Clinical and genetic characteristics of global cohort of 132 individuals with Janus kinase-3 deficiency

Polyakova Ekaterina[1]PhD, Pac Malgorzata[2]MD,PhD, Dąbrowska-Leonik Nel[2]MD,PhD, Delavari Sama[3]MD,PhD, Rezaei Nima[3]MD,PhD, Abolhassani Hassan[3]MD,PhD, Tkemaladze Tinatin[4]MD,PhD, Kvilividze Oleg[5]MD,PhD, Pashchenko Olga E.[6]MD,PhD, Vakhlyarskaya Svetlana S.[7]MD,PhD, Kondratenko Irina V.[7]MD,PhD, Sakovich Inga S.[1], Belevtsev Mikhail[1]PhD, Tsekhanovich Dmitry A[1] , Aleshkevich Svetlana N.[1]MD,Geier Christoph B.[8]MD, Leiss-Piller Alexander[9], Çiğdem Aydoğmuş[10]MD,PhD, Pınar Gökmirza Özdemir[11]MD, PhD, Serdar Al[12]MD, PhD, Miller Rahim[13], Kiykim Ayca[14]MD, PhD, Baris Safa[15]MD, PhD, Notarangelo Luigi[16]MD, Gennery Andrew R[17]MD,PhD, Walter Jolan E.[13]MD,PhD, Sharapova Svetlana O.[1]PhD

1 – Research Department, Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Belarus. 2 – Department of Immunology, The Children's Memorial Health Institute, Warsaw, Poland.3 – Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.4 – Department of Molecular and Medical Genetics, Tbilisi State Medical University, Tbilisi, Georgia; Givi Zhvania Pediatric Academic Clinic, Tbilisi State Medical University, Tbilisi, Georgia.5 – Georgian Foundation for Genetic and Rare Diseases; School of Medicine, New Vision University, Tbilisi, Georgia6 – Immunology chair, Pirogov Russian National Research Medical University; Clinical Immunology and Rheumatology Department, Russian Children's Clinical Hospital of Pirogov Russian National Research Medical University, Moscow, Russian Federation.7 – Russian Children's Clinical Hospital of Pirogov Russian National Research Medical University, Clinical Immunology and Rheumatology Department, Moscow, Russian Federation.8 – Research Department, Immunology Outpatient Clinic, Vienna, Austria; Department of Rheumatology and Clinical Immunology, Faculty of Medicine, University of Freiburg; Center for Chronic Immunodeficiency, Faculty of Medicine, University of Freiburg, Freiburg, Germany.9 – Research Department, Immunology Outpatient Clinic, Vienna, Austria; Archimed Life Science GmbH, Vienna, Austria.10 – University of Health Sciences, Basaksehir Cam and Sakura City Hospital, Department of Pediatric Allergy and Immunology, Istanbul, Turkey.11 – Department of Pediatric Allergy and Immunology, Trakya University School of Medicine, Edirne, Turkey.12 – Department of Pediatric Allergy and Clinical Immunology, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey.13 – Division of Pediatric Allergy & Immunology, Department of Pediatrics, University of South Florida, St. Petersburg, FL, USA; Johns Hopkins All Children's Hospital Children's Research Institute St. Petersburg, FL14 – Istanbul University-Cerrahpasa, Cerrahpasa Medical School, Department of Pediatrics, Division of Pediatric Allergy and Immunology, Istanbul, Turkey.15 – Marmara University Hospital Pediatric Allergy and Immunology, Istanbul Jeffrey Modell Diagnostic and Research Center for IEI, Istanbul, Turkey.16 – Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.17 – Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK; Paediatric Stem Cell Transplant Unit, Great North Children's Hospital, Newcastle upon Tyne, UK.**

Background and aims

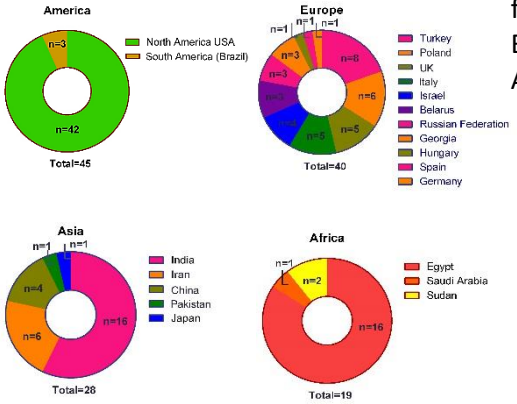
Janus kinase-3(*JAK3*) deficiency, first described in 1995, is an autosomal recessive inborn error of immunity that mostly results in variants of severe combined immunodeficiency (SCID). The frequency is estimated to account for 7-14% of heritable SCID, with sporadic cases in the Western world. Neither preferential "hot-spots" nor founder effects have yet been documented. Hereby, we aim to describe the global experience of JAK3-related diseases regarding clinical spectrum, genetic landscape, including founder variants and treatment strategies.

Materials and methods

We extracted clinical, genetic, immunological data from published cases on patients with CID/SCID phenotype caused by defects in the *JAK3* gene. The literature search included unpublished cases from collaborators, reports from meetings of the ESID, of the CIS, published data in the PubMed from 1995 to 2024.

Results

Our cohort includes 132 patients with 47 unique genetic defects, including 35 novel variants (18-homozygous, 17-heterozygous)



Forty five (35%) of patients from cohort were born to consanguineous parents in 31 families from Georgia (n=3,1-family), Russian Federation (n=3/2-family), Sudan (n=1), Turkey (n=8,5-family), Israel (n=4, 2 family), India (n=3, 2 family), Egypt (n=13, 8 family), UK (n=5, 4 family), China(n=1), Brazil(n=1), Spain(n=1), Italy (n=1), Pakistan(n=1), Saudi Arabia (n=1).

	Title	JAK3(n=132)
Zygosity genetic defect	Homozygote Compound Heterozygote Germline heterozygous gain of function	90 40 2
Omenn syndrome		6
Treatment	HSCT	61
Outcome	Died Alive	17 44

Conclusions

We describe for the first time a global cohort of JAK3 with 132 patients with founder effects in a subgroups. Patients were identified in four continents but is most common in countries with high rate of consanguinity. Founder effect was identified in 14 regions.

Presenting author: *Walter Jolan E.* e-mail: **Corresponding author: Svetlana Sharapova sharapovasv@gmail.com**

Clinical and genetic characteristics of global cohort of 132 individuals with Janus kinase-3 deficiency

14 – Istanbul University-Cerrahpasa, Cerrahpasa Medical School, Department of Pediatrics, Division of Pediatric Allergy and Immunology, Istanbul, Turkey.
15 – Marmara University Hospital Pediatric Allergy and Immunology, Istanbul Jeffrey Modell Diagnostic and Research Center for IEI, Istanbul, Turkey.
16 – Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.
17 – Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK; Paediatric Stem Cell Transplant Unit, Great North Children's Hospital, Newcastle upon Tyne, UK

Background and aims

Severe combined immunodeficiency with Janus kinase 3 (*JAK3*) deficiency has immunologic phenotype T-B+NK-, frequency~10% of SCID cases.

Materials and methods

We report on 10 patients (5 females and 5 males) from different ethnic groups with the SCID/CID phenotype (Fig1.).
In order to obtain a diagnosis, immunophenotyping of lymphocytes and molecular analysis using the Sanger sequencing and NGS were performed.

The *JAK3*-cohort included 10 patients from: the Republic of Belarus (2 - Eastern Slavs, 1- Arabs (Sudan origin), 1-Romany), the Russian Federation (3-Turkic), Georgia (3-Azerbaijani Georgians). (Fig1.).
Consanguineous marriages were confirmed in 5 out 7 families.

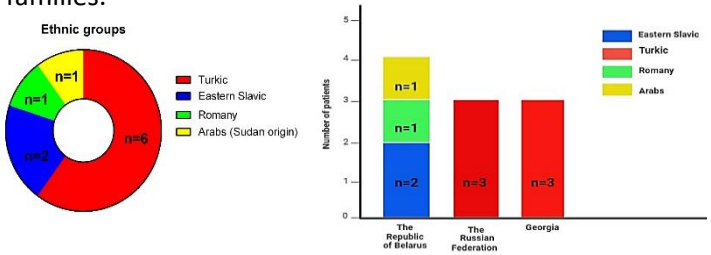


Fig. 1. The *JAK3*-cohort

Results

Genetic variants in the *JAK3* gene were identified in all families

Title		JAK3(n=10)
Immuno phenotype	T-B+NK- T-low B+NK- (CD3+CD8-)B+NK-	8 1 1
Type of mutation	Missense Frame shift Splicing site	2 6 2
Zygosity	Homozygote Compound Heterozygote	8 1 1
Pathogenicity (ACMG)	Pathogenic VUS Gain of function	2 7 1

1 patient underwent HSCT, 8 died at the age of 9(9-18) months, 2 are alive (1-preparing for HSCT).

Conclusions

Our study expands the mutational spectrum of *JAK3* deficiency. Pathogenic variants in the *JAK3* gene leading to combined immunodeficiency are accompanied by heterogeneity of immunological phenotypes, which creates the need for detailed immunological and molecular studies, especially in closed ethnic groups.

Corresponding author: *Ekaterina Polyakova* e-mail: polyakovakat86@gmail.com