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Meta-analysis of genome-wide association studies discovers multiple loci for chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is a common lymphoid malignancy with strong heritability. To further understand the genetic susceptibility for CLL and identify common loci associated with risk, we conducted a meta-analysis of four genome-wide association studies (GWAS) composed of 3,100 cases and 7,667 controls with follow-up replication in 1,958 cases and 5,530 controls. Here we report three new loci at 3p24.1 (rs9880772, *EOMES*, $P = 2.55 \times 10^{-11}$), 6p25.2 (rs73718779, *SERPINB6*, $P = 1.97 \times 10^{-8}$) and 3q28 (rs9815073, *LPP*, $P = 3.62 \times 10^{-8}$), as well as a new independent SNP at the known 2q13 locus (rs9308731, *BCL2L11*, $P = 1.00 \times 10^{-11}$) in the combined analysis. We find suggestive evidence ($P < 5 \times 10^{-7}$) for two additional new loci at 4q24 (rs10028805, *BANK1*, $P = 7.19 \times 10^{-8}$) and 3p22.2 (rs1274963, *CSRNP1*, $P = 2.12 \times 10^{-7}$). Pathway analyses of new and known CLL loci consistently show a strong role for apoptosis, providing further evidence for the importance of this biological pathway in CLL susceptibility.

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Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in western countries¹. Although advances in treatment options have been made, CLL remains an incurable malignancy. Genome-wide association studies (GWAS) have identified multiple susceptibility loci for CLL^{2–7} with at least three loci having more than one independent signal^{5,8}. However, these discovered loci only account for about a third of the estimated heritability attributed to common variants⁵. In a combined analysis of four GWAS and follow-up replication, including 3,888 cases and 12,539 controls of European ancestry, we recently discovered 11 independent single-nucleotide polymorphisms (SNPs) in nine novel loci associated with CLL risk⁵. To discover additional loci associated with susceptibility to CLL, we more than doubled our replication sample size in the present study, slightly increasing our statistical power, and investigated the association with 14 other promising SNPs identified from our GWAS meta-analysis.

Here, we identify four new independent SNPs in three novel loci as well as two promising new loci associated with the risk of CLL. Pathway analyses with these new loci as well as the previously identified loci suggest a strong role for the apoptosis in susceptibility to CLL, further enhancing our understanding.

Results

Discovery meta-analysis. We conducted a meta-analysis of four genome-wide association studies^{4,5,9} comprising 3,100 unrelated cases and 7,667 controls of European ancestry (see ‘Methods’ section, Supplementary Tables 1–3). As these studies used different commercial SNP microarrays, we imputed the ~8.5 million common SNPs present in the 1000 Genomes Phase 1 integrated data (version 3)¹⁰ for each study using IMPUTE2 (ref. 11; Supplementary Table 2) and tested for associations with CLL risk assuming a log-additive genetic model. After quality control exclusions, ~8.5 million SNPs with minor allele frequency >1% were meta-analysed in the discovery stage using a fixed effects model.

A quantile–quantile plot of the meta-analysis results in the discovery stage showed an enrichment of small P values from the fixed-effects model compared with the null distribution, which persisted even after removal of the known loci (Supplementary Fig. 1). There was little evidence for inflation due to population stratification ($\lambda = 1.028$). Under a log-additive genetic model, a total of 16 unique loci (defined as separated by at least 1 Mb) reached genome-wide significance ($P < 5 \times 10^{-8}$; Supplementary Fig. 2), all of which had been previously reported^{2,3,5,8}. For each previously reported locus, we identified the SNP with the strongest P value within 1 Mb of the published index SNP. Of the 29 published loci, 21 were at least suggestively associated with CLL under a log-additive model in our discovery meta-analysis with $P < 5 \times 10^{-7}$ (Supplementary Table 4). As the original reported SNPs at two loci (4q26 and 6q25.2) failed to show nominal significance ($P < 0.05$) in our study, we meta-analysed our results with the published results for known loci from two other GWAS^{6,7}. In this larger meta-analysis, 25 of the published loci were at least suggestively associated with CLL risk ($P < 5 \times 10^{-7}$) based on a fixed-effects model; however, both rs6858698 at 4q26 and rs11631963 at 15q25.2 showed attenuated odds ratios and weak P values even with this increased sample size ($P = 0.002$ and $P = 0.0003$, respectively; Supplementary Table 5), questioning the certainty of these loci.

Joint meta-analysis of the discovery and replication. To identify additional loci associated with CLL risk, four SNPs in known regions that appeared to be possible secondary signals ($r^2 < 0.1$ with the reported SNPs and $P < 5 \times 10^{-7}$ in the discovery meta-analysis) and 10 SNPs in novel regions that reached a

significance threshold of $P < 5 \times 10^{-6}$ in the discovery meta-analysis were taken forward for replication in 1,958 cases and 5,530 controls. In the joint meta-analysis of the discovery and replication, four SNPs were identified as genome-wide significant under a fixed-effects model, three in novel regions and one as a new independent SNP in the previously reported 2q13 region: 3p24.1 (rs9880772, *EOMES*, $P = 2.55 \times 10^{-11}$), 6p25.2 (rs73718779, *SERPINB6*, $P = 1.97 \times 10^{-8}$), 3q28 (rs9815073, *LPP*, $P = 3.62 \times 10^{-8}$) and 2q13 (rs9308731, *BCL2L11*, $P = 1.00 \times 10^{-11}$; Table 1, Fig. 1, Supplementary Table 6). The new 2q13 SNP, rs9308731, was weakly correlated with the two previously identified^{2,5} independent SNPs at 2q13, rs17483466 ($r^2 = 0.008$) and rs13401811 ($r^2 = 0.0005$); when the three 2q13 SNPs were included in the same logistic regression model, all three remained genome-wide significant (Supplementary Table 7). Genome-wide suggestive evidence ($P < 5 \times 10^{-7}$) was also found in the joint discovery/replication fixed-effects meta-analysis for two promising novel loci at 4q24 (rs10028805, *BANK1*, $P = 7.19 \times 10^{-8}$) and 3p22.2 (rs1274963, *CSRNP1*, $P = 2.12 \times 10^{-7}$; Table 1, Supplementary Fig. 3).

Discussion

All the three novel loci are located in or near genes implicated in apoptosis and/or immune function. The novel 3p24.1 SNP (rs9880772) resides 13 kb 5' of eomesodermin (*EOMES*), a member of the T-box gene family and a key regulator in cell-mediated immunity and CD8+ T-cell differentiation¹². *EOMES* is critical for lymphoproliferation due to Fas-deficiency¹³, which has been observed in inherited lymphoproliferative disorders associated with autoimmunity^{14,15}. Overexpression of *EOMES* has been observed among extranodal natural killer/T (NK/T)-cell and peripheral T-cell lymphomas¹⁶. Interestingly, highly correlated SNPs within the same 15 kb region 5' of *EOMES* have also been associated with two autoimmune diseases, rheumatoid arthritis¹⁷ (rs3806624, $r^2 = 0.96$) and multiple sclerosis¹⁸ (rs11129295, $r^2 = 0.72$), as well as Hodgkin's lymphoma¹⁹ (rs3806624, $r^2 = 0.96$), underscoring the importance of this genetic region for susceptibility to both lymphoma and autoimmune disease. Regions locally centromeric and telomeric of rs9880772 show strong regulation and promoter signatures by histone marks, DNaseI hypersensitivity and transcription factor binding sites, and the correlated SNP, rs3806624, is located within a poised promoter in the lymphoblastoid cell line, GM12878 (Supplementary Table 8).

The novel 6p25.2 SNP (rs73718779) is located within an intron of *SERPINB6*, which encodes a member of the serine protease inhibitor (serpin) superfamily. Although the physiological role of *SERPINB6* is not well understood, it inhibits cathepsin G²⁰, which activates the pro-apoptotic proteinase caspase 7 (ref. 21). In eQTL and methylation QTL analyses, we found that the T allele for rs6939693, an SNP completely correlated with rs73718779 ($r^2 = 1$), was associated with significantly reduced *SERPINB6* expression in blood in a weighted z-score meta-analysis ($P = 1.40 \times 10^{-52}$, Supplementary Table 9) and increased DNA methylation levels based on a linear mixed model ($P = 1.70 \times 10^{-11}$, Supplementary Table 10), suggesting strong potential functional relevance.

The 3q28 SNP (rs9815073) is an intronic variant within the LIM domain containing preferred translocation partner in lipoma gene (*LPP*). The SNP is located within a strong enhancer in the lymphoblastoid cell line, GM12878 (Supplementary Fig. 4). Moderately correlated SNPs in *LPP* have previously been associated with diseases related to autoimmunity and/or immune dysregulation, including celiac disease²² (rs1464510, $r^2 = 0.51$), allergy²³ (rs9860547, $r^2 = 0.68$) and vitiligo²⁴ (rs1464510, $r^2 = 0.51$). SNPs within this region have also been associated

with follicular lymphoma²⁵ (rs6444305, $r^2 = 0.001$) and B-cell lymphoma in Asians (rs6773854, $r^2 = 0.002$); however, the association with rs9815073 appears to be independent of both of these SNPs in the fixed-effects meta-analysis ($P_{rs9815073} = 9.11 \times 10^{-7}$ after conditioning on rs6444305 and $P_{rs9815073} = 5.11 \times 10^{-7}$ after conditioning on rs6773854 compared with $P_{rs9815073} = 5.35 \times 10^{-7}$ without adjustment).

The suggestive 4q24 SNP (rs10028805) is located within an intron of B-cell scaffold protein with ankyrin repeats 1 (*BANK1*), which encodes a protein adaptor that is predominantly expressed in B-cells. *BANK1* is a putative tumour suppressor gene in B-cell lymphomagenesis²⁶, and *BANK1*-deficient cells show enhanced CD40-mediated proliferation and survival with Akt activation²⁷. Rs10028805 is moderately correlated with rs10516487 ($r^2 = 0.70$), a non-synonymous SNP in exon 2 that has been associated with systemic lupus erythematosus²⁸ and shown to alter mRNA splicing and the quantity of the *BANK1* protein²⁹. Consistent with this, we observed rs10028805 to be associated with *BANK1* expression in lymphoblastoid cells ($P = 6.89 \times 10^{-13}$, Supplementary Table 11).

The 3p22.2 SNP (rs1274963) is an intronic variant in the gene *CSRNP1* (cysteine-serine-rich nuclear protein 1), which is induced by AXIN1, a scaffold protein that is a negative regulator of the Wnt/signalling pathway³⁰. A putative tumour suppressor with potential apoptosis activity³¹, *CSRNP1* plays an important role in the development of haematopoiesis progenitors in zebrafish³² and has been shown to be expressed in many tissues, with leukocytes being among those with the highest abundance³⁰. The SNP resides in an area with strong regulatory potential based on histone marks, DNaseI hypersensitivity and transcription factor binding sites (Supplementary Table 8) and is located within a strong enhancer in the lymphoblastoid cell line, GM12878 (Supplementary Fig. 4). Of potential functional relevance, in lymphocytes and blood, the rs1274963A risk allele was associated with reduced *WDR48* expression (Supplementary Tables 9 and 11), a gene shown to induce apoptosis and suppress tumour cell proliferation³³.

To explore potential biological pathways associated with the newly discovered loci as well as the previously established loci for CLL, we conducted pathway analyses using GRAIL³⁴, Webgestalt and GeneMania (see 'Methods' section). All the three pathway analyses identified apoptosis or apoptosis-related pathways as either the top key words (GRAIL, Supplementary Table 12, Fig. 2a) or their most significantly enriched pathway: regulation of apoptotic signalling (GeneMania, $P = 2.06 \times 10^{-17}$, false discovery rate-corrected hypergeometric test, Supplementary Table 13, Fig. 2b) and activation of pro-apoptotic gene products (Webgestalt, $P = 5.49 \times 10^{-11}$, false discovery rate-corrected hypergeometric test, Supplementary Table 14). Other enriched pathways included related apoptotic functions and pathways, such as cytochrome *c* release from mitochondria (Webgestalt, $P = 2.16 \times 10^{-6}$; GeneMania, $P = 7.50 \times 10^{-13}$) and mitochondrial outer membrane (Webgestalt, $P = 3.89 \times 10^{-6}$; GeneMania, $P = 7.18 \times 10^{-17}$; Supplementary Tables 13 and 14, Supplementary Fig. 5). Lymphocyte-related pathways, such as lymphocyte homeostasis (Webgestalt, $P = 2.16 \times 10^{-6}$), haematopoietic or lymphoid organ development (GeneMania, $P = 0.009$), and lymphoid (GRAIL) were also observed in all the three analyses.

We constructed a polygenetic risk score that included the four new SNPs from this study as well as 30 previously identified SNPs at known loci (Supplementary Table 5) to evaluate the possibility of risk stratification for CLL (see 'Methods' section). Those in the top 20% of the risk distribution had a 1.9-fold increased risk (95% confidence interval: 1.70–2.21) compared with those in the middle quintile of the distribution. The newly discovered SNPs explain ~1% of the familial risk. Together with the previously identified loci, we estimate that the identified loci for CLL thus far explain ~16.5% of the familial risk, which is similar to previous estimates^{5,6}.

In conclusion, our meta-analysis of GWAS identified four new independent SNPs and two additional promising loci for CLL, furthering our knowledge of the underpinnings of genetic susceptibility to CLL. Pathway analyses of known and new CLL

Table 1 | New loci and independent SNPs associated with CLL risk.

SNP	Cytoband	Nearest gene	Position	Stage	No. of cases	No. of controls	Risk allele/ other allele	RAF	OR	CI	P
<i>New loci</i>											
rs9880772	3p24.1	<i>EOMES</i>	27777779	Discovery	3,097	7,664	T/C	0.464	1.17	(1.10-1.24)	7.77E – 07
				Replication	1,935	5,414	T/C	0.467	1.23	(1.13-1.34)	4.67E – 06
				Combined	5,032	13,078	T/C	0.465	1.19	(1.13-1.25)	2.55E – 11
rs73718779	6p25.2	<i>SERPIN6</i>	2969278	Discovery	3,097	7,663	A/G	0.111	1.27	(1.16-1.40)	6.22E – 07
				Replication	1,871	4,107	A/G	0.109	1.21	(1.05-1.40)	0.008
				Combined	4,968	11,770	A/G	0.110	1.26	(1.16-1.36)	1.97E – 08
rs9815073	3q28	<i>LPP</i>	188115682	Discovery	3,098	7,663	C/A	0.651	1.20	(1.12-1.28)	5.35E – 07
				Replication	1,848	4,094	C/A	0.652	1.13	(1.03-1.25)	0.01
				Combined	4,946	11,757	C/A	0.651	1.18	(1.11-1.25)	3.62E – 08
<i>New independent SNP at known locus</i>											
rs9308731	2q13	<i>BCL2L1</i>	111908262	Discovery	3,100	7,665	A/G	0.541	1.19	(1.12-1.26)	4.71E – 08
				Replication	1,929	5,448	A/G	0.531	1.21	(1.10-1.32)	4.66E – 05
				Combined	5,029	13,113	A/G	0.537	1.19	(1.13-1.26)	1.00E – 11
<i>New suggestive loci ($P < 5 \times 10^{-7}$)</i>											
rs10028805	4q24	<i>BANK1</i>	102737250	Discovery	3,099	7,665	G/A	0.625	1.16	(1.09-1.23)	7.04E – 06
				Replication	1,876	4,107	G/A	0.621	1.15	(1.05-1.15)	0.003
				Combined	4,975	11,772	G/A	0.624	1.16	(1.10-1.22)	7.19E – 08
rs1274963	3p22.2	<i>CSRNP1</i>	39191029	Discovery	3,100	7,666	T/C	0.210	1.20	(1.12-1.29)	1.37E – 06
				Replication	1,938	5,402	T/C	0.204	1.13	(1.01-1.26)	0.03
				Combined	5,038	13,068	T/C	0.208	1.18	(1.11-1.25)	2.12E – 07

CI, confidence interval; OR, odds ratio; RAF, risk allele frequency among controls.

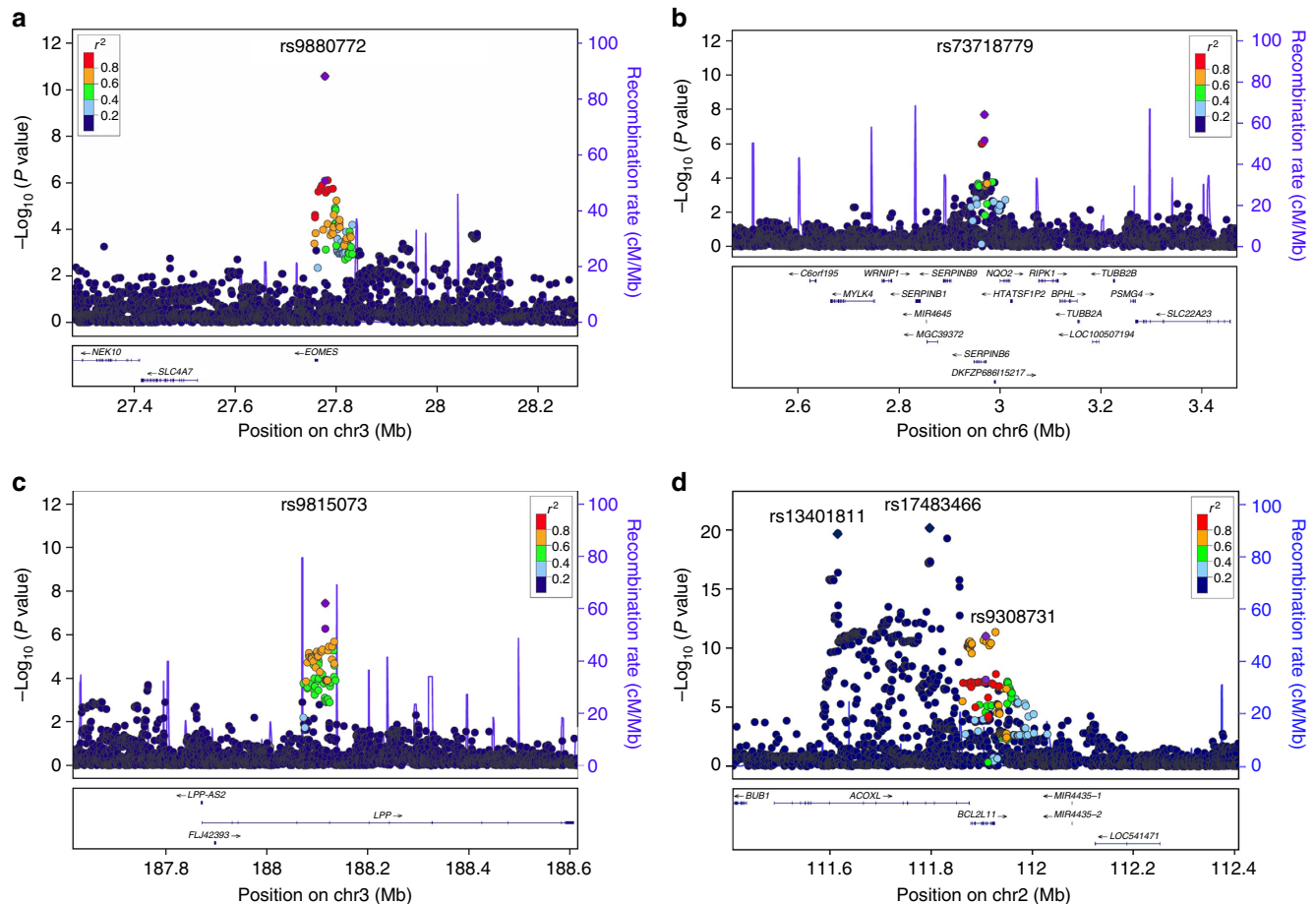


Figure 1 | Regional association plots of the three novel loci and new independent SNP at a known locus associated with the risk of CLL.

(a) Chromosome 3p24.1 (rs9880772), (b) chromosome 6p25.2 (rs73718779), (c) chromosome 3q28 (rs9815073) and (d) chromosome 2q13 (rs9308731). Shown are the $-\log_{10}$ association P values from the discovery fixed effects meta-analysis (dots) and combined discovery and replication fixed effects meta-analysis (diamonds). The lead SNPs are shown in purple. Estimated recombination rates (from 1000 Genomes) are plotted in blue. The SNPs surrounding the most significant SNP are colour-coded to reflect their correlation with this SNP. Pairwise r^2 values are from 1000 Genomes European data (March 2012 release). Genes, position of exons and direction of transcription from UCSC genome browser (genome.ucsc.edu) are noted. Plots were generated using LocusZoom (<http://csg.sph.umich.edu/locuszoom>).

loci point to regulation of apoptosis as one of the key biological processes underlying the genetic loci to date and suggest new avenues for disease prevention and treatment.

Methods

Discovery meta-analysis. Our discovery meta-analysis included four CLL GWAS of European ancestry: National Cancer Institute NHL GWAS (NCI GWAS)⁵, Utah Chronic Lymphocytic Leukemia GWAS (UTAH), Genetic Epidemiology of CLL Consortium GWAS (GEC)⁴, and Molecular Epidemiology of Non-Hodgkin Lymphoma GWAS (UCSF)⁹. Details of the case and control ascertainment and study design of the four GWAS, including the 22 studies that comprise the NCI GWAS, are described in Supplementary Table 1. In brief, CLL cases were ascertained from cancer registries, clinics or hospitals, or through self-report verified by medical and pathology reports. For the NCI GWAS, phenotype information for the cases was reviewed centrally at the International Lymphoma Epidemiology Consortium (InterLymph) Data Coordinating Center and harmonized according to the hierarchical classification proposed by the Interlymph Pathology Working Group based on the World Health Organization classification (2008)^{35,36}. All the studies obtained informed consent from their participants and approval from their respective Institutional Review Boards for this study⁵.

To maximize our statistic power, all cases with sufficient DNA and a subset of available controls were genotyped for this study. Subjects in these studies were genotyped using the Illumina OmniExpress, Omni2.5, HumanHap610K, HumanCNV360-Duo or Affymetrix 6.0. For the NCI GWAS, the majority of subjects were genotyped with the Illumina OmniExpress; however, a subset of controls ($N = 3,536$) and one case were genotyped using the Omni2.5, so to prevent potential platform artifacts, extensive quality control metrics were used, including the removal of assays with low completion rates or monomorphic calls from either

platform, before combining the data⁵. For all four GWAS, rigorous quality control metrics were applied to each study to ensure high quality results. Samples with poor call rates, gender discordance, abnormal heterozygosity or of non-European ancestry were excluded, and SNPs with a call rate $< 95\%$ or Hardy-Weinberg equilibrium P value $< 1 \times 10^{-6}$ were removed from the analysis (Supplementary Table 2).

Each GWAS was imputed separately using IMPUTE2 (ref. 11). In contrast to the previous study⁵ where a hybrid reference panel was used for imputation, all the studies in this analysis were imputed using the 1000 Genomes Project version 3 (March 2012 release) as the reference panel. Poorly imputed SNPs (INFO score < 0.3) and SNPs with minor allele frequency $< 1\%$ were excluded from each study, leaving roughly ~ 8.5 million SNPs for analysis. After quality control filters, a total of 3,100 cases and 7,667 controls across the four studies remained for analysis (Supplementary Table 3). For each study, principal component analyses were conducted separately. Association testing was conducted for each study separately using SNPTEST version 2, adjusting for age, sex and significant principal components ($P < 0.05$ in null model with age and sex). Meta-analyses were performed using the fixed-effects inverse variance method based on the beta estimates and standard errors from each study.

Replication and technical validation. Replication of potential novel SNPs was undertaken in 1,958 additional cases and 5,530 controls from six different studies (Supplementary Tables 1 and 3). Fourteen promising SNPs that reached a significance threshold of $P < 5 \times 10^{-6}$ in the discovery meta-analysis were taken forward for replication, including 10 SNPs in novel regions (defined as at least 1 Mb from a known CLL locus) and four SNPs in known regions that appeared to be possible secondary signals ($r^2 < 0.1$ with the reported SNPs and $P < 5 \times 10^{-7}$ in the discovery meta-analysis). To conduct conditional analyses with the potential secondary signals, the previously reported index SNP(s) in each of these four

from 593 participants. Subjects were genotyped with the Affymetrix Human SNP Array 6.0, and the 2.5 million SNPs available in the HapMap2 release were imputed. We updated the analysis by including more participants ($n = 717$) and expanded the scope of *cis*-meQTL to SNPs and CpG sites within 50 kb of each other. The association between the CLL-associated SNPs (as well as strongly correlated SNPs, $r^2 > 0.8$) and methylation beta values was tested using the linear mixed models, adjusting for family structure and other covariates including age, sex, recruitment centres and principal components. Finally, we also utilized HaploReg⁴⁴, a tool for exploring noncoding functional annotation using ENCODE data, to evaluate the genome surrounding our SNPs.

Pathway analyses. To explore potential biological pathways underlying known CLL loci to date, we conducted analyses using GRAIL³⁴, Webgestalt⁴⁵ and GeneMania⁴⁶. GRAIL³⁴ is a text-based mining tool that is used to evaluate the relationship between genes at different disease loci. Genes within 250 kb of known loci were included, and the 2006 text database was used to avoid overweighting the previously published loci. Webgestalt⁴⁵ is a web-based pathway analysis server offering hypergeometric tests for Gene Ontology (GO) term enrichments and visualization of enriched GO terms in a graph depicting the GO hierarchy. GeneMania⁴⁶ is a network-based analysis server that finds an expanded set of genes including the query genes and additional genes closely linked with the query genes via protein and genetic interactions, pathways, co-expression, co-localization and protein domain similarity. For both Webgestalt and GeneMania, the nearest gene for each locus was included. For all pathways analyses, only newly discovered loci and the previously identified loci that reached at least $P < 1 \times 10^{-5}$ in the combined meta-analysis with the published results from two other GWAS^{6,7} (Supplementary Table 5) were included.

Chromatin state dynamics analysis. To assess chromatin state dynamics, we used Chromos⁴⁷, which utilizes Chip-Seq data from ENCODE⁴⁸ on nine cell types: B-lymphoblastoid cells (GM12878), hepatocellular carcinoma cells (HepG2), embryonic stem cells (hESC), erythrocytic leukemia cells (hK562), umbilical vein endothelial cells (hUVEC), skeletal muscle myoblasts (hSMM), normal lung fibroblasts (hNHLF), normal epidermal keratinocytes (hNHEK) and mammary epithelial cells (hMEC). This programme uses pre-computed data with genome-segmentation performed using a multivariate hidden Markov-model to reduce the combinatorial space to a set of interpretable chromatin states. The output from Chromos lists data into 15 chromatin states corresponding to repressed, poised and active promoters, strong and weak enhancers, putative insulators, transcribed regions and large-scale repressed and inactive domains. For this study, we focused on the results observed for the lymphoblastoid cell line (GM12878).

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