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ORIGINAL ARTICLE

Germline Predisposition to Pediatric Lymphoid Malignancies: Genetic Tumor Syndromes Identified in a Single-Center Study

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SUMMARY

Background: **Germline predisposition (GP) is associated with a variety of hematolymphoid malignancies. While GP has been addressed mostly in myeloid malignancies, recent diagnostic systems have newly introduced GP in lymphoid malignancies; however, evidence and data are limited, particularly in pediatric patients. In this study, we investigated the frequency and characteristics of GP in pediatric lymphoid malignancies.**
Methods: **The study subjects were pediatric patients diagnosed with lymphoid malignancies by bone marrow (BM) study between April 2021 and August 2024 at Samsung Medical Center, Seoul, Korea. The clinical and laboratory data were retrospectively collected from medical records. Next generation sequencing (NGS) tests for somatic variants and GP variants were performed on DNA extracted from BM aspirate samples and cultured skin fibroblasts or peripheral blood in remission, respectively.**
Results: **During the study period, a total of 65 pediatric patients were diagnosed with lymphoid malignancies (age, 0 - 17 years, median 7 years; 38 male and 27 female patients). Fifty-three patients with B Lymphoblastic Leukemia (B-ALL, 85%), 3 with Burkitt lymphoma/leukemia (4.6%) and 9 with T Lymphoblastic Leukemia (T-ALL, 14%). Five patients (5/65; 7.7%) had germline tumor syndromes as GP: one each patient with *CBL* syndrome in B-ALL, *PTPN11*-associated Noonan syndrome in Burkitt lymphoma/leukemia, and Shwachman-Diamond syndrome in B-ALL, and two patients with Li-Fraumeni syndrome in B-ALL. No patient with T-ALL had GP.**
Conclusions: **We found that a significant proportion of pediatric lymphoid malignancies had GP. The data of our series, including the first report of Shwachman-Diamond syndrome in B-ALL, are believed to expand our knowledge on GP in pediatric lymphoid malignancies. Identification of GP by NGS panel tests is critical in pediatric lymphoid malignancies in order to tailor treatment plans and implement entity-specific surveillance recommendations.**
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Supplementary Data

Table S1. Genes included in somatic targeted next generation sequencing for lymphoid malignancies (n = 96).

ABL1	*CDKN1A*	*EZH2*	*IKZF1*	*NRAS*	*RPS19*
ABL2	*CDKN2A*	*FANCA*	*IL7R*	*NTRK1*	*RUNX1*
AKT1	*CDKN2B*	*FANCC*	*JAK1*	*NTRK3*	*SBDS*
ANKRD26	*CEBPA*	*FANCG*	*JAK2*	*PAX5*	*SETBP1*
ASXL1	*CRLF2*	*FBXW7*	*JAK3*	*PDGFRA*	*SF3B1*
ATM	*CSF1*	*FGFR1*	*KIT*	*PDGFRB*	*SH2B3*
BCOR	*CSF3R*	*FLT1*	*KMT2A*	*PHF6*	*SRSF2*
BCR	*DDX41*	*FLT3*	*KRAS*	*PIK3CA*	*STAG2*
BRAF	*DKC1*	*FLT4*	*MAP2K1*	*PPM1D*	*STAT3*
BRCA2	*DNMT3A*	*GATA1*	*MAP2K2*	*PRPF8*	*STK11*
CALR	*EBF1*	*GATA2*	*MET*	*PTEN*	*TET2*
CBFB	*ELANE*	*GATA3*	*MPL*	*PTPN11*	*TP53*
CBL	*EP300*	*HAX1*	*MYD88*	*RAF1*	*U2AF1*
CCND3	*EPOR*	*HRAS*	*NF1*	*RARA*	*WHSC1*
CDK4	*ERG*	*IDH1*	*NOTCH1*	*RB1*	*WT1*
CDK6	*ETV6*	*IDH2*	*NPM1*	*RET*	*ZRSR2*

Table S2. Genes included in targeted next-generation sequencing for germline predisposition to hematolymphoid malignancies (n = 93).

ANKRD26	*ETV6*	*FANCP*	*NBN*	*RPL5*	*TAZ*
AP3B1	*EZH2*	*FANCQ*	*NF1*	*RPS10*	*TERC*
ATM	*FANCA*	*G6PC3*	*NHP2*	*RPS17*	*TERT*
BLM	*FANCB*	*GATA1*	*NOP10*	*RPS19*	*TINF2*
BRCA1	*FANCC*	*GATA2*	*NRAS*	*RPS24*	*TP53*
CBL	*FANCD1*	*GFI1*	*PTPN11*	*RPS26*	*UBE2T*
CEBPA	*FANCD2*	*HAX1*	*RAB27A*	*RPS29*	*USB1*
CSF3R	*FANCE*	*JAK2*	*RAC2*	*RPS7*	*VPS13B*
CTC1	*FANCF*	*JAK3*	*RAD51*	*RTEL1*	*VPS45*
CXCR4	*FANCG*	*KANSL1*	*RAD51C*	*RUNX1*	*WAS*
DDX41	*FANCI*	*KRAS*	*RAF1*	*SBDS*	*WIPF1*
DIS3	*FANCJ*	*LAMTOR2*	*RFWD3*	*SH2B3*	*WRAP53*
DKC1	*FANCL*	*LIG4*	*RPL11*	*SLC37A4*	*XRCC2*
DNAJC21	*FANCM*	*LYST*	*RPL15*	*SLX4*	
EFL1	*FANCN*	*MAD2L2*	*RPL26*	*SOS1*	
ELANE	*FANCO*	*MPL*	*RPL35A*	*SRP72*	