyte subsets			
Total lymphocytes (/mm³)	2000-8000	1830	4110
CD3+ T cells (%)	55.6-86.2	52	71.6
CD3+ T cells (/mm³)	971-3685	951	2327
CD4+ T helper (%)	23.4-48.7	18,6	38
CD4+ T helper (/mm³)	445-1918	338	1235
CD8+ cytotoxic T (%)	16.8-46.5	29.6	29
CD8+ cytotoxic T (/mm³)	379-2084	541	942
B and NK cell parameters			
CD19+ B cells (%)	6.5-20.3	39.71	19.85
CD19+ B cells (/mm³)	122-755	726	645
CD19+ CD27+ IgD- (class-switched memory B cells) (%)	6.7-31.1	0.33	1.06
CD19+ CD27+ IgD- (class-switched memory B cells) (/mm³)	24-148	2	34
CD16+56+ NK cells (%)	4.0-29.0	2.5	12
CD16+56+ NK cells (/mm³)	105-1107	45	390

Notes: Complete blood count was performed using a Sysmex XN-series hematology analyzer. Lymphocyte subset analysis was performed by multicolor flow cytometry using a BD FACSCanto II cytometer.
Serum immunoglobulin levels (IgG, IgA, and IgM) were measured by nephelometry, and total IgE was quantified by chemiluminescent immunoassay.
Surface staining was performed using anti-CD3 (BD Biosciences, Cat# 555340) and anti-CD20 (BioLegend, clone 2H7, Cat# 302324) antibodies. Intracellular DOCK8 expression was assessed using a DOCK8-specific primary antibody (Santa Cruz Biotechnology, clone G-2, Cat# sc-376911) and a secondary antibody (BioLegend, clone RMG1, Cat# 406606).
HSCT: hematopoietic stem cell transplantation; Ig: immunoglobulin; NK: natural killer cells.

features. The diagnosis of such diseases necessitates awareness of phenotype and a decisive approach to order genetic and functional analyses. In the differential diagnosis, conditions that show clinical similarity to DOCK8 deficiency were considered. Each condition was excluded based on inheritance patterns, the absence of typical findings for respective diseases, or immunologic profiles.[6] Ultimately, definitive diagnosis was achieved through comprehensive genetic testing and flow cytometric demonstration of DOCK8 protein deficiency.

The diagnostic delay observed in this case—spanning 7 years from the onset of clinical manifestations to definitive diagnosis—reflects broader challenges in the recognition of inborn errors of immunity. Phenotypic overlap with common allergic and infectious conditions, limited access to specialized immunological services, and insufficient awareness among non-specialist practitioners contribute to delayed referral. In Turkey, as in many settings, comprehensive genetic and immunological evaluation remains largely concentrated in tertiary centers. The absence of systematic immunological screening in this patient during prolonged follow-up at a single center underscores the need for improved interdisciplinary coordination and earlier referral when primary immunodeficiency is suspected.

The majority of mutations affecting the *DOCK8* gene are reported as large deletions (12.4%), although nonsense (2.8%), missense (1.7%), and splice-site (2.8%) mutations are also identified.[7] In the present case, whole exome sequencing revealed a homozygous nonsense mutation in the *DOCK8* gene (c.5382C>A, p.Tyr1794*), which, based on our review of the literature, has not been reported previously for any phenotype in any classification. The variation is also not found in ClinVar archive and Human Gene Mutation *Database* (HGMD®). This variation is located in 42nd exon of the *DOCK8* gene, which has 48 exons (NM_203447.4). In the current literature, this variation is not reported yet, although one reported truncating variation within the same exon (rs775544616) was described multiple times for 'combined immunodeficiency due to DOCK8 deficiency'

phenotype in the ClinVar database. This variation is also reported by Jing et al. for DOCK8 deficiency.[8]

According to the ACMG guidelines, this variant fulfills the PVS1 and PM2 criteria and is therefore classified as potential pathogenic.[9] The pathogenicity of this variant was further supported by flow cytometric analysis, which demonstrated markedly reduced DOCK8 protein expression in patient's lymphocytes.

The identification of residual DOCK8 protein expression by flow cytometry, despite a truncating nonsense mutation, warrants comment. Three mechanisms may account for this finding. First, nonsense-mediated *messenger RNA* (mRNA) decay (NMD) is known to operate with variable efficiency across cell types and transcript contexts, and a subset of transcripts may escape degradation.[10] Second, non-canonical DOCK8 transcripts lacking exon 42—where the pathogenic variant resides—may produce a partial protein product detectable by the N-terminal-targeting antibody used in this study. Third, somatic reversion is previously documented in DOCK8 deficiency and may restore partial expression in a subpopulation of lymphocytes.[8] Notwithstanding this residual signal, the clinical and immunological phenotype, genotyping results, and the overall flow cytometric findings are collectively consistent with functionally significant DOCK8 deficiency.

In previously reported patient cohorts, common features of DOCK8 deficiency included eczema, recurrent infections, food allergies, mucocutaneous candidiasis, and growth retardation. Additionally, complications, such as bronchiectasis, pneumatocele, and malignancies, were described in some patients.[11] While the clinical findings of our patient were largely consistent with these phenotypes, the absence of bronchiectasis, molluscum contagiosum, or malignancy may be attributed to the timely initiation of supportive care once the diagnosis was established as well as the patient's younger age at the time of HSCT, compared to many reported cases. Nonetheless, it is also possible that the novel mutation identified in this patient was associated with the distinctive presentation.

The immunological profile, detailed in Table 1, was characterized by markedly elevated IgE, progressive eosinophilia, reductions in $CD3^+$, $CD4^+$, and Natural Killer (NK) cell counts, significantly diminished class-switched memory B cells, and low IgA—findings consistent with the heterogeneous immunological profiles reported previously in DOCK8 deficiency.[12]

Following the diagnosis, HSCT with an appropriate conditioning regimen is critical for improving disease prognosis.[13,14] In the present case, the reduced-intensity conditioning protocol led to successful full donor chimerism without complications, and no GvHD was observed during the 12-month post-transplant follow-up. This regimen is preferred in pediatric patients because of its favorable toxicity profile and the lack of need for pharmacokinetic monitoring.[15,16]

A limitation of this report is the absence of post-transplant flow cytometric analysis of DOCK8 protein expression. However, the achievement of full donor chimerism (99%) and the patient's clinical and immunological recovery provide indirect evidence of restored DOCK8 function.

Conclusion

We presented a pediatric patient with DOCK8 deficiency carrying a previously unreported pathogenic homozygous nonsense mutation, in which functional confirmation was achieved via demonstration of reduced protein expression. The initial management of this patient as a case of allergic and infectious disease, and the subsequent diagnostic delay until referral to an immunology center, illustrate that DOCK8 deficiency may be misclassified in routine clinical practice. This case underscores the need for heightened clinical awareness to facilitate earlier recognition of primary immunodeficiencies. Comprehensive genetic analysis and functional validation are essential for definitive diagnosis, and HSCT remains curative when performed in a timely manner.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that artificial intelligence-supported tools were used only for language editing, translation assistance, and improvement of English readability during the preparation of this manuscript. These tools were not used for data analysis, interpretation of findings, generation of scientific content, or reference selection. All references were manually checked for accuracy and appropriateness by the authors.

Competing Interests

The authors had no relevant financial interests to disclose.

Author Contributions

All authors contributed equally to this article.

Conflicts of Interest

None.

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