Compound Heterozygous Mutations in *DCLRE1C* Caused Leaky SCID Phenotype

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Inborn errors of immunity represent a heterogeneous group of disorders with variable clinical manifestations. Within this group of disorders, severe combined immunodeficiency (SCID) is the most profound disorder, where affected infants present clinically early in life, and have almost uniformly fatal outcome unless hematopoietic stem cell transplantation (HSCT) is performed. Gene therapy or enzyme replacement therapy are options in some specific SCID forms [1]. The estimated incidence of SCID in the United States is 1 in 58,000 live births, while in Israel the incidence is as high as 1 in 29,000 live births. This higher rate is due to a high rate of consanguineous marriages in certain communities [2].

SCID is caused by pathogenic genetic variants in more than 20 distinct genes, affecting either metabolism/protein synthesis, V(D)J recombination, cytokine signaling, or T-cell receptor signaling. The SCID immune-phenotype is defined according to the T, B, and NK presence or absence cell profile ($T^{-/+}B^{-/+}NK^{-/+}$) and is associated with the pathogenic mechanism. Different modes of inheritance are known to cause SCID including X-linked, autosomal recessive or, in some rare cases, compound heterozygote forms. Leaky SCID (CD3+ > 300 cells/mm^3), which is usually is caused by hypomorphic mutations, or SCID with residual immune function (e.g., SCID with maternally engrafted cells, SCID with specific gene defects such as MHC2 deficiency, ZAP70 deficiency) are challenging for diagnosis and patients sometimes display a diagnostic odyssey. The clinical presentation and the subsequent outcome for SCID differ markedly between patients diagnosed through newborn screening (NBS) or patients identified later in life based on their clinical symptoms. Infants detected via NBS are typically asymptomatic at the time of diagnosis, whereas those diagnosed later usually present at several months of age with severe infections, failure to thrive, and unfavorable reaction to live vaccines.

NBS for SCID relies on quantifying T-cell receptor excision circles (TRECs), a byproduct of the rearrangement process of T cells in the thymus, from dried blood spots collected on Guthrie cards. In brief, when T cells mature in the thymus, they rearrange their T-cell receptor genes and as part of this process, a small circle of DNA called a TREC is cut as a byproduct of the process and remains in the cell. TRECs are a highly sensitive and specific marker of thymus output and T-cell immunity. Before the introduction of NBS, SCID diagnosis was often delayed until clinical manifestations appeared or made in the context of a positive family history. Today, NBS promptly diagnoses infants soon after birth. In Israel, the NBS program for SCID was implemented in the end of 2015 [2]. To validate a positive case of SCID that is picked up in NBS, further immunology diagnostic laboratory studies are performed as well as genetic testing.

Since NBS started in Israel, the median age for diagnosis through NBS is 15 days compared to 5 months for the non-NBS identified patients [1]. Patients who have been identified through NBS experienced better overall survival rates (91% survival rate among infants who underwent HSCT). They have presented with fewer transplantation-related complications and have shown improved long-term outcomes [1]. Interestingly, 13 of the 32 SCID patients identified by the NBS program during the first 5 years had leaky SCID or SCID with residual cells. This group included patients with specific mutation in the *DCLRE1* gene (c.1299_1306dup-AGGATGCT, encoded the ARTEMIS protein) and in

the *IL7RA* gene (c.120C>G, p. F40L), or even SCID patients with *CORO1A* or *PSMB10* mutations [2].

We describe a case of an infant identified through the Israeli national NBS program who ultimately was diagnosed with *leaky* SCID due to compound heterozygous variants in *DCLRE1C gene*. Our case highlights the clinical and genetic spectrum of *leaky SCID* and underscores the importance of both NBS and comprehensive genetic confirmation in affected patients to achieve a favorable outcome.

PATIENT DESCRIPTION

A male infant was referred to the national NBS clinic for SCID at 14 days of age following identification of undetectable TRECs on NBS. The pregnancy was uneventful, gestational age 39 + 1, birth weight 3140 grams. He was discharged after 36 hours without complications. Both parents were healthy and non-consanguineous. There was no family history of immunodeficiency. Physical examination was unremarkable, with no dysmorphic features and no rash, no hepatosplenomegaly, and no signs of infection or concurrent secondary disease that could explain the abnormal NBS results. Initial laboratory evaluation revealed mild lymphopenia with a complete absence of B cells, reduced but not absence TRECs in peripheral blood, and normal T-cell receptor repertoire and low immunoglobulin levels [Table 1].

Based on the laboratory findings, the patient was managed as *suspected SCID*. Strict isolation was implemented, live vaccines were deferred, breastfeeding was discontinued (due to positive maternal IgG CMV serology), and prophylaxis with trimethoprim–sulfamethoxazole and fluconazole was initiated at one month of age.

Whole trio-exome sequencing with an extended immunodeficiency panel identified two heterozygous variants in the DCLRE1C gene, each inherited from a different parent: 1. c.730T>G (p.Cys244Gly), a missense variant in exon 12 (inherited from his father), and 2. complete deletion of exons 1–2/13 (inherited from his mother). The findings were consistent with compound heterozygosity in the DCLRE1C gene, in which biallelic pathogenic variants cause Athabascan-type SCID [3].

Repeated blood tests at 2 months of age [Table 1] showed consistent abnormal findings. Maternal engrafted T cells were excluded. Intravenous immunoglobulin (IVIG) replacement was initiated, and the patient was referred to the HSCT clinic. An adjusted HSCT conditioning protocol was advised since *ARTEMIS*-deficient patients are hypersensitive to ionizing radiation and alkylating agents [4].

At 3 months of age, our patient underwent an allogeneic HSCT transplant from a matched unrelated donor (11/12 HLA match, permissive DPB1 mismatch) using a fludarabine–treosulfan–ATG conditioning regimen per ESID guidelines [4]. The transplant was uneventful, and 6 months after the procedure, chimerism analysis in the patient's peripheral blood revealed 92% donor cells. During the next 12 months post-HSCT, the patient remained infection-free, achieved appropriate developmental milestones (walking and speaking single words by 15 months), and demonstrated normal growth (11.2 kg at 1.3 years). Prophylactic antibiotics were discon-

Table 1. Longitudinal immunologic and hematologic findings

	At 2 weeks of age	At 2 months of age	12 months post HSCT	Normal ranges
WBC (K/microL)	4.92	2.63	10.84	5.0–19.5
Abs Lymphocytes (K/microL)	1.65	1.31	7.02	2–8
CD3 T cells (cells/mm^3)	1653	789	5521	2500–5500
CD4 cells (cells/mm^3)	876	526	3407	436–1394
CD8 cells (cells/ mm^3)	446	250	1777	166–882
CD20 B cells (cells/mm^3)	5	29	773	50–300
CD16/56 NK cells (% of lymphocytes)	29%	33%	11%	6–30
IgG (mg/dl)	613	401	606	470–1230
IgA (mg/dl)	< 23	< 23	43.6	21–145
IgM (mg/dl)	20.9	< 18.4	66.8	45–169
Thymus output (TRECs) / copies per 0.5 mcg DNA	122	Not done	1608	> 400 copies
T cell receptor V beta repertoire / flow	polyclonal	polyclonal	polyclonal	polyclonal

HSCT = hematopoietic stem cell transplantation, TRECs = T-cell receptor excision circles, WBC = white blood cell count

tinued, and he began catching up with immunizations. Immune work up a year after transplant revealed 100% donor cells, with a complete reconstitution of the immune system [Table 1].

COMMENT

Leaky SCID refers to cases caused by hypomorphic mutations, variants that result in partial, rather than complete, loss of gene function that retains some function allowing partial immune function and variable disease presentations. An example would be missense mutations or nonsense mutations at the end of the gene, mutations in promoters or enhancer regions lower the amount of mRNA produced, or compound heterozygote mutations. These patients with hypomorphic mutations typically have detectable but dysfunctional T cells (often > 300 $CD3^+$ cells/μL) and present with variable clinical severity, from early severe infections to late-onset combined immunodeficiency.

Signs of Omenn syndrome, including itchy, erythematous skin, alopecia, hepatosplenomegaly, lymphadenopathy, and diarrhea, may be present. Often and in contrast to our case, these patients can evade a diagnosis in NBS and unfortunately are only diagnosed after developing clinical symptoms. In particular, patients with hypomorphic *DCLRE1C* mutations can present with variable clinical and laboratory findings at different ages, including Omenn syndrome, autoimmunity (e.g., cytopenia), dysregulated inflammation (e.g., inflammatory bowel disease), and/or lymphoproliferative disease. These patients display a helper T (Th)1-dominant immune response and increased IFN-γ and TFH cells ratio as a reason for chronic inflammation and autoimmunity developing before and even after HSCT [5].

Interestingly, gene therapy, which is currently under clinical trials, was successful in restoring a functional T-cell and B-cell compartment in a complete Artemis-deficient SCID but failed for unknown reasons in patients with the leaky phenotype.

We present a patient with heterozygotes change at the gene *DCLRE1C*, which is a key nuclease involved in the non-homologous end joining repair pathway on DNA double-stranded breaks and during V(D)J recombination [4]. The usual immune phenotype of these patients is $T^-B^-NK^+$, while our patient had small amount of T cells, with normal TCRVb repertoire. A genetic validation enabled us to unmask the hypomorphic nature of his genetic changes as a compound heterozygote. In *ARTEMIS*-deficient SCID patients, exposure to alkylating agents during HSCT conditioning has been associated with late complications such as dental agenesis, growth impairment, and renal dysfunction [4]. Genetic confirmation allows for tailored conditioning regimens that minimize toxicity [5]. This finding further validates the importance of reaching genetic diagnosis in every case of SCID.

Our case illustrates the transformative impact of national NBS for SCID and highlights the importance of integrating genetic confirmation into the diagnostic pathway. Genetic characterization of *leaky SCID* cases enables optimized therapeutic strategies and provides valuable insights into the spectrum of hypomorphic mutations underlying combined immunodeficiencies.

CONCLUSIONS

We described a newborn with compound heterozygous mutations in *DCLRE1C* causing a leaky SCID phenotype, which was detected by our national NBS program for SCID. Our case expands the clinical spectrum of SCID detectable by NBS and demonstrates the ability of the screening to detect milder or atypical forms, not only the classic phenotype. It highlights the importance of early detection of non-classic SCID infants preventing diagnostic delay and allowing early protective measures and earlier decisions about HSCT. Importantly, compound heterozygosity provides insight into the genotype–phenotype correlation and clarifies how specific combinations of mutations alter severity, contributing to better prediction of clinical outcomes.

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