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Title:

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

Date:

2017-01-01

Citation:

Bernatsky, S., García, H. A. V., Spinelli, J. J., Gaffney, P., Smedby, K. E., Ramsey-Goldman, R., Wang, S. S., Adami, H. O., Albanes, D., Angelucci, E., Ansell, S. M., WAsmann, Y., Becker, N., Benavente, Y., Berndt, S. I., Bertrand, K. A., Birmann, B. M., Boeing, H., Boffetta, P. ,... Zucca, M. (2017). Lupus-related single nucleotide polymorphisms and risk of diffuse large B-cell lymphoma. *Lupus Science and Medicine*, 4 (1), <https://doi.org/10.1136/lupus-2016-000187>.

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

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To cite: Bernatsky S, Velásquez García HA, Spinelli JJ, *et al.* Lupus-related single nucleotide polymorphisms and risk of diffuse large B-cell lymphoma. *Lupus Science & Medicine* 2017;4:e000187. doi:10.1136/lupus-2016-000187

► Additional material is available. To view please visit the journal online (<http://dx.doi.org/10.1136/lupus-2016-000187>).

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



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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
IL110	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 κ B 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*03:01. This allele is in strong linkage disequilibrium with HLA-B*08:01 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- κ B), 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 general¹⁴ (and specifically, in lymphoma¹⁵). 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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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

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 QLK4-CT-2000-00422 and FOOD-CT-2006-023103); the Spanish Ministry of Health (grant references CIBERESP, PI11/01810, PI14/01219, RCESP 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 2014SRG756) who had no role in the data collection, analysis or interpretation of the results; the NIH (contract NO1-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-EO-1303); the Health Research Board, Ireland and Cancer Research Ireland; Czech Republic supported by MH CZ—DRO (MMCI, 00209805) and by MEYS—NPS I—LO1413; Fondation de France and Association de Recherche Contre le Cancer.

GEC/Mayo GWAS: 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 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 (UL1 TR000135).

HPFS: The HPFS was supported in part by National Institutes of Health grants CA167552, CA149445, CA098122 and CA098566. 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 SPOR: NCI Specialized Programs of Research Excellence (SPOR) in Human Cancer (P50 CA97274); National Cancer Institute (P30 CA086862, P30 CA15083); Henry J. Predolin Foundation.

Italian GxE: Italian Association for Cancer Research (AIRC, Investigator Grant 11855) (PC); Fondazione Banco di Sardegna 2010–2012 and Regione Autonoma della Sardegna (LR7 CRP-59812/2012) (MGE).

Mayo Clinic Case-Control: National Institutes of Health (R01 CA92153); National Cancer Institute (P30 CA015083).

MCCS: The Melbourne Collaborative Cohort Study recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 209057, 251553 and 504711 and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry (VCR) and the Australian Institute of Health and Welfare (AIHW), including the National Death Index and the Australian Cancer Database.

MD Anderson: Institutional support to the Center for Translational and Public Health Genomics.

MSKCC: Geoffrey Beene Cancer Research Grant, Lymphoma Foundation (LF5541); Barbara K. Lipman Lymphoma Research Fund (74419); Robert and Kate Niehaus Clinical Cancer Genetics Research Initiative (57470); U01 HG007033; ENCODE; U01 HG007033.

NCI-SEER: Intramural Research Program of the National Cancer Institute, National Institutes of Health, and Public Health Service (N01-PC-65064, N01-PC-67008, N01-PC-67009, N01-PC-67010, N02-PC-71105). NHS—The NHS was supported in part by National Institutes of Health grants CA186107, CA87969, CA49449, CA149445, CA098122 and CA098566. We would like to thank the participants and staff of the Nurses' Health 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.

NSW: NSW was supported by grants from the Australian National Health and Medical Research Council (ID990920), the Cancer Council NSW, and the University of Sydney Faculty of Medicine.

NYU-WHS: National Cancer Institute (UM1 CA182934, P30 CA016087); National Institute of Environmental Health Sciences (ES000260).

PLCO: This research was supported by the Intramural Research Program of the National Cancer Institute and by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS.

SCALE: Swedish Cancer Society (2009/659), Stockholm County Council (20110209) and the Strategic Research Program in Epidemiology at Karolinska Institute. Swedish Cancer Society grant (02 6661). National Institutes of Health (5R01 CA69669-02); Plan Denmark. UCSF—UCSF and the UCSF NHL study were supported by the following grants (including joint grants to University California Berkley (Skibola and M. Smith)): NIH grant R01-CA45614; NCI grant R01 CA87014; NCI grant R03 CA89745; NCI 263-MQ-701711; NCI grant R01 CA122663; NCI grant R01 CA104682; NCI grant P01-CA34233.

UCSF2: The UCSF studies were supported by the NCI, National Institutes of Health, CA1046282 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 programme mandated by California Health and Safety Code Section 103885; 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, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #1U58 DP000807-01 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, 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 HCI 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 Burwen, 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/Howard 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

HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C and HHSN271201100004C.

YALE: National Cancer Institute (CA62006); National Cancer Institute (CA165923).

Competing interests None declared.

Ethics approval Each participating study's investigators obtained approval from human subjects review committees and informed consent from all participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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