



Meta- and Pooled Analyses

Tumor Necrosis Factor (*TNF*) and Lymphotoxin- α (*LTA*) Polymorphisms and Risk of Non-Hodgkin Lymphoma in the InterLymph Consortium

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In an International Lymphoma Epidemiology Consortium pooled analysis, polymorphisms in 2 immune-system-related genes, tumor necrosis factor (*TNF*) and interleukin-10 (*IL10*), were associated with non-Hodgkin lymphoma (NHL) risk. Here, 8,847 participants were added to previous data (patients diagnosed from 1989 to 2005 in 14 case-control studies; 7,999 cases, 8,452 controls) for testing of polymorphisms in the *TNF* -308G>A (rs1800629), lymphotoxin- α (*LTA*) 252A>G (rs909253), *IL10* -3575T>A (rs1800890, rs1800896), and nucleotide-binding oligomerization domain containing 2 (*NOD2*) 3020insC (rs2066847) genes. Odds ratios were estimated for non-Hispanic whites and several ethnic subgroups using 2-sided tests. Consistent with previous findings, odds ratios were increased for "new" participant *TNF*-308A carriers (NHL: per-allele odds ratio (OR_{allelic}) = 1.10, P_{trend} = 0.001; diffuse large B-cell lymphoma (DLBCL): OR_{allelic} = 1.23, P_{trend} = 0.004). In the combined population, odds ratios were increased for *TNF*-308A carriers (NHL: OR_{allelic} = 1.13, P_{trend} = 0.0001; DLBCL: OR_{allelic} = 1.25, P_{trend} = 3.7×10^{-6} ; marginal zone lymphoma: OR_{allelic} = 1.35, P_{trend} = 0.004) and *LTA* 252G carriers (DLBCL: OR_{allelic} = 1.12, P_{trend} = 0.006; mycosis fungoides: OR_{allelic} = 1.44, P_{trend} = 0.015). The *LTA* 252A>G/*TNF* -308G>A haplotype containing the *LTA*/*TNF* variant alleles was strongly associated with DLBCL (P = 2.9×10^{-8}). Results suggested associations between *IL10* -3575T>A and DLBCL (P_{trend} = 0.02) and *IL10* -1082A>G and mantle cell lymphoma (P_{trend} = 0.04). These findings strengthen previous results for DLBCL and the *LTA* 252A>G/*TNF* -308A locus and provide robust evidence that these *TNF*/*LTA* gene variants, or others in linkage disequilibrium, are involved in NHL etiology.

lymphoma; lymphoma, non-Hodgkin; lymphotoxin-alpha; meta-analysis; polymorphism, genetic; polymorphism, single nucleotide; tumor necrosis factor-alpha

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; HIV, human immunodeficiency virus; IL10, interleukin-10; LTA, lymphotoxin- α ; MZL, marginal zone lymphoma; NCI, National Cancer Institute; NOD2, nucleotide-binding oligomerization domain containing 2; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; SLL, small lymphocytic lymphoma; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor; UCSF, University of California, San Francisco.

There is evidence that genetic susceptibility plays a role in lymphomagenesis. Population-based studies show 2-fold risk elevations for non-Hodgkin lymphoma (NHL) among

persons with a family history of hematopoietic malignancies (1, 2). Furthermore, findings from case-control studies suggest associations between a small but growing number of

common genetic variants and risk of NHL (3). Immune system deregulation is an established risk factor for NHL, and common variations among immune-response genes are of particular interest in understanding the pathogenesis of lymphoma. Specifically, inflammatory response genes may play a role in chronic antigenic stimulation, which is a key mechanism for lymphomagenesis. Whereas immune signatures have been reported for follicular and Burkitt's lymphoma (4, 5), specific expression signatures involving genes that mediate inflammation have been reported in diffuse large B-cell lymphoma (DLBCL) (6).

We previously reported statistically significant associations between variants in 2 proinflammatory cytokine genes, tumor necrosis factor- α (*TNF* -308G>A) and interleukin-10 (*IL10* -3575T>A), and DLBCL among 3,586 Caucasian NHL cases and 4,018 Caucasian controls enrolled in 8 case-control studies that are part of the International Lymphoma Epidemiology (InterLymph) Consortium (7). An association between these single nucleotide polymorphisms (SNPs) and DLBCL, but not follicular lymphoma, indicated that genetic variation in inflammatory mediators such as *TNF* and *IL10* may play an essential role in DLBCL etiology. In our initial pooled analysis, we also noted statistically significant associations between DLBCL and 2 other polymorphisms in genes that contribute to nuclear factor- κ B activation, lymphotoxin- α (*LTA* 252A>G) and a C insertion that results in a frame-shift mutation in exon 11 of the nucleotide-binding oligomerization domain containing 2 (*NOD2*) gene (3020insC) (7). However, *LTA* 252A>G is in linkage disequilibrium with *TNF* -308G>A, and a haplotype analysis could not separate effects of risk for these 2 variants. The results for *NOD2* were limited by the rarity of the SNP (<1% frequency of homozygote variants). Furthermore, the sample was not large enough for us to evaluate the above associations with less common NHL subtypes or in other ethnic groups.

To confirm our initial findings, we evaluated *TNF* -308G>A, *IL10* -3575T>A, and *LTA* 252G>A in 6,601 human immunodeficiency virus (HIV)-negative non-Hispanic white participants (3,278 NHL cases and 3,323 controls) from 8 study centers not included in the previous pooled analyses (7). We then pooled all InterLymph study data (7,999 NHL cases and 8,452 controls) from 14 European, Canadian, Australian, and US case-control studies to increase precision and statistical power for analyzing the associations of the *TNF* -308G>A, *IL10* -3575T>A, *LTA* 252G>A, and *NOD2* 3020insC SNPs with NHL. We further extended our analyses to include other, rarer subtypes of NHL and other ethnic groups—that is, black, Hispanic, and Asian populations.

MATERIALS AND METHODS

Participating InterLymph studies

Participating studies from the InterLymph Consortium included the York, United Kingdom, lymphoma study (8); the Connecticut Women's NHL Study from Yale University (9); the National Cancer Institute (NCI)/Surveillance, Epidemiology, and End Results (SEER) Multi-Center Case-

Control Study (10); the Mayo Clinic NHL study (11); the New South Wales, Australia, lymphoma study (12); the British Columbia, Canada, NHL study (13); the University of California, San Francisco (UCSF)/University of California, Berkeley studies of NHL (2 studies, hereafter called UCSF1 and UCSF2) (14–16); and studies from Spain, Germany, France, the Czech Republic, Ireland, and Italy (Sardinia) that were part of a multicenter European study (EpiLymph) (17) (Table 1). Demographic data, including age at diagnosis for cases and age at interview for controls, sex, self-reported race and Hispanic/Latino ethnicity (or geographic ancestry for the EpiLymph and British Columbia studies), HIV status, histologic subtype classification and/or *International Classification of Diseases for Oncology* code for lymphoma diagnoses, and genotype data for the *TNF* -308G>A (rs1800629), *LTA* 252A>G (rs909253), *IL10* -3575T>A (rs1800890), *IL10* -1082A>G (rs1800896), and *NOD2* 3020insC (rs2066847) polymorphisms were obtained for each study. Cases were diagnosed with incident lymphoma between 1989 and 2005. Analyses were restricted to participants aged ≥ 18 years and to patients diagnosed with NHL, as some studies included other lymphatic malignancies. (See Table 1 for individual study characteristics.) Data were further restricted to HIV-negative, non-Hispanic white participants for the primary analyses. Hispanic ethnicity was defined per the US definition as someone of Mexican, Puerto Rican, or Latin-American descent—that is, an admixed population of Native American, Caucasian, and black/African ancestry. Therefore, Caucasian participants from EpiLymph Spain were included in the analyses of non-Hispanic whites, with the exception of several participants who met the definition of Hispanic ethnicity based on their parental ancestry information.

Histologic subtypes were grouped for analyses using the pathology coding scheme developed by InterLymph collaborators and study pathologists, which was based on the current World Health Organization classification (18). Outcomes for which results are presented include NHL and broad categories of NHL by cell lineage (B-cell, T-cell, and unknown), as well as specific subtypes, including DLBCL, follicular lymphoma, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma, marginal zone lymphoma (MZL) (further subdivided into extranodal MZL and other MZL), lymphoplasmacytic lymphoma, mycosis fungoides, and peripheral T-cell lymphoma.

Genotyping

SNPs were genotyped using either TaqMan (Applied Biosystems, Foster City, California) or Pyrosequencing (Qiagen NV, Hilden, Germany) (all EpiLymph studies). Assay conditions for TaqMan assays are available on the NCI's SNP500Cancer Web site (<http://snp500cancer.nci.nih.gov>). All laboratories genotyped a quality control set of DNA samples from 102 ethnically diverse individuals that had been previously sequenced and genotyped on 1 or more platforms to ensure consistent genotype calls. Genotyping was assessed and verified for accuracy across laboratories.

Table 1. Characteristics of Studies Included in Pooled Analyses of the Relation of *TNF*, *LTA*, *IL10*, and *NOD2* Genetic Polymorphisms to Non-Hodgkin Lymphoma, International Lymphoma Epidemiology Consortium, 1989–2005

Study (Ref.) ^a	No. Genotyped		Characteristics
	Cases (n = 7,999)	Controls (n = 8,452)	
EpiLymph studies (17)			
Spain	591	631	Both sexes, all subtypes, hospital-based controls
France	210	172	Both sexes, all subtypes, hospital-based controls
Germany	670	664	Both sexes, all subtypes, population-based controls
Sardinia, Italy	39	113	Both sexes, CLL only, population-based controls
Ireland	147	131	Both sexes, all subtypes, hospital-based controls
Czech Republic	292	260	Both sexes, all subtypes, hospital-based controls
York, United Kingdom (8)	777	824	Both sexes, predominantly diffuse large B-cell and follicular lymphomas; controls selected from general practice lists
New South Wales, Australia (12)	561	506	Both sexes, CLL not included, population-based controls
British Columbia, Canada (13)	797	793	Both sexes, all subtypes, population-based controls
NCI/SEER (United States) (10)	1,151	956	Both sexes, all subtypes, population-based controls
Yale University (New Haven, Connecticut) (9)	518	597	Women only, all subtypes, population-based controls
Mayo Clinic (Rochester, Minnesota) (11)	476	484	Both sexes, all subtypes, population-based controls
UCSF (San Francisco, California) (14–16)			
UCSF1	481	948	Both sexes, all subtypes, population-based controls
UCSF2	1,289	1,373	Both sexes, all subtypes, population-based controls

Abbreviations: CLL, chronic lymphocytic leukemia; ICDO-2, *International Classification of Diseases for Oncology*, Second Edition; *IL10*, interleukin-10; *LTA*, lymphotoxin- α ; NCI, National Cancer Institute; *NOD2*, nucleotide-binding oligomerization domain containing 2; SEER, Surveillance, Epidemiology, and End Results; *TNF*, tumor necrosis factor; UCSF, University of California, San Francisco.

^a Studies that contributed new data for these analyses: EpiLymph studies from France, Italy (Sardinia), Ireland, and the Czech Republic; New South Wales; British Columbia (for *TNF* and *IL10*-1082A>G single nucleotide polymorphisms); Mayo Clinic; and UCSF2. The Sardinia study center within EpiLymph contributed only patients who had been diagnosed with CLL (ICDO-2 code 9823) and their matched population-based controls. Studies included in the first pooled analyses included: EpiLymph Spain, EpiLymph Germany, United Kingdom, British Columbia, NCI/SEER, Yale, and UCSF1. In all studies, investigators had reviewed and classified the non-Hodgkin lymphoma subtypes for participating cases as part of the confirmation of non-Hodgkin lymphoma diagnoses. Prior to pooling, for the UCSF, New South Wales, Yale, and British Columbia studies, an expert review of diagnostic materials and/or pathology reports was conducted, and cases were coded per the working formulation, the Revised European-American Lymphoma classification, or the World Health Organization classification; for the EpiLymph studies, all cases were histologically confirmed (immunohistochemistry/flow cytometry was completed for 99%); and for the NCI/SEER study, all cases were histologically confirmed by each center's registry and were coded per the ICDO-2.

Statistical analyses

Statistical analyses were conducted using SAS, version 9 (SAS Institute Inc., Cary, North Carolina) and the haplo.stat 1.3.8 and metaplot packages in R, version 2.7.1 (R Foundation for Statistical Computing, Vienna, Austria). Risk estimates were obtained from unconditional logistic regression models, adjusted for age, sex, and study center. Heterogeneity of effects across studies was determined using a logit model in PROC GLIMMIX, where study center was included as a random variable. The contribution of individual studies to the overall effect estimates was assessed in sensitivity analyses. For each polymorphism, genotype was coded as an ordinal variable based on the number of variant alleles (0, 1, 2) and also as a dichotomous variable, assuming dominant inheritance (heterozygous/homozygous variant vs. homozygous wild-type genotypes). The most common homozygous genotype among control participants was used as the referent group. Tests for linear trend in risk

estimates were based on the Wald chi-squared statistic from adjusted logistic regression models, where genotype was included as an ordinal variable. Adjusted polytomous generalized logit regression models for categorical outcomes were used to determine heterogeneity of SNP effects across the DLBCL and follicular lymphoma subtypes.

Haplotype analyses of *TNF* and *IL10* genes were conducted using the R package haplo.stat (19). Gene-gene interaction between *TNF* and each of the *IL10* SNPs was assessed by comparing the difference in the -2 log-likelihoods from the main-effects and interaction models to a chi-squared statistic with degrees of freedom equal to the difference in the number of terms between the nested models. We also analyzed categorical variables of the joint *TNF* and *IL10* SNP genotypes grouped, where homozygous wild types for both SNPs were the referent group.

The large size of the pooled sample also allowed for exploratory analyses of genotype effects for NHL and common NHL subtypes (DLBCL and follicular lymphoma)

Table 2. Adjusted Odds Ratios in Validation Studies for Risk of All Non-Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma Associated With Polymorphisms in the *TNF* and *LTA* Genes, International Lymphoma Epidemiology Consortium, 1989–2005^a

Polymorphism and Genotype	Controls (n = 3,323)		All Non-Hodgkin Lymphoma (n = 3,278)				Diffuse Large B-Cell Lymphoma (n = 856)				Follicular Lymphoma (n = 715)			
	No.	%	No.	%	OR ^b	95% CI	No.	%	OR ^b	95% CI	No.	%	OR ^b	95% CI
<i>TNF</i> –308G>A (rs1800629)														
GG	2,297	71	2,162	68	1.0		543	65	1.0		489	71	1.0	
AG	858	27	899	28	1.09	0.98, 1.22	258	31	1.21	1.02, 1.44	167	24	0.86	0.71, 1.05
AA	79	2	130	4	1.69	1.27, 2.25	32	4	1.58	1.04, 2.42	32	5	1.69	1.09, 2.60
AG/AA	937	29	1,029	32	1.10	1.03, 1.27	290	35	1.23	1.06, 1.47	199	29	0.93	0.78, 1.12
<i>P</i> for trend ^c					0.001				0.004				0.83	
<i>LTA</i> –252A>G (rs909253)														
AA	1,242	46	1,133	43	1.0		271	40	1.0		245	45	1.0	
AG	1,148	43	1,172	45	1.08	0.96, 1.22	324	48	1.22	1.02, 1.46	236	44	0.93	0.76, 1.14
GG	295	11	311	12	1.12	0.93, 1.34	85	12	1.22	0.93, 1.61	59	11	0.89	0.65, 1.23
AG/GG	1,441	54	1,483	57	1.09	0.98, 1.22	409	60	1.22	0.84, 1.77	295	55	0.92	0.76, 1.12
<i>P</i> for trend ^c					0.13				0.04				0.39	

Abbreviations: CI, confidence interval; *LTA*, lymphotoxin- α ; OR, odds ratio; *TNF*, tumor necrosis factor; UCSF, University of California, San Francisco.

^a Results were based on new data from the following studies: EpiLymph studies from France, Italy (Sardinia), Ireland, and the Czech Republic; New South Wales; British Columbia; Mayo Clinic; and UCSF2. Analyses were restricted to human immunodeficiency virus-negative non-Hispanic white study participants.

^b Adjusted for age (as a continuous variable), sex, and study center.

^c Based on a 2-sided test for trend in the odds ratio when genotype was modeled as an ordinal variable.

among blacks/African Americans (NCI/SEER, Yale, and UCSF studies), Asians (British Columbia, NCI/SEER, New South Wales, and UCSF studies), and Hispanic whites (EpiLymph Spain, NCI/SEER, Yale, and UCSF studies). Of a total of 16,451 participants (7,999 cases and 8,452 controls), 14,498 HIV-negative non-Hispanic whites (7,034 cases and 7,464 controls), representing 88% of the total study population, were included in the overall analyses; of these, 6,601 (45.5%) had not been included in the earlier analyses (7). Investigators from several studies included in the initial pooled report (7) subsequently published additional study-specific findings (20, 21) that were included here. Data from the New South Wales and Mayo Clinic studies that were not included in the report were subsequently published separately (22, 23).

Participants at each study site provided written informed consent prior to interview and biospecimen collection. Procedures and protocols were approved by committees for the protection of human subjects at each institution.

Quality control assessment

To ensure that genotyping results were consistent across studies, each laboratory analyzed the same set of DNA samples from 102 ethnically diverse individuals as had previously been sequenced and genotyped for all SNPs on 1 or more platforms as part of the SNP500Cancer project (<http://snp500cancer.nci.nih.gov>) (24). The samples were obtained from the Coriell Institute for Medical Research (Camden, New Jersey; <http://www.coriell.org/>). We assessed concor-

dance across laboratories and rechecked quality control data for assays not in Hardy-Weinberg equilibrium (defined as $P < 0.05$) to confirm accuracy.

RESULTS

Table 1 shows characteristics of the individual studies that provided data for this project. This includes studies that contributed data to the initial InterLymph pooled analysis (7) and studies contributing new data (8,847 participants) to the current pooled analysis that comprised the validation study population.

Validation study population

These analyses included 6,601 HIV-negative non-Hispanic white participants (3,278 cases and 3,323 controls) from 8 study centers (EpiLymph studies in France, Italy, Ireland, and the Czech Republic; New South Wales; British Columbia; Mayo Clinic; and UCSF2) who were not included in the initial pooled analyses (7). Results from analyses restricted to these newly included cases and controls showed increasing risks of NHL and DLBCL among carriers of the *TNF* –308AA genotype (odds ratio (OR) = 1.69 ($P_{\text{trend}} = 0.001$) and OR = 1.58 ($P_{\text{trend}} = 0.004$), respectively; Table 2). Although the *TNF* –308AA genotype also was associated with an increased risk of follicular lymphoma (OR = 1.69, 95% confidence interval (CI): 1.09, 2.60), no effect on risk was observed for the –308GA genotype, nor was there a significant risk increase by allele ($P_{\text{trend}} = 0.84$).

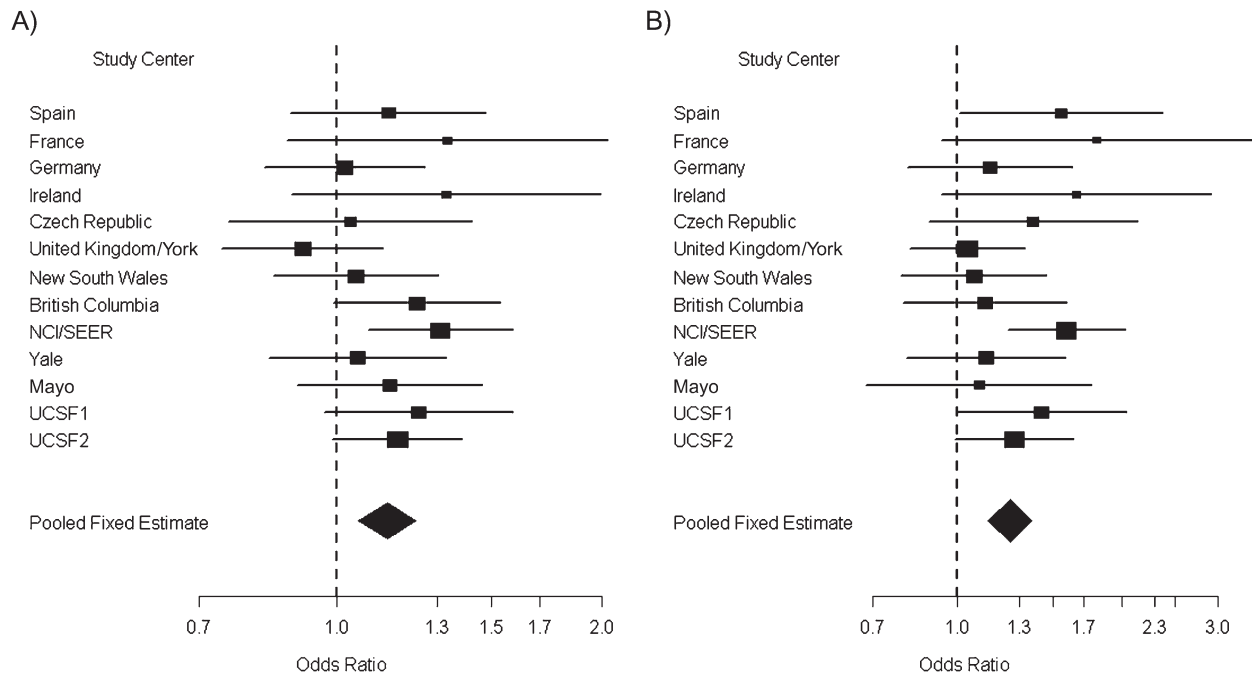


Figure 1. Odds ratios for the risks of A) all non-Hodgkin lymphoma and B) diffuse large B-cell lymphoma associated with tumor necrosis factor (*TNF*) -308G>A genotypes in individual studies (squares) and a pooled analysis (diamonds), International Lymphoma Epidemiology Consortium, 1989–2005. The sizes of the rectangles for individual studies are proportional to the weight (sample size) of each individual study in the pooled estimate. Odds ratios were derived from age- and sex-adjusted log-additive unconditional logistic regression models. Mayo, Mayo Clinic study; NCI/SEER, National Cancer Institute/Surveillance, Epidemiology, and End Results study; UCSF1 and UCSF2, University of California, San Francisco, studies 1 and 2; Yale, Yale University study. Bars, 95% confidence interval.

We also found that the *LTA* 252AG genotype was associated with an increased risk of DLBCL (OR = 1.22, 95% CI: 1.02, 1.46; $P_{\text{trend}} = 0.04$). *IL10* -1082A>G and -3575T>A SNP frequencies were similar between cases and controls. The positive associations between the *TNF* -308AA and *LTA* 252GG genotypes and risk of DLBCL are consistent with our previous report (7) (*TNF* -308AA: OR = 1.65, 95% CI: 1.16, 2.34; *LTA* 252GG: OR = 1.47, 95% CI: 1.18, 1.84) and justified pooling of the new and previous data to increase precision and statistical power, especially for analyses of rarer subtypes and smaller ethnic subgroups.

Population demographic characteristics and NHL subtypes

Of the combined 14,498 HIV-negative non-Hispanic white participants, ages at diagnosis ranged from 18 years to 89 years, with a median age at diagnosis of 60 years (interquartile range, 19 years). There were slightly more men (52%) than women (48%) in the pooled case group. Per the Inter-Lymph pathology group classification of NHL subtypes (18), 77% of cases were of B-cell lineage (of these, 34% were DLBCL, 26% were follicular lymphoma, and 16% were CLL/SLL), 5% of lymphomas were of T-cell lineage (of these, 35% were mycosis fungoides and 58% were peripheral T-cell lymphoma), and 18% were unclassified.

SNP and haplotype results among non-Hispanic whites

TNF -308G>A. For each study center, all SNPs were in Hardy-Weinberg equilibrium in the non-Hispanic white controls ($P \geq 0.01$). Increased NHL risk was observed for carriers of the variant allele for *TNF* -308G>A per allele, OR = 1.13; $P_{\text{trend}} = 0.0001$ (see Web Table 1, which is posted on the *Journal's* Web site (<http://aje.oxfordjournals.org/>)). Consistent with *TNF* -308G>A results for all NHL, increasing risks also were observed for B-cell NHL (per allele, OR = 1.12; $P_{\text{trend}} = 0.0007$), DLBCL (per allele, OR = 1.25; $P_{\text{trend}} = 3.7 \times 10^{-6}$), and other MZL (per allele, OR = 1.35; $P_{\text{trend}} = 0.004$). When study center was modeled as a random variable, the EpiLymph France, EpiLymph Italy, NCI/SEER, and UCSF1 study effects were significantly different from the average effect across studies. However, exclusion of data from these studies resulted in small changes in the odds ratio estimates obtained from the adjusted models with study center included as a fixed-effect variable. Figure 1 shows the study-specific and pooled adjusted risk estimates from fixed-effect models for *TNF* -308G>A for all NHL and DLBCL. No associations with *TNF* -308G>A were observed with CLL/SLL or with lymphomas broadly grouped as being of T-cell lineage. However, results from analyses of specific T-cell subtypes showed some evidence of an increasing risk of mycosis fungoides with *TNF* -308A (per allele, OR = 1.46; $P = 0.026$). Furthermore, polytomous analyses showed that

Table 3. Adjusted Odds Ratios for Risk of All Non-Hodgkin Lymphoma and Diffuse Large B-Cell Lymphoma Associated With *LTA* 252A>G/*TNF* -308G>A and *IL10*-1082A>G/*IL10*-3575T>A Haplotypes, International Lymphoma Epidemiology Consortium, 1989–2005

Haplotype	All Non-Hodgkin Lymphoma				P Value	Diffuse Large B-Cell Lymphoma				P Value
	Frequency, %		OR ^a	95% CI		Frequency, %		OR ^a	95% CI	
	Cases	Controls				Cases	Controls			
<i>LTA</i> 252A>G/ <i>TNF</i> -308G>A										
AG	66.3	67.7	1.0			64.3	67.7	1.0		
GG	16.0	16.6	0.99	0.93, 1.06	0.78	16.0	16.6	1.01	0.91, 1.12	0.85
GA	17.4	15.5	1.14	1.07, 1.22	4.3×10^{-5}	19.4	15.5	1.31	1.19, 1.44	2.9×10^{-8}
AA	0.2	0.2	0.99	0.58, 1.70	0.97	0.3	0.2	1.50	0.73, 3.08	0.26
Global score P value ^b	4.1×10^{-4}					2.5×10^{-7}				
<i>IL10</i> -1082A>G/ <i>IL10</i> -3575T>A										
AT	51.7	53.0	1.0			50.5	53.0	1.0		
GA	38.5	37.0	1.07	1.02, 1.13	0.01	40.3	37.0	1.14	1.06, 1.23	7.2×10^{-4}
GT	9.4	9.5	1.01	0.92, 1.10	0.84	8.8	9.5	0.97	0.85, 1.10	0.62
AA	0.3	0.4	0.80	0.53, 1.19	0.27	0.4	0.4	1.05	0.60, 1.84	0.86
Global score P value ^b	0.039					0.005				

Abbreviations: CI, confidence interval; *IL10*, interleukin-10; *LTA*, lymphotoxin- α ; OR, odds ratio; *TNF*, tumor necrosis factor.

^a Estimates were derived from the additive model with adjustment for sex, age, and study center, using the most common haplotype as the reference group.

^b Based on a 2-sided global score test.

lymphoma risk for persons with the *TNF* -308 A allele differed between DLBCL patients and follicular lymphoma patients ($P = 0.0002$).

LTA 252A>G, *IL10* -1082A>G, *IL10* -3575T>A, and *NOD2* 3020insC. Although there was no association between risk of all NHL and polymorphisms in *LTA* 252A>G, *IL10* -1082A>G, *IL10* -3575T>A, or *NOD2* 3020insC, there was evidence of associations with specific NHL subtypes (Web Table 1 (<http://aje.oxfordjournals.org/>)). Results showed increased DLBCL risk for carriers of variant alleles for *LTA* 252A>G (per allele, OR = 1.12; $P_{\text{trend}} = 0.006$) and *IL10* -3575T>A (per allele, OR = 1.10; $P_{\text{trend}} = 0.02$). In addition, increasing risk estimates were observed for mantle cell lymphoma with *IL10* -1082A>G (per allele, OR = 1.30; $P_{\text{trend}} = 0.04$), where risk was increased 67% among persons with the GG genotype, and for extranodal MZL, where risk was increased 88% among persons with the *IL10* -3575AA genotype (per allele, OR = 1.30). Furthermore, the *LTA* 252GG genotype was associated with mycosis fungoides (per allele, OR = 1.44; $P_{\text{trend}} = 0.015$), where risk was increased more than 2-fold. A nearly 9-fold increased risk of MZL among persons who were homozygous-variant for *NOD2* 3020insC also was observed (OR = 8.82, 95% CI: 2.33, 33), but results were based on few homozygous insC cases and controls (per allele, OR = 1.49; $P_{\text{trend}} = 0.03$). No associations were found between *TNF*, *IL10*, and *NOD2* polymorphisms and CLL/SLL risk. In polymorphic analyses, lymphoma risk differed between DLBCL and follicular lymphoma patients among carriers of the variant allele for *LTA* 252A>G ($P = 0.002$) but not for *IL10* -3575T>A ($P = 0.24$).

Haplotypes. *LTA/TNF* haplotype analyses showed that the most common haplotype (67%) in the study population

included the wild-type allele (AG) for both SNPs (Table 3). The adjusted overall global score statistic indicated that haplotype frequencies differed between NHL cases and control participants ($P = 4.1 \times 10^{-4}$). Most pronounced were results for DLBCL, where we observed a 31% increased risk of DLBCL among carriers of both variant alleles (GA) as compared with AG carriers (Table 3; adjusted $P = 2.9 \times 10^{-8}$). Haplotype analyses of the *IL10* -1082A>G and *IL10* -3575T>A SNPs showed that the most common haplotype (52%) was that with the wild-type alleles (AT) of both SNPs (Table 3). Haplotype frequencies differed between NHL cases and controls (adjusted global score statistic: $P = 0.04$). Carriers of the *IL10* GA haplotype versus the AT haplotype had an increased risk of DLBCL (OR = 1.14, 95% CI: 1.06, 1.23; $P = 7.2 \times 10^{-4}$).

Analyses of ethnic subgroups

There were nearly 600 Asian participants (289 cases and 286 controls from the New South Wales, British Columbia, NCI/SEER, and UCSF studies), more than 350 black/African-American participants (140 cases and 227 controls from the NCI/SEER, Yale, and UCSF studies), and more than 350 white participants of Hispanic/Latino ethnicity (172 cases and 206 controls from the EpiLymph Spain, NCI/SEER, Yale, and UCSF studies) in the analysis, affording us an opportunity to explore associations between the variants under study and NHL (overall and the most common subtypes) within these ethnic groups. Exploratory analyses (see Web Tables 2–4 (<http://aje.oxfordjournals.org/>)) suggested that among black/African-American participants, the *TNF*-308A allele conferred a nearly 3-fold increased risk of DLBCL ($P_{\text{trend}} = 0.02$) (Web Table 2). Among Hispanic

white participants, exploratory analyses showed a nearly 2-fold increased risk of B-cell lymphoma (Web Table 3), largely for the DLBCL subtype, among persons who carried either *IL10* variant allele. In contrast, reduced risk of B-cell lymphoma was observed among Asian participants with the *TNF*-308A allele (Web Table 4).

DISCUSSION

This study provides further evidence that variant alleles in *LTA* 252A>G, *IL10* -3575T>A, and (particularly) *TNF* -308G>A are associated with an increased risk of DLBCL in non-Hispanic white populations, as indicated in a previous analysis by the InterLymph Consortium (7). By pooling all of the cases and controls in the largest genetic study of NHL to date, we were able to investigate the influence of these SNPs on rarer subtypes of NHL. Here, we found that the *TNF* -308A allele was positively associated with risks of MZL and mycosis fungoides in non-Hispanic whites. These findings suggest a potentially common proinflammatory etiology in the pathogenesis of DLBCL, MZL, and mycosis fungoides. Moreover, in analyses of other ethnic groups, the *TNF* -308A allele conferred an increased risk of DLBCL in blacks and reduced risks of all NHL and B-cell lymphoma in Asians. Among Hispanic white participants, a nearly 2-fold increased risk of B-cell lymphoma also was observed, particularly for DLBCL, in persons who carried the *IL10* -1082A>G or *IL10* -3575T>A variant alleles. This study highlights the effect of genetic variation in the *TNF*, *LTA*, *IL10*, and *NOD2* genes on risk of DLBCL and rare subtypes of lymphoma, as well as risk of B-cell lymphoma in other ethnic groups.

Because of linkage disequilibrium, we were unable to unambiguously determine whether the *LTA* and *TNF* SNPs exerted independent effects on NHL risk (linkage disequilibrium: $D' = 1.0$, $r^2 = 0.38$). However, in haplotype analyses, we found that persons with the GA haplotype (variant alleles for *LTA* 252A>G and *TNF*-308G>A) had an increased risk of DLBCL ($P = 2.9 \times 10^{-8}$; Table 3), whereas the AA haplotype (wild type for *LTA* and variant for *TNF*) did not influence DLBCL risk. This suggests an independent effect of the *TNF*-308G>A SNP on DLBCL risk; functional studies will be needed to dissect the effects of these variants. Because the *TNF/LTA* locus lies in the major histocompatibility complex class III region and is in long-range linkage disequilibrium with a highly conserved ancestral haplotype, these alleles may be linked to causal major histocompatibility complex SNPs or allelotypes that are part of an extended haplotype. Studies show that Caucasian populations carry an 8.1 ancestral haplotype containing the *TNF* -308A allele (*2), HLA-A1-B8-TNF-308*2-DR3-DQ2 (25), that has been implicated in susceptibility to autoimmune diseases, including rheumatoid arthritis, Crohn's disease, and systemic lupus erythematosus (26, 27). In contrast, the *TNF* -308A allele occurs as part of a 58.1 ancestral haplotype, HLA-A33-B58-TNF-308*2-DR3, that is found in Asian populations (28). Further studies will be needed to determine whether these extended haplotypes might explain the differences observed between the *TNF*-308A allele and

risk of lymphoma in Caucasians and Asians. Moreover, fine mapping and functional studies of SNPs across this region will be required to determine whether the *TNF* -308G>A and *LTA* 252A>G SNPs constitute distinct susceptibility alleles or whether they are linked to other causal major histocompatibility complex loci.

The *TNF* -308A allele enhances transcriptional activation (29, 30) and *TNF*- α production (30) and has been implicated as a pathogenic mediator of numerous cancers (31). As a major proinflammatory cytokine, *TNF*- α may function as a bridge between inflammation and cancer through its roles in promoting cell transformation, proliferation, survival, invasion, and angiogenesis. Our findings suggest that this proinflammatory mechanism may provide a T-cell-fueled proinflammatory milieu that may be involved in the pathogenesis of DLBCL, and possibly MZL and mycosis fungoides, although validation studies of this association will be required for these rare NHL subtypes. Interleukin-10 plays an antiinflammatory role by down-regulating proinflammatory cytokines, including *TNF*- α (32). Because the *IL10* -3575A allele results in decreased interleukin-10 production (33), this allele also may provide a proinflammatory milieu that can favor neoplastic transformation to DLBCL and MZL, particularly extranodal MZL. Based on findings from a recent genome-wide association study of NHL, genetic variation in the class II major histocompatibility complex is associated with risk of follicular lymphoma but not DLBCL (34). Furthermore, sustained B-lymphocyte activation and proliferation may be involved in the pathogenesis of follicular lymphoma and not DLBCL. This is based on genetic association studies in which gene variants that augment humoral immune T-helper cell 2 responses and dampen inflammatory T-helper cell 1 responses are associated with increased risk of follicular lymphoma but not DLBCL (3).

Given the low frequency of the *NOD2* mutation in our non-Hispanic white controls, a large consortial study such as this was required to detect the association between the homozygous variant genotype and NHL and MZL risk. *NOD2* plays an important role in the inflammatory response (35). Gastric MZL is associated with *Helicobacter pylori* infection and chronic inflammation. Thus, the *NOD2* mutation may provide a proinflammatory milieu that promotes MZL. Because this is a relatively rare mutation, the results of our analysis should be interpreted with caution.

Results from this large pooled study allowed us to test a priori hypotheses to confirm and validate our earlier findings. The larger sample size also afforded us a unique opportunity to explore associations within rare subtypes and by ethnicity. However, underlying population stratification, even in relatively homogeneous populations, may influence results. Restricting the data to non-Hispanic Caucasians and adjusting for study site in our analyses helped us diminish possible effects due to underlying population stratification. In addition, we tested multiple hypotheses in our analyses by ethnicity, with some analyses being constrained by small sample sizes. Thus, our exploratory results should be interpreted conservatively and warrant further investigation and validation.

This study provides novel insights into mechanisms of lymphomagenesis involving signaling pathways that affect inflammation and immunity by regulating nuclear factor- κ B-mediated processes. These pathways contribute to the development, survival, and attenuation of specific subtypes of NHL. The findings also underline the importance of large, pooled consortial studies in generating robust genetic association results. Continued efforts to dissect linkage disequilibrium patterns, particularly between TNF and the major histocompatibility complex region, and potential risk differences by ethnicity will be critical for pinpointing the causal variant(s) in NHL etiology. Finally, the InterLymph consortium is now preparing to carry out studies of gene-environment interactions, with a particular focus on SNPs in the *TNF/LTA* and *IL10* genes and environmental exposures (including obesity, sun exposure, and history of autoimmune disease) that have shown an association in previous InterLymph pooled analyses (36–38). This ongoing, well-powered consortial effort is likely to further our understanding of the fundamental processes that contribute to lymphomagenesis.

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