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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 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.

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),[3] 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.[4] All of these SNPs have been strongly associated with lupus risk, with a p value of 1×10^{-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 α 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

Gene	Chromosome	SNP	Allele* DLBCL SLE ref.		DLBCL OR	DLBCL 95% CI	p Value* DLBCL
CD40	20	rs4810485	T	T	C	1.088 (1.017 to 1.162)	0.013355
HLA	6	rs1270942	G	G	A	1.171 (1.010 to 1.357)	0.036172
TNFSF4	1	rs2205960	A	A	G	1.074 (0.998 to 1.156)	0.054899
IRF5	7	rs12537284	A	A	G	1.081 (0.992 to 1.179)	0.076450
ILI10	1	rs3024505	A	A	G	1.102 (0.898 to 1.353)	0.352319
BANK1	4	rs10516487	A	A	G	1.035 (0.969 to 1.106)	0.303231
Mir146a	5	rs57095329	G	G	A	1.020 (0.756 to 1.377)	0.896089
ITGAM	16	rs9888739	T	T	C	1.008 (0.923 to 1.102)	0.851519
IFIH1	2	rs1990760	T	T	C	1.037 (0.978 to 1.101)	0.223359
TNFAIP3	6	rs7749323	A	A	G	1.053 (0.884 to 1.253)	0.564425
NCF2	1	rs17849502	T	G	G	1.050 (0.892 to 1.236)	0.554699
STAT4	2	rs7582694	G	C	C	1.110 (0.977 to 1.260)	0.108048
PTPN22	1	rs2476601	G	A	A	1.043 (0.937 to 1.161	0.441704
TYK2	19	rs280519	G	A	A	1.016 (0.959 to 1.077)	0.582604
PHRF1/IRF7/ KIAA1542	11	rs4963128	C	T	T	1.018 (0.956 to 1.085)	0.570646
CD44	11	rs507230	A	G	G	1.000 (0.941 to 1.062)	0.987988
XKR6	8	rs6985109	A	G	G	1.040 (0.981 to 1.103)	0.187826
JAZF1	7	rs849142	C	T	T	1.012 (0.903 to 1.134)	0.836267
UBE2L3	22	rs463426	C	G	T	1.060 (0.938 to 1.197)	0.349982
BLK	8	rs7812879	C	A	T	1.058 (0.956 to 1.172)	0.276113
FCGR2A, FCGR3B	1	rs1801274	G	T	A	1.023 (0.913 to 1.147)	0.693045
IKZF1	7	rs4917014	G	C	T	1.020 (0.916 to 1.138)	0.710394
LYN	8	rs7829816	G	C	A	1.031 (0.959 to 1.107)	0.411987
TNIP1	5	rs10036748	T	G	C	1.015 (0.950 to 1.085)	0.652213
IRF8	16	rs2280381	T	A	C	1.096 (0.933 to 1.287)	0.265341
ATG5	6	rs548234	T	G	C	1.033 (0.936 to 1.140)	0.518828
PXK	3	rs6445975	T	C	G	1.011 (0.945 to 1.083)	0.743076
IL2/IL21	4	rs907715	T	G	C	1.033 (0.967 to 1.104)	0.339144

*With 28 comparisons, an α 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.[5] In their assessment of genetic risk overlap between rheumatoid arthritis (RA) and haematological cancers, Okada *et al*[6] 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.[7] 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.[8] In recent DLBCL GWAS analyses, HLA-B 08-01 reached genome-wide significance.[4] 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.[9] 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).[10] Tumour necrosis factor ligand superfamily involvement has been suggested in the pathology of malignant lymphomas.[11] 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.[12]

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).[13] 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.[2] 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[14] (and specifically, in lymphoma[15]). 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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