

Brief report

Human leukocyte antigen class I and II alleles in non-Hodgkin lymphoma etiology

Sophia S. Wang,¹ Amr M. Abdou,² Lindsay M. Morton,³ Rasmi Thomas,² James R. Cerhan,⁴ Xiaojiang Gao,² Wendy Cozen,⁵ Nathaniel Rothman,³ Scott Davis,⁶ Richard K. Severson,⁷ Leslie Bernstein,¹ Patricia Hartge,³ and Mary Carrington^{2,8}

¹Division of Cancer Etiology, Department of Population Sciences, City of Hope, Duarte, CA; ²Cancer and Inflammation Program, Laboratory of Experimental Immunology, SAIC-Frederick Inc, NCI-Frederick, MD; ³Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD; ⁴College of Medicine, Mayo Clinic, Rochester, MN; ⁵Norris Comprehensive Cancer Center, University of Southern California, Los Angeles; ⁶Fred Hutchinson Cancer Research Center and University of Washington, Seattle; ⁷Department of Family Medicine and Public Health Sciences, Wayne State University and Karmanos Cancer Institute, Detroit, MI; and ⁸Ragon Institute of the Massachusetts General Hospital, Massachusetts Institute of Technology and Harvard University, Boston

Genome-wide association and candidate gene studies implicate different genetic variants within the 6p21 chromosomal region with different non-Hodgkin lymphoma (NHL) subtypes. Complementing these efforts, we conducted human leukocyte antigen (HLA) class I and class II genotyping among 610 NHL cases and 555 controls of non-Hispanic white de-

scendent from a US multicenter study. Allele-disease associations were assessed by logistic regression for NHL and its subtypes. Statistically significant associations between HLA and NHL subtypes include *HLA-DRB1*0101* for follicular lymphoma (odds ratio [OR] = 2.14, $P < .001$), *HLA-DRB1*0401* for diffuse large B-cell lymphoma (DLBCL; OR = 0.45, $P = .006$),

and *HLA-DRB1*13* and follicular lymphoma (OR = 0.48, $P = .008$). We further observed significant heterozygote advantage for HLA class I alleles and NHL, and particularly DLBCL (P trend = .01 for elevated risk with increasing number of homozygous alleles). Our results support a role for HLA in the etiology of NHL and its subtypes. (*Blood*. 2010;115(23):4820-4823)

Introduction

There is growing evidence indicating that genetic variation in the 6p21 chromosomal region is important in non-Hodgkin lymphoma (NHL) etiology. To date, implicated single nucleotide polymorphisms (SNPs) appear to vary by NHL subtype. A genome-wide association study reported rs6457327 on 6p21.33 (located near psoriasis susceptibility region 1 [*PSORS1*]) to be associated with susceptibility for follicular lymphoma.¹ A consortium effort reported that a tumor necrosis factor (*TNF*) promoter polymorphism (*TNF* G-308A) on chromosome 6p21.3 was associated with increased risk of diffuse large B-cell lymphoma (DLBCL) and marginal zone lymphoma.^{2,3}

The 6p21 chromosomal region houses the major histocompatibility complex which plays a critical role in host immune responses to viral and other pathogens. The human leukocyte antigen (*HLA*) genes are the most polymorphic human genes, presumably because they encode for variations that influence the specificity of the antigenic epitopes bound and presented to T cells. In general, *HLA* class I molecules (*HLA-A*, *-B*, and *-C*) present foreign antigens to CD8⁺ cytotoxic T lymphocytes (CTL), and *HLA* class II molecules (*HLA-DR*, *-DQ*, and *-DP*) present antigenic peptides to CD4⁺ T-helper cells.

Here, we present data from 610 NHL cases and 555 controls of non-Hispanic white descent who participated in a US population-based case-control study where *HLA* class I (A, B, C) and class II *DRB1* alleles were genotyped and evaluated for their role in NHL etiology.

Methods

The multicenter National Cancer Institute–Surveillance, Epidemiology and End Results (NCI-SEER) NHL case-control study population comprised 1321 NHL cases identified in 4 SEER registries (Iowa; Detroit, MI; Los Angeles, CA; Seattle, WA) aged 20 to 74 years and newly diagnosed between July 1998 and June 2000.^{4,5} Cases had no evidence of HIV infection. A total of 1057 population controls were identified by random digit dialing (< 65 years) and from Medicare eligibility files (> 65 years). Written informed consent was obtained from each participant before interview in accordance with the Declaration of Helsinki, and institutional review board approval was obtained from each participating study center and from the National Institutes of Health (NIH). All study participants were asked to provide a venous blood or mouthwash buccal cell sample. The present analysis was conducted on study participants who provided blood (773 cases, 668 controls). Data from the 610 cases and 555 controls who self-reported to be non-Hispanic white and from whom sufficient DNA were available for *HLA* allelotyping are included in the present manuscript (population characteristics are presented in supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

Pathology information was derived from abstracted reports by the local diagnosing pathologist. All cases were histologically confirmed and coded according to the International Classification of Diseases for Oncology⁶ (ICD, 2nd Edition) and updated to the World Health Organization (WHO)/ICD-O-3. We evaluated risk for NHL and the histologic subtypes DLBCL, follicular lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

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Table 1. HLA class I and II allele-disease associations with NHL overall and NHL subtypes (adjusted for age, sex, study site)

Exposure	Status	Control, n (%)	NHL, n (%)	DLBCL, n (%)	OR (95% CI)	P	Follicular, n (%)	OR (95% CI)	P	CLL/SLL, n (%)	OR (95% CI)	P
HLA class I												
<i>HLA-A*2601</i>	Absent	512 (96)	531 (92)	150 (91)	1.00 (ref)		151 (93)	1.00 (ref)		73 (89)	1.00 (ref)	
	Present	23 (4)	46 (8)	15 (9)	1.88 (1.12-3.16)	.02	11 (7)	1.61 (0.76-3.42)	.2	9 (11)	2.69 (1.18-6.11)	.02
<i>HLA-A*2302</i>	Absent	493 (92)	546 (95)	159 (96)	1.00 (ref)		151 (93)	1.00 (ref)		78 (95)	1.00 (ref)	
	Present	42 (8)	31 (5)	6 (4)	0.67 (0.41-1.09)	.1	11 (7)	0.88 (0.44-1.77)	.7	4 (5)	*	*
<i>HLA-B*3503</i>	Absent	512 (95)	567 (98)	161 (98)	1.00 (ref)		162 (99)	1.00 (ref)		78 (95)	1.00 (ref)	
	Present	25 (5)	13 (2)	4 (2)	0.44 (0.22-0.87)	.02	1 (1)	*	*	4 (5)	*	*
<i>HLA-B*5101</i>	Absent	496 (92)	520 (90)	143 (87)	1.00 (ref)		146 (90)	1.00 (ref)		76 (93)	1.00 (ref)	
	Present	41 (8)	60 (10)	22 (13)	1.45 (0.95-2.21)	.08	17 (10)	1.34 (0.73-2.47)	.3	6 (7)	0.92 (0.37-2.25)	.8
<i>HLA-Cw*0304</i>	Absent	433 (81)	490 (84)	145 (87)	1.00 (ref)		141 (87)	1.00 (ref)		67 (83)	1.00 (ref)	
	Present	102 (19)	91 (16)	21 (13)	0.8 (0.58-1.1)	.2	22 (14)	0.69 (0.41-1.14)	.1	14 (17)	0.86 (0.46-1.61)	.6
<i>HLA-Cw*0701</i>	Absent	386 (72)	387 (67)	107 (64)	1.00 (ref)		111 (68)	1.00 (ref)		57 (70)	1.00 (ref)	
	Present	149 (28)	194 (33)	59 (36)	1.3 (1.01-1.69)	.04	52 (32)	1.19 (0.81-1.75)	.4	24 (30)	1.08 (0.64-1.81)	.8
<i>HLA-Cw*1502</i>	Absent	520 (97)	554 (95)	155 (93)	1.00 (ref)		157 (96)	1.00 (ref)		78 (96)	1.00 (ref)	
	Present	15 (3)	27 (5)	11 (7)	1.76 (0.92-3.37)	.09	6 (4)	1.23 (0.46-3.33)	.7	3 (4)	*	*
HLA class II												
<i>HLA-DRB1*0101</i>	Absent	432 (83)	437 (79)	122 (80)	1.00 (ref)		105 (70)	1.00 (ref)		68 (83)	1.00 (ref)	
	Present	88 (17)	113 (21)	31 (20)	1.26 (0.92-1.72)	.1	46 (30)	2.14 (1.4-3.26)	< .001	14 (17)	0.95 (0.51-1.78)	.9
<i>HLA-DRB1*0401</i>	Absent	414 (80)	460 (84)	137 (90)	1.00 (ref)		118 (78)	1.00 (ref)		67 (82)	1.00 (ref)	
	Present	106 (20)	90 (16)	16 (10)	0.78 (0.57-1.07)	.1	33 (22)	1.12 (0.72-1.76)	.6	15 (18)	0.93 (0.5-1.7)	.8
<i>HLA-DRB1*0403</i>	Absent	515 (99)	535 (97)	150 (98)	1.00 (ref)		146 (97)	1.00 (ref)		81 (99)	1.00 (ref)	
	Present	5 (1)	15 (3)	3 (2)	2.71 (0.97-7.58)	.06	5 (3)	3.45 (0.95-12.47)	.06	1 (1)	*	*
<i>HLA-DRB1*13</i>	Absent	403 (77)	456 (83)	127 (83)	1.00 (ref)		133 (88)	1.00 (ref)		70 (85)	1.00 (ref)	
	Present	117 (23)	94 (17)	26 (17)	0.71 (0.52-0.97)	.03	18 (12)	0.48 (0.28-0.82)	.008	12 (15)	0.59 (0.31-1.13)	.1
<i>HLA-DRB1*1301</i>	Absent	463 (89)	504 (92)	142 (93)	1.00 (ref)		145 (96)	1.00 (ref)		77 (94)	1.00 (ref)	
	Present	57 (11)	46 (8)	11 (7)	0.74 (0.49-1.11)	.1	6 (4)	0.35 (0.15-0.83)	.02	5 (6)	0.54 (0.21-1.39)	.2
<i>HLA-DRB1*1302</i>	Absent	469 (90)	507 (92)	139 (91)	1.00 (ref)		142 (94)	1.00 (ref)		76 (93)	1.00 (ref)	
	Present	51 (10)	43 (8)	14 (9)	0.81 (0.52-1.24)	.3	9 (6)	0.61 (0.29-1.28)	.2	6 (7)	0.72 (0.3-1.76)	.5
<i>HLA-DRB1*1303</i>	Absent	507 (98)	542 (99)	152 (99)	1.00 (ref)		148 (98)	1.00 (ref)		80 (98)	1.00 (ref)	
	Present	13 (3)	8 (1)	1 (1)	0.54 (0.22-1.32)	.2	3 (2)	*	*	2 (2)	*	*

HLA indicates human leukocyte antigen; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; OR, odds ratio; CI, confidence intervals; and ref, referent.

*ORs not calculated for cells with less than 5 people.

DNA were extracted using Puregene Autopure DNA extraction kits (Gentra Systems). Four-digit *HLA* class I (A, B, C) and class II genotyping (*DRB1*) was conducted at NCI-Frederick (Frederick, MD) according to sequence-specific oligonucleotide probe (SSOP) hybridization and sequence-based typing protocols developed by the 13th International Histocompatibility Workshop.⁷ Agreement for quality control duplicates (n = 100) was more than 99%.

We first calculated *HLA-A*, *-B*, *-C*, and *-DRB1* allele frequencies and evaluated the statistical differences between cases and controls using the χ^2 test for significance or by the Fisher exact test when a cell contained fewer than 5 subjects. Only for alleles found to be significantly different between case and control groups were odds ratios (ORs) and 95% confidence intervals (CIs) subsequently calculated to determine the magnitude and precision of associations. To test whether there was heterozygote advantage, we determined whether an increase in disease risk was observed for those who were homozygous at *HLA* loci. We assessed zygosity by calculating ORs and 95% CIs for individual *HLA* loci (eg, *HLA-A*, *-B*, *-C*, or *-DRB1*) and for combined zygosity across the 3 class I *HLA* loci. All risk estimates are adjusted for the study design variables: sex, age (< 45, 45-64, 65+ years), education (< 12, 12-15, > 15 years), and study center (Detroit, Iowa, Los Angeles, Seattle). All logistic regression models were unconditional and conducted using SAS 9.1.3 (SAS Institute). All tests of statistical significance were 2-sided.

Results and discussion

HLA class II alleles

*HLA-DRB1*13* alleles were inversely associated with overall NHL risk (OR = 0.71, 95% CI = 0.52-0.97) and most notably for follicular lymphoma (OR = 0.48, 95% CI = 0.28-0.82; Table 1). Of the *HLA-DRB1*13* alleles, the association was most pronounced for *HLA-DRB1*1301* and follicular lymphoma (OR = 0.35, 95% CI = 0.15-0.83). *HLA-DRB1*0401* was significantly associated with DLBCL (OR = 0.45, 95% CI = 0.26-0.79), while *HLA-DRB1*0101* was significantly associated with follicular lymphoma (OR = 2.14, 95% CI = 1.40-3.26). No significant associations were observed for any *HLA-DRB1* alleles and CLL/SLL.

HLA class I alleles

Presence of *HLA-A*2601* and *HLA-Cw*0701* alleles was associated with increased NHL risk and *HLA-B*3503* was associated with decreased NHL risk. The *HLA* class I alleles were largely consistent in the direction of association by subtype. Similarly, although statistically significant associations were observed and most pronounced for *HLA-B*5101* and *HLA-Cw*1502* with DL-

BCL, the direction of the associations was also consistent for follicular lymphoma and for NHL overall though not statistically significant.

Allele frequencies for *HLA* class I *A*, *B*, *C* and class II *DRB1* alleles are shown in supplemental Table 2.

Zygosity (heterozygote advantage)

No significant increases in risk for NHL, DLBCL, or follicular lymphoma were observed for homozygosity at individual *HLA* loci (Table 2). However, increasing risks for NHL and DLBCL with increasing numbers of homozygous class I loci were observed. Compared with persons heterozygous in 2 or more *HLA* class I loci, persons homozygous at 2 *HLA* class I loci had a 1.81-fold risk (95% CI = 0.78-4.17) for DLBCL, and persons homozygous at all 3 *HLA* class I loci had a 3.66-fold risk (95% CI = 1.15-11.7) for DLBCL (*P* trend = .01). Results were more pronounced (*P* trend = .007) in analyses not restricted to non-Hispanic white (supplemental Table 3).

Overall, associations observed for *HLA* class II alleles were more striking for NHL subtypes than for NHL overall. Most notable were the increased risks observed with *HLA-DRB1*0101* and follicular lymphoma and *HLA-DRB1*0401* with DLBCL, and the risk decrease observed between *HLA-DRB1*13* alleles and follicular lymphoma. Our results add further evidence of a role for *HLA* in NHL risk and suggest that these associations may be specific to certain NHL subtypes.

Our results are consistent with our knowledge of NHL; *HLA* class II molecules present antigens to CD4⁺ T cells and are fundamental to immune responses to external pathogens and autoimmunity, 2 well-recognized risk factors for NHL.⁸ Specifically, the implicated alleles have been previously linked with autoimmune conditions, many of which are also established or hypothesized risk factors for NHL, including systemic lupus erythematosus (*HLA-DRB1*0301*, *HLA-B*0801*), Sjogren syndrome (*HLA-DRB1*0301*, *HLA-B*0801*), celiac disease (*HLA-DRB1*0301*), rheumatoid arthritis (*HLA-DRB1*0101* and **0401*), and type 1 diabetes (*HLA-DRB1*0401* and **0301*).⁹ Previous risk reductions have also been reported for several other diseases in association with *HLA-DRB1*13* alleles, including autoimmune conditions (eg, rheumatoid arthritis¹⁰ and multiple sclerosis¹¹) and infectious diseases (eg, hepatitis B infection,¹²⁻¹⁴ hepatitis C infection,^{15,16} and human papillomavirus¹⁷). Ours is the first such report for NHL.

Table 2. Effect of homozygosity at each of the three HLA class I loci -A, -B, and -C and level of homozygosity on the risk for NHL, DLBCL, and follicular lymphoma, compared to persons not homozygous for specified loci (adjusted for age, sex, and study center)

		Controls		NHL		DLBCL		Follicular	
		n	(%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
<i>HLA-A</i>	No	452	(84)	484 (84)	1.00 (referent)	137 (83)	1.00 (referent)	142 (88)	1.00 (referent)
	Yes	83	(16)	93 (16)	1.04 (0.75-1.43)	28 (17)	1.11 (0.69-1.78)	20 (12)	0.74 (0.44-1.26)
<i>HLA-B</i>	No	503	(94)	537 (93)	1.00 (referent)	149 (90)	1.00 (referent)	151 (93)	1.00 (referent)
	Yes	34	(6)	43 (7)	1.18 (0.74-1.89)	16 (10)	1.67 (0.89-3.13)	12 (7)	1.22 (0.61-2.45)
<i>HLA-C</i>	No	487	(91)	516 (89)	1.00 (referent)	146 (88)	1.00 (referent)	146 (90)	1.00 (referent)
	Yes	48	(9)	65 (11)	1.23 (0.83-1.83)	20 (12)	1.40 (0.80-2.45)	17 (10)	1.11 (0.61-2.02)
No. of class I loci (<i>HLA-A</i> , <i>-B</i> , or <i>-C</i>)	0 or 1	505	(96)	532 (93)	1.00 (referent)	149 (91)	1.00 (referent)	151 (93)	1.00 (referent)
	2	17	(3)	31 (5)	1.69 (0.92-3.10)	9 (5)	1.81 (0.78-4.17)	8 (5)	1.37 (0.57-3.28)
	3	6	(1)	12 (2)	1.94 (0.72-5.25)	6 (4)	3.66 (1.15-11.7)	3 (2)	1.81 (0.43-7.59)
	<i>P</i> trend				0.04		0.01		0.3

HLA indicates human leukocyte antigen; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; OR, odds ratio; CI, confidence interval; and ref, referent.

Our results also suggest that heterozygote advantage may exist at *HLA* class I loci for NHL and DLBCL, as previously demonstrated for some autoimmune conditions (eg, psoriatic arthritis¹⁸) and infectious diseases (eg, hepatitis B and HIV¹⁹). Because *HLA* class I heterozygotes would in principle present a broader range of peptides for antigen presentation to cytotoxic T lymphocytes or CD8⁺ T cells than homozygotes, our results support the hypothesis that such advantages afforded from a broad and more productive immune response for a more diverse array for pathogens and infectious diseases²⁰ may also decrease NHL risk. As infectious diseases are a well-known etiologic cause of NHL, our results warrant further investigation. No heterozygote advantage was observed found for *HLA-DRB1* alleles and NHL (data not shown).

In summary, our results support a role for *HLA* in NHL etiology, and are consistent with the mounting evidence that calls for a targeted and comprehensive evaluation of the variation in the 6p21 chromosomal region in NHL etiology.^{1-3,5} Our results also emphasize the importance of pursuing parallel efforts of a priori regions of interest such as *HLA* to complement ongoing agnostic approaches in genetic discoveries.

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Authorship

Contribution: S.S.W. and M.C. designed the research; L.M.M., J.R.C., W.C., N.R., S.D., R.K.S., L.B., and P.H. designed and conducted the parent NHL study from which this analysis was based; A.M.A., R.T., X.G., and M.C. performed the research/HLA genotyping; S.S.W. and M.C. conducted data analysis; and all authors participated in manuscript preparation.

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Correspondence: Sophia S. Wang, PhD, Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute and the City of Hope, Duarte, CA 91010; e-mail: sowang@coh.org.