



Published in final edited form as:

*Br J Haematol.* 2009 June ; 145(5): 614–623. doi:10.1111/j.1365-2141.2009.07675.x.

## Risk of non-Hodgkin lymphoma in association with germline variation in complement genes

James R Cerhan<sup>1</sup>, Anne J. Novak<sup>2</sup>, Zachary S. Fredericksen<sup>3</sup>, Alice H. Wang<sup>3</sup>, Mark Liebow<sup>4</sup>, Timothy G. Call<sup>2</sup>, Ahmet Dogan<sup>5</sup>, Thomas E. Witzig<sup>2</sup>, Stephen M. Ansell<sup>2</sup>, Thomas M. Habermann<sup>2</sup>, Neil E. Kay<sup>2</sup>, and Susan L. Slager<sup>3</sup>

<sup>1</sup>Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota, 55905

<sup>2</sup>Division of Hematology, Department of Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, 55905

<sup>3</sup>Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota, 55905

<sup>4</sup>Division of General Internal Medicine, Department of Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, 55905

<sup>5</sup>Division of Hematopathology, Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota, 55905

### Summary

Germline mutations in complement genes have been associated with susceptibility to infections and autoimmune diseases, conditions that are associated with non-Hodgkin lymphoma (NHL) risk. To test the hypothesis that common genetic variation in complement genes affect risk of NHL, we genotyped 167 single nucleotide polymorphisms (SNPs) from 31 genes in 441 NHL cases and 475 controls. Principal components (PC) and haplotype analyses were used for gene-level tests of NHL risk, while individual SNPs were modeled as having a log-additive effect. In gene level PC analyses, *C2* ( $p=0.023$ ), *C5* ( $p=0.0032$ ) and *C9* ( $p=0.020$ ) were associated with NHL risk; haplotype analyses showed similar results, as well as a haplotype association for *C7* ( $p=0.046$ ). When all 4 genes were considered simultaneously, only *C5* and *C9* remained significant ( $p<0.05$ ). In SNP level results from these genes, 10 SNPs had a  $p<0.05$ . However, after correcting for multiple testing, only the *C5* SNPs rs7026551 ( $q=0.015$ ; OR=1.54, 95% CI 1.21-1.95) and rs2416810 ( $q=0.015$ ; OR=1.57; 95% CI 1.22-2.01), and the *C9* SNP rs187875 ( $q=0.015$ ; OR=0.68; 95% 0.56-0.84) remained noteworthy. Associations were similar for the common NHL subtypes. In summary, we provide evidence for a role of genetic variation in complement genes, particularly *C5* and *C9*, and NHL risk.

### Keywords

non-Hodgkin lymphoma; genetic variation; complement genes; epidemiology

---

Correspondence: James R. Cerhan, MD, PhD, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Phone: (507) 538-0499; Fax: (507) 266-2478; cerhan.james@mayo.edu.

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

## Introduction

Non-Hodgkin lymphoma (NHL) is the most commonly diagnosed hematologic malignancy in the United States, and the lifetime odds of developing NHL is 1 in 47 for men and 1 in 55 for women (Jemal, *et al* 2008). Lymphomagenesis is closely related to suppression of the cellular immune system, particularly in the setting of chronic antigenic stimulation (driving proliferation of the B-cell compartment) and genetic instability (from V(D)J recombination, somatic hypermutation, and class-switch recombination) (Shaffer, *et al* 2002). The strongest known epidemiologic risk factors for NHL are immune suppressed states due to primary immune deficiency diseases or acquired immune alterations (e.g., iatrogenic suppression in solid organ transplantation; disease-related); the risk of developing NHL in these patients is ten to several hundred times greater than the general population (Alexander, *et al* 2007). Other putative immune and inflammation-related risk factors for NHL include autoimmune diseases, atopy, asthma, later birth order, as well as infectious agents for specific NHL subtypes (Alexander, *et al* 2007, Chiorazzi and Ferrarini 2003). The latter epidemiologic data supporting a prominent role for immune dysfunction in the etiology of NHL leads to the hypothesis that NHL risk may be associated with variation in polymorphic genes that modulate immune function and regulation and response to inflammatory stimuli, for which there are growing empiric data (Cerhan, *et al* 2007a, Rothman, *et al* 2006, Skibola, *et al* 2007).

The complement system comprises a group of more than 30 proteins in a tightly regulated pathway of plasma proteins and membrane-bound regulators and receptors (Figure I) (Markiewski and Lambris 2007). Complement has long been known to play a central role in the innate immune response and functions to protect the host from pathogenic microorganisms. Complement has been further shown to play a prominent role as a mediator of inflammation, in the removal of immune complexes and apoptotic cells, and as a regulator of the immune response, including T-cell responses (Barrington, *et al* 2001, Kemper and Atkinson 2007, Markiewski and Lambris 2007). Complement can also target and remove tumor cells (Gorter and Meri 1999), although recent evidence suggest that in other settings it may also play a role in augmenting tumor growth (Markiewski, *et al* 2008). Germline mutations in complement genes have been associated with susceptibility to infections and autoimmune diseases (Crawford and Alper 2000, O'Neil 2000), conditions that have also been associated with NHL risk in many studies (Alexander, *et al* 2007). We therefore evaluated the hypothesis that common genetic variation in complement genes is associated with risk of NHL. We have previously reported our top results from an evaluation of 1253 immune genes (Cerhan, *et al* 2007a); here we report the specific results for the complement pathway also generated from that study, which have not been previously published.

## Materials and methods

### Study population and data collection

This study was reviewed and approved by the Human Subjects Institutional Review Board at the Mayo Clinic, and all participants provided written, informed consent. Full details of this on-going, clinic-based case-control study conducted at the Mayo Clinic in Rochester, Minnesota have been previously reported (Cerhan, *et al* 2007a). Briefly, we offered enrollment to consecutive patients with newly diagnosed (within nine months of first diagnosis), histologically-confirmed Hodgkin and non-Hodgkin lymphoma (including the subtype of chronic lymphocytic leukemia/small lymphocytic lymphoma) who were aged 20 years or older, HIV negative, and a resident of Minnesota, Iowa or Wisconsin at the time of diagnosis. All cases were reviewed and confirmed by a hematopathologist, and classified

according to the WHO criteria (Jaffe, *et al* 2001). Of the 956 eligible cases, 626 (65%) participated.

Clinic-based controls were selected from patients visiting the Mayo Clinic Department of Medicine for a pre-scheduled general medical exam. Eligibility requirements included being 20 years or older and a resident of Minnesota, Iowa or Wisconsin; patients were excluded if they had prior diagnoses of lymphoma, leukemia, or HIV infection. Controls were randomly selected and frequency matched to our cases by 5-year age group, gender, and region of residence. Of the 818 eligible controls, 572 (70%) participated.

All participants were asked to complete a self-administered risk-factor questionnaire and provide a blood sample. DNA was extracted using a standard procedure (Genra Inc., Minneapolis, MN). This (Phase 1) analysis included 498 cases and 497 controls enrolled from 9/1/02 through 9/30/05 and who had a DNA sample available at the time of genotyping (10/1/2005).

### Genotyping

This analysis of complement genes is part of a larger genotyping project to assess the role of immune and other candidate genes in the etiology of NHL. All of the genes and SNPs reported here were from the ParAllele (now Affymetrix) Immune and Inflammation SNP panel that included 1253 genes and 9412 SNPs, and full details of genotyping (including quality controls) for this panel have been previously published (Cerhan, *et al* 2007a). Briefly, genes were selected for their involvement in inflammation and immunity, and tagging SNPs for the 1253 genes were selected using CEPH (European-American) and Yoruba (African) samples from release 16 of the HapMap Consortium (The International HapMap Consortium 2003). Tagging SNPs covered 5 kb up and downstream of each gene with minor allele frequency (MAF)  $\geq 0.05$  and pairwise  $r^2$  threshold of 0.8. In addition, the panel included 748 validated non-synonymous SNPs. Genotyping was conducted at the Affymetrix facility using the Molecular Inversion Probe (MIP) genotyping technology (Hardenbol, *et al* 2005). Overall, the sample success rate was 98.75%, the assay call rate was 99.13%, and the concordance rate (based on 48 duplicates) was 98.95%. For this analysis, a total of 916 people (441 cases and 475 controls) passed all quality control measures, had NHL (Hodgkin lymphoma excluded) and were available for analysis (Cerhan, *et al* 2008).

### Statistical analysis

Allele frequencies from cases and controls were estimated using observed genotype frequencies. The genotype frequencies in the controls were compared to allele frequencies expected under Hardy-Weinberg Equilibrium using a Pearson goodness-of-fit test or Fisher's exact test (MAF < 0.05). In this analysis, there were 8 SNPs from the candidate genes that had a Hardy-Weinberg p-value of  $p < 0.05$  (see supplementary Table I); none of these SNPs were excluded from the analysis. We restricted our analyses to subjects whose self-reported race was Caucasian. Furthermore, we previously tested and found no evidence of population stratification in our data (Cerhan, *et al* 2007a, Cerhan, *et al* 2007b) using STRUCTURE (Pritchard, *et al* 2000).

Two methods were used to analyze the association of each gene with risk of NHL: haplotype and principal components analysis. For the haplotype analysis, all SNPs from a gene with HWE p-value for the controls greater than 0.0001 were used to determine haplotype frequencies, and a global score test was used, as implemented in the S-plus program *Haplo.stats* (Schaid, *et al* 2002). As a global gene test, we used principal components to create uncorrelated components that are linear combinations of the SNPs from a gene. These

components were then ranked according to the amount of the total SNP variance explained. The resulting smallest subset of components that accounted for at least 90% of the variability amongst the SNPs was included in a multivariable logistic regression model. A likelihood ratio test was then used to jointly test the significance of the selected principal components. This method decreases the dimensionality of the correlated SNPs by reducing the number of independent degrees of freedom (Gauderman, *et al* 2007). Gene level tests with  $p < 0.05$  were declared of interest.

Individual SNPs were examined using unconditional logistic regression to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) separately for heterozygotes and minor allele homozygotes, using homozygotes for the major allele as the reference. Each polymorphism was modeled as gene-dosage effect (i.e., a p-trend) in which the rare variant allele is arbitrarily chosen as the “high-risk” allele and the scores take on values of 0, 1, or 2 corresponding to the number of copies of the high-risk alleles. SNPs with a  $p < 0.05$  in the setting of a global gene test of  $p < 0.05$  were declared of interest. In exploratory analyses, we reported subtype results for SNPs declared of interest, as well as investigated logistic regression models that simultaneously modeled effects from multiple genes.

To assess the robustness of our results we calculated the tail strength for the genes and SNPs that we evaluated (Taylor and Tibshirani 2006). The tail strength assesses the overall statistical significance of testing for no association across all the SNPs or genes evaluated. A tail strength  $> 0$  indicates that you observe more significant findings than what is expected by chance. We also calculated q-values (Storey 2002) for the SNP level tests. A q-value is the expected proportion of false positives among significant results; q-values  $< 0.05$  were declared to be of interest.

Analyses were conducted using SAS (SAS Institute, Cary, NC, Version 8, 1999), S-Plus (Insightful Corp, Seattle, WA, Version 7.05, 2005), and R software systems. All analyses were adjusted for the design variables of age, gender, and county of residence.

## Results

There were 441 cases and 475 controls available for analysis. Compared to controls, cases were slightly younger (60.1 versus 61.7 years) and were less likely to have attended graduate or professional school (13.8% versus 20.3%), but were similar with respect to gender (58% of cases and 55% of controls were male) and state of residence (65% of cases and 67% of controls were from Minnesota) (See Supplemental Table II). The most common NHL subtypes were CLL/SLL (N=123), follicular (N=113), and DLBCL (N=69).

We evaluated 31 genes (Table I) from the complement pathway (Figure I). Gene coverage ranged from 5% to 100%, with a median coverage of 67% (Table II). Coverage was defined as the number of SNPs accounted for by a successfully genotyped tagSNP divided by the total number of SNPs, as defined by HapMap, within each complement gene. In gene level analysis, *C2*, *C5*, and *C9* were significant at a nominal  $p < 0.05$  in principal components analysis, which was in agreement with the haplotype results (Table II). In addition, *C7* was also statistically significantly associated with NHL risk in haplotype analysis ( $p = 0.046$ ) but not in the principle components analysis ( $p = 0.11$ ). The tail strength of this set of 31 genes from the principal components analysis was 0.26 (95% CI -0.09, 0.61). Simultaneous inclusion of the *C2* SNP ( $p = 0.068$ ) and the principal components for *C5* ( $p = 0.028$ ), *C7* ( $p = 0.19$ ), and *C9* ( $p = 0.044$ ) in the same statistical model suggested that the strongest signal ( $p < 0.05$ ) was from *C5* and *C9* (results not shown).

In Table III we report the SNP-level results for these 4 genes, and in Table IV we report the NHL subtype-specific results for SNPs that were significant at  $p < 0.05$  in Table III. For *C2*

we only genotyped one SNP (gene coverage, 25%) and this variant was associated with increased NHL risk overall (ordinal OR=1.32; 95% CI 1.04, 1.69). NHL subtype results were consistent with the overall associations reported in Table III.

For *C5*, 4 of the 14 typed SNPs had a  $p < 0.05$ , including 3 intronic SNPs and one non-synonymous coding SNP (rs17612), which leads to a missense protein change (Glu1437Asp). The latter variant was associated with an increased risk of NHL (ordinal OR=1.64; 95% CI 1.14, 2.35). The subtype results for the 4 SNPs from *C5* were generally consistent with the risk estimates for overall NHL, although the ORs were somewhat stronger (but not significantly so) for CLL/SLL.

For *C7*, 2 of the 12 typed SNPs had a  $p < 0.05$ , including one intronic SNP (ordinal OR=1.26; 95% CI 1.01, 1.58) and one non-synonymous coding SNP (OR=1.30; 95% CI 1.03, 1.62); the latter SNP is associated with a missense protein change (Thr587Pro). Both SNPs showed similar patterns for each of the NHL subtypes.

For *C9*, 3 of the 7 typed SNPs had a  $p < 0.05$ , and all were intronic. Subtype results were similar with overall results for the SNP rs187875, and variable for the other two SNPs.

With the exception of a SNP in *CR1*, no other SNPs in genes from the complement pathway were significant at  $p < 0.05$ . The tail strength test for the 167 SNPs was 0.14 (95% CI, -0.01, 0.29), and 3 of the SNPs had  $q$ -values  $< 0.05$ : rs7026551 from *C5* ( $q = 0.015$ ), rs2416810 from *C5* ( $q = 0.015$ ), and rs187875 from *C9* ( $q = 0.015$ ).

*C5* is adjacent to *TRAF1*, which we previously reported to be associated with risk of NHL in this study (Cerhan, *et al* 2007a). Figure II shows the  $p$ -values and LD pattern for the SNPs genotyped across this region, and suggests there are multiple signals across this region of the genome. When all significant SNPs in *C5* and *TRAF1* were included in the same logistic model, none of the SNPs were individually significant at  $p < 0.05$ .

## Discussion

In our analysis of genetic variation in the complement pathway and risk of NHL, we found evidence at the gene and SNP level for an association of *C2*, *C5*, *C7*, and *C9* with risk of NHL, and after accounting for multiple testing, SNPs from *C5* and *C9* remained noteworthy. Our results were broadly similar for the major NHL subtypes of CLL/SLL, follicular NHL and DLBCL, suggesting that these genes may play a general role in lymphomagenesis, although relatively small numbers for the selected subtypes and lack of data on the rarer subtypes makes this conclusion preliminary. Strengths of this study include the use of newly diagnosed patients from a regionally-defined clinic population, central pathology review, careful matching of clinic controls, and extensive quality controls for data collection and genotyping. Population stratification is unlikely to explain our results based on our restriction to Caucasians in the study and lack of evidence using the STRUCTURE program. However, by limiting to Caucasians of mainly northern European ancestry, we recognize that our results do not readily generalize to other racial and ethnic groups.

Both false positive and false negative results are a concern in association studies. To address false positive concerns generated from multiple testing, we first calculated the tail strength at both the gene and SNP level and found support that both the collection of genes and SNPs provide a clear signal over chance, although the 95% confidence intervals did not exclude zero. We also calculated  $q$ -values for individual SNPs, and two SNPs from *C5* and a single SNP from *C9* remained noteworthy at  $q < 0.05$ . False negatives are also a potential concern. While our analysis included nearly all of the genes from the complement pathway, the tagSNP coverage was variable (5 to 100%) and only 8 genes had  $\geq 80\%$  coverage, although



the median coverage was reasonable (67%). For lower coverage genes in particular, we cannot rule out a genetic association. There may be other genetic mechanisms (e.g., copy number variants) by which these genes could influence NHL. Ultimately, replication in independent populations will be required.

C2 is part of the classical pathway of the complement system, and activated C1 cleaves C2 into C2a and C2b, and C2a leads to the activation of C3 (Figure I). Deficiency in C2 is the most frequently inherited complement deficiency, affecting 1 in 20,000 Caucasians (Jonsson, *et al* 2005), and more than 90% of all C2 deficiency cases are thought to be due to a 28 base pair deletion in C2 gene of the HLA-B\*18,S042,DRB1\*15 MHC haplotype (Johnson, *et al* 1992). Approximately 50% of C2 deficient persons develop severe and/or repeated infections or an autoimmune disease, most commonly systemic lupus erythematosus, Henoch-Schonlein purpura, or polymyositis (Jonsson, *et al* 2005). Of additional interest, in age-related macular degeneration, a chronic degenerative disease thought to be due to chronic inflammation from deposition of complement proteins, a common risk haplotype and two protective haplotypes have been identified based on variants in *CFB* (L9H, R32Q) and *C2* (E318D, intron 10) (Gold, *et al* 2006), which was confirmed in a second study (Maller, *et al* 2006). None of our SNPs were in LD with these SNPs. Both *CFB* and *C2* are closely located to both the MHC class III region and the *TNF* loci. Thus, further characterization of this region is of high priority to identify one or more SNPs that could play a causal role in NHL.

C5 is composed of 2 disulfide-linked polypeptide chains, alpha (C5a) and beta (C5b), and is activated after cleavage by C3b (Figure I). C5a is a highly potent mediator of acute inflammatory reactions, while C5b-C9 compose the membrane attack complex (MAC), which can lead to direct lysis of target cells by complement-dependent cytotoxicity (CDC) (Guo and Ward 2005, Kemper and Atkinson 2007). C5a is a strong chemoattractant for a variety of inflammatory cells (neutrophils, eosinophils, monocytes, and T-lymphocytes), up-regulates expression of adhesion molecules on endothelial cells, and induces the release of a number of pro-inflammatory cytokines and chemokines including IL-1, IL-6, MCP-1, and TNF $\alpha$  (Guo and Ward 2005, Markiewski and Lambris 2007). C5a also mediates effector T-cell apoptosis, further emphasizing the importance of the complement pathway in regulating T-cell responses (Lalli, *et al* 2008). C5a is involved in sepsis, allergy and asthma (Guo and Ward 2005), and also appears to contribute to tumor growth in mice models, with the latter effect primarily due to the impact of C5a on the host microenvironment rather than tumor cells (Markiewski, *et al* 2008). Deficiencies of C5b-C9 are associated with recurrent and clinically mild to moderate infections by *Neisseria* species, particularly meningococcal and gonococcal (O'Neil 2000). Complement-mediated signaling can override the intracellular inhibitory mechanisms that maintain clonal anergy in B cells, and exposure to complement fixing bacteria may increase the risk of autoimmunity (Lyubchenko, *et al* 2007). Taken together, this suggests the hypothesis that inadequate control of infections may result in chronic B-cell receptor stimulation or T-cell/B-cell interactions and the subsequent development of a malignant clone.

C5 has also been identified as a susceptibility locus in asthma (Ober, *et al* 1998, Wjst, *et al* 1999) and hepatic fibrosis (Hillebrandt, *et al* 2005). Furthermore, one of the top hits from a recent genome-wide association study (GWAS) of rheumatoid arthritis (RA) identified a SNP in the intragenic region between *C5* and *TRAF1* (Plenge, *et al* 2007), which was further confirmed in a candidate gene study (Kurreaman, *et al* 2007). We previously identified *TRAF1*, which is involved in TNF signaling, as a top candidate gene in an analysis of over 1200 immune genes (Cerhan, *et al* 2007a). The combined results, shown in Figure II, suggest several SNPs that are of interest across this region; however, none of our SNPs were

in LD with the SNP from the RA GWAS. Since both genes are plausible candidates for both RA and NHL, and further fine mapping and functional studies are warranted.

Many types of solid tumors and hematologic malignancies have been shown to express molecules that regulate the complement cascade, including CD46, CD55, and CD59, and this may allow tumor cells to escape complement attack (Gorter and Meri 1999). We did not find evidence for genetic variation in these molecules impacting risk of NHL, but given that complement-dependent cellular cytotoxicity (CDCC) may be relevant to the mechanism of action for monoclonal antibody therapy in NHL including CLL/SLL (e.g., Rituximab), the role of genetic variation of these genes in NHL prognosis remains to be evaluated.

The role of genetic variation in immune genes and risk of NHL is still limited, but several patterns are emerging, including a role for genes encoding pro-inflammatory cytokines (Cerhan, *et al* 2007a, Rothman, *et al* 2006, Skibola, *et al* 2007). Furthermore, there are suggestions that genes involved in innate immunity, including *TLR2*, *TLR4*, *TLR6* and *CARD15* may also be susceptibility loci (Cerhan, *et al* 2007a, Forrest, *et al* 2006, Nieters, *et al* 2006, Wang, *et al* 2006). Complement activation can be initiated by the interaction of pattern recognition receptors such as TLRs, and given the central role of complement in innate immunity and the critical link it provides to adaptive immunity, further evaluation of this pathway is warranted.

In summary, we provide the first evidence for a role of genetic variation in complement genes, particularly *C5* and *C9*, and risk of NHL. These initial findings require replication, and the *C5-TRAF1* region in particular will require fine mapping to identify any causal variants.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

This study was funded, in part, by the National Institutes of Health (R01 CA92153; P50 CA97274). We thank Sondra Buehler for her editorial assistance.

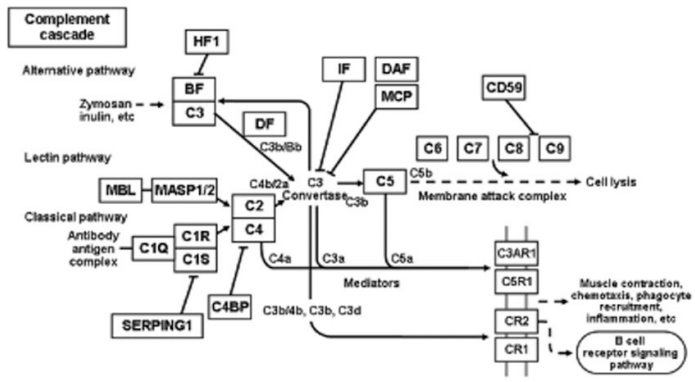
## References

- Alexander DD, Mink PJ, Adami HO, Chang ET, Cole P, Mandel JS, Trichopoulos D. The non-Hodgkin lymphomas: A review of the epidemiologic literature. *International Journal of Cancer*. 2007; 120:1–39.
- Barrington R, Zhang M, Fischer M, Carroll MC. The role of complement in inflammation and adaptive immunity. *Immunological Reviews*. 2001; 180:5–15. [PubMed: 11414363]
- Cerhan JR, Ansell SM, Fredericksen ZS, Kay NE, Liebow M, Call TG, Dogan A, Cunningham JM, Wang AH, Liu-Mares W, Macon WR, Jelinek D, Witzig TE, Habermann TM, Slager SL. Genetic variation in 1253 immune and inflammation genes and risk of non-Hodgkin lymphoma. *Blood*. 2007a; 110:4455–4463. [PubMed: 17827388]
- Cerhan JR, Liu-Mares W, Fredericksen ZS, Novak AJ, Cunningham JM, Kay NE, Dogan A, Liebow M, Wang AH, Call TG, Habermann TM, Ansell SM, Slager SL. Genetic variation in tumor necrosis factor and the nuclear factor- $\kappa$ B canonical pathway and risk of non-Hodgkin's Lymphoma. *Cancer Epidemiology, Biomarkers & Prevention*. 2008; 17:3161–3169.
- Cerhan JR, Wang S, Maurer MJ, Ansell SM, Geyer SM, Cozen W, Morton LM, Davis S, Severson RK, Rothman N, Lynch CF, Wacholder S, Chanock SJ, Habermann TM, Hartge P. Prognostic significance of host immune gene polymorphisms in follicular lymphoma survival. *Blood*. 2007b; 109:5439–5446. [PubMed: 17327408]

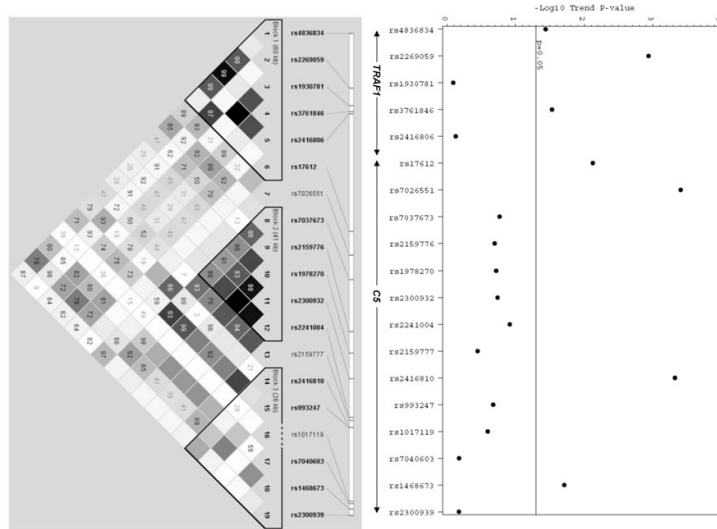
- Chiorazzi N, Ferrarini M. B cell chronic lymphocytic leukemia: lessons learned from studies of the B cell antigen receptor. *Annual Review of Immunology*. 2003; 21:841–894.
- Crawford K, Alper CA. Genetics of the complement system. *Reviews in Immunogenetics*. 2000; 2:323–338. [PubMed: 11256743]
- Forrest MS, Skibola CF, Lightfoot TJ, Bracci PM, Willett EV, Smith MT, Holly EA, Roman E. Polymorphisms in innate immunity genes and risk of non-Hodgkin lymphoma. *British Journal of Haematology*. 2006; 134:180–183. [PubMed: 16740140]
- Gauderman WJ, Murcay C, Gilliland F, Conti DV. Testing association between disease and multiple SNPs in a candidate gene. *Genetic Epidemiology*. 2007; 31:383–395. [PubMed: 17410554]
- Gold B, Merriam JE, Zernant J, Hancox LS, Taiber AJ, Gehrs K, Cramer K, Neel J, Bergeron J, Barile GR, Smith RT, Hageman GS, Dean M, Allikmets R. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. *Nature Genetics*. 2006; 38:458–462. [PubMed: 16518403]
- Gorter A, Meri S. Immune evasion of tumor cells using membrane-bound complement regulatory proteins. *Immunology Today*. 1999; 20:576–582. [PubMed: 10562709]
- Guo RF, Ward PA. Role of C5a in inflammatory responses. *Annual Review of Immunology*. 2005; 23:821–852.
- Hardenbol P, Yu F, Belmont J, Mackenzie J, Bruckner C, Brundage T, Boudreau A, Chow S, Eberle J, Erbilgin A, Falkowski M, Fitzgerald R, Ghose S, Iartchouk O, Jain M, Karlin-Neumann G, Lu X, Miao X, Moore B, Moorhead M, Namsaraev E, Pasternak S, Prakash E, Tran K, Wang Z, Jones HB, Davis RW, Willis TD, Gibbs RA. Highly multiplexed molecular inversion probe genotyping: over 10,000 targeted SNPs genotyped in a single tube assay. *Genome Research*. 2005; 15:269–275. [PubMed: 15687290]
- Hillebrandt S, Wasmuth HE, Weiskirchen R, Hellerbrand C, Keppeler H, Werth A, Schirin-Sokhan R, Wilkens G, Geier A, Lorenzen J, Kohl J, Gressner AM, Matern S, Lammert F. Complement factor 5 is a quantitative trait gene that modifies liver fibrogenesis in mice and humans. *Nature Genetics*. 2005; 37:835–843. [PubMed: 15995705]
- Jaffe, ES.; Harris, N.; Stein, H.; Vardiman, J. World Health Organization classification of tumours pathology and genetics, tumours of hematopoietic and lymphoid tissues. IARC Press; Lyon: 2001.
- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA: A Cancer Journal for Clinicians*. 2008; 58:71–96. [PubMed: 18287387]
- Johnson CA, Densen P, Hurford RK Jr, Colten HR, Wetsel RA. Type I human complement C2 deficiency. A 28-base pair gene deletion causes skipping of exon 6 during RNA splicing. *Journal of Biological Chemistry*. 1992; 267:9347–9353. [PubMed: 1577763]
- Jonsson G, Truedsson L, Sturfelt G, Oxelius VA, Braconier JH, Sjöholm AG. Hereditary C2 deficiency in Sweden: frequent occurrence of invasive infection, atherosclerosis, and rheumatic disease. *Medicine (Baltimore)*. 2005; 84:23–34. [PubMed: 15643297]
- Kemper C, Atkinson JP. T-cell regulation: with complements from innate immunity. *Nature Reviews Immunology*. 2007; 7:9–18.
- Kurreeman FA, Padyukov L, Marques RB, Schrodi SJ, Seddighzadeh M, Stoeken-Rijsbergen G, van der Helm-van Mil AH, Allaart CF, Verduyn W, Houwing-Duistermaat J, Alfredsson L, Begovich AB, Klareskog L, Huizinga TW, Toes RE. A candidate gene approach identifies the TRAF1/C5 region as a risk factor for rheumatoid arthritis. *PLoS Medicine*. 2007; 4:e278. [PubMed: 17880261]
- Lalli PN, Strainic MG, Yang M, Lin F, Medof ME, Heeger PS. Locally produced C5a binds to T cell-expressed C5aR to enhance effector T-cell expansion by limiting antigen-induced apoptosis. *Blood*. 2008; 112:1759–1766. [PubMed: 18567839]
- Lyubchenko T, Dal Porto JM, Holers VM, Cambier JC. Cutting edge: Complement (C3d)-linked antigens break B cell anergy. *Journal of Immunology*. 2007; 179:2695–2699.
- Maller J, George S, Purcell S, Fagerness J, Altshuler D, Daly MJ, Seddon JM. Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. *Nature Genetics*. 2006; 38:1055–1059. [PubMed: 16936732]



- Markiewski MM, DeAngelis RA, Benencia F, Ricklin-Lichtsteiner SK, Koutoulaki A, Gerard C, Coukos G, Lambris JD. Modulation of the antitumor immune response by complement. *Nature Immunology*. 2008; 9:1225–1235. [PubMed: 18820683]
- Markiewski MM, Lambris JD. The role of complement in inflammatory diseases from behind the scenes into the spotlight. *American Journal of Pathology*. 2007; 171:715–727. [PubMed: 17640961]
- Nieters A, Beckmann L, Deeg E, Becker N. Gene polymorphisms in Toll-like receptors, interleukin-10, and interleukin-10 receptor alpha and lymphoma risk. *Genes and Immunity*. 2006; 7:615–624. [PubMed: 16971956]
- O'Neil KM. Complement deficiency. *Clinical Reviews in Allergy and Immunology*. 2000; 19:83–108. [PubMed: 11107496]
- Ober C, Cox NJ, Abney M, Di Rienzo A, Lander ES, Changyaleket B, Gidley H, Kurtz B, Lee J, Nance M, Pettersson A, Prescott J, Richardson A, Schlenker E, Summerhill E, Willadsen S, Parry R. Genome-wide search for asthma susceptibility loci in a founder population. The Collaborative Study on the Genetics of Asthma. *Human Molecular Genetics*. 1998; 7:1393–1398. [PubMed: 9700192]
- Plenge RM, Seielstad M, Padyukov L, Lee AT, Remmers EF, Ding B, Liew A, Khalili H, Chandrasekaran A, Davies LR, Li W, Tan AK, Bonnard C, Ong RT, Thalamuthu A, Pettersson S, Liu C, Tian C, Chen WV, Carulli JP, Beckman EM, Altshuler D, Alfredsson L, Criswell LA, Amos CI, Seldin MF, Kastner DL, Klareskog L, Gregersen PK. TRAF1-C5 as a risk locus for rheumatoid arthritis—a genome-wide study. *New England Journal of Medicine*. 2007; 357:1199–1209. [PubMed: 17804836]
- Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. *Genetics*. 2000; 155:945–959. [PubMed: 10835412]
- Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, Spinelli JJ, Willett E, De Sanjose S, 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. *The Lancet Oncology*. 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. *American Journal of Human Genetics*. 2002; 70:425–434. [PubMed: 11791212]
- Shaffer AL, Rosenwald A, Staudt LM. Lymphoid malignancies: the dark side of B-cell differentiation. *Nature Reviews Immunology*. 2002; 2:920–932.
- Skibola CF, Curry JD, Nieters A. Genetic susceptibility to lymphoma. *Haematologica*. 2007; 92:960–969. [PubMed: 17606447]
- Storey JD. A direct approach to false discovery rates. *J R Statist Soc B*. 2002; 64:479–498.
- Taylor J, Tibshirani R. A tail strength measure for assessing the overall univariate significance in a dataset. *Biostatistics*. 2006; 7:167–181. [PubMed: 16332926]
- The International HapMap Consortium. The International HapMap Project. *Nature*. 2003; 426:789–796. [PubMed: 14685227]
- 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 Research*. 2006; 66:9771–9780. [PubMed: 17018637]
- Wjst M, Fischer G, Immervoll T, Jung M, Saar K, Rueschendorf F, Reis A, Ulbrecht M, Gomolka M, Weiss EH, Jaeger L, Nickel R, Richter K, Kjellman NI, Griese M, von Berg A, Gappa M, Riedel F, Boehle M, van Koningsbruggen S, Schoberth P, Szczepanski R, Dorsch W, Silbermann M, Wichmann HE, et al. A genome-wide search for linkage to asthma. *German Asthma Genetics Group. Genomics*. 1999; 58:1–8. [PubMed: 10333435]



**Figure 1. Schematic of the complement pathway**  
 Adapted from KEGG: Kyoto Encyclopedia of Genes and Genomes  
 (<http://www.genome.jp/kegg/>).



**Figure 2. *TRAF1* and *C5* gene structure and tagSNPs mapping**  
 Top:  $-\log_{10}$  p-value for tagSNPs, ordered by position; Bottom: Linkage disequilibrium plot of genotyped SNPs (numbers,  $|D'|$  values; darker shading higher  $r^2$  values of correlation between SNP).

**Table I**

Candidate genes evaluated from the complement pathway

Gene (alias)	Name	Gene ID*	Chromosome
<i>C1QB</i>	complement component 1, q subcomponent, B chain	713	1p36.12
<i>C1QC</i>	complement component 1, q subcomponent, C chain	714	1p36.11
<i>C1QTNF7</i>	C1q and tumor necrosis factor related protein 7	114905	4p16-p15
<i>C1RL</i>	complement component 1, r subcomponent-like	51279	12p13.31
<i>C1S</i>	complement component 1, s subcomponent	716	12p13
<i>C2</i>	complement component 2	717	6p21.3
<i>C3</i>	complement component 3	718	19p13.3-p13.2
<i>C3AR1</i>	complement component 3a receptor 1	719	12p13.31
<i>C4BPA</i>	complement component 4 binding protein, alpha	722	1q32
<i>C4BPB</i>	complement component 4 binding protein, beta	725	1q32
<i>C5</i>	complement component 5	727	9q33-q34
<i>C5AR1</i>	complement component 5a receptor 1	728	19q13.3-q13.4
<i>C6</i>	complement component 6	729	5p13
<i>C7</i>	complement component 7	730	5p13
<i>C8B</i>	complement component 8, beta polypeptide	732	1p32
<i>C9</i>	complement component 9	735	5p14-p12
<i>CD46 (MCP)</i>	CD46 molecule, complement regulatory protein	4179	1q32
<i>CD55 (DAF)</i>	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	1604	1q32
<i>CD59</i>	CD59 molecule, complement regulatory protein	966	11p13
<i>CD93 (C1QR1)</i>	CD93 molecule	22918	20p11.21
<i>CFB</i>	complement factor B	629	6p21.3
<i>CFD</i>	complement factor D (adipsin)	1675	19p13.3
<i>CFH</i>	complement factor H	3075	1q32
<i>CFHR1</i>	complement factor H-related 1	3078	1q32
<i>CFHR5</i>	complement factor H-related 5	81494	1q22-q23
<i>CLU</i>	Clusterin	1191	8p21-p12
<i>CR1</i>	complement component (3b/4b) receptor 1 (Knops blood group)	1378	1q32
<i>CR2</i>	complement component (3d/Epstein Barr virus) receptor 2	1380	1q32
<i>MASP2</i>	mannan-binding lectin serine peptidase 2	10747	1p36.3-p36.2
<i>MBL2</i>	mannose-binding lectin (protein C) 2, soluble (opsonic defect)	4153	10q11.2-q21
<i>SERPING1</i>	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hereditary)	710	11q12-q13.1

\* As defined in Entrez Gene

Table II

Gene-level results, Mayo Case-Control Study of NHL, 2002-2005

Gene (alias)	HapMap SNPs, N	SNPs genotyped, N	Gene coverage* SNPs p<0.05, N	Principal Components Analysis		Haplotype Analysis*	
				DF	p-value	N	p-value
<i>CTQB</i>	11	1	9%	1	0.43	0	0
<i>CTQC</i>	21	2	67%	2	0.15	3	0.13
<i>CTQTNF7</i>	122	12	92%	5	0.58	24	0.81
<i>CTRL</i>	20	1	5%	1	0.96	0	0
<i>CJS</i>	18	3	78%	1	0.96	3	0.65
<b>C2</b>	<b>20</b>	<b>1</b>	<b>25%</b>	<b>1</b>	<b>0.023</b>	<b>0</b>	<b>0</b>
<i>C3</i>	58	9	29%	6	0.83	34	0.29
<i>C3ARI</i>	5	2	100%	2	0.55	2	0.55
<i>C4BPA</i>	36	6	81%	4	0.29	19	0.45
<i>C4BPB</i>	13	1	77%	1	0.27	0	0
<b>C5</b>	<b>78</b>	<b>14</b>	<b>67%</b>	<b>4</b>	<b>0.0032</b>	<b>12</b>	<b>0.015</b>
<i>C5ARI</i>	6	2	100%	2	0.53	2	0.53
<i>C6</i>	84	15	83%	5	0.35	11	0.57
<b>C7</b>	<b>104</b>	<b>12</b>	<b>71%</b>	<b>5</b>	<b>0.11</b>	<b>21</b>	<b>0.046</b>
<i>C8B</i>	36	8	69%	5	0.39	22	0.33
<b>C9</b>	<b>57</b>	<b>7</b>	<b>39%</b>	<b>4</b>	<b>0.020</b>	<b>14</b>	<b>0.0078</b>
<i>CD46</i>	31	5	61%	2	0.10	5	0.14
<i>CD55</i>	27	2	96%	1	0.61	2	0.30
<i>CD59</i>	47	7	57%	4	0.46	10	0.35
<i>CD93</i>	18	1	11%	1	0.16	0	0
<i>CFB</i>	21	3	33%	3	0.18	3	0.19
<i>CFD</i>	9	1	11%	1	0.13	0	0
<i>CFH</i>	75	11	92%	4	0.91	11	0.26
<i>CFHR1</i>	3	1	33%	1	0.12	0	0
<i>CFHR5</i>	28	5	79%	3	0.67	4	0.82
<i>CLU</i>	22	6	68%	3	0.75	11	0.78
<i>CRI</i>	72	12	83%	5	0.48	20	0.28



Gene (alias)	HapMap SNPs, N	SNPs genotyped, N	Gene coverage*	SNPs p<0.05, N	Principal Components Analysis		Haplotype Analysis*	
					DF	p-value	N	p-value
<i>CR2</i>	43	9	63%	0	3	0.74	10	0.24
<i>MASP2</i>	12	1	58%	0	1	0.24	0	0
<i>MBL2</i>	45	5	44%	0	4	0.37	8	0.50
<i>SERPING1</i>	13	2	69%	0	2	0.74	3	0.56

\* As defined in Entrez Gene

\* SNPs from HapMap version Build 36 dbSNP 126, MAF>0.05, r<sup>2</sup> 0.8 and Caucasian

\* Gene coverage is defined as =(total HapMap SNPs – size of bins not tagged) / total HapMap SNPs

\* Number of haplotypes

**Table III**

SNP level associations from genes with  $p < 0.05$  from the gene level test (principal components or haplotype)

Gene	SNP ID*	Type*	Minor Allele Frequency		Adjusted OR (95% Confidence Interval)			p-trend
			Cases	Contr	Per copy of variant allele	1 copy of variant allele	2 copies of variant allele	
C2	Rs7746553	intronic	0.19	0.15	1.32 (1.04, 1.69)	1.50 (1.12, 2.01)	1.17 (0.56, 2.41)	0.023
	Rs17612	coding-ns	0.09	0.05	1.64 (1.14, 2.35)	1.63 (1.09, 2.42)	2.81 (0.54, 14.7)	0.0075
C5	Rs7026551	intronic	0.22	0.16	1.54 (1.21, 1.95)	1.66 (1.25, 2.22)	1.84 (0.91, 3.71)	0.00039
	rs7037673	intronic	0.42	0.45	0.88 (0.73, 1.06)	1.01 (0.75, 1.36)	0.73 (0.50, 1.08)	0.17
	rs2159776	intronic	0.43	0.46	0.89 (0.74, 1.07)	0.81 (0.60, 1.10)	0.80 (0.55, 1.16)	0.20
	rs1978270	intronic	0.36	0.39	0.88 (0.73, 1.07)	0.88 (0.66, 1.16)	0.78 (0.52, 1.17)	0.19
	rs2300932	intronic	0.37	0.40	0.88 (0.73, 1.06)	0.88 (0.67, 1.18)	0.77 (0.52, 1.15)	0.18
	rs2241004	intronic	0.36	0.39	0.86 (0.71, 1.04)	0.88 (0.66, 1.17)	0.73 (0.48, 1.09)	0.12
	rs2159777	intronic	0.49	0.47	1.09 (0.91, 1.31)	1.25 (0.91, 1.70)	1.18 (0.81, 1.70)	0.36
	<b>Rs2416810</b>	intronic	<b>0.20</b>	<b>0.14</b>	<b>1.57 (1.22, 2.01)</b>	<b>1.74 (1.30, 2.33)</b>	<b>1.52 (0.67, 3.45)</b>	<b>0.00048</b>
	rs993247	intronic	0.45	0.47	0.89 (0.74, 1.07)	1.04 (0.77, 1.41)	0.77 (0.53, 1.11)	0.21
	rs1017119	intronic	0.01	0.01	1.69 (0.68, 4.20)	1.69 (0.68, 4.20)		0.25
C7	rs7040603	intronic	0.23	0.24	0.95 (0.76, 1.19)	0.98 (0.75, 1.30)	0.82 (0.44, 1.56)	0.67
	<b>Rs1468673</b>	intronic	<b>0.44</b>	<b>0.39</b>	<b>1.26 (1.04, 1.52)</b>	<b>1.44 (1.07, 1.93)</b>	<b>1.48 (1.00, 2.20)</b>	<b>0.020</b>
	rs2300939	intronic	0.06	0.06	1.09 (0.74, 1.60)	1.13 (0.76, 1.70)	0.58 (0.05, 6.47)	0.67
	rs3792633	intronic	0.16	0.16	0.96 (0.74, 1.24)	0.88 (0.65, 1.17)	1.51 (0.60, 3.83)	0.75
	rs10512750	intronic	0.21	0.20	1.04 (0.83, 1.30)	1.25 (0.94, 1.67)	0.67 (0.35, 1.28)	0.75
	rs10512751	intronic	0.17	0.18	0.88 (0.69, 1.12)	0.77 (0.58, 1.03)	1.33 (0.59, 3.00)	0.30
	rs2455314	intronic	0.40	0.43	0.85 (0.70, 1.02)	0.88 (0.65, 1.17)	0.71 (0.48, 1.05)	0.090
	rs1450656	intronic	0.37	0.38	0.94 (0.77, 1.13)	0.87 (0.66, 1.16)	0.92 (0.61, 1.39)	0.50
	rs1063499	coding-ns	0.40	0.43	0.84 (0.69, 1.01)	0.88 (0.66, 1.18)	0.69 (0.46, 1.02)	0.069
	rs3805215	intronic	0.23	0.25	0.87 (0.70, 1.08)	0.92 (0.70, 1.21)	0.67 (0.37, 1.21)	0.21
C7	rs324058	intronic	0.23	0.24	0.99 (0.80, 1.23)	1.08 (0.81, 1.42)	0.85 (0.49, 1.48)	0.96
	<b>Rs13157656</b>	coding-ns	<b>0.27</b>	<b>0.22</b>	<b>1.30 (1.03, 1.62)</b>	<b>1.35 (1.03, 1.78)</b>	<b>1.45 (0.75, 2.80)</b>	<b>0.025</b>
	<b>Rs3805221</b>	intronic	<b>0.28</b>	<b>0.24</b>	<b>1.26 (1.01, 1.58)</b>	<b>1.28 (0.98, 1.68)</b>	<b>1.54 (0.84, 2.81)</b>	<b>0.037</b>
	rs3805226	intronic	0.08	0.10	0.85 (0.62, 1.16)	0.93 (0.65, 1.33)	0.40 (0.10, 1.51)	0.31
rs8264	mrna-utr	0.18	0.18	1.03 (0.81, 1.31)	1.13 (0.85, 1.51)	0.72 (0.33, 1.57)	0.84	

Gene	SNP ID*	Type*	Minor Allele Frequency			Adjusted OR (95% Confidence Interval)				p-trend
			Cases	Contr	Per copy of variant allele	1 copy of variant allele	2 copies of variant allele			
<i>C9</i>	rs3776541	intronic	0.07	0.06	1.24 (0.87, 1.78)	1.10 (0.74, 1.66)	3.53 (0.71, 17.66)	0.23		
	<b>Rs187875</b>	intronic	<b>0.34</b>	<b>0.42</b>	<b>0.68 (0.56, 0.84)</b>	<b>0.61 (0.45, 0.81)</b>	<b>0.51 (0.33, 0.80)</b>	<b>0.00024</b>		
	<b>Rs261752</b>	intronic	<b>0.43</b>	<b>0.49</b>	<b>0.78 (0.64, 0.94)</b>	<b>0.68 (0.50, 0.93)</b>	<b>0.62 (0.42, 0.91)</b>	<b>0.0099</b>		
	rs696758	intronic	0.07	0.06	1.32 (0.92, 1.91)	1.13 (0.75, 1.71)	7.19 (0.86, 60.12)	0.14		
	<b>Rs3776526</b>	intronic	<b>0.28</b>	<b>0.32</b>	<b>0.80 (0.65, 0.98)</b>	<b>0.92 (0.70, 1.22)</b>	<b>0.52 (0.32, 0.85)</b>	<b>0.029</b>		
	rs1421094	intronic	0.38	0.37	1.03 (0.86, 1.25)	1.01 (0.76, 1.34)	1.09 (0.73, 1.61)	0.72		
	rs700228	intronic	0.01	0.01	1.35 (0.53, 3.48)	1.35 (0.53, 3.48)		0.53		

\* Reference sequence ID from dbSNP

\* Type: int, intronic; coding-rs, non-synonymous coding; nma-utr, variation in transcript, but not in coding region interval.

**Table IV**

Adjusted ORs (95% confidence interval) for selected SNPs by NHL subtype\*

Gene	SNP ID	CLL/SLL			Follicular Lymphoma			DLBCL		
		Per copy of variant allele	p-trend	Per copy of variant allele	p-trend	Per copy of variant allele	p-trend	Per copy of variant allele	p-trend	
C2	rs7746553	1.56 (1.01, 2.41)	0.32	1.69 (1.07, 2.66)	0.0021	1.75 (1.02, 3.03)	0.0021	1.75 (1.02, 3.03)	0.17	
	rs17612	2.90 (1.73, 4.84)	0.00009	1.04 (0.53, 2.04)	0.43	1.45 (0.67, 3.13)	0.43	1.45 (0.67, 3.13)	0.18	
C5	rs7026551	2.25 (1.46, 3.45)	0.00006	1.35 (0.86, 2.12)	0.22	1.64 (0.95, 2.83)	0.22	1.64 (0.95, 2.83)	0.13	
	rs2416810	2.25 (1.46, 3.47)	0.0001	1.49 (0.95, 2.34)	0.19	1.73 (0.99, 3.01)	0.19	1.73 (0.99, 3.01)	0.067	
C7	rs1468673	2.06 (1.27, 3.33)	0.015	1.18 (0.75, 1.86)	0.91	1.54 (0.85, 2.76)	0.91	1.54 (0.85, 2.76)	0.15	
	rs1063499	0.62 (0.40, 0.96)	0.0021	1.37 (0.85, 2.20)	0.83	0.86 (0.48, 1.55)	0.83	0.86 (0.48, 1.55)	0.51	
C9	rs13157656	1.65 (1.09, 2.49)	0.062	1.49 (0.97, 2.29)	0.028	1.56 (0.92, 2.64)	0.028	1.56 (0.92, 2.64)	0.12	
	rs3805221	1.52 (1.01, 2.30)	0.12	1.33 (0.87, 2.04)	0.074	1.56 (0.92, 2.66)	0.074	1.56 (0.92, 2.66)	0.089	
C9	rs187875	0.65 (0.42, 1.00)	0.0071	0.67 (0.43, 1.05)	0.013	0.48 (0.28, 0.85)	0.013	0.48 (0.28, 0.85)	0.073	
	rs261752	0.96 (0.59, 1.54)	0.39	0.78 (0.49, 1.25)	0.026	0.45 (0.25, 0.81)	0.026	0.45 (0.25, 0.81)	0.075	
	rs3776526	0.96 (0.63, 1.45)	0.088	1.22 (0.79, 1.87)	0.45	0.80 (0.46, 1.37)	0.45	0.80 (0.46, 1.37)	0.21	

\* OR adjusted for age and sex; SNPs are those with p<0.05 from Table III.