

LYMPHOID NEOPLASIA

Genome-wide association study implicates immune dysfunction in the development of Hodgkin lymphoma

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KEY POINTS

- Variation at 6p21.31, 6q23.3, 11q23.1, 16p11.2, and 20q13.12 influences risk for HL.
- Genetic predisposition implicates germinal center dysfunction, disrupted T-cell function, and NF- κ B activation in the pathogenesis of HL.

To further our understanding of inherited susceptibility to Hodgkin lymphoma (HL), we performed a meta-analysis of 7 genome-wide association studies totaling 5325 HL cases and 22 423 control patients. We identify 5 new HL risk loci at 6p21.31 (rs649775; $P = 2.11 \times 10^{-10}$), 6q23.3 (rs1002658; $P = 2.97 \times 10^{-8}$), 11q23.1 (rs7111520; $P = 1.44 \times 10^{-11}$), 16p11.2 (rs6565176; $P = 4.00 \times 10^{-8}$), and 20q13.12 (rs2425752; $P = 2.01 \times 10^{-8}$). Integration of gene expression, histone modification, and in situ promoter capture Hi-C data at the 5 new and 13 known risk loci implicates dysfunction of the germinal center reaction, disrupted T-cell differentiation and function, and constitutive NF- κ B activation as mechanisms of predisposition. These data provide further insights into the genetic susceptibility and biology of HL. (*Blood*. 2018;132(19):2040-2052)

Introduction

Hodgkin lymphoma (HL) comprises classical HL (cHL; ~95% of cases) and nodular lymphocyte predominant HL (~5% of cases).¹ Although cHL and nodular lymphocyte-predominant HL are defined by the Hodgkin and Reed-Sternberg (HRS) cell and the lymphocyte-predominant cell, respectively, both diseases are thought to arise from the malignant transformation of germinal center B cell.^{2,3} Furthermore, both cHL and nodular lymphocyte-predominant HL demonstrate a paucity of these neoplastic B cells within a background of reactive inflammatory cells that includes large populations of CD4⁺ T cells.^{4,5}

A viral or infectious agent has long been considered a major etiological factor for HL, with Epstein-Barr virus (EBV) being the posited infectious agent.^{6,7} However, the EBV genome is only identifiable in a variable number of HL cases, and epidemiological data support a causal role for the virus in EBV-positive HL only.⁸ Evidence for genetic susceptibility to HL is provided by the elevated familial risk, as well as the high concordance between monozygotic twins.^{9,10} More

recently, genome-wide association studies (GWAS) have confirmed an HLA association for HL and have identified single nucleotide polymorphisms (SNPs) at 13 non-HLA loci influencing risk.^{11,12}

To gain further insight into HL susceptibility, we have conducted a meta-analysis of data from 7 independent GWAS and report 5 new HL risk loci.¹¹⁻¹³ Integration of gene expression, histone modification, and in situ promoter capture Hi-C data (PCHI-C) at the 5 new and the 13 known risk loci provides evidence for cell-type specificity in B and T cells and implicates dysfunction of the germinal center reaction, disrupted T-cell differentiation and function, and constitutive NF- κ B activation as mechanisms by which loci influence HL risk.

Materials and methods

Ethics

Collection of patient samples and associated clinicopathological information was undertaken with written informed consent. Relevant ethical review boards approved the individual studies in

accordance with the tenets of the Declaration of Helsinki (UK-GWAS MREC 03/1/096, German-GWAS University of Heidelberg 104/2004, and UK-GWAS-NSHLG MREC 09/MRE00/72). The diagnosis of HL in all cases was established in accordance with World Health Organization guidelines.

GWAS

We used GWAS data generated on 3 nonoverlapping case-control series of Northern European ancestry, which have been the subject of previous analyses (supplemental Tables 1 and 2, available on the *Blood* Web site).¹¹ The UK-GWAS was based on 622 cases ascertained through the Royal Marsden Hospital National Health Service Trust Family History study during 2004 to 2008,¹⁴ and 5677 control patients from the UK Wellcome Trust Case Control Consortium 2.¹⁵ The German-GWAS comprised 1001 cases ascertained by the German Hodgkin Study Group during 1998 to 2007, and 2092 control patients from the Heinz Nixdorf Recall study.¹⁶ The UK-NSHLG-GWAS used 1717 cases ascertained through the National Study of Hodgkin Lymphoma Genetics (<https://www.ukctg.nihr.ac.uk>) from 2010 to 2013.¹¹ Control patients comprised 2976 cancer-free men recruited by the PRACTICAL Consortium, the UK Genetic Prostate Cancer Study (UKGPCS; age <65 years), a study conducted through the Royal Marsden NHS Foundation Trust and Study of Epidemiology & Risk Factors in Cancer, recruited via general practitioner practices in East Anglia (2003-2009); and 4446 cancer-free women from across the United Kingdom via the Breast Cancer Association Consortium. Details of the genotyping platform and quality control measures applied to each of the 3 GWAS have been described previously and are detailed in supplemental Tables 3 and 4.^{11,14,17,18} Briefly, individuals with a low call rate (<95%), as well as all individuals evaluated to be of non-European ancestry, were excluded (supplemental Figure 1). Eigenvectors for the GWAS data sets were inferred using smartpca (part of EIGENSOFT) by merging cases and controls with phase 3 HapMap samples.¹⁹ For apparent first-degree relative pairs, we excluded the control from a case-control pair or the individual with the lower call rate (supplemental Table 3). SNPs with a call rate below 95% were excluded, as were those with a minor allele frequency <0.01 or displaying deviation from Hardy-Weinberg equilibrium (ie, $P < 10^{-6}$; supplemental Table 4). GWAS data were phased with SHAPEIT3,²⁰ and imputed to more than 10 million SNP, using IMPUTE4 v1.0.²¹ and a merged reference panel consisting of data from 1000 Genomes Project (phase 3)²² and UK10K (EGAD00001000776).²³ Imputation was conducted separately for each study from a set of SNPs common to cases and controls. Poorly imputed SNPs (defined by an information measure < 0.80) were excluded. Tests of association between SNPs and HL were performed using logistic regression under an additive genetic model in SNPTTESTv2.5.2.²⁴ The adequacy of the case-control matching was evaluated using Q-Q plots of test statistics (supplemental Figure 2). The inflation factor λ_{1000} was based on the 90% least-significant SNP scaled to 1000 cases and 1000 controls.

In addition to analyzing data from these 3 GWAS, we made use of preprocessed association test statistics for HL risk from a meta-analysis of 3 additional GWAS (USC-IARC-UC-GWAS) comprising 1816 HL cases and 7879 control individuals,^{12,25,26} and an analysis of 432 HL cases and 337 208 unaffected individuals¹³ from the UK Biobank, accessed through the Global Biobank Engine.

Meta-analysis

Meta-analyses were performed under a fixed-effects model, using META v1.7.²⁴ Cochran's Q-statistic to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation resulting from heterogeneity were calculated; an I^2 value at least 75% is considered to be characteristic of large heterogeneity.²⁷ Where the same controls were used in both the UK-GWAS and the USC-IARC-UC GWAS, these controls were excluded from the UK-GWAS association analysis.

Cell culture

L-428 HL cells were obtained from Deutsche Sammlung von Mikroorganismen und Zellkulturen and were cultured at 37°C in RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum (Thermo Fisher Scientific). Cell line identity was confirmed by STR-profiling. Cells were regularly tested for mycoplasma contamination (PromoCell, PK-CA91).

Chromatin immunoprecipitation-seq analysis

L-428 Chromatin immunoprecipitation (ChIP)-seq was performed on H3K27Ac and H3K4me3 for using antibodies obtained from Diagenode. Briefly, after cell lysing, sonication of nuclei was performed (UCD-300, BioRuptor) to obtain 150- to 500-bp fragments. ChIP reaction was performed on a Diagenode SX-8G IP-Star Compact using Diagenode automated Ideal Kit reagents (C01010011). Protein A beads were incubated for 10 hours with 3 to 6 μ g antibody and 2 to 4 million sonicated cell lysate. ChIP samples were de-cross-linked at 65°C for 4 hours and subsequently treated for 30 minutes with RNase Cocktail and proteinase K. DNA was then purified (MiniElute PCR purification kit, Qiagen), followed by library preparation according to manufacture (HTP Illumina library preparation kit, KAPA Biosystems). Fourteen cycles of polymerase chain reaction were performed, followed by size selection for 200- to 400-bp fragments and final library purification (GeneRead Size Selection kit, 301 Qiagen). ChIP libraries were sequenced using HiSeq 2000 (Illumina) with 100-bp single-ended reads. Generated raw reads were filtered for quality (Phred33 ≥ 30) and length ($n \geq 32$), and adapter sequences were removed using Trimmomatic v0.2235. Reads passing filters were then aligned to the human reference (hg19), using BWA v0.6.1. Peak calls are obtained using MACS2 v 2.0.1.

Histone modification data from primary blood cells H3K27Ac and H3K4me3 data from more than 100 samples from more than 30 cell types from the Blueprint Epigenome Consortium were analyzed.²⁸

Cell-specificity analysis

Overlap enrichment analysis of HL risk SNPs with H3K4me3 and H3K27Ac peaks was performed as described by Trynka et al.²⁹ Briefly, we evaluated whether the HL risk SNPs and SNPs in linkage disequilibrium ($LD; r^2 > 0.8$) with the sentinel SNP were enriched at H3K4me3 and H3K27Ac ChIP-seq peaks in blood cells and the HRS cell line L-428 by a permutation procedure with 10^5 iterations.

Promoter capture Hi-C

In situ Hi-C libraries for L-428 were prepared as previously described.^{30,31} Briefly, 25 million cells were fixed in 1% formaldehyde for 10 minutes. Cross-linked DNA was digested with *HindIII* (NEB, R0104), and chromatin ends were filled and marked

with biotin-14-dATP (Thermo Fisher, 19524-016). The resulting blunted ended fragments were ligated at 16°C in the nucleus with T4 DNA ligase (NEB, M0202) to minimize random ligation. DNA purified after cross-linking was reversed by proteinase K (Ambion, AM2546) treatment. DNA was sheared by sonication (Covaris, M220), and 200- to 650-bp fragments were selected. Biotin tag DNA was pulled down with streptavidin beads and ligated with Illumina paired-end adapters (Illumina). Six cycles of polymerase chain reaction were performed to amplify libraries before capture. Promoter capture was based on 32 313 biotinylated 120-mer RNA baits (Agilent Technologies), targeting both ends of *HindIII* restriction fragments that overlap Ensembl promoters of protein-coding, noncoding, antisense, snRNA, miRNA, and snoRNA transcripts (supplemental Data). After library enrichment, a postcapture polymerase chain reaction amplification step was carried out using 6 amplification cycles. Hi-C and PCHI-C libraries were sequenced using HiSeq 2000 technology (Illumina). Reads were aligned to the GRCh37 build using Bowtie2 v2.2.6,³² and identification of valid di-tags was performed using HiCUP v0.5.9.³³ To declare significant contacts, HiCUP output was processed using ChICAGO v1.1.8.³⁴ Data from 3 independent biological replicates were combined to define a definitive set of contacts. Publicly accessible PCHI-C data generated in B- and T-cell populations were downloaded from the Open Science Framework.³⁵

Chromatin interactions relevant to HL risk loci were defined as contacts overlapping with HL risk SNPs and SNPs in LD ($r^2 > 0.8$ with the sentinel SNP), with promoters within a 2-Mb window of the sentinel SNP, and with a score of at least 5.0.³⁴ Plotting of HL association data and chromatin contacts was performed using visPIL.³⁶

Expression quantitative trait loci analysis

An analysis of associations between the SNPs ($r^2 > 0.8$) at each locus and tissue-specific changes in gene expression was performed using summary statistics from 3 publicly available resources: lymphoblastoid cell line (LCL) expression from the MuTHER (n = 825) consortium³⁷; LCL expression from the GTEx consortium (n = 114)³⁸; and CD4⁺ and CD8⁺ T cells from 313 individuals.³⁹ Statistical significance was assigned after correcting for the number of probes at each locus (microarray) or the number of transcripts at each locus (RNA-seq) for each expression data set.

Genetic correlation with infection

To estimate the genetic correlation between specific infections and all HL, and nodular sclerosis HL (NSHL) and mixed cellularity HL (MCHL) subtypes,⁴⁰ we used LD score regression. Summary statistics for self-reported infectious diseases from more than 200 000 participants in 23andMe included⁴¹ chickenpox, shingles, cold sores, mononucleosis, mumps, hepatitis B, plantar warts, positive tuberculosis test results, *Streptococcus* throat infection, scarlet fever, pneumonia, bacterial meningitis, yeast infections, urinary tract infections, tonsillectomy, childhood ear infections, myringotomy, measles, hepatitis A, rheumatic fever, common colds, rubella, and chronic sinus infection.

Mendelian randomization

We performed 2-sample Mendelian randomization using SNPs associated with specific infection-related traits (ie, $P \leq 5.0 \times 10^{-8}$) as instrumental variables.⁴¹ We analyzed infection-related traits for

which more than 2 SNPs had been shown to be associated with the specific infection (tonsillectomy, mumps infection, childhood ear infection, and yeast infections). To avoid colinearity between SNPs for each trait, we excluded SNPs that were correlated (ie, $r^2 \geq 0.01$) within each trait and only considered the SNPs with the strongest effect on the trait for use as instrumental variables. Where data on an instrumental variable was not present in the outcome trait, a proxy was used ($r^2 > 0.6$). Details of the instrumental variables used are detailed in supplemental Data. For each SNP, we recovered the chromosome position, risk allele, association estimates (per allele log-odds ratio [OR]), and standard errors. The allele that was associated with increased risk for the exposure was considered the effect allele. The ORs of HL, NSHL, and MCHL per unit of standard deviation increment for each infection-related trait were estimated using the Mendelian randomization R package.⁴² Given that traits analyzed are binary outcomes, the maximum likelihood method was employed with the resulting causal effect estimate representing the odds for HL risk per unit increase in the log-OR for infection-related trait.

Results

Association analysis

We analyzed summary level GWAS data generated on HL cases and controls of European ancestry¹¹ from 3 sources (supplemental Tables 1-4): 2 GWAS of UK cases and controls and 1 GWAS of German cases and controls, totaling 3077 cases and 14 546 control patients (Discovery GWAS)¹¹; the Stanford Global Biobank Engine, an analysis of 432 HL cases from the UK Biobank¹³; and a meta-analysis of 3 published HL GWAS totaling 1816 HL cases and 7879 control patients (USC-IARC-UC-GWAS).^{12,25,26}

In a meta-analysis of data from the 7 studies, we identified new genome-wide significant associations for HL (Figure 1; Table 1) at 6p21.31 (rs649775; $P = 2.11 \times 10^{-10}$, marking *ITPR3-UQCC2-IP6K3*), 6q23.3 (rs1002658; $P = 2.97 \times 10^{-8}$, marking *OLIG3-TNFAIP3*), 11q23.1 (rs7111520; $P = 1.44 \times 10^{-11}$, marking *POU2AF1*), 16p11.2 (rs6565176; $P = 4.00 \times 10^{-8}$, marking *MAPK3-CORO1A*), and 20q13.13 (rs2425752; $P = 2.01 \times 10^{-8}$, marking *NCOA5-CD40*). In addition, we identified a promising association at 1p13.2 (rs2476601; $P = 4.20 \times 10^{-7}$, marking *PTPN22*).

The bimodal incidence of HL and the higher rate of NSHL and EBV-negative HL in young adults suggest differences in the etiology of HL subtypes.⁸ Case-only analysis, however, provided no evidence for an age or histological subtype association for the 5 new-risk SNPs. (supplemental Tables 5 and 6).

Cell specificity of associations

Trynka et al have recently shown that chromatin marks highlighting regulatory regions overlap with phenotype-associated variants in a cell-type-specific manner.²⁹ To examine for cell-type specificity of the 5 new and 13 known HL risk loci, we analyzed H3K4me3 and H3K27Ac chromatin marks, which annotate regulatory regions, in more than 125 samples from 38 hematopoietic cell types from BLUEPRINT^{28,29} and the HRS cell line L-428. The H3K27Ac histone mark is predominantly associated with enhancers, and of all the histone marks, it demonstrates the greatest enrichment of promoter-interacting regions.³⁵ The H3K4me3

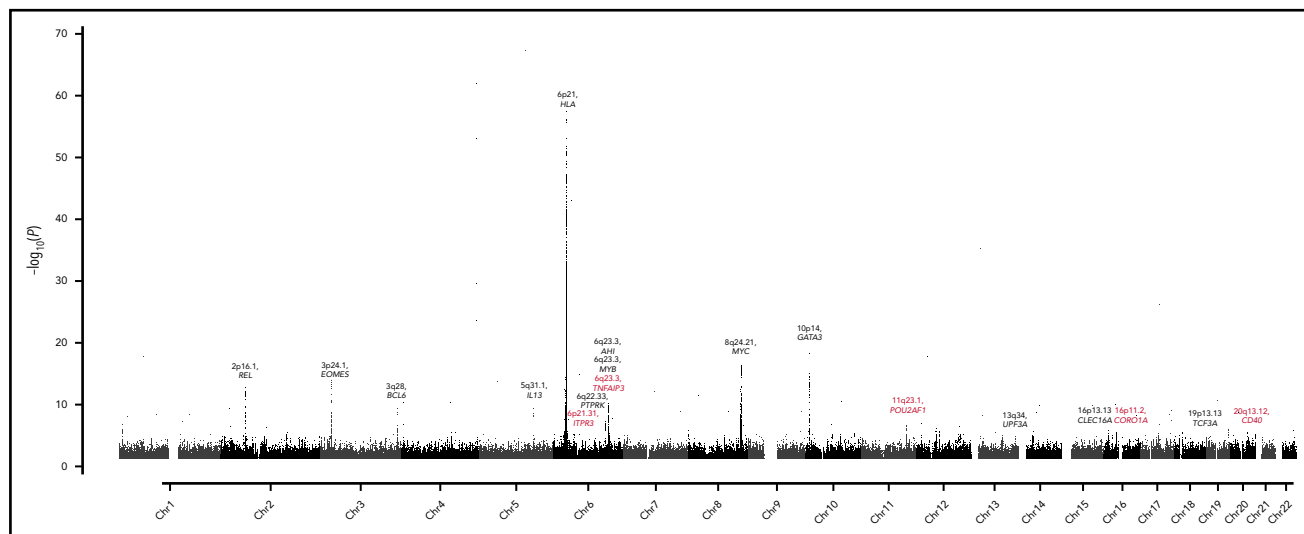


Figure 1. Genome-wide meta-analysis P values of Hodgkin's lymphoma risk ($-\log_{10}P$, y-axis) plotted against their chromosomal positions (x-axis). Novel HL risk loci and candidate gene are in orange.

histone mark is predominantly associated with promoters and transcribed regions and has previously been shown to be the most phenotypically cell-type-specific.^{29,43} Cell types showing the strongest enrichment of risk SNPs at H3K4me3 marks were CD4⁺ T cells from venous blood ($P = 2.9 \times 10^{-3}$), CD3⁺CD4⁺CD8⁺ positive thymocytes ($P = 5.7 \times 10^{-3}$), and tonsillar-derived germinal center B cell ($P = 6.3 \times 10^{-3}$; supplemental Table 7). Cell types with the strongest enrichment of risk SNPs at H3K27Ac marks were CD8⁺ T cells from venous blood ($P = 3.0 \times 10^{-4}$), CD3⁺CD4⁺CD8⁺ thymocytes ($P = 5.6 \times 10^{-4}$), CD4⁺ thymocytes ($P = 2.7 \times 10^{-3}$), and L-428 ($P = 7.9 \times 10^{-3}$; supplemental Table 8). Based on the colocalization of variants with active chromatin marks, we calculated an enrichment score for each genetic association (Figure 2).²⁹ High SNP regulatory scores were also shown in T cells at 3p24.1, 6q22.33, 6q23.3, and 10p14 risk loci; in B cells at 2p16.1, 3q28, 8q24.21, 11q23.1, and 20q13.12 risk loci; and in HRS cells at 3p24.1, 5q31.1, 6q22.33, 6q23.3, 10p14, 13q34 16p13.13, and 20q13.12.

Identification of candidate target genes at HL risk loci

Most GWAS loci map to noncoding regions of the genome and influence gene regulation.⁴⁴ Hence, to gain insight into the biological mechanisms for the associations at the 5 new and 13 known HL risk loci, we first performed expression quantitative trait locus (eQTL) analysis on expression data in B-cell LCLs and in CD4⁺ and CD8⁺ T cells. We identified eQTLs in LCLs at 6p21.31 (*ITPR3*), 6q23.3 (*AH1*, *ALDH8A1*), 10p14 (*GATA3*), 11q23.1 (*COLCA1*, *COLCA2*), 13q34 (*UPF3A*, *CDC16*), 16p13.13 (*SOCS1*), 16p11.2 (*MAPK3*, *BOLA2*), and 20q13.12 (*WFDC10B*); in CD4⁺ T cells at 6q23.3 (*AH1*) and 13q34 (*CDC16*); and in CD8⁺ T cell at 3p24.1 (*EOMES*), 6q23.3 (*AH1*), and 13q34 (*CDC16*; Table 2; supplemental Tables 9 and 10).

Chromatin looping interactions between enhancer elements and promoters are central to regulation of gene expression.⁴⁵ To link risk loci to candidate target genes, we analyzed PCHI-C data. First, we examined physical interactions at genomic regions annotated by HL risk loci (including variants with an $r^2 > 0.8$),

using publicly accessible PCHI-C in naive and total B cells, as well as CD4⁺ and CD8⁺ T cells.³⁵ Second, we generated and analyzed PCHI-C data for the HRS cell line L-428. We observed concordance between H3K27Ac peaks and chromatin contacts in B, T, and HRS cells for specific HL risk loci. Notable chromatin contacts were found in the B lineage at 2p16.1 (*REL*), 6p21.31 (*BAK1*), 8q24.21 (*MYC*, *PVT1*), 13q34 (*RASA3*), 16p13.13 (*RMI2*), and 20q13.12 (*CD40*); in the T-lineage at 3p24.1 (*EOMES*, *AZI2*), 6p21.31 (*BAK1*), 6q22.33 (*THEMIS*, *PTPRK*), 6q23.3 (*MYB*), 13q34 (*RASA3*), and 16p13.13 (*SOCS1*, *RMI2*); and in L-428 at 3p24.1 (*AZI2*, *CMC1*), 6q23.3 (*MYB*), 6q23.3 (*TNFAIP3*), and 16p13.13 (*SOCS1*, *RMI2*; Table 2; supplemental Figure 3; supplemental Data).

Shared susceptibility with infection

The association between EBV with HL, coupled with epidemiological reports of HL also being associated with non-EBV infections,⁴⁶⁻⁴⁹ suggests shared susceptibility a priori. Support for such an assertion is provided by a recent report implicating a number of the HL loci, including 6q23.3, 16p11.2, and 20q13.12, as well as the HLA region, as determinants of risk for infection.⁴¹

To investigate coheritability between HL and susceptibility to infection, we implemented cross-trait LD score regression.⁴⁰ Using summary-level GWAS data, we estimated genetic correlations between HL and more than 20 self-reported infections in 200 000 23andMe participants.⁴¹ Overall, no statistically significant correlation was shown between any specific infection and HL, NSHL, or mixed cellularity HL (supplemental Table 11). Following on from this, for infections with greater than 2 genetically defined instrumental variables, we performed a Mendelian randomization analysis to identify a potential causal relationship with HL. For tonsillectomy, yeast infections, and childhood ear infections, no statistically significant associations were demonstrated (supplemental Table 12). A nominally significant positive association between self-reported mumps infection and HL was found ($P = .04$); however, this was not significant after correction for multiple testing.

Table 1. Summary results for newly identified Hodgkin lymphoma risk loci

| Locus | Nearest genes* | Risk | | Discovery GWAS meta-analysis | | | UK Biobank | | USC-IARC-UC-GWAS | | Meta-analysis | | | |
|---------------------|--------------------------|---------------|---------------------|------------------------------|------------------|-------------------------|------------|------------------|-------------------------|-------------------|--------------------------|------------------|------------------|------------------|
| | | Allele (freq) | Position (hg19, bp) | P | OR (95% CI) | P | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | I ² % | P _{het} |
| 1p13.2, rs2476601 | PTPN22 | A (0.12) | 114377568 | 3.92 × 10 ⁻³ | 1.15 (1.04-1.26) | 3.21 × 10 ⁻⁴ | — | 1.42 (1.17-1.72) | 3.70 × 10 ⁻³ | 1.24 (1.07-1.44)† | 4.20 × 10 ⁻⁷ | 1.21 (1.12-1.30) | 20 | .29 |
| 6p21.31, rs649775 | ITPR3- UQC2- IP6K3 | A (0.11) | 33684313 | 4.00 × 10 ⁻⁶ | 1.25 (1.14-1.38) | — | — | — | 8.22 × 10 ⁻⁶ | 1.36 (1.19-1.55) | 2.11 × 10 ⁻¹⁰ | 1.29 (1.19-1.40) | 0 | .54 |
| 6q23.3, rs1002658 | OLIG3- TNFAIP3 | T (0.18) | 137981584 | 3.86 × 10 ⁻⁶ | 1.19 (1.11-1.28) | — | — | — | 2.15 × 10 ⁻³ | 1.18 (1.06-1.31) | 2.97 × 10 ⁻⁸ | 1.19 (1.12-1.26) | 0 | .53 |
| 11q23.1, rs7111520 | POU2AF1 | A (0.70) | 111249611 | 4.33 × 10 ⁻⁷ | 1.17 (1.10-1.24) | — | — | — | 4.39 × 10 ⁻⁶ | 1.24 (1.13-1.35) | 1.44 × 10 ⁻¹¹ | 1.19 (1.13-1.25) | 0 | .68 |
| 16p11.2, rs6565176 | MAPK3- CORO1A | T (0.48) | 30174926 | 8.64 × 10 ⁻⁶ | 1.14 (1.08-1.21) | 3.44 × 10 ⁻⁴ | — | 1.28 (1.10-1.23) | — | — | 4.00 × 10 ⁻⁸ | 1.16 (1.10-1.22) | 0 | .46 |
| 20q13.12, rs2425752 | NCOA5- CD40 | T (0.23) | 44702120 | 2.23 × 10 ⁻⁴ | 1.13 (1.06-1.20) | 2.94 × 10 ⁻⁴ | — | 1.30 (1.12-1.50) | 3.77 × 10 ⁻³ | 1.14 (1.09-1.20) | 2.01 × 10 ⁻⁸ | 1.15 (1.10-1.21) | 56 | .06 |

freq, frequency; I², proportion of the total variation resulting from heterogeneity.
*Genes at each risk locus are given for identification purposes only and does not necessarily indicate biological functionality.
†Summary statistics from 1200 patients with cHL and 6417 control patients.²⁶

Table 2. Integration of expression quantitative trait loci, histone modification, promoter capture Hi-C data at non-HLA Hodgkin lymphoma risk loci to identify candidate causal genes at Hodgkin lymphoma risk loci

| Locus | Sentinel SNP | Position, (bp, hg19) | Gene(s) in LD block | Coding variant(s) | Promoter/UTR variant(s) | Expression quantitative trait loci in LCLs | Expression quantitative trait loci in T cell | H3K27Ac histone peak* | Hi-C contact(s) in naive or total B cells | Hi-C contact(s) in T cells | Hi-C contact(s) in HRS cell | Evidence of perturbation in HL | Candidate biological mechanism |
|---------|--------------|----------------------|---------------------|-------------------|-------------------------|--|---|--|---|---|-----------------------------|--------------------------------|---|
| 2p16.1 | rs2420518 | 61054980 | | | | | | Naive B cell | REL | REL | | REL ⁸⁴ | Constitutive NF-κB activation (REL) ⁷² . Altered B-cell differentiation and germinal center reaction (REL) ⁹⁰ |
| 3p24.1 | rs3806624 | 27764623 | EOMES | | EOMES, (3'-UTR) | | EOMES (t) (CD8 ⁺) | Effector memory CD8 ⁺ T cell, plasma cell, L-428 | AZI2, CMC1, NEK10, OXSM, NGLY1, ZCWPW2 | EOMES, AZI2, CMC1, NEK10, OXSM, NGLY1, ZCWPW2 | AZI2, CMC1 | EOMES ⁸⁵ | Exhausted CD8 T-cell phenotype (EOMES) ^{81,82} . Constitutive NF-κB activation (AZI2) ⁷³ |
| 3q28 | rs4459895 | 187954414 | LPP | | | | | CD38 ⁺ naive B cell, naive B cell, germinal center B cell, L-428 | | | | BCL6 ⁸⁴ | Dysfunction of B-cell germinal center reaction (BCL6, mir-28) ^{51,52} |
| 5q31.1 | rs848 | 131996500 | IL-13 | (p.Gln144Arg) | IL-13, (3'-UTR) | | | L-428 | | | | IL-13 ⁹⁰ | Altered CD4 ⁺ T-cell function (IL-13) ⁹² |
| 6p21.31 | rs649775 | 33684313 | ITPR3, UQC22, ITPK3 | | ITPK3, (3'-UTR) | ITPR3 (t) | | CD4 ⁺ T cell, CD8 ⁺ T cell, effector memory CD8 ⁺ T cell, naive B cell, class-switched memory B cell | BAK1, SYNGAP1, GGNBP1, LINC00336 | BAK1, GRM4, SYNGAP1, KIFC1, CUTA, PHF1, GGNBP1, LINC00336 | | | Altered B-cell differentiation (ITPR3) ⁸⁸ |
| 6q22.33 | rs9482849 | 128288536 | PTPRK | | | | | CD4 ⁺ T cell, central memory CD4 ⁺ T cell, CD8 ⁺ T cell, effector memory CD8 ⁺ T cell, L-428 | PTPRK, THEMIS | | | PTPRK ⁸⁹ | Altered T-cell differentiation (PTPRK, THEMIS) ^{83,84} |
| 6q23.3 | rs9402684 | 135419305 | HBS1L | | | | | CD3 ⁺ CD4 ⁺ CD8 ⁺ thymocyte, CD3 ⁺ CD4 ⁺ CD8 ⁺ thymocyte, CD4 ⁺ T cell, central memory CD4 ⁺ T cell, effector memory CD8 ⁺ T cell, germinal center B cell, plasma cell, L-428 | MYB, | | MYB, | | Altered T-cell differentiation (MYB) ^{85,86} . Altered B-cell differentiation and germinal center reaction (MYB) ⁸⁴ |
| 6q23.3 | rs6928977 | 135626348 | AHI1 | | | AHI1 (t), ALDH8A1 (t) | AHI1 (CD4 ⁺ and CD8 ⁺) (t) | CD3 ⁺ CD4 ⁺ CD8 ⁺ thymocyte | | | | | Altered T-cell differentiation (AHI1) ⁸⁶ |
| 6q23.3 | rs1002658 | 137981584 | | | | | | L-428 | RP11-204P2.3 | | TNFAIP3, | TNFAIP3 ⁷⁸ | Constitutive NF-κB activation (TNFAIP3) ⁸⁴ |
| 8q24.21 | rs34748721 | 129195943 | | | | | | naive B cell, class switched memory B cell | CASC11, MYC, PVT1, RNU1-108P, MIR1207 | | | MYC ⁹¹ | Dysfunction of B-cell germinal center reaction (MYO) ^{85,86} |

*SNPs ($r^2 < 2.5$ kilobases from ChIP-seq peak).

Table 2. (continued)

| Locus | Sentinel SNP | Position, (bp, hg19) | Gene(s) in LD block | Coding variant(s) | Promoter/UTR variant(s) | Expression quantitative trait loci in LCLs | Expression quantitative trait loci in T cell | H3K27Ac histone peak* | Hi-C contact(s) in naive or total B cells | Hi-C contact(s) in T cells | Hi-C contact(s) in HRS cell | Evidence of perturbation in HL | Candidate biological mechanism |
|----------|--------------|----------------------|---------------------|-------------------|-------------------------|--|---|--|---|---|-----------------------------|---|--|
| 10p14 | rs2388486 | 8099021 | GATA3 | | | GATA3(l) | | CD3 ⁺ CD4 ⁺ CD8 ⁺ thymocyte, CD3 ⁺ CD4 ⁺ CD8 ⁺ thymocyte, CD4 ⁺ T cell, CD8 ⁺ T cell, effector memory CD8 ⁺ T cell, germinal center B cell | | | | GATA3 ⁹² | Altered T-cell differentiation (GATA3) ⁹⁷ |
| 10p14 | rs3781093 | 8101927 | GATA3 | | | GATA3 (l) | | CD4 ⁺ T cell, CD8 ⁺ T cell | | | | GATA3 | Altered CD4 ⁺ T-cell differentiation (GATA3) ⁹⁷ . Altered B-cell differentiation (GATA3) ⁹⁵ |
| 11q23.1 | rs7111520 | 111249611 | POU2AF1 | | | COLCA1 (t), COLCA2 (t) | | CD4 ⁺ T cell, central memory CD4 ⁺ T cell, CD8 ⁺ T cell, CD38 ⁺ B cell, CD38 ⁺ naive B cell, naive B cell, germinal center B cell, unswitched memory B cell, class switched memory B cell, plasma cell | FDX1 | FDX1, PPP3R1B, ALG9, FDXACB1, DIXDC1 | | POU2AF1 ⁹⁴ | Dysfunctional germinal center reaction (POU2AF1) ⁹⁶ |
| 13q34 | rs112998813 | 115059729 | UPF3A | | | CDC16 (t), UPF3A (l) | CDC16 (CD4 ⁺ and CD8 ⁺ T) | CD4 ⁺ T cell, central memory CD4 ⁺ T cell, CD8 ⁺ T cell, effector memory CD8 ⁺ T cell, CD38 ⁺ naive B cell, naive B cell, germinal center B cell, unswitched memory B cell, class-switched memory B cell, plasma cell | | RASA3, TMEM255B, GAS46 | | CDC16 ⁹⁵ | Disrupted cell cycle regulation (CDC16) ⁹⁵ . Dysfunction of mRNA surveillance (UPF3A) ⁹⁶ |
| 16p13.13 | rs34972832 | 11198938 | CLEC16A | | | SOCST1 (t) | | CD4 ⁺ T cell, central memory CD4 ⁺ T cell, CD8 ⁺ T cell, effector memory CD8 ⁺ T cell, naive B cell, germinal center B cell, class switched memory B cell, plasma cell, L-424 | RM12 | SOCST1, RM12, PRM2, PRM3, TNF2, HNRNPC4 | SOCST1, RM12 | SOCST1 ⁹⁰ | T-cell dysfunction (SOCST1) ⁹⁰ . Altered T-cell differentiation (CLEC16A) ⁹⁰ . B-cell dysfunction (CLEC16A) ⁹⁷ . Genomic instability (RM12) ⁹⁸ |
| 16p11.2 | rs6565176 | 30174926 | CORO1A | | CORO1A (5'-UTR) | MAPK3 (l), BOLA2 (l) | | CD4 ⁺ T cell, CD8 ⁺ T cell, effector memory CD8 ⁺ T cell, naive B cell, class-switched memory B cell | | | | MAPK3 ⁹⁹ , CORO1A ¹⁰⁰ | T-cell dysfunction (CORO1A and MAPK3) ^{99,100,101} . Dysfunction of B-cell germinal center reaction (MAPK3) ^{99,101,102} |
| 19p13.3 | rs2012125 | 1630341 | TCF3A | | | | | CD38 ⁺ B cell, naive B cell, class-switched memory B cell | | | | | Dysfunction of B-cell germinal center reaction (TCF3A) ¹⁰³ |
| 20q13.12 | rs2425752 | 44702120 | NCOA5, CD40 | | | WFDC108 (t) | | Central memory CD4 ⁺ T cell, CD8 ⁺ T cell, effector memory CD8 ⁺ T cell, naive B cell, germinal center B cell, L-428 | CD40 | TP53RK | | CD40 ¹⁰⁴ | Dysfunctional germinal center reaction (CD40) ^{98,104} . Constitutive NF-κB activation (CD40) ^{93,96} |

*SNPs ($r^2 < 2.5$ kilobases from ChIP-seq peak).

had limited power. It is, however, possible that pleiotropism between the 6p21.1, 6q23.3, 16p11.2, and 20q13.12 risk loci for HL and tonsillectomy is consistent with some form of a shared biological basis. This is intriguing, as tonsillectomy has previously been linked to HL in some epidemiological observational studies.⁴⁶

In summary, our study provides further evidence for inherited susceptibility to HL and support for cell-type specificity at HL risk loci. Furthermore, through the integration of gene expression, histone modification and *in situ* PCHi-C data, our data highlight dysfunction of the germinal center reaction, perturbed T-cell function, and constitutive NF- κ B activation as mechanisms by which genetic risk loci influence HL pathogenesis.

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Authorship

Contribution: A.S., K.H., and R.S.H. designed and provided overall project management; A.S. and R.S.H. drafted the manuscript; A.J.S., N.O., and R.S.H. provided samples for UK-GWAS and UK-NSHLG-GWAS;

D.F.E., P.D.P.P., A.M.D., J.P., F.C., R.E., Z.K.-J., K.M., N.P., and D.C. provided control samples for the UK-NSHLG-GWAS; A.S. and P.J.L. performed bioinformatic and statistical analysis; A.S. and P.B. performed sample and laboratory coordination; A.S. and R.C. provided clinical data on the UK samples; A.S. and G.O. performed capture Hi-C experiments; F.H. and T.P. performed ChIP-seq experiments; H.T. and A.F. performed bioinformatic and statistical analyses; P.H. and M.M.N. were responsible for German-GWAS analysis; K.-H.J. provided the German control samples; and E.P.v.S. and A.E. were responsible for German patients with HL.

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Footnotes

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ChIP-seq data from the Blueprint Epigenome Consortium are available from <http://dcc.blueprint-epigenome.eu/#/home>.

Hi-C data from the Blueprint Epigenome Consortium are available from <https://osf.io/u8tzip/>.

ChIP-seq data for the HRS cell line L-428 are deposited under the accession number EGAS00001003033.

Hi-C data for the HRS cell line L-428 are deposited in the European Genome-Phenome Archive under accession number EGAS00001003032.

Summary statistics for genetic susceptibility to infection-related traits are available upon request from 23andMe. Please visit [research/23andme.com/collaborate](http://research.23andme.com/collaborate) to request access to these datasets.

The online version of this article contains a data supplement.

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