SLAVIC FOUNDER MUTATION p.S44R IN IL7RA GENE IN CHILDREN WITH POSTMORTEM DIAGNOSIS SEVERE COMBINED IMMUNODEFICIENCY

Polyakova E.A.[1]PhD, Sakovich I.S.[1], Geier Christoph B.[2]MD, Leiss-Piller A.[2], Kupchinskaya A. N.[1], Kostuchenko L.V.[3]MD, PhD, Migas A.A.[1], Rozhko O.N.[4] MD, Hilfanova A.M.[5] MD, PhD, Mikhalevskaya T.M.[1] MD, Kugeiko T. B.[1] MD, Belevtsev M.V. PhD[1], Naumchik I.V.[6]MD, PhD, Golovatya E.I.[6]MD, PhD, Prebushenia O.V. [6]MD, PhD, Boyarchyk O.R.[7]MD, PhD, Hariyan T.[7]MD, PhD, Varabyou D.S.[8]PhD, Aleinikova O.V. [1]MD, PhD, Lisuk P.N. [10], Dudash P.I. [11], Walter J.E.[9]MD, PhD, Sharapova S.O.[1]PhD

1 – Research Department, Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Minsk region, Belarus, 2 – Research Department, Immunology Outpatient Clinic, Vienna, Austria, 3 – Pediatric department, West-Ukrainian Specialized Children's Medical Center, Lviv, Ukraine, 4 – Department Pediatric immunology, Regional Children's Clinical Hospital, Brest, Belarus, 5 – Department of Pediatric Infectious Diseases and Pediatric Immunology, Shupyk National Healthcare University of Ukraine, Kiev, Ukraine, 6 – Research Department, Republican Medical Center «Mother and Child», Minsk, Belarus, 7 – Department of Children's Diseases and Pediatric Surgery, I.Horbachevsky Ternopil National Medical University, Ternopil, Ukraine., 8 – Department of Ecologic Geography, Belarusian State University, Minsk, Belarus., 9 – University of South Florida at Johns Hopkins All Children's Hospital, Saint Petersburg, FL, USA., 10 – Department of Pediatric Pathology. Regional Pathology bureau. Brest, Belarus,11 – Pediatric Laboratory. Regional Pathologoanatomic bureau. Lviv, Ukraine

Background

Severe combined immunodeficiency with IL-7Rα-chain deficiency has immunologic phenotype T-B+NK+, frequency~10% of SCID cases

Methods

We conducted a multicenter retrospective study, enrolling patients' DNA with clinically suspected-SCID without genetic confirmation from Belarus(n=22) and Ukraine(n=24); children were selected from the mortality lists who died before the age of 1 year due to complications from generalized infections in infants (21–DNA was obtained from newborn cards, 16–FFPE, 2–FFT,1–FT,6–PB). We investigated a NGS PID panel of 102-SCID/CID genes. Identified genetic variant were confirmed by Sanger sequencing.

Result

We studied DNA from 20 females and 26 males. In 19/46 patients' DNA TREC/KRECs were determined, TRECs–mediana-4.2x10^3(0-2.0x10^4)/10^6leukocytes) and KREC–mediana-4.6x10^3(0-3.9x10^4)/10^6leukocytes). In three patients with T-B+SCID, TREC were undetectable and KREC-normal were (8.2x10^3(2.7x10^3-2.1x10^4)/10^6leukocytes.

In 2/4 patients, the genetic variant of p.S44R in the IL7Ra gene was detected in the homozygous state, in 2 of patients-in the heterozygous state, one patient had heterozygous compound with other mutations in the IL7Ra gene : p.C57R, p. R206Q (Figure 1-4)

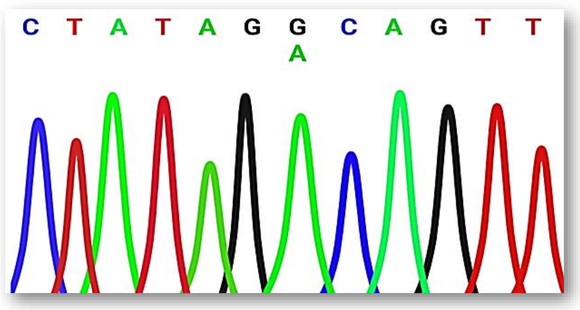
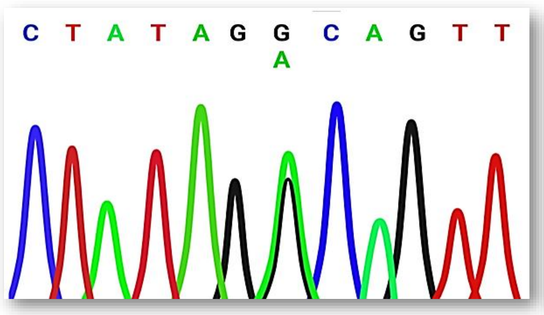


Fig.1. Sanger sequencing results in **P1, P2** with the homozygous mutations in the IL7Ra gene (variant c.132C>G, p.S44R)



The search for a heterozygous compound continues

Fig.2. Sanger sequencing results in P3 with the heterozygous mutation in the IL7Ra gene (variant c.132C>G, p.S44R)

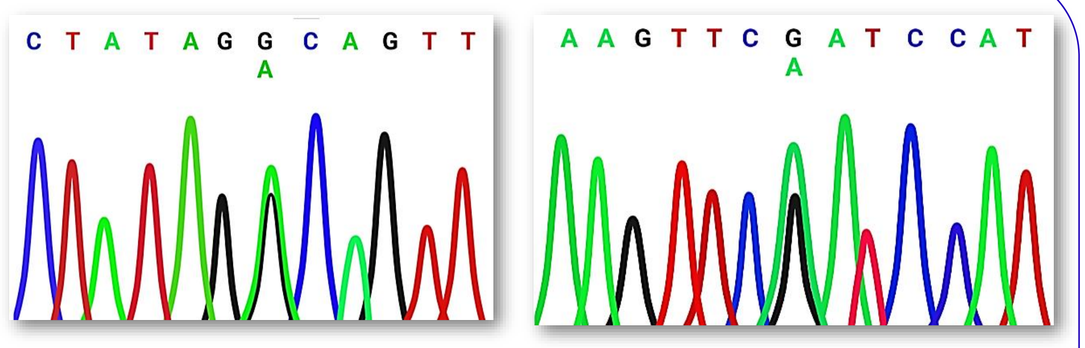


Fig.3. Sanger sequencing results in **P4**, with the heterozygous compound in the IL7Ra gene (variant c.132C>G, p.S44R; c. 617 G>A, p. R206Q).

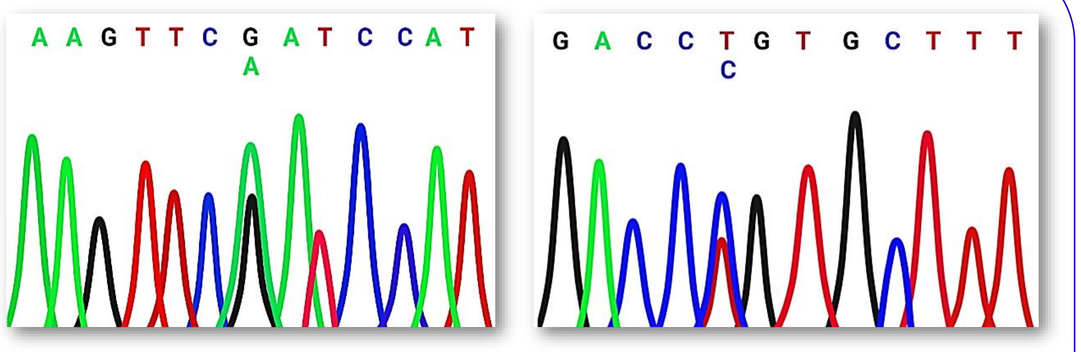


Fig.4. Sanger sequencing results in **P5**, with the heterozygous compound in the IL7Ra gene (variant ; c. 617 G>A, p. R206Q; c.169T>C, p.C57R

The IL7Ra gene variant	p.S44R	p.R206Q	p.C57R
Frequencies (gnomAD)	Variant not found	0.000048	Variant not found
Clinvar	No data available	Uncertain Significance	Uncertain Significance
Path. scores	10/8	16/1	14/4

Conclusion

Based on our data, a repeated substitution in the IL7Ra gene may be classified as mutation and may have the "founder effect" in East Slavic countries

Corresponding autor e-mail: Polyakovakat86@gmail.com