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Genetic variation in Th1/Th2 pathway genes and risk of non-Hodgkin lymphoma: A pooled analysis of three population-based case-control studies

Qing Lan[1], **Sophia S. Wang**[1,2], **Idan Menashe**[1], **Bruce Armstrong**[3], **Yawei Zhang**[4], **Patricia Hartge**[1], **Mark P. Purdue**[1], **Theodore R. Holford**[4], **Lindsay M. Morton**[1], **Anne Kricker**[3], **James R. Cerhan**[5], **Andrew Grulich**[6], **Wendy Cozen**[7], **Shelia H Zahm**[1], **Meredith Yeager**[8], **Claire M. Vajdic**[9], **Maryjean Schenk**[10], **Brian Leaderer**[4], **Jeff Yuenger**[8], **Richard K. Severson**[11], **Nilanjan Chatterjee**[1], **Stephen J. Chanock**[1,8], **Tongzhang Zheng**[4,*], and **Nathaniel Rothman**[1,*]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Rockville, MD

[2]Division of Etiology, Department of Population Sciences, City of Hope, Duarte, CA

[3]Sydney School of Public Health, The University of Sydney, Sydney, New South Wales, Australia

[4]Department of Epidemiology and Public Health, Yale School of Medicine, New Haven, CT

[5]Mayo Clinic, College of Medicine, Rochester, MN

[6]National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, New South Wales, Australia

[7]Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA

[8]Core Genotyping Facility, Advanced Technology Center, National Cancer Institute, NIH, DHHS, Gaithersburg, MD

[9]UNSW Cancer Research Centre, Prince of Wales Clinical School, University of New South Wales, Sydney, Australia

[10]Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA

[11]Department of Family Medicine and Karmanos Cancer Institute, Wayne State University, Detroit, MI

Abstract

The balance between Th1 and Th2 activity is critical in lymphoid cell development and differentiation. Immune dysfunction underlies lymphomagenesis, so an alteration in the regulation of key Th1/Th2 cytokines may lead to the development of non-Hodgkin lymphoma (NHL). To study the impact of polymorphism in Th1/Th2 cytokines on NHL risk, we analyzed 145 tag single nucleotide polymorphisms (SNPs) in 17 Th1/Th2 cytokine and related genes in three population-based case-control studies (1,946 cases and 1,808 controls). Logistic regression was used to compute odds ratios (OR) for NHL and four major NHL subtypes in relation to tag SNP genotypes and haplotypes. A gene-based analysis adjusting for the number of tag SNPs genotyped in each gene showed significant associations with risk of NHL combined and one or more NHL subtypes

Author for correspondence: Qing Lan, M.D., Ph.D., Occupational & Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, MSC 7240, 6120 Executive Blvd., EPS 8109, Bethesda, Maryland 20892-7240, Telephone: 301-435-4706, Fax: 301-402-1819, qingl@mail.nih.gov.
*co-senior authors.

for Th1 (*IL12A* and *IL12RB1)* and Th2 *(IL4, IL10RB,* and *IL18)* genes. The strongest association was for *IL12A* rs485497, which plays a central role in bridging the cellular and humoral pathways of innate resistance and antigen-specific adaptive immune responses (allele risk OR=1.17; P(trend)=0.00099). This SNP was also associated specifically with risk of follicular lymphoma (allele risk OR=1.26; P(trend)=0.0012). These findings suggest that genetic variation in Th1/Th2 cytokine genes may contribute to lymphomagenesis.

Keywords

Non-Hodgkin lymphoma; single nucleotide polymorphisms; immunogenetics; case-control study

Introduction

Disruption of host immunity is one of the strongest known risk factors for non-Hodgkin lymphoma (NHL). An essential aspect of immune regulation involves maintaining homeostasis between T-helper 1 (Th1) and T-helper 2 (Th2) activation, controlling both lymphoid cell development and differentiation (Chiu and Weisenburger, 2003; Hartge et al., 1994; Neurath et al., 2002). Th1 cells are primarily responsible for the development of cell mediated immunity, whereas Th2 cells are involved in antibody production and humoral immune responses. Cytokines mediate the immune responses by Th1 or Th2 type. Because immune dysfunction is thought to be the underlying basis of lymphomagenesis, alteration in the regulation and expression of key Th1/Th2 cytokines could play an important role in the pathogenesis of NHL.

Single nucleotide polymorphisms (SNPs) in Th1/Th2 cytokines (*IL4*, *IL10*, *IL12*, *IL18*) have been shown to influence gene expression (Arimitsu et al., 2006; Hoffmann et al., 2001; Keen, 2002) and have been associated with risk of a number of autoimmune conditions (Lee et al., 2007; Pawlik et al., 2005; Hirschfield et al., 2009) and cancers (Wei et al., 2007; Rothman et al., 2006; Chen et al., 2009b; Lan et al., 2006). For example, we previously reported that variants in *IL10* and *IL4* were significantly associated with risk of NHL and/or its subtypes in a population-based case-control study among women in Connecticut (Yale NHL study) (Lan et al., 2006) and that variants in *IL10* were associated with risk of NHL in a population-based case-control study of NHL in New South Wales, Australia (Purdue et al., 2007) and in pooled analyses conducted by the International Lymphoma Consortium study that included data from the three studies in the current report (Rothman et al., 2006). To comprehensively evaluate the role that genetic variation in Th1/Th2 genes plays in lymphomagenesis, we genotyped tag SNPs in a candidate gene study of 17 key cytokine genes in 1,946 NHL cases and 1,808 controls pooled from three independent population-based case-control studies conducted in the US and Australia.

Materials and methods

Study population

Three population-based case-control studies of NHL participated in this pooled analysis: the National Cancer Institute (NCI)-Surveillance Epidemiology and End Results (SEER) NHL case-control study, conducted within the SEER registry catchment areas of Iowa, Detroit, Los Angeles and Seattle (Wang et al., 2006); the Connecticut case-control NHL study, conducted among female residents of Connecticut (Lan et al., 2006); and the New South Wales (NSW) case-control study, conducted among residents of New South Wales and the Australian Capital Territory, Australia (Purdue et al., 2007). All three studies included first primary NHL cases only, and population controls that were frequency-matched to cases. Selected characteristics for each study are presented in Table 1. The protocols for each study

were approved by all relevant institutional review boards. All study participants provided informed consent, in accordance with the Declaration of Helsinki.

NHL Pathology Classification

In the NCI-SEER study, all cases were histologically confirmed by the local diagnosing pathologist. In the Connecticut study, all cases were confirmed by central review of diagnostic slides by two independent expert hematopathologists. In the NSW study, all cases were histologically confirmed by the local diagnosing pathologist, and a confirmatory central pathology review was performed for cases whose diagnosis was judged by an expert hematopathologist to be <90% certain on review of the diagnostic pathology report. NHL pathology subtypes were classified based on the World Health Organization classification using the International Lymphoma Epidemiology Consortium (InterLymph) guidelines (Morton et al., 2007). In the present analyses, we evaluated NHL overall and the four most common NHL subtypes: diffuse large B-cell lymphoma (DLBCL) (31%), follicular lymphoma (28%), marginal zone lymphoma (8%), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (8%) (Tables 1).

Biological samples, genotyping, and quality control

DNA was extracted from blood or buccal cell samples. Genotyping was conducted at the National Cancer Institute Core Genotyping Facility (Advanced Technology Center, Gaithersburg, MD; http://snp500cancer.nci.nih.gov). Tag SNPs were chosen from the designable set of common SNPs (minor allele frequency (MAF)>5%) genotyped in the Caucasian (CEU) population sample of the HapMap Project (Data Release 20/Phase II, NCBI Build 35 assembly, dbSNPb125) using the software Tagzilla (http://tagzilla.nci.nih.gov/), which implements a tagging algorithm based on the pair wise binning method of Carlson *et al*. (Carlson et al., 2004). For each gene, SNPs within the region spanning 20kb 5' of the start of transcription (exon 1) to 10kb 3' of the end of the last exon were grouped using a binning threshold of r^2>0.8. When there were multiple transcripts available for genes, only the primary transcript was assessed. SNPs with a low completion rate (<90% of the full panel of 1536 tag SNPs) were excluded. QC duplicates and replicates from each study were genotyped and blinded to laboratory personnel. SNPs with a concordance of <95% in the study-specific QC samples as well as a low completion rate (<90% of the samples) were excluded. In total, 145 tag SNPs in 17 Th1/Th2 cytokine genes were analyzed (Supplementary Table 1).

Statistical methods

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for the genotype-specific risks of NHL for each SNP for the heterozygote and less common homozygote genotypes, with the more common homozygote as the baseline category. Models were adjusted for age, race, sex and study center. Polytomous multivariate unconditional logistic regression models were used to evaluate the effect among different NHL subtypes.

To evaluate the significance of the association between each gene region and NHL risk, we used a minimum p-value ("minP test") to assess the smallest p-trend within each gene region. The minP test uses permutation-based re-sampling methods (10,000 permutations) (Chen et al., 2006) that adjusts for both the number of tag SNPs in each gene, as well as for correlations between SNPs genotyped for each gene region, while taking into account the underlying linkage disequilibrium pattern

To obtain a gene-level summary of association, the minP value was computed ("minP test"), which evaluates the statistical significance of the smallest p-trend within each gene region

(determined by dichotomous logistic regression, comparing NHL or NHL subtypes to controls) by permutation-based resampling methods (10,000 permutations) that automatically adjusts for both the number of tag SNPs in each gene, as well as for correlations between SNPs genotyped for each gene region, while taking into account the underlying linkage disequilibrium pattern (Chen et al., 2006). Further, to assess the robustness of our findings for each gene and NHL risk, false discovery rates (FDR) (Benjamini and Hochberg, 1995) were calculated for each minP test for all NHL to take into account multiple comparisons across the 17 Th1/Th2 genes that were tested. A SNP association with a FDR value < 0.2 was considered a noteworthy finding with a relatively lower probability of being a false discovery. The FDR was also calculated for the trend test for each SNP genotyped.

A haplotype analysis among non-Hispanic Caucasians was carried out using an expectation-maximization (EM) algorithm(Excoffier and Slatkin, 1995) and HaploStats (R version 1.2.0) (R Development Core Team, 2004; Schaid et al., 2002), but did not reveal additional insights beyond those obtained from the SNP and gene-based analyses (data not shown).

Results

Cases and controls were comparable both overall and in each study with respect to age, sex, race, and study. Population characteristics and histologic subtype frequencies were generally similar across the three studies (Table 1). Results for each SNP for all NHL sorted by $P_{(trend)}$, for all NHL by study, and for major NHL subtypes are shown in Supplementary Tables 2, 3 and 4, respectively.

We observed evidence for association at the gene-level for *IL12A* and *IL12RB1*, Th1 genes, and *IL4*, *IL10RB*, and *IL18*, Th2 genes, with significance levels <0.05 by the minP test (Table 2). In addition, there was evidence for associations at the gene level for Th2 genes with DLBCL (*IL4* and *IL18*) and marginal zone lymphoma (*IL4*) and the Th1 gene *IL12A* with follicular lymphoma (Table 2). Results for the most significant SNP in each gene that was significant based on the minP test are presented in Table 3 and Table 4. Within genes showing an association with NHL, *L12A* rs485497 and *IL4* rs2243263 were associated with increased risk, and *IL12RB1* rs12564159, *IL10RB* rs1058867, and *IL18* rs243908 were associated with a decreased risk of NHL overall and/or with one or more of the subtypes (Tables 3 and 4). Risk estimates were in the same direction and moderately consistent in magnitude across the three studies for SNPs in *IL12A*, *IL4*, and *IL18* (Table 3). All of these SNPs except *IL18* rs243908 were associated with altered risk of follicular lymphoma (Table 4).

The strongest association for tag SNPs was in *IL12A* rs485497, which plays a central role in bridging the cellular and humoral pathways of innate resistance and antigen-specific adaptive immune responses (allele risk OR 1.17; 95% CI, 1.07–1.28, P(trend) = 0.00099) (Supplementary Table 2). This variant was related to follicular lymphoma in particular (allele risk OR 1.26; 95% CI, 1.10–1.45, P(trend) = 0.0012), although there was not statistically significant heterogeneity for this SNP across the four subtypes (Supplementary Table 4).

Discussion

We carried out the first comprehensive evaluation of genetic variation in Th1 and Th2 genes and risk of NHL. The comparison of 1946 cases and 1808 controls from three population-based case-control studies of NHL suggests that variants in Th1/Th2 genes may play a role in lymphomagenesis. In particular, SNPs in the Th1 genes *IL12A*, and *IL12RB1* and in the

Th2 genes *IL4*, *IL10RB*, and *IL18* were associated with risk of NHL overall and with one or more subtypes.

IL12 plays a central role in bridging the cellular and humoral pathways of innate resistance and antigen-specific adaptive immune responses (Trinchieri, 1995). IL12 is produced primarily by antigen-presenting cells and exerts immunoregulatory effects on T and natural killer (NK) cells by inducing rapid IFN-γ production (Trinchieri, 1995). Its immunological functions are mediated through high-affinity binding to the IL12 receptor, IL12RB1 and IL12RB2. Inherited deficiencies of *IL12*, *IL12* receptor, and IFN-γ have been associated with increased susceptibility to severity of mycobacterial and other infectious diseases (Filipe-Santos et al., 2006). Mutations in the *IL12RB1* gene encoding the IL12Rβ1 chain is the most common genetic disorder associated with mycobacterial disease (Fieschi et al., 2003).

IL18 is a critical cytokine regulator that stimulates both Th1 and Th2-type immune responses, depending on its cytokine milieu (Nakanishi et al., 2001). Working together with IL12, IL18 can stimulate T cells, produce IFN-γ (Yamanaka et al., 2006), and suppress IL4-dependent immunoglobulin E (IgE) production from B cells. However, in the absence of IL12, IL18 seems to favor a Th2 response. High levels of IL18 alone can lead to increased IgE levels and induce IL4 and IL13 production by basophils, mast cells, and $CD4^+$ T cells (Yamanaka et al., 2006). It has been reported that polymorhpisms in *IL18* significantly affect IL18 production (Arimitsu et al., 2006). Further, *IL18* variants have been associated in some reports with risk of asthma (Higa et al., 2003; Harada et al., 2009), lupus nephritis (Chen et al., 2009a), childhood lymphomas (Andrie et al., 2009), epithelial ovarian cancer (Palmieri et al., 2008), colorectal cancer (Nikiteas et al., 2007), prostate cancer (Liu et al., 2007), and esophageal squamous cell carcinoma (Wei et al., 2007). The *IL18* variant identified in our study is in moderate LD with variants that have been associated with these diseases.

IL4 is a key regulator in the inhibition of Th1 cells and stimulation of a Th2 type of immune response. IL4 also has many additional biological roles, including stimulation of activated B-cell and T-cell proliferation and differentiation of CD4+ T-cells into Th2 cells, which are capable of producing both IL4 and IFN-γ. *IL4* polymorphisms have been shown to alter gene expression *in vivo* and *in vitro* (Rockman et al., 2003) and have been associated in some reports with juvenile idiopathic arthritis, severity of infection with respiratory syncytial virus in young children, asthma, fungal infection with *Candida albicans* in patients with leukemia, atopy, and inflammatory bowel disease (Murtaugh et al., 2009). We previously reported that a SNP in *IL4* (rs2243248) was associated with risk of NHL in the Connecticut study (Lan et al., 2006). In the current study, *IL4* rs2243248 was also associated with risk of NHL even though the p trend from this SNP is not the lowest p value among all SNPs we genotyped in this gene. It is in moderate LD with the *IL4* SNP (rs2243263) that has the lowest p value for trend in this report ($r = 0.38$, $D' = 0.8$). The magnitude of risk estimates for these two SNPs were very similar. The results from this study provide additional evidence that genetic variation in *IL4* plays a role in the etiology of NHL and warrants further investigation.

There is substantial evidence in support of a role for IL10 in lymphomagenesis. We previously contributed data from the three case-control studies in this report to pooled analyses of the International InterLymph Consortium of case-control studies of NHL and results suggest an association between variants in *IL10* and risk of NHL overall and for DLBCL in particular and possibly other subtypes (Rothman et al., 2006; Skibola et al., 2010). We found a similar association for *IL10* rs1800890 and DLBCL in the three studies included in this report (Supplementary Table 4). Polymorphisms in genes encoding the *IL10*

receptor could interrupt IL10 mediated immune regulation and alter risk for NHL. Our findings in *IL10RB* support this hypothesis.

In summary, Th/Th2 cytokine genes play a critical role in mediating Th1/Th2 pathways, apoptotic potential, and regulation of inflammation. Any perturbation of homeostasis of the immune system could potentially alter risk for NHL. Our study provides evidence that common genetic variants in Th1 (*IL12A* and *IL12RB1*) and Th2 (*IL4*, *IL10RB*, and *IL18*) genes are associated with risk of NHL and one or more subtypes. Additional studies are needed to replicate and extend these findings, which will be facilitated by genome-wide scan efforts of NHL currently underway (Di Bernardo et al., 2008; Skibola et al., 2009;Conde et al., 2010) and being planned. If these findings are replicated in a larger study population, a comprehensive strategy of fine mapping across risk-related genes to identify potential functional SNPs should be pursued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Reference List

Andrie E, Michos A, Kalampoki V, Pourtsidis A, Moschovi M, Polychronopoulou S, thanasiadou-Piperopoulou F, Kalmanti M, Hatzakis A, Paraskevis D, Nieters A, Petridou ET. Genetic variants in immunoregulatory genes and risk for childhood lymphomas. Eur. J Haematol. 2009; 83:334–342. [PubMed: 19508433]

Arimitsu J, Hirano T, Higa S, Kawai M, Naka T, Ogata A, Shima Y, Fujimoto M, Yamadori T, Hagiwara K, Ohgawara T, Kuwabara Y, Kawase I, Tanaka T. IL-18 gene polymorphisms affect IL-18 production capability by monocytes. Biochem. Biophys. Res. Commun. 2006; 342:1413–1416. [PubMed: 16516851]

Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: a Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society B. 1995; 57:289–300.

Carlson CS, Eberle MA, Rieder MJ, Yi Q, Kruglyak L, Nickerson DA. Selecting a maximally informative set of single-nucleotide polymorphisms for association analyses using linkage disequilibrium. Am. J. Hum. Genet. 2004; 74:106–120. [PubMed: 14681826]

Chen BE, Sakoda LC, Hsing AW, Rosenberg PS. Resampling-based multiple hypothesis testing procedures for genetic case-control association studies. Genet. Epidemiol. 2006; 30:495–507. [PubMed: 16755536]

Chen DY, Hsieh CW, Chen KS, Chen YM, Lin FJ, Lan JL. Association of interleukin-18 promoter polymorphisms with WHO pathological classes and serum IL-18 levels in Chinese patients with lupus nephritis. Lupus. 2009a; 18:29–37. [PubMed: 19074166]

Chen X, Han S, Wang S, Zhou X, Zhang M, Dong J, Shi X, Qian N, Wang X, Wei Q, Shen H, Hu Z. Interactions of IL-12A and IL-12B polymorphisms on the risk of cervical cancer in Chinese women. Clin. Cancer Res. 2009b; 15:400–405. [PubMed: 19118071]

Chiu BC, Weisenburger DD. An update of the epidemiology of non-Hodgkin's lymphoma. Clin. Lymphoma. 2003; 4:161–168. [PubMed: 14715098]

Conde L, Halperin E, Akers NK, Brown KM, Smedby KE, Rothman N, Nieters A, Slager SL, Brooks-Wilson A, Agana L, Riby J, Liu J, Adami HO, Darabi H, Hjalgrim H, Low HQ, Humphreys K, Melbye M, Chang ET, Glimelius B, Cozen W, Davis S, Hartge P, Morton LM, Schenk M, Wang SS, Armstrong B, Kricker A, Milliken S, Purdue MP, Vajdic CM, Boyle P, Lan Q, Zahm SH, Zhang Y, Zheng T, Becker N, Benavente Y, Boffetta P, Brennan P, Butterbach K, Cocco P, Foretova L, Maynadie M, De SS, Staines A, Spinelli JJ, Achenbach SJ, Call TG, Camp NJ, Glenn M, Caporaso NE, Cerhan JR, Cunningham JM, Goldin LR, Hanson CA, Kay NE, Lanasa MC, Leis JF, Marti GE, Rabe KG, Rassenti LZ, Spector LG, Strom SS, Vachon CM, Weinberg JB, Holly EA, Chanock S, Smith MT, Bracci PM, Skibola CF. Genome-wide association study of follicular lymphoma identifies a risk locus at 6p21.32. Nat. Genet. 2010; 42:661–664. [PubMed: 20639881]

Di Bernardo MC, Crowther-Swanepoel D, Broderick P, Webb E, Sellick G, Wild R, Sullivan K, Vijayakrishnan J, Wang Y, Pittman AM, Sunter NJ, Hall AG, Dyer MJ, Matutes E, Dearden C, Mainou-Fowler T, Jackson GH, Summerfield G, Harris RJ, Pettitt AR, Hillmen P, Allsup DJ, Bailey JR, Pratt G, Pepper C, Fegan C, Allan JM, Catovsky D, Houlston RS. A genome-wide association study identifies six susceptibility loci for chronic lymphocytic leukemia. Nat. Genet. 2008; 40:1204–1210. [PubMed: 18758461]

Excoffier L, Slatkin M. Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population. Mol. Biol. Evol. 1995; 12:921–927. [PubMed: 7476138]

Fieschi C, Dupuis S, Catherinot E, Feinberg J, Bustamante J, Breiman A, Altare F, Baretto R, Le DF, Kayal S, Koch H, Richter D, Brezina M, Aksu G, Wood P, Al-Jumaah S, Raspall M, Da Silva Duarte AJ, Tuerlinckx D, Virelizier JL, Fischer A, Enright A, Bernhoft J, Cleary AM, Vermylen C, Rodriguez-Gallego C, Davies G, Blutters-Sawatzki R, Siegrist CA, Ehlayel MS, Novelli V, Haas WH, Levy J, Freihorst J, Al-Hajjar S, Nadal D, De M, V, Jeppsson O, Kutukculer N, Frecerova K, Caragol I, Lammas D, Kumararatne DS, Abel L, Casanova JL. Low penetrance, broad resistance, and favorable outcome of interleukin 12 receptor beta1 deficiency: medical and immunological implications. J Exp. Med. 2003; 197:527–535. [PubMed: 12591909]

Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de BL, Feinberg J, Jouanguy E, Boisson-Dupuis S, Fieschi C, Picard C, Casanova JL. Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin. Immunol. 2006; 18:347–361. [PubMed: 16997570]

Harada M, Obara K, Hirota T, Yoshimoto T, Hitomi Y, Sakashita M, Doi S, Miyatake A, Fujita K, Enomoto T, Taniguchi M, Higashi N, Fukutomi Y, Nakanishi K, Nakamura Y, Tamari M. A functional polymorphism in IL-18 is associated with severity of bronchial asthma. Am J Respir. Crit Care Med. 2009; 180:1048–1055. [PubMed: 19745201]

Hartge P, Devesa SS, Fraumeni JF Jr. Hodgkin's and non-Hodgkin's lymphomas. Cancer Surv. 1994; 19–20:423–453.

Higa S, Hirano T, Mayumi M, Hiraoka M, Ohshima Y, Nambu M, Yamaguchi E, Hizawa N, Kondo N, Matsui E, Katada Y, Miyatake A, Kawase I, Tanaka T. Association between interleukin-18 gene polymorphism 105A/C and asthma. Clin. Exp. Allergy. 2003; 33:1097–1102. [PubMed: 12911784]

Hirschfield GM, Liu X, Xu C, Lu Y, Xie G, Lu Y, Gu X, Walker EJ, Jing K, Juran BD, Mason AL, Myers RP, Peltekian KM, Ghent CN, Coltescu C, Atkinson EJ, Heathcote EJ, Lazaridis KN, Amos CI, Siminovitch KA. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. N. Engl. J Med. 2009; 360:2544–2555. [PubMed: 19458352]

Hoffmann SC, Stanley EM, Darrin CE, Craighead N, DiMercurio BS, Koziol DE, Harlan DM, Kirk AD, Blair PJ. Association of cytokine polymorphic inheritance and in vitro cytokine production in anti-CD3/CD28-stimulated peripheral blood lymphocytes. Transplantation. 2001; 72:1444–1450. [PubMed: 11685118]

Keen LJ. The extent and analysis of cytokine and cytokine receptor gene polymorphism. Transpl. Immunol. 2002; 10:143–146. [PubMed: 12216945]

Lan Q, Zheng T, Rothman N, Zhang Y, Wang SS, Shen M, Berndt SI, Zahm SH, Holford TR, Leaderer B, Yeager M, Welch R, Boyle P, Zhang B, Zou K, Zhu Y, Chanock S. Cytokine polymorphisms in the Th1/Th2 pathway and susceptibility to non-Hodgkin lymphoma. Blood. 2006; 107:4101–4108. [PubMed: 16449530]

Lee CC, Lin WY, Wan L, Tsai Y, Lin YJ, Tsai CH, Huang CM, Tsai FJ. Interleukin-18 gene polymorphism, but not interleukin-2 gene polymorphism, is associated with rheumatoid arthritis. Immunogenetics. 2007; 59:433–439. [PubMed: 17396252]

Liu Y, Lin N, Huang L, Xu Q, Pang G. Genetic polymorphisms of the interleukin-18 gene and risk of prostate cancer. DNA Cell Biol. 2007; 26:613–618. [PubMed: 17688413]

Morton LM, Turner JJ, Cerhan JR, Linet MS, Treseler PA, Clarke CA, Jack A, Cozen W, Maynadie M, Spinelli JJ, Costantini AS, Rudiger T, Scarpa A, Zheng T, Weisenburger DD. Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). Blood. 2007; 110:695–708. [PubMed: 17389762]

Murtaugh MP, Johnson CR, Xiao Z, Scamurra RW, Zhou Y. Species specialization in cytokine biology: is interleukin-4 central to the T(H)1-T(H)2 paradigm in swine? Dev. Comp Immunol. 2009; 33:344–352. [PubMed: 18761033]

Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 regulates both Th1 and Th2 responses. Annu. Rev. Immunol. 2001; 19:423–474. [PubMed: 11244043]

Neurath MF, Finotto S, Glimcher LH. The role of Th1/Th2 polarization in mucosal immunity. Nat. Med. 2002; 8:567–573. [PubMed: 12042806]

Nikiteas N, Yannopoulos A, Chatzitheofylaktou A, Tsigris C. Heterozygosity for interleukin-18 -607 A/C polymorphism is associated with risk for colorectal cancer. Anticancer Res. 2007; 27:3849–3853. [PubMed: 18225542]

Palmieri RT, Wilson MA, Iversen ES, Clyde MA, Calingaert B, Moorman PG, Poole C, Anderson AR, Anderson S, nton-Culver H, Beesley J, Hogdall E, Brewster W, Carney ME, Chen X, Chenevix-Trench G, Chang-Claude J, Cunningham JM, Dicioccio RA, Doherty JA, Easton DF, Edlund CK, Gayther SA, Gentry-Maharaj A, Goode EL, Goodman MT, Kjaer SK, Hogdall CK, Hopkins MP, Jenison EL, Blaakaer J, Lurie G, McGuire V, Menon U, Moysich KB, Ness RB, Pearce CL, Pharoah PD, Pike MC, Ramus SJ, Rossing MA, Song H, Terada KY, Vandenberg D, Vierkant RA, Wang-Gohrke S, Webb PM, Whittemore AS, Wu AH, Ziogas A, Berchuck A, Schildkraut JM. Polymorphism in the IL18 gene and epithelial ovarian cancer in non-Hispanic white women. Cancer Epidemiol. Biomarkers Prev. 2008; 17:3567–3572. [PubMed: 19064572]

Pawlik A, Wrzesniewska J, Florczak M, Gawronska-Szklarz B, Herczynska M. The -590 IL-4 promoter polymorphism in patients with rheumatoid arthritis. Rheumatol. Int. 2005; 26:48–51. [PubMed: 15660235]

Purdue MP, Lan Q, Kricker A, Grulich AE, Vajdic CM, Turner J, Whitby D, Chanock S, Rothman N, Armstrong BK. Polymorphisms in immune function genes and risk of non-Hodgkin lymphoma: findings from the New South Wales non-Hodgkin Lymphoma Study. Carcinogenesis. 2007; 28:704–712. [PubMed: 17056605]

R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2004

Rockman MV, Hahn MW, Soranzo N, Goldstein DB, Wray GA. Positive selection on a human-specific transcription factor binding site regulating IL4 expression. Curr. Biol. 2003; 13:2118–2123. [PubMed: 14654003]

Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, Spinelli JJ, Willett E, De SS, Cocco P, Berndt SI, Brennan P, Brooks-Wilson A, Wacholder S, Becker N, Hartge P, Zheng T, Roman E, Holly EA, Boffetta P, Armstrong B, Cozen W, Linet M, Bosch FX, Ennas MG, Holford TR, Gallagher RP, Rollinson S, Bracci PM, Cerhan JR, Whitby D, Moore PS, Leaderer B, Lai A, Spink C, Davis S, Bosch R, Scarpa A, Zhang Y, Severson RK, Yeager M, Chanock S, Nieters A. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006; 7:27–38. [PubMed: 16389181]

Schaid DJ, Rowland CM, Tines DE, Jacobson RM, Poland GA. Score tests for association between traits and haplotypes when linkage phase is ambiguous. Am. J. Hum. Genet. 2002; 70:425–434. [PubMed: 11791212]

Skibola CF, Bracci PM, Halperin E, Conde L, Craig DW, Agana L, Iyadurai K, Becker N, Brooks-Wilson A, Curry JD, Spinelli JJ, Holly EA, Riby J, Zhang L, Nieters A, Smith MT, Brown KM. Genetic variants at 6p21.33 are associated with susceptibility to follicular lymphoma. Nat. Genet. 2009; 41:873–875. [PubMed: 19620980]

Skibola CF, Bracci PM, Nieters A, Brooks-Wilson A, De SS, Hughes AM, Cerhan JR, Skibola DR, Purdue M, Kane E, Lan Q, Foretova L, Schenk M, Spinelli JJ, Slager SL, De Roos AJ, Smith MT, Roman E, Cozen W, Boffetta P, Kricker A, Zheng T, Lightfoot T, Cocco P, Benavente Y, Zhang Y, Hartge P, Linet MS, Becker N, Brennan P, Zhang L, Armstrong B, Smith A, Shiao R, Novak AJ, Maynadie M, Chanock SJ, Staines A, Holford TR, Holly EA, Rothman N, Wang SS. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. Am J Epidemiol. 2010; 171:267–276. [PubMed: 20047977]

Trinchieri G. Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. Annu. Rev. Immunol. 1995; 13:251–276. [PubMed: 7612223]

Wang SS, Cerhan JR, Hartge P, Davis S, Cozen W, Severson RK, Chatterjee N, Yeager M, Chanock SJ, Rothman N. Common genetic variants in proinflammatory and other immunoregulatory genes and risk for non-Hodgkin lymphoma. Cancer Res. 2006; 66:9771–9780. [PubMed: 17018637]

Wei YS, Lan Y, Liu YG, Tang H, Tang RG, Wang JC. Interleukin-18 gene promoter polymorphisms and the risk of esophageal squamous cell carcinoma. Acta Oncol. 2007; 46:1090–1096. [PubMed: 17851835]

Yamanaka K, Clark R, Dowgiert R, Hurwitz D, Shibata M, Rich BE, Hirahara K, Jones DA, Eapen S, Mizutani H, Kupper TS. Expression of interleukin-18 and caspase-1 in cutaneous T-cell lymphoma. Clin. Cancer Res. 2006; 12:376–382. [PubMed: 16428475]

Table 1

Demographic and pathology characteristics of study participants in the NCI-SEER, Connecticut, and New South Wales NHL case-control studies, by study and pooled

	NCI-SEER*		Yale		New South Wales		Pooled	
	Control	Case	Control	Case	Control	Case	Control	Case
	n=828	n=990	n=515	n=436	n=465	n=520	n=1808	n=1946
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Sex								
Male	443 (53)	536 (54)	-	-	268 (58)	304 (58)	711 (39)	840 (43)
Female	385 (47)	454 (46)	515 (100)	436 (100)	197 (42)	216 (42)	1097 (61)	1106 (57)
Age (years)								
< 50	203 (25)	277 (28)	98 (19)	86 (20)	107 (23)	121 (23)	408 (23)	484 (25)
50–59	177 (21)	235 (24)	97 (19)	89 (20)	135 (29)	171 (33)	409 (23)	495 (25)
60–69	285 (34)	311 (31)	120 (23)	110 (25)	151 (32)	154 (30)	556 (31)	575 (30)
70+	163 (20)	167 (17)	200 (39)	151 (35)	72 (16)	74 (14)	435 (24)	392 (20)
Race								
White	669 (81)	858 (87)	484 (94)	420 (96)	459 (99)	507 (98)	1612 (89)	1785 (92)
Black	112 (13)	64 (6)	14 (3)	13 (3)	-	-	126 (7)	77 (4)
Asian	16 (2)	32 (3)	3 (0.6)	1 (0.2)	6 (1)	13 (2)	25 (1)	46 (2)
Other/Unknown	31 (4)	36 (4)	14 (3)	2 (0.5)	-	-	45 (3)	38 (2)
Ethnicity								
Hispanic	41 (5)	52 (5)	18 (4)	6 (1)	-	-	59 (3)	58 (3)
Non-Hispanic	787 (95)	936 (95)	491 (95)	427 (98)	465 (100)	520 (100)	1743 (96)	1883 (97)
Unknown		2 (0.2)	6 (1)	3 (1)			6 (0.3)	5 (0.3)
Study Site								
Detroit	139 (17)	197 (20)	-	-	-	-	139 (8)	197 (10)
Iowa	246 (30)	301 (30)	-	-	-	-	246 (14)	301 (16)
L.A.	199 (24)	234 (24)	-	-	-	-	199 (11)	234 (12)
Seattle	244 (29)	258 (26)	-	-	-	-	244 (13)	258 (13)
Connecticut	-	-	515 (100)	436 (100)	-	-	515 (28)	436 (22)
N.S.W.	-	-	-	-	446 (96)	496 (95)	446 (25)	496 (26)
A.C.T.	-	-	-	-	19 (4)	24 (5)	19 (1)	24 (1)

	NCI-SEER*		Yale		New South Wales		Pooled	
	Control	Case	Control	Case	Control	Case	Control	Case
	n=828	n=990	n=515	n=436	n=465	n=520	n=1808	n=1946
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
NHL Subtype								
DLBCL	-	294 (30)	-	137 (31)	-	169 (33)	-	600 (31)
Follicular	-	246 (25)	-	103 (24)	-	191 (37)	-	540 (28)
CLL/SLL	-	101 (10)	-	43 (10)	-	17 (3)	-	161 (8)
Mantle Cell	-	40 (4)	-	10 (2)	-	19 (4)	-	69 (4)
Marginal Zone	-	82 (8)	-	29 (7)	-	49 (9)	-	160 (8)
LPL	-	24 (2)	-	9 (2)	-	23 (4)	-	56 (3)
MF/SS	-	18 (2)	-	10 (2)	-	3 (1)	-	31 (2)
Burkitt	-	11 (1)	-	0	-	3 (1)	-	14 (1)
Peripheral T	-	41 (4)	-	14 (3)	-	7 (1)	-	62 (3)
NOS	-	133 (13)	-	81 (19)	-	39 (7)	-	253 (13)
DNA Source								
Blood	598 (72)	688 (70)	515 (100)	436 (100)	465 (100)	520 (100)	1578 (87)	1644 (85)
Buccal	230 (28)	302 (30)	-	-	-	-	230 (13)	302 (15)

*Abbreviations: National Cancer Institute (NCI); non-Hodgkin lymphoma (NHL); Surveillance, Epidemiology, and End Results (SEER).

Table 2

Results for the minimum P value (minP test)* for 17 candidate Th1 and/or Th2 genes evaluated in the pooled analysis for NHL overall and by subtype

Candidate gene	NHL	DLBCL	FL	MZL	CLL
Th1					
IL2	0.75	0.64	0.87	0.70	0.39
IL12A¶	**0.021**¥	0.69	**0.015**	0.14	0.83
IL12B	0.59	0.51	0.58	0.99	0.86
IL12RB1†	**0.012**¥	0.15	0.092	0.43	0.12
IL12RB2	0.23	0.14	0.39	0.11	0.076
Th2					
IL13/IL4‡	**0.046**¥	**0.041**	0.35	**0.019**	0.13
IL4R	0.56	0.59	0.36	0.83	0.32
IL5	0.15	0.26	0.70	0.15	0.19
IL10/IL19	0.23	0.14	0.25	0.44	0.57
IL10RA	0.36	0.38	0.33	0.20	0.89
IL10RB§	**0.038**¥	0.40	0.08	0.41	0.72
IL18€	**0.044**¥	**0.023**	0.92	0.15	0.31
Th1/Th2					
CD5	0.17	0.28	0.11	0.48	0.90
CD28	0.98	0.63	0.97	0.15	0.59
IL9	0.079	0.14	0.18	0.17	0.61

*Bold type indicates P value of <0.05. The minP test assesses the true statistical significance of the smallest P(trend) within each gene (determined by dichotomous logistic regression, comparing NHL or NHL subtypes to controls; Analysis based on permutation-based resampling methods (10,000 permutations) that automatically adjust for the number of tag SNPs tested within that gene and the underlying linkage disequilibrium pattern (Chen et al., 2006). NHL indicates non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; and CLL/SLL chronic lymphocytic leukemia/small lymphocytic lymphoma.

Significant p-trend in logistic regression analyses:

¶IL12A: significant SNPs for NHL, rs485497; Follicular, rs485497, rs583911.

†IL12RB1: significant SNPs for NHL, rs2305742.

‡*IL4*: significant SNPs for NHL, rs2243263, rs2243248; DLBCL, rs2243263, rs2243248; MZL, rs2243291.

§ IL10RB: significant SNPs for NHL, rs1058867, rs2834176, rs2040107.

€ IL18: significant SNPs for NHL, rs243908, rs1946519; DLBCL, rs243908.

¥ FDR value based on testing all minP values < 0.20.

Table 3

Results for individual SNP for NHL in the pooled analysis, overall and by study*

						NCI SEER				Connecticut				New South Wales			
Genotype	**Controls (%)**	**Cases (%)**	**OR (95% CI)**	**p**	**FDR value**	**Control (%)**	**cases (%)**	**OR (95% CI)**	**P**	**Control (%)**	**cases (%)**	**OR (95% CI)**	**p**	**Control (%)**	**cases (%)**	**OR (95% CI)**	**p**
IL12A (rs485497)																	
GG	506 (28)	461 (24)				242 (29)	240 (24)			134 (26)	103 (24)			130 (28)	118 (23)		
AG	894 (50)	952 (49)	1.12 (0.96–1.31)	0.16		423 (51)	471 (48)	1.04 (0.83–1.31)	0.75	252 (49)	211 (48)	1.08 (0.78–1.49)	0.65	219 (47)	270 (52)	1.35 (0.99–1.84)	0.06
AA	403 (22)	526 (27)	1.37 (1.14–1.65)	**0.00097**		162 (20)	273 (28)	1.51 (1.15–1.99)	**0.0033**	127 (25)	122 (28)	1.29 (0.9–1.86)	0.17	114 (25)	131 (25)	1.24 (0.87–1.78)	0.23
AG or AA	1297 (72)	1478 (76)	1.19 (1.03–1.39)	**0.020**		585 (71)	744 (76)	1.16 (0.94–1.45)	0.18	379 (74)	333 (76)	1.15 (0.85–1.55)	0.38	333 (72)	401 (77)	1.31 (0.98–1.76)	0.06
Trend				**0.00099**	0.14				**0.0039**				0.17				0.22
*IL12RB1 (*rs2305741)																	
AA	1143 (64)	1287 (67)				509 (63)	659 (68)			332 (65)	292 (67)			302 (65)	336 (65)		
AC	563 (31)	566 (29)	0.86 (0.75–1)	**0.046**		263 (32)	276 (29)	0.76 (0.61–0.93)	**0.009**	159 (31)	129 (30)	0.92 (0.69–1.22)	0.56	141 (30)	161 (31)	1.04 (0.79–1.38)	0.76
CC	83 (5)	66 (3)	0.67 (0.48–0.94)	**0.020**		40 (5)	30 (3)	0.52 (0.32–0.86)	**0.010**	21 (4)	14 (3)	0.8 (0.4–1.62)	0.53	22 (5)	22 (4)	0.9 (0.49–1.66)	0.74
AC or CC	646 (36)	632 (33)	0.84 (0.73–0.96)	**0.013**		303 (37)	306 (32)	0.73 (0.59–0.89)	**0.0018**	180 (35)	143 (33)	0.91 (0.69–1.19)	0.48	163 (35)	183 (35)	1.02 (0.79–1.33)	0.86
Trend				**0.0047**	0.20				**0.00070**				0.43				0.99
IL4 (rs2243263)																	
GG	1425 (79)	1458 (76)				636 (78)	737 (76)			399 (78)	319 (74)			390 (84)	402 (77)		
CG	351 (20)	444 (23)	1.28 (1.09–1.51)	**0.0022**		169 (21)	223 (23)	1.21 (0.96–1.52)	0.11	109 (21)	107 (25)	1.22 (0.9–1.66)	0.20	73 (16)	114 (22)	1.53 (1.1–2.12)	**0.011**
CC	20 (1)	19 (1)	1.03 (0.54–1.97)	0.92		12 (1)	11 (1)	0.94 (0.4–2.19)	0.89	6 (1)	5 (1)	1 (0.3–3.31)	1.00	2 (0)	3 (1)	1.49 (0.25–9)	0.66
CG or CC	371 (21)	463 (24)	1.27 (1.09–1.49)	**0.0028**		181 (22)	234 (24)	1.19 (0.95–1.49)	0.13	115 (22)	112 (26)	1.21 (0.9–1.64)	0.22	75 (16)	117 (23)	1.53 (1.11–2.11)	**0.010**
Trend				**0.0056**	0.20				0.19				0.26				**0.012**
IL10RB (rs1058867)																	
AA	566 (31)	683 (35)				237 (29)	346 (35)			162 (32)	130 (30)			167 (36)	207 (40)		
AG	897 (50)	964 (50)	0.91 (0.79–1.06)	0.23		425 (51)	491 (50)	0.83 (0.67–1.03)	0.10	249 (48)	239 (55)	1.15 (0.86–1.55)	0.34	223 (48)	234 (45)	0.85 (0.64–1.12)	0.24
GG	343 (19)	295 (15)	0.74 (0.61–0.9)	**0.0024**		166 (20)	151 (15)	0.68 (0.51–0.9)	**0.0070**	103 (20)	66 (15)	0.8 (0.54–1.18)	0.25	74 (16)	78 (15)	0.86 (0.59–1.25)	0.43
AG or GG	1240 (69)	1259 (65)	0.87 (0.75–1)	**0.044**		591 (71)	642 (65)	0.79 (0.64–0.97)	**0.025**	352 (68)	305 (70)	1.05 (0.79–1.39)	0.73	297 (64)	312 (60)	0.85 (0.66–1.1)	0.22
Trend				**0.0037**	0.20				**0.0060**				0.43				0.30
IL18 (rs243908)																	
AA	831 (46)	958 (49)				376 (45)	483 (49)			247 (48)	223 (51)			208 (45)	252 (49)		

						NCI SEER				Connecticut				New South Wales			
Genotype	**Controls (%)**	**Cases (%)**	**OR (95% CI)**	**p**	**FDR value**	**Control (%)**	**cases (%)**	**OR (95% CI)**	**P**	**Control (%)**	**cases (%)**	**OR (95% CI)**	**p**	**Control (%)**	**cases (%)**	**OR (95% CI)**	**p**
AG	777 (43)	803 (41)	0.88 (0.76–1)	0.057		370 (45)	413 (42)	0.85 (0.7–1.04)	0.11	209 (41)	176 (40)	0.89 (0.68–1.17)	0.42	198 (43)	214 (42)	0.89 (0.68–1.16)	0.39
GG	194 (11)	175 (9)	0.77 (0.61–0.97)	**0.025**		81 (10)	90 (9)	0.86 (0.61–1.2)	0.36	59 (11)	36 (8)	0.64 (0.41–1.02)	0.06	54 (12)	49 (10)	0.75 (0.49–1.15)	0.18
AG or GG	971 (54)	978 (51)	0.85 (0.75–0.97)	**0.018**		451 (55)	503 (51)	0.85 (0.71–1.03)	0.10	268 (52)	212 (49)	0.84 (0.65–1.09)	0.18	252 (55)	263 (51)	0.86 (0.67–1.11)	0.24
Trend				**0.0093**	0.22				0.14				0.070				0.16

* Abbreviations: National Cancer Institute (NCI); non-Hodgkin lymphoma (NHL); Surveillance, Epidemiology, and End Results (SEER). P values less than 0.05 are bold.

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Table 4

Results for selected individual SNP from the pooled analysis for NHL subtypes*

Genotype	Controls (%)	DLBCL			Follicular			Marginal zone lymphoma			CLL/SLL			
		Cases (%)	OR (95% CI)	P	Cases (%)	OR (95% CI)	P	Cases (%)	OR (95% CI)	P	Cases (%)	OR (95% CI)	P	P†
IL12A (rs485497)														
GG	506 (28)	148 (25)			116 (22)			39 (24)			41 (26)			
AG	894 (50)	294 (49)	1.08 (0.86–1.35)	0.52	268 (50)	1.27 (0.99–1.63)	0.062	81 (51)	1.1 (0.73–1.64)	0.65	75 (47)	1.02 (0.68–1.52)	0.93	0.67
AA	403 (22)	156 (26)	1.25 (0.96–1.63)	0.10	153 (28)	1.59 (1.2–2.11)	**0.0012**	40 (25)	1.18 (0.74–1.89)	0.49	44 (28)	1.33 (0.84–2.11)	0.22	0.47
AG or AA	1297 (72)	450 (75)	1.13 (0.91–1.4)	0.27	421 (78)	1.37 (1.08–1.73)	**0.0093**	121 (76)	1.12 (0.77–1.65)	0.55	119 (74)	1.11 (0.76–1.62)	0.58	
Trend				0.11			**0.0012**			0.50			0.22	0.47
IL12RB1 (rs2305742)														
AA	1143 (64)	394 (67)			364 (68)			106 (67)			107 (67)			
AC	563 (31)	171 (29)	0.84 (0.69–1.04)	0.11	149 (28)	0.79 (0.64–0.99)	**0.038**	50 (31)	0.94 (0.66–1.34)	0.74	47 (30)	0.86 (0.6–1.23)	0.41	0.85
CC	83 (5)	22 (4)	0.73 (0.45–1.19)	0.21	23 (4)	0.82 (0.51–1.33)	0.42	3 (2)	0.38 (0.12–1.23)	0.11	5 (3)	0.61 (0.24–1.55)	0.30	0.65
AC or CC	646 (36)	193 (33)	0.83 (0.68–1.01)	0.068	172 (32)	0.8 (0.65–0.98)	**0.033**	53 (33)	0.87 (0.61–1.23)	0.43	52 (33)	0.83 (0.58–1.17)	0.29	
Trend				0.057			**0.050**			0.21			0.22	1.00
IL4 (rs2243263)														
GG	1425 (79)	436 (74)			410 (76)			123 (78)			118 (74)			
CG	351 (20)	144 (25)	1.42 (1.13–1.78)	**0.0023**	124 (23)	1.33 (1.05–1.69)	**0.018**	34 (22)	1.12 (0.75–1.68)	0.57	39 (25)	1.33 (0.91–1.96)	0.14	0.77
CC	20 (1)	7 (1)	1.31 (0.54–3.17)	0.55	4 (1)	0.82 (0.27–2.45)	0.72	1 (1)	0.69 (0.09–5.22)	0.72	2 (1)	1.29 (0.29–5.69)	0.74	0.85
CG or CC	371 (21)	151 (26)	1.41 (1.13–1.76)	**0.0021**	128 (24)	1.31 (1.03–1.65)	**0.025**	35 (22)	1.1 (0.74–1.64)	0.63	41 (26)	1.33 (0.91–1.94)	0.14	
Trend				**0.0031**			**0.047**			0.72			0.15	0.68
IL10RB (rs1058867)														
AA	566 (31)	203 (34)			211 (39)			58 (36)			54 (34)			
AG	897 (50)	305 (51)	0.99 (0.81–1.22)	0.94	246 (46)	0.79 (0.63–0.97)	**0.029**	82 (51)	0.91 (0.64–1.3)	0.61	85 (53)	0.97 (0.68–1.4)	0.88	0.34
GG	343 (19)	91 (15)	0.78 (0.59–1.04)	0.087	82 (15)	0.69 (0.51–0.92)	**0.012**	20 (13)	0.6 (0.35–1.02)	0.057	22 (14)	0.65 (0.39–1.09)	0.10	0.76
AG or GG	1240 (69)	396 (66)	0.93 (0.77–1.14)	0.51	328 (61)	0.76 (0.62–0.93)	**0.0080**	102 (64)	0.83 (0.59–1.17)	0.28	107 (66)	0.88 (0.62–1.25)	0.49	
Trend				0.14			**0.0055**			0.077			0.15	0.65
IL18 (rs243908)														
AA	831 (46)	312 (52)			251 (47)			85 (53)			74 (46)			
AG	777 (43)	235 (39)	0.78 (0.64–0.95)	**0.015**	225 (42)	0.91 (0.74–1.12)	0.38	62 (39)	0.77 (0.55–1.09)	0.14	68 (43)	0.96 (0.68–1.36)	0.83	0.51

Genotype	Controls (%)	DLBCL			Follicular			Marginal zone lymphoma			CLL/SLL			
		Cases (%)	OR (95% CI)	P	Cases (%)	OR (95% CI)	P	Cases (%)	OR (95% CI)	P	Cases (%)	OR (95% CI)	P	p†
GG	194 (11)	50 (8)	0.68 (0.49–0.96)	**0.028**	62 (12)	1.04 (0.75–1.44)	0.80	12 (8)	0.6 (0.32–1.12)	0.11	18 (11)	1 (0.58–1.72)	1.00	0.12
AG or GG	971 (54)	285 (48)	0.76 (0.63–0.92)	**0.0047**	287 (53)	0.94 (0.77–1.14)	0.51	74 (47)	0.74 (0.53–1.02)	0.070	86 (54)	0.97 (0.7–1.35)	0.86	
Trend				**0.0042**			0.82			**0.052**			0.92	0.092

*Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); National Cancer Institute (NCI); non-Hodgkin lymphoma (NHL); Surveillance, Epidemiology, and End Results (SEER). P values less than 0.05 are bold.

†The test for homogeneity among the NHL subtypes was conducted using the codominant model and the test for trend (additive model).