HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2020 October 05.

Published in final edited form as:

Cancer Causes Control. 2020 May ; 31(5): 451–462. doi:10.1007/s10552-020-01266-4.

Infectious mononucleosis, immune genotypes, and non-Hodgkin lymphoma (NHL): an InterLymph Consortium study

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Abstract

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10552-020-01266-4) contains supplementary material, which is available to authorized users.

Purpose—We explored the interaction between non-Hodgkin lymphoma (NHL), infectious mononucleosis (IM) history, and immune-related genotypes in a pooled case–control analysis.

Methods—A total of 7,926 NHL patients and 10,018 controls from 12 case–control studies were included. Studies were conducted during various time periods between 1988 and 2008, and participants were 17–96 years of age at the time of ascertainment/recruitment. Self-reported IM history and immune response genotypes were provided by the InterLymph Data Coordinating Center at Mayo Clinic. Odds ratios (OR) were estimated using multivariate logistic regression, and interactions were estimated using the empirical Bayes method. *P*ACT was used to account for multiple comparisons.

Results—There was evidence of an interaction effect between IM history and two variants on T-cell lymphoma (TCL) risk: rs1143627 in *interleukin-1B* (*IL1B*) ($p_{\text{interaction}} = 0.04$, $\text{OR}_{\text{interaction}} = 0.09$, 95% confidence interval [CI] 0.01, 0.87) and rs1800797 in *interleukin-6* (*IL6*) ($p_{\text{interaction}} = 0.03$, $\text{OR}_{\text{interaction}} = 0.08$, 95% CI 0.01, 0.80). Neither interaction effect withstood adjustment for multiple comparisons. There were no statistically significant interactions between immune response genotypes and IM on other NHL subtypes.

Conclusions—Genetic risk variants in *IL1B* and *IL6* may affect the association between IM and TCL, possibly by influencing T-cell activation, growth, and differentiation in the presence of IM, thereby decreasing risk of immune cell proliferation.

Keywords

Infectious mononucleosis; Non-Hodgkin lymphoma; T-cell lymphoma; Interleukin-1beta (*IL1B*); Interleukin-6 (*IL6*); Gene–environment interaction

Introduction

Non-Hodgkin lymphoma (NHL) comprises a group of lymphoid malignancies with distinct histopathologies and risk patterns originating from B- (~ 80%) and T-lymphocytes (~ 20%) [1]. Genetic or acquired immunodeficiency is the strongest risk factor, but more subtle immune alterations may also play a role in pathogenesis [2]. For example, there is a strong positive association between NHL and autoimmune disease [3, 4] and an inverse association with atopy [5]. In addition to evidence of familiality for overall and subtype-specific NHL risk [6, 7], variants in and near genes related to innate and adaptive immunity (*IL1RN, FCGR2A, TNFA*, *HLA Class I* and *II*) [8–10] have been implicated as potential risk factors.

Several infectious agents, including Epstein–Barr virus (EBV) [11], Hepatitis C virus [12], and Helicobacter pylori [13], contribute to NHL etiology through various mechanisms including direct transformation of lymphocytes, immunosuppression, chronic B-cell activation, and innate immune stimulation [14]. EBV, a ubiquitous member of the human herpesvirus family, induces B-cell growth by expression of viral proteins and non-coding RNAs [15]. The viral DNA persists as an episome in the host memory B-cell DNA after infection where it remains latent in the presence of a competent cytotoxic T-cell response. When acquired early in life, primary EBV infection is generally asymptomatic or causes a mild, non- specific, febrile illness [16]. In industrialized countries and populations of higher socioeconomic status (SES), primary infection is often delayed until adolescence or young

adulthood. From 25 to 74% of those experiencing delayed primary infection develop infectious mononucleosis (IM), a moderate to severe clinical syndrome characterized by fever, tonsillar pharyngitis, and lymphadenopathy [17–19]. The severity of primary EBV infection and the development of IM are attributable, at least in part, to an amplified EBV-specific CD8 +, and to a lesser extent, CD4 + T-cell response which is not observed in those whose EBV seroconversion occurs asymptomatically [20–22]. Propensity to develop the syndrome is influenced by genetic factors related to immune response [23, 24].

In the largest pooled case–control study of NHL conducted to date from the International Lymphoma Epidemiology Consortium (InterLymph), Becker et al. [25] observed a positive association between self-reported IM history and risk of all NHL (OR 1.26, 95% CI 1.01, 1.57). When stratified by subtype, associations were observed between IM and T-cell lymphoma (TCL) and a B-cell category combining chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), prolymphocytic lymphoma (PLL), and mantle cell lymphoma (MCL) [25]. Mechanisms for this association have not been explored.

Studies indicating familial IM clustering and higher concordance for IM risk among monozygotic compared to dizygotic twin pairs suggest a role for genetic susceptibility in IM etiology [26, 27]. However, little is known about the influence of genetic factors on IM risk or their role in modifying the possible association between IM and NHL. Many of the genetic risk loci identified for NHL and NHL subtypes in previous InterLymph studies are in or near genes related to immune response that might also influence the association between IM and NHL risk [8,9, 28–32].

In this InterLymph study, we examined the joint effects of IM history and 12 candidate immune-related genetic variants on the risk of NHL.

Methods

Study population

Participants included NHL patients and controls contributed from case–control studies at InterLymph Consortium member sites. All 12 studies (from 10 countries) had approval from their respective National or Institutional Review Boards, and participants provided signed informed consent according to the WMA Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects in 1964.

Seven participating sites used population-based ascertainment (population-based case–control studies: British Columbia Cancer Agency BC [Canada]; Scandinavian Lymphoma Etiology: SCALE [Denmark, Sweden]; University of California San Francisco: UCSF [USA]; National Cancer Institute Surveillance, Epidemiology, and End Results: NCI-SEER [USA]; Epilymph-Germany; and Yale [USA]). Cases from these sites were ascertained from population-based cancer registries or national health systems, and controls were recruited from the same source population as the cases (census or random digit dialing rosters or from the same national health system clinic practice, respectively).

Five sites used clinic or hospital-based ascertainment (clinic-based case–control studies: Epilymph-Spain, Epilymph-France, Epilymph-Ireland, Epilymph-Czech Republic, and Mayo Clinic). Patients at these sites were identified from clinic or hospital records and controls were identified from other patients without cancer attending the same clinics.

Studies were conducted during various time periods between 1988 and 2008, and participants were 17–96 years of age at the time of ascertainment/recruitment. A summary of study details is provided in Supplemental Table 1 with additional details available in previous InterLymph publications [4, 5, 10, 25, 29–43].

InterLymph Consortium member studies were selected for inclusion based on the availability of self-reported IM history and candidate variant genotypes from at least 50% of participants. Participants who had missing data for age at enrollment, sex, SES, or IM history were excluded. Because the number of non-white participants in member studies was small and would require stratification for genetic analyses, we limited the study to white participants. Consistent with previous InterLymph analyses, participants who reported IM diagnosis less than 2 years before NHL diagnosis were excluded [25].

Data collection

The InterLymph Data Coordinating Center (Mayo Clinic, Rochester, MN) harmonized data submitted by each study site into a de-identified, pooled dataset for analysis. Information on demographics, family structure (number of siblings and birth order), and IM history was self-reported using questionnaires [1]. Ethnicity/race was available for eleven of the twelve study centers included in the analysis, with the participants from most of these European, US, and Canadian studies being non-Hispanic white. Participants with missing race/ethnicity were included from SCALE (n = 5,683), Mayo Clinic (n = 28), Yale (n = 3), and NCI-SEER-Seattle and Iowa (n = 20) studies since the majority of the population in these study areas is non-Hispanic white; otherwise, those with missing race were excluded. Socioeconomic status (SES) was categorized based on years of education (low: 0–12 years, high school or less; medium: 13–15 years, some college; high: 16 + years, college degree or more) or tertiles of the SES variable submitted by each individual study center.

The pooled analysis used existing genotype data on variants selected a priori based on results from previous functional analyses, association with NHL, or role in pro-/anti-inflammatory pathways [8, 9, 28–30]. The effects of these 12 genetic variants located in or near nine immune response genes were assessed: *IL1A*-889C>T (rs1800587), *IL1B*–511C>T (rs16944), *IL1B*–31T>C (rs1143627), *IL1RN*–9589A>T (rs454078), *IL2*–384T>G (rs2069762), *IL6*–174G>C (rs1800795), *IL6*–597G>A (rs1800797), *IL10*–3575T>A (rs1800890), *IL10* –1082A>G (rs1800896), *TNF* –308G>A (rs1800629), *HLA class I* C>A (rs6457327), and *HLA class II* T>G (rs10484561). Genotyping was performed using either TaqMan (Applied Biosystems, Inc., Foster City, California), Pyrosequencing (Qiagen NV, Hilden, Germany), or Illumina Goldengate (Illumina, Inc., San Diego, California) genotyping assays. Additional technical details about genotyping methods used in each contributing study are included in previous publications [8, 29, 30, 33, 44].

All NHL diagnoses were confirmed by pathology report review, with the majority re-reviewed by a hematopathologist, depending on the study. NHL subtypes were classified according to the World Health Organization (WHO) classification in 2001 and 2008 [45–47] and include chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL: ICD-O-3 codes 9670, 9823), diffuse large B-cell lymphoma (DLBCL: 9679, 9680, 9684), follicular lymphoma (FL: 9690, 9691, 9695, 9698), mantle cell lymphoma (MCL: 9673), TCL (9702, 9705, 9708, 9709, 9714, 9716, 9717, 9718, 9719, 9729, 9827, 9834), and all NHL combined (defined by the above ICDO3 codes and 9671, 9675, 9687, 9689, 9699, 9700, 9701, 9728, 9826, 9832, 9833, 9591, and 9727). Patients with AIDS-related lymphomas were excluded.

Statistical analysis

Candidate variants in linkage disequilibrium (LD)—SNP Annotation and Proxy Search (SNAP) [48] was used to assess LD via correlations between all pairs of candidate variants in the same gene.

Main effect NHL associations—Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between IM and NHL and for associations between candidate genetic variants and NHL. Consistent with other InterLymph publications [29, 30], all genetic variants were coded as dichotomous variables assuming a dominant model (absence or presence of minor allele). All models were adjusted for age at NHL diagnosis/enrollment, sex, study center, and SES.

Gene–environment interaction in NHL risk—The effect of interaction between IM and immune-related genotypes on NHL risk was assessed using the empirical Bayes approach described by Mukherjee et al. [49]. Sensitivity analyses were then performed using unconditional logistic regression to test the association between IM and NHL stratified by each candidate variant genotype. Models were adjusted for the covariates listed above. Associations were examined for all NHL combined and by NHL subtype.

Sensitivity analysis and multiple comparisons—All genetic data were assessed for deviations from allele frequencies expected under Hardy–Weinberg equilibrium among controls, and a sensitivity analysis was conducted in which we excluded study centers from the analysis of the specific genetic variants for which within-center allele frequencies were inconsistent with Hardy–Weinberg equilibrium at $p < 0.05$. Additional sensitivity analyses were conducted excluding studies using clinic-based control recruitment methods.

All statistical tests were two-sided. For genetic analyses, the p_{ACT} statistic was used to account for multiple comparisons and correlated tests from variants within the same region [50]. Uncorrected p values are reported in tables. For those associations with uncorrected p values < 0.05, p_{ACT} statistics are noted in the text. Statistical analysis was performed using Stata, version 13 (StataCorp, LP, College Station, TX).

Results

Main NHL associations

A total of 7,926 NHL patients and 10,018 controls from 12 InterLymph studies met the inclusion criteria. The distribution of NHL patients and controls by selected demographic and clinical characteristics is shown in Table 1. The majority (83%) of patients were diagnosed with mature B-cell lymphoma (Table 2); the remainder were diagnosed with mature T-cell (6%), precursor cell (1%), and missing subtype/not otherwise specified (NOS) lymphomas (10%).

Analysis with SNAP indicated candidate risk variants in *IL1B* (r^2_{IL1B}: rs16944, rs1143627 = 0.96) and in *IL6* (r^2_{IL6}: rs1800795, rs1800797 = 0.97) were in high LD, and candidate variants in *IL10* were in moderate LD (r^2_{IL10}: rs1800890, rs1800896 = 0.66).

After adjustment for multiple comparisons, we observed strong main effects for associations between *HLA* variants and NHL (rs6457327 $p_{ACT} < 0.001$ and rs10484561 $p_{ACT} = 0.004$) and an *IL1RN* variant and NHL (rs454078, $p_{ACT} = 0.04$) (Supplemental Table 2). A history of IM was associated with all NHL combined ($p_{Bon} = 0.06$) and strongly associated with CLL/SLL ($p_{Bon} = 0.04$) and MCL ($p_{Bon} = 0.01$) (Supplemental Table 3). The direction of the association between IM and NHL risk was consistent when restricted to population-based case–control studies (not shown in tables). Thus, the main effects of genotype and IM for associations with all NHL and NHL subtypes were largely consistent with previously reported results from a subset of the same InterLymph studies [8, 9, 25, 28–31].

Gene–IM interaction and NHL risk

There was an interaction effect between a genetic variant in the *IL1B* gene (rs1143627C) and IM history on TCL risk ($OR_{interaction} = 0.09$, 95% CI 0.01, 0.87, $p = 0.04$) risk. We also observed interaction between rs1800797A in the *IL6* gene and IM on TCL risk ($OR_{interaction} = 0.08$, 95% CI 0.01, 0.80, $p = 0.04$) (Table 3). Neither of the associations persisted after adjustment for multiple comparisons ($p_{ACT} > 0.05$). These results were directionally consistent when restricted to population-based case–control studies. Associations between IM history and T-cell lymphoma, stratified by *IL1B* and *IL6* genotypes, are shown in Supplemental Table 4. For each *IL1B or IL6* variant, participants with the minor allele had a lower risk of NHL. However, effect estimates are unstable due to low sample sizes in strata comprised of IM-positive TCL patients. No interaction was observed between other candidate variants and NHL or NHL subtypes ($p \geq 0.05$).

Conclusions

IM was associated with an increased risk of TCL in the original main effects InterLymph paper [25] and with a 32% ($p = 0.17$) increased risk among our subset of InterLymph participants. The minor allele in variant rs1143627 in the promoter region of the *IL1B* gene appeared to attenuate the effect of IM on TCL risk as did the minor allele in variant rs1800797 in the promoter region of the *IL6* gene, although the interaction effects for both variants did not persist after adjustment for multiple comparisons.

IL1B, the cytokine encoded by the *IL1B* gene, is an inflammatory response and fever mediator, and contributes to several lymphocyte activities including growth and differentiation of B-cells [51], proliferation of T-helper Type 2 (Th2) clones [52], and activation of Th17 cells [53]. We observed a suggestive interaction effect of similar magnitude between rs16944, an *IL1B* variant highly correlated with rs1143627, and TCL. IL1B is required for T-cell activation in some immune responses [54, 55] and thus could contribute to increased T-cell replication. The minor alleles of the two *IL1B* variants examined in our study are associated with lower expression of IL1B [56] and may decrease T-cell activation in the setting of IM. This decrease in activation may, in turn, attenuate the effects of the amplified T-cell response in IM. rs16944 has also been associated with uncontrolled EBV replication in liver transplant patients, who later develop post-transplant lymphoproliferative disorder [57], suggesting a link between IL1B and dysfunctional control of EBV. There was also suggestive association between the functional variant rs1800797 in the *IL6* gene promoter region and risk of TCL. Through complex interactions with nearby variants, rs1800797 regulates the gene that encodes the inflammatory cytokine IL6, which influences growth and differentiation of T-cells, among many other immune functions [58, 59].

In the presence of the significant T-cell expansion associated with IM, the identified variants in *IL1B* and *IL6* may reduce T-cell cell proliferation and subsequent mutation or oncogenic rearrangement. These findings may extend to other settings in which the T-cell compartment undergoes significant expansion, in particular, during primary or reactivated viral infections. Follow-up of these observations in a targeted study is warranted because of the potential biological pathway.

A limitation of our study is reliance on self-reported IM history, which could be affected by recall bias. However, IM is a severe and debilitating syndrome of relatively long duration, interrupting young adult life; therefore, it is unlikely that a participant would forget this experience.

Although the results can be generalized to adults of European descent living in the United States and Europe, the limited number of ethnically diverse participants enrolled in these studies and the exclusion of HIV/AIDS-related lymphomas and post-transplant lymphomas limits generalizability to other groups. Because NHL patients were recruited after the onset of disease, those with longer post-diagnosis survival times were more likely to enroll in the study and complete questionnaires. This ascertainment bias prevents us from generalizing to NHL patients with very short survival times, although rapid case ascertainment methods at individual study sites dampened the impact of this bias. In general, survival times for TCL patients are shorter than those for B-cell lymphoma patients [60, 61]. Among the sample of TCL participants, the majority were diagnosed with peripheral T-cell (51%) or mycosis fungoides/Sézary syndrome (MF/SS, 33%). Survival times for these subtypes vary significantly depending on stage at presentation and disease-specific factors (e.g., level of skin involvement by patch or plaque in MF/SS) [62, 63]. The introduction of new treatments such as Rituximab during the recruitment window for our study may have had additional impact on the subtypes of NHL patients we were able to recruit for study inclusion. Follow-

up analyses are warranted to determine whether the effect modification we identified applies to patients presenting with advanced or aggressive disease.

Furthermore, data from sites using clinic-based recruitment methods for enrolling controls are subject to Berkson's bias since patient controls are likely to be sicker than the general population from which cases were ascertained. Many admitting conditions of clinic-based controls may have some immune component which can obscure the effect of immune-related genetic variants on NHL and IM. Results of sensitivity analyses excluding sites using clinic-based control recruitment were directionally consistent with results using the full dataset, indicating the effect of Berkson's bias on our study results was minimal.

Our study was underpowered to detect an interaction between uncommon variants and IM within rare NHL subtype strata after adjusting for multiple comparisons. For example, in order to achieve 80% power for detecting an interaction odds ratio of 0.09 for rs1143627 at $\alpha = 0.05$ after accounting for multiple comparisons, we would have needed 518 genotyped TCL patients. Thus, even with the overall large numbers of cases and controls in the study, there was inadequate power to detect associations by subtype.

In summary, this study was the first to explore possible interaction between immune response genotypes and IM history on NHL risk [64]. The results from our study may have broader implications for understanding how certain genotypes modulate the impact of various infectious agents on NHL etiology. The identified variants in *IL1B* and *IL6* may influence T-cell activation, growth, and differentiation in the presence of the massive T-cell expansion associated with IM leading to decreased immune cell proliferation. Although we observed a possible interaction that affected the risk of a rare NHL subtype, our study was underpowered to overcome multiple comparisons. Confirmation will require a well-characterized, targeted study with larger numbers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Annalie Landgren and Aaron Norman for supporting the InterLymph Consortium. In addition, the authors would like to acknowledge the support of the InterLymph Data Coordinating Center at Mayo Clinic as well as the Ulla and Mogens Folmer Andersen's Foundation.

Funding This work was supported by awards from National Cancer Institute/National Institutes of Health (N01-CN-75014-20, P30CA014089, R01 CA186646, P30 CA13148, R21 CA155951, U54 CA118948, CA45614, CA87014, CA104682, and CA154643); Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR), CERCA Programme/Generalitat de Catalunya for institutional support (2017SGR1085); Spanish Ministry of Economy and Competitiveness—Carlos III Institute of Health cofunded by FEDER funds/European Regional Development Fund (ERDF)—a way to build Europe (PI14/01219); Centro de Investigación Biomédica en Red: Epidemiología y Salud Pública (CIBERESP, Spain); the Canadian Institutes for Health Research (CIHR); Canadian Cancer Society; and Michael Smith Foundation for Health Research [British Columbia]). The collection of cancer incidence data used in the UCSF study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement 5NU58DP003862-04/DP003862; and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California (NHL MultiCenter Case-Control Study site), and contract HHSN261201000034C awarded to the Public Health Institute.

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Table 1

Demographic characteristics of non-Hodgkin lymphoma patients and controls

	Controls (*n* = 10,018)		NHL Patients (*n* = 7,926)	
	Negative IM history *n* (%)	Positive IM history *n* (%)	Negative IM history *n* (%)	Positive IM history *n* (%)
Study center				
BC	604 (6)	35 (7)	566 (8)	42 (10)
EpiLymph-Czech Republic	289 (3)	8 (2)	165 (2)	5 (1)
EpiLymph-France	250 (3)	5 (1)	198 (3)	3 (1)
EpiLymph-Germany	628 (7)	21 (4)	435 (6)	18 (4)
EpiLymph-Ireland	198 (2)	5 (1)	116 (2)	11 (3)
EpiLymph-Italy	331 (3)	3 (1)	177 (2)	2 (0)
EpiLymph-Spain	603 (6)	5 (1)	418 (6)	6 (1)
Mayo Clinic	1,014 (11)	85 (16)	779 (10)	80 (20)
NCI-SEER	378 (4)	25 (5)	543 (7)	48 (12)
Scale	2,830 (30)	106 (20)	2,653 (35)	94 (23)
UCSF	1,752 (18)	189 (36)	946 (13)	63 (15)
Yale	620 (7)	34 (7)	523 (7)	35 (9)
SES[a]				
Low	3,282 (35)	63 (12)	3,037 (40)	74 (18)
Medium	3,169 (33)	146 (28)	2,400 (32)	134 (33)
High	3,046 (32)	312 (60)	2,082 (28)	199 (49)
Birth order				
First/only	3,318 (35)	182 (35)	2,555 (34)	149 (37)
2nd	2,412 (25)	154 (30)	1,781 (24)	115 (28)
3rd	1,278 (13)	83 (16)	1,031 (14)	50 (12)
4th	1,653 (17)	57 (11)	1,392 (19)	40 (10)
Missing	836 (9)	45 (9)	760 (10)	53 (13)
Number of siblings				
0	394 (4)	24 (5)	255 (3)	23 (6)
1	1,578 (17)	110 (21)	1,144 (15)	71 (17)

	Controls (*n* = 10,018)				NHL Patients (*n* = 7,926)			
	Negative IM history		Positive IM history		Negative IM history		Positive IM history	
	n (%)		*n* (%)		*n* (%)		*n* (%)	
2	2,147 (23)		159 (31)		1,603 (21)		118 (29)	
3	4,673 (49)		189 (36)		3,908 (52)		153 (38)	
Missing	705 (7)		39 (7)		609 (8)		42 (10)	
Sex								
Male	5,018 (53)		260 (50)		4,052 (54)		186 (46)	
Female	4,479 (47)		261 (50)		3,467 (46)		221 (54)	
	Mean ± SD	Med (IQR)	Mean ± SD	Med (IQR)	Mean ± SD	Med (IQR)	Mean ± SD	Med (IQR)
Age at NHL diagnosis/interview	57 ± 15	60 (21)	46 ± 15	47 (22)	60 ± 12	62 (17)	52 ± 13	53 (19)

Table 2

Subtypes among non-Hodgkin lymphoma patients

	n **(%)**
B-cell	
DLBCL	2246 (28)
CLL/SLL/B-PLL/MCL	1470 (19)
Follicular	1691 (21)
MZL	447 (6)
MCL	325 (4)
LPL/Waldenstrom	228 (3)
Hairy cell	75 (1)
Burkitt	63 (1)
Precursor B-cell	40 (1)
Burkitt-like	27 (0.3)
B-cell NOS	534 (7)
Total B-cell	7146 (90)
T-cell	
Peripheral T-cell	262 (3)
MF/SS	166 (2)
Precursor T-cell	26 (0.3)
Nasal NK	17 (0.2)
Large granular	7 (0.1)
T-PLL	4 (0.1)
T-cell NOS	27 (0.3)
Total T-cell	509 (6)
NOS[a]	210 (3)
Missing[a]	61 (1)

B-PLL B-cell prolymphocytic leukemia, *CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *LPL* lymphoplasmacytic lymphoma, *MCL* mantle cell lymphoma, *MF/SS* mycosis fungoides/ Sézary syndrome, *MZL* marginal zone lymphoma, *NK* natural killer cell, *NOS* not otherwise specified, *T-PLL* T-cell prolymphocytic leukemia

[a]Patients missing a subtype were excluded from subtype-specific analyses

Table 3

Interaction between history of infectious mononucleosis and candidate risk variants [*IL1A* (rs1800587), *IL1B* (rs16944, rs1143627), *IL1RN* (rs454078), *IL2* (rs2069762), *IL6* (rs1800795, rs1800797), *IL10* (rs1800896, rs1800890), *TNFA* (rs1800629), *HLA* I (rs6457327), and *HLA* II (rs10484561)] on risk of non-Hodgkin lymphoma by subtype: empirical Bayes estimates of interaction effects

NHL subtype	Variant	Genotyped Controls *n*	Genotyped NHL patients *n*	Interaction OR[a]	Interaction 95% CI	Interaction *p* value[b]
All NHL	*IL1A*-889C>T (rs1800587)	2,317	2,084	1.13	[0.69, 1.87]	0.62
	IL1B-511C>T (rs16944)	1,280	1,311	0.66	[0.35, 1.22]	0.18
	IL1B-31T>C (rs1143627)	3,715	3,130	0.76	[0.57, 1.02]	0.06
	IL1RN-9589A>T (rs454078)	2,319	2,068	1.02	[0.62, 1.67]	0.94
	IL2–384T>G (rs2069762)	2,320	2,080	0.99	[0.62, 1.57]	0.96
	IL6-174G>C (rs1800795)	2,347	2,099	1.08	[0.77, 1.52]	0.64
	IL6-597G>A (rs1800797)	3,852	3,304	1.10	[0.81, 1.49]	0.55
	IL10-1082A>G (rs1800896)	4,173	3,472	0.81	[0.59, 1.10]	0.18
	IL10-3575T>A (rs1800890)	5,914	5,629	0.80	[0.57, 1.13]	0.21
	TNF-308G>A (rs1800629)	5,562	5,546	0.86	[0.59, 1.27]	0.46
	HLA: C>A (rs6457327)	2,963	2,457	1.07	[0.65, 1.76]	0.78
	HLA: T>G (rs10484561)	3,989	3,176	0.93	[0.62, 1.40]	0.74
CLL/SLL	*IL1A*-889C>T (rs1800587)	2,317	366	1.03	[0.45, 2.35]	0.95
	IL1B-511C>T (rs16944)	1,280	117	1.30	[0.22, 7.56]	0.77
	IL1B-31T>C (rs1143627)	3,715	646	0.96	[0.49, 1.87]	0.90
	IL1RN-9589A>T (rs454078)	2,319	364	1.81	[0.80, 4.07]	0.15
	IL2–384T>G (rs2069762)	2,320	365	1.77	[0.79, 3.98]	0.17
	IL6-174G>C (rs1800795)	2,347	364	1.13	[0.49, 2.57]	0.78
	IL6-597G>A (rs1800797)	3,852	666	0.89	[0.45, 1.76]	0.73
	IL10-1082A>G (rs1800896)	4,173	669	0.80	[0.39, 1.62]	0.53
	IL10-3575T>A (rs1800890)	5,914	1,204	0.68	[0.37, 1.24]	0.21
	TNF-308G>A (rs1800629)	5,562	1,186	0.89	[0.47, 1.71]	0.73
	HLA: C>A (rs6457327)	2,963	389	1.05	[0.36, 3.02]	0.93
	HLA: T>G (rs10484561)	3,989	623	0.54	[0.20, 1.50]	0.24
DLBCL	*IL1A*-889C>T (rs1800587)	2,317	541	0.98	[0.48, 2.01]	0.96

NHL subtype	Variant	Genotyped Controls	Genotyped NHL patients	Interaction	Interaction	Interaction
		n	*n*	OR[a]	95% CI	*p* value[b]
	IL1B-511C>T (rs16944)	1,280	384	0.75	[0.34, 1.68]	0.49
	IL1B-31T>C (rs1143627)	3,715	877	0.61	[0.34, 1.08]	0.09
	IL1RN-9589A>T (rs4540078)	2,319	530	0.83	[0.41, 1.68]	0.61
	IL2-384T>G (rs2069762)	2,320	538	2.02	[0.99, 4.13]	0.05
	IL6-174G>C (rs1800795)	2,347	537	0.83	[0.43, 1.60]	0.59
	IL6-597G>A (rs1800797)	3,852	922	0.92	[0.52, 1.64]	0.78
	IL10-1082A>G (rs1800896)	4,173	928	1.10	[0.58, 2.09]	0.78
	IL10-3575T>A (rs1800890)	5,914	1,496	0.74	[0.45, 1.21]	0.23
	TNF-308G>A (rs1800629)	5,562	1,447	0.72	[0.42, 1.23]	0.23
	HLA: C>A (rs6457327)	2,963	701	0.66	[0.32, 1.37]	0.26
	HLA: T>G (rs10484561)	3,989	840	1.05	[0.51, 2.17]	0.89
FL	*IL1A*-889C>T (rs1800587)	2,317	527	1.18	[0.58, 2.41]	0.64
	IL1B-511C>T (rs16944)	1,280	331	0.53	[0.20, 1.36]	0.19
	IL1B-31T>C (rs1143627)	3,715	706	0.98	[0.54, 1.77]	0.95
	IL1RN-9589A>T (rs4540078)	2,319	526	0.63	[0.31, 1.29]	0.21
	IL2-384T>G (rs2069762)	2,320	528	0.69	[0.35, 1.35]	0.28
	IL6-174G>C (rs1800795)	2,347	533	1.34	[0.69, 2.60]	0.39
	IL6-597G>A (rs1800797)	3,852	757	1.78	[0.94, 3.39]	0.08
	IL10-1082A>G (rs1800896)	4,173	750	0.67	[0.37, 1.20]	0.18
	IL10-3575T>A (rs1800890)	5,914	1,125	0.89	[0.51, 1.54]	0.68
	TNF-308G>A (rs1800629)	5,562	1,130	0.91	[0.50, 1.65]	0.75
	HLA: C>A (rs6457327)	2,963	510	1.65	[0.72, 3.79]	0.24
	HLA: T>G (rs10484561)	3,989	696	0.86	[0.46, 1.62]	0.64
MCL	*IL1A*-889C>T (rs1800587)	2,317	103	2.24	[0.48, 10.33]	0.30
	IL1B-511C>T (rs16944)	1,280	61	0.25	[0.02, 3.07]	0.28
	IL1B-31T>C (rs1143627)	3,715	146	1.35	[0.33, 5.57]	0.68
	IL1RN-9589A>T (rs4540078)	2,319	102	1.24	[0.28, 5.53]	0.78
	IL2-384T>G (rs2069762)	2,320	103	0.74	[0.16, 3.43]	0.70
	IL6-174G>C (rs1800795)	2,347	105	0.28	[0.06, 1.24]	0.09
	IL6-597G>A (rs1800797)	3,852	159	0.29	[0.08, 1.11]	0.07

NHL subtype	Variant	Genotyped Controls *n*	Genotyped NHL patients *n*	Interaction OR[a]	Interaction 95% CI	Interaction *p* value[b]
	IL10-1082A>G (rs1800896)	4,173	171	0.70	[0.15, 3.22]	0.64
	IL10-3575T>A (rs1800890)	5,914	285	0.59	[0.20, 1.77]	0.35
	TNF-308G>A (rs1800629)	5,562	279	3.27	[1.06, 10.05]	0.04
	HLA: C>A (rs6457327)	2,963	116	2.75	[0.34, 22.05]	0.34
	HLA: T>G (rs10484561)	3,989	158	0.29	[0.04, 2.33]	0.24
T-Cell	*IL1A*-889C>T (rs1800587)	2,317	127	2.76	[0.36, 21.42]	0.33
	IL1B-511C>T (rs16944)	1,280	97	0.01	[0.00, 2.55]	0.10
	IL1B-31T>C (rs1143627)	3,715	206	**0.09**	**[0.01, 0.87]**	**0.04**
	IL1RN-9589A>T (rs454078)	2,319	125	0.37	[0.05, 2.75]	0.33
	IL2–384T>G (rs2069762)	2,320	127	0.71	[0.12, 4.36]	0.71
	IL6-174G>C (rs1800795)	2,347	129	0.05	[0.00, 1.01]	0.05
	IL6-597G>A (rs1800797)	3,852	219	**0.08**	**[0.01, 0.80]**	**0.03**
	IL10-1082A>G (rs1800896)	4,173	233	0.89	[0.16, 5.04]	0.90
	IL10-3575T>A (rs1800890)	5,914	378	1.07	[0.36, 3.16]	0.91
	TNF-308G>A (rs1800629)	5,562	369	1.20	[0.39, 3.71]	0.75
	HLA: C>A (rs6457327)	2,963	183	3.36	[0.48, 23.47]	0.22
	HLA: T>G (rs10484561)	3,989	210	1.82	[0.31, 10.58]	0.50

CI confidence interval, *CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *MCL* mantle cell lymphoma, *OR* odds ratio

[a] Interaction ORs, CIs, and *p* values calculated using empirical-Bayes method adjusted for age, sex, study center, and socioeconomic status

[b] Significant values are shown in bold but did not retain significance after accounting for multiple comparisons using pACT statistic