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A pooled analysis of three studies evaluating genetic variation in innate immunity genes and non-Hodgkin lymphoma risk

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Summary

Genetic variation in immune-related genes may play a role in the development of non-Hodgkin lymphoma (NHL). To test the hypothesis that innate immunity polymorphisms may be associated with NHL risk, we genotyped 144 tag single nucleotide polymorphisms (tagSNPs) capturing common genetic variation within 12 innate immunity gene regions in three independent population-based case-control studies (1946 cases and 1808 controls). Gene-based analyses found *IL1RN* to be associated with NHL risk (minP = 0.03); specifically, *IL1RN* rs2637988 was associated with an increased risk of NHL (per-allele odds ratio = 1.15, 95% confidence interval = 1.05 – 1.27; $p_{\text{trend}} = 0.003$), which was consistent across study, subtype, and gender. *FCGR2A* was also associated with a decreased risk of the follicular lymphoma NHL subtype (minP = 0.03). Our findings suggest that genetic variation in *IL1RN* and *FCGR2A* may play a role in lymphomagenesis. Given that conflicting results have been reported regarding the association between *IL1RN* SNPs and NHL risk, a larger number of innate immunity genes with sufficient genomic coverage should be evaluated systematically across many studies.

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Keywords

non-Hodgkin lymphoma; immune; innate immunity; genetic variation; single nucleotide polymorphisms

Introduction

Although the aetiology of non-Hodgkin lymphoma (NHL) is poorly understood, known risk factors include immune-related factors, such as severe immunodeficiency and selected infectious agents (Muller *et al*, 2005). As having a family history of hematopoietic malignancy is also an established risk factor for NHL (Chatterjee *et al*, 2004; Wang *et al*, 2007), inherited germline genetic variation in immune-related genes may influence NHL susceptibility.

Candidate-gene association studies of NHL have focused on cytokines, secreted proteins that play a critical role in regulating the immune system. While some cytokines, such as tumour necrosis factor (*TNF*) and interleukin 10 (*IL10*), have been the subject of extensive investigation (Lan *et al*, 2006; Rothman *et al*, 2006; Wang *et al*, 2006; Skibola *et al*, 2010; Wang *et al*, 2009), others have been examined by only a few studies, or not at all. The innate immunity pathway, which is involved in the clearance of non-specific antigens and interacts with the adaptive immune system during chronic inflammation (Kabelitz & Medzhitov, 2007), may also play a role in NHL risk (Forrest *et al*, 2006; Andrieu *et al*, 2009). Genes involved in the innate immunity pathway include those with roles in the biological response to activation of the nuclear factor (NF)- κ B pathway, such as specific cytokines [i.e. the interleukin 1 (*IL1*) family, interleukin 6 (*IL6*)], chemokines [i.e. interleukin 8 (*IL8*)], and adhesion molecules [i.e. the inter-cellular adhesion molecule family (*ICAM*), Fc region receptor II-a (*FCGR2A*)] (Ghosh *et al*, 1998; Bonizzi & Karin, 2004). Cytokines, chemokines, and adhesion molecules found in the innate immunity pathway may be involved in NHL risk through various mechanisms of altered immune function. Certain cytokines, for example, influence immune pathways through their regulation of cell-mediated (Th1) and humoral (Th2) balance, which is associated with haematopoiesis (Lucey *et al*, 1996; Hofmann *et al*, 2002). Chemokines and adhesion molecules also exert influence on immune function through their regulation of leucocytes, tumour proliferation, and metastasis (Langer & Chavakis, 2009; Mantovani *et al*, 2006). To investigate further the possible associations of immunoregulatory genes, and innate immunity genes in particular, with NHL risk, we genotyped tagging single nucleotide polymorphisms (tagSNPs) summarizing common variation in 12 gene regions (*FCGR2A*, *ICAM1/ICAM4/ICAM5*, *IL15*, *IL1A/IL1B*, *IL1R1*, *IL1R2*, *IL1RN*, *IL6*, *IL6R*, *IL8*, *CXCR1 [IL8RA]/CXCR2 [IL8RB]*, *JAK3*) in a pooled analysis of three independent population-based case-control studies.

Methods

Our study population comprised of three independent population-based case-control studies: the National Cancer Institute (NCI) – Surveillance Epidemiology and End Results (SEER) NHL case-control study (Wang *et al*, 2006), the Connecticut NHL case-control study (Lan *et al*, 2006), and the New South Wales (NSW) NHL case-control study (Purdue *et al*, 2007). All three studies included only newly diagnosed NHL cases, and population controls were frequency matched to cases (Supplemental Table I). The protocols for each study were approved by their respective Institutional Review Boards and all study participants provided informed consent.

All cases were histologically confirmed by the local diagnosing pathologist in the NCI-SEER study and by central review by two independent pathologists in the Connecticut study. In the NSW study, all cases were histologically confirmed by the local diagnostic pathologist, and a confirmatory central pathology review was performed for cases with <90% certainty to be NHL. NHL subtypes were categorized according to the World Health Organization classification using the International Lymphoma Epidemiology Consortium (InterLymph) guidelines (Morton *et al*, 2007).

DNA was extracted from blood (NCI-SEER; Connecticut; NSW) or buccal cells (NCI-SEER). In total, 144 tagSNPs in 12 gene regions were genotyped (Supplemental Table 2). TagSNPs were chosen from the designable set of common SNPs (minor allele frequency >5%) genotyped in the Caucasian population sample (CEU) of the HapMap Project (Data Release 20/Phase II, NCBI Build 35 assembly, dpSNPb125) using Tagzilla (<http://tagzilla.nci.nih.gov/>), which implements a tagging algorithm based on the pairwise binning method (Carlson *et al*, 2004). For each gene region, SNPs located within 20 kb 5' of the start of transcription (exon 1) and 10 kb 3' of the end of the last exon were grouped and selected using a binning threshold of $r^2 > 0.8$. When there were multiple transcripts available for the gene, the primary transcript was assessed. TagSNPs were genotyped using an oligo pool assay (OPA) on the Illumina GoldenGate platform investigating genetic variants from multiple candidate pathways at the NCI Core Genotyping Facility (Gaithersburg, MD).

Subjects with OPA-wide sample completion rates <90% were excluded from analysis (15 cases, 17 controls). Thus, genotyping of the 144 tagSNPs was successful for 1946 cases and 1808 controls. Hardy-Weinberg equilibrium (HWE) for each tagSNP was tested in non-Hispanic Caucasian controls using Fisher's exact test; two tagSNPs (rs3917296, rs17202249) deviated substantially from HWE ($p < 0.001$) (Supplemental Table II).

Associations of each tagSNP with NHL risk were estimated by odds ratios (OR) and 95% confidence intervals (CI) calculated using unconditional logistic regression. The homozygote of the common allele was used as the reference group and age, ethnicity, gender, and study centre were controlled in the analysis. Gene-dose effects were estimated by a linear trend test based on the number of variant alleles present (0, 1, 2). Analyses were also done restricted to non-Hispanic Caucasians and stratified by gender. Polytomous regression models were used to evaluate SNP effects among specific NHL subtypes [diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)]. To assess the significance of the association with NHL for SNPs within each gene region, the minP test was used. This test assesses the significance of the minimum p-value in each gene region using a permutation-based resampling procedure (10,000 permutations) that takes into account the number of tagSNPs genotyped in each gene region and their underlying linkage disequilibrium structure (Chen *et al*, 2006). P values ≤ 0.05 were considered significant. Finally, haplotypes with frequencies greater than 1% were assessed for *IL1RN* among non-Hispanic Caucasians using a three-SNP sliding window approach (Huang *et al*, 2007) and a global score test (Schaid *et al*, 2002). Haplotype ORs and 95% CIs were adjusted for age, gender, and study centre.

Results

The allele distribution among cases and controls, as well as the NHL risk associated with all 144 genotyped tagSNPs, is provided in Supplemental Table III. Supplemental Table IV describes the associations between each tagSNP and each NHL subtype. Of the 12 gene regions evaluated, only *IL1RN* was associated with NHL overall (minP = 0.03) (Table I). Three of the 17 *IL1RN* SNPs (rs17042888, rs2637988, rs315949), which were in high

linkage disequilibrium (LD) with each other ($D' \geq 0.92$), were associated with NHL ($p_{\text{trend}} < 0.05$) with rs2637988 being the most significant (Supplemental Table III; Figure 1). The G variant at rs2637988 was associated with a per-allele 15% increased risk of NHL ($OR_{\text{per-allele}} = 1.15$, 95%CI = 1.05 – 1.27; $p_{\text{trend}} = 0.003$). This association was consistent across study, subtype, gender, and among non-Hispanic Caucasians (Figure 1, Supplemental Tables III–IV). Haplotype analyses of *IL1RN* did not provide any additional information beyond that in the individual tagSNP analyses. *IL1RN* rs454078, which was in high LD and moderate correlation with rs2637988 ($D' = 0.90$; $r^2 = 0.46$), was not statistically associated with NHL ($OR_{\text{per-allele}} = 1.08$, 95%CI = 0.97 – 1.20; $p_{\text{trend}} = 0.18$) (Supplemental Table III).

FCGR2A was associated with follicular lymphoma ($\text{minP} = 0.03$) (Table 1), with the G variant of rs1801274 associated with decreased risk ($OR_{\text{per-allele}} = 0.81$, 95%CI = 0.71 – 0.94; $p_{\text{trend}} = 0.005$) (Supplemental Table IV). The direction and magnitude of association with FL for this tagSNP was similar across all three studies (NCI-SEER: $OR_{\text{per-allele}} = 0.82$, 95%CI = 0.67 – 1.02; $p_{\text{trend}} = 0.07$; Connecticut: $OR_{\text{per-allele}} = 0.89$, 95%CI = 0.63 – 1.24; $p_{\text{trend}} = 0.48$; NSW: $OR_{\text{per-allele}} = 0.77$, 95%CI = 0.60 – 0.99; $p_{\text{trend}} = 0.04$).

Discussion

Our evaluation of associations between common genetic variation in innate immunity genes and risk of NHL found that *IL1RN* and *FCGR2A* may be important to the aetiology of lymphoma. *IL1RN*, along with *IL1A* and *IL1B*, make up the interleukin 1 (*IL1*) gene family cluster on chromosome 2q. Specifically, *IL1RN* is known to alter *IL1B* expression levels (Santtila *et al*, 1998), leading to a modulation of a variety of *IL1*-related immune and inflammatory responses, which may affect the risk of haematopoietic cancers (Bastion *et al*, 1997; Elahi *et al*, 2005; Parker *et al*, 1994). Further, variants in *IL1* genes have been associated with susceptibility to and clearance of infectious agents (Witkin *et al*, 2002). Genetic variation in *IL1RN* and risk of NHL has been evaluated with conflicting results (Hoeft *et al*, 2008; Rollinson *et al*, 2003; Rothman *et al*, 2006; Wu *et al*, 2004). Similar to our results, two studies found *IL1RN* SNPs to be associated with an increased risk of NHL (Hoeft *et al*, 2008) and gastric marginal lymphomas (Rollinson *et al*, 2003). Two additional studies did not replicate these findings for NHL (3586 cases, 4018 controls) (Rothman *et al*, 2006) or gastric mucosa-associated lymphoid tissue lymphoma (75 cases and 321 controls) (Wu *et al*, 2004). However, the larger study, involving a pooled analysis of eight case-control studies (including the NCI-SEER and Connecticut studies) within the Interlymph Consortium, did find a borderline-significant association with NHL risk for rs454078 ($p_{\text{trend}} = 0.06$) (Rothman *et al*, 2006). Given that rs454078 is moderately correlated with rs2637988 ($r^2 = 0.46$ among controls in our pooled analysis), it is possible that our *IL1RN* findings and the Interlymph finding reflect the same signal, which is better captured by the SNPs in our OPA.

Our observed association between *FCGR2A* and follicular lymphoma may be of biological importance as *FCGR2A* codes for a receptor necessary for the binding of IgG to the surface of phagocytes (Salmon *et al*, 1996) and *FCGR2A* rs1801274 has been found to affect processes associated with innate immunity (Karassa *et al*, 2004; Lehrnbecher *et al*, 1999). Specifically, the R131H substitution of *FCGR2A* rs1801274 affects the Fc region of the IgG receptor and determines the affinity of *FCGR2A* for IgG subclasses (Bournazos *et al*, 2009). This variant is capable of binding to and mediating phagocytosis with IgG2 (Warmerdam *et al*, 1990), potentially leading to altered immune response to infectious agents and activation of B-cells and overproduction of cytokines (Koene *et al*, 1997; Warmerdam *et al*, 1991; Maxwell *et al*, 1999; Asano *et al*, 2009). The association between rs1801274 and follicular lymphoma was previously reported in the NCI-SEER study (Wang *et al*, 2006) and the NSW study (Purdue *et al*, 2007).

Our study's main strength is the evaluation of these associations in a large, pooled sample from three independent case-control studies. While the use of the gene-based permutation analysis aids in the identification of a gene's true significance, it is possible that some associations that are significant at the SNP level but deemed non-significant at the gene level are true positive findings. Similarly, it is possible that some of our findings, even though significant at the gene level, are false positives. Another concern is the low participation rates of our three study populations; however, bias in our results is unlikely, because genotype frequencies among controls have been found to be very similar despite varying participation rates (Bhatti *et al.*, 2005). Finally, it is unlikely that population stratification would explain our results given that we adjusted for ethnicity and study centre in our main effects analyses, and our associations were consistently observed across most studies and when restricted to non-Hispanic Caucasians.

In conclusion, findings from our pooled analysis of three case-control studies evaluating genetic variation in innate immunity genes provide further evidence that variation in *IL1RN* and *FCG2A* influence lymphoma susceptibility. However, our results should be viewed as exploratory until a larger number of innate immunity genes are evaluated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Risk of NHL associated with *IL1RN* rs2637988, by study, NHL subtype, gender, and ethnicity, based on the additive model.*

*Square symbols represent odds ratios (OR), with the size proportional to the number of cases and horizontal lines representing the 95% confidence intervals; Abbreviations: non-Hodgkin lymphoma (NHL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); marginal zone lymphoma (MZL); chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL); National Cancer Institute - Surveillance Epidemiology and End Results (NCI-SEER); New South Wales (NSW).

Table 1

Gene-based permutation test (minP) for p-trends of innate immunity tagSNPs for NHL and NHL subtypes*

Gene Region	Number of SNPs	NHL			DLBCL			FL			MZL			CLL/SLL		
		minP	minP	minP	minP	minP	minP	minP	minP	minP	minP	minP	minP	minP	minP	minP
<i>IL1RN</i>	17	0.03 [‡]	0.23	0.18	0.57	0.17										0.17
<i>FCGR2A</i>	9	0.08	0.43	0.03 [‡]	0.11	0.98										0.98
<i>JAK3</i>	14	0.10	0.17	0.88	0.72	0.70										0.70
<i>IL1RI</i>	18	0.10	0.35	0.11	0.18	0.35										0.35
<i>IL1R2</i>	15	0.42	0.17	0.65	0.93	0.17										0.17
<i>IL6R</i>	12	0.45	0.35	0.86	0.68	0.99										0.99
<i>ICAM1/ICAM4/ICAM5</i>	9	0.54	0.51	0.15	0.28	0.06										0.06
<i>IL15</i>	5	0.61	0.66	0.83	0.59	0.05										0.05
<i>IL6</i>	17	0.61	0.49	0.54	0.54	0.31										0.31
<i>CXCR1/CXCR2</i>	8	0.72	0.58	0.88	0.12	0.98										0.98
<i>IL1A/IL1B</i>	16	0.77	0.33	0.72	0.61	0.30										0.30
<i>IL8</i>	4	0.87	0.99	0.36	0.80	0.83										0.83

* Abbreviations: non-Hodgkin lymphoma (NHL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); marginal zone lymphoma (MZL); chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)

[‡]Three SNPs (rs17042888, rs2637988, rs315949) were associated with NHL (ptrend < 0.05)

[‡]Three SNPs (rs1801274, rs10800309, rs12139150) were associated with FL (ptrend < 0.05)