Genome-wide association study of classical Hodgkin lymphoma identifies key regulators of disease susceptibility

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Several susceptibility loci for classical Hodgkin lymphoma have been reported. However, much of the heritable risk is unknown. Here, we perform a meta-analysis of two existing genome-wide association studies, a new genome-wide association study, and replication totalling 5,314 cases and 16,749 controls. We identify risk loci for all classical Hodgkin lymphoma at 6q22.33 (rs9482849, \( P = 1.52 \times 10^{-8} \)) and for nodular sclerosis Hodgkin lymphoma at 3q28 (rs4459895, \( P = 9.43 \times 10^{-17} \)), 6q23.3 (rs6928977, \( P = 4.62 \times 10^{-11} \)), 10p14 (rs3781093, \( P = 9.49 \times 10^{-13} \)), 13q34 (rs112998813, \( P = 4.58 \times 10^{-8} \)) and 16p13.13 (rs34972832, \( P = 2.12 \times 10^{-8} \)). Additionally, independent loci within the HLA region are observed for nodular sclerosis Hodgkin lymphoma (rs9269081, HLA-DPB1*03:01, Val86 in HLA-DRB1) and mixed cellularity Hodgkin lymphoma (rs1633096, rs13196329, Val86 in HLA-DRB1). The new and established risk loci localise to areas of active chromatin and show an over-representation of transcription factor binding for determinants of B-cell development and immune response.
Classical Hodgkin lymphoma (cHL) is a lymphoid malignancy of germinal centre (GC) B-cell origin, which is characterised by Hodgkin and Reed–Sternberg (HRS) cells with a dominant background population of reactive inflammatory cells. Of the four major subtypes of cHL, nodular sclerosis Hodgkin lymphoma (NSHL) and mixed cellularity Hodgkin lymphoma (MCHL) account for 65% and 20% of cHL, respectively. While Epstein–Barr virus (EBV) infection is causally associated with a subset of cHL cases, proportionally higher in MCHL, no other environmental factor has thus far been robustly linked to cHL risk.

Evidence for inherited genetic influence on susceptibility to cHL is provided by the familial risk and the high concordance power of published studies is limited. Although projections indicate that additional non-HLA loci account for 65% and 20% of cHL, respectively. Results

Association analysis. We analysed GWAS data from three studies of European ancestry: a new GWAS from the UK National Study of Hodgkin Lymphoma Genetics (NSHLG) and two previously reported GWAS (Supplementary Table 1). After quality control the three studies provided SNP genotypes on 3,077 cases and 13,680 controls (Supplementary Tables 2, 3, 4; Supplementary Fig. 1). To increase genomic resolution, we imputed >10 million SNPs using the 1000 Genomes Project and the UK10K data as reference. Quantile–quantile (Q–Q) plots for SNPs with minor allele frequency (MAF) > 0.05% post imputation did not show evidence of substantive over-dispersion (λ ~ 1.03–1.09; Supplementary Fig. 2). An overview of the analysis strategy is outlined in Supplementary Fig. 3. Meta-analysing the association test results from the three GWAS into a joint discovery set, we calculated joint odds ratios and 95% confidence intervals for each SNP and associated per-allele P-value for all cHL, NSHL and MCHL cases vs. controls (Supplementary Fig. 4).

In this analysis, associations for the established non-HLA risk loci at 2p16.1, 3p24.1, 5q31.1, 6q23.3, 6q24.21, 10p14 and 19p13 were consistent in direction and magnitude of effect with previously reported studies (Supplementary Fig. 4; Supplementary Table 5).

We sought validation of association SNPs with a P-value from the meta-analysis under a fixed-effects model at P < 1.0 × 10^{-7} and P < 1.0 × 10^{-6} for loci not previously associated with cHL and NSHL risk, respectively, by genotyping two additional independent series (Supplementary Table 1), totalling 2,237 cases and 3,069 controls (Table 1; Supplementary Table 6). Where the strongest signal was provided by an imputed SNP, we confirmed the fidelity of imputation by genotyping (Supplementary Table 7). In the combined meta-analysis, we identified genome-wide significant associations for cHL (Table 1; Supplementary Tables 8 and 9), at 3q28 (rs4459895, P = 4.45 × 10^{-18}), 6q22.33 (rs9482849, P = 1.52 × 10^{-10}), 6q23.3 (rs6928977, P = 1.24 × 10^{-10}) and 10p14.

### Table 1 Summary results for newly identified risk loci

| Nearest gene | Risk allele (frequency) | Discovery GWAS meta-analysis | UK Replication 1 | UK Replication 2 | Meta-analysis |
|--------------|-------------------------|-------------------------------|------------------|------------------|-------------|
|              |                         | P-value OR (95% CI)           | P-value OR (95% CI) | P-value OR (95% CI) | P-value OR (95% CI) |
| rs3781093    |                         |                               |                   |                   |             |
| rs6928977    |                         |                               |                   |                   |             |
| rs9482849    |                         |                               |                   |                   |             |
| rs4459895    |                         |                               |                   |                   |             |

The risk allele is the allele corresponding to the estimated odds ratio. Frequency of the risk allele is from the CEU population from 1000 Genomes Project.

### Table 2

| Position | Discovery GWAS meta-analysis | UK Replication 1 | UK Replication 2 | Meta-analysis |
|----------|-----------------------------|------------------|------------------|-------------|
|          | P-value OR (95% CI)         | P-value OR (95% CI) | P-value OR (95% CI) | P-value OR (95% CI) |
| rs3781093| rs4459895                  | 4.16 × 10^{-10}  | 6.85 × 10^{-9}   | 4.45 × 10^{-10} |
| rs6928977| rs9482849                  | 5.02 × 10^{-8}   | 1.10 × 9.10^{-6} | 1.52 × 10^{-8} |
| rs9482849| rs4459895                  | 2.91 × 10^{-6}   | 0.78 = 1.06 (0.70-1.61) | 0.39 |
| rs4459895| rs9482849                  | 1.66 × 10^{-8}   | 0.01 = 1.14 (1.03-1.36) | 0.85 |
| rs9482849| rs4459895                  | 9.34 × 10^{-10}  | 0.03 = 1.10 (1.02-1.24) | 0.04 |
| rs4459895| rs9482849                  | 2.48 × 10^{-12}  | 0.11 = 1.32 (1.25-1.44) | 64.01 |
| rs9482849| rs4459895                  | 1.96 × 10^{-12}  | 0.00 = 1.16 (1.05-1.4) | 0.01 |
| rs4459895| rs9482849                  | 8.34 × 10^{-10}  | 0.03 = 1.12 (1.3-1.65) | 0.04 |
| rs9482849| rs4459895                  | 0.92 = 0.99 (0.80-1.22) | 0.16 | 0.01 |
| rs4459895| rs9482849                  | 1.45 × 10^{-8}   | 1.15 (1.07-1.23)   | 0.03  |
| rs9482849| rs4459895                  | 7.47 × 10^{-7}   | 1.10 (1.05-1.34)   | 0.09  |
| rs4459895| rs9482849                  | 6.45 × 10^{-7}   | 1.07 (1.05-1.34)   | 0.13  |
| rs9482849| rs4459895                  | 1.66 × 10^{-10}  | 1.15 (1.07-1.23)   | 0.03  |
| rs4459895| rs9482849                  | 2.48 × 10^{-12}  | 1.15 (1.07-1.23)   | 0.01  |
| rs9482849| rs4459895                  | 1.96 × 10^{-12}  | 1.15 (1.07-1.23)   | 0.04  |
| rs4459895| rs9482849                  | 8.34 × 10^{-10}  | 1.15 (1.07-1.23)   | 0.04  |
| rs9482849| rs4459895                  | 0.92 = 0.99 (0.80-1.22) | 0.16 | 0.01 |
| rs4459895| rs9482849                  | 1.45 × 10^{-8}   | 1.15 (1.07-1.23)   | 0.03  |
| rs9482849| rs4459895                  | 7.47 × 10^{-7}   | 1.15 (1.07-1.23)   | 0.09  |
| rs4459895| rs9482849                  | 6.45 × 10^{-7}   | 1.15 (1.07-1.23)   | 0.13  |

The nearest gene may not be the functional gene.
Relationship between the new risk SNPs and phenotype. A hallmark of cHL epidemiology is the bimodal age-specific incidence and it has been argued that the disease in young adults and older adults is aetiologically different; in particular there is a low incidence and it has been argued that the disease in young adults and observed in HRS cells20, 21. Intriguingly, the rs3781093 risk allele is associated with intron 3 of AHI1 and T-cell lymphoma14, 15. The 13q34 association marked by rs3781093 maps intronic of GATA3 and is therefore strong candidates for cHL susceptibility. Hence, to gain insight into the biological function of these new risk SNPs, we interrogated publicly accessible expression data on lymphoblastoid cell lines (LCLs)16, 17. We used the summary data-based Mendelian randomisation (SMR) analysis to test for pleiotropy between GWAS signal and cis-expression quantitative trait (eQTL) for genes within 1 Mb of the sentinel SNP at each locus to identify a causal relationship25. At 6q23.3 and 10p14, significant eQTLs were observed with AH11 (P_SMR = 8.63 × 10⁻⁶; Supplementary Table 11 and Supplementary Fig. 5) and GATA3 (P_SMR = 4.70 × 10⁻⁵; Supplementary Table 11 and Supplementary Fig. 5).

Since spatial proximity between specific genomic regions and chromatin looping interactions are central for the regulation of gene expression, we identified patterns of chromatin interactions at candidate causal SNPs by analysing promoter capture Hi-C data on GM12878 as a source of B-cell information26. Looping chromatin interactions were shown at 3q28 (rs4459895), 6q23.3 (rs6928977), 10p14 (rs3781093) and 16p13.13 (rs34972832). While no significant eQTL was shown for these chromatin looping interactions they involved a number of genes with biological relevance to cHL development (Fig. 1). At 3q28, the looping interaction implicates BC6 and mir-28, which have well documented roles in B-cell tumour biology and GC B-cell development27, 28. At 6q23.3, we observed interactions with promoter sequences upstream in MYB and ALDH8A1. At 10p14, both risk SNPs encompass a region that interacts with TAF3, which encodes transcriptional initiation factor TFIIID subunit 3. TAF3 forms part of the transcription initiation factor TFIIID and is necessary for haematopoiesis29. Finally, we observed interactions at the 16p13.13 risk locus with RMI2 (encoding RecQ mediated genome instability 2) (Fig. 1). RMI2 is an essential component of the Bloom helicase-double Holliday junction dissolvosome and is responsible for genomic stability30.

Across the new and established risk loci for cHL we confirmed a significant enrichment of DNase hypersensitivity in GM12878 cells (false discovery rate (FDR) adjusted P-value = 0.0035), as well as enhancer elements in primary B-cells (FDR adjusted P-value = 0.00064) and GM12878 cells (FDR adjusted P-value = 0.015)31. Analysis of ChIP-seq data on 82 transcription factors (TFs) showed an over-representation of the binding of TFs that play a central role in B-cell signalling-networks such as RELA (nuclear factor NF-kappa-B p65), EBF1 (early B-cell factor 1), RUNX3 (runt-related transcription factor 3) and BATF (basic leucine zipper transcription factor, ATF-like) (Fig. 2). Collectively, these observations support the assertion that risk loci for cHL mediate their effects through B-cell developmental networks, and are strongly involved in transcriptional initiation and enhancement.

Biological inference. Five of the six new risk SNPs localise in or near genes which have either been previously implicated in the development of cHL or have established roles in B-cell development and are therefore strong candidates for cHL susceptibility. Specifically, the 6q22.33 association marked by rs9482849 maps intergenically to THEMIS (thymocyte-expressed molecule involved in selection) and PTPRK (receptor-type tyrosine protein phosphatase kappa) (Fig. 1). Downregulation of PTPRK by the EBV-encoded EBNA1 contributes to the growth and survival of HRS cells13. The 6q23.3 association defined by rs6928977 localises to intron 3 of AHI1 (abelson helper integration site-1) (Fig. 1) which has been implicated in the development of both B- and T-cell lymphoma14, 15. The 13q34 association marked by rs112998813 is located in intron 5 of UPE3A (Fig. 1), a regulator of nonsense transcripts16. The LD region of association also harbours CDC16 (cell division cycle protein 16). CDC16, a subunit of the anaphase-promoting complex17, targets cell cycle regulatory proteins for proteasome degradation, thereby allowing cell cycle progression, and is downregulated in HRS cells18. At 16p13.13, the rs34972832 association for NSHL maps to intron 18 of CLEC16A (C-type lectin domain family 1, Fig. 1) whose loss of function affects both B-cell number and function19. The 10p14 association marked by rs3781093 maps intronic of GATA3 (Fig. 1). Transcriptional repression of GATA3 is essential for early B-cell commitment, and aberrant GATA3 expression has been observed in HRS cells20, 21. Intriguingly, the rs3781093 risk allele for NSHL has previously been demonstrated to be protective for paediatric B-cell acute lymphoblastic leukaemia (ALL)22.

To the extent that they have been deciphered, many GWAS risk loci map to non-coding regions of the genome and influence gene regulation. Hence, to gain insight into the biological mechanisms for the associations of the newly identified risk SNPs, we interrogated publicly accessible expression data on lymphoblastoid cell lines (LCLs)23, 24. We used the summary data-based Mendelian randomisation (SMR) analysis to test for pleiotropy between GWAS signal and cis-expression quantitative trait (eQTL) for genes within 1 Mb of the sentinel SNP at each locus to identify a causal relationship25. At 6q23.3 and 10p14,
**Fig. 1** Regional plots of association results and recombination rates for the newly identified classical Hodgkin lymphoma (NSHL) risk loci. Results for a 3q28 (rs4459895) and nodular sclerosis Hodgkin lymphoma (NSHL) risk, b 6q22.33 (rs9482849) and classical Hodgkin lymphoma (cHL) risk, c 6q23.3 (rs6928977) and NSHL risk, d 10p14 (rs3781093) and NSHL risk, e 13q34 (rs112998813) and NSHL risk, and f 16p13.13 (rs34972832) and NSHL risk. Plots show association results of both genotyped (triangles) and imputed (circles) single-nucleotide polymorphisms (SNPs) in the genome-wide association study samples and recombination rates. $-\log_{10} P$-values ($y$-axes) of the SNPs are shown according to their chromosomal positions ($x$-axes). The sentinel SNP in each combined analysis is shown as a large circle or triangle and is labelled by its rsID. The colour intensity of each symbol reflects the extent of LD with the top SNP, white ($r^2 = 0$) through to dark red ($r^2 = 1.0$). Genetic recombination rates, estimated using 1000 Genomes Project samples, are shown with a light blue line. Physical positions are based on NCBI build 37 of the human genome. Also shown are the relative positions of genes and transcripts mapping to the region of association. Genes have been redrawn to show their relative positions; therefore maps are not to physical scale. The middle track represents the chromatin state segmentation track (ChromHMM) for lymphoblastoid cells using data from the HapMap ENCODE Project. The top track represents capture Hi-C promoter contacts in GM12878 cells. The colour intensity of each contact reflects the interaction score.
The physical chromosomal position. The physical positions are based on NCBI build 36 of the human genome. The region.

(b2) Results of the HLA region after conditioning on rs1633096. (b3) Results of the HLA region after conditioning on rs1633096 and rs13196329. (a3) Results of the HLA region after conditioning on rs9269081 and HLA-DPB1*03:01. (b1) Unconditioned test of the HLA region. (a2) Results of the HLA region.

Co-heritability with autoimmune disease. Although not universal, some epidemiological studies have reported associations between cHL and various autoimmune diseases, raising the possibility of common genetic susceptibility and hence common

Environmental interactions having an impact on cHL risk. The currently identified non-HLA risk loci thus only account for around 12% of the additive heritable risk.

Discussion

To our knowledge, we have performed the largest GWAS of cHL to date, identifying six new non-HLA risk loci. The availability of comprehensive reference panels for the HLA region has allowed us to delineate class I and class II associations for NSHL and MCHL, substantiating recent documented differences between these cHL histologies.

Although functional analyses are required to determine the biological basis of HLA association signals, we have demonstrated that these risk loci are enriched for regulatory elements in B-cells. Moreover, they feature an over-representation of key B-cell TF binding, notably RELA, RUNX3, EBF1 and BATF. RELA is a TF involved in NF-κB heterodimer formation. HRS cells show high constitutive activity of NF-κB (both canonical and non-canonical pathways), which promotes cell survival and growth through inducing anti-apoptotic and pro-proliferative gene programs. Inhibition of NF-κB in HRS cells leads to caspase-independent apoptosis. EBF1 cooperates with E2A and PAX5 to regulate B-cell maturation. Its expression in HRS cells is low, which is thought to contribute to the loss of normal B-cell phenotype. RUNX3 has important roles in B-cell maturation and down-regulation of RUNX1 by RUNX3 is required for EBV-driven LCL

Fig. 1 Manhattan plot representation of the step-wise conditional logistic regression of risk of a nodular sclerosis Hodgkin lymphoma and b mixed cellularity Hodgkin lymphoma within the human leukocyte antigen (HLA) region. (a) Unconditioned test of the HLA region. (a2) Results of the HLA region after conditioning on rs9269081. (a3) Results of the HLA region after conditioning on rs9269081 and HLA-DPB1*03:01. (b1) Unconditioned test of the HLA region. (b2) Results of the HLA region after conditioning on rs1633096. (b3) Results of the HLA region after conditioning on rs1633096 and rs13196329. Physical positions are based on NCBI build 36 of the human genome. The \(-\text{log}_{10} P\) values are plotted against their physical chromosomal position. The broken red line represents the genome-wide level of significance (P < 5 × 10^{-8})

\(P = 0.04\) and a negative correlation between cHL and UC (\(r_g = -0.23, P = 0.01\)).

\(P = 0.035, P = 0.04\) and a negative correlation between cHL and UC (\(r_g = -0.23, P = 0.01\)).
growth. BATF also appears to co-ordinate B-cell maturation, and is highly expressed in HRS cells.

The strong HLA associations we identified for NSHL and MCHL support recent observations for distinct class I and class II relationships for these B-cell subtypes. Specifically, the class II NSHL association marked by rs9269081 is in strong LD with the previously identified risk SNP rs6903608 (r² = 0.92, D’ = 1.0) for EBV-negative NSHL. For MCHL the class I association rs1633096 shows correlation with the previously identified marker SNP rs2734986 (pairwise r² = 0.41, D’ = 0.97) for EBV-positive cHL. A class I association for MCHL is consistent with a high EBV positivity and supports the notion of defective cytotoxic T-cell lymphocyte responses in EBV-infected HRS cells. Variation within the class I HLA region alters the risk of autoimmune diseases, but the underlying biological mechanism of these associations has yet to be fully defined. The class II HLA association for NSHL and MCHL risk, comprising both coding variants and non-coding SNPs, may explain the importance of CD4+ T follicular helper (Tfh) cells in cHL pathogenesis. In the GC, there is a requirement for CD4+ Tfh cells to interact with GC B-cells through the Tfh-cell antigen receptor (TCR) and HLA class II proteins for normal plasma and memory cells formation.

It is therefore plausible that variation in peptide binding and expression of the HLA class II proteins contributes to cHL pathogenesis through interaction with CD4+ Tfh cells. Such a model is supported by the observation of variation at position 86 of HLA-DRB1 influencing TCR Vα gene expression, the predominance of CD4+ T-cells in cHL tumours, the reliance of HRS cells on the micro-environment for survival, and the loss of MHC class II expression on HRS cells, the last of which is associated with adverse prognosis. An alternative explanation for the class II HLA association in cHL is the involvement of an unidentified pathogen playing a causative role in cHL. Amino-acid variants and SNPs within HLA-DRB1 modulate humoral immune responses to common viruses, such as influenza A and JC polyomavirus.

Consistent with such a model, dimorphic variation at position 86 of HLA-DRB1, which we identify as influencing risk of NSHL and MCHL, modulating the anchoring pocket of the antigen binding site, and influencing the conformation of peptide–DR protein complexes while maintaining a T-cell response.

In our analysis we noted a reciprocal relationship between NSHL risk and ALL risk at 10p14, which are malignancies derived from B-cells at different stages of maturation, and cell proliferation. Our observation leads to speculation of a significant temporal effect of genetic variation at this locus in response to an environmental or mutational insult.

Although supported by a contemporaneous study and requiring further validation, we found evidence for common genetic susceptibility between cHL and MS, thus raising the possibility of shared environmental risk factors. A potential biological basis for susceptibility between cHL and MS, thus raising the possibility of subtypes, which are reflective of differences in tumour aetiology.

**Methods**

**Ethics.** Collection of patient samples and associated clinico-pathological 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-NSHL GREC 09/MREC0072). The diagnosis of cHL (i.e., excluding cases with nodular lymphocyte predominant HLN), NSHL and MCHL (ICD-10-CM 041.1-3) in all cases was established in accordance with World Health Organisation guidelines.

**Genome-wide association studies.** Primary study: We analysed constitutional DNA from 1,171 cases ascertained through the NSHLG (http://www.pub.ukcrn.org.uk) from 2010 to 2013. These are detailed in Supplementary Table 1. Cases were genotyped using the Illumina Oncosarray (Illumina Inc.). Controls which were also genotyped using the oncoarray comprised: (1) 2,976 cancer-free men recruited from the UK-TCGA Consortium (UK-TCGA); (2) UK General Prostate Cancer Study (UKGPCS) (age < 65 years, a study conducted through the Royal Marsden NHS Foundation Trust and SEARCH (Study of Epidemiology & Risk Factors in Cancer), recruited via GP practices in East Anglia (2003–2009), (2) 4,446 cancer-free women from across the UK via the Breast Cancer Association Consortium (BCAC). GWAS studies: We used GWAS data generated in two case-control series of Northern European ancestry, which have been the subject of previous analyses that are summarised in Supplementary Table 1. Briefly: (1) The UK-GWAS was based on 622 cases ascertained through the Royal Marsden Hospital National Health Service Trust Family History study during 2004–2008, and 5,677 controls from the UK Wellcome Trust Case Control Consortium 2 (WTCCC2) and (2) the German-GWAS comprised 1,001 cases ascertained by the German Hodgkin Study Group during 1998–2007, and 1,226 controls from the Heinz Nixdorf Recall (HNR) study.

**GWAS and meta-analysis.** Standard quality control measures were applied to each of the three GWAS (Supplementary Tables 2, 3 and 4), which, specifically, individuals with a low call rate (<95%) as well as all individuals evaluated to be of non-European ancestry (using UCSC Genome Browser and the 1000 Genomes Project). GWAS data were imputed to >10 million SNP with IMPUTE2 v2.34 software, using a merged reference panel consisting of data from 10,000 Genomes Project (phase 1 integrated release 3, March 2012) and UK10K (ALSPAC, EGAS00001000090, EGAD00001000195 and TwinsUK EGAS00010001018/EGAS0001000194 studies) and TwinsUK EGAS00001001018/EGAS0001000194 studies) and TwinsUK EGAS000010001018/EGAS0001000194 studies. HLA imputation was conducted using SNP2HLA and the Type 1 Diabetes Genetics Consortium reference panel of 5,225 individuals of European descent. The number of variants in the HLA imputation recovered with an information measure > 0.80 were 8,436, 8,506 (95% of total variants) and 8,599 (96% of total variants) in the UK-GWAS, German-GWAS and UK-GWAS data sets, respectively. Imputation was conducted separately for each study, and in the data, were pruned to a common set of SNPs between cases and controls prior to imputation. Poorly imputed SNPs defined by an information measure < 0.80 were excluded. Tests of association between SNPs and cHL were performed using logistic regression under an additive genetic model in PLINK 1.07. The adequacy of SNP imputation was evaluated using Q–Q plots of test statistics (Supplementary Fig. 2). The inflation factor λ was based on the 90% least-significant SNP. Where appropriate, principal components, generated using common SNPs, were included in the analysis to limit the effects of cryptic population stratification that otherwise might cause inflation of test statistics. The two GWAS data sets were imputed with the use of EIGENSOFT by merging cases and controls with Phase III HapMap samples. LD metrics were calculated in vcftools v0.1.12b67, using UK10K merged 10,000 Genomes Project data and plotted using viPiG.

**Replication studies and technical validation.** The eight SNPs in the most promising loci (Table 1; Supplementary Table 6), were taken forward for de novo replication in an additional 1,284 cases from the NSHLG and 2,504 controls from the UK widening replication 1 series (Supplementary Table 1). After this six SNPs were genotyped in an additional replication series, (UK replication 2 series) comprising 953 cases and 565 controls from the Scotland and Newcastle Epidemiological Study of Hodgkin Disease (SNEHD), the Young Adult Hodgkin Case-Control Study (YHCSCs) and the Epidemiology and Cancer Statistics Group Lymphoma Case-Control Study (ELCCs; Supplementary data files) (SNEHD, YHCSCs and ELCCs, respectively). Full details of the SNEHD, YHCSCs and ELCCs studies have previously been reported. Briefly, SNEHD involved ascertainment of incident cases from Scotland and Northern England during 1993–1997. YHCSCs was based on newly diagnosed cases aged 16–24 years from Northern England during 1991–1995. ELCCs comprised cases residing in the north or parts of southern England aged 16–69 years with newly diagnosed, non-human immunodeficiency virus-related cHL during 1998–2003. UK population controls matched to cases on age, sex and area of residence were obtained from SNEHD, YHCSCs and ELCCs. The EBV status of cHL tumours in the UK replication 2 series was determined by immunohistochemical staining for EBV latent membrane protein 1 and EBV-encoded RNA in situ hybridisation using sections of paraffin-embedded material.
The fidelity of GWAS imputation was assessed by the concordance between imputed and directly genotyped SNP in a subset of samples (Supplementary Table 7). Replication genotyping of UK samples was performed using competitive allele-specific PCR KASP chemistry (LGC, Hertfordshire, UK). Primers, probes, and conditions are detailed in Supplementary Table 14. Call rates for SNP genotypes were >95% in each of the replication series. To ensure the quality of genotyping in assays, at least two negative controls and a set of duplicates were genotyped (concordance >99%).

Meta-analysis. Meta-analyses were performed under a fixed-effects model using META v1.674. Briefly, if $b_{xy}$ is the effect size of SNP (gene expression) on $y$ (slope of $y$ regressed on the genetic value of $x$), $b_{x}$ is the effect of $x$ on $y$, and $b_{z}$ is the effect of $z$ on $y$. Therefore $b_{xy} = (b_{x}b_{z})/b_{z}$ is the effect of $x$ on $y$. To distinguish pleiotropy from linkage where the top associated cis-eQTL is in LD with two causal variants, one affecting gene expression the other affecting trait, we tested for heterogeneity in dependent instruments, using multiple SNPs in each eQTL region. Under the hypothesis of pleiotropy, $b_{xy}$ values for SNPs in LD with the causal variant will be identical. Thus testing against the null hypothesis that there is a single causal variant is equivalent to testing heterogeneity in the $b_{xy}$ values estimated for multiple SNPs in the cis-eQTL region using HEIDI.

Expression quantitative trait locus analysis. To examine the relationship between SNP genotype and gene expression, we carried out SMR analysis as per Zhu et al.2016. Briefly, if $b_{x}$ is the effect size of a SNP (gene expression) on $y$ (slope of $y$ regressed on the genetic value of $x$), $b_{x}$ is the effect size of $x$ on $y$, and $b_{z}$ is the effect of $z$ on $y$. Therefore $b_{xy} = (b_{x}b_{z})/b_{z}$ is the effect of $x$ on $y$. To distinguish pleiotropy from linkage where the top associated cis-eQTL is in LD with two causal variants, one affecting gene expression the other affecting trait, we tested for heterogeneity in dependent instruments, using multiple SNPs in each eQTL region. Under the hypothesis of pleiotropy, $b_{xy}$ values for SNPs in LD with the causal variant will be identical. Thus testing against the null hypothesis that there is a single causal variant is equivalent to testing heterogeneity in the $b_{xy}$ values estimated for multiple SNPs in the cis-eQTL region using HEIDI.

Chromatin state dynamics. Enrichment of cHL risk SNPs with DNAse and enhancer-conducting factors using HaploReg v3.12. The overlap of cHL risk SNPs with enhancers in GM12878 cell is compared to a background model of all 1000 Genomes Project variants with a frequency above 5% in any population. The enrichment relative to these background frequencies was performed using a binomial test and a FDR P-value was subsequently calculated; we considered an FDR <0.05 as being significant.

To examine enrichment in specific TF binding across risk loci, we adapted the variant set enrichment method of Cowper-Sal lari et al.78. For each locus, a region of strong LD (defined as $r^2 > 0.8$ and $D’ > 0.8$) was determined, and these SNPs were termed the associated variant set (AVS). TF ChIP-seq uniform peak data were obtained from ENCODE for the GM12878 cell line, and input data was used as a control for background. For each marker, the overlap of the SNPs in the AVS and the binding sites was determined to produce a mapping tally. A null distribution was produced by randomly selecting SNPs with the same LD structure (generated from 1000 Genomes Project and UK10K data) as the risk associated SNP, and the null mapping tally was calculated. This process was repeated 10,000 times, and an approximate P-value was calculated as the proportion of permutations where the null mapping tally was greater or equal to the AVS mapping tally. An enrichment score was calculated by the tallies to the median of the null distribution. Thus the enrichment score is the number of standard deviations of the AVS mapping tally from the mean of the null distribution tallies.

Promoter capture Hi-C data. To map risk SNPs to interactions involving promoter contacts and identify genes involved in cHL susceptibility, we analysed promoter capture Hi-C data on the LCL cell line GM12878 as a model B-cell26. Reads from technical replicates (E-MTAB-2323) were combined before processing with HiCUP79. Significant interactions (i.e., score ≥ 5) on two biological replicates were determined using CHICAGO80.

Co-heritability of Hodgkin lymphoma with autoimmune disease. We utilised LD regression to estimate genetic correlation between individual autoimmune diseases and cHL. NSHL and MCHL35. Summary statistics for published studies of coeliac disease34, systemic lupus erythematous37, primary biliary cirrhosis39, rheumatoid arthritis36, MS38 and UC40 were downloaded from the ImmunoBase website (http://www.immunobase.org/).

Heritability analysis. We used genome-wide complex trait analysis to estimate the polygenic variance (i.e., heritability) ascribable to all genotyped and imputed GWAS SNPs25. SNPs were excluded based on low MAF <0.01, poor imputation (info score < 0.9) and evidence of departure from HWE ($P < 0.05$). Individuals were excluded for poor imputation and where two individuals were closely related. A genetic relationship matrix of pairs of samples was used as input for the restricted maximum likelihood analysis to estimate the heritability explained by the selected set of SNPs. To transform the estimated heritability to the liability scale, we used the lifetime risk, for cHL, which is estimated to be 0.002 by SEER (https://seer.cancer.gov/statfacts/html/hodg.html).

Data availability. Genotype data that support the findings of this study have been deposited in the European Genome-phenome Archive (EGA) under accession codes EGAD00000000022 and EGAD00000000024.

Sequencing data, which forms the reference panel for imputation, have been deposited in the European Genome-phenome Archive (EGA) under accession codes EGAS00001000090, EGAD00001000195, EGAS00001000108.

Transcriptional profiling data from the MuTHER consortium that support the findings of this work have been deposited in the European Bioinformatics Institute (Part of the European Molecular Biology Laboratory, EMBL-EBI) under accession code E-TABM-1140.

Transcriptional profiling data from the Genotype-Tissue Expression (GTEx) project, that support the findings of this work are available here: https://www.gtexportal.org/.

Transcription factor binding data that support the findings of this work are available here: http://genome.ucsc.edu/ENCODE/downloads.html.

Promoter capture Hi-C data in GM12878 cells that support the findings of this work have been deposited in the European Bioinformatics Institute (Part of the European Molecular Biology Laboratory, EMBL-EBI) under accession code E-MTAB-2323.

The remaining data contained within the paper and supplementary files are available from the author upon request.

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A.S., R.S.H. and K.H. designed and provided overall project management. A.S. and R.S.H. drafted the manuscript. In the UK, R.S.H. and A.S. performed database development and oversaw laboratory analyses; R.H.A.J.S. and N.O. provided samples for UK-GWAS and UK-NSHL-GWAS, L.W., and R.C. provided samples on UK-GWAS and UK-NSHL-GWAS. D.E., P.P., A.D., J.P., F.C., R.E., Z.K.-J., K.M. and N.P. provided control samples for the UK-NSHL-GWAS. A.S. performed bioinformatic and statistical analysis. In the UK P.L., G.O. and O.L. performed additional bioinformatic analyses. P.B. and A.S. performed sample and laboratory coordination. A.H. performed validation genotyping. For UK Replication 2, A.L. and D.M. prepared samples, T.L., E.K., E.R., D.M. and A.S. performed sample and laboratory coordination. A.H. performed validation genotyping. For UK Replication 2, A.L. and D.M. prepared samples, T.L., E.K., E.R., D.M. and A.S. performed sample and laboratory coordination. A.H. performed validation genotyping.
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