B-Cell NHL Subtype Risk Associated with Autoimmune Conditions and PRS

Sophia S. Wang[1], Claire M. Vajdic[2], Martha S. Linet[3], Susan L. Slager[4], Jenna Voutsinas[1], Alexandra Nieters[5], Delphine Casabonne[6,7], James R. Cerhan[4], Wendy Cozen[8], Graciela Alarcón[9], Otoniel Martínez-Maza[10,11,12], Elizabeth E. Brown[13,14], Paige M. Bracci[15], Jennifer Turner[16,17], Henrik Hjalgrim[18], Parveen Bhatti[19], Yawei Zhang[20], Brenda M. Birmann[21], Christopher R. Flowers[22], Ora Paltiel[23], Elizabeth A. Holly[15], Eleanor Kane[24], Dennis D. Weisenburger[25], Marc Maynadié[26], Pierluigi Cocco[27], Lenka Foretova[28], Elizabeth Crabb Breen[29], Qing Lan[3], Angela Brooks-Wilson[30], Anneclaire J. De Roos[31], Martyn T. Smith[32], Eve Roman[24], Paolo Boffetta[33,34], Anne Kricker[35], Tongzhang Zheng[36], Christine F. Skibola[22], Jacqueline Clavel[37], Alain Monnereau[37,38], Stephen J. Chanock[3], Nathaniel Rothman[3], Yolanda Benavente[6,7], Patricia Hartge[3], and Karin E. Smedby[39]

ABSTRACT

Background: A previous International Lymphoma Epidemiology (InterLymph) Consortium evaluation of joint associations between five immune gene variants and autoimmune conditions reported interactions between B-cell response-mediated autoimmune conditions and the rs1800629 genotype on risk of B-cell non–Hodgkin lymphoma (NHL) subtypes. Here, we extend that evaluation using NHL subtype-specific polygenic risk scores (PRS) constructed from loci identified in genome-wide association studies of three common B-cell NHL subtypes.

Methods: In a pooled analysis of NHL cases and controls of Caucasian descent from 14 participating InterLymph studies, we evaluated joint associations between B-cell–mediated autoimmune conditions and tertile (T) of PRS for risk of diffuse large B-cell lymphoma (DLBCL; $n = 1{,}914$), follicular lymphoma ($n = 1{,}733$), and marginal zone lymphoma (MZL; $n = 407$), using unconditional logistic regression.

Results: We demonstrated a positive association of DLBCL PRS with DLBCL risk [T2 vs. T1: OR = 1.24; 95% confidence interval (CI), 1.08–1.43; T3 vs. T1: OR = 1.81; 95% CI, 1.59–2.07; *P*-trend (P_{trend}) < 0.0001]. DLBCL risk also increased with increasing PRS tertile among those with an autoimmune condition, being highest for those with a B-cell–mediated autoimmune condition and a T3 PRS [OR = 6.46 vs. no autoimmune condition and a T1 PRS, $P_{trend} < 0.0001$, *P*-interaction ($P_{interaction}$) = 0.49]. Follicular lymphoma and MZL risk demonstrated no evidence of joint associations or significant $P_{interaction}$.

Conclusions: Our results suggest that PRS constructed from currently known subtype-specific loci may not necessarily capture biological pathways shared with autoimmune conditions.

Impact: Targeted genetic (PRS) screening among population subsets with autoimmune conditions may offer opportunities for identifying those at highest risk for (and early detection from) DLBCL.

[1]Division of Health Analytics, Department of Computational and Quantitative Medicine, Beckman Research Institute of the City of Hope, Monrovia, California. [2]Centre for Big Data Research in Health, The University of New South Wales, Sydney, New South Wales, Australia. [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland. [4]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota. [5]The Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany. [6]Unit of Infections and Cancer, Epidemiology, Public Health, Cancer Prevention and Palliative Care Program – Epibell, IDIBELL, Institut Català d' Oncologia/IDIBELL, Barcelona, Spain. [7]The Biomedical Research Centre Network for Epidemiology and Public Health (CIBERESP), Madrid, Spain. [8]Chao Family Comprehensive Cancer Center, University of California, Irvine, Irvine, California. [9]Division of Clinical Immunology and Rheumatology, Department of Medicine, Heersink School of Medicine, The University of Alabama at Birmingham, Birmingham, Alabama. [10]Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California. [11]Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California. [12]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, California. [13]Department of Pathology, Heersink School of Medicine, The University of Alabama at Birmingham, Birmingham, Alabama. [14]O'Neal Comprehensive Cancer Center, The University of Alabama at Birmingham, Birmingham, Alabama. [15]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California. [16]Department of Histopathology, Douglass Hanly Moir Pathology, Sydney, New South Wales, Australia. [17]Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, New South Wales, Australia. [18]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark. [19]British Columbia Cancer Research Center, Vancouver, British Columbia, Canada. [20]Department of Cancer Prevention and Control at the National Cancer Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. [21]Channing Division of Network Medicine, Department of Medicine Research, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. [22]Winship Cancer Institute, Emory University, Atlanta, Georgia. [23]Department of Hematology, The Hebrew University-Hadassah Braun School of Public Health and Community Medicine, Hadassah University Medical Center, Jerusalem, Israel. [24]Department of Health Sciences, University of York, York, United Kingdom. [25]Department of Pathology, City of Hope, Duarte, California. [26]Registry of Hematological Malignancies of Cote d'Or, INSERM U1231, Burgundy University and University Hospital, Dijon, France (Maynadie). [27]Occupational Health Section, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy. [28]Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic. [29]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California. [30]Department of Biomedical Physiology and Kinesiology, Faculty of Science, Simon Fraser University, Vancouver, British Columbia, Canada. [31]Department of Environmental and Occupational Health, Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania. [32]Division of

Introduction

Since its inception in 2001, the International Lymphoma Epidemiology (InterLymph) Consortium has sought to identify genetic and nongenetic risk factors for non–Hodgkin lymphoma (NHL) and its heterogenous subtypes by conducting pooled analyses comprising thousands of patients and controls from case–control epidemiologic studies across multiple countries (https://epi.grants.cancer.gov/interlymph). Consortium members have demonstrated statistical associations between autoimmune conditions and NHL subtypes (1–3), most notably between B-cell–mediated autoimmune conditions and diffuse large B-cell lymphoma (DLBCL) and marginal zone lymphoma (MZL; refs. 4, 5). Although autoimmune conditions are generally rare, their individual associations with NHL subtypes are among the most robust and strongest (e.g., over 2-fold) in NHL etiology (1). In contrast, genome-wide association studies (GWAS) have identified statistically significant associations with NHL subtypes for multiple common genetic susceptibility loci, but their associations have largely exhibited modest magnitudes of risk (e.g., less than 2-fold; refs. 6–11), as is typical for genetic associations studies.

In a previous InterLymph Consortium evaluation of joint associations between autoimmune conditions and five putative susceptibility loci among genes potentially linked with immune function, we demonstrated a statistically significant interaction between *TNF -308G-A* (rs1800629) and B-cell–mediated autoimmune conditions for DLBCL risk (3). Since that publication, several other NHL GWASs have yielded multiple highly significant susceptibility loci; notably, the growing list of implicated putative loci differs by NHL subtype. Here, we construct polygenic risk scores (PRS) derived from NHL subtype-specific GWAS results for three common NHL subtypes, including DLBCL, follicular lymphoma, and MZL, and evaluate the joint associations between these subtype-specific PRS and autoimmune conditions to determine whether autoimmune conditions and genetic susceptibility to these NHL subtypes share common biological underpinnings.

Materials and Methods

Study population

The present analysis included data from 14 case–control studies that previously participated in an InterLymph Consortium (https://epi.grants.cancer.gov/interlymph/) pooled analysis of autoimmune conditions in relation to NHL risk (Supplementary Table S1; refs. 1–3; 12–25). As previously described, NHL cases and controls from the 14 studies were eligible if they were: age 17 years or older, not known to be human immunodeficiency virus (HIV)-positive, and had no history of organ transplantation (3). Among the eligible participants, inclusion further required genotype data from NHL GWAS studies published from 2014 to 15 (6–8). To minimize confounding by race, the GWAS studies were conducted among Caucasians. Specifically, ancestry was assessed using the Genotyping Library and Utilities (GLU- http://code.google.com/p/glu-genetics/) struct.admix module based on the method by Pritchard and colleagues (26) and participants with less than 80% European ancestry were excluded (6). The final study sample for the present analysis thus reflects a subset of those from previously published studies who also had DNA and passed quality control for GWAS analyses. A comparison of select demographic characteristics of participants included in this analysis and those in our previous publication is summarized in Supplementary Table S2 (3). The final analytic dataset comprised 5,886 cases and 5,687 controls.

Exposure assessment

As previously described, harmonization of autoimmune conditions was conducted previously as part of a consortium-wide effort and detailed in the resulting publications (1, 3). Briefly, self-reported history of autoimmune conditions was collected in each participating study using structured questionnaires during in-person or telephone interviews. In most studies (70%), respondents were asked whether any autoimmune condition had been diagnosed by a physician. Consistent with the original InterLymph Consortium study on autoimmune conditions (1), we included the following: primary Sjögren syndrome, systemic lupus erythematosus (SLE), 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 disease, ulcerative colitis, autoimmune hemolytic anemia, and Hashimoto thyroiditis. No imputation was conducted for missing data; studies and individuals with missing data were excluded from each of the respective analyses. Based on this harmonization, autoimmune conditions were then categorized 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 (3). 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, dermatologic, hematologic, neurologic, and endocrine organs. B-cell–mediated autoimmune conditions included autoimmune hemolytic anemia, Hashimoto thyroiditis, primary Sjögren syndrome, SLE, rheumatoid arthritis, pernicious anemia, and myasthenia gravis. T-cell–mediated autoimmune conditions included systemic sclerosis or scleroderma, poly- or dermatomyositis, immune thrombocytopenic

Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, California. [33]Stony Brook Cancer Center, Stony Brook University, Stony Brook, New York. [34]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy. [35]Sydney School of Public Health, The University of Sydney, Sydney, New South Wales, Australia. [36]Department of Epidemiology, School of Public Health, Brown University, Providence, Rhode Island. [37]Centre of Research in Epidemiology and Statistics (CRESS), UMR1153, INSERM, Université de Paris, Paris, France. [38]Registre des Hémopathies Malignes de la Gironde, Institut Bergonié, University of Bordeaux, Inserm, Team EPICENE, UMR 1219, Paris, France. [39]Division of Clinical Epidemiology, Department of Medicine Solna, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Sophia S. Wang, Division of Health Analytics, Department of Computational and Quantitative Medicine, Beckman Research Institute of the City of Hope, 1218 South 5th Avenue, Monrovia, CA 91016. Phone: 626-471-7316; Fax: 626-471-7308; E-mail: sowang@coh.org

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purpura, type-1 diabetes, multiple sclerosis, celiac disease, psoriasis, sarcoidosis, Crohn disease, and ulcerative colitis. These categorizations were based on the type of primary immune response believed to be involved in mediating autoimmunity. Categorizations by organ involvement (multiple-organ– versus primarily single-organ–targeted) were also evaluated (Supplementary Table S3; ref. 3). Because the focus of the present manuscript is on the three major B-cell lymphoma subtypes, our analyses and results are focused on the B-cell–mediated autoimmune conditions for which prior associations were reported (3).

PRS

GWAS data were ascertained through a number of efforts and platforms, including Illumina 317K [Scandinavian Lymphoma *Etiology* (SCALE) study], Illumina Human CNV370-Duo BeadChip [University of California, San Francisco (UCSF), San Francisco, CA), OmniExpress [NCI–Surveillance Epidemiology and End Results (SEER); New South Wales, Australia; Yale, New Haven, CN; British Columbia, Canada; UCSF, United Kingdom], Illumina660 (Mayo Clinic), Sequenom MassARRAY iPLEX (SF1B), Illumina GoldenGate, and Pyrosequencing (EpiLymph). Collectively, we included loci for which call rates were ≥95% and sample completion rates were ≥90% (6–9). To evaluate the genome across studies, we thus imputed all GWAS data using the 1000 Genomes Project (1kGP) v.3 (March 2012 release, http://www.1000genomes.org/) reference panel and IMPUTE2 (http://mathgen.stats.ox.ac.uk/impute/impute_v2.html). The imputation analysis was restricted to common SNPs (cut-off minor allele frequency > 0.01 with imputation accuracy INFO score >0.3). Wherever possible, either the best directly genotyped SNP or the most significant imputed SNP (with information score > 0.8) for the locus was used. We note that genotyping of SNPs by TaqMan (Applied Biosystems) in a subset of subjects yielded more than 88.9% concordance with the imputed dosages (median concordance = 99.6%), indicating that imputation accuracy was high (4, 7, 8).

SNPs included for each PRS comprised those statistically significantly associated with the respective NHL subtype in recently published GWAS that included InterLymph studies. Specifically, we included the following SNPs and corresponding reported ORs to derive subtype-specific PRS: DLBCL [rs116446171 (OR = 2.2), rs2523607 (OR = 1.32), rs79480871 (OR = 1.34); rs13255292 (OR = 1.22); rs4733601 (OR = 1.18)] (6); follicular lymphoma [rs4938573 (OR = 1.34), rs4937362 (OR = 1.19), rs6444305 (OR = 1.21), rs17749561 (OR = 1.34), rs13254990 (OR = 1.18), rs12195582/rs115374828 (OR = 1.44)] (7); and MZL [rs9461741 (OR = 2.66), rs2922994/rs116778584 (OR = 1.64)] (8). For each SNP, there was no statistically significant heterogeneity by study (6–8).

To construct the PRS, homozygous risk alleles were assigned a value of 2, heterozygotes a value of 1, and homozygous nonrisk alleles a value of 0 (27, 28). This value was subsequently multiplied by the log of the published OR, and the resulting values were summed across all SNPs included in each subtype-specific PRS. Subtype-specific PRSs were then categorised into tertiles using the PRS distribution among controls for each subtype. We note that numbers of controls vary for each NHL subtype due to the different numbers of participants with complete data for each of the SNPs required to construct the given PRS.

NHL classification

NHL subtypes were grouped as per InterLymph Pathology Working Group guidelines (29–31). Results are presented for two NHL subtypes for which associations with several autoimmune conditions have been consistently reported: DLBCL and MZL. We also included follicular lymphoma because we previously observed an excess risk of follicular lymphoma among those with a history of Sjogren syndrome (32) and an association with autoimmune conditions among those with a variant rs1800629 allele (3). Our analytic dataset included 1914 DLBCLs, 1733 follicular lymphomas, and 407 MZLs.

Statistical methods

Independent associations

We first confirmed associations between autoimmune conditions and NHL subtypes in our subset of eligible cases and controls. Unconditional logistic regression, adjusted for age as a continuous variable, sex, and geographical region/study center (Supplementary Table S2), were used to calculate ORs and 95% confidence intervals (CI) as estimates of NHL subtype risk. ORs and 95% CIs for each NHL subtype were similarly calculated for each subtype-specific PRS, comparing tertiles (T) 2 and T3 to T1. We calculated P-trend (P_{trend}) using the Wilcoxon rank-sum test across the ordered categories to measure whether magnitudes of risk across PRS tertiles T2 and T3 yielded a significant trend. For both independent models (e.g., models examining only autoimmune conditions or PRS), we adjusted for age. Potential confounders, such as socioeconomic status, smoking status, and family history of hematologic malignancies did not change risk estimates more than 10% and were thus not retained in any of the models. Heterogeneity was evaluated using χ^2 tests of interaction between the studies and variables of interest; as there was no strong evidence of heterogeneity by study or any other variable of interest, all data were examined in a logistic regression model (by subtype).

Stratified associations

We tested for associations between PRS and autoimmune conditions on an additive scale for each subtype (DLBCL, follicular lymphoma, MZL) by calculating ORs and 95% CIs relative to those without autoimmune conditions and a PRS in T1 as the common referent group (**Tables 1–3**). We calculated P_{trends} (Wilcoxon rank-sum test) across ordered categories to test for trends. Potential interaction on the multiplicative scale was assessed by stratifying on PRS tertile within each category of autoimmune condition. The *P* value for interaction was estimated using the Wald test for homogeneity of the associations of autoimmune conditions with NHL subtype risk by PRS tertile. Parallel analyses by individual SNPs were also conducted (Supplementary Tables S4–S6).

All analyses were conducted using SAS 9.3 (SAS Institute, Inc.). All tests were two-sided and $P < 0.05$ were considered statistically significant. For *P*-interactions ($P_{interactions}$) < 0.05, Bonferoni adjustment was applied to account for multiple comparisons.

Results

NHL cases and controls representing 14 participating InterLymph Consortium studies in North America, Europe, and Australia were included, comprising 1,914 DLBCL (5,257 controls), 1,733 follicular lymphoma (5,338 controls), and 407 MZL (2,883 controls; Supplementary Table S1). As noted, controls differed by subtype due to differences in the available SNP data to construct the corresponding PRS across participants. Comparisons with our previous publication showed similar distributions of sex, socioeconomic status, and smoking; in addition to being restricted to Caucasian race, the present population was slightly older (Supplementary Table S2).

DLBCL

The highest magnitude of (nongenetic) DLBCL risk was observed for individuals with B-cell–mediated autoimmune conditions (OR =

Table 1. Main and stratified associations for DLBCL risk by autoimmune condition and DLBCL PRS in participating InterLymph Consortium studies.

Autoimmune conditions	DLBCL PRS	Controls	DLBCL	OR (95% CI)	$P_{interaction}$[a]
None		5,064	1,808	1.00 (Ref)	
Any		193	106	**1.42 (1.10–1.83)**	–
No B-cell conditions		5,046	1,796	1.00 (Ref)	
B-cell conditions		53	50	**2.90 (1.94–4.35)**	–
No multiple organs		5,053	1,797	1.00 (Ref)	
Multiple organs		64	46	**2.24 (1.50–3.33)**	–
None/any	T1	1,965	549	1.00 (Ref)	
	T2	1,717	578	**1.24 (1.08–1.43)**	
	T3	1,575	787	**1.81 (1.59–2.07)**	–
None	T1	1,888	513	1.00 (Ref)	
	T2	1,656	550	**1.25 (1.09–1.44)**	
	T3	1,520	745	**1.82 (1.59–2.08)**	
Any	T1	77	36	1.52 (0.99–2.33)	
	T2	61	28	**1.73 (1.07–2.79)**	$P_{interaction}$
	T3	55	42	**2.65 (1.71–4.10)**	= 0.82
No B-cell conditions	T1	1,881	512	1.00 (Ref)	
	T2	1,647	545	**1.24 (1.08–1.43)**	
	T3	1,518	739	**1.80 (1.57–2.07)**	
B-cell conditions	T1	22	18	**2.94 (1.52–5.70)**	
	T2	18	14	**3.27 (1.56–6.84)**	$P_{interaction}$
	T3	13	18	**6.46 (3.04–13.7)**	= 0.49
No multiple organs	T1	1,885	512	1.00 (ref)	
	T2	1,650	544	**1.24 (1.08–1.43)**	
	T3	1,518	741	**1.81 (1.58–2.07)**	
Multiple organs	T1	31	17	**2.18 (1.16–4.11)**	
	T2	19	12	**2.54 (1.17–5.48)**	$P_{interaction}$
	T3	14	17	**5.92 (2.80–12.5)**	= 0.34

Note: See Supplementary Table S3 for definition of autoimmune condition categories.
[a]Wald test for homogeneity.

2.90; 95% CI, 1.94–4.35) or autoimmune conditions that affected multiple organs (OR = 2.24; 95% CI, 1.50–3.33). We also observed an increased DLBCL risk with increasing tertile of DLBCL PRS (vs. T1, T2: OR = 1.24; 95% CI, 1.08–1.43; T3: OR = 1.81; 95% CI, 1.59–2.07; **Table 1**). DLBCL risk among those with no B-cell–mediated autoimmune conditions increased in a dose-dependent manner for each subsequent level of PRS ($P_{trend} < 0.0001$). Among those with B-cell–mediated autoimmune conditions, ORs were further elevated, with the highest magnitude of DLBCL risk among those with a PRS in T3 (OR = 6.46; 95% CI, 3.04–13.7), compared with the referent group. A similar pattern of elevated DLBCL risk was observed for autoimmune conditions affecting multiple organs and increasing PRS, though we note that B-cell–mediated autoimmune conditions comprise approximately 80% of autoimmune conditions affecting multiple organs (**Table 1**). There was no statistically significant evidence for interaction with the PRS (**Table 1**) or in any analyses stratified by the individual SNPs (Supplementary Table S4).

Follicular lymphoma

No association with any category of autoimmune conditions was observed. However, the PRS for follicular lymphoma demonstrated an increasing trend in risk with each PRS tertile (vs. T1, T2: OR = 2.38; 95% CI, 2.03–2.80; T3 OR = 4.89; 95% CI, 4.18–5.73; $P_{trend} < 0.0001$; **Table 2**). Evaluation of stratified associations showed that the increasing follicular lymphoma risk by PRS did not differ by autoimmune condition category. Evaluation of autoimmune associations by individual loci yielded a significant $P_{interaction}$ for rs115374828, whereby associations between autoimmune conditions and follicular lymphoma risk were observed and significant only among those with the CC genotype (Supplementary Table S5). However, we note the $P_{interaction}$ was not statistically significant after adjustment for multiple comparisons.

MZL

MZL risk was significantly elevated specifically among those reporting B-cell–mediated autoimmune conditions (OR = 5.88; 95% CI, 3.55–9.74) and conditions that affect multiple organ systems (OR = 4.96; 95% CI, 3.04–8.12; **Table 3**). We observed no association with increasing tertile of the MZL PRS. Evaluation of autoimmune conditions by PRS yielded statistically significant risk increases for B-cell–mediated conditions and conditions affecting multiple organ systems, regardless of PRS tertile. Further evaluation of associations for autoimmune conditions by individual SNPs did not yield evidence of individual SNP-level interaction (Supplementary Table S6).

Discussion

In this analysis, we observed DLBCL risk to be positively associated with increasing PRS tertiles among those with a history of B-cell–related autoimmune conditions. We did not observe significant joint associations between individual SNPs and autoimmune conditions for increased DLBCL, follicular lymphoma, or MZL risk. Although increased follicular lymphoma risk related to autoimmune conditions appeared restricted to one locus (rs115374828), the $P_{interaction}$ was not statistically significant. For MZL, the lack of joint association between the PRS and history of autoimmune conditions was not entirely

Table 2. Main and stratified association for follicular lymphoma risk by autoimmune condition and follicular lymphoma PRS in participating InterLymph Consortium studies.

Autoimmune conditions	FL PRS	Controls	FL	OR (95% CI)	$P_{interaction}$[a]
None		5,142	1,666	1.00 (Ref)	
Any		196	67	0.91 (0.67–1.23)	–
No B-cell conditions		5,123	1,660	1.00 (Ref)	
B-cell conditions		51	19	1.12 (0.65–1.93)	–
No multiple organs		5,131	1,661	1.00 (Ref)	
Multiple organs		65	18	1.10 (0.66–1.82)	–
None/any	T1	2,367	298	1.00 (Ref)	
	T2	1,680	549	**2.38 (2.03–2.80)**	
	T3	1,127	832	**4.89 (4.18–5.73)**	**–**
None	T1	2,352	292	1.00 (Ref)	
	T2	1,675	543	**2.37 (2.01–2.79)**	
	T3	1,115	829	**4.99 (4.24–5.86)**	
Any	T1	87	12	1.01 (1.68–4.84)	
	T2	**55**	**24**	**2.85 (1.97–5.22)**	$P_{interaction}$
	T3	**54**	**31**	**3.21 (1.07–1.37)**	= 0.30
No B-cell conditions	T1	2,345	292	1.00 (Ref)	
	T2	1,666	543	**2.37 (2.01–2.79)**	
	T3	1,112	825	**4.98 (4.23–5.85)**	
B-cell conditions	T1	22	6	1.96 (0.77–5.02)	
	T2	14	6	**3.61 (1.33–9.76)**	$P_{interaction}$
	T3	15	7	**2.92 (1.15–7.39)**	= 0.10
No multiple organs	T1	2,346	292	1.00 (Ref)	
	T2	1,672	543	**2.36 (2.01–2.78)**	
	T3	1,113	826	**4.98 (4.24–5.86)**	
Multiple organs	T1	30	8	2.02 (0.89–4.58)	
	T2	18	10	**4.15 (1.79–9.61)**	$P_{interaction}$
	T3	17	5	2.11 (0.75–5.94)	= 0.20
No organ-specific conditions	T1	2,349	291	1.00 (Ref)	
	T2	1,668	545	**2.39 (2.03–2.81)**	
	T3	1,113	825	**4.99 (4.24–5.97)**	
Organ-specific conditions	T1	59	6	0.73 (0.31–1.72)	
	T2	38	15	**2.44 (1.28–4.66)**	$P_{interaction}$
	T3	38	26	**3.57 (2.07–6.17)**	= 0.78

[a]Wald test for homogeneity.

surprising given the lack of association between the PRS and MZL risk in our population.

As a reflection of the currently established genetic risk, the PRS provides improved statistical power for evaluating joint associations. This power is evident with the significant increase in the magnitudes of risk for each PRS tertile for DLBCL and follicular lymphoma. The suggestive joint association between DLBCL PRS and autoimmune conditions supports the hypothesis that susceptibility loci identified to date independently contribute to DLBCL susceptibility in an additive manner to having autoimmune conditions. It remains to be determined whether their associations are within shared biological pathways, but the additive effects at a minimum suggest that their associations are not overlapping. This is supported by the curious observation that while HLA associations have been reported for both DLBCL and various autoimmune conditions, these associated loci remain distinct for both outcomes. Even each of the purported loci comprising the DLBCL PRS appear to function independently from one another at the moment. Briefly, the susceptibility locus at 6p25.3 (rs116446171) maps near exocyst complex component 2 (EXOC2) which functions at the interface between host defense and cell death regulation and interacts with Ral proteins, which play a crucial role in the maintenance of epithelial cell polarity, cell motility, and cytokinesis, and in proliferation and metastasis (4). The two 8q24.21 variants, rs13255292 and rs4736601, are in close proximity to PVT1, an ncRNA implicated in MYC (oncogene) activation. The susceptibility locus at 2p23.3 (rs79480871) maps near nuclear receptor coactivator 1 (NCOA1) and intersectin 2 (ITSN2). *NCOA1* acts as a transcriptional coactivator for steroid and nuclear hormone receptors and *ITSN2* encodes a protein involved in clathrin-mediated endocytosis (4). The HLA-B SNP rs2523607 (*HLA-B*08:01*) plays a central role in presenting intracellularly processed self or foreign antigens to $CD8^+$ cytotoxic T lymphocytes and is carried by the ancestral 8.1 haplotype which has been associated with other autoimmune conditions, such as type-I diabetes. The additive effects between autoimmune conditions and the DLBCL PRS thus appears statistical in nature; larger sample sizes would be required to determine whether biological or multiplicative interaction with specific loci could pinpoint biological pathways of interest and high susceptibility.

Though confirmation is required, the association between rs115374828 and autoimmune conditions and follicular lymphoma is worth noting; rs115374828 reflects *HLA DRB1* loci, which has also been implicated in various autoimmune conditions (33, 34), providing plausible biological rationale for a joint association. Although we broadly categorized autoimmune conditions by their purported biological pathways to enhance power, a similar task cannot yet be taken with susceptibility loci, as the culpable loci and their functions remain

Table 3. Main and stratified associations for MZL risk by autoimmune condition and MZL PRS in participating InterLymph Consortium studies.

Autoimmune conditions	MZL PRS	Controls	MZL	OR (95% CI)	$P_{interaction}$[a]
None		2,774	376	1.00 (ref)	
Any		109	31	**1.97 (1.33–2.94)**	–
No B-cell conditions		2,764	373	1.00 (ref)	
B-cell conditions		28	24	**5.88 (3.55–9.74)**	–
No multiple organs		2,770	374	1.00 (ref)	
Multiple organs		33	24	**4.96 (3.04–8.12)**	–
None/any	T1	2,123	294	1.00 (ref)	
	T2	586	86	1.10 (0.84–1.43)	
	T3	174	27	1.09 (0.71–1.68)	–
None	T1	2,046	272	1.00 (ref)	
	T2	567	80	1.10 (0.83–1.44)	
	T3	161	24	1.10 (0.70–1.74)	
Any	T1	77	22	**2.13 (1.28–3.55)**	
	T2	19	6	**2.64 (1.02–6.83)**	$P_{interaction}$ = 0.58
	T3	13	3	1.42 (0.39–5.10)	
No B-cell conditions	T1	2,037	272	1.00 (ref)	
	T2	566	78	1.06 (0.81–1.40)	
	T3	161	23	1.48 (0.66–1.67)	
B-cell conditions	T1	16	17	**7.95 (3.79–16.7)**	
	T2	7	5	**6.07 (1.80–20.5)**	$P_{interaction}$ = 0.21
	T3	5	2	2.59 (0.48–13.9)	
No multiple organs	T1	2,042	272	1.00 (ref)	
	T2	567	79	1.08 (0.82–1.42)	
	T3	161	23	1.05 (0.66–1.67)	
Multiple organs	T1	19	18	**7.43 (3.74–14.8)**	
	T2	9	4	**4.90 (1.44–16.7)**	$P_{interaction}$ =0.27
	T3	5	2	3.24 (0.60–17.5)	
No organ-specific conditions	T1	2,040	268	1.00 (ref)	
	T2	566	77	1.06 (0.80–1.40)	
	T3	161	24	1.11 (0.70–1.75)	
Organ-specific conditions	T1	60	5	0.59 (0.23–1.51)	
	T2	11	2	1.26 (0.27–5.88)	$P_{interaction}$ =0.80
	T3	8	1	0.65 (0.08–5.27)	

[a]Wald test for homogeneity.

largely speculative. This is consistent with a recent analysis of InterLymph Conosrtium data by Din and colleagues (35) which showed that the PRS of each of three autoimmune conditions that most consistently demonstrate an association with NHL risk (RA, SLE, MS) was not associated with risk of any major NHL subtype, and that PRS of NHL subtypes were, likewise, not associated with these three autoimmune conditions. With little overall overlap evident among the respective lists of GWAS-identified susceptibility loci, identifying novel ways to pinpoint common but specific biologic processes (e.g., chronic inflammation) may reveal critical interactions and show a causative cascade effect (35). This notion is consistent with the recent report by Ben Eli (2019) that found family history of lymphoma to be associated with NHL, family history of autoimmune conditions to be associated with autoimmune conditions, but family history of autoimmune conditions not to be associated with NHL and vice versa (36)

Study limitations include the use of self-reported autoimmune conditions (although most studies queried for personal history of physician-diagnosed conditions; ref. 3), the low prevalence of autoimmune conditions, and lack of data on severity or treatment; it is possible that true interactions with individual conditions might exist (e.g., for Sjogren syndrome and MZL), for which we lack the power to investigate. Another limitation is the target population in which our study was conducted, as the eligible studies were generally conducted in geographical areas with small minority populations. Our evaluation of PRS for MZL was limited, with only two confirmed SNPs to date and a small sample size. In addition, there is also clinical and biological heterogeneity within MZL that has not yet been evaluated in the context of GWAS. This is also applicable to DLBCL where tumor molecular subtypes such as cell of origin (37) or double hit status (38) used to subclassify DLBCL cases into clinically meaningful categories was not available.

Ongoing efforts include the identification of additional genetic susceptibility loci for NHL subtypes through an expanded GWAS with additional studies. Despite the large sample size compiled from our present consortial collaboration and the strength of our biologically-based groupings of autoimmune conditions to enhance power, even larger sample sizes are needed to confirm these results and to power further exploration of specific autoimmune conditions with specific genetic loci. Moreover, additional loci from these analyses will refine the PRS and may prove instrumental for identifying common pathways of interest that contribute to disease risk. Clinically, leveraging a refined PRS coupled with established risk factors (e.g., autoimmune conditions) may also prove relevant for identifying those with autoimmune conditions who are at highest risk for developing DLBCL based on their genetic profile. It is not implausible to envision enhanced screening among targeted populations, such as those with

specific autoimmune conditions known to be at highest risk for DLBCL so that early diagnosis may improve subsequent prognosis. Future efforts to expand the evaluation of NHL risk factors to include potential similar immune responses (e.g., infections) may also be warranted.

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Authors' Contributions

S.S. Wang: Conceptualization, resources, formal analysis, supervision, funding acquisition, methodology, writing–original draft, project administration, writing–review and editing. **C.M. Vajdic:** Data curation, writing–review and editing. **M.S. Linet:** Conceptualization, data curation, writing–review and editing. **S.L. Slager:** Data curation, writing–review and editing. **J. Voutsinas:** Formal analysis, writing–review and editing. **A. Nieters:** Conceptualization, data curation, writing–review and editing. **D. Casabonne:** Data curation, writing–review and editing. **J.R. Cerhan:** Conceptualization, data curation, writing–review and editing. **W. Cozen:** Conceptualization, data curation, writing–review and editing. **G. Alarcón:** Conceptualization, formal analysis, methodology, writing–review and editing. **O. Martínez-Maza:** Methodology, writing–review and editing. **E.E. Brown:** Methodology, writing–review and editing. **P.M. Bracci:** Data curation, writing–review and editing. **J. Turner:** Data curation, writing–review and editing. **H. Hjalgrim:** Conceptualization, data curation, methodology, writing–review and editing. **P. Bhatti:** Data curation, writing–review and editing. **Y. Zhang:** Data curation, writing–review and editing. **B.M. Birmann:** Data curation, methodology, writing–review and editing. **C.R. Flowers:** Conceptualization, methodology, writing–review and editing. **O. Paltiel:** Methodology, writing–review and editing. **E.A. Holly:** Data curation, writing–review and editing. **E. Kane:** Data curation, writing–review and editing. **D.D. Weisenburger:** Methodology, writing–review and editing. **M. Maynadié:** Data curation, writing–review and editing. **P. Cocco:** Data curation, writing–review and editing. **L. Foretova:** Data curation, writing–review and editing. **E.C. Breen:** Conceptualization, methodology, writing–review and editing. **Q. Lan:** Writing-review and editing. **A. Brooks-Wilson:** Data curation, writing–review and editing. **A.J. De Roos:** Methodology, writing–review and editing. **M.T. Smith:** Data curation. **E. Roman:** Data curation, writing–review and editing. **P. Boffetta:** Data curation, writing–review and editing. **A. Kricker:** Data curation, writing–review and editing. **T. Zheng:** Data curation, writing–review and editing. **C.F. Skibola:** Writing-review and editing. **J. Clavel:** Data curation, writing–review and editing. **A. Monnereau:** Data curation, writing–review and editing. **S.J. Chanock:** Data curation, funding acquisition, writing–review and editing. **N. Rothman:** Data curation. **Y. Benavente:** Data curation, writing–review and editing. **P. Hartge:** Conceptualization, data curation, methodology, writing–review and editing. **K.E. Smedby:** Conceptualization, data curation, methodology, writing–original draft, writing–review and editing.

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