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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Lymphoid Malignancy Risk with Rare Inherited Variants in Known Cancer Predisposition Genes

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Introduction

Lymphoid malignancy (LM) is a heterogenous neoplasm with respect to biology, aggressiveness, and treatment with over 100 subtypes, including Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM). Genome-wide association studies have identified common variants associated with risk of specific LM subtypes, but less is known about the contribution of rare inherited pathogenic variants (PV) in the genetic architecture of LM risk. Rare PV have been shown to contribute to the genetic architecture of solid tumor cancer risk, many of which have been found in genes that are important to the DNA-damage repair (DDR) pathway (e.g., *BRCA1, BRCA1, ATM*). Here, we investigated the prevalence of PV in cancer predisposition genes regularly included on multi-gene panel testing based on NCCN guidelines and correlated with risk of LM overall and by common subtypes.

Methods

In this association study, cases were newly diagnosed lymphomas (excluding chronic lymphocytic leukemia) from Mayo Clinic who were enrolled between 2002 and 2015 in the Lymphoma SPORE Molecular Epidemiology Resource (MER) and MM from Mayo Clinic enrolled primarily between 1998 and 2022 in a clinical registry. Controls were from the Mayo Clinic Biobank who were enrolled between 2009 and 2016, from which we excluded individuals with a history of hematologic malignancy. All participants provided a blood sample for whole exome sequencing, performed by Regeneron on an Illumina NovaSeq panel (mean coverage of 48X). Variants were called using GATK v4 and variant annotation was performed using BioR. All loss-of-function variants (i.e., nonsense, frameshift, and consensus splice sites) and pathogenic missense in 19 cancer predisposition genes with a minor allele frequency < 0.5% were included in the analyses. Logistic regression was used to estimate odds ratio (OR) and 95% confidence intervals (CI) for the association between mutation status by gene (burden test) and risk of LM overall, and by subtype that had more than 5 mutation carriers. All analyses were adjusted for age (at diagnosis for cases and at enrollment for controls) and sex.

Results

A total of 6990 cases and 42432 controls were included. Median age was 63 years for both cases and controls (case range 18-94 years, control range 18-99 years). Males accounted for 58.5% (n=4090) of the cases and 41.7% (n=17762) of the controls. MM accounted for 31% (n=2138) of the cases, followed by diffuse large B-cell lymphoma (DLBCL, n=1146) and follicular

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lymphoma (FL, n=1132) each accounting for 16% of cases. *CHEK2* (1.0%), *ATM* (0.4%), *BRCA2* (0.4%), and *BRCA1* (0.3%) had the most PV carriers in controls; these frequencies are in the range of published control populations. A total of 1816 (3.7%) individuals had a PV across the 19 genes, with 4.7% of cases and 3.5% of controls carrying any PV (OR=1.34, 95% CI: 1.18-1.51). *ATM* (OR=1.86, 95% CI: 1.36-2.49), *CHEK2* (OR=1.74, 95% CI: 1.42-2.13) and *TP53* (OR=9.07, 95% CI: 4.51-18.87) were all significantly associated with increased risk of LM overall (Figure 1). When investigating subtypes (Table 1), *CHEK2* (OR=1.93, 95% CI: 1.23-2.89) and *TP53*(OR=10.97, 95% CI: 3.06-31.43) were significantly associated with DLBCL. *ATM* (OR=2.22, 95% CI: 1.13-3.90) was significantly associated with FL. *ATM* (OR=1.97, 95% CI: 1.16-3.12), *CHEK2* (OR=1.75, 95% CI: 1.24-2.41) and *TP53* (OR=7.67, 95% CI: 2.43-20.72) were significantly associated with MM and *ATM* (OR=8.62, 95% CI: 4.47-15.12), *NBN* (OR=6.94, 95% CI: 2.41-15.76) and *TP53* (OR=38.30, 95% CI: 10.27-116.69) were significantly associated with mantle cell lymphoma (MCL). When subset to LM cases overall, there was no evidence of enrichment for young onset (age <60 years), male sex, or family history of hematologic malignancy between PV carriers and non-PV carriers. However, FL cases with an *ATM* PV tended to be less than 60 years (OR=3.21, P=0.09) compared to non- *ATM* PV carriers. Similarly, MM cases with a *TP53* PV tended to be less than 60 years of age (OR=7.39, P=0.07) compared non-carriers.

Discussion

In this large case-control study, PV in established cancer predisposition genes were associated with increased risk of LM overall, demonstrating that rare inherited variants may play an important etiologic role. This study also suggests that PV in cancer predisposition genes may be subtype specific. These results will help inform LM risk for individuals who undergo genetic testing of cancer predisposition genes.

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Figure 1. Forest plot of risk of lymphoid malignancy overall by cancer predisposition gene

Gene	Cases N (%)	Controls N (%)	OR (95% CI)	P-value
ATM	57 (0.8%)	186 (0.4%)	1.86 (1.36,2.49)	5.63e-05
BARD1	4 (0.1%)	46 (0.1%)	0.54 (0.16,1.34)	0.24
BRCA1	19 (0.3%)	113 (0.3%)	0.99 (0.59,1.58)	0.97
BRCA2	24 (0.3%)	175 (0.4%)	0.87 (0.55,1.33)	0.55
BRIP1	14 (0.2%)	110 (0.3%)	0.77 (0.42,1.3)	0.36
CDKN2A	0 (0.0%)	3 (0.0%)	NA	NA
CHEK2	125 (1.8%)	425 (1.0%)	1.74 (1.42,2.13)	9.06e-08
MLH1	1 (0.0%)	14 (0.0%)	NA	NA
MRE11	10 (0.1%)	58 (0.1%)	1.05 (0.5,1.98)	0.89
MSH2	1 (0.0%)	8 (0.0%)	NA	NA
MSH6	4 (0.1%)	54 (0.1%)	0.45 (0.14,1.1)	0.12
NBN	17 (0.2%)	84 (0.2%)	1.17 (0.67,1.92)	0.57
NF1	1 (0.0%)	18 (0.0%)	NA	NA
PALB2	7 (0.1%)	56 (0.1%)	0.75 (0.31,1.55)	0.48
PTEN	1 (0.0%)	1 (0.0%)	NA	NA
RAD50	15 (0.2%)	90 (0.2%)	1.04 (0.57,1.74)	0.9
RAD51C	9 (0.1%)	38 (0.1%)	1.48 (0.67,2.95)	0.3
RAD51D	2 (0.0%)	18 (0.0%)	NA	NA
TP53	20 (0.3%)	13 (0.0%)	9.07 (4.51,18.87)	1.07e-09

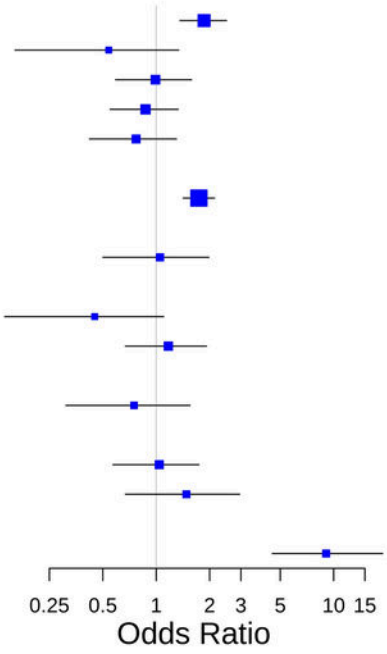

Table 1. Risk of lymphoid malignancy subtype by select cancer predisposition genes

Subtype	OR (95% CI)		
	ATM	*CHEK2*	*TP53*
Overall	1.86 (1.36-2.49)	1.74 (1.42-2.13)	9.07 (4.51-18.87)
DLBCL	--	1.93 (1.23-2.89)	10.97 (3.06-31.43)
FL	2.22 (1.13-3.90)	--	--
MM	1.97 (1.16-3.12)	1.75 (1.24-2.41)	7.67 (2.43-20.72)
MCL	8.62 (4.47-15.12)	--	38.30 (10.27-116.69)

Figure 1

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