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Original Article

Association Analysis of Polymorphisms in Inflammation-Related Genes with Non-Hodgkin Lymphoma Susceptibility

Nguyen Hoang Giang[1], Nguyen Trong Ha[2], Nguyen Thi Xuan[1,*]

[1]*Institute of Genome Research, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Hanoi, Vietnam*

[2]*103 Hospital, Vietnam Military Medical University, 261 Phung Hung, Ha Dong, Hanoi, Vietnam*

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Abstract: Non-Hodgkin's lymphoma (NHL) is a common hematological malignancy that develops in the lymphatic system. *A20*, *CYLD*, *IFN-γ*, *JAK2*, *PI3KCA*, and *TP53* are known as inflammation-related genes in autoimmune diseases and cancers. In the end, 126 patients with NHL and 109 healthy individuals with well-characterized clinical profiles were enrolled. Twelve variants in the above genes were determined by the Kompetitive allele-specific PCR (KASP) assay. As a result, among genotyped 12 SNPs, the AG genotype of the rs280500 in the *TYK2* gene showed significantly higher frequency in the patient group compared to healthy individuals (P=0.05). In addition, no significant differences in genotype frequencies of the other SNPs were found between the two groups. In conclusion, the rs280500 in the *TYK2* gene was the risk variant for NHL susceptibility and additionally contributed to understanding the genetic basis of NHL.

Keyword: A20, JAK2, KASP assay, TYK2.

1. Introduction

Non-Hodgkin's lymphoma (NHL) is a common hematological malignancy that develops in the lymphatic system and originates from B cell precursors. NHL is associated with its increased risk in patients with autoimmune and inflammatory diseases [1]. In NHL, activations of the nuclear factor kappa B (NF-κB) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathways are considered pathogenic hallmarks

* Corresponding author.
E-mail address: xuannt@igr.ac.vn

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by modulating expressions of inflammation and apoptosis-related genes [2], resulting in the uncontrolled proliferation of lymphoma cells. Metastasis and infiltration of lymphoma cells lead to progression and poor prognosis in NHL [3]. Among NHL, diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive clinical course and accounts for about 30-40% of all lymphomas worldwide [4]. The heterogeneity of DLBCL is reflected in disease pathogenesis, phenotypic properties, oncogenic survival pathways, and clinical responses to therapy [4]. According to Hans' criteria by gene expression profiling, DLBCLs were subclassified into germinal center B cell-like (GCB) and activated B cell-like (ABC) subtypes, with about 10–15% of cases being unclassifiable. The ABC DLBCL subtype is the most resistant DLBCL to current therapies and has poorer clinical outcomes and inferior survival than those with the GCB subtype [5]. Unlike DLBCL, peripheral T cell NHL (T-NHL) is an aggressive and uncommon malignancy derived from mature T cells and less frequent than B-cell NHL in all populations worldwide [2].

The immunogenetic investigations revealed that inflammation-related genes, including tumor necrosis factor α-induced protein 3 *(TNFAIP3, A20),* tumor suppressor cylindromatosis *(CYLD),* interferon *(IFN)γ*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha *(PI3KCA),* Janus kinase *(JAK)2*, tyrosine kinase *(TYK)2* and tumor protein *(TP)53* are associated with the survival, proliferation, and progression of tumor cells [6-16]. In our recent study, inactivations of *A20* and *CYLD* lead to the pathogenesis of lymphomas [17-19]. Moreover, several polymorphisms are indicated to be associated with the development of blood cancers. *A20* rs661561 is the risk variant of T-cell acute lymphocytic leukemia [15]. *JAK2* rs10974947 is associated with polycythemia vera [13]. The *IFNγ* rs2069718 is linked to the survival of NHL patients [9]. The *TP53* rs1042522 is associated with the risk of NHL in China [10], but does not influence the survival of NHL patients in European Caucasians [6].

In addition, the remaining SNPs are related to the development of other cancers. The *PI3KCA* rs6443624, *JAK2* rs7849191, and *TYK2* rs280500 SNPs are associated with the risk of breast cancer [12, 14]. In contrast, the *PI3KCA* rs6443624 decreases the risk of bladder cancer in the Iranian population [7]. The *A20* rs77191406 is the risk variant of rheumatoid arthritis and systemic lupus erythematosus patients [16], which are important risks of secondary cancers [1]. The *CYLD* rs12324931 is found to link to inflammatory bowel disease [8].

In this study, genotypes of 12 variants located in nine genes, including *A20* (rs661561, rs77191406, and rs2230926); *CYLD* (rs12324931 and rs773685620); *IFN-γ* (rs2069718); *JAK2* (rs7849191, rs10974947 and rs2274471); *PI3KCA* (rs6443624); *TYK2* (rs280500) and *TP53* (rs1042522) all were examined by the Kompetitive allele-specific PCR (KASP) assay in 126 patients with NHL and 109 healthy individuals to evaluate the association of these polymorphisms with the risks of NHL.

2. Materials and Methods

2.1. Patients and Control Subjects

Fresh peripheral blood samples were collected from 126 untreated patients diagnosed with NHL, at the National Hospital of Haematology and Blood Transfusion and the 103 Military Hospital, Hanoi, Vietnam. The control group comprised 109 healthy subjects. No individuals in the control population took any medication or suffered from any known acute or chronic disease. All patients and volunteers gave written consent to participate in the study. Person care and experimental procedures were performed according to the Vietnamese law for the welfare of humans and were approved by the Ethical Committee of Institute of Genome Research, Vietnam Academy of Science and

Technology under number 03-2021/NCHG-HĐĐĐ.

2.2. SNP Genotyping

Total DNA was extracted from whole blood samples by using Gene JET Whole Blood Genomic DNA Purification Kit (Thermo Fisher Scientific, USA) following the manufacturer's instructions. DNA samples were normalized to 50 ng/µl per sample for SNP genotyping, which was identified by the "Amplifluor and Kompetitive allele-specific PCR" (KASP, LGC Biosearch Technologies) method. Each reaction of the KASP assay contained 2.5 µL Mastermix (LGC Genomics, UK), 0.07 µL KASP assay mix and 2.5 µL genomic DNA. The following cycling conditions were used for the reaction: 15 min at 94 °C; 10 touchdown cycles of 20 s at 94 °C, 60 s 57 °C (dropping 0.6 °C per cycle); and amplification of 35 cycles of 20 s at 94 °C, 60s at 57 °C). In the end, raw data of reactions were analyzed by cluster plot analysis using Kraken software (LGC Genomics, UK) for identified genotypes.

Samples were loaded on The Fluidigm 96.96 Dynamic ArrayTM IFC and genotypes were identified by Data Collection Software on the BioMark system (Fluidigm Corp.). The genotyping mix was prepared by combining the KASP Master mix containing two allele-specific primers and a common reverse primer. The genotype of each variant was identified by calculating FAM and HEX fluorescence signals. The KASP primers were ordered directly from the LGC Biosearch Technologies. For quality control, we repeatedly genotyped 10% of the total samples by Sanger sequencing. The primer information is listed in Table 1. The concordance rate of these repeated samples reached 100%, which suggested that the genotyping results were reliable.

2.3. Statistics

The genotype frequencies among NHL patients and the control group were calculated by using the Crosstabs with chi-square ($\chi 2$) analysis. $P<0.05$ was considered statistically significant.

Table 1. Primer sequences used for Sanger sequencing

Gene	SNP	Forward (5'→3')	Reverse (5'→3')	Amplicon size (bp)
A20	rs661561	GCTCCCCTTAGAACTGGAATG	AACCAAGCAAGTCACAGAACAA	626
A20	rs77191406	CCAGGTGGCCTTAGAAAGCA	GGTCCTCAGGAAAGGAACCG	393
A20	rs2230926	AGCTAGAACCAAGGTCCCCT	GGGGGAAAAACCTACCCGAG	461
CYLD	rs12324931	GACGTATATGAGTATAAGGGTGGCA	GGATCTCACAGGTTATCCAGCA	233
CYLD	rs773685620	TCAAGGTTTCACTGACGGGG	CCCCTGTTCTATTTCAATGCTCC	548
IFN-γ	rs2069718	ACACCAAATCCAAAACGAGTGAA	CTGTAATCCCCCAGCCATCC	354
JAK2	rs10974947	ACGGTCAACTGCATGAAACA	GTAGAGGAGCCTCTGTGTAACC	686
JAK2	rs2274471	GTAGCCGGTGGGTGTTATCT	TCGCCTTTACTGCAGCGATA	436
JAK2	rs7849191	AGTACCAGCTGATCATGGCTTAAT	TGTCCTGGGATTCACACAGTA	359
PI3KCA	rs6443624	TGTCAGTTCTCCCTGTTCTCA	AGACAAGAGGCCCTGAAAGC	484
TYK2	rs280500	ACAGGCAGATGTGGTCAAACA	TCCTAGGCTTTGGGGAGTCA	352
TP53	rs1042522	TCCCAAGCAATGGATGATTT	GCCAGGCATTGAAGTCTCAT	314

3. Results and Discussion

Among 12 SNPs genotyped, the 4 SNPs, including *A20* rs2230926, *CYLD* rs12324931, *CYLD* rs773685620, and *JAK2* rs7849191 were not found in NHL patients and healthy controls in this study. Differently, the *JAK2* rs7849191 with the MAF of 0.308 in the Vietnamese population is reported in the NCBI database. The discrepancy may be due to the limited sample size or different regions of the samples.

The genotype distributions of the 8 remaining SNPs, except for the TYK2 rs280500 in the control group were by Hardy-Weinberg equilibrium (HWE) ($p > 0.05$) (Table 2). Besides, the minor allele frequencies (MAFs) of all 8 SNPs did not show significant differences between the two groups (Table 2).

Table 2. General information on the studied single nucleotide polymorphisms (SNPs)

Gene/SNP	Type of Variant	Allele	MAF		HWE (*p*-Value)		
			Controls	Patients	Controls	Patients	All population
A20/ rs661561	Intron	A>C	0.83486239	0.869048	0.7751	0.9921	0.8882
A20/ rs77191406	3′ UTR	C>T	0.02293578	0.039683	0.9704	0.8980	0.8801
IFN-γ/rs2069718	Intron	A>G	0.18807339	0.186508	0.5080	0.7191	0.3816
JAK2/rs10974947	Intron	G>A	0.16055046	0.202381	0.4374	0.4912	0.2407
JAK2/rs2274471	Intron	A>G	0.14678899	0.142857	0.9609	0.1738	0.3061
PI3KCA/rs6443624	Intron	C>A	0.17889908	0.134921	0.6153	0.2160	0.9462
TYK2/rs280500	5′ UTR	A>G	0.03211009	0.06746	0.0237	0.7191	0.8729
TP53/rs1042522	Missense	G>C	0.5	0.440476	0.3563	0.9468	0.7554

MAF: Minor allele frequency; HWE: Hardy-Weinberg equilibrium was checked by Chi-squared test.

Importantly, the AG genotype of the rs280500 in the *TYK2* gene was significantly more frequent in the patient group (13.5%) compared to healthy individuals (4.6%, Table 3 and Figure 1). In addition, no significant differences in genotype frequencies of the 7 other SNPs were found between the two groups (Table 3 and Figure 1). Similar to a study in European Caucasians [6], the *TP53* rs1042522 is not associated with the risk of NHL in this population, whereas it is a high risk of NHL in China [10].

The *TYK2* rs280500 was reported for the first time in this study to be the risk variant for NHL. Differently, carriers of this variant are at high risk of breast cancer [12] and the presence of this SNP was not found in 155 patients with acute myeloid leukemia and 110 patients with lymphocytic leukemia in our study, suggesting that the rs280500 SNP could be associated with significant risk of NHL, but not leukemia.

Table 3. Genotype frequencies of SNPs in NHL patients and control individuals

SNP	Gene	Test model	Controls (n=109)	NHL Patients (n=126)	OR	95% CI	*p*-Value
rs661561	*A20*	AA	4 (3.67%)	2 (1.58%)	1		
		AC	28 (25.69%)	29 (23.02%)	2.0714	0.3510 - 12.2229	0.695(1)
		CC	77 (70.64%)	95 (75.4%)	2.4675	0.4402 - 13.8326	0.439(1)
rs77191406	*A20*	CC	104 (95.41%)	116 (92.06%)	1		
		CT	5 (4.59%)	10 (7.94%)	1.7931	0.5935 - 5.4175	0.568(1)
rs2069718	*IFN-γ*	AA	70 (64.22%)	82 (65.08%)	1		

		AG	37 (33.95%)	41 (32.54%)	0.9459	0.5474 - 1.6347	1[(2)]
		GG	2 (1.83%)	3 (2.38%)	1.2805	0.2080 - 7.8827	1[(1)]
rs10974947	*JAK2*	GG	75 (68.81%)	78 (61.91%)	1		
		GA	33 (30.29%)	45 (35.71%)	1.3112	0.7567 - 2.2721	0.368[(2)]
		AA	1 (0.9%)	3 (2.38%)	2.8846	0.2935 - 28.3519	0.606[(1)]
rs2274471	*JAK2*	AA	79 (72.48%)	90 (71.43%)	1		
		AG	28 (25.69%)	36 (28.57%)	1.1286	0.6325 - 2.0136	0.752[(2)]
		GG	2 (1.83%)	0 (0%)	0.1757	0.0083 - 3.7147	0.497[(1)]
rs6443624	*PI3KCA*	CC	75 (68.8%)	92 (73.02%)	1		
		CA	29 (26.6%)	34 (26.98%)	0.9558	0.5342 - 1.7100	0.874[(2)]
		AA	5 (4.6%)	0 (0%)	0.0742	0.0040 - 1.3635	0.058[(1)]
rs280500	*TYK2*	AA	103 (94.5%)	109 (86.5%)	1		
		AG	5 (4.6%)	17 (13.5%)	3.2128	1.1437 - 9.0253	0.05[(1)]
		GG	1 (0.9%)	0 (0%)	0.3151	0.0127 - 7.8222	1[(1)]
rs1042522	*TP53*	GG	31 (28.44%)	37 (28.24%)	1		
		GC	47 (43.12%)	67 (51.15%)	1.1944	0.6518 - 2.1886	0.735[(2)]
		CC	31 (28.44%)	27 (20.61%)	0.7297	0.3614 - 1.4736	0.557[(1)]

Position refers to the GRCh38.p10 assembly; *p*-values were calculated by either Fisher's exact test [(1)] or Chi-squared test [(2)]; $p < 0.05$ (in bold) indicates statistical significance from healthy donors; OR: Odds ratio; 95% CI: 95% confidence interval of odds ratio.

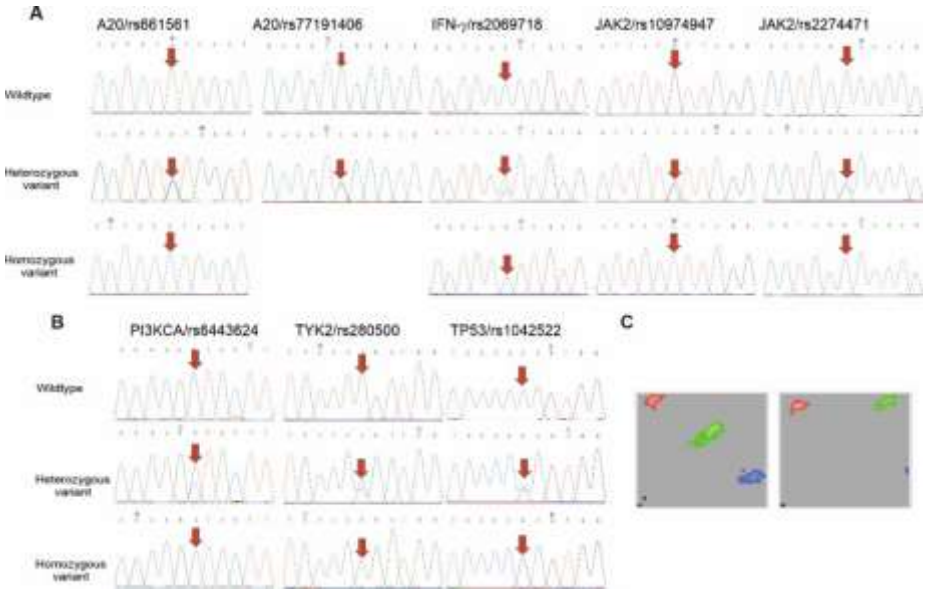

Figure 1. Polymorphisms of immune-related genes in NHL patients and controls.

Unlike the effects of the SNPs in *A20, IFN-γ, JAK2, PI3KCA*, and *TP53* genes on the development of NHL, Zhu et al., indicated that carriers of the CC genotype of the *A20* rs661561 variant are at risk of T-cell acute lymphoblastic leukemia patients [15]. *A20* rs77191406 is a prognostic marker for rapid malignancy progression and poor survival of rheumatoid arthritis and systemic lupus erythematosus patients [16]. The *IFNγ* rs2069718 is associated with NHL patients' survival [9] and the risk of developing severe COVID-19 disease, which is caused by abnormally high levels of cytokines such as IFN-γ, IL-6, and TNF-α [20].

A-B. Partial sequence chromatograms of wildtype (1st panels) and variant (2nd and 3rd panels) genotypes of the SNPs rs661561 and rs77191406 in *A20* gene, rs2069718 in *IFN-γ* gene, rs10974947 and rs2274471 in *JAK2* gene (A) and the SNPs rs6443624 in *PI3KCA* gene, rs280500 in *TYK2* gene and rs1042522 in *TP53* gene (B) are shown. Arrows indicate the location of the base changes. **C.** Representative results of two original scatter plots by KASP genotyping assay. The homozygous wild-type genotypes presented by FAM-only signals (orange dots) were shown in the upper left area, the heterozygous genotypes presented by FAM and HEX signals (green dots) were shown in the middle area, and the homozygous genotypes presented by HEX-only signals (blue dots) were shown in the lower right area. No-template control groups (NTC) were shown in the lower left area (grey dots).

In addition, carriers of the *JAK2* rs10974947 are linked to polycythemia vera susceptibility [13]. The *PI3KCA* rs6443624 SNP is at high risk of breast cancer [14] and decreased risk of bladder cancer [7].

Based on the results attained in this finding, we indicated that the rs280500 in the *TYK2* gene was the risk variant for NHL susceptibility and additionally contributed to understanding the genetic basis of NHL.

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