Case Report:

CD3ε gene variant causing typical SCID and Omenn syndrome in patients from two unrelated families

Saddiq Habiballah[*1,2,3] , Ashwag Alsaidalani[1,2], Jumanah Nassar[4] , Abdulsalam O. Alsulami[1] ,Ryan A. Ahyed[5], Mohammed Nashawi[1,3,6]

1. Department of Pediatrics, King Abdulaziz University, Faculty of Medicine, Jeddah, KSA.
2. Pediatric Allergy/Immunology, King Abdulaziz University HospitalJeddah, KSA.
3. Immunology Unit, King Fahd Medical Research Center, Jeddah, KSA.
4. Batarjee Medical School, Jeddah, KSA.
5. Department of Radiology, King Abdulaziz University, Faculty of Medicine, Jeddah, KSA.
6. Pediatric Rheumatology, King Abdulaziz University Hospital, Jeddah, KSA, Jeddah, KSA .

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Corresponding author:
Saddiq Bader Habiballah, MBBS, FABP, FABAI sbhabiballah@kau.edu.sa

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Abstract:

Severe combined immune deficiencies (SCIDs) are a group of rare diseases that impact the immune system. Depending on the underlying gene defects, SCIDs exhibit various clinical and immunological phenotypes. Multiple gene defects have been linked to the presentation of SCIDs, including typical SCIDs and Omenn syndrome. Typical SCIDs manifest early in life with recurrent infections caused by opportunistic pathogens. Omenn syndrome is characterized by a clinical triad of erythroderma, hepatosplenomegaly, and lymphadenopathy, commonly accompanied by peripheral eosinophilia and elevated IgE levels. Here, we present two unrelated families (2 siblings & one patient from a different family), all of the same ethnicity and race, who presented with variable clinical and laboratory presentations of severe combined immunodeficiency (SCID) while harboring the same missense, homozygous variant in the CD3**ε** gene (P.Gly94Ala), previously classified as a variant of unknown significance. Our case series shows a potentially disease-causing variant that was previously classified as a variant of unknown significance, in addition to suggesting a treatment for Omenn syndrome-related immune dysregulation using corticosteroids as a monotherapy. We concluded that a defect in the CD3**ε** gene can result in classical SCID, along with features of Omenn syndrome that may arise from this genetic defect. A heightened level of suspicion is crucial for diagnosing SCID cases, as various presentations can emerge from the same genetic variant.

Keywords:

SCID, Omenn syndrome, CD3**ε**, Middle Eastern and North Africa, immune dysregulation

Introduction:

Severe combined immunodeficiencies (SCIDs) are a rare group of heterogeneous disorders with variable clinical presentation.[1] The Primary Immune Deficiency Treatment Consortium (PIDTC) classifies those diseases into typical and atypical based on the total T cell number and other criteria.[2] Omenn syndrome is a form of atypical SCID first reported by Gilbert Omenn in 1965.[3] The triad of generalized erythroderma, lymphadenopathy, and hepatosplenomegaly characterizes its clinical presentation. In most cases, significant eosinophilia and elevated IgE accompany that triad.[4] Among the SCID-causing genes, Recombination activating gene 1 (RAG1) mutations are the most reported underlying variants for Omenn syndrome.[2,5] The Middle East/North African region (MENA) has a very high consanguinity rate, ranging between 20% and 50%, with Saudi Arabia reaching a 60% consanguinity rate in marriages.[6] As a result, a study conducted by Al Sukaiti showed a predominance of autosomal inherited genes in SCID-diagnosed cases.[7] T-cell receptor (TCR) plays a major role in thymic selection, T-cell maturation, and differentiation. Any defect in one of the chains of the TCR-CD3 complex can present clinically as SCID.[8] All the reported defects of the TCR-CD3 complex are inherited in an autosomal recessive fashion and present with typical SCID with immune phenotyping of T-B+NK+.[8,9] CD3**ε** is one of four subunits forming the TCR complex.[9] So far, at least eight variants in the CD3**ε** gene have been reported to be disease-causing, but none have been reported in Omenn syndrome patients.[8] Omenn syndrome patients may require immunosuppressive therapy for their immune dysregulation phenotype, which requires a well-thought-out plan to avoid unnecessary immune suppression in an already immunodeficient patient.[10] Hematopoietic stem cell transplantation (HSCT) is considered curative in SCIDs if done early in life before infectious complications and end-organ irreversible damage take place.[2]

We present three patients (2 siblings and one patient from an unrelated family) with very different clinical and immunophenotyping presentations who harbor the same CD3**ε** genetic variant, which has not been previously reported as pathogenic. To our knowledge, we are reporting the first case series of Omenn syndrome associated with a CD3**ε** mutation.

Case description:

Our first patient (P1) was a twenty-two-month-old Arabian male born to a consanguineous couple. At the age of one

month, he developed severe dermatitis that did not respond to topical therapies. Subsequently, at the age of four months, he developed severe diarrhea after the second dose of the live attenuated rotavirus vaccine and has had persistent loose stool. When he reached the age of nine months, he met the definition of failure to thrive as his weight was persistently under the third percentile for age and gender. He experienced his first pneumonia and oral thrush at that age, which became frequent since then, requiring frequent admissions to the intensive care unit without the need for intubation or mechanical ventilation, and here, when immune phenotyping took place, as shown in Table 1.

Table 1: Demographics, laboratory, and radiological data.

	P1	P2	P3
Gender	**Male**	**Female**	**Male**
Age at presentation	9 months	3 months	2 weeks
Hgb	11.1 g/dL (9.6-15.6)	**7.8 g/dL** (12-15)	17.2 g/dl (10-20)
PLT	295 K/uL (150-450)	384 K/uL (150-450)	**449** (150-350)
WBC	4.08 K/uL (5.5-17.5)	**56.70 K/uL** (4.5-13.5)	9.52 K/uL (5-19)
ALC	**1.55 K/uL** (4-10.5)	**40.63 K/uL** (1.5-6.8)	4.40 K/ul (3-16)
AEC	**0.17 K/uL** (0.2-0.8)	**2.31 K/uL** (0.2-0.8)	**2.66 K/uL** (0.1-1)
ANC	1.44 K/uL (1-8.5)	7.2 K/uL (1-8.5)	1.95 K/uL (1-9)
CRP	**11.8 mg/L** (0-3)	**35.9 mg/L** (0-3)	**27 mg/L** (0-3)
IgG	**2000 mg/dl** (400-600)	**1190 mg/dl** (400-600)	-----
IgM	Not done	**108 mg/dl** (24-89)	-----
IgA	Not done	**50 mg/dl** (4.6-46)	-----
IgE	Not done	**>5000 KU/L** (0.18-3.67)	**219.3 K/uL** (0-15)
CD3+	**338 cell/mm^3** (1400-8000)	5833 cell/mm^3 (2200-9200)	2093 cell/mm^3 (2000-3410)
CD3+CD4+	**27 cell/mm^3** (900-5500)	5655 cell/mm^3 (1600-6500)	1151 cell/mm^3 (732-1270)
CD3+CD8+	**27 cell/mm^3** (400-2300)	**295 cell/mm^3** (300-3400)	230 cell/mm^3 (230-837)
CD4+/CD8+ ratio	1	**19.2**	**5**
CD19+	**284 cell/mm^3** (600-3100)	1330 cell/mm^3 (520-2300)	233 cell/mm^3 (233-775)
CD56+	486 cell/mm^3 (97-2000)	**4254 cell/mm^3** (97-2000)	116 cells/mm^3 (116-800)
Spleen size on ultrasound	5.2 cm (<6.5 cm)	**7 cm** (<6.5 cm)	6 cm (<6.5 cm)
Thymus shadow on X ray	**Absent**	**Absent**	**Absent**
Thymus index on ultrasound	Not done	**12cm^2**(reference value of 25.4±9.4 cm3)	**15.2 cm^2** (reference value of 25.4±9.4 cm^3)

***Hgb: Hemoglobin, PLT: platelets, WBC: White blood cells, ALC: Absolute lymphocyte count, AEC: Absolute eosinophil count, ANC: Absolute neutrophil count, CRP: C-reactive protein.**

His tonsils were not appreciable on examination, and his chest X-ray confirmed the absence of his thymic shadow, with a CT scan showing central bronchiectasis. The Whole Exome Sequencing (WES) was performed in a clinically accredited diagnostic laboratory, which is internationally recognized. Details regarding sequencing and variant interpretation followed standard diagnostic protocols. The sequence revealed a missense homozygous variant in the CD3**ε** gene (P.Gly94Ala)(Table 2).

Table 2: Identified CD3ε variant information.

Gene & (transcript)	cDNA change	Amino acid change	Molecular consequence	Zygosity	MAF*	Classification and (CADD** score)	Subcellular location
CD3E (NM_000733.4)	c.281G>C	P. Gly94Ala	Missense	Homozygous	0%	VUS (21.8)	Extracellular

MAF (minor allele frequency) based on data from GnomAD. *(Deleterious: >=20, Likely deleterious: 10-19, Unlikely deleterious: <10).**

Considering these findings, he started receiving bacterial and fungal prophylaxis in addition to immunoglobulin replacement therapy as a case of SCID with possible maternal engraftment. As HSCT is the treatment of choice for SCID, the preparation process for HSCT started. However, unfortunately, he succumbed to Klebsiella Pneumoniae sepsis at the age of twenty-two months before getting his transplantation.

The second patient (P2) is currently a ten-month-old Arabian female born to a consanguineous couple. Around the age of three months, she presented with continuous fever, generalized erythroderma, alopecia, and lymphadenopathy with hepatosplenomegaly. Laboratory work showed anemia, thrombocytosis, and significant leukocytosis with lymphocyte predominance and elevated eosinophil count. Her total IgE, IgG, IgA, and IgM were significantly elevated. Chest X-ray showed an absent thymic shadow, confirmed by chest ultrasound showing thymic hypoplasia. Despite a normal lymphocyte subset other than a significantly elevated natural killer count (T+B+NK+) (Table 1), her case presentation was convincing for Omenn syndrome with immune dysregulation, and she was treated as such. She was started on a prophylactic regimen for bacteria and fungi in addition to immunoglobulin replacement. After a negative infectious workup, the team started her on high-dose methylprednisolone pulse (30 mg/kg/day) for three days, followed by a daily

dose of 1 mg/kg of oral prednisolone, which was weaned slowly to 0.25 mg/kg over time, stabilizing her clinically with no more fever and normalizing laboratory parameters. Her lymphadenopathy and erythroderma continued to wax and wane on the steroid regimen. The whole exome sequence was done following the same protocol described in P1, which revealed a missense homozygous variant in the CD3**ε** gene (P.Gly94Ala)(Table 2). This patient underwent haploidentical bone marrow transplantation at another center and is currently doing well without immunoglobulin replacement, exhibiting full donor chimerism, along with complete resolution of her erythroderma, alopecia, and lymphadenopathy.

P3 is a sibling of P2. He presented at the age of 2 weeks with lethargy, fever, and skin rash. Because of the known diagnosis of his sister, Omenn syndrome was highly suspected as an underlying etiology in addition to rhino/enterovirus infection, confirmed by qPCR. His immunophenotyping is shown in Table 1. The thymus ultrasound showed an atrophied thymus. Targeted genetic sequencing for the CD3**ε** gene confirmed the presence of the same mutation found previously in P1 and P2 (Table 2). He had been started on methylprednisolone pulse therapy followed by oral steroids with a remarkable clinical response, and is currently in the process of HSCT.

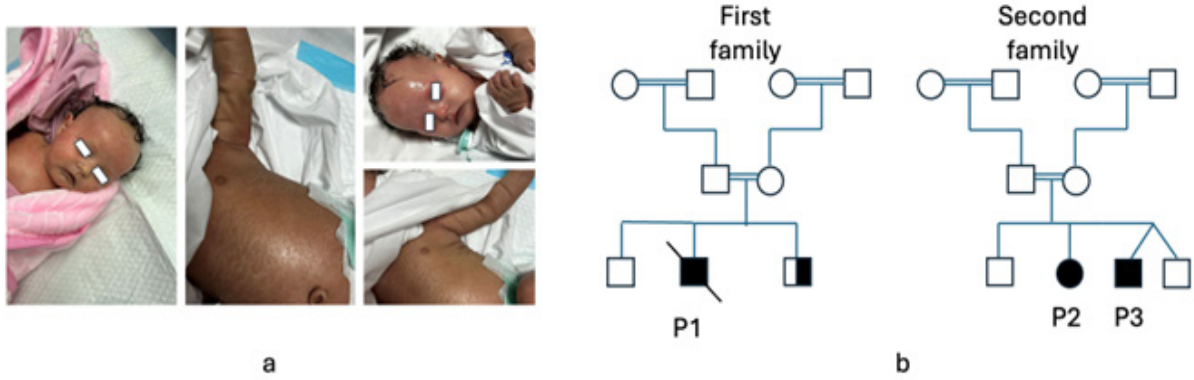


Figure 1. a) Erythroderma, alopecia, and axillary lymph node enlargement of P2. b) Families' pedigrees

Discussion:

Severe combined immune deficiencies (SCIDs) are a group of heterogeneous diseases where the phenotype highly depends on the underlying genotype.[1] Early diagnosis and management of those diseases are paramount in decreasing the associated morbidity and mortality.[1] Diagnosing these disorders needs a high index of suspicion, as they present with widely variable clinical

and immunophenotypic presentations. The PIDTC classifies SCID disorders based on the total CD3+ count, the presence of a pathogenic genetic variant, and the presence or absence of transplacentally acquired maternal engraftment (TME), categorizing them into typical and atypical SCIDs, in addition to Omenn syndrome.[2] Omenn syndrome is a clinical syndrome characterized by the triad of erythroderma, hepatosplenomegaly, and lymphadenopathy, in addition to significant eosinophilia and elevated IgE levels.[4] While X-linked inherited genetic defects are the most common for SCIDs in the West, AR-inherited defects are frequent in the MENA region due to the high consanguinity rate.[6] Reported defects of the TCR-CD3 complex are AR-inherited ones, causing typical SCIDs[11]. Heterodimerization of those chains is essential for signal transduction, T-cell development, and activation.[11] Subsequently, mutations in all CD3 chains have caused a typical T-B+NK+ SCID phenotype.[9]

Our first patients had the classical clinical presentation of typical SCID with frequent sinopulmonary and opportunistic infections,[2] in addition to the absence of thymic shadow on X-ray and the presence of a possibly damaging variant of CD3**ε**[12] Despite our belief that this patient has typical SCID with maternal engraftment, we were unable to prove this hypothesis due to the lack of engraftment testing at our center and in the surrounding area. As stated previously, defects in the CD3**ε**chain usually spare B cells and cause T-B+NK+ SCID; our patient unexpectedly had a T-B-NK+ phenotype not matching his genotype. Obtaining a B-cell memory panel and BCR repertoire can explore this further; those tests are unavailable at the center. The authors do not have a specific explanation for his elevated IgG and very low B cell numbers, as no cases of CD3**ε** defects were reported to have similar immunological phenotypes. The presentation of P2 and her sibling, P3, is more consistent with Omenn syndrome, characterized by immune dysregulation features. P2 presented with skin and lymphoproliferative manifestations, whereas P3's presentation was more of a mixed between infectious and immune dysregulation process. Their normal total peripheral CD3+ cells can be explained by oligoclonal expansion, which unfortunately could not be confirmed. To complete the diagnostic criteria suggested by the PIDTC for Omenn syndrome, we should have performed a T-cell naïve panel and confirmed the absence of TME with oligoclonality; however, these tests were unavailable. While RAG1 mutations

cause most of the Omenn syndrome phenotypes in T+B-NK+, other genes have been reported, including JAK3, IL-7R, and ZAP70, among others, which exhibit different immune phenotypes.[5] Oligoclonality of T-cells and peripheral expansion of those clones in the setting of low T-regulatory cell (Treg) numbers contributes to the clinical and immunological phenotype of Omenn syndrome.[10] We identified a potentially damaging variant in the CD3**ε** gene, which has not been previously reported as a cause of Omenn syndrome. We controlled our patients' immune dysregulation using corticosteroids as monotherapy without the need for combined therapy with cyclosporin or other immunosuppressive medications.[13]

The true prevalence of SCID-causing genes in the Middle Eastern and North African (MENA) region remains unclear due to the limited availability of genetic testing. However, a study led by Al-Sukaiti in Oman demonstrated that autosomal recessive (AR) inherited genes were more prevalent than X-linked (XL) inherited ones, a finding attributed to this region's high consanguinity rates.[7] Given the shared cultural and demographic factors, including consanguinity, among MENA countries, it is reasonable to extrapolate these findings to the broader region. However, further region-wide studies are needed to confirm this generalization.

Our patients are of the same ethnicity and race, and they all exhibited the same homozygous missense variant in the transmembrane region of the CD3**ε** chain (Ig-like domain) (c.281G>C, P.Gly94Ala). This variant has not been documented in public databases, and several in-silico prediction tools indicate it is damaging. It is likely to destabilize the protein. This amino acid change impacts the extracellular domain of the CD3**ε** protein, probably disrupting signal transmission. As a result, it may impair the protein's function, contributing to the SCID phenotype by interfering with the proper assembly or function of the TCR-associated CD3 complex. This variant is probably more common in this population as a heterozygote, and as shown in our cases, a homozygous variant could be damaging and disease-causing. This homozygosity is perhaps linked to the high rate of consanguinity and inter-familial marriages within this specific ethnicity. Despite all patients sharing the same genetic variant, their clinical presentations varied. This exemplifies the complexity of immune system-related genes and suggests that other factors, such as immunological redundancy, environmental influences, and epigenetics, can cause the same genetic

defect to manifest differently.

As the presentation of SCID-related diseases has many nuances, a high index of suspicion is needed to diagnose and treat such rare diseases and presentations.

Participation consents:

Both families consented to writing their case reports, and the parents of P2 gave special consent to share the image.

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References:

1. Cirillo E, Cancrini C, Azzari C, et al. Clinical, Immunological, and Molecular Features of Typical and Atypical Severe Combined Immunodeficiency: Report of the Italian Primary Immunodeficiency Network. Front Immunol. 2019;10:1908. doi:10.3389/fimmu.2019.01908
2. Dvorak CC, Haddad E, Heimall J, et al. The diagnosis of severe combined immunodeficiency (SCID): The Primary Immune Deficiency Treatment Consortium (PIDTC) 2022 Definitions. J Allergy Clin Immunol. 2023;151(2):539-546. doi:10.1016/j.jaci.2022.10.022
3. Elnour IB, Ahmed S, Halim K, Nirmala V. A rare primary immunodeficiency disorder. SULTAN QABOOS Univ Med J. 2007;7(2):P. 133-138.
4. Al-Hammadi S. Unusual presentation of Omenn syndrome: case report. World Allergy Organ J. 2015;8:A248. doi:10.1186/1939-4551-8-S1-A248
5. Tsilifis C, Spegarova JS, Good R, et al. Omenn Syndrome in Two Infants with Different Hypomorphic Variants in Janus Kinase 3. J Clin Immunol. 2024;44(4):98. doi:10.1007/s10875-024-01699-5
6. Al-Mousa H, Al-Dakheel G, Jabr A, et al. High Incidence of Severe Combined Immunodeficiency Disease in Saudi Arabia Detected Through Combined T Cell Receptor Excision Circle and Next Generation Sequencing of Newborn Dried Blood Spots. Front Immunol. 2018;9:782. doi:10.3389/fimmu.2018.00782
7. Al Sukaiti N, Ahmed K, Alshekaili J, Al Kindi M, Cook MC, Farsi TA. A Decade Experience on Severe

Combined Immunodeficiency Phenotype in Oman, Bridging to Newborn Screening. Front Immunol. 2021;11:623199. doi:10.3389/fimmu.2020.623199

8. Setia P, Bargir UA, Aluri J, et al. Novel CD3Z and CD3E Deficiency in Two Unrelated Females. J Clin Immunol. 2021;41(5):1116-1118. doi:10.1007/s10875-021-01010-w
9. Erman B, Fırtına S, Fışgın T, Bozkurt C, Çipe FE. Biallelic Form of a Known CD3E Mutation in a Patient with Severe Combined Immunodeficiency. J Clin Immunol. 2020;40(3):539-542. doi:10.1007/s10875-020-00752-3
10. Lev A, Simon AJ, Amariglio N, Rechavi G, Somech R. Selective clinical and immune response of the oligoclonal autoreactive T cells in Omenn patients after cyclosporin A treatment. Clin Exp Immunol. 2012;167(2):338-345. doi:10.1111/j.1365-2249.2011.04508.x
11. Basile GDS, Geissmann F, Flori E, et al. Severe combined immunodeficiency caused by deficiency in either the δ or the ε subunit of CD3. J Clin Invest. 2004;114(10):1512-1517. doi:10.1172/JCI200422588
12. McWilliams LM, Dell Railey M, Buckley RH. Positive Family History, Infection, Low Absolute Lymphocyte Count (ALC), and Absent Thymic Shadow: Diagnostic Clues for All Molecular Forms of Severe Combined Immunodeficiency (SCID). J Allergy Clin Immunol Pract. 2015;3(4):585-591. doi:10.1016/j.jaip.2015.01.026
13. Meyer-Bahlburg A. Treatment with cyclosporin A in a patient with Omenn's syndrome. Arch Dis Child. 2002;87(3):231-233. doi:10.1136/adc.87.3.231