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THE IMPORTANCE OF SCREENING IN PREVENTING INTENSIVE CARE ADMISSIONS FOR SEVERE COMBINED IMMUNODEFICIENCY (SCID): LESSONS FROM A HIGH-CONSANGUINITY COHORT

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Background: Severe combined immunodeficiency (SCID) represents a group of treatable disorders leading to frequent infections, malignancies, and even death if left untreated. Without newborn screening (NBS), infants develop severe recurrent infections that require emergency intensive care (NICU/PICU) admissions, often ending in death before a diagnosis is made. Ethnic Azerbaijanis represent a highly consanguineous, isolated minority residing mostly in the southern part of Georgia. The prevalence of rare genetic immunodeficiencies has never been studied in this population. We have identified several seemingly unrelated families with homozygous *ADA* and *JAK3* mutations from this community, all of whom died within several months after birth due to SCID, whereas early identification could have led to life-saving interventions. Based on these findings, SCID may be heavily underdiagnosed in this region.

Methods: We analyzed the clinical and genetic records of ethnic Azerbaijani SCID patients hospitalized in the NICU/PICU to document disease severity, hospital course, and underlying mutations. Diagnosis was established via immune profiling and genetic testing (whole exome sequencing). To assess the approximate incidence of SCID in ethnic minorities residing in southern Georgia, we are currently performing retrospective screening of ethnic Azerbaijani newborns' dried blood spot cards using TREC/KREC assays.

Results and Discussion: In one ethnic Azerbaijani family, three siblings aged 4, 8, and 7 months, died of recurrent respiratory infections and low count of T and B lymphocytes, suggesting of SCID. Genetic testing revealed a homozygous *JAK3*, c.1383dup p.(Leu462Alafs*58) pathogenic variant in the third sibling. Another infant patient from the Dmanisi region was admitted at 7 weeks with severe pneumonia, respiratory failure, sepsis, and peritonitis; immunological assays were suggestive of SCID. Further genetic testing confirmed a homozygous *ADA*, c.44A>T

p.(His15Leu) variant. The other unrelated infant from Marneuli with immunodeficiency also had the same recurrent *ADA* variant. The occurrence of this rare *ADA* variant in two unrelated families from neighboring regions (60 km distance between Dmanisi and Marneuli), may indicate on a founder effect. This finding raises the possibility that other children with SCID in the region remain undiagnosed and underscores the importance of timely recognition and genetic testing.

Conclusion: Our finding suggest that recurrent homozygous mutations in seemingly unrelated families may be due to founder effect. Moreover, SCID may be underdiagnosed among ethnic minorities residing in southern Georgia, emphasizing the urgency and cost-effectiveness of introducing SCID into national NBS. Implementing routine TREC/KREC newborn screening will enable early presymptomatic diagnosis, avoid emergency PICU/NICU admissions, and ensure life-saving curative treatment before severe infections occur. Precise molecular diagnosis also enables genetic counselling of families and informed decision-making for reproductive risk management.

Keywords: Newborn screening, severe combined immunodeficiency, intensive care, consanguinity, TREC/KREC, *ADA* deficiency, *JAK3*