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Two Cases of Severe Combined Immunodeficiency Disease with No Known Variants Identified in Genes Associated with Immunodeficiencies

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Research Abstract Title

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IRB Number: N/A, consent obtained from families

Describe role of Submitting/Presenting Trainee in this project (limit 150 words):
I was directly involved in the patient care of Case 2 and indirectly in the care of Case 1. I composed the abstract below in collaboration with my mentors, and I presented the work at the North American Immuno-Hematology Clinical Education and Research Symposium in Columbus Ohio.

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background:
Traditionally, cases of severe combined immunodeficiency (SCID) are classified immunophenotypically based on the lymphocyte subsets affected. More recently, there has been an increasing effort to classify SCID by its genetic etiology as genotype influences treatment options and predicts prognosis. However, in approximately 10-15% of SCID cases no genetic defect is identified.

Objectives/Goal:
We report two challenging cases of SCID with novel findings without identifiable genetic defects.

Methods/Design:
Case 1: An intrauterine growth restricted (IUGR), 34-week male infant presented with multiple congenital anomalies (severe micrognathia requiring tracheostomy, cleft palate, agenesis of the corpus callosum, sensorineural hearing loss, intestinal malrotation, nephrotic syndrome, pulmonary valve stenosis and skeletal dysplasia). He was severely lymphopenic, and immune workup led to a phenotypic diagnosis of T-B+NK+ SCID. He underwent a matched-sibling donor bone marrow transplant without conditioning which led to donor T-cell engraftment. At 6 months of life, he presented with respiratory failure due to staphylococcal tracheitis and died. Case 2: A term female IUGR infant presented at birth with thrombocytopenia and severe lymphopenia. Immune workup led to a phenotypic diagnosis of leaky T-B-NK+ SCID. She developed progressive hypoxic respiratory failure secondary to pulmonary

arterial hypertension (PAH) and required cannulation to extracorporeal membrane oxygenation (ECMO). After ECMO decannulation, she died at 5 weeks of age from refractory PAH.

Results:

On exome sequencing, no reportable variants were identified in genes associated with SCID in either case. In Case 1, exome sequencing identified 10 variants of unknown significance (VUS) (Table 1), one of which, a hemizygous variant in *SEPT6*, c.44G>A (p.Arg15Gln), is particularly intriguing as this gene is involved in neural tube development and lymphocyte migration. In case 2, exome sequencing identified 3 VUS (Table 1), one of which, a heterozygous variant in *PSMB8*, c.265G>T (p.Asp89Tyr), is of interest as it was found to be a *de novo* mutation in a highly evolutionarily conserved amino acid residue and was located within a gene involved in immunoproteasome formation.

Conclusions:

Despite advancements in the classification of SCID through identification of genetic defects, these cases with non-diagnostic genetic work up highlight the limitation of presently available clinical genomic testing.