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## "Omenn Syndrome Associated with Novel Variants in DNA LIGASE I"

INTRODUCTION: Immunodeficiency associated with pathogenic variants in *LIG1*, which encodes DNA ligase 1, has only been reported in eight patients. While cases demonstrate a wide spectrum of clinical and immunologic severity, only one previously published case presented with Omenn Syndrome. Omenn Syndrome is an atypical form of severe combined immunodeficiency (SCID) in which aberrant autoreactive T cells attack multiple systems including skin, gut, and internal organs. We present an infant with fatal Omenn Syndrome who was found to have two heterozygous variants of uncertain significance in *LIG1*.

CASE PRESENTATION: A 28-week gestational age male developed a rash at approximately 1 month of age. He eventually developed severe exfoliative dermatitis, erythroderma, hair loss, diarrhea, hepatosplenomegaly, and lymphadenopathy. Due to his impaired skin integrity, he developed significant fluid volume loss, hyperkalemia, and acute renal failure. While his absolute lymphocyte count (ALC) was normal upon transfer, flow cytometry revealed exceedingly low B cells, NK cells, and naïve T cells. The total CD3 T cell count was normal with predominance of effector/memory (CD45RO) markers and elevated double negative T cells. Despite a normal CD3 count, naïve T cells expressing CD4/CD45RA were profoundly low (30 cells/uL, 7% of CD4 cells) consistent with SCID. Activated T cells expressing HLADR were significantly elevated and the infant developed eosinophilia, supporting the clinical presentation of Omenn Syndrome. There was no evidence of maternal engraftment. Cytomegalovirus PCR was negative. He developed profound cystic encephalomalacia and succumbed to his numerous complications at 5 months of age. Whole exome sequencing (WES) revealed two variants of uncertain significance in *LIG1* which, to our knowledge, have not been previously published: deletion c.1088-2_1094delAGGTCGGCA in exon 13, a canonical splice site variant; and a missense mutation c.2312 G>A in exon 24 for which in silico predictors suggest deleterious effect. Neither variant is present in large population cohorts.

DISCUSSION: Based on the profound immunologic defects in this patient, limited reports of SCID caused by *LIG1*, these specific variants not being found in the general population, and WES not revealing other mutations in known immunodeficiency genes, we suspect that these are pathogenic variants. Omenn Syndrome is exceedingly elusive, as aberrant autoreactive T cells may proliferate to the degree that both the absolute lymphocyte count and the total CD3 enumeration may be normal, as in this case. This presentation emphasizes the need for including naïve T cell markers when flow is performed, the need for TREC newborn screening, and the need for *LIG1* to be added to commercially available SCID gene panels.