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HLA class I and II diversity contributes to the etiologic heterogeneity of non-Hodgkin lymphoma subtypes

A full list of authors and affiliations appears at the end of the article.

Abstract

A growing number of loci within the human leukocyte antigen (HLA) region have been implicated in non-Hodgkin lymphoma (NHL) etiology. Here, we test a complementary hypothesis of "heterozygote advantage" regarding the role of HLA and NHL, whereby HLA diversity is beneficial and homozygous HLA loci are associated with increased disease risk. HLA alleles at class I and II loci were imputed from genome-wide association studies (GWAS) using SNP2HLA for: 3,617 diffuse large B-cell lymphomas (DLBCL), 2,686 follicular lymphomas (FL), 2,878 chronic lymphocytic leukemia/small lymphocytic lymphomas (CLL/SLL), 741 marginal zone lymphomas (MZL), and 8,753 controls of European descent. Both DLBCL and MZL risk were elevated with homozygosity at class I HLA-B and -C loci (OR DLBCL=1.31, 95% CI=1.06–1.60; OR MZL=1.45, 95% CI=1.12–1.89) and class II HLA-DRB1 locus (OR DLBCL=2.10, 95% CI=1.24–3.55; OR MZL= 2.10, 95% CI=0.99–4.45). Increased FL risk was observed with the overall increase in number of homozygous HLA class II loci (p-trend<0.0001, FDR=0.0005). These results support a role for HLA zygosity in NHL etiology and suggests that distinct immune pathways may underly the etiology of the different NHL subtypes.

INTRODUCTION

Genome-wide association studies (GWAS) have identified a growing list of common susceptibility loci modestly associated with risk of non-Hodgkin lymphomas (NHLs) including several *HLA* (human leukocyte antigen) genetic variants on chromosome 6p21, a region that is critical for innate and adaptive immune responses. Putative NHL susceptibility loci either directly implicate genes within the Major Histocompatibility Complex (MHC) or appear in strong linkage disequilibrium (LD) with extended *HLA* haplotypes (1–5). Interestingly, there is little convincing overlap of the identified *HLA* susceptibility loci among the NHL subtypes, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), suggesting that disparate aspects of the MHC and resulting immune responses are involved in the etiology of each NHL subtype.

The *HLA* genes are the most polymorphic in the human genome and specific *HLA* loci determine the antigens that are bound by antigen presenting cells (e.g., B cells and dendritic cells) and presented to T cells to elicit immune responses. Functionally, HLA molecules are

[+]To whom correspondence should be addressed: Sophia S. Wang, Ph.D., Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute of the City of Hope, 1500 East Duarte Road, Duarte, CA 91010, Phone: (626) 471-7316, Fax: (626) 471-7308, sowang@coh.org.

critical for the host immune response. HLA class I molecules present foreign antigens primarily to cytotoxic T-cells that in response kill these target cells, while HLA class II molecules stimulate antibody production in response to specific antigens.

Reduced diversity, as defined by homozygosity at each co-dominant *HLA* loci, might adversely affect the host's ability to recognize a more diverse array of foreign antigens and thereby increase subsequent disease burden. This concept is supported by *a priori* research that has examined effects of *HLA* zygosity on infectious disease, whereby a lack of *HLA* class I and II diversity has been associated with increased risk HIV and hepatitis B virus infection (6–8).

Given the growing evidence that genetic variation within *HLA* genes play in the etiology of NHL subtypes (1–4, 9), we specifically aimed to test whether lack of *HLA* diversity - as measured by *HLA* homozygosity – was associated with increased NHL risk. Specifically, we posit that associations with HLA Class II, which primarily presents peptides derived from extracellular sources, would implicate a role in infectious disease etiology. On the other hand, associations with HLA Class I, which primarily presents peptides derived from intracellular sources, would suggest a role in related conditions, such as autoimmune or atopic conditions. We present here results from a pooled analysis of 25 studies from North America, Europe, and Australia where we measured the associations between *HLA* class I and/or class II zygosity and four main NHL subtypes.

MATERIALS AND METHODS

Study sample

Our study sample comprises the same study participants of European descent that were included in the original GWAS efforts from which 25 studies participated. Specifically, adults diagnosed with incident, non-HIV-related B-cell NHL of mostly European descent, ascertained from cancer registries, clinics, or hospitals or through self-report were included and where diagnoses were verified by medical and pathology reports (1–4). Study designs included prospective cohort studies, population- and hospital-based case-control studies, and clinic-based studies. Original details of design methods for each study and of each GWAS have been described previously (1–4).

This study was approved by the City of Hope Institutional Review Board. Each participating study obtained approval from human subjects review committees and written informed consent from all participants. A de-identified pooled dataset with individual-level data on genotypes, demographic characteristics, and NHL subtypes of cases was provided by the InterLymph Data Coordinating Center (Mayo Clinic, Rochester, MN).

Genotyping

GWAS platforms used include the Illumina 317K, Illumina HumanHap 610K, Illumina HumanHap 660W, Illumina Human CNV370-Duo BeadChip, Affymetrix SNP 6.0, and the Illumina OmniExpress (Table 1). Quality control metrics employed (e.g., QQ plots and Eigenstrat results) and main results of each GWAS have been previously described in-depth (1–4).

HLA imputation

As reported by Skibola et al (2), classical *HLA* alleles were imputed at *HLA* class I (*HLA-A*, *HLA-B*, *HLA-C*) and class II loci (*HLA-DQA1*, *HLA-DQB1*, *HLA-DRB1*, *HLA-DPA1, HLA-DPB1*) using SNP2HLA and a reference panel from the Type 1 Diabetes Genetics Consortium that comprised 5,225 individuals of European descent who were typed for *HLA-A, B, C, DQA1, DQB1, DRB1, DPA1, DPB1* 4 digit alleles. We note that the SNP2HLA reference panel is typed both for a panel of MHC SNPs and using classical *HLA* typing; the imputation algorithms used thus rely on both methodologies particularly when only SNPs are available. A comparison of imputed *HLA* alleles to 4-digit *HLA* sequencing data available for a subset of samples showed high concordance: *HLA-A* (97.3%), *B* (98.5%), *C* (98.1%) and *DRB1* (97.5%). In all, 201 classical *HLA* alleles (two- and four-digit resolution) were successfully imputed (info score r^2>0.3 for alleles) and available for analysis. Because of the strong LD between the *HLA* class II A1 and B1 loci (e.g., *HLA-DQA1* and *DQB1*), we present results for each of the B1 loci (*HLA-DQB1*, *HLA-DRB1*, *HLA-DPB1)* since there were fewer homozygous B1 loci than A1 loci. For each *HLA* locus, individuals were coded as homozygote (for any allele) or heterozygote, as determined from the imputed alleles. All results presented are based on four-digit resolution.

NHL Classification

NHL subtypes were harmonized at the InterLymph Data Coordinating Center using the InterLymph Pathology Working Group guidelines (10,11), which are based on the World Health Organization classification (12).

Final analytic sample

Data for *HLA* loci were directly imputed from the original GWAS SNP panels and evaluated for the 3,617 DLBCL, 2,686 FL, 2,878 CLL/SLL, 741 MZL, and 8,753 controls. We note that, as with the original GWAS manuscripts, the specific numbers of controls differed by NHL subtype, due to different study inclusion and control selection criteria for each NHL subtype analyses, as described by the original GWAS publications (enumerated in Table 2).

Statistical analysis

Heterozygosity and homozygosity at each individual *HLA* locus and the number of homozygous loci for class I loci (*A, B, C*) and class II loci (*DQB1, DRB1, DPB1*) were determined; odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as estimates of NHL risk with heterozygotes as the referent category, adjusted for sex, age, study, GWAS platform, and ancestry (with principal components as conducted for each subtype-specific GWAS and previously published (1–4). For analyses of MZL, adjustment by geographic region was conducted due to sample size restrictions (instead of by individual study). In addition to calculating the risk estimates for each additional number of homozygous loci, we further calculated the p-trend.

To further describe associations of zygosity by loci, we conducted joint effects analyses for *HLA* class I loci and class II loci. Each *HLA* loci (class I or II) was conducted in a stratified manner whereby heterozygotes for all loci were the referent groups and all combinations of homozygosity among the loci were evaluated. For example, to pinpoint whether *HLA* class I

associations were attributable to *HLA* Class I B or C loci, we modeled as one covariate, 4 levels/combinations for *HLA-B* and *-C* (e.g., homozygous for both *HLA-B* and *–C*, homozygous only for *HLA-B*, homozygous for only *HLA-C*, and heterozygous for both), with heterozygote for both *HLA-B* and *-C* as reference (Table 3). For the associated p-trends reported in Table 3, each category is modeled based on ordinal variable in the order listed in the table, with heterozygosity at all loci as the referent group in a logistic regression model. For each p-trend, we also present the linearized additive relative-risk-per-locus, reflecting the slope of the trend-line.

Platform-specific results are shown in a Supplemental Table 1. Additional sensitivity analysis included evaluation of potential confounders, including evaluation of associations by previously implicated autoimmune conditions and *HLA* loci associated with specific NHL subtypes. We conducted stratified analysis to evaluate whether *HLA* zygosity associations were present among participants with and without autoimmune conditions (generally, and by specific conditions); similarly stratified analyses were conducted among participants with and without previously identified SNPs associated with NHL subtypes. We further calculated the risks, adjusting for autoimmune conditions and for all reported genetic susceptibility loci (for each NHL subtype). As neither variable altered the odds ratio >10%, those data are not presented. Analyses that restricted studies to population-based controls only also did not have measurable effect on the results. Finally, to evaluate the probability that some of our results could be due to chance, we used the Benjamini-Hochberg method to calculate the false discovery rate (FDR) and applied it to the p-trends as this allows for the fewest number of comparisons and thus degrees of freedom to assess the additive model.

Unconditional logistic regression models were applied using SAS 9.4 (SAS Institute). All tests of statistical significance were 2-sided.

RESULTS

The numbers of European cases and controls from each of the 25 studies in North America, Europe, and Australia for which *HLA* class I and II loci were evaluated are detailed in Table 1.

DLBCL

Elevated DLBCL risks of 20–50% were observed for homozygosity for individual *HLA* class I (*B* and *C*) and/or class II loci (*DRB1* and *DQB1*) (Table 2). DLBCL risk also increased with increasing number of homozygous class I loci (p-trend=0.0008; FDR p=0.003) and class II loci (p-trend<0.0001; FDR p=0.0005) (Table 2). Although homozygosity for *HLA-A* had a borderline non-significant effect for increasing DLBCL risk, joint analyses suggested that the 30% risk increase observed with two or more homozygote loci (Table 2) was attributable to homozygosity at the *HLA-B* and *-C* locus (OR=1.31, 95% CI=1.06–1.60, Table 3). Similarly, for class II loci, joint analysis showed statistically significant associations for homozygosity specifically at the *HLA-DRB1* locus (OR=2.10, 95% CI=1.24–3.55) as significantly increased risk was observed only in combination with homozygous *HLA-DRB1* locus (Table 3).

FL

There were no significant associations between zygosity at *HLA* class I loci and FL risk (Table 2). Statistically significant 24–54% increases, however, were observed for FL risk for each of the three *HLA* class II loci. Further, FL risk increased with the total number of homozygous *HLA* class II loci (p-trend<0.0001; FDR p=0.0005), with an odds ratio of 1.89 (95% CI=1.37–2.61) for those fully homozygous compared with those fully heterozygous at all three *HLA* class II loci. Joint analyses additionally supported a statistically significant increased risk for FL with overall homozygosity at the *HLA* class II loci (p-trend<0.0001; FDR p=0.0005, Table 3).

MZL

Homozygosity at *HLA* class I loci *HLA-B* (OR=1.34, 95% CI=1.01–1.78) and *–C* (OR=1.33, 95% CI=1.04–1.70) but not *-A* (OR=1.06, 95% CI=0.82–1.38) increased MZL risk (Table 2). Stratified analysis supported independent associations for both *HLA-B* and *–C* and MZL (Table 3). Homozygosity at *HLA* class II loci increased MZL risk (Table 2), but only the association with *HLA-DRB1* reached statistical significance (OR=1.45, 95% CI-1.12–1.89, Table 2). Analyses considering single locus homozygosity provided evidence of a role for *HLA-DRB1* in increasing MZL risk (Table 3).

CLL/SLL

Modest CLL/SLL risk increases were observed for *HLA-A* (OR=1.19, 95% CI=1.02–1.38), *HLA-DRB1* (OR=1.19, 95% CI=1.00–1.42) and *HLA-DQB1* (OR=1.20, 95% CI=1.03–1.39) (Table 2). Increasing CLL/SLL risk was not observed with increasing number of homozygote class I or class II loci, though when evaluating total numbers of class I and II loci altogether, a borderline significant increased risk was observed for those with all five homozygote class I and II loci (OR=1.57, 95% CI=1.04–2.38, p-trend = 0.029; FDR=0.055) (Table 2). We were unable to isolate CLL/SLL associations with *HLA* zygosity to any singular locus (Table 3).

DISCUSSION

Based on the largest number of NHL subtypes to date for whom imputed HLA data is available, we demonstrate that *HLA* homozygosity plays a role in four B-cell NHL subtypes, and that the associations between homozygosity at *HLA* Class I and/or Class II loci are distinct by these subtypes. Specifically, FL risk was associated with homozygosity at *HLA* class II loci, but not Class I loci. CLL/SLL risk appeared to be associated (borderline) with homozygosity at either *HLA* Class I or Class II loci. In contrast, while both DLBCL and MZL were associated with zygosity at *HLA* Class I and Class II loci, the associations appeared specific to Class I *HLA-B* and *–C* loci and to the Class II *HLA-DRB1* locus. We note that the p-trends evaluated for each additional homozygous loci remained statistically significant after adjust for multiple comparisons, with exception of that for CLL/SLL. Our results add to the growing body of literature implicating different roles for *HLA* class I and II loci, key modulators of human immune response, in the heterogeneous etiologies of B-NHL subtypes (1–4). Our results also add to the current literature which points to similarities in the etiologic profiles of DLBCL and MZL (13). Overall, these data support

the importance of *HLA* diversity in NHL etiology, with the type of *HLA* diversity potentially varying by NHL subtype.

The underlying hypothesis regarding the role of *HLA* zygosity and disease is that homozygosity at *HLA* loci reduces the diversity of peptides that can be presented, with the hypothesis that these peptides can reflect etiologic agents such as infectious diseases, self-antigens for atopic or autoimmune conditions, and even cancerous cells. At present, there is a growing body of literature supporting that *HLA* heterozygotes are more resistant to infectious diseases, and the corollary, that *HLA* homozygotes are more susceptible to infectious diseases. Specifically, *HLA* class I heterozygote advantage (e.g., presenting greater diversity of antigenic peptides to CD8+ cytotoxic T lymphocytes) has been demonstrated for slowing progression to AIDS (6), whereas heterozygotes at *HLA* class II loci appear to have greater ability in clearing HBV infection (8) and HCV infection (14) than homozygotes. *HLA-DRB1* heterozygosity has also been reported to confer favorable outcome (e.g., against end-stage liver disease) among HCV-infected liver transplant recipients (15). There are also reports evaluating *HLA* zygosity as a key contributor in autoimmune conditions. For example, reports of heterozygote advantage for class II loci and inflammatory bowel disease (16) and for class I loci and psoriatic arthritis (17) have both been published. Specific associations between *HLA* zygosity and NHL have been limited to reports of CLL. Evidence of the importance of *HLA* zygosity include reports that homozygosity at *HLA-A*, *-B*, and *-DRB1* are associated with CLL (18) and with CLL disease progression (19–20), with the hypothesis that limited *HLA* diversity provided an advantage of the tumor to escape the immune response.

HLA heterozygote advantage is posited to work in concert with specific allele associations (as opposed to exclusively) (21); our results thus complement ongoing efforts that have identified the most role that specific *HLA* alleles have on NHL subtype risk. In sensitivity analysis, we evaluated the effect of known HLA associations and, in stratified and adjusted analysis, did not find that these associations diminish the reported association between *HLA* zygosity and NHL subtypes. Further evaluation into how these complementary associations act in concert are thus warranted and inclusion of *HLA* zygosity in the construct of genetic risk scores for each NHL subtype should be considered.

Further research to understand the association – or independence - between *HLA* zygosity with infections and autoimmune conditions and NHL risk are also needed (21–24). For example, efforts to evaluate autoimmune conditions linked to class II alleles (e.g., Sjögren syndrome, systemic lupus erythromatosus, and rheumatoid arthritis) (23) with class II zygosity in relation to FL risk could provide potential insight regarding immune mechanisms modulating FL risk. A particularly pressing research question is understanding what are the underlying mechanisms of individual allele-associations and how are they distinct from *HLA* zygosity associations. Similar efforts to identify commonalities between autoimmune and infectious disease associations with *HLA* loci and zygosity among other NHL subtypes are also warranted. Finally, extension of these efforts towards understanding the genetic and structural variants and HLA expression are also required to fully understand the implication of *HLA*-allelic associations in the context of overall class I or II zygosity.

Study strengths include the large sample size available to evaluate individual NHL subtypes which no studies have been able to do adequately to date (25). Potential study limitations include possible misclassification of *HLA* alleles due to imputation, although direct comparison of a subset with genotyped *HLA* alleles showed >97% concordance (2). While the present analysis leverages the available GWAS data through imputation of *HLA* alleles, we recognize that confirmation with direct *HLA* allelotyping may provide additional levels of information not ascertained in imputed data.

Our study's restriction to individuals of European ancestry requires our results to be replicated for other racial or ethnic groups, as the associations may not apply universally to all ethnic groups. However, as demonstrated for HLA associations in autoimmune conditions, fine-mapping studies show that the same amino acid changes contribute to disease in both European and Asian populations (26), implicating similar underlying biologic mechanisms for disease etiology. Studies limitations also include our inability to evaluate heterogeneity within NHL subtypes, either defined molecularly, by infectious etiology, or by organ site.

In summary, our results add to the growing evidence of *HLA* alleles as susceptibility loci in the etiology of B-cell NHL subtypes. In addition to ongoing fine-mapping studies being conducted as follow-up to GWAS, our results here suggest that functional studies aiming to understand the underlying biology of zygosity and NHL subtype risk will also be important. Additional efforts to evaluate larger-scale zygosity, such as of immune genes and perhaps the entire genome may prove important in understanding the full extent of the role diversity of the immune response plays in lymphoma etiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Sophia S. Wang[1,+], Mary Carrington[2], Sonja I. Berndt[3], Susan L. Slager[4], Paige M. Bracci[5], Jenna Voutsinas[1], James R. Cerhan[4], Karin E. Smedby[6,7], Henrik Hjalgrim[8,9], Joseph Vijai[10], Lindsay M. Morton[3], Roel Vermeulen[11,12], Ora Paltiel[13], Claire M. Vajdic[14], Martha S. Linet[3], Alexandra Nieters[15], Silvia de Sanjose[16,17], Wendy Cozen[18], Elizabeth E. Brown[19], Jennifer Turner[21,22], John J. Spinelli[23,24], Tongzhang Zheng[25], Brenda M. Birmann[26], Christopher R. Flowers[27], Nikolaus Becker[28], Elizabeth A. Holly[5], Eleanor Kane[20], Dennis Weisenburger[29], Marc Maynadie[30], Pierluigi Cocco[31], Demetrius Albanes[3], Stephanie J. Weinstein[3], Lauren R. Teras[32], W. Ryan Diver[32], Stephanie J. Lax[20], Ruth C. Travis[33], Rudolph Kaaks[28], Elio Riboli[34], Yolanda Benavente[16,17], Paul Brennan[35], James McKay[36], Marie-Hélène Delfau-Larue[36,37], Brian K. Link[38], Corrado Magnani[39], Maria Grazia Ennas[40], Giancarlo Latte[41], Andrew L. Feldman[42], Nicole Wong Doo[43], Graham G. Giles[43,44], Melissa C. Southey[45], Roger L. Milne[43,44], Kenneth Offit[9], Jacob Musinsky[9], Alan A. Arslan[46,47,48], Mark P. Purdue[3], Hans-Olov Adami[50], Mads Melbye[8,51], Bengt Glimelius[52], Lucia Conde[53], Nicola J. Camp[54], Martha Glenn[54],

Karen Curtin[54], Jacqueline Clavel[55,56], Alain Monnereau[55,56,57], David G. Cox[58], Hervé Ghesquières[59,60], Gilles Salles[60,61], Paulo Bofetta[62], Lenka Foretova[63], Anthony Staines[64], Scott Davis[65], Richard K. Severson[66], Qing Lan[3], Angela Brooks-Wilson[67,68], Martyn T Smith[69], Eve Roman[20], Anne Kricker[70], Yawei Zhang[71,72], Peter Kraft[73], Stephen J. Chanock[3], Nathaniel Rothman[3], Patricia Hartge[3], and Christine F. Skibola[27]

Affiliations

[1]Department of Population Sciences, Beckman Research Institute and the City of Hope, Duarte, California [2]Cancer and Inflammation Program, Leidos Biomedical Research Inc., Frederick National Laboratory for Cancer Research, Frederick, MD and Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD [4]Department of Health Sciences Research, Mayo Clinic, Rochester, MN [5]Department of Epidemiology and Biostatistics, University of California–San Francisco, San Francisco, CA [6]Department of Medicine Solna, unit of clinical epidemiology, Karolinska Institutet, Stockholm, Sweden [7]Hematology Center, Karolinska University Hospital, Stockholm, Sweden [8]Department of Epidemiology Research, Division of Health Surveillance and Research, Statens Serum Institut, Copenhagen, Denmark [9]Department of Hematology, Rishospitalet, Copenhagen, Denmark [10]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City, NY [11]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands [12]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands [13]Braun School of Public Health and Community Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel [14]Centre for Big Data Research in Health, The University of New South Wales, Sydney, New South Wales, Australia [15]Centre for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Baden-Württemberg, Germany [16]Unit of Infections and Cancer, Cancer Epidemiology Research Programme, Institut Català d' Oncologia, IDIBELL, 08908 L'Hospitalet de Llobregat, Barcelona, Spain [17]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain [18]Norris Comprehensive Cancer Center, Keck School of Medicine of USC, Departments of Preventive Medicine and Pathology, University of Southern California, Los Angeles, CA [19]Department of Pathology, School of Medicine and the UAB Comprehensive Cancer Center, The University of Alabama at Birmingham, Birmingham, AL [20]Department of Health Sciences, University of York, York, United Kingdom [21]Department of Histopathology, Douglass Hanly Moir Pathology, Sydney, Australia [22]Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia [23]Cancer Control Research, British Columbia Cancer Agency, Vancouver, British Columbia, Canada [24]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada [25]Department of Epidemiology, School of Public Health, Brown University, Providence, RI [26]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA [27]Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA [28]Division of Clinical Epidemiology, German Cancer

Research Centre, Heidelberg, Baden-Württemberg, Germany [29]Department of Pathology, City of Hope, Duarte, California [30]Registry of Hematological Malignancies of Cote d'Or, INSERM UMR1231, University of Burgundy and Dijon University Hospital, Dijon, France [31]Department of Public Health, Clinical and Molecular Medicine, University of Cagliari, Cagliari, Italy [32]Epidemiology Research Program, American Cancer Society, Atlanta, GA [33]Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom [34]School of Public Health, Imperial College London, London, United Kingdom [35]International Agency for Research on Cancer, Lyon, France [36]Department of Immunology, CHU Henri Mondor, Créteil, France [37]INSERM U 955, CHU Henri Mondor, Créteil, France [38]Department of Internal Medicine, Carver College of Medicine, The University of Iowa, Iowa City, IA [39]Center of Oncological Prevention (CPO) Piemonte and Unit of Medical Statistics and Epidemiology, Department Translational Medicine, University of Piemonte Orientale, Novara, Italy [40]Department of Biomedical Science, University of Cagliari, Monserrato, Cagliari, Italy [41]Division of Hematology, S. Francesco Hospital, Nuoro, Italy [42]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN [43]Cancer Epidemiology & Intelligence Division, Cancer Council Victoria, Melbourne, Australia [44]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia [45]Genetic Epidemiology Laboratory, Department of Pathology, University of Melbourne, Melbourne, Victoria, Australia [46]Department of Obstetrics and Gynecology, New York University School of Medicine, New York City, NY [47]Department of Environmental Medicine, New York University School of Medicine, New York City, NY [48]Perlmutter Cancer Center, NYU Langone Medical Center, New York City, NY [49]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden [50]Department of Medicine, Stanford University School of Medicine, Stanford, CA [51]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden [52]Bill Lyons Informatics Centre, UCL Cancer Institute, University College London, WC1E 6DD, London, United Kingdom [53]Department of Internal Medicine, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT [54]Epidemiology of Childhood and Adolescent Cancers Group, Inserm, Center of Research in Epidemiology and Statistics Sorbonne Paris Cité (CRESS), Paris, France [55]Université Paris Descartes, Paris, France [56]Registre des hémopathies malignes de la Gironde, Institut Bergonié, University of Bordeaux, Inserm, Team EPICENE, UMR 1219, France [57]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom. Cancer Research Center of Lyon, INSERM UMR1052, Center Léon Bérard, Lyon, France [58]Department of Hematology, Centre Léon Bérard, Lyon, France [59]Laboratoire de Biologie Moléculaire de la Cellule UMR 5239, Centre National de la Recherche Scientifique, Pierre benite Cedex, France [60]Department of Hematology, Hospices Civils De Lyon, Centre Hospitalier Lyon-Sud and Université Claude Bernard, Lyon, France [61]The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York City, New York [62]Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, MF MU,

Brno, Czech Republic [63]School of Nursing and Human Sciences, Dublin City University, Dublin, Ireland [64]Fred Hutchinson Cancer Research Center & School of Public Health and Community Medicine, University of Washington, Seattle, WA [65]Department of Family Medicine and Public Health Sciences, Wayne State University, Detroit, MI [66]Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, British Columbia, Canada [67]Genome Sciences Centre, BC Cancer Agency, Vancouver, British Columbia, Canada [68]Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, CA [69]Sydney School of Public Health, The University of Sydney, Sydney, Australia [70]Department of Surgery, Yale School of Medicine, New Haven, CT [71]Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT [72]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA [73]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

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Table 1

Genome wide association studies (GWAS) included in the evaluation of human leukocyte antigen (HLA) homozygosity and risk of four non-Hodgkinlymphoma (NHL) subtypes: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma(CLL/SLL), and marginal zone lymphoma (MZL).

Study Name	Study Abbreviation	GWAS Platform	NHL Cases				Controls (n=8753)
			DLBCL (n=3617)	FL (n=2686)	CLL/SLL (n=2878)	MZL (n=741)	
Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study	ATBC	Illumina OmniExpress	43	17	50	1	238
British Columbia Non-Hodgkin Lymphoma Study	BCCA	Illumina OmniExpress	92	98	26	40	109
American Cancer Society Cancer Prevention Study-II Nutrition Cohort	CPS-II	Illumina OmniExpress	188	141	251	52	220
Treatment program of DLBCL patients from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) consisting in LNH03-1B, 2B, 3B, 39B, 6B and 7B.	GELA	Illumina HumanHap 610K	549	0	0	0	0
Epidemiology & Genetics Unit Lymphoma Case-Control study	ELCCS	Illumina OmniExpress	229	182	0	0	245
Environmental and genetic risks factors study in adult lymphoma	ENGELA	Illumina OmniExpress	56	30	44	5	63
European Prospective Investigation into Cancer, Chronic Diseases, Nutrition and Lifestyles	EPIC	Illumina OmniExpress	46	46	72	8	265
Epilymph case-control study in six European countries	EpiLymph	Illumina OmniExpress	198	123	158	59	211
Genetic Epidemiology of CLL (GEC) Consortium	GEC	Affymetrix 6.0	0	0	391	0	296
Health Professionals Follow-up Study	HPFS	Illumina OmniExpress	12	5	19	5	85
Iowa-Mayo SPORE Molecular Epidemiology Resource	IOWA-MAYO SPORE	Illumina OmniExpress	146	228	242	112	0
Multicenter Italian study on gene-environment interactions in lymphoma etiology: translational aspects	Italian GxE	Illumina OmniExpress	16	16	5	6	45

Study Name	Study Abbreviation	GWAS Platform	NHL Cases				Controls (n=8753)
			DLBCL (n=3617)	FL (n=2686)	CLL/SLL (n=2878)	MZL (n=741)	
Mayo Clinic Case-Control Study of NHL and CLL	MAYO-Case-Control	Illumina OmniExpress	25	245	132	75	343
Mayo Clinic Case-Control Study of NHL and CLL	MAYO-Case-Control	Illumina HumanHap 660W	393	0	0	0	172
The Melbourne Collaborative Cohort Study	MCCS	Illumina OmniExpress	71	58	57	8	75
Memorial-Sloan Kettering Lymphoproliferative Disorders Study	MSKCC	Illumina OmniExpress	175	174	36	47	4
National Cancer Institute-Surveillance, Epidemiology, and End Results Interdisciplinary Case-Control Study of Non-Hodgkin's Lymphoma	NCI-SEER	Illumina OmniExpress	251	217	86	62	270
Nurses' Health Study	NHS	Illumina OmniExpress	28	24	18	12	88
New South Wales non-Hodgkin lymphoma study	NSW	Illumina OmniExpress	115	146	13	34	154
New York University Women's Health Study	NYU-WHS	Illumina OmniExpress	8	11	10	6	53
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	PLCO	Illumina OmniExpress	153	115	278	26	3076
Scandinavian Lymphoma Epidemiology Study	SCALE	Illumina OmniExpress	405	0	395	64	291
Scandinavian Lymphoma Epidemiology Study	SCALE	Illumina HumanHap 317K	0	376	0	0	791
Molecular Epidemiology of non-Hodgkin lymphoma 1	UCSF1	Illumina OmniExpress	38	7	22	91	10
Molecular Epidemiology of non-Hodgkin lymphoma 1	UCSF1	Illumina HumanCNV370-Duo	254	210	213	0	749
Molecular Epidemiology of non-Hodgkin lymphoma 2	UCSF2	Illumina OmniExpress	0	119	0	0	349
Utah Chronic Lymphocytic Leukemia Study	UTAH	Illumina HumanHap 610K	0	0	321	0	405
Population-based NHL case-control study in Connecticut women	YALE	Illumina OmniExpress	126	98	39	28	146

Table 2

Effect of homozygosity at the three HLA class I loci *-A, -B* and *-C* and three HLA class I loci *-DRB1, DQB1,* and *DPB1* on susceptibility to four NHL subtypes (DLBCL, FL, CLL/SLL, and MZL) in Caucasian participants within participating lymphoma genome-wide association studies (analyses adjusted for sex, study or region, age, and ancestry/principal components).

		Controls (n=6912)		DLBCL (n=3617)			Controls (n=7880)		FL (n=2686)			Controls (n=7441)		CLL/SLL (n=2878)			Controls (n=5991)		MZL* (n=741)		
		n	%	n	%	OR (95% CI)	n	%	n	%	OR (95% CI)	n	%	n	%	OR (95% CI)	n	%	n	%	OR (95% CI)
Class I locus																					
HLA-A	Heterozygote	6039	89	3096	86	1.00 (ref)	6843	88	2330	88	1.00 (ref)	6504	89	2460	87	1.00 (ref)	5244	89	649	89	1.00 (ref)
	Homozygote	756	11	484	14	1.14 (0.98–1.34)	923	12	313	12	1.03 (0.88–1.21)	821	11	378	13	**1.19 (1.02–1.38)**	646	11	78	11	1.06 (0.82–1.38)
HLA-B	Heterozygote	6430	93	3297	91	1.00	7330	93	2469	92	1.00 (ref)	6916	93	2656	92	1.00 (ref)	5576	93	675	91	1.00 (ref)
	Homozygote	476	7	318	9	**1.22 (1.01–1.47)**	544	7	216	8	1.14 (0.94–1.38)	519	7	221	8	1.04 (0.87–1.26)	411	7	66	9	**1.34 (1.01–1.78)**
HLA-C	Heterozygote	6238	90	3182	88	1.00	7112	90	2383	89	1.00 (ref)	6719	90	2576	90	1.00 (ref)	5414	90	651	88	1.00 (ref)
	Homozygote	674	10	435	12	**1.20 (1.02–1.41)**	768	10	302	11	1.13 (0.96–1.34)	722	10	301	10	1.10 (0.94–1.29)	577	10	90	12	**1.33 (1.04–1.70)**
Total # of homozygous Class I loci	0	5535	80	2792	77	1.00	6266	80	2121	79	1.00 (ref)	5965	80	2225	77	1.00 (ref)	4805	80	586	79	1.00 (ref)
	1	950	14	524	14	1.05 (0.90–1.21)	1120	14	361	64	0.98 (0.84–1.13)	1009	14	457	70	**1.19 (1.03–1.36)**	822	14	94	13	0.97 (0.76–1.23)
	2	297	4	187	5	**1.33 (1.05–1.69)**	342	4	132	5	1.18 (0.93–1.51)	323	4	130	5	1.08 (0.85–1.37)	256	4	37	5	1.16 (0.80–1.68)
	3	130	2	114	3	1.31 (0.95–1.81)	152	2	72	3	1.29 (0.93–1.79)	144	2	66	2	1.16 (0.83–1.62)	108	2	24	3	**2.13 (1.33–3.42)**
	p-trend					***0.0008***					*0.12*					*0.0518*					***0.026***
	OR per locus					1.11 (1.03–1.19)					1.06 (0.98–1.15)					1.08 (1.00–1.16)					1.08 (1.00–1.16)
Class II locus																					
HLA-DRB1	Heterozygote	6331	92	3173	88	1.00 (ref)	7212	92	2339	87	1.00 (ref)	6810	92	2583	90	1.00 (ref)	5500	92	663	89	1.00 (ref)
	Homozygote	561	8	435	12	**1.51 (1.27–1.78)**	648	8	338	13	**1.54 (1.31–1.82)**	608	8	286	10	**1.19 (1.00–1.42)**	480	8	78	11	**1.45 (1.12–1.89)**
HLA-DQB1	Heterozygote	6137	89	3055	84	1.00 (ref)	6999	89	2255	84	1.00 (ref)	6603	89	2494	87	1.00 (ref)	5310	89	638	98	1.00 (ref)
	Homozygote	773	11	561	16	**1.30 (1.12–1.51)**	879	11	431	16	**1.42 (1.23–1.65)**	836	11	384	13	**1.20 (1.03–1.39)**	681	11	10	2	1.20 (0.95–1.52)
HLA-DPB1	Heterozygote	5544	80	2817	78	1.00 (ref)	6292	80	2064	77	1.00 (ref)	5972	80	2320	81	1.00 (ref)	4809	80	582	79	1.00 (ref)
	Homozygote	1356	20	798	22	1.05 (0.93–1.19)	1576	20	620	23	**1.24 (1.10–1.40)**	1455	20	554	19	0.92 (0.81–1.04)	1176	20	158	21	1.13 (0.93–1.38)
Total # of homozygous Class II loci	0	4889	71	2341	65	1.00 (ref)	5545	71	1694	63	1.00 (ref)	5255	71	1994	70	1.00 (ref)	4247	71	501	68	1.00 (ref)
	1	1428	21	830	23	1.08 (0.95–1.22)	1656	21	660	25	**1.28 (1.14–1.45)**	1543	21	586	20	0.95 (0.84–1.08)	1241	21	159	21	1.08 (0.89–1.31)
	2	426	6	344	10	**1.51 (1.25–1.83)**	493	6	239	9	**1.47 (1.21–1.78)**	462	6	224	8	1.20 (0.99–1.46)	363	6	60	8	**1.42 (1.05–1.91)**
	3	136	2	91	3	1.30 (0.92–1.82)	153	2	82	3	**1.89 (1.37–2.61)**	143	2	62	2	1.10 (0.77–1.57)	123	2	20	3	1.48 (0.89–2.43)
	p-trend					***<0.0001***					***<0.0001***					*0.1924*					***0.0124***
	OR per locus					1.15 (1.07–1.23)					1.24 (1.15–1.32)					1.04 (0.97–1.12)					1.15 (1.03–1.28)

		Controls (n=6912)		DLBCL (n=3617)			Controls (n=7880)		FL (n=2686)			Controls (n=7441)		CLL/SLL (n=2878)			Controls (n=5991)		MZL* (n=741)		
		n	**%**	**n**	**%**	**OR (95% CI)**	**n**	**%**	**n**	**%**	**OR (95% CI)**	**n**	**%**	**n**	**%**	**OR (95% CI)**	**n**	**%**	**n**	**%**	**OR (95% CI)**
Total # of homozygous Class I or Class II loci	0	3972	59	1866	52	1.00 (ref)	4486	58	1390	53	1.00 (ref)	4275	59	1569	56	1.00 (ref)	3446	59	407	56	1.00 (ref)
	1	1750	26	992	28	1.11 (0.98–1.25)	2029	26	710	27	**1.13 (1.00–1.28)**	1880	26	767	27	1.07 (0.95–1.20)	1528	26	181	25	1.03 (0.85–1.25)
	2	625	9	407	11	**1.32 (1.11–1.58)**	741	10	293	11	**1.22 (1.03–1.45)**	683	9	284	10	1.11 (0.94–1.32)	538	9	71	10	1.16 (0.87–1.53)
	3	232	3	128	4	0.96 (0.73–1.27)	259	3	130	5	**1.55 (1.19–2.00)**	247	3	106	4	1.10 (0.84–1.44)	204	3	39	5	**1.52 (1.04–2.21)**
	4	98	1	82	2	**1.92 (1.30–2.81)**	114	1	58	2	**1.94 (1.32–2.85)**	111	2	49	2	1.06 (0.71–1.57)	83	1	16	2	**1.84 (1.04–3.27)**
	5+	84	1	92	3	**1.72 (1.19–2.49)**	100	1	50	2	**1.50 (1.02–2.22)**	87	1	49	2	**1.57 (1.04–2.38)**	70	1	12	2	1.64 (0.86–3.13)
	p-trend					**<0.0001**					**<0.0001**					**0.029**					**0.0024**
	OR per locus					1.10 (1.06–1.16)					1.13 (1.08–1.18)					1.05 (1.01–1.10)					1.12 (1.04–1.20)

*adjusted by geographic region (continent) rather than study

Table 3

Effects of zygosity by individual HLA Class I and Class II loci, for DLBCL, MZL, FL, and CLL/SLL (analyses adjusted for sex,age, study/region, and ancestry/principal components).

			Controls (n=6912)		DLBCL (n=3617)			Controls (n=7880)		FL (n=2686)			Controls (n=5991)		MZL* (n=741)			Controls (n=7441)		CLL/SLL (n=2878)		
			n	%	n	%	OR (95% CI)	n	%	n	%	OR (95% CI)	n	%	n	%	OR (95% CI)	n	%	n	%	OR (95% CI)
Class I locus																						
HLA-B	***HLA-C***																					
Heterogyzote	Heterozygote		6133	89	3127	87	1.00 (ref)	6992	89	2350	88	1.00 (ref)	5321	89	637	86	1.00 (ref)	6608	89	2520	88	1.00 (ref)
Heterogyzote	Homozygote		297	4	170	5	1.07 (0.83–1.36)	338	4	119	4	1.01 (0.79–1.29)	255	4	38	5	1.28 (0.89–1.85)	308	4	135	5	1.19 (0.94–1.50)
Homozygote	Heterozygote		100	1	53	1	0.89 (0.58–1.38)	115	1	33	1	0.81 (0.51–1.28)	89	1	14	2	1.27 (0.70–2.30)	106	1	55	2	1.10 (0.75–1.62)
Homozygote	Homozygote		376	5	265	7	**1.31 (1.06–1.60)**	429	5	183	7	1.23 (1.00–1.52)	322	5	52	7	**1.38 (1.01–1.90)**	413	6	166	6	1.04 (0.84–1.29)
		p-trend					*0.02*					*0.1258*					*0.02*					*0.43*
		p-trend OR					*1.08 (1.01–1.15)*					*1.05 (0.99–1.13)*					*1.12 (1.02–1.24)*					*1.03 (0.96–1.10)*
Class II locus																						
HLA-DPB1	***HLA-DQB1***	***HLA-DRB1***																				
Heterozygote	Heterozygote	Heterozygote	4889	72	2341	65	1.00 (ref)	5545	71	1694	63	1.00 (ref)	4247	71	501	68	1.00 (ref)	5255	71	1994	70	1.00 (ref)
Heterozygote	Heterozygote	Homozygote	52	1	42	1	**2.10 (1.24–3.55)**	62	1	48	2	**2.60 (1.66–4.06)**	42	1	9	1	2.10 (0.99–4.45)	61	1	39	1	**1.76 (1.09–2.86)**
Heterozygote	Homozygote	Heterozygote	239	3	149	4	1.01 (0.77–1.33)	263	3	122	5	**1.33 (1.03–1.73)**	213	4	24	3	0.80 (0.51–1.26)	257	3	110	4	1.15 (0.88–1.49)
Heterozygote	Homozygote	Homozygote	345	5	277	8	**1.54 (1.25–1.91)**	403	5	195	7	**1.42 (1.14–1.76)**	297	5	48	6	**1.43 (1.03–2.00)**	378	5	172	6	1.12 (0.90–1.39)
Homozygote	Heterozygote	Heterozygote	1137	17	639	18	1.05 (0.92–1.21)	1331	17	490	18	**1.21 (1.06–1.39)**	986	17	126	17	1.11 (0.89–1.37)	1225	17	437	15	0.88 (0.76–1.01)
Homozygote	Heterozygote	Homozygote	28	0	24	1	1.44 (0.77–2.71)	30	0	13	0	1.33 (0.66–2.68)	18	0	1	0	0.62 (0.08–4.82)	26	0	13	0	1.15 (0.54–2.48)
Homozygote	Homozygote	Heterozygote	53	1	43	1	1.38 (0.82–2.33)	60	1	31	1	**1.88 (1.14–3.10)**	48	1	11	1	1.54 (0.75–3.16)	58	1	39	1	**1.78 (1.11–2.85)**
Homozygote	Homozygote	Homozygote	136	2	91	3	1.30 (0.92–1.82)	153	2	82	3	**1.89 (1.37–2.61)**	123	2	20	3	1.48 (0.90–2.44)	143	2	62	2	1.10 (0.77–1.57)
		p-trend					*0.0091*					*<0.0001*					*0.04*					*0.95*
		p-trend OR					*1.04 (1.01–1.06)*					*1.07 (1.05–1.10)*					*1.04 (1.00–1.09)*					*1.00 (0.97–1.03)*