Lupus-related single nucleotide polymorphisms and risk of diffuse large B-cell lymphoma


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ABSTRACT

Objective: Determinants of the increased risk of diffuse large B-cell lymphoma (DLBCL) in SLE are unclear. Using data from a recent lymphoma genome-wide association study (GWAS), we assessed whether lupus-related single nucleotide polymorphisms (SNPs) were also associated with DLBCL.

Methods: GWAS data on European Caucasians from the International Lymphoma Epidemiology Consortium (InterLymph) provided a total of 3857 DLBCL cases and 7666 general-population controls. Data were pooled in a random-effects meta-analysis.

Results: Among the 28 SLE-related SNPs investigated, the two most convincingly associated with risk of DLBCL included the CD40 SLE risk allele rs4810485 on chromosome 20q13 (OR per risk allele=1.09, 95% CI 1.02 to 1.16, p=0.0134), and the HLA SLE risk allele rs1270942 on chromosome 6p21.33 (OR per risk allele=1.17, 95% CI 1.01 to 1.36, p=0.0362). Of additional possible interest were rs2205960 and rs12537284. The rs2205960 SNP, related to a cytokine of the tumour necrosis factor superfamily TNFSF4, was associated with an OR per risk allele of 1.07, 95% CI 1.00 to 1.16, p=0.0549. The OR for the rs12537284 (chromosome 7q32, IRF5 gene) risk allele was 1.08, 95% CI 0.99 to 1.18, p=0.0765.

Conclusions: These data suggest several plausible genetic links between DLBCL and SLE.

Several recent studies have highlighted an increased risk of haematological malignancies, particularly non-Hodgkin’s lymphoma (NHL), in patients with SLE. 1, 2 The determinants of the increased risk of NHL in SLE are unclear. The most common type of NHL in SLE (as in the general population) is the diffuse large B-cell lymphoma (DLBCL)
 subtype. Using data from a recent NHL genome-wide association study (GWAS), our objective was to determine if certain SLE-related single nucleotide polymorphisms (SNPs) were also associated with the risk of DLBCL.

We focused on 28 SNPs independently associated with SLE in European Caucasians. All of these SNPs have been strongly associated with lupus risk, with a p value of $1 \times 10^{-7}$ or stronger. Our hypothesis was that these SNPs would also be associated with DLBCL risk.

**METHODS**

GWAS data on European Caucasians from the International Lymphoma Epidemiology Consortium (InterLymph http://www.epi.grants.cancer.gov/InterLymph) studies and participating cohort studies were based on a total of 3857 DLBCL cases and 7666 controls. Each participating study’s investigators obtained approval from human subjects review committees and informed consent from all participants. De-identified data were provided by the InterLymph Data Coordinating Center (Mayo Clinic, Rochester, Minnesota, USA).

For each SLE-related SNP, the ORs and 95% CIs were computed using a log-additive logistic regression model. Results from three previously conducted DLBCL GWAS studies were pooled in a random-effects meta-analysis. With 28 comparisons, an $\alpha$ of 0.05 would correspond to a Bonferroni-corrected p value of 0.0018.

**RESULTS**

Among the 28 SLE-related SNPs investigated (table 1), the two most convincingly associated with risk of DLBCL when correcting for multiple comparisons included the CD40 SLE risk allele rs4810485 on chromosome 20q13 (OR per risk allele=1.09, 95% CI 1.02 to 1.16, p=0.0134) and the HLA SLE risk allele rs1270942 on chromosome 6p21.33 (OR per risk allele 1.17, 95% CI 1.01 to 1.36, p=0.0362). Two other SNPs were of additional possible interest in DLBCL, with 95% CIs that just barely included the null value. The rs2205960 SNP, related to a cytokine of the tumour necrosis factor superfamily TNFSF4, was associated with an OR per risk allele of 1.07, 95% CI 1.00 to 1.16, p=0.0549. The OR for the SLE interferon regulatory factor (IRF5) risk allele was 1.08, 95% CI 1.01 to 1.17, p=0.0362.

**Table 1** SLE-related single nucleotide polymorphisms (SNPs) and ORs for diffuse large B-cell lymphoma (DLBCL) in European Caucasians in InterLymph data

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>SNP</th>
<th>Allele*</th>
<th>DBLCL SLE ref.</th>
<th>DBLCL OR</th>
<th>DBLCL 95% CI</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD40</td>
<td>20</td>
<td>rs4810485</td>
<td>T T C</td>
<td>1.08 (1.01 to 1.16)</td>
<td>0.013355</td>
<td></td>
<td></td>
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<tr>
<td>HLA</td>
<td>6</td>
<td>rs1270942</td>
<td>G G A</td>
<td>1.17 (1.01 to 1.35)</td>
<td>0.036172</td>
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<td></td>
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<tr>
<td>TNFSF4</td>
<td>1</td>
<td>rs2205960</td>
<td>A A G</td>
<td>1.07 (0.99 to 1.15)</td>
<td>0.054899</td>
<td></td>
<td></td>
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<tr>
<td>IRF5</td>
<td>7</td>
<td>rs12537284</td>
<td>A A G</td>
<td>1.08 (0.99 to 1.17)</td>
<td>0.076450</td>
<td></td>
<td></td>
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<tr>
<td>IL110</td>
<td>1</td>
<td>rs3024505</td>
<td>A A G</td>
<td>1.10 (0.98 to 1.35)</td>
<td>0.352319</td>
<td></td>
<td></td>
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<tr>
<td>BANK1</td>
<td>4</td>
<td>rs10516487</td>
<td>A A G</td>
<td>1.03 (0.96 to 1.10)</td>
<td>0.303231</td>
<td></td>
<td></td>
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<tr>
<td>Mir146a</td>
<td>5</td>
<td>rs57095329</td>
<td>G G A</td>
<td>1.02 (0.75 to 1.37)</td>
<td>0.860689</td>
<td></td>
<td></td>
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<tr>
<td>ITGAM</td>
<td>16</td>
<td>rs9888739</td>
<td>T T C</td>
<td>1.00 (0.92 to 1.10)</td>
<td>0.851519</td>
<td></td>
<td></td>
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<tr>
<td>IFIH1</td>
<td>2</td>
<td>rs1990760</td>
<td>T T C</td>
<td>1.03 (0.97 to 1.10)</td>
<td>0.223359</td>
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<tr>
<td>TNFAIP3</td>
<td>6</td>
<td>rs7749323</td>
<td>A A G</td>
<td>1.05 (0.84 to 1.25)</td>
<td>0.564425</td>
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<tr>
<td>NCF2</td>
<td>1</td>
<td>rs17849502</td>
<td>T G G</td>
<td>1.05 (0.89 to 1.23)</td>
<td>0.554699</td>
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<tr>
<td>STAT4</td>
<td>2</td>
<td>rs7582694</td>
<td>G C C</td>
<td>1.11 (0.97 to 1.26)</td>
<td>0.108048</td>
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<tr>
<td>PTPN22</td>
<td>1</td>
<td>rs2476601</td>
<td>G A A</td>
<td>1.04 (0.93 to 1.16)</td>
<td>0.441704</td>
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<tr>
<td>TYK2</td>
<td>19</td>
<td>rs280519</td>
<td>G A A</td>
<td>1.01 (0.95 to 1.07)</td>
<td>0.582604</td>
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<tr>
<td>PHRF1/IRF7/JIAA1542</td>
<td>11</td>
<td>rs4963128</td>
<td>C T T</td>
<td>1.01 (0.95 to 1.08)</td>
<td>0.570646</td>
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<td></td>
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</tbody>
</table>

*With 28 comparisons, an $\alpha$ of 0.05 would correspond to a Bonferroni-corrected p value of 0.0018.
rs12537284 (chromosome 7q32, gene) was 1.08, 95% CI 0.99 to 1.18, p=0.0765. A table presenting the study-specific contributions to the meta-analysis is provided in the online supplemental material.

**DISCUSSION**

Multiple studies have highlighted an increased risk of haematological malignancies, particularly NHL, in patients with SLE. To date, the reason for this excess risk has remained elusive. Recently, advances have been made in our understanding of lymphoma risk in other autoimmune rheumatic diseases, such as primary Sjögren’s syndrome, where the majority of patients with mucosa-associated lymphoid tissue (MALT) lymphoma have either germline polymorphisms of TNFAIP3 related to the A20 protein important in nuclear factor κB activation or somatic alterations of the gene within the lymphoma tissue. In their assessment of genetic risk overlap in autoimmune rheumatic diseases, Okada et al. found that polymorphisms of TNFAIP3 were common to both RA and Hodgkin’s lymphoma. Our analyses did not confirm a strong relationship between the lupus-related TNFAIP3 SNP rs7749323 specifically for DLBCL, but this may be a power issue, or may reflect the importance of different pathways for different haematological risk profiles across different autoimmune rheumatic diseases. Of note, our analyses were done in Caucasian populations; several non-Caucasian race/ethnic groups (eg, blacks, Asians) may have different genetic risk profiles and clinical presentations, thus future analyses could consider these populations as well. We have previously shown that the increased risk of lymphoma in SLE is similar across white, black and Asian patients. In addition, it may be that specific genetic risk factors for different clinical SLE manifestations may drive some of the risk of lymphoma, although we were unable to investigate that hypothesis here.

Existing data do suggest that some human leukocyte antigen (HLA) polymorphisms influence risk of DLBCL. In recent DLBCL GWAS analyses, HLA-B*08:01 reached genome-wide significance. In SLE, the strongest association in HLA is for the Class II allele DRB1*0301. This allele is in strong linkage disequilibrium with HLA-B*0801 in Caucasians so we are likely tagging the same HLA effect. CD40, a member of the tumour necrosis superfamily, plays a central role in regulating immune cells; CD40 is expressed on several B-cell neoplasms including DLBCL. Data have suggested a possible role for functional polymorphisms (specifically, C vs T, rs1883832) in the TNFRSF5 gene encoding CD40 in lymphomas originating within the germinal centre (both DLBCL and follicular). Tumour necrosis factor ligand superfamily involvement has been suggested in the pathology of malignant lymphomas. Furthermore, in human NHL B-cell lines, IRF5 initiates a regulatory cascade by inducing the transcription factor activator protein 1 (AP-1) and cooperating with nuclear factor kappa B (NF-κB), which appears to represent a potentially important tumour promoting role of IRF5 in lymphoma.

Not all of the excess risk of haematological malignancies in SLE is necessarily due to genetic factors; exposures within the environment may also be at play. However, in the InterLymph Subtypes pooling project, autoimmune diseases as a risk for lymphoma appeared to be independent of other potentially shared environmental risk factors (body mass index, sun, alcohol, occupation, etc). In the work of Ekström Smedby et al., SLE was associated with a 2.7-fold increase in risk of NHL risk overall; this was highest among patients with SLE of short duration (2–5 years), but a near twofold increase was also observed with more than 10 years of disease. Use of corticosteroid and immunosuppressive drugs categorically was not clearly linked to higher or lower risk, but analyses were not detailed. Two very comprehensive case-control studies of SLE-related medications have suggested a link between cyclophosphamide (used intravenously in severe or resistant forms of SLE, especially nephritis) and haematological malignancies in general and specifically, in lymphoma. Fortunately, lymphoma after cyclophosphamide SLE treatment is a relatively uncommon outcome. Future studies of interactions between genetic factors and drug exposures may be warranted.

In conclusion, we studied a large GWAS datasets and found several plausible pathways linking DLBCL and SLE. Given that cyclophosphamide exposure in SLE is also associated with DLBCL risk, future studies might be able to explore whether these genetic risk factors may aid in risk stratification and decision-making when cyclophosphamide treatment is being considered for severe forms of SLE.

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Lupus Science & Medicine

Contributors All authors contributed to study design and/or data collection and/or analysis. All authors contributed to the manuscript and approve the final version.

Funding Support for the logistical needs of the InterLymph Consortium is provided by NCI’s Division of Cancer Epidemiology and Genetics (DCEG), the Epidemiology and Genomics Research Program (EGRP) of the Division of Cancer Control and Population Sciences (DCCPS), the International Agency for Research on Cancer (IARC) and the Leukaemia Research Fund.

Support for individual studies

ATBC: The α-Tocopherol, β-Carotene Cancer Prevention Study is supported by the Intramural Research Program of the U.S. National Cancer Institute, National Institutes of Health and by U.S. Public Health Service contract HHSN261201500005C from the National Cancer Institute, Department of Health and Human Services.

BC: Canadian Institutes for Health Research (CIHR); Canadian Cancer Society; Michael Smith Foundation for Health Research.

CPS-II: The Cancer Prevention Study-II (CPS-II) Nutrition Cohort is supported by the American Cancer Society. Genotyping for all CPS-II samples were supported by the Intramural Research Program of the National Institutes of Health, NCI, Division of Cancer Epidemiology and Genetics. The authors would also like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries and cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries and cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results programme.

ELCSS: Bloodwise (formerly Leukaemia & Lymphoma Research); grant reference 0073.

ENGELA: Association pour la Recherche contre le Cancer (ARC), Institut National du Cancer (INCa), Fondation de France, Fondation contre la Lymphome et le Myélome (FLM).
Leucémie, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES).

EPIC: Coordinated Action (Contract #006438, SP23-CT-2005-006438); HuGeF (Human Genetics Foundation), Torino, Italy; Cancer Research UK; Danish Cancer Society.

EpiLymph: European Commission (grant references OL4-KT-2000-00422 and FOOD-CT-2006-023103); the Spanish Ministry of Health (grant references CIBERESP, PI11/01810, PI14/01219, RCESEP C03/09, RTICESP C03/10 and RTIC RD06/0020/0095), the Marató de TV3 Foundation (grant reference 051210), the Agència de Gestió d'Ajuts Universitaris de Recerca—Generalitat de Catalunya (grant reference 2014SGR756) who had no role in the data collection, analysis or interpretation of the results; the NIH (contract N01-CO-12400); the Compagnia di San Paolo—Programma Oncologia; the Federal Office for Radiation Protection grants STsCh4261 and STsch4420; the José Carreras Leukemia Foundation grant DJCLS-R12/23, the German Federal Ministry for Education and Research (BMBF-01-E0-1303); the Health Research Board, Ireland and Cancer Research Ireland; Czech Republic supported by MH CZ—DRO (MMCI, 200920085) and by MEYS—NPS I—L01413; Fondation de France and Association de Recherche Contre le Cancer.

GEC/Mayo GWS: National Institutes of Health (CA118444, CA148690, CA92153), Intramural Research Program of the NIH, National Cancer Institute. Veterans Affairs Research Service. Data collection for Duke University was supported by a Leukemia & Lymphoma Society Cancer Career Development Award, the Bernstein Family Fund for Leukemia and Lymphoma Research and the National Institutes of Health (K08CA134919), National Center for Advancing Translational Science (UL1TR000135).

HPFS: The HPFS was supported in part by National Institutes of Health grants CA167552, CA149445, CA098812 and CA099866. We would like to thank the participants and staff of the Health Professionals Follow-up Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

Iowa-Mayo SPORE: NCI Specialized Programs of Research Excellence (SPORE) in Human Cancer (P50 CA97274); National Cancer Institute (P30 CA050536); Iowa Cancer Center (P30 CA15083); Henry J. Prendel Foundation.

Italian GxE: Italian Association for Cancer Research (AIRC, Investigator Grant (SPORE) in Human Cancer (P50 CA97274); National Cancer Institute (P30 CA15083); National Institutes of Health (R01 CA45614; NCI grant R01 CA87014; NCI grant R03 CA89745; NCI R01 CA122663; NCI grant R01 CA104682; NCI grant P01-CA43233).

UCSF2: The UCSF studies were supported by the NCI, National Institutes of Health, CA104628 and CA154643. The collection of cancer incidence data used in this study was supported by the California Department of Health Services as part of the state-wide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program under contract HHSN26120100014C awarded to the Cancer Prevention Institute of California, contract HHSN26120100003C awarded to the University of Southern California, and contract HHSN26120100003C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention’s National Program of Cancer Registries, under agreement #U156 DP000807-01 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the authors, and endorsement by the California Department of Health Services, the National Cancer Institute, or the Centers for Disease Control and Prevention or their contractors and subcontractors is neither intended nor should be inferred.

UTAH/Sheffield: National Institutes of Health CA134674. Partial support for data collection at the Utah site was made possible by the Utah Population Database (UPDB) and the Utah Cancer Registry (UCR). Partial support for all datasets within the UPDB is provided by the Huntsman Cancer Institute (HCI) and the NCI Cancer Center Support grant, P30 CA42014. The UCR is supported in part by NIH contract HHSN261201000026C from the National Cancer Institute SEER Program with additional support from the Utah State Department of Health and the University of Utah. Partial support for data collection in Sheffield, UK was made possible by funds from Yorkshire Cancer Research and the Sheffield Experimental Cancer Medicine Centre. We thank the NCRI Haemato-Oncology Clinical Studies Group, colleagues in the North Trent Cancer Network the North Trent Haemato-Oncology Database.

WHI: WHI investigators are: Program Office—(National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Dale Burven, Joan McGowan, Leslie Ford, and Nancy Geller; Clinical Coordinating Center—(Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg; Investigators and Academic Centers—(Brigham and Women’s Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Harvard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (Women’s Health Initiative Memory Study—(Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts
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