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Polymorphisms in Pattern-Recognition Genes in the Innate Immunity System and Risk of Non-Hodgkin Lymphoma

Wei Hu[1,*], **Bryan A. Bassig**[1], **Jun Xu**[1], **Tongzhang Zheng**[2], **Yawei Zhang**[2], **Sonja I. Berndt**[1], **Theodore R. Holford**[2], **H. Dean Hosgood III**[1], **Brian Leaderer**[2], **Meredith Yeager**[1], **Idan Menashe**[1], **Peter Boyle**[3], **Kaiyong Zou**[4], **Yong Zhu**[2], **Stephen Chanock**[1], **Qing Lan**[1], **Nathaniel Rothman**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, Maryland [2]Division of Environmental Health Sciences, Yale University School of Public Health, New Haven, Connecticut [3]International Agency for Research on Cancer, Lyon, France [4]Department of Molecular, Cellular, and Developmental Biology, Yale University, New Haven, Connecticut

Abstract

The pattern-recognition pathway plays an important role in infection recognition and immune responses, and previous studies have suggested an association between genetic variation in innate immunity genes and non-Hodgkin lymphoma (NHL). We evaluated NHL risk associated with genetic variation in pattern-recognition genes using data from a case-control study of NHL conducted in Connecticut women. Single nucleotide polymorphisms (SNPs) in 27 pattern-recognition genes were genotyped in 432 Caucasian incident NHL cases and 494 frequency-matched controls. Unconditional logistic regression was used to compute odds ratios (ORs) for NHL and common NHL subtypes in relation to individual SNPs and haplotypes. A gene-based analysis that adjusted for the number of tagSNPs genotyped in each gene showed a significant association with over-all NHL for the *MBP* gene ($P = 0.028$), with the diffuse large B-cell lymphoma (DLBCL) subtype for the *MASP2* gene ($P = 0.011$), and with the follicular lymphoma (FL) subtype for *DEFB126* ($P = 0.041$). A SNP-based analysis showed that *MBP* rs8094402 was associated with decreased risks of overall NHL (allele risk OR = 0.72, *P*-trend = 0.0018), DLBCL (allele risk OR = 0.72, *P*-trend = 0.036), and FL (allele risk OR = 0.67, *P*-trend = 0.021), while *MASP2* rs12711521 was associated with a decreased risk of DLBCL (allele risk OR = 0.57, *P*-trend = 0.0042). We also observed an increased risk of FL for *DEFB126* rs6054706 (allele risk OR = 1.39, *P*-trend = 0.033). Our results suggest that genetic variation in pattern-recognition genes is

[*]Correspondence to: Wei Hu, National Cancer Institute, Division of Cancer Epidemiology and Genetics, Environmental and Occupational Epidemiology Branch, 6120 Executive Blvd, EPS 5103, Bethesda, MD 20892-7240. wei.hu@nih.gov.

AUTHOR CONTRIBUTIONS

Drs T. Zheng, Y. Zhang, T. Holford, P. Boyle, S. Cha-nock, Q. Lan, N. Rothman, S. Berndt, B. Leaderer, M. Yeager, K. Zou, and Y. Zhu were involved in the conception and design of the study. Drs W. Hu, B. Bassig, J. Xu, D. Hosgood, I. Menashe, Q. Lan, and N. Rothman conducted data analysis and/or were involved in the interpretation of the data and results. Drs W. Hu, B. Bassig, J. Xu, Q. Lan, and N. Rothman wrote the first draft of the manuscript and/or assisted in the preparation of the final manuscript. All the listed authors have reviewed and approved the final version of the manuscript.

Additional Supporting Information may be found in the online version of this article.

associated with the risk of NHL or specific NHL subtypes, but these preliminary findings require replication in larger studies.

Keywords

pattern recognition; NHL; MBP; MASP2; innate immunity

INTRODUCTION

Prior epidemiological evidence has indicated that some infections may increase the risk of non-Hodgkin lymphoma (NHL). The incidence of NHL is 70 times greater in HIV-infected individuals than in the general population [Grulich et al., 2007], and NHL is classified as an AIDS-defining criterion [Epeldegui et al., 2010]. In particular, several case–control studies including a large pooled study from InterLymph have suggested a moderate, but consistent association of hepatitis C virus (HCV) infection with an increased risk in NHL [de Sanjose et al., 2008; Franceschi et al., 2011]. Furthermore, there is evidence in chronic hepatitis C patients of enhanced genetic expression of genes related to NHL, strongly suggesting the possible relationship between chronic HCV infection and B-lymphomagenesis [Ito et al., 2010]. A similar association was observed in a population with confirmed chronic hepatitis B virus infection [Engels et al., 2010].

The innate immunity system is the first line of host defense to clear nonspecific antigens after exposure to microorganisms and interacts with the adaptive immune system during physiological and chronic inflammation [Kabelitz and Medzhitov, 2007]. The general strategy of innate immune detection is to recognize microbial molecules that are conserved across broad taxa by a limited number of receptors [Beutler, 2004]. Pattern-recognition receptors (PRR) of the innate immune system recognize invariant structures, which are referred to as pathogen-associated molecular patterns (PAMPs). PAMPs are perceived by the innate immune system as signs of infection, and their recognition via PRR induces an immune response [Friese et al., 2004].

The association between NHL risk and immune dysfunction may be modified by variation in genes involved in the regulation of the immune system [Cerhan et al., 2007]. A previous study that examined variants within genes associated with immunity and inflammation and risk of NHL using a panel of 9,412 single-nucleotide polymorphisms (SNPs) from 1,253 genes did identify several genes important in the inflammatory and innate immune response, including *TRAF, RIPK3, BAT2,* and *TLR6,* which were associated with the risk of NHL or specific subtypes [Cerhan et al., 2007]. A few studies also provide evidence that genetic variation in immune response and innate immunity genes are associated with NHL [Forrest et al., 2006; Lan et al., 2006; Purdue et al., 2007; Rothman et al., 2006; Wang et al., 2007; Cerhan et al., 2009] and with subtypes of NHL [Di Bernardo et al., 2008; Skibola et al., 2009; Crowther-Swanepoel et al., 2010; Lan et al., 2010]. However, few studies have comprehensively examined the association between pattern-recognition genes and lymphoma risk except for only focusing on toll-like receptors, a group of PRRs [Nieters et al., 2006; Purdue et al., 2009].

To test the hypothesis that genetic variation in pattern-recognition genes is associated with lymphomagenesis, we evaluated genetic polymorphisms in 27 pattern-recog-nition genes and 285 SNPs using data from a case-control study of women conducted in Connecticut.

METHODS

Study Population

Detailed methods of this case–control study of NHL have been previously described [Lan et al., 2006]. Briefly, the study included female patients aged 21–84 years-old with histologically confirmed NHL (ICD-O: M-9590–9642, 9690–9701, and 9740–9750) who were identified from the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource and without a previous diagnosis of cancer except for nonmelanoma skin cancer. Population-based controls with a Connecticut address were identified through random digit dialing (<65 years of age) or via files from the Health Care Financing Administration (≥65 years of age). Study controls were frequency matched to cases by age in 5-year strata. Participation rates for study controls were 69% for those contacted via random digit dialing and 47% among those identified through medical records. From 1995 to 2005, 601 eligible NHL cases (72% of all eligible cases) and 717 qualified controls participated in this study.

Informed consent was obtained for each participant who agreed to participate in the study, and the study was reviewed and approved by the Institutional Review Board at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute (NCI).

Blood Samples and Genotyping

At the time of the interview, eligible blood samples were obtained from 461 (76.7%) consenting cases and 535 (74.6%) consenting controls, and DNA was extracted from samples using a phenol-chloroform extraction method. Genotyping was conducted at the NCI Core Genotyping Facility (Advanced Technology Center, Gaithersburg, MD) using an Illumina GoldenGate platform. DNA from 448 cases and 525 controls was successfully genotyped. Duplicate samples from 100 study participants and 40 replicate samples from each of the two blood donors were interspersed throughout the plates used for genotype analysis for quality-control purposes. In total, 285 SNPs from 27 pattern-recognition genes were considered. The completion rate for all SNPs was greater than 97%, and the concordance rate for quality control samples was greater than 95% for all assays.

Statistical Analysis

For each SNP, Hardy–Weinberg equilibrium (HWE) was assessed in non-Hispanic white controls using a chi-square test. SNPs with a *P*-value > 0.01 from the chi-square test were considered to be in HWE. To test for an association with NHL at the gene level, a minimum *P*-test ("minP") based on permutation resampling was conducted to assess the true statistical significance of the smallest *P*-trend within each gene region [Chen et al., 2006]. This approach adjusts for the number of tagSNPs tested within each gene region as well as the underlying linkage disequilibrium pattern [Chen et al., 2006]. The minP test was

additionally conducted for the most prevalent NHL subtypes in the study population, including diffuse large B-cell lymphoma (DLBCL; 32.4%), follicular lymphoma (FL; 23.8%), marginal zone lymphoma (MZL; 6.7%), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 11.3%).

Unconditional logistic regression was used to estimate odds ratios (ORs) and calculate 95% confidence intervals (CIs) for individual SNPs and NHL, adjusted for age. The models compared the variant allele homozygote and heterozygote to the common allele homozygote, which served as the reference group. A linear trend test assuming an additive genetic model was conducted by assigning an ordinal value of 1, 2, or 3 corresponding to the homozygous wild-type, heterozygote, and homozygous variant genotype, respectively. These scores were then modeled as a continuous variable. Stratified analyses by NHL subtype were conducted for DLBCL, FL, MZL, and CLL/SLL, using all controls in order to maximize statistical power. The false-discovery rate (FDR) was applied to the minP test in order to account for multiple comparisons ($P < 0.2$ considered significant). We examined the haplotype block structure for pattern-recognition genes that were significant in the overall or subtype analysis using Haploview 4.2. Individual haplotype frequencies were estimated using the expectation-maximization algorithm [Excoffier and Slatkin, 1995], and unconditional logistic regression was used to estimate the effect of individual haplotypes, using the most frequent haplotype as the reference group. All analyses in this study were limited to Caucasians for a final sample size of 432 cases and 494 controls. Statistical analysis was conducted using Statistical Analysis Software version 9.1.3 (SAS Institute Cary, NC).

RESULTS AND DISCUSSION

Of the 285 SNPs tested, 4 were not in HWE (Supporting Information Table SII) However, none of the significant findings were located in these genes. Cases and controls were similar with respect to age, level of education, and having a family history of cancer (Table I).

The *MBP* (myelin basic protein) gene region was significantly associated with overall NHL in gene level analyses ($P = 0.028$; Supporting Information Table SI). In addition, there was evidence of an association with DLBCL for *MASP2 (*$P = 0.011$) and with FL for the *DEFB126 (*$P = 0.041$) gene regions (Supporting Information Table SI). However, none of these significant associations at the gene level identified from the minP test withstood adjustment for the FDR.

The most significant SNPs within these genes are shown in Tables II and III. *MBP* rs8094402 was associated with a significantly decreased risk of overall NHL (per allele risk OR = 0.72, 95% CI = 0.58–0.88, *P*-trend = 0.0018; Table II) and the DLBCL (per allele risk OR = 0.72, 95% CI = 0.53–0.98, *P*-trend = 0.036; Table II) and FL subtypes (per allele risk OR = 0.67, 95% CI = 0.47–0.94, *P*-trend = 0.021; Table II)], adjusted for age. The *MBP* GG homozygous variant genotype (referent = AA and AG) was significantly associated with a decreased risk of overall NHL (OR = 0.35, 95% CI = 0.21–0.59, $P = 0.000069$), while no significant association was observed for the *MBP* AG genotype (Table II). Furthermore, the decrease in risk associated with the *MBP* GG genotype was statistically significant for the

DLBCL (OR = 0.14, 95% CI = 0.04–0.47, $P = 0.0013$) and FL (OR = 0.27, 95% CI = 0.09–0.76, $P = 0.013$) subtypes (Table II), but not for MZL (OR = 0.54, 95% CI = 0.12–2.32, $P = 0.40$) or CLL/SLL (OR = 0.30, 95% CI = 0.07–1.26, $P = 0.10$; Table III). A decreased risk of the DLBCL subtype for *MASP2* rs12711521 (allele risk OR = 0.57, 95% CI = 0.39–0.84, *P*-trend = 0.0042; Table II) and an increased risk of the FL subtype for *DEFB126* rs6054706 (allele risk OR = 1.39, 95% CI = 1.03–1.88, *P*-trend = 0.033; Table II) were further observed.

After adjustment for multiple comparisons using the FDR, however, only the *MBP* GG genotype remained statistically significant. Haplotype analyses were consistent with the results of the individual SNP analyses and did not provide additional insight into these associations (data not shown).

We found that several SNPs in genes involved in the pattern-recognition pathway were associated with overall NHL risk or specific NHL subtypes in women. Our results extend the existing knowledge that genetic variation in genes of the innate immune system may confer susceptibility to NHL, and our comprehensive evaluation of the pattern-recognition pathway specifically indicates that variation in these genes may be important with respect to lymphomagenesis. In particular, our results are suggestive of a potential role of the *MBP* and *MASP2* genes in overall NHL risk as well as for the DLBCL subtype.

Golli-myelin basic proteins encoded by *MBP* are found in both the immune system and the nervous system of humans. Previous evidence has indicated that golli-MBP acts as an autoantigen and plays a role in T-cell function and specifically may regulate T-cell activation [Feng, 2007]. Golli proteins have been shown to negatively regulate T-cell activation through modulation of calcium homeostasis [Feng et al., 2006]. T-cells are part of the innate immune response, as they express a restricted T-cell receptor repertoire, which is used as a PRR [Holt-meier and Kabelitz, 2005]. Therefore, genetic variation in MBP resulting in differential expression of MBP protein could influence the immune response by either enhancing or inhibiting T-cell activation. A previous study that examined polymorphisms in genes involved in innate immunity and susceptibility to benzene-induced hemato-toxcity indicated that variation in the *MBP* gene was significantly associated with white blood cells counts [Shen et al., 2011]. Several studies have also indicated that *MBP* is associated with cancer risk. Specifically, a case-control study of breast cancer in Korean women indicated that the *MBP* gene was associated with breast cancer [Lee et al., 2009], and *MBP* was also significantly associated with childhood leukemia risk after correction for multiple comparisons [Han et al., 2010].

MASP2, a serine protease, plays an important role in the activation of the complement system via mannose-binding lectin [Medzhitov and Janeway, 2000; Ip et al., 2009], as it translates the recognition of microorganisms by pattern-recognition molecules, that is, MBL, H-ficolin, L-ficolin, and M-ficolin, into initiation of the complement system [Thiel et al., 2009]. It was previously reported that variation in complement genes may be related to NHL risk, and given the involvement of the complement system in infectious and inflammatory processes, the complement system may be related to lymphomagenesis [Bassig et al., 2012]. A study of 106 donor-patient sibling pairs undergoing conventional myeloablative allogeneic

stem-cell transplantation has shown that polymorphisms responsible for MASP2 deficiency are independent predictive factors for invasive fungal infections following allo-SCT [Granell et al., 2006]. Higher MASP2 was also associated with better event-free survival in pediatric patients with hematologic malignancies, especially lymphoma [Zehnder et al., 2009].

The protein encoded by the *DEFB126* gene is a member of the beta defensin protein family. Defensins are cysteine-rich cationic polypeptides that play a role in host defense from invading microorganisms and are catego rized as either α-defensins or β-defensins [Yang et al., 1999]. β-Defensins have been demonstrated to interact with the chemokine receptor CCR6 and may have a role in initiating the adaptive immune response [Yang et al., 1999]. There is limited previous evidence concerning disease associations with the *DEFB126* genetic region, specifically, although a study of glioma susceptibility observed a significant association with the *DEFB126/127* genetic region in analyses restricted to glioblastoma [Rajaraman et al., 2009].

In conclusion, we observed an association at the gene level with *MBP* for overall NHL and with *MASP2* and *DEFB126* for DLBCL and FL, respectively. Although our study was of modest size for a rare cancer, we lacked the statistical power to fully consider specific NHL subtypes, and therefore our results require replication. Nevertheless, our results are suggestive of a potential role of PRRs in susceptibility to overall NHL or for specific NHL subtypes, particularly for *MBP* and *MASP2.* To our knowledge, this is the first study to comprehensively evaluate genetic variation in pattern-recognition pathway genes and risk of NHL. However, because of the small sample size, future studies with a larger number of subtype specific cases should evaluate these associations more closely.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE I.

Demographic Characteristics of Cases and Controls in a Case-Control Study of NHL in Connecticut Women

	Cases	Controls
Demographic characteristic	***n* = 432**	***n* = 494**
Age (years)		
<50	86 (20%)	93 (19%)
50–69	210 (49%)	212 (43%)
70+	136 (31%)	189 (38%)
Education		
<12 years	53 (12%)	55 (11%)
12 years-College	327 (76%)	368 (74%)
Graduate or other	52 (12%)	71 (14%)
Family history of cancer[a]		
No	88 (21%)	122 (25%)
NHL	9 (2%)	2 (0.4%)
Other cancer	335 (78%)	370 (75%)

[a]Family history of cancer in first degree relatives.

TABLE II.

Association Between the Most Significant SNPs and Overall NHL or NHL Subtypes (Overall NHL, DLBCL, and FL)

		NHL				DLBCL				FL			
SNP	**Genotype**	**Control (%)**	**Case (%)**	**OR (95% CL)**	***P* value**	**Control (%)**	**Case (%)**	**OR (95% CL)**	***P* value**	**Control (%)**	**Case (%)**	**OR (95% CL)**	***P* value**
MBP rs8094402	AA	194 (40)	192 (46)	1.0 (ref.)	—	194 (40)	58 (43)	1.0 (ref.)	—	194 (40)	48 (48)	1.0 (ref.)	—
	AG	225 (47)	209 (50)	0.93 (0.71–1.23)	0.61	225 (47)	75 (55)	1.13 (0.76–1.68)	0.54	225 (47)	49 (49)	0.87 (0.55–1.36)	0.54
	GG	62 (13)	21 (5)	0.34 (0.20–0.58)	**0.000071**	62 (13)	3 (2)	0.15 (0.05–0.51)	**0.0022**	62 (13)	4(4)	0.25 (0.09–0.72)	**0.010**
	AG or GG	287 (60)	230 (55)	0.80 (0.62–1.05)	0.10	287 (60)	78 (57)	0.91 (0.62–1.34)	0.64	287 (60)	53 (52)	0.73 (0.47–1.13)	0.16
	Trend	481	422	0.72 (0.58–0.88)	**0.0018**	481	136	0.72 (0.53–0.98)	**0.036**	481	101	0.67 (0.47–0.94)	**0.021**
	AA or AG	419 (87)	401 (95)	1.0 (ref.)	—	419 (87)	133 (98)	1.0 (ref.)	—	419 (87)	97 (96)	1.0 (ref.)	—
	GG	62 (13)	21 (5)	0.35 (0.21–0.59)	**0.000069**	62 (13)	3 (2)	0.14 (0.04–0.47)	**0.0013**	62 (13)	4(4)	0.27 (0.09–0.76)	**0.013**
MASP2 rs12711521	AA	290 (61)	278 (66)	1.0 (ref.)	—	290 (61)	100 (74)	1.0 (ref.)	—	290 (61)	62 (61)	1.0 (ref.)	—
	AC	162 (34)	126 (30)	0.81 (0.61–1.08)	0.16	162 (34)	32 (24)	0.56 (0.36–0.87)	**0.011**	162 (34)	31 (31)	0.92 (0.57–1.49)	0.74
	CC	23 (5)	17 (4)	0.77 (0.40–1.48)	0.44	23 (5)	3 (2)	0.37 (0.11–1.26)	0.11	23 (5)	8(8)	1.66 (0.70–3.93)	0.25
	AC or CC	185 (39)	143 (34)	0.81 (0.61–1.07)	0.13	185 (39)	35 (26)	0.54 (0.35–0.82)	**0.0045**	185 (39)	39 (39)	1.02 (0.65–1.59)	0.95
	Trend	475	421	0.84 (0.67–1.06)	0.14	475	135	0.57 (0.39–0.84)	**0.0042**	475	101	1.10 (0.77–1.58)	0.59
DEFB126 rs6054706	TT	156 (32)	116 (28)	1.0 (ref.)	—	156 (32)	53 (40)	1.0 (ref.)	—	156 (32)	23 (23)	1.0 (ref.)	—
	CT	221 (46)	212 (51)	1.30 (0.96–1.77)	0.092	221 (46)	60 (45)	0.79 (0.52–1.21)	0.28	221 (46)	49 (49)	1.51 (0.88–2.60)	0.13
	CC	104 (22)	89 (21)	1.17 (0.81–1.70)	0.40	104 (22)	21 (16)	0.60 (0.34–1.05)	0.075	104 (22)	28 (28)	1.93 (1.05–3.56)	**0.035**
	CT or CC	325 (68)	301 (72)	1.26 (0.94–1.68)	0.12	325 (68)	81 (60)	0.73 (0.49–1.09)	0.12	325 (68)	77 (77)	1.64 (0.99–2.73)	0.055
	Trend	481	417	1.10 (0.91–1.32)	0.31	481	134	0.78 (0.59–1.02)	0.069	481	100	1.39 (1.03–1.88)	**0.033**

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P values < 0.05 are shown in bold.

TABLE III.

Association Between the Most Significant SNPs and NHL Subtypes (MZL and CLL/SLL)

		MZL				CLL/SLL			
SNP	**Genotype**	**Control (%)**	**Case (%)**	**OR (95% CL)**	***P* value**	**Control (%)**	**Case (%)**	**OR (95% CL)**	***P* value**
MBP rs8094402	AA	194 (40)	11 (39)	1.0 (ref.)	—	194 (40)	25 (51)	1.0 (ref.)	—
	AG	225 (47)	15 (54)	1.10 (0.49–2.47)	0.81	225 (47)	22 (45)	0.75 (0.41–1.37)	0.34
	GG	62 (13)	2(7)	0.56 (0.12–2.63)	0.47	62 (13)	2(4)	0.26 (0.06–1.12)	0.070
	AG or GG	287 (60)	17 (61)	0.99 (0.45–2.17)	0.98	287 (60)	24 (49)	0.64 (0.36–1.16)	0.14
	Trend	481	28	0.88 (0.49–1.58)	0.66	481	49	0.63 (0.39–1.01)	0.056
	AA or AG	419 (87)	26 (93)	1.0 (ref.)	—	419 (87)	47 (96)	1.0 (ref.)	—
	GG	62 (13)	2 (7)	0.54 (0.12–2.32)	0.40	62 (13)	2(4)	0.30 (0.07–1.26)	0.10
MASP2 rs12711521	AA	290 (61)	21 (72)	1.0 (ref.)	—	290 (61)	31 (63)	1.0 (ref.)	—
	AC	162 (34)	6(21)	0.55 (0.22–1.39)	0.20	162 (34)	17 (35)	1.01 (0.54–1.89)	0.97
	CC	23 (5)	2 (7)	1.25 (0.27–5.72)	0.78	23 (5)	1 (2)	0.41 (0.05–3.17)	0.40
	AC or CC	185 (39)	8 (28)	0.64 (0.27–1.47)	0.29	185 (39)	18 (37)	0.93 (0.51–1.72)	0.83
	Trend	475	29	0.78 (0.39–1.57)	0.49	475	49	0.87 (0.52–1.48)	0.62
DEFB126 rs6054706	TT	156 (32)	8 (29)	1.0 (ref.)	—	156 (32)	14 (29)	1.0 (ref.)	—
	CT	221 (46)	13 (46)	1.19 (0.48–2.94)	0.71	221 (46)	23 (48)	1.17 (0.58–2.35)	0.65
	CC	104 (22)	7 (25)	1.38 (0.48–3.95)	0.55	104 (22)	11 (23)	1.19 (0.52–2.72)	0.69
	CT or CC	325 (68)	20 (71)	1.25 (0.54–2.91)	0.61	325 (68)	34 (71)	1.18 (0.61–2.26)	0.62
	Trend	481	28	1.18 (0.70–1.98)	0.54	481	48	1.09 (0.73–1.64)	0.67