Positive newborn screen: a case of a novel variant in *DCLRE1C* in a patient with SCID

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ABSTRACT

Background: Artemis enzyme, encoded by the *DCLRE1C* gene, is essential to V(D)J recombination in both T and B lymphocytes. Artemis functions as an important component of the nonhomologous end-joining DNA double-strand break repair pathway. Artemis deficiency leads to a T-B-NK+ severe combined immune deficiency (SCID) associated with radiosensitivity.

Clinical presentation: We present a case of a positive newborn screen for SCID in a patient who was subsequently shown to have a T-B-NK+ phenotype. Further immune evaluation showed profound T and B lymphopenia, near-absent response to mitogen stimulation, and absent immunoglobulins A and M. Genetic investigation demonstrated a novel and putative pathogenic variant in the *DCLRE1C* gene.

Conclusion: This case identifies a novel variant in the *DCLRE1C* gene in a patient with SCID identified by newborn screening.

Statement of novelty: This case report identifies a novel variant in the *DCLRE1C* gene in a patient with T-B-NK+ SCID.

Introduction

The Artemis enzyme, encoded by *DCLRE1C*, is essential for successful V(D)J recombination in both T and B lymphocytes. Artemis is a necessary component of the nonhomologous end-joining DNA double-strand break repair pathway. Specifically, it is an endonucleolytic enzyme, required for the opening of hairpin structures that are created by RAG1/RAG2 specific DNA cleavage. The *DCLRE1C* gene was first cloned in 2001 after having been mapped to the short arm of chromosome 10 (Moshous et al. 2001).

Artemis deficiency is the most common form of radiosensitive severe combined immunodeficiency (SCID), and patients have been shown to present with features of severe immunodeficiency in infancy (Woodbine et al. 2010). Defects in this pathway lead to a T-B-NK+ SCID, as in our patient, described below. Hypomorphic pathogenic variants in *DCLRE1C* can result in residual enzymatic activity leading to Omenn syndrome (Mancebo et al. 2011), and combined immune deficiency which can present much later in life (Lee et al. 2013).

Pannicke et al. (2010) examined the frequencies of clinically-identified pathogenic variants in the *DCLRE1C* gene in 29 patients. The most frequent genetic changes were gross changes in exon 1–3 or 1–4. They observed 13 different missense and nonsense

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point mutations, 9 of which had not been previously described. Recently, another case of Artemis deficiency SCID was found to be caused by a compound heterozygous change in *DCLRE1C* (Sundin et al. 2019). The variant found in our case (homozygous missense variant p.Gly118Glu) was not reported among these pathogenic variants, making this a novel variant in a patient with Artemis deficiency.

A different missense pathogenic variant at the same amino acid residue (p.Gly118Val) has been reported as homozygous in a patient with radiosensitive SCID (Felgentreff et al. 2015). Functional studies have shown that the p.Gly118Val variant has a functional impact on the DNA repair abilities of the *DCLRE1C* protein. Given that this region encodes an amino acid essential for Artemis function, we postulate that a variant in this region could be deleterious for maintenance of the protein structure and for interaction with other proteins.

Functional and clinical presentation

An 11-day old female presented to the Immunology Clinic due to a positive newborn screen for SCID. Guthrie blood spot PCR results were flagged for undetectable T-cell Receptor Excision Circle (TREC) level.

The patient was born at 39 weeks to a G1P0 mother after an uncomplicated pregnancy. The mother was not on any medications and had prenatal care throughout her pregnancy. There were no complications or resuscitation required at birth. Birthweight was 3.12 kg and the patient was breastfeeding well. There was no history of fever, diarrhea, or rash. The patient was not on any medications and was unimmunized.

The family history was significant for consanguinity. Parents are of Indian descent and are first cousins. The father has a history of inflammatory bowel disease for which he requires immunomodulating therapy with Infliximab. The mother is medically well. This is mother's first pregnancy and the couple's first child. There was no known history of immunodeficiency, early infant deaths, leukemia, or lymphoma in the family. There is no other autoimmunity in the family. Parents each have both male and female siblings who are healthy and have healthy children.

On initial examination, vital signs were stable and there were no dysmorphic features. The patient looked well and was in no distress. Lymph nodes were not palpable. The oropharynx was clear. Cardiovascular and respiratory examination were unremarkable. There was no hepatosplenomegaly and no rash. Neurological examination was within normal limits.

Maternal CMV IgG was positive, thus breastfeeding was stopped, and formula feeding was initiated. Pneumocystis prophylaxis and immunoglobulin replacement were commenced pending definitive management.

Laboratory investigations

Initial investigations demonstrated lymphopenia at 1.2×10^9/L, which subsequently decreased to 0.7×10^9/L on repeat 3 days later. Quantitative lymphocyte immunophenotyping could not be completed using the laboratory apparatus due to profound lymphopenia. On microscopic evaluation, the laboratory was able to report absent B and T cells, and that the few visible lymphocytes appeared to be CD3-/CD16+/CD56+ NK cells. T-cell mitogen stimulation index to Phytohemagglutinin was profoundly low at 2.3. IgA was <0.07 g/L, IgM < 0.04 g/L and IgG was 5.96 g/L. Due to difficulties with blood draw, further testing on CD45RA/RO and TCRV beta were not able to be done. PCR-based testing was negative for CMV, EBV and HIV.

A primary immunodeficiency genetic testing panel interrogating 274 genes was completed by Blueprint Genetics. Analysis revealed a homozygous missense variant, c.353G>A (p.Gly118Glu), in exon 5 of the *DCLRE1C* gene. This variant has not been previously reported in individuals affected with Artemis deficiency (Pannicke et al. 2010). This variant has also not been observed in the presumed healthy control databases.

Given the laboratory results of lymphopenia and SCID diagnosis, the patient was referred to the regional transplant centre and underwent hematopoietic stem cell transplant (HSCT) using a matched unrelated donor.

Conclusion

In summary, we present the case of an infant with absent TRECs and T-B-NK+ SCID, found to have a

novel variant in the *DCLRE1C* gene, exon 5, c.353G>A (p.Gly118Glu) resulting in Artemis deficiency SCID. The patient's clinical phenotype, in addition to the previously published body of literature on the *DCLRE1C* gene and Artemis deficiency, points to the possible pathogenicity of this variant. Functional studies are needed to ascertain the role of this variant in our patient's presentation.

Disclosures

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