Uncovering Germline Leukemia Predisposition through Integrated Clinical and Somatic Genomic Analysis

K. Wypyszczak[1], K. Miarka-Walczyk[1], Z. Urbańska[1], M. Michalak[2], J. Trelińska[2], M. Lejman[3], M. Ussowicz[4], I. Dachowska-Kałwak[4], A. Kołtan[5], M. Hennig[6], D. Januszkiewicz-Lewandowska[7], J. Bulsa[8], A. Królak[9], W. Bal[10], M. Wołowiec[11], E. Ulińska[12], W. Młynarski[2], A. Pastorczak[1]

[1] Medical University of Lodz, Department of Genetic Predisposition to Cancer, Lodz, Poland
[2] Medical University of Lodz, Department of Pediatrics, Oncology and Hematology, Lodz, Poland
[3] Medical University of Lublin, Independent Laboratory of Genetic Diagnosis, Lublin, Poland monika.lejman@umlub.pl
[4] **Supraregional Centre for Paediatric Oncology "Cape of Hope"**, Department of Bone Marrow Transplantation, Oncology and Pediatric Hematology, Wroclaw Medical University, Wrocław, Poland,
[5] Department of Pediatric Hematology and Oncology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Bydgoszcz, Poland [6] Klinika Pediatrii, Hematologii, Onkologii i immunologii, Uniwersyteckie Centrum Kliniczne, Gdańsk, Poland
[7] Oncology Clinic, Karol Marcinkowski Clinical Hospital, Poznan, Poland [8] Independent Public Clinical Hospital No. 1 in Zabrze, Department of Pediatrics, Hematology and Pediatric Oncology, Zabrze [9] Department of Pediatrics and Pediatric Hemato-Oncology, Pomeranian Medical University in Szczecin, Szczecin, Poland [10] Clinic of Pediatric Oncohematology, Clinical Provincial Hospital No. 2 in Rzeszów, Rzeszów, Poland
[11] Subdepartment of Clinical Oncology and Pediatrics, Department of Pediatric Oncology, Hematology, Clinical Transplantology and Pediatrics, Medical University of Warsaw, Warsaw, Poland
[12] Department of Pediatric Oncology, Hematology, Clinical Transplantology and Pediatrics, Medical University of Warsaw, Warsaw, Poland

MEDICAL UNIVERSITY OF LODZ

INTRODUCTION

Cancer predisposition syndromes account for approximately 6% of hematological malignancies in children, yet most pediatric patients diagnosed with leukemia do not undergo routine germline genetic screening.

AIM

Our objective was to identify germline cancer-predisposing variants in pediatric patients with ALL who either fulfilled established clinical criteria for genetic predisposition syndromes or harbored variants suggestive of constitutional origin that were incidentally detected during routine somatic sequencing performed as part of ALL diagnostics.

METHODS

We retrospectively enrolled 118 patients (aged 1–18 years) treated for acute lymphoblastic leukemia (ALL). Phenotype-driven germline genetic testing, including targeted sequencing and whole-exome sequencing, was performed in 53 individuals who met the criteria established by Jongmans et al. An additional 65 patients were included based on somatic findings suggestive of a potential germline origin, identified through RNA sequencing of the leukemic transcriptome.

CONCLUSIONS

Integrating somatic genome analysis with a thorough phenotypic assessment facilitates the identification of inherited predispositions to childhood leukemia. Leukemia predisposition syndrome (LPS) were associated with unfavorable outcome of childhood ALL

RESULTS

INCIDENCE OF LEUKEMIA PREDISPOSING SYNDROMES (LPS)

Of the 118 patients enrolled in the study, 35 (29,7%) were found to harbor variants associated with cancer predisposition, 27 (22.9%) of whom carried variants linked specifically to acute lymphoblastic leukemia. Among phenotypically selected patients, LPS were predominantly identified in the presence of comorbidities (n = 11, 68.7%).

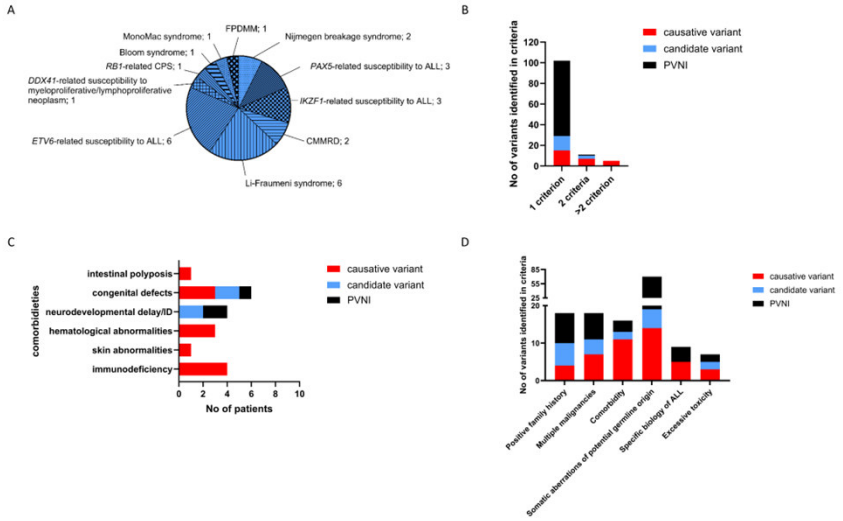

Figure 2 (A) The incidence of the leukemia predisposing syndromes (LPS) in the study cohort with the number of individuals diagnosed with specific entity. (B) The distribution of the identified leukemia predisposing and candidate gene variants depending on the number of inclusion criteria met. (C) The number of patients harboring causative and candidate leukemia predisposing gene variants according to the specific comorbidities coexisting with ALL. (D). Identification of candidate and causative gene variants across defined inclusion criteria.

ALL OUTCOME DEPENDING ON LPS

Children harboring a confirmed genetic variants predisposing to ALL showed significantly inferior overall survival outcomes and an increased risk of relapse.

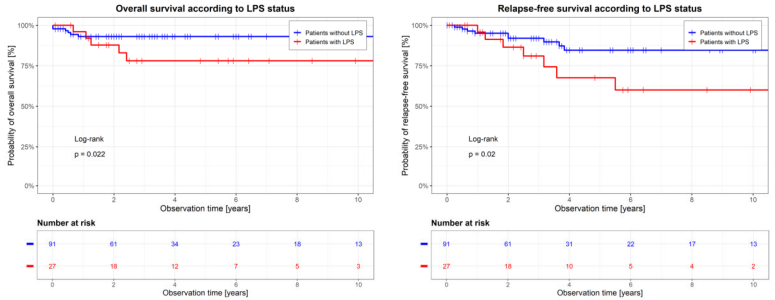

Figure 2. Kaplan-Meier curves displaying the probability of overall and relapse-free survivals among pediatric patients diagnosed with ALL with (red line) or without leukemia predisposing syndrome (LPS) (blue line).

NOVEL – CANDIDATE VARIANTS FOR ALL PREDISPOSITION

Four patients carried heterozygous, likely pathogenic variants of possible leukemia predisposing effect that need to be further verified using functional studies

Table 1 Novel likely pathogenic candidate gene variants for ALL predisposition

GENE	HGVSc	HGVSp	Zygosity	ACMG classification
NARS1	NM_004539.3:c.713G>A	p.Arg238Gln	heterozygous	LIKELY PATHOGENIC
TOM1	NM_001135732.1:c.1369C>T	p. Arg457*	heterozygous	LIKELY PATHOGENIC
NTRK3	NM_001012338.2:c.1745G>A	p.Arg582Gln	heterozygous	VUS
CLPB	NM_030813.4:c.2124delG	p.*708Tyr	heterozygous	LIKELY PATHOGENIC

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CONTACT INFORMATION

kamila.wypyszczak@umed.lodz.pl

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