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


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 certain 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.

CrossMark

Received 29 September 2016
Revised 18 November 2016
Accepted 30 November 2016
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

**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>DLBCL SLE ref.</th>
<th>DLBCL OR</th>
<th>DLBCL 95% CI</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD40</td>
<td>20</td>
<td>rs4810485</td>
<td>T</td>
<td>T</td>
<td>C</td>
<td>1.088 (1.017 to 1.162)</td>
<td>0.013355</td>
</tr>
<tr>
<td>HLA</td>
<td>6</td>
<td>rs1270942</td>
<td>G</td>
<td>G</td>
<td>A</td>
<td>1.171 (1.010 to 1.357)</td>
<td>0.036172</td>
</tr>
<tr>
<td>TNFSF4</td>
<td>1</td>
<td>rs2205960</td>
<td>A</td>
<td>A</td>
<td>G</td>
<td>1.074 (0.998 to 1.156)</td>
<td>0.054899</td>
</tr>
<tr>
<td>IRF5</td>
<td>7</td>
<td>rs12537284</td>
<td>A</td>
<td>A</td>
<td>G</td>
<td>1.081 (0.992 to 1.179)</td>
<td>0.076450</td>
</tr>
<tr>
<td>IL110</td>
<td>1</td>
<td>rs3024505</td>
<td>A</td>
<td>A</td>
<td>G</td>
<td>1.102 (0.898 to 1.353)</td>
<td>0.352319</td>
</tr>
<tr>
<td>BANK1</td>
<td>4</td>
<td>rs10518648</td>
<td>A</td>
<td>A</td>
<td>G</td>
<td>1.035 (0.969 to 1.106)</td>
<td>0.303231</td>
</tr>
<tr>
<td>Mir146a</td>
<td>5</td>
<td>rs57095329</td>
<td>G</td>
<td>G</td>
<td>A</td>
<td>1.020 (0.756 to 1.377)</td>
<td>0.896098</td>
</tr>
<tr>
<td>ITGAM</td>
<td>16</td>
<td>rs9888739</td>
<td>T</td>
<td>T</td>
<td>C</td>
<td>1.008 (0.923 to 1.102)</td>
<td>0.851159</td>
</tr>
<tr>
<td>IFI1</td>
<td>1</td>
<td>rs1990760</td>
<td>T</td>
<td>T</td>
<td>C</td>
<td>1.037 (0.978 to 1.101)</td>
<td>0.223359</td>
</tr>
<tr>
<td>TNFAIP3</td>
<td>6</td>
<td>rs7749323</td>
<td>A</td>
<td>A</td>
<td>G</td>
<td>1.053 (0.884 to 1.253)</td>
<td>0.564425</td>
</tr>
<tr>
<td>NCF2</td>
<td>1</td>
<td>rs17849520</td>
<td>T</td>
<td>G</td>
<td>G</td>
<td>1.050 (0.892 to 1.236)</td>
<td>0.554699</td>
</tr>
<tr>
<td>STAT4</td>
<td>2</td>
<td>rs7582694</td>
<td>G</td>
<td>C</td>
<td>C</td>
<td>1.110 (0.977 to 1.260)</td>
<td>0.108048</td>
</tr>
<tr>
<td>PTPN22</td>
<td>1</td>
<td>rs2476601</td>
<td>G</td>
<td>A</td>
<td>A</td>
<td>1.043 (0.937 to 1.161)</td>
<td>0.441704</td>
</tr>
<tr>
<td>TYK2</td>
<td>19</td>
<td>rs280519</td>
<td>G</td>
<td>A</td>
<td>A</td>
<td>1.016 (0.959 to 1.077)</td>
<td>0.582604</td>
</tr>
<tr>
<td>PHRF1/IRF7/</td>
<td>11</td>
<td>rs4963128</td>
<td>C</td>
<td>T</td>
<td>T</td>
<td>1.018 (0.956 to 1.085)</td>
<td>0.570646</td>
</tr>
<tr>
<td>KIAA1542</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD44</td>
<td>11</td>
<td>rs507230</td>
<td>A</td>
<td>G</td>
<td>G</td>
<td>1.000 (0.941 to 1.062)</td>
<td>0.987988</td>
</tr>
<tr>
<td>XKR6</td>
<td>8</td>
<td>rs6985109</td>
<td>A</td>
<td>G</td>
<td>G</td>
<td>1.040 (0.981 to 1.103)</td>
<td>0.187826</td>
</tr>
<tr>
<td>JAZF1</td>
<td>7</td>
<td>rs849142</td>
<td>C</td>
<td>T</td>
<td>T</td>
<td>1.012 (0.903 to 1.134)</td>
<td>0.836267</td>
</tr>
<tr>
<td>UBE2L3</td>
<td>22</td>
<td>rs463426</td>
<td>C</td>
<td>G</td>
<td>G</td>
<td>1.060 (0.938 to 1.197)</td>
<td>0.349982</td>
</tr>
<tr>
<td>BLK</td>
<td>8</td>
<td>rs7812879</td>
<td>C</td>
<td>A</td>
<td>T</td>
<td>1.058 (0.956 to 1.172)</td>
<td>0.276113</td>
</tr>
<tr>
<td>FCGR2A,FCGR3B</td>
<td>1</td>
<td>rs1801274</td>
<td>G</td>
<td>T</td>
<td>A</td>
<td>1.023 (0.913 to 1.147)</td>
<td>0.693045</td>
</tr>
<tr>
<td>IZK1F</td>
<td>7</td>
<td>rs4917014</td>
<td>G</td>
<td>C</td>
<td>T</td>
<td>1.020 (0.916 to 1.138)</td>
<td>0.710394</td>
</tr>
<tr>
<td>LYN</td>
<td>8</td>
<td>rs7829816</td>
<td>G</td>
<td>C</td>
<td>A</td>
<td>1.031 (0.959 to 1.107)</td>
<td>0.411987</td>
</tr>
<tr>
<td>TNFIP1</td>
<td>5</td>
<td>rs10036748</td>
<td>T</td>
<td>G</td>
<td>C</td>
<td>1.015 (0.950 to 1.085)</td>
<td>0.652213</td>
</tr>
<tr>
<td>IRF8</td>
<td>16</td>
<td>rs2280381</td>
<td>T</td>
<td>A</td>
<td>C</td>
<td>1.093 (0.933 to 1.287)</td>
<td>0.265341</td>
</tr>
<tr>
<td>ATG5</td>
<td>6</td>
<td>rs548234</td>
<td>T</td>
<td>G</td>
<td>C</td>
<td>1.033 (0.936 to 1.140)</td>
<td>0.518928</td>
</tr>
<tr>
<td>PKX</td>
<td>3</td>
<td>rs6445975</td>
<td>T</td>
<td>C</td>
<td>G</td>
<td>1.011 (0.945 to 1.083)</td>
<td>0.743076</td>
</tr>
<tr>
<td>IL2/IL21</td>
<td>4</td>
<td>rs907715</td>
<td>T</td>
<td>G</td>
<td>C</td>
<td>1.033 (0.967 to 1.104)</td>
<td>0.339144</td>
</tr>
</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. In their assessment of genetic risk overlap between rheumatoid arthritis (RA) and haematological cancers, 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 with 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 factor 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 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.

**Author affiliations**

1Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, Canada
2BC Cancer Research Centre and School of Population and Public Health, University of British Columbia, Vancouver, Canada
3Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA
4Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, and Hematology Center, Karolinska University Hospital, Stockholm, Sweden
5Feinberg School of Medicine, Northwestern University, Chicago, USA
6Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, Duarte, USA
7Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
8Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA
9Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, USA
10Hematology Unit, Ospedale Oncologico di Riferimento Regionale ‘A. Buscino’, Cagliari, Italy
11Department of Medicine, Mayo Clinic, Rochester, USA
12Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Jacksonville, USA
13Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
14Cancer Epidemiology Research Programme, Catalan Institute of Oncology-IDIBELL, L’Hospital de Llobregat, Barcelona, Spain
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 by the National Cancer Institute Surveillance Epidemiology and End Results programme.

ELCCS: 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...
REFERENCES

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


*Lupus Sci Med* 2017 4:
doi: 10.1136/lupus-2016-000187

Updated information and services can be found at:
http://lupus.bmj.com/content/4/1/e000187

These include:

**References**

This article cites 15 articles, 6 of which you can access for free at:
http://lupus.bmj.com/content/4/1/e000187?BIBL

**Open Access**

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

To request permissions go to: http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to: http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to: http://group.bmj.com/subscribe/
Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

Lupus Nephritis (11)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/