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Germline lymphoma-predisposing variants: impact on age of cancer diagnosis and survival in pediatric patients

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Running heads: Germline predisposition to childhood lymphomas

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Up to 10% of paediatric malignancies occur in individuals carrying germline gene variants conferring cancer predisposing syndromes (CPS)[1–3]. In paediatric lymphomas, inherited susceptibility is particularly relevant in the context of inborn errors of immunity, including DNA repair disorders, in which impaired immune surveillance and genomic instability promote lymphomagenesis[1–3]. As their clinical presentation manifestations may be subtle or limited, the underlying cancer predisposition may be unrecognized at the time of lymphoma diagnosis[1–3]. The increasing availability of next-generation sequencing (NGS) has enabling comprehensive detection of germline variants and refinement of genotype-phenotype correlations[2,4–9]. Recognition of an underlying CPS has immediate clinical implications, including adaptation of treatment intensity, anticipation of excessive toxicity, surveillance, management of comorbidities, and genetic counselling[2]. Here, we investigated germline predisposition to lymphoma in a cohort of children subjected to phenotype-driven genetic testing.

The project was initiated in July 2019 after approval of Bioethics Committee of the Medical University of Łódź (RNN/309/19/KE). 14 Polish paediatric haemato-oncology departments were asked to report patients meeting ≥1 inclusion criteria: **C1.** positive family history of cancer [≥1 first-degree relative diagnosed with cancer ≤45y.o.; ≥2 relatives (≥1 second-degree) in the same lineage diagnosed with cancer ≤45y.o.; or parental consanguinity], **C2.** specific histopathological subtypes of lymphoma [predefined entities: T-cell lymphoblastic lymphoma (T-LBL), diffuse large B-cell lymphoma (DLBCL) and rare entities reviewed case-by-case: subcutaneous panniculitis-like T-cell lymphoma, cutaneous T-cell lymphoma, blastic plasmacytoid dendritic cell neoplasm, primary mediastinal large B-cell lymphoma). A histopathological diagnosis of T-LBL was used as an inclusion criterion because of the notably high prevalence of congenital DNA repair defects[10] and secondary malignancies among patients with this diagnosis[11]. **C3.** multiple primary malignancies (≥1 lymphoma and ≥1 diagnosed ≤18 years), **C4.** congenital anomalies/comorbidities (as originally described[12]), **C5.** excessive treatment-related toxicity (≥1 AE ≥4CTCAE or ≥3 AEs ≥3CTCAE inconsistent with the used treatment). Recruitment was criterion-based, but not population-wide screening; patients could also be enrolled retrospectively if eligibility became apparent during follow-up, e.g. after a second malignancy or newly recognized family history.

Additionally, for subsequent comparative analyses of overall survival and event-free survival, defined as relapse, second malignancy, or death, we obtained nationwide data on 305 paediatric B-cell lymphoma cases and 153 T-LBL treated in Poland during the same period (subsequently referred as *unselected lymphoma cohort*).

Patients with a phenotype suggestive of a genetic syndrome underwent targeted NGS (Table S1), while all remaining individuals were analysed by whole-exome sequencing [WES; SureSelect Human All Exon V7 (Agilent Technologies, CA, USA); NovaSeq 6000 (Illumina, CA, USA), 2 × 150 bp; median coverage ×200]. In patients with a positive family history, affected and unaffected relatives were also analysed. In selected cases, copy number analysis using CytoScan HD (Thermo Fisher, MA, USA) arrays was performed (Figure 1). Bioinformatic analysis was conducted using hg19 and the DRAGEN Germline Pipeline. Variants were filtered based on predefined gene lists, population frequency, conservation score, in-silico functional predictions and interpreted according to ACMG guidelines. Selected variants were validated by Sanger sequencing. Candidate variants were defined as likely pathogenic variants or variant of uncertain significance in biologically relevant genes with predicted functional consequences compatible with the presumed disease mechanism (loss or gain-of-function promote carcinogenesis) and ≥1 supporting feature: proximity to known somatic hotspots, genotype-phenotype concordance or familial segregation with malignancies. Candidate variants have not been validated in vitro therefore require further functional studies.

Among the study participants, 50 males (68%), the median age at diagnosis of lymphoma was 8 years (IQR: 5–13). The most commonly reported tumour types were: Hodgkin lymphoma (HL; 27 patients, 36%), T-LBL (13 patients, 18%), and DLBCL (11 patients, 15%). Unless otherwise specified, percentages in the following paragraphs refer to families.

C2 was the most frequent inclusion criterion reported in 33 (56%) families followed by C4 in 22 (37%) families, C1 in 18 (31%), C3 in 16 (27%; Figure 2) families, and C5 in 9 (15%) families were noted. Notably, more than 1 inclusion criterion was met in 29 families (49%), while more than 2 were identified

in 9 families (15%). Among patients meeting more than two criteria, the most frequent constellation involved the co-occurrence of a C2, C3, and C4 (33%).

The most prevalent lymphoma subtype was T-LBL (12 families, 36%), DLBCL (10 families, 30%), and primary mediastinal B-cell lymphoma (PMBL; 7 families, 21%). Additionally, blastic plasmacytoid dendritic cell neoplasms (2 families, 6%), cutaneous lymphoma (1 family, 3%), and subcutaneous panniculitis-like T-cell lymphoma (1 family, 3%) were observed. Pedigrees of families with cancer diagnosis in multiple relatives are shown in Figure S1. In thirteen families, both parent and child(ren) were diagnosed with lymphomas, with the father being affected in the majority of cases (n=9, 69%). Only siblings were involved in 3 families (17%). The remaining pedigrees are shown as Figure S1L&R.

C4 primarily conferring immunodeficiencies were observed in ten families (45%), followed by colon polyposis, reported in four families (18%). In addition, autism, skin abnormalities, and hearing loss were each identified in two families (9%).

Regarding the C3 incidence, acute leukaemias were diagnosed in 6 families (38%: 5 cases of lymphoblastic origin, 1 of myeloid immunophenotype), and brain tumours were present in 4 patients (25%; 3 out of 4 high-grade gliomas and 1 hemangioblastoma). Furthermore, there were single cases of multiple lymphomas (HL and DLBCL), Ewing sarcoma, hepatoblastoma, teratoma, thyroid cancer, ovarian tumor, liver cancer, and Wilms tumor (6%) (Figure 2A).

Adequate-quality germline material suitable for NGS was available for 58 patients from 48 families (81%), all of whom underwent genetic testing. Causative pathogenic variants were found in 10 families (21% of tested families), the variants particularly affecting DNA repair genes: MMR genes (4 families), *ATM* gene (2 families), *BLM* gene (1 family; Supplementary Excel Table). Additionally, germline pathogenic variants predisposing to cancer but only possibly contributing to lymphoma development were identified in two families, involving the *TP53* (family 9) *and CHEK2* (family 10) genes.

In the remaining 9 (19%) families, we identified gene variants that may possibly contribute to lymphoma development, including two patients with monoallelic pathogenic variants within the *BRCA1*

gene (Family 17 and Family 18) and a patient with HL and secondary Ewing sarcoma carrying a heterozygous variant of unknown significance in *PALB2* gene (Family 14). We consider the germline variants involving: *LCK* (NM_005356.5:c.1176C>G; p.Asn392Lys, het), *NTRK3* (NM_001012338.2:c.1745G>A; p.Arg582Gln, het), and *CHD8* (NM_001170629:c.6614delC; het) were the most promising candidates for further functional testing. *LCK* encodes key kinase in T-cell receptor signalling. The variant lies within the kinase domain, and was detected in a patient with immunodeficiency and panniculitis-like T-cell lymphoma, with segregation compatible with autosomal dominant inheritance with incomplete penetrance[13]. The *NTRK3* p.Arg582Gln affects the tyrosine kinase domain of TrkC, a functionally relevant hotspot involved in oncogenic signalling through Erk1/2, PLC-γ, and AKT pathways, and was identified in a patient with multiple malignancies, although germline *NTRK3* variants have not been established as a cause of lymphoproliferative disease. The *CHD8* p.Pro2205LeufsTer57 variant represents a loss-of-function alteration in a gene involved in chromatin remodelling and transcriptional regulation. It is somatically affected in Burkitt lymphoma, and matched the patient phenotype including macrocephaly, macrosomia, autism (OMIM# 615032)[14].

Despite performing a three-step diagnostic procedure with targeted NGS, WES, and microarrays on a pre-selected group of patients, we were unable to identify either causative variants or other variants potentially associated with CPS in the majority of families (n=29, 60%). The only notable pattern in our cohort was the overrepresentation of HL among families in whom no causative or candidate variants were identified.

The highest probability of identifying a lymphoma predisposing variant was observed among families meeting at least three inclusion criteria (see **Figure 2B**). In this group, 7 (78%) families carried a causative variant. Interestingly, among families meeting at least two inclusion criteria, the detection rate of causative variants was 31% (8 families) - a rate comparable to or even slightly lower than those observed in multiple malignancies, excessive toxicity, congenital abnormalities/specific dysfunctions, and a specific histopathology.

In Kaplan-Meier time-to-event analysis, patients with causative germline variants showed the steepest decline, indicating the earliest onset of malignancy, followed by patients with candidate variants and those without an identified predisposing variant (log-rank p=0.007; Figure 2C). Consistently, the median age at first cancer diagnosis was 5 years (IQR: 4-6.75) in patients with a causative variant, 10 years (IQR: 7.5-10.7) with a candidate variant, and 11 years (IQR: 5.75-14) in those with no germline predisposition identified. A similar pattern was observed for lymphoma-free survival, with the shortest lymphoma-free interval in patients carrying causative variants (log-rank p=0.013; Figure 2D). The median ages at first lymphoma diagnosis were 6.5 years (IQR: 4.5-7), 10 years (IQR: 7.5-11.5), and 11 years (IQR: 5.75-14), respectively. Furthermore, the carriers of causative or candidate variants did not show unfavourable overall survival when compared to the unselected lymphoma cohort (p=0.067). They had, however, significantly poorer event-free survival: 5-year EFS was 71.4% (95% CI 44.7%-100.0%), 100.0% (95% CI 100.0%-100.0%), and 90.7% (95% CI 87.8%–93.7%); p<0.001; Figure 2E). Importantly, lymphoma subtype distribution differed between groups, with enrichment of T-LBL and DLBCL among causative-variant carriers and a more heterogeneous spectrum among candidate-variant carriers. Therefore, histology may represent a potential confounder. Given the limited number of cases within individual histological subtypes, the study was underpowered to perform a multivariable analysis assessing the independent effect of germline lymphoma predisposition on survival.

In conclusion, our study demonstrates that a phenotype-driven approach to germline analysis facilitates the identification of inherited predisposition in paediatric lymphoma. Improving clinician awareness, standardizing phenotypic assessment, and implementing dedicated diagnostic algorithms are essential to optimize the identification and management of affected patients.

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Table 1. Molecular and clinical characteristics of 10 families (1-10) with members carrying pathogenic or likely pathogenic CPS variants and 9 (11-19) families with variants potentially contributing to lymphoma development.

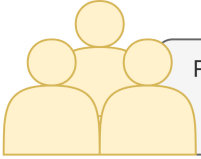
Family number	Number of lymphoma patients	Pathogenic variant	Zygosity [(c) het-(compound) heterozygous]	Origin [M-maternal;P – paternal]	C1. positive familial history	C2. specific histopathological types of lymphoma	C3. multiple malignancies	C4. congenital abnormalities or specific dysfunctions	C5. Excessive toxic complications
1.	2	*PMS2* (NM_000535:c.1296delC p.(Asn432LysfsTer16) & ex. 10-15 deletion)	C het	M/P	2 brothers	T-LBL	T-LBL and HGG	N.A.	N.A.
2.	1	*PMS2* (NM_000535:c.1185delC; p.(Met396TrpfsTer2) with exon 1-10 deletion	C het	P/M	N.A.	T-LBL	T-LBL and HGG	Colon polyps	N.A.
3.	1	*PMS2* (NM_000535:c.1939A>T; p.(Lys647Ter) with deletion of exons 8-14)	C het	M/P	N.A.	T-LBL	B-ALL, T-LBL	Immunodeficiency	Yes*
4.	1	*MSH6* (NM_001406815: c.1135_1139delAGAGA; p.(Arg379_Asp380delinsTer) & c.2277_2293del; p.(Glu760ProfsTer6))	C het	De novo/M	N.D	T-LBL	B-All, T-LBL + T-ALL, HGG	Colon polyps and café-au-lait spots	N.A.
5.	1	*ATM* (NM_000051:c.434T>G; p.(Leu145Arg) with deletion of exons 40-64)	C het	N.D.	N.D	DLBCL	N.A.	Immunodeficiency	Yes**
6.	1	*ATM* (NM_000051:c.601C>T;p.(Gln201Ter) & c.5932G>T; p.(Glu1978Ter))	C het	P/M	N.D	N.D	N.D	Neurological dysfunction, conjunctival telangiectasias	N.A.
7.	1	*BLM* (NM_000057:c.1642C>T; p.(Gln548Ter) & c.2833G>A; p.(Ala945Thr))	C het	N.D.	N.A.	T-LBL	N.A.	N.A.	Yes***
8.	1	*CXCR4* (NM_003467:c.1012dup; p.(Ser338PhefsTer6))	Het	M	2 brothers, mother	DLBCL	N.A.	Neutropenia and hearing loss	N.A.
9.	1	*TP53* (NM_000546:c.155_164delAATGGTTCAC; p.(Gln52LeufsTer68))	Het	M	Mother (breast cancer)	N.A.	Hepatoblastoma, EBV(+) PTLD;	Colon polyps	N.A.
10.	1	*CHEK2* (NM_001005735:C.573+1G>A; p.(Ser471Phe))	Het	N.D.	N.A.	N.A.	HL, thyroid cancer	N.A.	N.A.
11.	1	*NTRK3* (NM_001012338:c.1745G>A; p.(Arg582Gln))	Het	M	N.A.	DLBCL	B-ALL, DLBCL	N.A.	N.A.
12.	1	*LCK* (NM_005356:c.1176C>G; p.(Asn392Lys))	Het	P	N.A.	Subcutaneous panniculitis-like T-cell lymphoma	N.A.	Immunodeficiency	N.A.
13.	1	*CHD8* (NM_001170629:c.6614delC; p.(Pro2205LeufsTer57))	Het	N.D.	N.A.	N.A	N.D	Macrocephaly, macrosomia, and autism	N.A.
14.	2	*PALB2* (NM_024675.1:c.110G>A; p.(Arg37His))	Het	P	HL	N.A.	Daughter:HL and Ewing sarcoma	N.A.	N.A.
15.	1	*MLH3* (NM_001040108:c.3483delC; p.(Ser1161ArgfsTer8)); *CHEK2* (NM_001005735:c.1412C>T; p.(Ser471Phe))	Het; Het	N.D.	N.A.	BPDCN	N.A.	N.A.	N.A.
16.	1	*MSH4* (NM_002440:c.1505G>A; p.(Arg502Lys))	Het	N.D.	N.A.	N.A.	N.A.	Immunodeficiency	Yes****
17.	1	*BRCA1* (c.4035delA; p.(Glu1346LysfsTer20))	Het	P	N.A.	T-LBL with T-ALL	T-LBL and AML	N.A.	Yes*****
18.	1	*BRCA1* (NM_007300:c.3756_3759del; p.(Ser1253ArgfsTer10))	Het	N.D.	N.A.	N.A.	N.A.	N.A.	Yes******
19.	1	*LAX1* (NM_017773.3:c.295C>T; p.(Arg99Ter))	Het	M(-), no biologic material from father	Father kidney cancer	N.A.	N.A.	N.A.	N.A.

Legend: B-LBL – B-lymphoblastic lymphoma, BPDCN – blastic plasmacytoid dendritic cell neoplasm, DLBCL – Diffuse large B-cell lymphoma, het – heterozygous, HL – Hodgkin lymphoma, MCL – Mantle cell lymphoma, N.A. – Non-applicable, T-LBL – T-lymphoblastic lymphoma, WT – Wilms tumor; * At initial diagnosis: severe myelotoxicity (CTCAE grade 4), invasive fungal infection with CNS abscesses (CTCAE grade 4), pneumonia requiring intravenous antibiotics (CTCAE grade 3); additionally, facial hyperpigmentation during maintenance chemotherapy (CTCAE grade 2); ** During treatment with the B-HR arm of the Inter-B-NHL-COP 2010 protocol (with dose reductions of methotrexate and cyclophosphamide), the patient experienced: leukopenia and neutropenic fever (CTCAE grade 3), urinary tract infection (CTCAE grade 3), oral mucosal damage (CTCAE grade 3), recurrent thrombocytopenia and anemia (CTCAE grade 3), and paroxysmal hypertension (CTCAE grade 3); *** During the first month of treatment with the EURO-LB 02 protocol, significant hematologic toxicities were observed, including anemia (CTCAE grade 3), neutropenic fever (CTCAE grade 3), and thrombocytopenia (CTCAE grade 4), as well as sepsis requiring catecholamine support (CTCAE grade 4); **** During treatment, on day 15 of the first OEPA cycle, a right-sided pneumothorax with slight leftward mediastinal shift was diagnosed. Chest drainage was performed with good effect; ***** During treatment according to the AIEOP-BFM ALL2017 protocol, the patient experienced neutropenic fever (CTCAE grade 3), Salmonella infection (CTCAE grade 3), urinary tract infection (CTCAE grade 3), pneumonia (CTCAE grade 3), and hepatotoxicity (CTCAE grade 3); ****** Symptoms observed from day 27 of treatment according to the EURO-LB 02 protocol included: severe hepatotoxicity (grade 4), ascites requiring drainage (grade 3), laparotomy wound dehiscence (grade 3), hematuria with a large bladder clot requiring surgical intervention (grade 3), peritonitis/abdominal fluid necessitating reoperation (grade 3), and pancreatic injury (grade 4). Additional findings included leukopenia (grade 4), thrombocytopenia (grade 3), anemia (grade 3), and accompanying febrile neutropenia (grade 3).

Figures Legend

Figure 1. Study work-flow. Legend: CMMRD, constitutional mismatch repair deficiency; NBS, Nijmegen breakage syndrome; WES, whole-exome sequencing; MLPA, multiplex ligation-dependent probe amplification.

Figure 2. Summary of clinical and genetic features and their relationships: **A.** Swimmer's plot depicting incidence of secondary malignancies in the study cohort; **B.** The frequency of causative and candidate variants depending on the number of met inclusion criteria and on the particular clinical criterion; Kaplan-Meier estimates of age at **C.** first cancer and **D.** first lymphoma diagnosis according to germline variant status; and **E.** event-free survival (defined as relapse, second malignancy, or death) between patients harboring causative or candidate variants in comparison with a representative pediatric cohort diagnosed with lymphomas. Legend: AML - acute myeloid leukemia; B-ALL - B-cell lymphoblastic leukemia; DLBCL- Diffuse large B-cell lymphoma; FL - Follicular lymphoma; HL- Hodgkin lymphoma; N.D.- Not determined; T-LBL- T-lymphoblastic lymphoma.



Project initiated in July 2019 across 14/17 Polish pediatric hemato-oncology departments and ended 2023

Survey data collection
(74 patients from 59 families)

Collection of germline material
(58 patients from 48 families)

Assessment of the clinical risk of lymphoma development in the course of a specific genetic syndrome

Phenotype of a specific genetic syndrome

Otherwise

Targeted DNA sequencing (initially 20 families)

Whole exome sequencing (initially 28 families)

In the presence of genetic indications following a negative result of targeted DNA sequencing

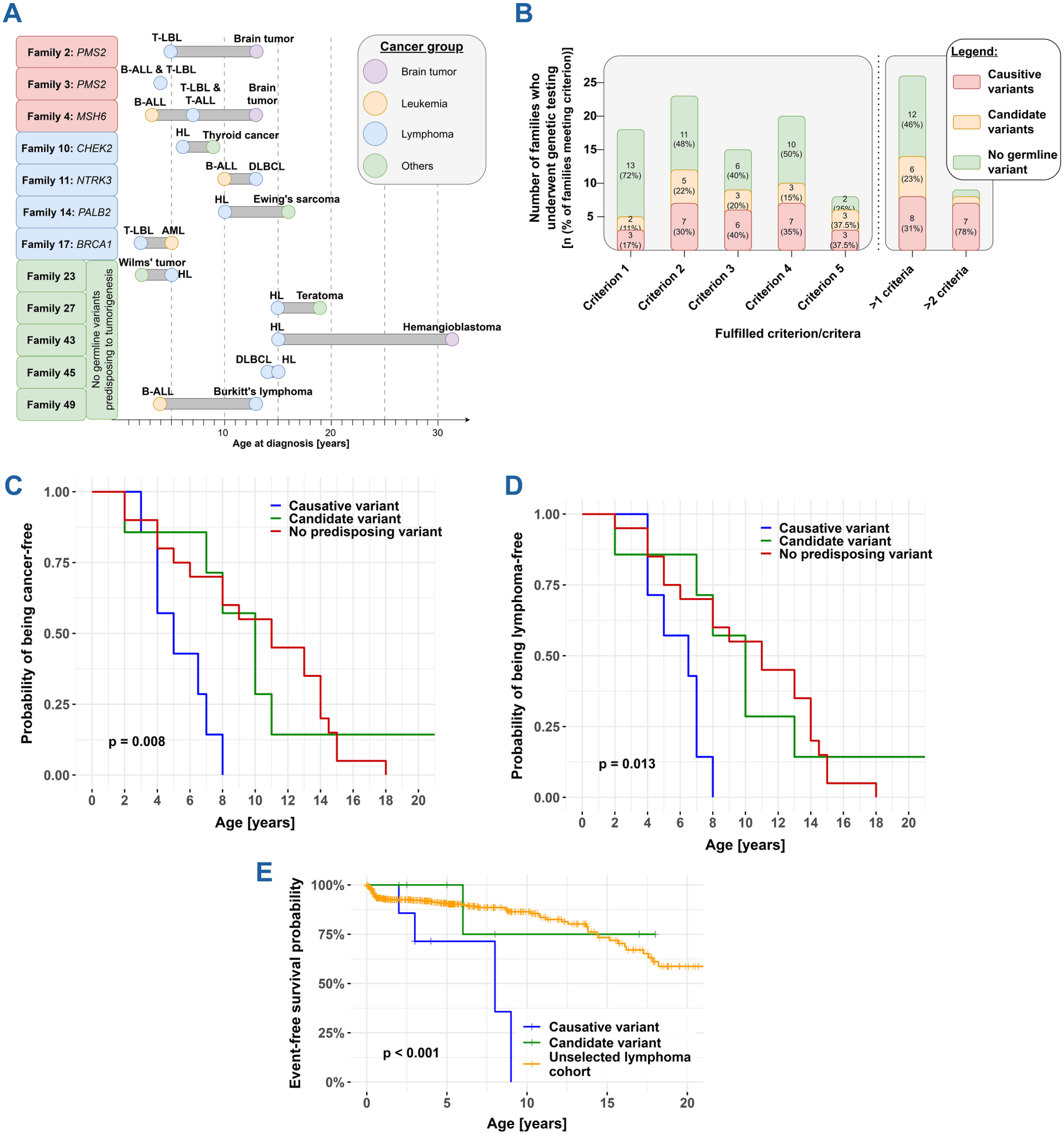
Analysis of DNA sequencing results

Verification by direct Sanger sequencing

5 families with a suggestive phenotype and a monoallelic defect, intellectual disability, or congenital anomalies – chromosomal microarray testing (CytoScan HD)

2 families with a CMMRD phenotype and a heterozygous PMS2 variant – MLPA testing

Statistical analysis of the obtained results


A
Family 2: PMS2
Family 3: PMS2
Family 4: MSH6
Family 10: CHEK2
Family 11: NTRK3
Family 14: PALB2
Family 17: BRCA1
Family 23
Family 27
Family 43
Family 45
Family 49
No germline variants predisposing to tumorigenesis
T-LBL
Brain tumor
B-ALL & T-LBL
T-LBL & T-ALL
B-ALL
Brain tumor
HL
Thyroid cancer
B-ALL
DLBCL
HL
Ewing's sarcoma
T-LBL
AML
Wilms' tumor
HL
HL
Teratoma
HL
Hemangioblastoma
DLBCL
HL
B-ALL
Burkitt's lymphoma
10
20
30
Age at diagnosis [years]
Cancer group
Brain tumor
Leukemia
Lymphoma
Others
B
Number of families who underwent genetic testing [n (% of families meeting criterion)]
25
20
15
10
5
13 (72%)
2 (11%)
3 (17%)
11 (48%)
5 (22%)
7 (30%)
6 (40%)
3 (20%)
6 (40%)
10 (50%)
3 (15%)
7 (35%)
2 (25%)
3 (37.5%)
3 (37.5%)
12 (46%)
6 (23%)
8 (31%)
7 (78%)
Criterion 1
Criterion 2
Criterion 3
Criterion 4
Criterion 5
>1 criteria
>2 criteria
Fulfilled criterion/critera
Legend:
Causitive variants
Candidate variants
No germline variant
C
Probability of being cancer-free
1.00
0.75
0.50
0.25
0.00
p = 0.008
Causative variant
Candidate variant
No predisposing variant
0
2
4
6
8
10
12
14
16
18
20
Age [years]
D
Probability of being lymphoma-free
1.00
0.75
0.50
0.25
0.00
p = 0.013
Causative variant
Candidate variant
No predisposing variant
0
2
4
6
8
10
12
14
16
18
20
Age [years]
E
Event-free survival probability
100%
75%
50%
25%
0%
p < 0.001
Causative variant
Candidate variant
Unselected lymphoma cohort
0
5
10
15
20
Age [years]

Germline Lymphoma Predisposing Variants: Impact on Age at Cancer Diagnosis and Survival in Pediatric Patients. Supplementary data

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Table S1. The list of cancer-predisposing genes used in the study.

Gene	Location	Name	OMIM#	Inheritance
A2ML1	12p13.31	Noonan syndrome		AD
ABCB11	2q31.1	Cholestasis, progressive familial intrahepatic, Hepatocellular carcinoma, Cholangiocarcinoma	601847	AR
ACD	16q22.1	Dyskeratosis congenital 6, 616553; Dyskeratosis congenital 7, 616553; Hoyeraal-Hreidarsson syndrome	609377, 609377	AD/AR
ALK	2p23.2-p23.1	Neuroblastoma, susceptibility to, 3	613014	AD
AMELX	Xp22.1-Xp22.3			
AMELY	Yp 11.2			
ANKRD26	10p12.1	Thrombocytopenia 2	188000	AD
APC	5q21-q22	FAMILIAL ADENOMATOUS POLYPOSIS 1; FAP1	175100	AD
ARID1A	1p36.11	Brain tumors, somatic		
ASXL1	20q11.21	Bohring-Opitz syndrome	605039	AD
ATM	11q22.3	Ataxia-telangiectasia	607585	AR
ATP11C	Xq27.1	Hemolytic anemia		AD
ATR	3q23	Seckel syndrome 1	210600	AR
ATRX	Xq21.1	Alpha-thalassemia/mental retardation syndrome	301040	XLD
AUTS2	7q11.22	autism, ALL- somatic		AD
AXIN2	17q24.1	oligodentia-colorectal cancer syndrome	608615	AD
BAP1	3p21.1	Tumor predisposition syndrome	614327	AD
BAP1	3p21.1	Tumor predisposition syndrome	614327	AD
BARD1	2q35	{Breast cancer, susceptibility to}	114480	AD, SMu
BCOR	Xp11.4	Solid tumors, somatic		
BLM	15q26.1	Bloom Syndrome	604610	AR
BMPR1A	10q23.2	Polyposis, juvenile intestinal	174900	AD
BRAF	7q34	Cardiofaciocutaneous syndrome	115150	AD
BRCA1	17q21.31	Fanconi anemia, complementation group S	617883	AR
BRCA2	13q13.1	Fanconi anemia, complementation group D1	605724	AR
BRIP1	17q23.2	Fanconi anemia, complementation group J	609054	AR
BUB1B	15q15.1	Wilms Tumor, Rhabdomyosarcoma, Myeloid hematological malignancy		AR
BUB3	10q26.13	Predisposition to adenocarcinoma		AD
CBL	11q23	Noonan syndrome		AD
CCND1	11q13.3	{von Hippel-Lindau syndrome, modifier of}	193300	AD
CDC73	1q25	Hyperparathyroidism-jaw tumor syndrome		AD
CDH1	16q22.1	Gastric cancer, hereditary diffuse, with or without cleft lip and/or palate	137215	AD
CDK4	12q14.1	Melanoma, cutaneous malignant, 3	609048	AD
CDKN1B	12p13.1	Multiple endocrine neoplasia, type IV	610755	AD
CDKN1C	11p15.5	Beckwith-Wiedemann syndrome	130650	AD
CDKN2A	9p21.3	Pancreatic cancer/melanoma syndrome	606719	AD
CEBPA	19q13.11	Familial MDS (Myelodysplastic syndromes); acute myeloid leukemia (AML)	601626	AD
CEP57	11q21	Mosaic variegated aneuploidy syndrome 2	614114	AR

CHEK2	22q12.1	{Breast cancer, susceptibility to}	114480	AD
CLCN5	Xp11.4	Ependymoma		AD
COL7A1	3p21.31	Epidermolysis bullosa, Squamous cell carcinmona (skin)		AD, AR
CREBBP	16p13.3	Rubinstein-Taybi syndrome 1	180849	AD
CTNNB1	3p22.1	Solid tumors		AD
CYLD	16q12.1	Brooke-Spiegler syndrome	605041	AD
DDB2	11p11.2	Xeroderma pigmentosum, group E, DDB-negative subtype	278740	AR
DDX3X	Xp11.4	Brain tumors, somatic		
DDX41	5q35.3	{Myeloproliferative/lymphoproliferative neoplasms, familial (multiple types), susceptibility to}	616871	AD
DICER1	14q32.13	Pleuropulmonary blastoma	601200	AD
DIS3L2	2q37.1	Perlman syndrome	267000	AR
DKC1	Xq28	Dyskeratosis congenita, X-linked	305000	XLR
DOCK8	9p24.3	HyperIgE syndrome, Squamous cell carcinoma, Lymphoma		AR
EBF1	5q33.3	ALL, somatic		
EGFR	7p11.2	{Nonsmall cell lung cancer, susceptibility to}	211980	AD, SMu
ELANE	19p13.3	Severe congenital neutropenia		AD
EP300	22q13.2	Rubinstein-Taybi syndrome 2	613684	AD
EPCAM	2p21	Colorectal cancer, hereditary nonpolyposis, type 8	613244	
ERCC2	19q13.32	Xeroderma pigmentosum, group D	278730	AR
ERCC3	2q14.3	Xeroderma pigmentosum, group B	610651	AR
ERCC4	16p13.12	Xeroderma pigmentosum, type F/Cockayne syndrome	278760	AR
ERCC5	13q33.1	Xeroderma pigmentosum, group G/Cockayne syndrome	278780	AR
ETV6	12p13.2	Leukemia, acute myeloid, somatic	601626	AD
EXT1	8q24.11	Exostoses, multiple, type 1	133700	AD
EXT2	11p11.2	Exostoses, multiple, type 2	133701	AD
EZH2	7q36.1	Weaver syndrome	277590	AD
FAH	15q25.1	Tyrosinemia, Hepatocellular carcinoma		AR
FANCA	16q24.3	Fanconi anemia, complementation group A	227650	AR
FANCB	Xp22.2	Fanconi anemia, complementation group B	300514	XLR
FANCC	9q22.32	Fanconi anemia, complementation group C	227645	AR
FANCD2	3p25.3	Fanconi anemia, complementation group D2	227646	AR
FANCE	6p21.31	Fanconi anemia, complementation group E	600901	AR
FANCF	11p14.3	Fanconi anemia, complementation group F	603467	
FANCG	9p13.3	Fanconi Anemia;Fanconi anemia, complementation group G, 614082		AR
FANCI	15q26.1	Fanconi anemia, complementation group I	609053	AR
FANCL	2p16.1	Fanconi Anemia;Fanconi anemia, complementation group L, 614083		AR
FANCM	14q21.2	Fanconi Anemia;Fanconi anemia, complementation group M, 614087		AR
FBXW7	4q31.3	Wilms tumor		AD
FH	1q43	Leiomyomatosis and renal cell cancer	150800	AD
FLCN	17p11.2	Birt-Hogg-Dube syndrome	135150	AD
GATA2	3q21.3	GATA2 deficiency (MonoMac syndrome)	137295	AD

GBA	1q21	Gauchers type 1, Myeloma, Lymphoma, Hepatocellular carcinoma		AR
GJB2	13q12.11	Keratosis-icthyosis-deafness syndrome (KID), Squamous cell carcinoma		AD
GPC3	Xq26.2	Simpson-Golabi-Behmel syndrome, type 1	312870	XLR
H3F3A	1q42.12	Glioblastoma		AD
HFE	6p22.2	Haemochromatosis, Hepatocellular carcinoma, Cholangiocarcinoma		AR
HMBS	11q23.3	Porphyria (AI), hepatocellular carcinoma		AD
HOXB13	17q21-q22	{Prostate cancer, hereditary, 9}	610997	
HRAS	11p15.5	Myelodysplastic syndrome (MDS), Adult		AD
IKZF1	7p12.2	IKAROS deficiency	603023	AD
ITK	5q33.3	Lymphoproliferative syndrome 1, Hodgkins lymphoma		
JAK1	1p31.3	JAK1 GOF	147795	AD GOF/AR
JAK2	9p24.1	Polycythemia vera, somatic	263300	AD
JAK3	19p13.11	JAK3 deficiency	600173	AR
KDM3B	5q31.2	Wilms tumor		AD
KDM6A	Xp11.3	Kabuki Syndrome 2 due to KDM6A deficiency	300128	XL (females may be affected)
KIF1Bϐ	1p36.22	Predisposition to neuroblastoma		AD
KIT	4q12	Mastocytosis, cutaneous	154800	AD
KMT2A	11q23.3	Wiedemann-Steiner syndrome		AD
KMT2D	12q13.12	Kabuki Syndrome 1 due to KMT2D deficiency	602113	AD
KRAS	12p12.1	RAS associated lymphoproliferative disease, 614470; RALD		Unknown
LIG4	13q33.3	DNA ligase IV deficiency	601837	AR
LZTR1	22q11.21	{Schwannomatosis-2, susceptibility to}	615670	AD
MAD2L2	1p36.22	Fanconi anemia, complementation group V	617243	AR
MAP2K1	15q22.31	Cardiofaciocutaneous syndrome 3	615279	AD
MAX	14q23.3	{Pheochromocytoma, susceptibility to}	171300	AD
MED12	Xq13.1	Brain tumors, somatic		
MEF2D	1q22	ALL, somatic		
MEN1	11q13.1	Multiple endocrine neoplasia 1	131100	AD
MET	7q31	Renal cell cancer (papillary carcinoma)		AD
MET	11p15.4	Delta-beta thalassemia	141749	AD
MLH1	3p21.3	MMR deficiency syndrome (biallelic mutations) Lynch syndrome / Hereditary Non-Polyposis Colon Cancer (monoallelic mutations)		AD, AR
MLH1	2p21-p16	Colorectal cancer, hereditary nonpolyposis, type 1	120435	AD
MLH3	14q24.3	Colorectal cancer, hereditary nonpolyposis, type 7	614385	AD
MLLT3				
MRE11	11q21	Ataxia-telangiectasia-like disorder 1 604391;AT-like disorder		AR
MSH2	2p21-p16	Colorectal cancer, hereditary nonpolyposis, type 1	120435	AD
MSH6	2p16.3	MSH6	600678	AR

MTAP	9p21.3	Diaphyseal medullary stenosis with malignant fibrous histiocytoma (DMS-MFH), malignant fibrous histiocytoma (sarcoma)		AD
MUTYH	1p34.1	Adenomas, multiple colorectal	608456	AR
NBN	8q21.3	Nijmegen breakage syndrome	602667	AR
NF1	17q11.2	Neurofibromatosis, type 1	162200	AD
NF2	22q12.2	Neurofibromatosis, type 2	101000	AD
NHP2	5q35.3	Dyskeratosis congenita, autosomal recessive 2	613987	AR
NOP10	15q14	Dyskeratosis congenita, autosomal recessive 1	224230	AR
NRAS	1p13.2	Myelodysplastic syndrome (MDS), Paediatric		AD
NSD1	5q35.3	Sotos syndrome 1	117550	AD
NTHL1	16p13.3	Colorectal cancer, multi-tumor predisposition syndrome		AR
NYNRIN	14q12	Wilms tumor, rhabdoid tumor		AR
PALB2	16p12.2	Fanconi anemia, complementation group N	610832	AD/AR
PAX5	9p13.2	{Leukemia, acute lymphoblastic, susceptibility to, 3}	615545	AD
PDGFRA	4q12	Gastrointestinal stromal tumor, somatic	606764	
PHF6	Xq26.2	Borjeson-Forssman-Lehmann syndrome	301900	XLR
PHOX2B	4p13	{Neuroblastoma, susceptibility to, 2}	613013	
PMS2	7p22.1	PMS2 Deficiency	600259	AR
POLD1	19q13.33	PPAP (polymerase proofreading associated polyposis), Colorectal cancer, Endometrial cancer		AD
POLE	12q24.33	PPAP (polymerase proofreading associated polyposis)		AR, AD
POLH	6p21.1	Xeroderma pigmentosa V, Squamous cell cancer (skin)		AR
PRKAR1A	17q24.2	Carney complex, type 1		
PRKCD	3p21.1	PRKCD deficiency	176977	AR
PRKDC	8q11.21	DNA PKcs deficiency	176977	AR
PTCH1	9q22.32	Basal cell nevus syndrome	109400	AD
PTCH2	1p34.1	Basal cell nevus syndrome	109400	AD
PTEN	10q23.31	PTEN Deficiency (LOF)	601728	AD
PTPN11	12q24.13	LEOPARD syndrome 1 151100;Metachondromatosis 156250;Noonan syndrome 1 163950;Myelodysplastic syndrome (MDS), Paediatric		AD
RAD50	5q31.1	Nijmegen breakage syndrome-like disorder		
RAD51A	15q15.1	Fanconi anemia, complementation group R	617244	AD
RAD51C	17q22	Fanconi anemia, complementation group O	613390	AR
RAD51D	17q12	{Breast-ovarian cancer, familial, susceptibility to, 4}	614291	
RAF1	3p25.2	Noonan syndrome 5	611553	AD
RAG1	11p12	RAG1 deficiency	179615	AR
RAG2	11p13	RAG2 deficiency	179616	AR
RB1	13q14.2	Retinoblastoma	180200	AD
RECQL4	8q24.3	Rothmund-Thomson syndrome	268400	AR
RET	14q13.3	{Thyroid cancer, nonmedullary, 1}	188550	AD
RFWD3	16q23.1	Fanconi anemia, complementation group W	617784	AR
RHBDF2	17q25.1	Tylosis with esophageal cancer	148500	AD
RIT1	1q22	Noonan syndrome 8	615355	AD

RMRP	9p13.3	Cartilage-hair hypoplasia syndrome, Non-Hodgkin lymphoma Squamous carcinoma (bcc) Leukemia		AR
RPL11	19q13.2	Diamond-Blackfan anemia 1	105650	AD
RPL26	17p13.1	Diamond-Blackfan anemia 11	614900	AD
RPL35A	3q29	Diamond-Blackfan anemia 5	612528	AD
RPL5	1p22.1	Diamond-Blackfan anemia 6	612561	AD
RPS10	6p21.31	Diamond-Blackfan anemia 9	613308	AD
RPS17	15q25.2	Diamond-Blackfan anemia 4	612527	AD
RPS19	19q13.2	Diamond-Blackfan anemia 1	105650	AD
RPS24	10q22.3	Diamond-blackfan anemia 3	610629	AD
RPS26	12q13.2	Diamond-Blackfan anemia 10	613309	AD
RPS7	2p25.3	Diamond-Blackfan anemia 8	612563	AD
RRAS	19q13.33	Noonan sydrome		AD
RUNX1	21q22.12	Platelet disorder, familial, with associated myeloid malignancy	601399	AD
SAMD9	7q21.2	SAMD9	617053	AD (GOF)
SAMD9L	7q21.2	SAMD9L	159550	AD (GOF)
SBDS	7q11.21	Shwachman-Diamond syndrome	260400	AR
SDHAF2	11q12.2	Paragangliomas 2	601650	AD
SDHB	1p36.13	Paragangliomas 4	115310	AD
SDHC	1q23.3	Paragangliomas 3	605373	AD
SDHD	11q23.1	Paragangliomas 1, with or without deafness	168000	AD
SERPINA1	14q32.13	Alpha1 antitrypsin deficiency, Hepatocellular carcinoma		AR
SETBP1				
SH2B3	10q21	{Leukemia, acute lymphocytic, susceptibility to, 1}	613065	
SH2D1A	Xq25	Lymphoproliferative disease, Lymphoma		XLR
SLC25A13	7q21.3	Citrullinaemia, Hepatocellular carcinoma		AR
SLX4	16p13.3	Fanconi anemia, complementation group P	613951	AR
SMAD4	18q21.2	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome	175050	AD
SMARCA4	19p13.2	{Rhabdoid tumor predisposition syndrome 2}	613325	AD
SMARCB1	22q11.23	{Rhabdoid tumor predisposition syndrome 1}	609322	AD
SMARCE1	17q21.2	{Meningioma, familial, susceptibility to}	607174	AD
SOS1	2p22.1	Noonan syndrome 4; Gingival fibromatosis 1		AD
SOS2	14q21.3	Noonan syndrome 9	616559	AD
SRY	Yp11.31	Gonadoblastoma		Y-LINKED
STAT3	17q21.1	Hyper-immunoglobulin E syndrome, Lymphoma		AD
STK11	19p13.3	Peutz-Jeghers syndrome	175200	AD
SUFU	10q24.32	Medulloblastoma, desmoplastic	155255	AD/AR
TERC	3q26.2	AD-DKC due to TERC deficiency	602322	AD
TERT	5p15.33	AD/AR-DKC due to TERT deficiency	187270	AD/ AR
TFRC	3q29	TFRC deficiency	616740	AR
TGFBR1	9q22.33	Multiple self-healing squamous epithelioma (MSSE) Ferguson-Smith syndrome		AD
TINF2	14q12	AD-DKC due to TINF2 deficiency	604319	AD

TJP2	9q21.11			
TMEM127	2q11.2	{Pheochromocytoma, susceptibility to}	171300	AD
TNFRSF6	10q23.31	Autoimmune lymphoproliferative syndrome, Lymphoma		AD
TP53	17p13.1	Li-Fraumeni syndrome	151623	AD
TRIM28	19q13.4	Wilms Tumor		AD
TRIM37	17q22	Mulibrey-nanism, Wilms tumor		AR
TSC1	9q34.13	Tuberous sclerosis-1	191100	AD
TSC2	12q15	{TSC2 angiomyolipomas, renal, modifier of}	613254	AD
TYK2	19p13.2	Tyk2 deficiency	176941	AR
UBE2T	1q32.1	Fanconi anemia, complementation group T	616435	AR
UROD	1p34.1	Porphyria (cutanea tarda), hepatocellular carcinoma		AR, AD
VHL	3p25.3	von Hippel-Lindau syndrome	193300	AD
WAS	Xp11.23	Wiskott-Aldrich syndrome	300392	XL
WRN	8p12	Werner syndrome	277700	AR
WT1	11p13	Denys-Drash syndrome	194080	AD
XPA	9q22.33	Xeroderma pigmentosum, group A	278700	AR
XPC	3p25.1	Xeroderma pigmentosum, group C	278720	AR
XRCC2	7q36.1	Fanconi anemia, complementation group U	617247	AR

Legend: AD- autosomal dominant, AR- autosomal recessive, GOF – gain of function, XL- X-chromosome linked.

Table S2 (provided as an Excel file). The summary of the studied families and includes the bioinformatic scoring of the variants presented in this study.

Figure S1. Genetic pedigrees displaying patients with a positive family history of cancer. Legend: BL – Burkitt lymphoma; DLBCL – Diffuse large B-cell lymphoma; FL – Follicular lymphoma; HL – Hodgkin lymphoma; N.D. – Not determined; T-LBL – T-lymphoblastic lymphoma.