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Polymorphisms in Complement System Genes and Risk of Non-Hodgkin Lymphoma

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Abstract

The complement system plays an important role in inflammatory and immune responses, and recent evidence has suggested that it may also play a role in lymphomagenesis. We evaluated the association between genetic variation in complement system genes and risk of non-Hodgkin lymphoma (NHL) in a population-based case–control study conducted among women in Connecticut. Tag SNPs in 30 complement genes were genotyped in 432 Caucasian incident cases and 494 frequency-matched controls. A gene-based analysis that adjusted for the number of tag SNPs genotyped in each gene showed a significant association with NHL overall ($P = 0.04$) as well as with diffuse large B-cell lymphoma (DLBCL) ($P = 0.01$) for the *C1RL* gene. A SNP-based analysis showed that a C>T base substitution for *C1RL* rs3813729 (odds ratio $(OR)_{CT} = 0.60$, 95% confidence interval (CI) = 0.42–0.87, $P_{trend} = 0.0062$) was associated with a decreased risk of overall NHL, as well as for DLBCL ($OR_{CT} = 0.39$, 95% CI = 0.20–0.73; $P_{trend} = 0.0034$). Additionally, SNPs (*C2* rs497309, A>C and *C3* rs344550, G>C) in two complement genes were positively associated with marginal zone lymphoma (MZL) and *C1QG* was associated with CLL/SLL, but these results were based on a limited number of cases. Our results suggest a potential role of the complement system in susceptibility to NHL; however, our results should be viewed as exploratory and further replication is needed to clarify these preliminary findings.

Keywords

lymphoma; *C1RL*; innate immunity; SNP

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

INTRODUCTION

Infections and autoimmune disorders have been shown to be positively associated with non-Hodgkin lymphoma (NHL), supporting the potential connection between immune status and lymphomagenesis [Cuttner et al., 2005; Smedby et al., 2006; Engels, 2007]. There is preliminary evidence from association studies that genetic variation in immune response and innate immunity genes are associated with NHL [Forrest et al., 2006; Lan et al., 2006; Rothman et al., 2006; Purdue et al., 2007; Wang et al., 2007].

The complement system plays a vital role in the immune response, particularly in innate immunity. Specifically, complement aids to regulate and coordinate inflammatory responses through the facilitation of leukocyte extravasation, chemotactic response mechanisms, and clearance of apoptotic cells and immune complexes [Markiewski and Lambris, 2007]. While the complement system in general may be involved in immune surveillance and thereby mediate protection from cancer, other evidence has challenged this notion [Markiewski et al., 2008; Markiewski and Lambris, 2009b; Rutkowski et al., 2010]. In particular, complement may also facilitate sustained angiogenesis and cellular proliferation, as well as the dysregulation of mitogenic signaling pathways [Rutkowski et al., 2010]. Moreover, complement protein C5a specifically has been demonstrated to enhance tumor growth through the recruitment and activation of myeloid-derived suppressor cells [Markiewski et al., 2008], and other experimental evidence has suggested an association between complement activation and specific tumor types [Markiewski and Lambris, 2009a].

Few epidemiological studies have directly assessed the relationship between variation in complement genes and cancer. Variant genotypes in the *C3* gene were recently positively associated with lung cancer mortality [Suadicani et al., 2011], and a previous study found an increased and decreased risk of NHL for single nucleotide polymorphisms (SNPs) in complement genes *C5* (rs7026551, rs2416810) and *C9* (rs187875), respectively [Cerhan et al., 2009]. Given the involvement of the complement system in infectious and inflammatory processes, and its association with autoimmune disease [Chen et al., 2010], further examination of the potential association between NHL and genetic variation in complement system genes is warranted. Here, we report the associations between NHL and genetic polymorphisms in 30 complement genes using data from a population-based case–control study conducted in Connecticut.

METHODS

Study Population

The methods for this case–control study of NHL have been previously described [Morton et al., 2003]. Briefly, cases were identified through the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource between 1996 and 2000 and included female patients aged 21–84 years with histologically confirmed, incident NHL (ICD-O, M-9590–9642, 9690–9701, 9740–9750). Pathology slides (or tissue blocks) from all cases were obtained from the original pathology departments and specimens were classified using the World Health Organization NHL classification system by central review. Patients with a previous history of cancer besides nonmelanoma skin cancer were not eligible. Of 832 eligible cases, 601 (72%) completed in-person interviews. 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; currently known as The Centers for Medicare and Medicaid Services), and were enrolled over the same time period as cases. Study controls were frequency matched to cases by age in five year strata. Participation rates for study controls were 69% for those contacted via random digit dialing, and 47% among those identified through health care records.

Informed consent was obtained for each participant, 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, blood samples were obtained from 461 (76.7%) consenting cases and from 535 (74.6%) consenting controls. 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 submitted for genotyping. Duplicate samples from 100 study participants and 40 replicate samples from each of two groups of non-Hispanic white volunteer blood donors who were not enrolled in the study were interspersed throughout the plates used for genotype analysis for quality control purposes. In total, 225 SNPs from 30 complement genes or genes in the same region were considered. Genes involved in the activation of the complement system as well as those previously suggested to influence lymphoma risk were evaluated (Supporting Information Table S1). The completion rate for all SNPs was greater than 95%, and the concordance rate for quality control samples was greater than 94% for all assays.

Statistical Analysis

Hardy–Weinberg equilibrium (HWE) was assessed in non-Hispanic white controls for each SNP 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 tag SNPs 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%), follicular lymphoma (FL) (24%), marginal zone lymphoma (MZL) (7%), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (11%).

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 referent 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 complement 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. We limited analyses 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 (Cary, NC).

RESULTS

Of the 225 SNPs considered, 4 were not in HWE (Supporting Information Table SII). However, none of our significant findings were located in these genes or gene regions. Cases and controls were similar with respect to age, level of education, and having a family history of cancer (Table I).

At the gene level, the *C1RL* gene region was significantly associated with overall NHL ($P = 0.04$), as well as with DLBCL ($P = 0.01$) (Supporting Information Table SI). In addition, there was evidence of an association with CLL/SLL for *C1QG* ($P = 0.04$), and with MZL for the *C2* ($P = 0.02$) and *C3* ($P = 0.03$) gene regions (Supporting Information Table SI). However, none of these significant associations at the gene level remained after accounting for the FDR. The most significant SNPs within these genes are shown in Tables II and III. Within the *C1RL* gene, a C>T base substitution for *C1RL* rs3813729 was associated with a significantly decreased risk of overall NHL ($OR_{CT} = 0.60$, 95% CI = 0.42–0.87; $P_{trend} = 0.0062$), as well as a decreased risk of DLBCL ($OR_{CT} = 0.39$, 95% CI = 0.20–0.73; $P_{trend} = 0.0034$; Table II) adjusted for age. An increased risk of the CLL/SLL subtype was associated with an A>G base substitution for *C1QG* rs12756603 ($OR_{AG/GG} = 2.35$, 95% CI = 1.29–4.26; $P_{trend} = 0.0048$; Table III), and two SNPs in the *C2* (rs497309; A>C) and *C3* (rs344550; G>C) gene regions were significantly associated with an increased risk of MZL (Table III). Stratified analyses by menopausal status, family history of cancer, and having a history of an inflammatory disorder were explored for our positive SNP results and overall NHL but these analyses did not meaningfully impact our findings (data not shown).

Haplotype analyses were consistent with the results of the individual SNP analyses and did not provide additional insight into these associations (data not shown).

DISCUSSION

Our results suggest a potential role of the *C1RL* gene in overall NHL risk as well as for DLBCL. Although the observed associations did not withstand adjustment for multiple testing, these genes were chosen for analysis based on high prior with risk of NHL. Our results extend previous preliminary evidence concerning a potential role of the complement system in susceptibility to NHL, and warrant replication in future studies including in different ethnic groups.

C1RL (complement component 1, r-subcomponent like) is a serine protease which is homologous to complement component *C1r* [Ligoudistianou et al., 2005]; however, its precise function has not been fully elucidated. *C1RL* has been shown to possess catalytic activity against pro-C1s and therefore may be involved in the activation of the classical complement pathway; however, this activity has not been observed in all studies [Wicher and Fries, 2004; Ligoudistianou et al., 2005]. *C1RL* also appears to mediate the proteolytic cleavage of a proform of haptoglobin in the endoplasmic reticulum [Wicher and Fries, 2004]. Haptoglobin is a glycoprotein whose concentration increases during inflammation, and in addition has several immunomodulatory functions including regulation of T-cell mediated immune responses [Arredouani et al., 2003; Quaye, 2008].

Interestingly, serum levels of haptoglobin-related protein have been shown to be higher in lymphoma patients relative to controls, and distinct haptoglobin phenotypes contribute to several infectious, inflammatory, and hematologic disorders [Epelbaum et al., 1998; Sadrzadeh and Bozorgmehr, 2004]. No association between *C1RL* and NHL was observed in the previous study which considered this relationship. However, only one SNP (rs3782928) from this gene was genotyped resulting in 5% coverage for this locus [Cerhan

et al., 2009]. Consistent with this study, our analysis revealed no association between this SNP and overall NHL or specific subtypes.

We observed an association at the gene level for *C1QG* with CLL/SLL, and for *C2* and *C3* with MZL. However, given the small number of cases of each of these subtypes, future studies with a larger number of subtype specific cases (i.e., pooling studies) should evaluate these associations more closely. Cerhan et al. [2009] found one SNP (rs7746553) in the *C2* gene that was positively associated with NHL, but there was no association with the *C3* gene. Each of these genes is involved in the activation of the classical pathway of the complement system, and thus may have important implications for the immune response. Deficiencies in C2 protein, in particular, have long been associated with autoimmune disease, including systemic lupus erythematosus, and infections [Jonsson et al., 2005; Truedsson et al., 2007]. Similarly, genetic variation in the *C3* gene has been associated with several inflammatory conditions [Hasegawa et al., 2004; Miyagawa et al., 2008; Purwar et al., 2009].

Given common associations with autoimmune disease and infections, the associations with overall NHL and particular subtypes observed in our study for specific complement genes are biologically plausible, but require further investigation and replication in order to rule out the possibility of chance findings. To date, several small genome-wide association studies (GWAS) of specific NHL subtypes have been conducted [Di Bernardo et al., 2008; Skibola et al., 2009; Conde et al., 2010; Crowther-Swanepoel et al., 2010]. These and future large scale GWAS of NHL will help clarify our findings and provide further insight into the role of the complement system in susceptibility to overall NHL and NHL subtypes. Moreover, while our study had limited power to conduct stratified analyses, further investigation of potential interactions between complement genes and conditions related to inflammatory status are warranted. It is plausible that the risk of NHL associated with complement genes may be higher in patients with a history of certain infections or autoimmune diseases, or in the case of differences in inflammatory status due to factors such as menopausal state, although this was not apparent in our exploratory analyses.

In summary, our results suggest a potential role of the complement system in susceptibility to NHL, particularly for *C1RL*. This is one of only two studies to comprehensively evaluate genetic variation in complement genes and risk of NHL. However, due to the small sample size for NHL subtypes, additional studies are needed to clarify this relationship.

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

Demographic characteristic	Cases, *n* = 432	Controls, *n* = 494
Age (years)		
<50	86 (20%)	93 (19%)
50–70	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 (20%)	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

Logistic Regression Analysis of Selected SNPs and Risk of Overall NHL, Diffuse Large B-cell Lymphoma (DLBCL), and Follicular Lymphoma (FL)

			Overall NHL			DLBCL			FL		
SNP	**Genotype**	**Controls (%)**	**Cases (%)**	**OR (95% CI)**	***P***	**Cases (%)**	**OR (95% CI)**	***P***	**Cases (%)**	**OR (95% CI)**	***P***
C1RL rs3813729	CC	375 80)	362 (87)	1.0 (ref)		123 (91)	1.0 (ref)		83 (84)	1.0 (ref)	
	CT	94 (20)	56 (13)	0.60 (0.42–0.87)	0.0062	12 (9)	0.39 (0.20–0.73)	0.0034	16 (16)	0.71 (0.40–1.28)	0.26
	TT	0	0	—	—	0	—	—	0	—	—
	CT or TT	94 (20)	56 (13)	0.60 (0.42–0.87)	0.0062	12 (9)	0.39 (0.20–0.73)	0.0034	16 (16)	0.71 (0.40–1.28)	0.26
	Trend	469	418	0.60 (0.42–0.87)	0.0062	135	0.39 (0.20–0.73)	0.0034	99	0.71 (0.40–1.28)	0.26
C1QG rs12756603	AA	350 (73)	302 (71)	1.0 (ref)		92 (67)	1.0 (ref)		75 (74)	1.0 (ref)	
	AG	120 (25)	110 (26)	1.06 (0.78–1.43)	0.72	42 (31)	1.30 (0.85–1.98)	0.23	22 (22)	0.84 (0.50–1.41)	0.51
	GG	12 (2)	11 (3)	1.01 (0.44–2.34)	0.98	3 (2)	1.03 (0.28–3.75)	0.96	4 (4)	1.36 (0.42–4.39)	0.61
	AG or GG	132 (27)	121 (29)	1.05 (0.79–1.41)	0.74	45 (33)	1.27 (0.84–1.92)	0.25	26 (26)	0.89 (0.54–1.46)	0.64
	Trend	482	423	1.04 (0.80–1.34)	0.77	137	1.20 (0.84–1.73)	0.32	101	0.96 (0.63–1.45)	0.83
C2 rs497309	AA	405 (84)	341 (80)	1.0 (ref)		106 (77)	1.0 (ref)		87 (86)	1.0 (ref)	
	AC	75 (16)	80 (19)	1.29 (0.91–1.83)	0.15	30 (22)	1.55 (0.96–2.50)	0.07	13 (13)	0.86 (0.45–1.63)	0.64
	CC	2 (0.4)	3 (0.7)	1.58 (0.26–9.55)	0.62	1 (0.7)	1.68 (0.15–18.86)	0.68	1 (0.99)	1.89 (0.17–21.17)	0.61
	AC or CC	77 (16)	83 (20)	1.30 (0.92–1.83)	0.13	31 (23)	1.56 (0.97–2.49)	0.07	14 (14)	0.89 (0.48–1.66)	0.72
	Trend	482	424	1.29 (0.93–1.79)	0.13	137	1.52 (0.97–2.37)	0.07	101	0.94 (0.52–1.67)	0.82
C3 rs344550	GG	198 (41)	170 (40)	1.0 (ref)		49 (36)	1.0 (ref)		49 (49)	1.0 (ref)	
	CG	220 (46)	190 (45)	1.00 (0.75–1.33)	0.99	65 (47)	1.18 (0.78–1.80)	0.43	41 (41)	0.74 (0.46–1.17)	0.20
	CC	64 (13)	62 (15)	1.15 (0.77–1.73)	0.50	23 (17)	1.44 (0.81–2.57)	0.21	11 (11)	0.72 (0.35–1.47)	0.37
	CG or CC	284 (59)	252 (60)	1.03 (0.79–1.35)	0.81	88 (64)	1.24 (0.84–1.84)	0.29	52 (51)	0.73 (0.47–1.13)	0.16
	Trend	482	422	1.05 (0.87–1.27)	0.59	137	1.20 (0.91–1.58)	0.20	101	0.81 (0.58–1.12)	0.20

TABLE III

Logistic Regression Analysis of Selected SNPs and Risk of Marginal Zone Lymphoma (MZL) and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

			MZL			CLL/SLL		
SNP	**Genotype**	**Controls (%)**	**Cases (%)**	**OR (95% CI)**	***P***	**Cases (%)**	**OR (95% CI)**	***P***
C1RL rs3813729	CC	375 (80)	24 (83)	1.0 (ref)		41 (85)	1.0 (ref)	
	CT	94 (20)	5 (17)	0.76 (0.28–2.07)	0.60	7 (15)	0.66 (0.29–1.52)	0.33
	TT	0	0	—	—	0	—	—
	CT or TT	94 (20)	5 (17)	0.76 (0.28–2.07)	0.60	7 (15)	0.66 (0.29–1.52)	0.33
	Trend	469	29	0.76 (0.28–2.07)	0.60	48	0.66 (0.29–1.52)	0.33
C1QG rs12756603	AA	350 (73)	22 (79)	1.0 (ref)		26 (53)	1.0 (ref)	
	AG	120 (25)	6 (21)	0.81 (0.32–2.05)	0.65	20 (41)	2.27 (1.22–4.21)	0.0097
	GG	12 (2)	0	—	—	3 (6)	3.09 (0.81–11.82)	0.10
	AG or GG	132 (27)	6 (21)	0.71 (0.28–1.81)	0.48	23 (47)	2.35 (1.29–4.26)	0.0051
	Trend	482	28	0.67 (0.29–1.57)	0.36	49	2.01 (1.24–3.26)	0.0048
C2 rs497309	AA	405 (84)	17 (59)	1.0 (ref)		44 (90)	1.0 (ref)	
	AC	75 (16)	12 (41)	4.21 (1.91–9.31)	0.00038	5 (10)	0.62 (0.24–1.63)	0.34
	CC	2 (0.4)	0	—	—	0	—	—
	AC or CC	77 (16)	12 (41)	4.09 (1.85–9.03)	0.00049	5 (10)	0.61 (0.23–1.59)	0.31
	Trend	482	29	3.52 (1.67–7.43)	0.00093	49	0.61 (0.24–1.56)	0.30
C3 rs344550	GG	198 (41)	5 (18)	1.0 (ref)		23 (47)	1.0 (ref)	
	CG	220 (46)	15 (54)	2.85 (1.01–8.03)	0.047	20 (41)	0.80 (0.42–1.50)	0.48
	CC	64 (13)	8 (29)	5.80 (1.80–18.64)	0.0032	6 (12)	0.85 (0.33–2.18)	0.73
	CG or CC	284 (59)	23 (82)	3.45 (1.28–9.29)	0.014	26 (53)	0.81 (0.45–1.46)	0.48
	Trend	482	28	2.37 (1.36–4.15)	0.0024	49	0.88 (0.57–1.37)	0.57

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