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Original Contribution

Associations of Non-Hodgkin Lymphoma (NHL) Risk With Autoimmune Conditions According to Putative NHL Loci

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Autoimmune conditions and immune system–related genetic variations are associated with risk of non-Hodgkin lymphoma (NHL). In a pooled analysis of 8,692 NHL cases and 9,260 controls from 14 studies (1988–2007) within the International Lymphoma Epidemiology Consortium, we evaluated the interaction between immune system genetic variants and autoimmune conditions in NHL risk. We evaluated the immunity-related single nucleotide polymorphisms rs1800629 (tumor necrosis factor gene (*TNF*) G308A), rs1800890 (interleukin-10 gene (*IL10*) T3575A), rs6457327 (human leukocyte antigen gene (*HLA*) class I), rs10484561 (*HLA* class II), and rs2647012 (*HLA* class II)) and categorized autoimmune conditions as primarily mediated by B-cell or T-cell responses. We constructed unconditional logistic regression models to measure associations between autoimmune conditions and NHL with stratification by genotype. Autoimmune conditions mediated by B-cell responses were associated with increased NHL risk, specifically diffuse large B-cell lymphoma (odds ratio (OR) = 3.11, 95% confidence interval (CI): 2.25, 4.30) and marginal zone lymphoma (OR = 5.80, 95% CI: 3.82, 8.80); those mediated by T-cell responses were associated with peripheral T-cell lymphoma (OR = 2.14, 95% CI: 1.35, 3.38). In the presence of the rs1800629 AG/AA genotype, B-cell-mediated autoimmune conditions increased NHL risk (OR = 3.27, 95% CI: 2.07, 5.16; *P*-interaction = 0.03) in comparison with the GG genotype (OR = 1.82, 95% CI: 1.31, 2.53). This interaction was consistent across major B-cell NHL subtypes, including marginal zone lymphoma (*P*-interaction = 0.02) and follicular lymphoma (*P*-interaction = 0.04).

autoimmune conditions; environment; genetics; interaction; human leukocyte antigen; lymphoma, non-Hodgkin; tumor necrosis factor

Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; *HLA*, human leukocyte antigen gene; *IL10*, interleukin-10 gene; InterLymph, International Lymphoma Epidemiology; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; OR, odds ratio; SNP, single nucleotide polymorphism; *TNF*, tumor necrosis factor gene.

Non-Hodgkin lymphomas (NHLs) are a histologically and genetically heterogeneous group of malignancies originating from B- and T-lymphocytes. They account for approximately 3% of the worldwide cancer burden and show global variations in patterns of incidence (1). Populations at high risk of developing NHL include persons with severe immune system

dysregulation—resulting, for example, from human immunodeficiency virus infection, immunosuppressive therapy following solid organ transplantation, or an inherited immunodeficiency syndrome (2). In the absence of these high-risk conditions, there are relatively few established risk factors for NHL; however, autoimmune conditions have been shown to confer approximately 2- to 10-fold increased risks of NHL in both clinical and epidemiologic studies (2–5).

Autoimmune conditions affect approximately 3% of the general population and represent a group of over 80 disorders in which an individual elicits an immune response to his/her own tissues, resulting in inflammation and chronic antigenic stimulation (6, 7). Autoimmune conditions can be broadly categorized on the basis of whether they are mediated by predominantly B-cell responses or T-cell responses (8–12), although there is overlap in the immune effector mechanisms that mediate different autoimmune conditions. These diseases can also be categorized as those that affect multiple organs (e.g., systemic lupus erythematosus) and those that primarily target specific organs or tissues (e.g., celiac disease). A large epidemiologic evaluation of autoimmune conditions and NHL risk comprising 12,982 NHL cases and 16,441 controls was conducted by the International Lymphoma Epidemiology (InterLymph) Consortium (1983–2004) (12). In line with other analyses (3, 13, 14), it implicated Sjögren syndrome and systemic lupus erythematosus in increased B-cell NHL risk and celiac disease and psoriasis in increased T-cell NHL risk. A variety of factors have been proposed that may mediate the associations between autoimmune conditions and NHL risk, including those inherent to the pathology of autoimmune conditions or inherent to external factors such as disease-modifying immunosuppressive drugs or Epstein-Barr virus infection (2). Recent evidence favors an important role for inflammatory activity and disease severity in both organ-specific and systemic autoimmune processes in determining the risk of NHL (15, 16).

The InterLymph Consortium investigators have also identified common susceptibility immune-response gene loci that are associated with NHL, including 4 variants located in 6p21.3 and rs1800890 (interleukin-10 gene (*IL10*) T3575A) (17–21). The 4 single nucleotide polymorphisms (SNPs) in the 6p21.3 region include rs1800629 (tumor necrosis factor gene (*TNF*) G308A), located in the human leukocyte antigen gene (*HLA*) class III region; rs10484561 and rs2647012 (19, 20), which are in high linkage disequilibrium with the extended haplotypes *DRB1*01:01-DQA1*01:01-DQB1*05:01* and *DRB1*15-DQA1*01-DQB1*06:02*, respectively (19), in the *HLA* class II region; and rs6457327 (21), which is near *HLA-C* in the *HLA* class I region. The high relevance of *HLA* loci in the risk of several autoimmune conditions is well established (22). Although genome-wide association studies conducted by our research group and others have continued to uncover novel loci (23–29), these efforts have been accomplished primarily with genotyping restricted to NHL cases and have been derived from a combination of study designs, including cohort studies and clinical case series where exposure data on autoimmune conditions are not systematically collected. Thus, in the present analysis our efforts were focused on the first 5 putative NHL loci identified in the published literature, for which we have complete exposure (e.g., harmonized autoimmune conditions) and genotyping data on both NHL cases and controls from participating InterLymph studies. This analysis combined cleaned and harmonized data derived from previous InterLymph studies that evaluated the main associations of autoimmune conditions (12) and genetic associations (17, 18) with NHL etiology. Thus, a case-control study of gene-environment interaction that comprised research included in the current genome-wide association studies would not be possible because of the lack of uniform information on autoimmune conditions from the majority of cohort and clinical studies and because of the lack of genotyping or exposure information from matched controls.

Our goal in the present study was to determine whether a positive history of autoimmune disease and variation in rs1800890, rs1800629, rs10484561, rs2647012, or rs6457327 contributed to NHL risk either independently, thereby suggesting distinct pathways of pathogenesis, or jointly, thereby suggesting a common pathway. We conducted a pooled analysis of 8,692 NHL cases and 9,260 controls from 14 participating studies with data available on both genetic variation and autoimmune conditions. We evaluated gene-environment interaction by testing whether the associations between autoimmune conditions and NHL risk differed among persons who possessed 1 (or 2) of the implicated risk variants and those who had no risk alleles (30, 31). Specifically, we evaluated the risk of autoimmune conditions and NHL according to putative NHL risk loci. These analyses were conducted within participating InterLymph Consortium studies, for which data on both autoimmune conditions and the 5 genetic loci were readily available and had been harmonized in cases and controls.

METHODS

Study population

We included data from 14 individual case-control studies in the InterLymph Consortium (www.epi.grants.cancer.gov/InterLymph) (Table 1). Case participants from these studies were included if they met the following criteria for eligibility: diagnosis of incident NHL between 1988 and 2007; age 17 years or older; no known human immunodeficiency virus positivity; no history of organ transplantation; available data regarding personal history of 1 or more autoimmune conditions; and genotype information for 1 or more genetic variants of interest. Details on the design methods for each of the participating studies have been previously provided (3, 12, 17–20, 32–43). Selected demographic characteristics of study participants are summarized in Table 1 and Web Table 1 (available at http://aje.oxfordjournals.org/).

This analysis was approved by the City of Hope Institutional Review Board Committee (Duarte, California). Each participating study's investigators obtained approval from human subjects review committees and informed consent from all participants. A deidentified pooled data set with study-level individual information on self-reported autoimmune conditions, genotypes, study-specific matching variables, demographic characteristics, potential confounders, and NHL subtypes was provided by the InterLymph Data Coordinating Center (Mayo Clinic, Rochester, Minnesota).

Table 1. Select Characteristics of Studies Included in a Pooled Analyses of Autoimmune Conditions and Implicated Immunity Genes (rs1800629 (*TNF* G308A), rs1800890 (*IL10 T3575A*), and rs10484561, rs2647012, and rs6457327 (*HLA* Classes I and II)), InterLymph Consortium, 1988–2007

Study Name	Study Location	Dates of Analysis	Age Range, years	Matching Variables	Gene(s) Studied			Cases		Controls		
					TNF	*IL10*	*HLA*	No.	Participation Rate, %	No.	Participation Rate, %	Source
British Columbia	Vancouver, Victoria, British Columbia	2000–2004	20–80	Age, sex, region	x	x	x	754	79	779	46	Random selection from client registry of Ministry of Health
EpiLymph	Czech Republic	2001–2003	19–82	Age, sex, region	x	x	x	180	90	260	60	Hospital-based[a]
	France	2000–2003	18–82	Age, sex, region	x	x	x	156	91	169	74	Hospital-based[a]
	Germany	1999–2002	18–82	Age, sex, region	x	x	x	494	87	668	44	Random selection from population registries
	Ireland	1998–2004	21–85	Age, sex, region	x	x	x	96	90	131	75	Hospital-based[a]
	Italy	1998–2004	25–77	Age, sex, region			x	85	93	193	66	Random selection from population registries
	Spain	1998–2003	17–96	Age, sex, region	x	x	x	378	82	572	96	Hospital-based[a]
Mayo Clinic	Rochester, Minnesota	2002–2007	18–75	Age, sex, region	x	x	x	848	67	1,095	70	Clinic-based
NCI-SEER	Detroit, Michigan; Iowa; Los Angeles, California; Seattle, Washington	1998–2001	20–74	Age, sex, study site	x	x	x	1,161	76	937	52	Age <65 years: RDD; age ≥65 years: random selection from CMMS
SCALE Study	Denmark and Sweden	1999–2002	18–75	Age, sex, country	x	x	x	2,567	81	2,001	71	Random selection from population registries
United Kingdom	Parts of North and South West England	1998–2003	25–64	Age, sex region	x	x		515	75	522	71	Random selection from general practice lists
UCSF-1	San Francisco, California	1988–1993	21–74	Age, sex, region	x	x	x	378	72	810	78	Age <65 years: RDD; age ≥65 years: random selection from CMMS
Yale University	New Haven, Connecticut	1995–2001	23–86	Age (only women)	x	x	x	520	72	618	RDD: 69 CMMS: 47	Age <65 years: RDD; age ≥65 years: random selection from CMMS
New South Wales	Australia	2000–2001	20–74	Age, sex, region	x	x	x	560	85	505	61	Electoral rolls

Abbreviations: CMMS, Centers for Medicare and Medicaid Services; *HLA*, human leukocyte antigen gene; *IL10*, interleukin-10 gene; NCI, National Cancer Institute; RDD, random digit dialing; SCALE, Scandinavian Lymphoma Etiology; SEER, Surveillance, Epidemiology, and End Results; *TNF*, tumor necrosis factor gene; UCSF, University of California, San Francisco.

[a] Patients admitted to a hospital for an infectious, parasitic, mental, nervous, circulatory, digestive, endocrine, metabolic, or respiratory condition.

Table 2. Categorization of Autoimmune Conditions in a Pooled Analyses of Autoimmune Conditions and Implicated Immunity Genes, by Immune Response and Organ Involvement, InterLymph Consortium, 1988–2007

Subcategory	Associated Autoimmune Condition(s)	% of Category
Immune response		
B-cell responses	Autoimmune hemolytic anemia	7.6
	Hashimoto's thyroiditis/hypothyroidism	2.6
	Myasthenia gravis	2.4
	Pernicious anemia	7.4
	Rheumatoid arthritis	42.6
	Sjögren's syndrome	16.6
	Systemic lupus erythematosus	20.8
T-cell responses	Celiac disease	6.3
	Dermatomyositis/polymyositis	3.1
	Immune thrombocytopenic purpura	0.5
	Inflammatory bowel disease (ulcerative colitis, Crohn's disease)	24.7
	Multiple sclerosis	3.2
	Psoriasis	49.0
	Sarcoidosis	4.0
	Systemic sclerosis/scleroderma	1.2
	Type 1 diabetes	8.0
Organ involvement		
Involvement of multiple organs	Rheumatoid arthritis	43.1
	Sjögren's syndrome	16.8
	Systemic lupus erythematosus	21.0
	Dermatomyositis/polymyositis	7.2
	Sarcoidosis	9.3
	Systemic sclerosis/scleroderma	2.7
Targeted toward a single organ or system		
Pancreas	Type 1 diabetes	100
Gastrointestinal/hepatobiliary	Pernicious anemia	9.4
	Celiac disease	18.5
	Inflammatory bowel disease (Crohn's disease, ulcerative colitis)	72.1
Dermatological	Psoriasis	100
Hematological	Autoimmune hemolytic anemia	87.9
	Immune thrombocytopenic purpura	12.1
Neurological	Myasthenia gravis	24.3
	Multiple sclerosis	75.7
Endocrine	Hashimoto's thyroiditis/hypothyroidism	100

Exposure assessment

Self-reported history of autoimmune conditions was recorded in each participating study using structured questionnaires during in-person or telephone interviews (12). In most studies (70%), respondents were asked whether any autoimmune condition had been diagnosed by a physician. Consistent with the previous InterLymph Consortium study (12), we examined the following: primary Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis or scleroderma, poly- or dermatomyositis, immune thrombocytopenic purpura, type 1 diabetes (defined as diabetes diagnosed at age ≤30 years), pernicious anemia, multiple sclerosis, myasthenia gravis, celiac disease, psoriasis, sarcoidosis, Crohn's disease, ulcerative colitis, autoimmune hemolytic anemia, and Hashimoto's thyroiditis. Rheumatoid arthritis was restricted to participants who indicated that they were receiving treatment (any treatment) for their disease, to improve the specificity of self-reported diagnoses of rheumatoid arthritis (44–46).

We assessed the duration of autoimmune conditions as the interval (in years) between self-reported age at onset of the autoimmune condition and age at diagnosis of NHL (cases) or age at interview (controls). Participants with an unknown date of autoimmune disease diagnosis or those diagnosed within 2 years of their NHL diagnosis (or 2 years of interview for controls) were excluded from the analysis, to minimize the inclusion of autoimmune paraneoplastic phenomena arising due to incipient, as-yet-undiagnosed NHL.

To facilitate the interpretation of any identified associations and to improve statistical power for evaluating gene-environment interactions, we categorized autoimmune conditions on the basis of the type of primary immune response involved in mediating autoimmunity: specifically, predominance of B-cell activation versus predominance of T-cell activation, based on a consensus panel comprised of rheumatologists, immunologists, and hematologist-oncologists. Conditions included in each pathway category are delineated in Table 2. Autoimmune conditions were also categorized by organ involvement as multiple-organ-targeted versus primarily single-organ-targeted, with further organ-specific evaluations for pancreatic, gastrointestinal/hepatobiliary, dermatological, hematological, neurological, and endocrine organs (Table 2). In other words, conditions in which multiple organ systems were the targets of the autoimmune process were classified as having multiple-organ involvement, whereas those in which the target of the autoimmune process was 1 organ or system (regardless of whether the disease itself might then affect multiple organs, as in diabetes) were classified as having single-organ involvement.

Genotyping

Genotyping data were collected for rs1800890 (*IL10* T3575A), rs1800629 (*TNF* G308A), rs10484561, rs2647012, and rs6457327 (Table 1). Genotyping methods have been previously described (18–20). Briefly, rs1800629 and rs1800890 were genotyped using either TaqMan (Applied Biosystems, Inc., Foster City, California) (all studies except EpiLymph) or Pyrosequencing (Qiagen NV, Hilden, Germany) (EpiLymph). Assay conditions for TaqMan assays are available on the National Cancer Institute's SNP500Cancer website (http://snp500cancer.nci.nih.gov). For quality control, each laboratory analyzed the same set of genotypes in DNA samples from 102 ethnically diverse individuals, obtained from the Coriell Institute for Medical Research (Camden, New Jersey; http://www.coriell.org/).

For *HLA* SNPs (rs6457327, rs10484561, and rs2647012), genotyping was conducted using the Illumina 317K (Illumina, Inc., San Diego, California; Scandinavian Lymphoma Etiology (SCALE) study), the Illumina Human CNV370-Duo BeadChip (Illumina, Inc.; University of California, San Francisco, study), TaqMan (Applied Biosystems, Inc.; National Cancer Institute–Surveillance, Epidemiology, and End Results (SEER) study, New South Wales study, Yale University study, British Columbia study, and University of California, San Francisco, study), the Illumina GoldenGate 1536 SNP Oligo Pool Assay (Illumina, Inc.; Mayo Clinic study), the Sequenom MassARRAY iPLEX (SF1B) (Sequenom, Inc., San Diego, California; University of California, San Francisco,

Table 3. Associations Between Categories of Autoimmune Conditions and Non-Hodgkin Lymphoma (All Types), Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma in a Pooled Analysis, InterLymph Consortium, 1988–2007

Autoimmune Condition Category	No. of Studies	Controls		Non-Hodgkin Lymphoma				Diffuse Large B-Cell Lymphoma				Follicular Lymphoma			
		Ever[a]	Never[a]	Ever	Never	OR[b]	95% CI	Ever	Never	OR[b]	95% CI	Ever	Never	OR[b]	95% CI
Any autoimmune condition	14	396	8,864	501	8,191	1.26	1.09, 1.44	149	2,402	1.40	1.15, 1.70	83	2,001	0.89	0.69, 1.14
B-cell responses	14	91	8,864	192	8,191	2.25	1.74, 2.90	70	2,402	3.11	2.25, 4.30	24	2,001	1.07	0.67, 1.69
T-cell responses	14	316	8,864	327	8,191	1.00	0.85, 1.17	90	2,402	1.03	0.81, 1.32	62	2,001	0.85	0.64, 1.12
Multiple-organ-targeted	14	105	8,864	183	8,191	1.78	1.40, 2.28	59	2,402	2.30	1.65, 3.20	28	2,001	1.11	0.72, 1.70
Single-organ-targeted	14	304	8,864	334	8,191	1.07	0.91, 1.26	100	2,402	1.18	0.94, 1.49	58	2,001	0.81	0.61, 1.09
Pancreas	9	30	4,792	24	4,765	0.80	0.47, 1.39	7	1,441	0.79	0.34, 1.81	3	1,000	0.48	0.14, 1.60
GI/hepatobiliary	13	119	8,270	118	7,702	1.03	0.80, 1.34	39	2,247	1.26	0.87, 1.82	22	1,882	0.72	0.45, 1.14
Dermatological	9	140	5,145	169	4,486	1.08	0.86, 1.36	44	1,260	1.07	0.75, 1.51	26	888	0.86	0.56, 1.33
Hematological	8	6	3,474	15	2,416	3.32	1.27, 8.63	8	701	6.13	2.10, 17.9	1	527	0.60	0.07, 5.10
Neurological	13	13	7,801	13	7,369	1.01	0.46, 2.18	4	2,244	1.01	0.32, 3.12	5	1,786	1.29	0.46, 3.67
Endocrine	7	3	2,730	2	1,722	1.32	0.22, 8.06	0	524	—[c]	—	1	326	1.97	0.20, 19.7

Abbreviations: CI, confidence interval; GI, gastrointestinal; OR, odds ratio.

[a] Number of participants ever or never diagnosed with the specified condition(s).

[b] ORs and 95% CIs were calculated using joint fixed-effects unconditional logistic regression models. Results were adjusted for age, sex, race/ethnicity, and region/study center.

[c] Not calculated because of the small number of cases.

study), and (for rs10484561) the Illumina GoldenGate or Pyrosequencing (Qiagen NV; all EpiLymph studies), where call rates were ≥95% and sample completion rates were ≥90% (19, 20).

NHL classification

NHL subtypes were grouped using the InterLymph Pathology Working Group guidelines (47, 48), which are based on the World Health Organization classification (49). We present results for all NHL and for common subtypes, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, marginal zone lymphoma (MZL), and peripheral T-cell lymphoma.

Statistical methods

Confirming the main associations. We first evaluated the main associations between autoimmune conditions and all NHL and major NHL subtypes and between gene variants and NHL/NHL subtypes in the subset of 8,692 NHL cases and 9,260 controls from the InterLymph Consortium study population who had available genotyping data (of the original 12,982 NHL cases and 16,441 controls included in the previous evaluation of autoimmune conditions (12) (Web Tables 2 and 3)). We further evaluated the main association between autoimmune conditions and NHL according to immunology and pathology: autoimmune conditions largely mediated by B-cell responses versus those largely mediated by T-cell responses, based on our a priori categorization, and multiple-organ-targeted involvement versus single-organ-targeted involvement (Tables 3 and 4). We calculated pooled odds ratios and 95% confidence intervals for NHL risk using joint fixed-effects unconditional logistic regression models adjusting for age, sex, race/ethnicity, and region/study center. Other potential confounders, such as socioeconomic status, smoking status, and family history, did not change risk estimates by ≥10% and thus were not retained in the final model.

For each of the main analyses, we conducted χ^2 tests for heterogeneity between the studies to ensure that the data from disperse studies could be pooled.

Independence of genotypes and autoimmune conditions. We examined the association between the (dichotomized) variant alleles and risk of autoimmune conditions (as defined by B-cell- or T-cell-mediated immune response) among controls using unconditional logistic regression to calculate odds ratios and 95% confidence intervals (Web Table 4).

Associations with autoimmune conditions by genotype and P-interaction. We first evaluated interaction on the multiplicative scale. For each grouping of autoimmune conditions, we calculated odds ratios and 95% confidence intervals for all NHL and the major NHL subtypes according to dichotomized genotype. For this dichotomization, we modeled the genotypes in the dominant fashion based on our previous publications, which clearly indicated a dominant model of association (17, 18). The *P* value for interaction was estimated using the Wald test for homogeneity of the associations between autoimmune conditions and NHL risk according to genotype strata (Tables 5–9).

Table 4. Associations Between Categories of Autoimmune Conditions and Specific Subtypes of Non-Hodgkin Lymphoma in a Pooled Analysis, InterLymph Consortium, 1988–2007

Autoimmune Condition Category	No. of Studies	Controls		Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma				Marginal Zone Lymphoma				Peripheral T-Cell Lymphoma			
		Ever[a]	Never[a]	Ever	Never	OR[b]	95% CI	Ever	Never	OR[b]	95% CI	Ever	Never	OR[b]	95% CI
Any autoimmune condition	14	396	8,864	84	1,374	1.08	0.84, 1.39	43	500	1.87	1.34, 2.60	26	257	2.08	1.36, 3.18
B-cell responses	14	91	8,864	20	1,374	1.43	0.86, 2.39	33	500	5.80	3.82, 8.80	4	257	1.63	0.59, 4.50
T-cell responses	14	316	8,864	65	1,374	0.98	0.74, 1.30	12	500	0.67	0.38, 1.21	22	257	2.14	1.35, 3.38
Multiple-organ-targeted	14	105	8,864	23	1,374	1.13	0.71, 1.81	30	500	4.63	3.03, 7.06	5	257	1.70	0.68, 4.22
Single-organ-targeted	14	304	8,864	62	1,374	1.03	0.77, 1.37	14	500	0.82	0.47, 1.41	21	257	2.12	1.33, 3.39
Pancreas	9	30	4,792	10	960	2.10	1.00, 4.40	1	251	0.52	0.07, 3.87	0	171	—[c]	—
GI/hepatobiliary	13	119	8,270	14	1,331	0.77	0.44, 1.36	7	467	0.88	0.41, 1.91	11	241	3.24	1.71, 6.13
Dermatological	9	140	5,145	37	931	1.02	0.69, 1.49	4	226	0.66	0.24, 1.80	10	152	2.12	1.08, 4.17
Hematological	8	6	3,474	0	360	—	—	2	189	5.57	1.10, 28.3	1	86	10.10	1.14, 89.9
Neurological	13	13	7,801	2	1,108	1.40	0.30, 6.51	0	449	—	—	0	237	—	—
Endocrine	7	3	2,730	0	321	—	—	0	112	—	—	0	61	—	—

Abbreviations: CI, confidence interval; GI, gastrointestinal; OR, odds ratio.

[a] Number of participants ever or never diagnosed with the specified condition(s).

[b] ORs and 95% CIs were calculated using joint fixed-effects unconditional logistic regression models. Results were adjusted for age, sex, race/ethnicity, and region/study center.

[c] Not calculated because of the small number of cases.

Table 5. Associations Between Categories of Autoimmune Conditions and Non-Hodgkin Lymphoma and Specific Subtypes in a Pooled Analysis, According to rs1800629 (*TNF* G308A) Genotype, InterLymph Consortium, 1988–2007

Autoimmune Condition Category	rs1800629 Genotype												*P*-Interaction
	GG						AG/AA						
	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI	
	Ever[b]	Never[b]	Ever	Never			Ever	Never	Ever	Never			
Non-Hodgkin lymphoma													
Any autoimmune disease	307	5,288	247	5,701	1.18	0.99, 1.41	171	2,445	103	2,348	1.43	1.11, 1.85	0.19
B-cell	102	5,288	58	5,701	1.82	1.31, 2.53	84	2,445	25	2,348	3.27	2.07, 5.16	0.03
T-cell	213	5,288	196	5,701	1.00	0.81, 1.22	97	2,445	82	2,348	0.95	0.70, 1.29	0.83
Multiple organs	95	5,288	62	5,701	1.49	1.08, 2.07	81	2,445	32	2,348	2.42	1.59, 3.69	0.07
Single organ	220	5,288	191	5,701	1.08	0.88, 1.32	98	2,445	75	2,348	1.06	0.78, 1.45	0.97
Diffuse large B-cell lymphoma													
Any autoimmune disease	88	1,483	247	5,701	1.32	1.02, 1.70	53	773	103	2,348	1.56	1.10, 2.21	0.46
B-cell	37	1,483	58	5,701	2.66	1.73, 4.07	30	773	25	2,348	4.03	2.31, 7.01	0.21
T-cell	55	1,483	196	5,701	1.00	0.73, 1.36	30	773	82	2,348	1.08	0.70, 1.67	0.82
Multiple organs	30	1,483	62	5,701	1.91	1.22, 3.00	27	773	32	2,348	3.12	1.82, 5.36	0.14
Single organ	62	1,483	191	5,701	1.17	0.87, 1.58	32	773	75	2,348	1.20	0.78, 1.85	0.99
Follicular lymphoma													
Any autoimmune disease	51	1,367	247	5,701	0.80	0.58, 1.09	27	528	103	2,348	1.10	0.71, 1.72	0.25
B-cell	11	1,367	58	5,701	0.72	0.37, 1.39	12	528	25	2,348	2.06	1.01, 4.20	0.04
T-cell	42	1,367	196	5,701	0.83	0.59, 1.17	16	528	82	2,348	0.82	0.47, 1.43	0.94
Multiple organs	13	1,367	62	5,701	0.79	0.43, 1.44	12	528	32	2,348	1.79	0.90, 3.57	0.09
Single organ	40	1,367	191	5,701	0.81	0.57, 1.16	16	528	75	2,348	0.85	0.49, 1.49	0.91
CLL/SLL													
Any autoimmune disease	55	908	247	5,701	1.08	0.79, 1.49	27	390	103	2,348	1.20	0.76, 1.91	0.81
B-cell	12	908	58	5,701	1.25	0.65, 2.41	8	390	25	2,348	2.71	1.16, 6.33	0.22
T-cell	44	908	196	5,701	1.04	0.73, 1.48	19	390	82	2,348	0.90	0.53, 1.55	0.64
Multiple organs	13	908	62	5,701	1.05	0.56, 1.97	10	390	32	2,348	2.20	1.04, 4.69	0.34
Single organ	43	908	191	5,701	1.09	0.76, 1.55	17	390	75	2,348	0.88	0.50, 1.56	0.65
Marginal zone lymphoma													
Any autoimmune disease	21	316	247	5,701	1.42	0.89, 2.27	20	157	103	2,348	2.55	1.52, 4.28	0.06
B-cell	13	316	58	5,701	3.42	1.82, 6.42	18	157	25	2,348	8.47	4.45, 16.1	0.02
T-cell	8	316	196	5,701	0.70	0.34, 1.45	4	157	82	2,348	0.67	0.24, 1.87	0.99
Multiple organs	12	316	62	5,701	2.87	1.51, 5.43	16	157	32	2,348	5.80	3.07, 11.0	0.05
Single organ	9	316	191	5,701	0.82	0.41, 1.63	5	157	75	2,348	0.94	0.37, 2.40	0.82
Peripheral T-cell lymphoma													
Any autoimmune disease	15	168	247	5,701	1.87	1.08, 3.25	10	78	103	2,348	2.39	1.18, 4.82	0.47
B-cell	2	168	58	5,701	1.31	0.32, 5.46	2	78	25	2,348	2.55	0.59, 11.2	0.47
T-cell	13	168	196	5,701	1.94	1.07, 3.51	8	78	82	2,348	2.29	1.05, 4.99	0.63
Multiple organs	2	168	62	5,701	1.13	0.27, 4.70	3	78	32	2,348	2.82	0.83, 9.59	0.28
Single organ	13	168	191	5,701	2.01	1.11, 3.63	7	78	75	2,348	2.22	0.97, 5.07	0.78

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; OR, odds ratio; SLL, small lymphocytic lymphoma; *TNF*, tumor necrosis factor gene.

[a] ORs and 95% CIs were calculated using joint fixed-effects unconditional logistic regression models. Results were adjusted for age, sex, race/ethnicity, and region/study center.

[b] Number of participants ever or never diagnosed with the specified condition(s).

We further evaluated interaction on an additive scale and calculated odds ratios and 95% confidence intervals using a common referent group to evaluate joint associations between autoimmune conditions and variant genotypes, whereby persons without a variant genotype and without autoimmune conditions were the referent group (Table 10).

Table 6. Associations Between Categories of Autoimmune Conditions and Non-Hodgkin Lymphoma and Specific Subtypes in a Pooled Analysis, According to rs1800890 (*IL10* T3575A) Genotype, InterLymph Consortium, 1988–2007

Autoimmune Condition Category	rs1800890 Genotype												*P*-Interaction
	TT						AT/AA						
	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI	
	Ever[b]	Never[b]	Ever	Never			Ever	Never	Ever	Never			
Non-Hodgkin lymphoma													
Any autoimmune disease	175	2,942	141	3,361	1.30	1.03, 1.63	306	4,862	238	5,044	1.25	1.05, 1.49	0.70
B-cell	70	2,942	30	3,361	2.56	1.66, 3.97	114	4,862	60	5,044	2.01	1.46, 2.76	0.28
T-cell	116	2,942	115	3,361	1.03	0.79, 1.34	199	4,862	185	5,044	1.01	0.82, 1.24	0.89
Multiple organs	66	2,942	36	3,361	1.97	1.30, 2.98	108	4,862	68	5,044	1.61	1.18, 2.20	0.33
Single organ	118	2,942	108	3,361	1.12	0.86, 1.47	205	4,862	180	5,044	1.08	0.88, 1.34	0.84
Diffuse large B-cell lymphoma													
Any autoimmune disease	54	820	141	3,361	1.55	1.12, 2.15	92	1,482	238	5,044	1.36	1.05, 1.75	0.47
B-cell	25	820	30	3,361	3.48	2.01, 6.01	42	1,482	60	5,044	2.76	1.83, 4.16	0.37
T-cell	34	820	115	3,361	1.19	0.80, 1.78	56	1,482	185	5,044	1.02	0.75, 1.39	0.53
Multiple organs	22	820	36	3,361	2.65	1.53, 4.57	35	1,482	68	5,044	2.04	1.33, 3.11	0.31
Single organ	36	820	108	3,361	1.32	0.89, 1.95	63	1,482	180	5,044	1.18	0.87, 1.59	0.67
Follicular lymphoma													
Any autoimmune disease	29	703	141	3,361	0.94	0.62, 1.43	44	1,183	238	5,044	0.78	0.56, 1.09	0.39
B-cell	10	703	30	3,361	1.39	0.66, 2.91	11	1,183	60	5,044	0.75	0.39, 1.44	0.16
T-cell	22	703	115	3,361	0.90	0.56, 1.44	33	1,183	185	5,044	0.77	0.52, 1.12	0.52
Multiple organs	10	703	36	3,361	1.28	0.62, 2.62	13	1,183	68	5,044	0.80	0.44, 1.46	0.26
Single organ	22	703	108	3,361	0.92	0.57, 1.47	31	1,183	180	5,044	0.74	0.50, 1.09	0.39
CLL/SLL													
Any autoimmune disease	25	523	141	3,361	0.96	0.61, 1.51	57	793	238	5,044	1.24	0.91, 1.70	0.23
B-cell	6	523	30	3,361	1.49	0.60, 3.70	14	793	60	5,044	1.48	0.80, 2.74	0.88
T-cell	20	523	115	3,361	0.87	0.53, 1.44	43	793	185	5,044	1.14	0.80, 1.63	0.25
Multiple organs	6	523	36	3,361	1.15	0.47, 2.81	17	793	68	5,044	1.27	0.73, 2.21	0.56
Single organ	20	523	108	3,361	0.94	0.57, 1.55	40	793	180	5,044	1.15	0.79, 1.66	0.43
Marginal zone lymphoma													
Any autoimmune disease	15	195	141	3,361	1.75	1.00, 3.06	27	268	238	5,044	2.10	1.37, 3.22	0.53
B-cell	9	195	30	3,361	4.85	2.24, 10.5	23	268	60	5,044	6.38	3.84, 10.6	0.40
T-cell	7	195	115	3,361	1.01	0.46, 2.20	5	268	185	5,044	0.53	0.21, 1.30	0.28
Multiple organs	10	195	36	3,361	4.48	2.17, 9.25	19	268	68	5,044	4.78	2.80, 8.16	0.65
Single organ	5	195	108	3,361	0.77	0.31, 1.91	9	268	180	5,044	0.97	0.49, 1.94	0.69
Peripheral T-cell lymphoma													
Any autoimmune disease	6	112	141	3,361	1.21	0.52, 2.83	19	138	238	5,044	2.75	1.65, 4.59	0.12
B-cell	1	112	30	3,361	1.28	0.17, 9.59	3	138	60	5,044	1.90	0.59, 6.19	0.68
T-cell	5	112	115	3,361	1.18	0.47, 2.98	16	138	185	5,044	2.92	1.68, 5.08	0.12
Multiple organs	1	112	36	3,361	0.99	0.13, 7.38	4	138	68	5,044	2.17	0.78, 6.08	0.47
Single organ	5	112	108	3,361	1.25	0.50, 3.17	15	138	180	5,044	2.83	1.60, 5.00	0.18

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; *IL10*, interleukin-10 gene; OR, odds ratio; SLL, small lymphocytic lymphoma.

[a] ORs and 95% CIs were calculated using joint fixed-effects unconditional logistic regression models. Results were adjusted for age, sex, race/ethnicity, and region/study center.

[b] Number of participants ever or never diagnosed with the specified condition(s).

Analyses were conducted using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina). All tests were 2-sided, and *P*-interaction values less than 0.05 were considered statistically significant. To account for multiple comparisons, we applied a conservative Bonferroni correction for 5 tests at an overall α level of 0.05 to all analysis ($P = 0.01$). For evaluation of rs1800629

Table 7. Associations Between Categories of Autoimmune Conditions and Non-Hodgkin Lymphoma and Specific Subtypes in a Pooled Analysis, According to *HLA* Single Nucleotide Polymorphism rs6457327 Genotype, InterLymph Consortium, 1988–2007

Autoimmune Condition Category	rs6457327 Genotype												*P*-Interaction
	CC						AC/AA						
	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI	
	Ever[b]	Never[b]	Ever	Never			Ever	Never	Ever	Never			
Non-Hodgkin lymphoma													
Any autoimmune disease	70	1,677	61	1,973	1.30	0.91, 1.86	82	2,042	93	2,732	1.15	0.84, 1.56	0.47
B-cell	32	1,677	17	1,973	2.13	1.17, 3.89	41	2,042	26	2,732	1.94	1.17, 3.21	0.73
T-cell	40	1,677	46	1,973	0.98	0.64, 1.52	44	2,042	69	2,732	0.85	0.58, 1.26	0.53
Multiple organs	25	1,677	12	1,973	2.25	1.12, 4.54	34	2,042	23	2,732	1.71	1.00, 2.94	0.51
Single organ	47	1,677	51	1,973	1.06	0.70, 1.59	51	2,042	71	2,732	0.98	0.68, 1.42	0.64
Diffuse large B-cell lymphoma													
Any autoimmune disease	24	506	61	1,973	1.50	0.92, 2.44	26	572	93	2,732	1.33	0.85, 2.09	0.66
B-cell	13	506	17	1,973	2.98	1.42, 6.24	16	572	26	2,732	2.89	1.52, 5.48	0.87
T-cell	13	506	46	1,973	1.06	0.56, 1.98	11	572	69	2,732	0.77	0.40, 1.48	0.47
Multiple organs	9	506	12	1,973	2.79	1.15, 6.77	11	572	23	2,732	2.17	1.04, 4.51	0.64
Single organ	17	506	51	1,973	1.27	0.72, 2.23	16	572	71	2,732	1.11	0.63, 1.93	0.67
Follicular lymphoma													
Any autoimmune disease	14	427	61	1,973	0.95	0.51, 1.76	17	498	93	2,732	0.91	0.53, 1.55	0.86
B-cell	2	427	17	1,973	0.41	0.09, 1.85	6	498	26	2,732	0.95	0.38, 2.34	0.38
T-cell	12	427	46	1,973	1.11	0.57, 2.17	13	498	69	2,732	1.01	0.55, 1.86	0.78
Multiple organs	2	427	12	1,973	0.66	0.14, 3.09	8	498	23	2,732	1.51	0.66, 3.45	0.34
Single organ	12	427	51	1,973	0.96	0.49, 1.86	11	498	71	2,732	0.81	0.42, 1.56	0.65
CLL/SLL													
Any autoimmune disease	4	198	61	1,973	0.80	0.28, 2.28	5	270	93	2,732	0.61	0.24, 1.52	0.69
B-cell	2	198	17	1,973	1.57	0.35, 7.08	3	270	26	2,732	1.57	0.46, 5.31	0.96
T-cell	2	198	46	1,973	0.52	0.12, 2.19	2	270	69	2,732	0.30	0.07, 1.25	0.61
Multiple organs	1	198	12	1,973	1.33	0.17, 10.6	3	270	23	2,732	1.58	0.46, 5.39	0.85
Single organ	3	198	51	1,973	0.68	0.21, 2.26	2	270	71	2,732	0.31	0.07, 1.26	0.38
Marginal zone lymphoma													
Any autoimmune disease	7	137	61	1,973	1.55	0.69, 3.49	7	166	93	2,732	1.21	0.55, 2.66	0.52
B-cell	5	137	17	1,973	3.78	1.34, 10.7	4	166	26	2,732	2.37	0.81, 6.94	0.35
T-cell	2	137	46	1,973	0.59	0.14, 2.50	3	166	69	2,732	0.71	0.22, 2.29	0.91
Multiple organs	5	137	12	1,973	6.05	2.04, 18.0	1	166	23	2,732	0.66	0.09, 4.91	0.04
Single organ	2	137	51	1,973	0.51	0.12, 2.13	6	166	71	2,732	1.39	0.59, 3.25	0.30
Peripheral T-cell lymphoma													
Any autoimmune disease	2	60	61	1,973	1.14	0.27, 4.80	5	69	93	2,732	2.29	0.90, 5.86	0.43
B-cell	1	60	17	1,973	2.42	0.31, 18.9	1	69	26	2,732	1.67	0.22, 12.6	0.83
T-cell	1	60	46	1,973	0.72	0.10, 5.29	4	69	69	2,732	2.45	0.86, 6.95	0.30
Multiple organs	0	60	12	1,973	—[c]	—	2	69	23	2,732	3.63	0.83, 15.8	0.98
Single organ	2	60	51	1,973	1.35	0.32, 5.71	3	69	71	2,732	1.80	0.55, 5.89	0.78

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; *HLA*, human leukocyte antigen gene; OR, odds ratio; SLL, small lymphocytic lymphoma.

[a] ORs and 95% CIs were calculated using joint fixed-effects unconditional logistic regression models. Results were adjusted for age, sex, race/ethnicity, and region/study center.

[b] Number of participants ever or never diagnosed with the specified condition(s).

[c] Not calculated because of the small number of cases.

and rs200890, sensitivity analyses restricting the subjects to persons of European ancestry was conducted; because results did not vary by race (18), we used the data for all participants to maximize statistical power. Because the prior genotyping efforts for rs10484561, rs2647012, and rs6457327 were restricted to persons of European ancestry (19–21), all analyses

Table 8. Associations Between Categories of Autoimmune Conditions and Non-Hodgkin Lymphoma and Specific Subtypes in a Pooled Analysis, According to *HLA* Single Nucleotide Polymorphism rs2647012 Genotype, InterLymph Consortium, 1988–2007

Autoimmune Condition Category	rs2647012 Genotype												*P*-Interaction
	GG						AG/AA						
	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI	
	Ever[b]	Never[b]	Ever	Never			Ever	Never	Ever	Never			
Non-Hodgkin lymphoma													
Any autoimmune disease	150	1,853	69	1,350	1.36	1.00, 1.85	221	2,839	116	2,298	1.25	0.97, 1.59	0.78
B-cell	51	1,853	21	1,350	1.67	0.98, 2.84	82	2,839	34	2,298	2.05	1.34, 3.12	0.51
T-cell	106	1,853	53	1,350	1.18	0.83, 1.69	148	2,839	87	2,298	0.97	0.73, 1.30	0.49
Multiple organs	52	1,853	25	1,350	1.48	0.90, 2.45	82	2,839	42	2,298	1.53	1.03, 2.27	0.85
Single organ	105	1,853	47	1,350	1.29	0.89, 1.86	146	2,839	77	2,298	1.13	0.84, 1.52	0.68
Diffuse large B-cell lymphoma													
Any autoimmune disease	49	478	69	1,350	1.72	1.13, 2.59	57	732	116	2,298	1.25	0.88, 1.78	0.22
B-cell	22	478	21	1,350	2.97	1.54, 5.70	27	732	34	2,298	2.76	1.60, 4.78	0.84
T-cell	31	478	53	1,350	1.26	0.77, 2.08	36	732	87	2,298	0.95	0.62, 1.46	0.34
Multiple organs	19	478	25	1,350	2.28	1.18, 4.42	25	732	42	2,298	1.93	1.12, 3.32	0.73
Single organ	34	478	47	1,350	1.51	0.93, 2.47	37	732	77	2,298	1.12	0.73, 1.72	0.30
Follicular lymphoma													
Any autoimmune disease	24	526	69	1,350	0.85	0.51, 1.41	23	509	116	2,298	0.91	0.57, 1.46	0.78
B-cell	6	526	21	1,350	0.77	0.31, 1.94	7	509	34	2,298	1.03	0.45, 2.36	0.60
T-cell	20	526	53	1,350	0.90	0.51, 1.59	17	509	87	2,298	0.88	0.51, 1.52	0.99
Multiple organs	8	526	25	1,350	0.91	0.40, 2.04	8	509	42	2,298	0.89	0.40, 2.02	0.98
Single organ	18	526	47	1,350	0.88	0.48, 1.61	16	509	77	2,298	0.95	0.54, 1.65	0.79
CLL/SLL													
Any autoimmune disease	27	323	69	1,350	1.20	0.71, 2.02	46	625	116	2,298	1.00	0.67, 1.50	0.71
B-cell	6	323	21	1,350	0.91	0.33, 2.48	10	625	34	2,298	1.40	0.63, 3.08	0.54
T-cell	21	323	53	1,350	1.23	0.68, 2.23	37	625	87	2,298	0.90	0.58, 1.40	0.52
Multiple organs	7	323	25	1,350	0.86	0.35, 2.15	13	625	42	2,298	1.08	0.54, 2.14	0.77
Single organ	20	323	47	1,350	1.34	0.72, 2.50	37	625	77	2,298	0.98	0.61, 1.56	0.59
Marginal zone lymphoma													
Any autoimmune disease	8	107	69	1,350	1.42	0.65, 3.08	25	214	116	2,298	2.04	1.28, 3.25	0.33
B-cell	5	107	21	1,350	2.93	1.05, 8.17	21	214	34	2,298	6.24	3.49, 11.1	0.12
T-cell	3	107	53	1,350	0.69	0.21, 2.29	5	214	87	2,298	0.53	0.21, 1.33	0.75
Multiple organs	5	107	25	1,350	2.64	0.96, 7.26	19	214	42	2,298	4.66	2.60, 8.34	0.23
Single organ	3	107	47	1,350	0.74	0.22, 2.47	6	214	77	2,298	0.70	0.30, 1.64	0.97
Peripheral T-cell lymphoma													
Any autoimmune disease	6	53	69	1,350	2.11	0.85, 5.24	17	103	116	2,298	2.64	1.48, 4.72	0.60
B-cell	0	53	21	1,350	—[c]	—	3	103	34	2,298	2.48	0.71, 8.63	0.97
T-cell	6	53	53	1,350	2.80	1.11, 7.07	14	103	87	2,298	2.63	1.39, 4.96	0.97
Multiple organs	1	53	25	1,350	1.16	0.15, 9.03	3	103	42	2,298	1.66	0.48, 5.70	0.73
Single organ	5	53	47	1,350	2.35	0.86, 6.40	14	103	77	2,298	3.00	1.58, 5.69	0.62

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; *HLA*, human leukocyte antigen gene; OR, odds ratio; SLL, small lymphocytic lymphoma.

[a] ORs and 95% CIs were calculated using joint fixed-effects unconditional logistic regression models. Results were adjusted for age, sex, race/ethnicity, and region/study center.

[b] Number of participants ever or never diagnosed with the specified condition(s).

[c] Not calculated because of the small number of cases.

with these HLA SNPs were similarly restricted to persons of European ancestry. Additional sensitivity analyses were also applied to autoimmune conditions whereby more prevalent conditions that contributed to the distinct categories were excluded individually (e.g., rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythromatosus), in an attempt to

Table 9. Associations Between Categories of Autoimmune Conditions and Non-Hodgkin Lymphoma and Specific Subtypes in a Pooled Analysis, According to *HLA* Single Nucleotide Polymorphism rs10484561 Genotype, InterLymph Consortium, 1988–2007

Autoimmune Condition Category	rs10484561 Genotype												*P*-Interaction
	TT						GT/GG						
	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI	
	Ever[b]	Never[b]	Ever	Never			Ever	Never	Ever	Never			
Non-Hodgkin lymphoma													
Any autoimmune disease	322	4,717	209	4,952	1.19	0.98, 1.44	85	1,532	44	1,318	1.31	0.89, 1.94	0.68
B-cell	122	4,717	58	4,952	1.99	1.43, 2.78	29	1,532	15	1,318	1.40	0.73, 2.68	0.35
T-cell	212	4,717	161	4,952	0.90	0.72, 1.13	60	1,532	30	1,318	1.32	0.82, 2.10	0.17
Multiple organs	118	4,717	68	4,952	1.48	1.07, 2.03	28	1,532	13	1,318	1.56	0.79, 3.10	0.92
Single organ	214	4,717	147	4,952	1.06	0.84, 1.36	61	1,532	32	1,318	1.25	0.79, 1.98	0.51
Diffuse large B-cell lymphoma													
Any autoimmune disease	95	1,291	209	4,952	1.33	1.02, 1.75	25	430	44	1,318	1.35	0.79, 2.31	0.77
B-cell	44	1,291	58	4,952	2.76	1.80, 4.23	13	430	15	1,318	2.35	1.07, 5.18	0.86
T-cell	59	1,291	161	4,952	0.97	0.70, 1.35	14	430	30	1,318	1.05	0.53, 2.08	0.70
Multiple organs	39	1,291	68	4,952	1.90	1.23, 2.94	10	430	13	1,318	2.01	0.84, 4.83	0.81
Single organ	63	1,291	147	4,952	1.18	0.85, 1.63	17	430	32	1,318	1.24	0.66, 2.35	0.71
Follicular lymphoma													
Any autoimmune disease	36	829	209	4,952	0.91	0.63, 1.32	15	448	44	1,318	0.86	0.47, 1.58	0.87
B-cell	11	829	58	4,952	0.98	0.51, 1.90	3	448	15	1,318	0.44	0.12, 1.53	0.27
T-cell	27	829	161	4,952	0.90	0.59, 1.37	13	448	30	1,318	1.15	0.58, 2.27	0.52
Multiple organs	13	829	68	4,952	1.01	0.55, 1.85	5	448	13	1,318	0.89	0.31, 2.55	0.87
Single organ	25	829	147	4,952	0.90	0.58, 1.40	11	448	32	1,318	0.88	0.43, 1.80	0.97
CLL/SLL													
Any autoimmune disease	65	1,002	209	4,952	0.95	0.69, 1.33	13	228	44	1,318	1.19	0.58, 2.42	0.68
B-cell	14	1,002	58	4,952	1.20	0.62, 2.33	3	228	15	1,318	0.86	0.22, 3.40	0.64
T-cell	52	1,002	161	4,952	0.86	0.60, 1.24	10	228	30	1,318	1.32	0.58, 3.02	0.41
Multiple organs	15	1,002	68	4,952	0.78	0.42, 1.45	5	228	13	1,318	1.83	0.58, 5.83	0.35
Single organ	51	1,002	147	4,952	1.01	0.69, 1.49	8	228	32	1,318	0.92	0.38, 2.25	0.92
Marginal zone lymphoma													
Any autoimmune disease	31	337	209	4,952	1.79	1.19, 2.68	3	82	44	1,318	0.90	0.27, 3.01	0.28
B-cell	24	337	58	4,952	5.41	3.27, 8.95	2	82	15	1,318	1.80	0.39, 8.35	0.15
T-cell	8	337	161	4,952	0.57	0.28, 1.19	1	82	30	1,318	0.44	0.06, 3.33	0.82
Multiple organs	22	337	68	4,952	3.83	2.29, 6.42	2	82	13	1,318	2.01	0.43, 9.53	0.37
Single organ	9	337	147	4,952	0.73	0.37, 1.47	1	82	32	1,318	0.42	0.06, 3.16	0.61
Peripheral T-cell lymphoma													
Any autoimmune disease	20	170	209	4,952	2.03	1.22, 3.39	4	40	44	1,318	2.92	0.96, 8.87	0.66
B-cell	3	170	58	4,952	1.53	0.46, 5.11	1	40	15	1,318	2.44	0.30, 20.1	0.84
T-cell	17	170	161	4,952	2.08	1.20, 3.62	3	40	30	1,318	3.09	0.87, 11.0	0.62
Multiple organs	4	170	68	4,952	1.48	0.52, 4.25	0	40	13	1,318	—[c]	—	0.98
Single organ	16	170	147	4,952	2.18	1.24, 3.85	4	40	32	1,318	4.15	1.35, 12.8	0.37

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; *HLA*, human leukocyte antigen gene; OR, odds ratio; SLL, small lymphocytic lymphoma.

[a] ORs and 95% CIs were calculated using joint fixed-effects unconditional logistic regression models. Results were adjusted for age, sex, race/ethnicity, and region/study center.

[b] Number of participants ever or never diagnosed with the specified condition(s).

[c] Not calculated because of the small number of cases.

ensure that our associations based on these categories (e.g., B-cell response) were robust and not driven by any single condition.

RESULTS

These analyses comprised 8,692 NHL cases and 9,260 controls from 14 participating InterLymph Consortium studies

Table 10. Joint Associations Between Categories of Autoimmune Conditions and rs1800629 (*TNF* G308A) Genotype in the Risk of Non-Hodgkin Lymphoma and Specific Subtypes, InterLymph Consortium, 1988–2007

TNF G308A Genotype	Autoimmune Condition Category	Non-Hodgkin Lymphoma				Marginal Zone Lymphoma				Diffuse Large B-Cell Lymphoma			
		No. of Cases	No. of Controls	OR[a]	95% CI	No. of Cases	No. of Controls	OR[a]	95% CI	No. of Cases	No. of Controls	OR[a]	95% CI
GG	None	5,288	5,701	1.00	Referent	316	5,701	1.00	Referent	1,483	5,701	1.00	Referent
AG/AA	None	2,445	2,348	1.10	1.02, 1.18	157	2,348	1.23	1.01, 1.51	773	2,348	1.22	1.10, 1.35
GG	T-cell	213	196	0.99	0.81, 1.22	8	196	0.69	0.33, 1.41	55	196	1.00	0.74, 1.37
AG/AA	T-cell	97	82	1.05	0.77, 1.42	4	82	0.83	0.30, 2.30	30	82	1.31	0.85, 2.01
GG	B-cell	94	51	1.91	1.35, 2.71	13	51	3.79	2.01, 7.16	33	51	2.66	1.70, 4.18
AG/AA	B-cell	74	21	3.86	2.36, 6.31	16	21	13.70	6.86, 27.5	23	21	4.43	2.41, 8.16

Abbreviations: CI, confidence interval; OR, odds ratio; *TNF*, tumor necrosis factor gene.

[a] ORs and 95% CIs were calculated using joint fixed-effects unconditional logistic regression models. Results were adjusted for age, sex, race/ethnicity, and region/study center.

carried out in North America, Europe, and Australia that had collected information on autoimmune conditions and had genotyped at least one of the 5 SNPs of interest (Table 1). Thirteen of the 14 studies provided data on rs1800629 (*TNF* G308A) or rs1800890 (*IL10* T3575A) variants, and 13 of the 14 studies contributed data on the 3 *HLA* class I and class II SNPs (see Table 1). The included studies comprised 9 population-based case-control studies, 4 hospital-based case-control studies, and 1 clinic-based case-control study (Table 1).

In our evaluation of associations between autoimmune conditions and genetic variants among controls (Web Table 4), 2 statistically significant associations were identified: a relationship between hemolytic anemia and rs10484561 and a relationship between dermatomyositis/polymyositis and rs1800629. However, this is within the number of associations that one would expect to observe on the basis of chance alone. Because their inclusion did not alter the main associations between the immunity categories and NHL risk, we continued to include these conditions to retain a consistent definition of the immune-response categories throughout our analyses.

Main autoimmune condition–gene associations

In our subset of cases and controls, our results remained consistent with previously published autoimmune condition (Web Table 2) and genetic (Web Table 3) main associations.

We found statistically significant increased NHL risks among participants with autoimmune conditions that were mediated predominantly by B-cell responses (odds ratio (OR) = 2.25, 95% confidence interval (CI): 1.74, 2.90), that had multiple organ involvement (OR = 1.78, 95% CI: 1.40, 2.28), and that targeted hematological organs (OR = 3.32, 95% CI: 1.27, 8.63) (Table 3). These associations were consistent for DLBCL and MZL and were most pronounced for autoimmune conditions mediated by B-cell responses (OR = 3.11 (95% CI: 2.25, 4.30) and OR = 5.80 (95% CI: 3.82, 8.80), respectively) and single-organ-targeted (hematological) conditions (for DLBCL, OR = 6.13, 95% CI: 2.10, 17.9) (Tables 3 and 4). Associations with peripheral T-cell lymphoma were observed predominantly for autoimmune conditions mediated primarily by T-cell responses (OR = 2.14, 95% CI: 1.35, 3.38) and autoimmune conditions targeting specific organs (OR = 2.12, 95% CI: 1.33, 3.39), such as the gastrointestinal/hepatobiliary organ system (OR = 3.24, 95% CI: 1.71, 6.13) and the skin (i.e., psoriasis) (OR = 2.12, 95% CI: 1.08, 4.17) (Table 4). Although associations with hematological targeted conditions were also observed for MZL and peripheral T-cell lymphoma, those associations were based on only 1 and 2 cases, respectively.

Autoimmune condition–gene interactions (rs1800629 (*TNF* G308A) and rs1800890 (*IL10* T3575A))

Among persons with the rs1800629 (*TNF* G308A) AG/AA genotype, those with autoimmune conditions predominantly mediated by B-cell responses had a 3.27-fold increased NHL risk (95% CI: 2.07, 5.16), as compared with a 1.82-fold (95% CI: 1.31, 2.53) increased risk among persons with the GG genotype (P-interaction = 0.03) (Table 5). The increased risk of B-cell response conditions among persons with the AG/AA genotype was consistently observed across the major NHL subtypes, with significant interaction for follicular lymphoma ($P = 0.04$) and MZL ($P = 0.02$). Interactions observed for MZL were particularly pronounced, with 8-fold increased risks for autoimmune diseases mediated by B-cell responses among persons with the variant allele (or AG/AA genotype), compared with a 3-fold risk for persons with the GG genotype. Although no significant interaction was observed, increased risks of DLBCL and chronic lymphocytic leukemia/small lymphocytic lymphoma were also observed among persons with autoimmune conditions who harbored the rs1800629 (*TNF* G308A) allele, but not among those who did not carry the variant allele. These results were consistent in sensitivity analysis where individual autoimmune conditions were excluded, ensuring that our results were not driven by any single condition.

Consistent with results from the stratified analysis, in analysis using a single common referent group, the greatest risk of NHL was observed among persons who had both the rs1800629 AG/AA genotype and an autoimmune condition mediated by B-cell responses (OR = 3.86, 95% CI: 2.36, 6.31), as compared

with those with the GG genotype who did not have an autoimmune condition (Table 10). The increased risks among persons with both the AG/AA genotype and B-cell-mediated autoimmune conditions were particularly pronounced for DLBCL (OR = 4.43, 95% CI: 2.41, 8.16) and MZL (OR = 13.7, 95% CI: 6.86, 27.5).

No statistically significant interactions between rs1800890 (*IL10* T3575A) genotypes and autoimmune conditions were observed with either NHL overall or any NHL subtype (Table 6). The elevated risks of NHL, DLBCL, MZL, and peripheral T-cell lymphoma observed for autoimmune conditions were similar across rs1800890 genotypes.

HLA class I (rs6457327) and class II SNPs (rs2647012, rs10484561)

In general, we observed little evidence of interaction between autoimmune conditions and the rs6457327 SNP located in the *HLA* class I region near *HLA-C*. The main associations for relationships of any autoimmune condition, B-cell response conditions, and autoimmune conditions involving multiple organs with NHL and DLBCL did not differ by rs6457327 genotype status (Table 7). We observed no evidence of interaction between the rs2647012 or rs10484561 SNP and autoimmune conditions in the risk of NHL or any NHL subtype (Tables 8 and 9). Although we observed elevated risk for MZL when we restricted the analysis to the rs10484561 TT genotype, the low frequency of the GT/GG genotype and the few exposed MZL cases ($n = 1–3$) made these results tenuous.

DISCUSSION

We identified possible interactions between the rs1800629 (*TNF* G308A) allele and autoimmune conditions that predominantly involve B-cell responses in the risks of DLBCL and MZL. Because tumor necrosis factor α activates the nuclear factor-kB pathway, a central mechanism for inflammation and immune system status, interactions between *TNF* and autoimmune conditions would suggest a shared biological pathway linked to immune system activation (50). If this were true, our results would support possible synergy between a genetic propensity toward a chronic inflammatory state in *TNF* G308A carriers through heightened tumor necrosis factor α overexpression (51, 52) and the chronic inflammation and B-cell activation seen in persons with autoimmune conditions.

Recently, it has been noted that a distinct form of immune response characterized by inflammation, B-cell activation, and the production of inflammatory cytokines plays a central role in driving autoimmune responses (53–55). This immune response pattern has been termed T-helper 17 and is distinct from the earlier defined T-helper 1 and T-helper 2 immune response patterns. Interleukin-23 is involved in the promotion of T-helper 17 responses, which are mediated by the production of interleukin-17, interleukin-6, and tumor necrosis factor α. Thus, the potential interaction between autoimmune conditions characterized by B-cell-mediated responses and autoantibody production with the *TNF* genotype may suggest a potential role for T-helper 17 immune responses in the pathogenesis of both NHL and autoimmunity. Clinical studies that directly measure levels of inflammatory markers among persons with and without the *TNF* G308A allele and autoimmune conditions that involve B-cell activation would also be particularly useful and would aid in the understanding of NHL etiology.

The 3 *HLA* class I/II SNPs identified to date as susceptibility loci for NHL subtypes, including the SNP tagging *HLA-DRB1**01:01 (rs10484561), have largely been associated with follicular lymphoma (56, 57), although rs10484561 has also been implicated in DLBCL etiology (19–21). The SNPs rs10484561, rs2647012, and rs6457327 yielded no interactions with autoimmune conditions for DLBCL or follicular lymphoma, a finding that is consistent with results from a previously published analysis within a single study (31). Given the lack of association between autoimmune conditions and follicular lymphoma, the absence of an observed interaction is not unexpected. Additionally identified SNPs in chronic lymphocytic leukemia/small lymphocytic lymphoma etiology (23–25, 28, 58) were not included in the present analysis because of the lack of data among controls, the lack of data on autoimmune conditions among cases in non-InterLymph studies, and the lack of association between autoimmune conditions and chronic lymphocytic leukemia/small lymphocytic lymphoma, providing little justification for their inclusion.

Strengths of this analysis included the large sample size compiled in our international effort, permitting analysis by NHL subtype. To further enhance our statistical power and to address our biological hypothesis, we created biologically based categories for autoimmune conditions. These provided specificity by demonstrating that autoimmune conditions mediated by B-cell effector mechanisms increased risks of DLBCL and MZL and that those involving T-cell-mediated responses increased risk of peripheral T-cell lymphoma. When autoimmune conditions were categorized by whether or not they targeted a single organ and by the specific organs targeted, differential risks were observed; conditions affecting multiple organs were implicated in the risks of DLBCL and MZL, whereas single-organ-targeted autoimmune conditions were implicated in peripheral T-cell lymphoma. Our large sample size and novel use of biology-based categories allowed for the evaluation of statistically significant interactions between genotypes and autoimmune conditions. Given the rarity of autoimmune conditions, pooled analysis of individual data provide an optimal means of conducting such an investigation.

Several limitations of this study should be considered, including the use of self-reported data on autoimmune conditions (although most studies queried participants about their personal history of physician-diagnosed conditions (3)) and the relatively low prevalence of autoimmune conditions, which restricted our ability to evaluate interactions with individual autoimmune conditions. Similarly, we were unable to examine associations with the rarer B-cell and T-cell NHL subtypes. In addition, given the large number of tests conducted, we cannot exclude the possibility that our results were due to chance, as our *P*-interaction values did not reach the level of significance ($P = 0.01$) set for Bonferroni correction. Nevertheless, we believe that our results remain of high interest, as the differences in risk by genotype (e.g., higher risk among *TNF* G308A

variant genotypes AG/AA) and the subtypes for which differences were observed (e.g., DLBCL, MZL) were consistent with our strong a priori hypotheses. Finally, we acknowledge that survival bias is a concern in case-control studies of NHL, from which this analysis was derived. Epidemiologic studies that include more aggressive NHL subtypes such as DLBCL probably do suffer from survival bias, since some persons have died and others are too ill to participate. We acknowledge that the antigenic stimulus or other stimuli from autoimmune diseases that promote lymphomagenesis are probably part of a chronic process and may be limited to autoimmune diseases that progress over a longer time course. Therefore, patients with more advanced autoimmune diseases or more rapidly progressing NHL may have been less likely to participate in such epidemiologic studies. It is possible that participation based on severity of autoimmune diseases would be applicable to both cases and controls, in which case the participation/survival bias would have been nondifferential and would have biased our risk estimates toward the null. In the scenario in which aggressive lymphomas from severe autoimmune conditions were not included in our analysis, the bias would have been differential and would have pointed toward the null.

Our results support the need for expanded research on the potential overlap of autoimmune-condition biological pathways with lymphomagenesis (59). Future fine mapping efforts and functional studies of implicated SNPs (including that for *TNF*, where the functional role of the putative loci has not yet been fully deciphered) are also warranted (52). Future efforts that incorporate haplotype analyses, particularly within the *HLA* region, in which there is tight linkage disequilibrium, are also warranted. Expanded gene-environment evaluation of established risk factors may further prove fruitful in delineating key biological mechanisms involved in lymphomagenesis. Finally, follow-up of our results among large-scale cohorts with celiac disease or Sjögren's syndrome could also prove fruitful.

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