Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus

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Systemic lupus erythematosus (SLE; OMIM 152700) is a genetically complex autoimmune disease characterized by loss of immune tolerance to nuclear and cell surface antigens. Previous genome-wide association studies (GWAS) had modest sample sizes, reducing their scope and reliability. Our study comprised 7,219 cases and 15,991 controls of European ancestry: a new GWAS, meta-analysis with a published GWAS and a replication study. We have mapped 43 susceptibility loci,

including 10 novel associations. Assisted by dense genome coverage, imputation provided evidence for missense variants underpinning associations in eight genes. Other likely causal genes were established by examining associated alleles for *cis*-acting eQTL effects in a range of *ex vivo* immune cells. We found an over-representation (n=16) of transcription factors among SLE susceptibility genes. This supports the view that aberrantly regulated gene expression networks in multiple cell types in both the innate and adaptive immune response contribute to the risk of developing SLE.

SLE is a clinically heterogeneous disease with a strong genetic component, as demonstrated by the tenfold increase in concordance rates between monozygotic and dizygotic twins[1], and familial aggregation (sibling risk ratio, $\lambda_s = 29$)[2]. Since 2008, the field of SLE genetics has been transformed by GWA[3–8] and independent replication studies[9,10]. However, while the pace of discovery has been unprecedented, providing a richer understanding of lupus genetic etiology, these findings were driven by modestly-sized GWA studies, utilizing 1,800 European patients[3,4] and slightly fewer Asian cases[5,6]; they therefore had limited power to detect loci with relatively low odds ratios and/or minor allele frequencies[11]. The size of our study, coupled with a meta-analysis and replication study, has greatly increased the power to detect susceptibility loci.

We genotyped 4,946 individuals with SLE and 1,286 healthy controls using the Illumina HumanOmni1-Quad BeadChip. These data were combined with the genotypes of 5,727 healthy controls taken from the University of Michigan Health and Retirement Study (HRS), genotyped using the Illumina HumanOmni2.5 BeadChip. Following quality control (QC) analyses, our data comprised 4,036 SLE cases and 6,959 controls (1,260 controls mainly from southern Europe genotyped using the Omni1-Quad chip and 5,699 controls from the HRS cohort). The final SNP set comprised 644,674 markers that were present on both the Omni1-Quad and Omni2.5 chips (see Online Methods). Four principal components were

used as covariates to correct for population structure[12,13]. The genomic inflation factor[14,15] for our data, λ_{1000}, was 1.02, with λ_{GC} = 1.16.

Our analysis strategy is described in detail in Online Methods, and is shown schematically in Supplementary Fig. 1. This GWAS identified 25 loci (Table 1 and Supplementary Fig. 2a) of genome-wide significance ($P < 5 \times 10^{-08}$). Three of these associations are novel in SLE: rs6740462 and rs3768792 on chromosome 2p14 and 2q34, respectively and rs7726414 on chromosome 5q31.1.

To validate these findings, and to search for additional susceptibility loci, we carried out a meta-analysis of our GWAS results and those from an independent European SLE GWAS comprising 1,165 cases and 2,107 controls (the Hom *et al.*[4] study). Each of the 25 loci mapped in the original GWAS had genome-wide significant p-values in this meta-analysis (Supplementary Table 1), and are therefore considered to be associated with SLE. We then designed a replication study, with inclusion based on the meta-analysis of the two GWA studies. At loci with no published association in SLE, we adopted a threshold for inclusion of $P < 2.5 \times 10^{-05}$, while for loci with previously reported associations the threshold was set at $P < 1 \times 10^{-04}$ (see Online Methods for rationale). The 33 SNPs with *P*-values meeting these criteria were genotyped in our replication study (Supplementary Table 2), using a custom panel that also included 53 ancestry informative markers (see Online Methods). After applying QC measures, the replication data comprised 2,018 cases and 6,925 controls, none of which had been included in either GWAS (see Online Methods).

Finally, we carried out a post-replication meta-analysis of the results of our GWAS, the Hom *et al.* study and the replication study for those 33 SNPs, again applying the standard measure of genome-wide significance. The 18 SNPs (over and above the 25 already mapped) with *P*-values $< 5 \times 10^{-08}$ in this meta-analysis were also considered to be associated with SLE (Table 1 and Supplementary Fig. 2b). In addition to the three novel loci mapped in the GWAS, seven further variants, at loci hitherto not showing genome-wide

significant association in SLE, were mapped in the overall meta-analysis: rs564799 (3q25.33), rs3794060 (11q13.4), rs10774625 (12q14.1), rs4902562 (14q24.1), rs9652601 (7q32.1), rs2286672 (17p13.2) and rs887369 (Xp21.2). The heritability explained by these 43 validated susceptibility alleles is 19.3% [95% C.I. 14.1–25.5%], where the total heritability of lupus is estimated to be 66%[16]. This is a large increase on the 8.7% [5.33–12.96%] reported by So *et al*.[17] in 2011 using the same measure.

We imputed both the main GWAS and Hom *et al.* data to the density of the 1000 Genomes (1KG) study[18] and re-analyzed the data (see Online Methods). While no additional loci were identified, we did obtain stronger evidence in support of some loci, for example the signal at the *SPRED2* locus, at which the most associated 1KG variant, rs268134, was strongly replicated. In addition, the imputation enabled us to fine map associated loci and to determine whether multiple signals were present (Supplementary Tables 3a and 3b). We identified multiple independent association signals at the *TNFSF4, STAT4* and *IRF5* loci, as well as five independently associated SNPs at the MHC (see below).

Given that the SNP with the smallest *P*-value is not necessarily the true causal variant, we considered SNPs from the most associated to a defined cut-off as potentially causal in our subsequent analyses. Specifically, guided by previous work on functional annotation[19] (see Online Methods), the cut-off was defined as a Bayes Factor against the most significantly associated SNP equal to 0.34. Any SNPs in this set that were missense variants were considered more likely candidates than the most associated SNP. The results are summarized in Supplementary Tables 3c and 4, listing candidate causal missense variants in *PTPN22, FCGR2A, NCF2, TNFAIP3, WDFY4, IRF7, ITGAM* and *TYK2*.

MHC polymorphisms, including SNPs and classical human leukocyte antigen (HLA) alleles, have consistently been observed to be associated with SLE[20]. We imputed HLA alleles[21] in both the main GWAS and Hom *et al*. data, and incorporated them into our analysis of 1KG imputed data across the MHC (see Online Methods). Of the five MHC SNPs we find to be

independently associated with SLE (Supplementary Tables 3a and 3b), the class III SNP in *SLC44A4* (rs74290525) is the only association signal that is clearly independent of any HLA alleles. We find that rs74290525 is significantly associated not only when conditioning on each of the HLA genes separately, but even when conditioning on all 199 HLA alleles (see Supplementary Tables 5a–e), and is not in linkage disequilibrium (LD) with any HLA alleles ($R^2 < 0.1$ with each HLA allele). We find that the best model for association includes the HLA class I alleles *B*08:01*, *B*18:01,* the class II alleles *DQB1*02:01, DRB3*02:00* and *DQA*01:02*, and the class III SNP rs74290525, consistent with previous findings suggesting multiple SLE associations at the MHC[20] (Supplementary Tables 6a and 6b). LD between the five MHC SNPs and HLA alleles on known SLE risk haplotypes can be seen in Supplementary Table 6c.

In order to highlight potential causal genes at the susceptibility loci, the associated SNPs at each of the loci were tested for correlation with *cis*-acting gene expression in *ex vivo* naïve CD4+ T cells, B cells, natural killer (NK) cells, and stimulated and resting monocytes[22–24]. Figure 1 displays a heat map across cell types, showing genes exhibiting significant differential expression in relation to the SLE associated alleles. We calculated Regulatory Trait Concordance (RTC) scores[25] (see Supplementary Figs. 3a and b) to test the relationship between eQTLs driven by disease-associated alleles, and other, potentially stronger eQTLs, which we identified at each locus. The *cis* eQTLs were distributed across all cell types tested, some being common to all cell types, such as *UBE2L3* and *UHRF1BP1*, while others are more cell specific: *BLK* in B cells and *JAZF1* in T cells. In general directionality was consistent, although not in all cases: for example *ABHD6* showed reduced expression in monocytes and elevated expression in lymphocytes.

We note that some caution must be used when inferring causality, as the RTC score has a uniform distribution and so setting an RTC score threshold of 0.9 for example, sets the type I error rate to be 0.1. Furthermore, some low RTC scores were found in genes (e.g. *UBE2L3*) where the associated allele resides in a region with strong LD, and the haplotype bearing the

associated allele shows robust evidence of functional effects on gene expression[26]. We suggest that the gene expression analyses provide some support for likely causal genes, but we note that proof of true causality through altered gene expression will only be elucidated by additional experimentation.

We then integrated the results of these eQTL analyses and the coding variant analysis with an *in silico* survey of murine phenotype data resulting from targeting gene knockouts of genes within the associated SLE loci (Table 2). At some loci, these lines of evidence point to one likely causal gene: examples include *IFIH1, LYST, WDFY4* and *BANK1*. In other instances, we found evidence that supports the role of multiple genes as candidates at a given locus; for example, *ABHD6* (an enzyme involved in the endocannabinoid pathway) and *PXK* (a lymphocyte protein kinase)[3] both exhibit correlation of their expression with the associated SNP. Similarly, *TCF7* (coding a T cell transcription factor), implicated by the rs7726414 association, has been associated with type 1 diabetes[27]; however, we show that *SKP1* (which encodes a protein involved in the regulation of ubiquitination), within the same LD block exhibits a strong *cis* eQTL in monocytes and NK cells. rs9652601 resides within *CLEC16A*, a gene previously reported in association studies in other autoimmune diseases[28]; we present evidence suggesting that *SOCS1* (Suppressor of Cytokine Signaling 1) is a causal gene at this locus in SLE rather than *CLEC16A*. Our analyses have the advantage of including *cis* eQTLs based on *ex vivo* cells, rather than cell line data alone. Nevertheless, we acknowledge the restricted range and activation states of immune cell types available for eQTL analyses and the limited number of murine and other functional studies performed on genes at the loci.

The 10 previously unmapped SLE loci (shown in bold type in Table 1 and Supplementary Table 3a) encompass genes of diverse function. Those of note include *IKZF2* (Helios), which represents the third member of the Ikaros transcription factor family to be associated with SLE (in addition to *IKZF1* and *IKZF3*). The association signal in the phospholipase D2 (*PLD2*) is a missense variant (R172C), which may alter the function of the enzyme that plays

a role in leukocyte migration and apoptosis. The importance of IL12, a cytokine that plays a critical role in the generation of γ-interferon from Th1 T cells and NK cells, is highlighted by the association with *IL12A* (Table 1), and the suggestive associations at *IL12B* and the locus encoding the IL12 receptor, *IL12RB2* (Supplementary Table 2).

In view of the sexual dimorphism of SLE, the novel X chromosome association revealed by rs887369 is of note. We suggest that the gene *CXorf21* is likely to be etiological. While the function of this gene is unknown, it is among a limited set of genes that largely escape X-inactivation[29]. Sex chromosome dosage has been implicated in the genetic risk of SLE[30]. We observed an elevated prevalence of Klinefelter's syndrome[31] in male cases in our GWAS compared with the general population (see Online Methods) strengthening the sex chromosome dosage hypothesis. The only other gene close to rs887369 (Table 2) is *GK* (glycerol kinase) which does not escape X-inactivation, supporting *CXorf21* as a candidate gene.

Five other genes (*TNIP1, IKZF1, ETS1, WDFY4* and *ARID5B*) that we mapped are novel in European SLE, but had been previously shown to be associated with SLE in Chinese subjects[5,6]. SLE is more prevalent in non-European populations – our data suggest that locus heterogeneity among common genetic variants is unlikely to explain this differential prevalence.

We present all of our principal findings in Fig. 2. This figure indicates ten likely missense coding variants that contribute to SLE risk; these occur largely in genes encoding kinases and other enzymes. It was noted that 16 of the genes shown are transcription factors, an enrichment above the nine expected ($P = 2.3 \times 10^{-05}$, χ^2 test). We studied the distribution of the expression of these transcription factors in the *ex vivo* immune cell types examined for eQTLs; we found no evidence of skewed expression in any cell type. Our results suggest that an important facet in future exploration of SLE pathogenesis will be detailed scrutiny of *trans* eQTLs and regulatory expression networks in multiple immune cells.

URLs. Department of Twin Research, King's College London, TwinsUK samples, http://www.twinsuk.ac.uk; Ingenuity Pathway Analysis, http://www.ingenuity.com/; Immunobase, http://www.immunobase.org. Systems Biology and Complex Disease Genetics, http://insidegen.com .

Data access. Summary statistics from the GWAS will be released by deposition in ImmunoBase. All 1KG imputed summary statistics will also be available at http://insidegen.com/insidegen-LUPUS-data.html .

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Author contributions

TJV supervised the study. MEAR, JM, A-CS, LR and JEW provided samples. JB pre-processed the genotype data and carried out quality control analysis for the GWAS data. DLM, PT and JB carried out statistical analysis of the GWAS data. DLM and TJV designed the replication chip. DLM, PT and JB carried out QC analysis of the controls for the replication study. DLM carried out statistical analysis for the replication study. DLM and JB carried out statistical analysis of the 1000 Genomes data. DM, LC, JR, BPF and JCK carried out statistical analysis of the eQTL analysis. DSCG and CLP coordinated sample collection and genotyping. DLM, JB, DSCG, JDR and TJV wrote the manuscript. All authors have read and contributed to the manuscript.

Competing financial interests

The authors declare no competing financial interests.

References

1. Deapen, D. *et al.* A revised estimate of twin concordance in systemic lupus erythematosus. *Arthritis Rheum.* **35**, 311–318 (1992).
2. Alarcón-Segovia, D. *et al.* Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. *Arthritis Rheum.* **52**, 1138–1147 (2005).
3. Harley, J.B. *et al.* Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in *ITGAM*, *PXK*, *KIAA1542* and other loci. *Nat. Genet.* **40**, 204–210 (2008).
4. Hom, G. *et al.* Association of systemic lupus erythematosus with *C8orf13-BLK* and *ITGAM-ITGAX*. *New Engl. J. Med.* **358**, 900–909 (2008).
5. Yang, W. *et al.* Genome-wide association study in Asian populations identifies variants in *ETS1* and *WDFY4* associated with systemic lupus erythematosus. *PLoS Genet.* **6**, e1000841 (2010).
6. Han, J.-W. *et al.* Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. *Nat. Genet.* **41**, 1234–1237 (2009).

7. Graham, R.R. *et al.* Genetic variants near *TNFAIP3* on 6q23 are associated with systemic lupus erythematosus. *Nat. Genet.* **40**, 1059–1061 (2008).
8. Okada, Y. *et al.* A genome-wide association study identified *AFF1* as a susceptibility locus for systemic lupus eyrthematosus in Japanese. *PLoS Genet.* **8**, e1002455 (2012).
9. Gateva, V. *et al.* A large-scale replication study identifies *TNIP1*, *PRDM1*, *JAZF1*, *UHRF1BP1* and *IL10* as risk loci for systemic lupus erythematosus. *Nat. Genet.* **41**, 1228–1233 (2009).
10. Graham, D.S.C. *et al.* Association of *NCF2*, *IKZF1*, *IRF8*, *IFIH1*, and *TYK2* with systemic lupus erythematosus. *PLoS Genet.* **7**, e1002341 (2011).
11. Hirschhorn, J.N. & Daly, M.J. Genome-wide association studies for common diseases and complex traits. *Nat. Rev. Genet.* **6**, 95–108 (2005).
12. Price, A.L. *et al.* Principal components analysis corrects for stratification in genome-wide association studies. *Nat. Genet.* **38**, 904–909 (2006).
13. Devlin, B. & Roeder, K. Genomic control for association studies. *Biometrics* **55**, 997–1004 (1999).
14. Price, A.L., Zaitlen, N.A., Reich, D. & Patterson, N. New approaches to population stratification in genome-wide association studies. *Nat. Rev. Genet.* **11**, 459–463 (2010).
15. de Bakker, P.I.W. *et al.* Practical aspects of imputation-driven meta-analysis of genome-wide association studies. *Hum. Mol. Genet.* **17**, R122–R128 (2008).
16. Lawrence, J.S., Martins, C.L. & Drake, G.L. A family survey of lupus erythematosus. 1. Heritability. *J. Rheumatol* . **14**, 913–921 (1987).
17. So, H.-C., Gui, A.H.S., Cherny, S.S. & Sham, P.C. Evaluating the heritability explained by known susceptibility variants: a survey of ten complex diseases. *Genet. Epidemiol.* **35**, 310–317 (2011).
18. The 1000 Genomes Project Consortium. An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56–65 (2012).
19. Knight, J., Barnes, M.R., Breen, G. and Weale, M.E. Using functional annotation for the empirical determination of Bayes Factors for genome-wide association study analysis. *PLoS One* **6**, e14808 (2011).
20. Morris, D.L. *et al.* Unraveling multiple MHC gene associations with systemic lupus erythematosus: model choice indicates a role for HLA alleles and non-HLA genes in Europeans. *Am. J. Hum. Genet.* **91**, 778–793 (2012).
21. Dilthey, A.T., Moutsianas, L., Leslie, S. & McVean, G. HLA*IMP--an integrated framework for imputing classical HLA alleles from SNP genotypes. *Bioinformatics* **27**, 968–972 (2011).
22. Fairfax, B.P. *et al.* Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. *Science* **343**, 1118 (2014).
23. Fairfax, B.P. *et al.* Genetics of gene expression in primary immune cells identifies cell type-specific master regulators and roles of HLA alleles. *Nat. Genet.* **44**, 502–510 (2012).
24. Raj, T. *et al.* Polarization of the effects of autoimmune and neurodegenerative risk alleles in leukocytes. *Science* **344**, 519–523 (2014).
25. Nica, A.C. *et al.* Candidate causal regulatory effects by integration of expression QTLs with complex trait genetic associations. *PLoS Genet.* **6**, e1000895 (2010).
26. Lewis, M.J. *et al. UBE2L3* polymorphism amplifies NF-κB activation and promotes plasma cell development, linking linear ubiquitination to multiple autoimmune diseases. *Am J Hum Genet.* **96,** 221–34 (2015).

27. Noble, J.A. *et al.* A polymorphism in the *TCF7* gene, C883A, is associated with type 1 diabetes. *Diabetes* **52**, 1579–1582 (2003).
28. International Multiple Sclerosis Genetics Consortium (IMSGC). The expanding genetic overlap between multiple sclerosis and type I diabetes. *Genes Immun*. **10,** 11–14 (2009).
29. Zhang, Y. *et al.* Genes that escape X-inactivation in humans have high intraspecific variability in expression, are associated with mental impairment but are not slow evolving. *Mol. Biol. Evol.* **30**, 2588–2601 (2013).
30. Scofield, R.H. *et al.* Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus patients: support for the notion of a gene-dose effect from the X chromosome. *Arthritis Rheum.* **58**, 2511–2517 (2008).
31. Lanfranco, F., Kamischke, A., Zitzmann, M. & Nieschlag, E. Klinefelter's syndrome. *Lancet* **364**, 273–283 (2004).

Figure legends

Figure 1 Heat map for *cis*-acting gene expression RTC scores from *ex vivo* cells. The heat map includes all genes with evidence of *cis*-regulatory (+/– 1Mb) action by SLE associated SNPs in at least one cell type. The color represents a signed-RTC-score: a positive score indicates that the associated allele in the GWAS is positively correlated with gene expression; a negative score indicates that the associated allele in the GWAS is negatively correlated with gene expression. We set the RTC score to zero if the *P*-value for association was > 0.001. Colors represent the RTC-scores as follows: blue, RTC < –0.9 (GWAS risk allele reduces expression); green, RTC < –0.5 (GWAS risk allele reduces expression); yellow –0.5 < RTC < 0.5; orange, RTC > 0.5 (GWAS risk allele increases expression); red, RTC > 0.9 (GWAS risk allele increases expression). A white block indicates that data were not available for this cell type (see Supplementary Figure 4 for results on lymphoblastoid cell lines), either because the probe data failed QC or the probe was not present in the experiment platform. Clustering was performed on cell types, including only genes with data observed for all cell types (i.e., missing data did not inform cell clustering). Genes were clustered using all available data across cells (missing data were not included when determining distance between pairs of genes if eQTL results were not observed for one of the pairs).

Figure 2 Summary of functional role of likely causal genes in SLE and other autoimmune diseases. The concentric rings in the figure show several layers of evidence to support the functional annotation of likely causal genes for SLE listed in Table 2. The genes are illustrated clockwise in chromosomal order with the grey arcs delineating those loci for which several genes are implicated. **Inner Ring 1** - the gene's functional category, taken from Ingenuity Pathway Analysis; **Middle Ring 2** - the presence of a *cis*-acting eQTL (Figure 1) and/or coding variant and **Innermost Ring 3** - the number of autoimmune diseases (excluding SLE) in Immunobase - Type 1 diabetes (T1D), Celiac disease (CEL), Multiple Sclerosis (MS), Crohn's Disease (CRO), Primary Billiary Cirrhosis (PBC), Psoriasis (PSO), Rheumatoid Arthritis (RA), Ulcerative Colitis (UC), Ankylosing Spondylitis (AS), Autoimmune Thyroid Disease (ATD), Juvenile Idiopathic Arthritis (JIA), Alopecia Areata (AA), Inflammatory Bowel Disease (IBD), Narcolepsy (NAR), Primary Sclerosing Cholangitis (PSC), Sjögren's Syndrome (SJO), Systemic Scleroderma (SSc), Vitiligo (VIT) - previously reported to be associated with the gene.

Table 1: Allelic associations at SLE susceptibility loci following meta–analysis with replication study

SNP	Chr	Position (b37)	Locus[c]	GWAS		Hom *et al*. GWAS		Replication study		Post–replication study meta–analysis		
				P–value	Odds Ratio	P–value	Odds Ratio	P–value	Odds Ratio	P–value	Odds Ratio	95% CI
rs2476601	1	114,377,568	*PTPN22*	8.34E–13	1.39	9.06E–04	1.32	6.00E–15	1.54	1.10E–28	1.43	1.34 – 1.53
rs1801274	1	161,479,745	*FCGR2A*	6.05E–11	1.21	1.78E–02	1.13	8.38E–03	1.10	1.04E–12	1.16	1.11 – 1.21
rs704840	1	173,226,195	*TNFSF4*	1.65E–13	1.26	7.65E–05	1.25	2.32E–04	1.15	3.12E–19	1.22	1.17 – 1.27
rs17849501[a]	1	183,542,323	*SMG7 NCF2*	1.63E–59	2.24	3.96E–05	1.58	2.84E–30	2.08	3.45E–88	2.10	1.95 – 2.26
rs3024505	1	206,939,904	*IL10*	2.55E–03	1.12	3.99E–07	1.42	4.00E–03	1.15	4.64E–09	1.17	1.11 – 1.24
rs9782955	1	236,039,877	*LYST*	5.58E–04	1.12	3.93E–06	1.33	1.38E–03	1.15	1.25E–09	1.16	1.11 – 1.22
rs6740462[a]	**2**	**65,667,272**	***SPRED2***	**2.31E–08**	**1.20**	**9.55E–02**	**1.11**	**4.91E–01**	**0.97**	**2.67E–05**	**1.10**	**1.05 – 1.16**
rs2111485	2	163,110,536	*IFIH1*	3.44E–06	1.15	2.97E–03	1.17	6.52E–05	1.16	1.27E–11	1.15	1.11 – 1.20
rs11889341[a]	2	191,943,742	*STAT4*	1.17E–65	1.75	3.70E–13	1.54	2.16E–48	1.79	5.59E–122	1.73	1.65 – 1.81
rs3768792	**2**	**213,871,709**	***IKZF2***	**2.35E–08**	**1.26**	**5.49E–03**	**1.22**	**7.12E–05**	**1.22**	**1.21E–13**	**1.24**	**1.17 – 1.31**
rs9311676	3	58,470,351	*ABHD6 PXK*	5.37E–06	1.14	7.58E–02	1.10	1.45E–10	1.27	3.06E–14	1.17	1.13 – 1.22
rs564799	**3**	**159,728,987**	***IL12A***	**1.15E–06**	**1.15**	**2.83E–01**	**1.06**	**1.78E–04**	**1.15**	**1.54E–09**	**1.14**	**1.09 – 1.18**
rs10028805	4	102,737,250	*BANK1*	4.50E–10	1.21	4.68E–01	1.04	9.84E–11	1.28	4.31E–17	1.20	1.15 – 1.25
rs7726414	**5**	**133,431,834**	***TCF7 SKP1***	**9.17E–10**	**1.46**	**2.88E–01**	**1.14**	**3.97E–08**	**1.56**	**4.44E–16**	**1.45**	**1.32 – 1.58**
rs10036748	5	150,458,146	*TNIP1*	2.83E–18	1.32	3.36E–07	1.35	2.53E–24	1.50	1.27E–45	1.38	1.32 – 1.45
rs2431697	5	159,879,978	MIR146A	3.23E–14	1.25	2.22E–03	1.18	4.16E–14	1.32	8.01E–28	1.26	1.21 – 1.31
rs1270942	6	31,918,860	MHC class III[d]	1.70E–101	2.52	6.15E–13	1.75	7.43E–60	2.23	2.25E–165	2.28	2.15 – 2.42
rs9462027	6	34,797,241	*UHRF1BP1*	1.80E–05	1.14	1.47E–01	1.09	2.42E–04	1.15	7.55E–09	1.14	1.09 – 1.19
rs6568431	6	106,588,806	*PRDM1 ATG5*	4.33E–12	1.22	2.29E–03	1.17	No Data	No Data	5.04E–14	1.21	1.15 – 1.27
rs6932056[a]	6	138,242,437	*TNFAIP3*	1.23E–16	1.82	8.08E–03	1.47	1.20E–14	1.99	1.97E–31	1.83	1.65 – 2.02
rs849142	7	28,185,891	*JAZF1*	3.49E–05	1.13	4.23E–04	1.20	2.04E–04	1.14	8.61E–11	1.14	1.10 – 1.19
rs4917014	7	50,305,863	*IKZF1*	4.10E–05	1.14	3.25E–03	1.19	1.49E–09	1.27	6.39E–14	1.18	1.13 – 1.24
rs10488631	7	128,594,183	*IRF5*	2.66E–44	1.79	4.50E–17	1.93	2.86E–52	2.12	9.37E–110	1.92	1.81 – 2.03
rs2736340	8	11,343,973	*BLK*	2.14E–16	1.30	6.42E–05	1.27	No Data	No Data	6.28E–20	1.29	1.22 – 1.37
rs2663052[a]	10	50,069,395	*WDFY4*	1.59E–08	1.18	6.25E–02	1.10	No Data	No Data	5.25E–09	1.16	1.10 – 1.22
rs4948496	10	63,805,617	*ARID5B*	1.17E–06	1.15	5.76E–01	0.97	2.76E–08	1.22	1.04E–10	1.14	1.10 – 1.19

rs12802200[a]	11	566,936	*IRF7*	8.43E–09	1.24	2.03E–02	1.18	No Data	No Data	8.81E–10	1.23	1.15 – 1.31
rs2732549[a]	11	35,088,399	*CD44*	1.31E–10	1.21	1.51E–03	1.18	1.88E–13	1.31	1.20E–23	1.24	1.19 – 1.29
rs3794060	**11**	**71,187,679**	***DHCR7 NADSYN1***	**1.13E–04**	**1.13**	**8.18E–02**	**1.11**	**2.61E–23**	**1.47**	**1.32E–20**	**1.23**	**1.18 – 1.29**
rs7941765	11	128,499,000	*ETS1 FLI1*	9.82E–07	1.15	4.64E–03	1.17	1.55E–03	1.12	1.35E–10	1.14	1.10 – 1.19
rs10774625	**12**	**111,910,219**	***SH2B3***	**9.47E–08**	**1.17**	**4.32E–03**	**1.16**	**9.81E–02**	**1.06**	**4.09E–09**	**1.13**	**1.08 – 1.18**
rs1059312	12	129,278,864	*SLC15A4*	3.20E–06	1.14	3.97E–03	1.16	4.14E–07	1.20	1.48E–13	1.17	1.12 – 1.21
rs4902562	**14**	**68,731,458**	***RAD51B***	**4.85E–05**	**1.13**	**1.49E–02**	**1.14**	**5.78E–05**	**1.16**	**6.15E–10**	**1.14**	**1.09 – 1.19**
rs2289583[a]	15	75,311,036	*CSK*	9.35E–09	1.20	1.68E–02	1.14	2.12E–06	1.20	6.22E–15	1.19	1.14 – 1.24
rs9652601[a,b]	**16**	**11,174,365**	***CIITA SOCS1***	**3.86E–07**	**1.17**	**4.00E–01**	**1.05**	**2.71E–15**	**1.36**	**7.42E–17**	**1.21**	**1.15 – 1.26**
rs34572943[a,b]	16	31,272,353	*ITGAM*	1.74E–47	1.78	1.90E–07	1.52	1.04E–24	1.68	3.39E–76	1.71	1.61 – 1.81
rs11644034	16	85,972,612	*IRF8*	1.25E–15	1.34	9.81E–03	1.18	5.42E–04	1.16	9.58E–18	1.25	1.19 – 1.32
rs2286672[b]	**17**	**4,712,617**	***PLD2***	**5.81E–05**	**1.24**	**2.50E–02**	**1.24**	**2.35E–04**	**1.27**	**2.93E–09**	**1.25**	**1.16 – 1.35**
rs2941509	17	37,921,194	*IKZF3*	4.32E–06	1.41	2.34E–01	1.16	6.27E–04	1.35	7.98E–09	1.35	1.22 – 1.49
rs2304256[a]	19	10,475,652	*TYK2*	2.34E–12	1.26	1.51E–02	1.16	No Data	No Data	3.50E–13	1.24	1.17 – 1.31
rs7444[a,b]	22	21,976,934	*UBE2L3*	1.30E–13	1.28	1.89E–01	1.09	3.51E–11	1.32	1.84E–22	1.27	1.21 – 1.33
rs887369[a]	**X**	**30,577,846**	***CXorf21***	**9.25E–07**	**1.16**	**6.62E–02**	**1.23**	**4.55E–04**	**1.14**	**5.26E–10**	**1.15**	**1.10 – 1.21**
rs1734787[a]	X	153,325,446	*IRAK1 MECP2*	2.83E–11	1.57	8.58E–04	1.52	9.54E–06	1.20	1.78E–15	1.31	1.22 – 1.40

Novel SLE associations are shown in bold type.

[a] Imputed data in the Hom *et al* study. IMPUTE info scores: rs17849501 (0.78), rs6740462 (1.00), rs11889341 (0.99), rs6932056 (0.94), rs2663052 (1.00), rs12802200 (0.90), rs2732549 (1.00), rs2289583 (0.99), rs9652601 (1.00), rs34572943 (0.90), rs2304256 (0.95), rs7444 (1.00), rs887369 (0.83), rs1734787 (0.95).

[b] Imputed controls in the replication study. IMPUTE info scores: rs9652601(0.99), rs34572943 (0.91), rs2286672(0.88), rs7444 (0.99).

[c] For rationale for candidate gene selection at the associated loci see Table 2

[d] For more detailed analysis of MHC see text

Table 2: Candidate genes at SLE associated loci

Associated SNP	Chr	Genes within +/–200kb of SNP	Genes within same LD block as SNP[a]	Immune phenotype in murine model[b]	Coding variant	cis eQTLs with SNP	Functional and/or fine mapping studies and Reference		Likely causal genes[c]
rs2476601	1	*MAGI3, PHTF1, RSBN1, PTPN22, BCL2L15 AP4B1, DCLRE1B, HIPK1, OLFML3 MPZ, SDHC, C1orf192*	*RSBN1, PTPN22*	*PTPN22*	*PTPN22*		*PTPN22*	*32*	*PTPN22*
rs1801274	1	*FCGR2A, HSPA6, FCGR3A FCGR2B, FCGR2C, FCGR3B, FCRLA*	*FCGR2A*	*FCGR2A*	*FCGR2A*		*FCGR2A*	*33*	*FCGR2A*
				FCGR2B	*FCGR2B*	*FCGR2A, FCGR2B*	*FCGR2B*	*34*	*FCGR2B*
				FCGR3B	*FCGR3B*		*FCGR3B*	*35*	*FCGR3B*
rs704840	1	*TNFSF4*	*TNFSF4*	*TNFSF4*			*TNFSF4*	*36*	*TNFSF4*
rs17849501	1	*NMNAT2, SMG7, NCF2, ARPC5, RGL1 APOBEC4 RASSF5, EIF2D, DYRK3*	*SMG7, NCF2*	*RASSF5*	*NCF2*	*SMG7*	*NCF2*	*37*	*SMG7, NCF2*
rs3024505	1	*MAPKAPK2, IL10, IL19, IL20 IL24, FAIM3, PIGR, FCAMR*	*IL10*	*MAPKAPK2, IL10 FAIM3, FCAMR*			*IL10*	*38*	*IL10*
rs9782955	1	*LYST, NID1*	*LYST*	*LYST*		*LYST*	*LYST*	*39*	*LYST*
rs6740462	2	*ACTR2, SPRED2*	*SPRED2*						*SPRED2*
rs2111485	2	*DPP4, GCG, FAP, IFIH1, GCA, KCNH7*	*IFIH1*	*IFIH1*	*IFIH1*	*IFIH1*	*IFIH1*	*40*	*IFIH1*
rs11889341	2	*GLS, STAT1, STAT4, MYO1B*	*STAT4*	*STAT1, STAT4*			*STAT4*	*41*	*STAT4*
rs3768792	2	*IKZF2*	*IKZF2*	*IKZF2*			*IKZF2*	*42*	*IKZF2*
rs9311676	3	*ABHD6, RPP14, PXK, PDHB, KCTD6 ACOX2, FAM107A, FAM3D*	*PXK, PDHB*			*ABHD6, PXK*	*ABHD6*	*43*	*ABHD6, PXK*
							PXK	*44*	
rs564799	3	*SCHIP1, IL12A*	*IL12A*	*IL12A*		*IL12A*			*IL12A*
rs10028805	4	*BANK1*	*BANK1*	*BANK1*		*BANK1*	*BANK1*	*45*	*BANK1*
rs7726414	5	*C5orf15, VDAC1, TCF7, SKP1*	*TCF7, SKP1*	*TCF7*		*SKP1*			*TCF7, SKP1*
rs10036748	5	*IRGM, ZNF300, GPX3, TNIP1, ANXA6 CCDC69, GM2A, SLC36A3*	*TNIP1*	*TNIP1 ANXA6*			*TNIP1*	*46*	*TNIP1*
rs2431697	5	*C1QTNF2, C5orf54, SLU7, PTTG1, MIR146A, 3142*	*intergenic*	*PTTG1*			*MIR146A*	*47*	*MIR146A*
rs1270942	6	MHC[d]							
rs9462027	6	*C6orf106, SNRPC, UHRF1BP1 TAF11, ANKS1A*	*UHRF1BP1*			*UHRF1BP1, ANKS1A, C6orf106*	*UHRF1BP1*	*48*	*UHRF1BP1*
rs6568431	6	*PRDM1 ATG5*	*intergenic*	*PRDM1 ATG5*			*PRDM1*	*49*	*PRDM1, ATG5*
							ATG5	*50*	
rs6932056	6	*TNFAIP3 PERP*	*TNFAIP3*	*TNFAIP3 PERP*	*TNFAIP3*		*TNFAIP3*	*51*	*TNFAIP3*

rs849142	7	*JAZF1, CREB5*	*JAZF1*			*JAZF1*			*JAZF1*
rs4917014	7	*ZPBP, C7orf72, IKZF1*	*IKZF1*	*IKZF1*			*IKZF1*	*52*	*IKZF1*
rs10488631	7	*CALU, OPN1SW, CCDC136, FLNC ATP6V1F, IRF5, TNPO3, TSPAN33*	*IRF5, TNPO3*	*IRF5*		*IRF5, TNPO3*	*IRF5*	*53*	*IRF5*
rs2736340	8	*MTMR9, SLC35G5, C8orf12 FAM167A, BLK, GATA4*	*BLK*			*BLK, XKR6*	*BLK*	*54*	*BLK*
rs2663052	10	*WDFY4, LRRC18, VSTM4*	*WDFY4*		*WDFY4*	*WDFY4*	*WDFY4*	*55*	*WDFY4*
rs4948496	10	*ARID5B, RTKN2*	*ARID5B*	*ARID5B*					*ARID5B*
rs12802200	11	*B4GALNT4, PKP3, SIGIRR, ANO9, PTDSS2 RNH1, HRAS, LRRC56, C11orf35, RASSF7 PHRF1, IRF7, CDHR5, SCT, DRD4, DEAF1 EPS8L2, TMEM80, TALDO1*	*LRRC56, LMNTD2 RASSF7, MIR210HG PHRF1, IRF7, CDHR5*	*SIGIRR IRF7*	*IRF7*	*IRF7, RNH1, HRAS, RASSF7, PHRF1, and, TMEM80*	*IRF7*	*56*	*IRF7*
rs2732549	11	*APIP, PDHX CD44, SLC1A2*	*upstream, CD44*	*CD44*			*CD44*	*57*	*CD44*
rs3794060	11	*DHCR7, NADSYN1, KRTAP5*	*DHCR7, NADSYN1*			*DHCR7, NADSYN1*			*DHCR7, NADSYN1*
rs7941765	11	*ETS1, FLI1 CUX2*	*intergenic*	*ETS1 FLI1*			*ETS1 FLI1*	*58 59*	*ETS1 FLI1*
rs10774625	12	*FAM109A, SH2B3 ATXN2, BRAP*	*SH2B3, ATXN2*	*SH2B3*			*SH2B3*	*60*	*SH2B3*
rs1059312	12	*TMEM132C, SLC15A4, GLT1D1*	*SLC15A4*	*SLC15A4*		*SLC15A4*			*SLC15A4*
rs4902562	14	*RAD51B*	*RAD51B*						*RAD51B*
rs2289583	15	*LMAN1L, CPLX3, ULK3, SCAMP2 MPI, FAM219B, COX5A, RPP25 SCAMP5, PPCDC, C15orf39*	*SCAMP5, PPCDC*			*CSK, ULK3, MPI, FAM219B, C15orf39*	*CSK*	*61*	*CSK*
rs9652601	16	*CIITA, DEXI, CLEC16A, RMI2, SOCS1 TNP2, PRM3, PRM2*	*CLEC16A*	*CIITA SOCS1*		*SOCS1, RMI2*	*CIITA SOCS1*	*62 63*	*CIITA, SOCS1*
rs34572943	16	*ZNF668, ZNF646, PRSS53, VKORC1, BCKDK KAT8 PRSS8, PRSS36, FUS, PYCARD C16orf98, TRIM72, PYDC1, ITGAM ITGAX, ITGAD, COX6A2, ZNF843, ARMC5*	*ITGAM*	*ITGAM ITGAX ITGAD PYCARD*	*ITGAM*	*ITGAM, PYCARD*	*ITGAM*	*64*	*ITGAM*
rs11644034	16	*C16orf74, EMC8, COX4I1, IRF8*	*intergenic*	*IRF8*			*IRF8*	*65*	*IRF8*
rs2286672	17	*ALOX15, PELP1, ARRB2, MED11, CXCL16 ZMYND15, TM4SF5, VMO1, GLTPD2 PSMB6, PLD2, MINK1, CHRNE, C17orf107 GP1BA, SLC25A11, RNF167, PFN1, ENO3 SPAG7, CAMTA2, INCA1, KIF1C*	*PLD2*	*ALOX15 CXCL16 INCA1 KIF1C PLD2*	*PLD2*	*RNF167*			*PLD2*
rs2941509	17	*NEUROD2, PPP1R1B, STARD3, TCAP, PNMT PGAP3, ERBB2, MIEN1, GRB7, IKZF3, ZPBP2*	*ERBB2, HER–2, C17orf37 GRB7, IKZF3, ZNFN1A3*	*IKZF3*			*IKZF3*	*66*	*IKZF3*

		GSDMB, ORMDL3, LRRC3C, GSDMA	*ZBPB2, GSDMB*						
rs2304256	19	*DNMT1, S1PR2, MRPL4, ICAM1, ICAM4 ICAM5 ZGLP1, FDX1L, RAVER1, ICAM3, TYK2, CDC37 PDE4A, KEAP1, S1PR5, ATG4D, KRI1*	*TYK2*	*DNMT1, S1PR2 ICAM1, S1PR5 TYK2*	*TYK2*	*TYK2, ICAM3*	*TYK2*	*67*	*TYK2*
rs7444	22	*HIC2, RIMBP3C, UBE2L3, YDJC, CCDC116 SDF2L1, PPIL2, YPEL1, MAPK1*	*UBE2L3 YDJC*	*MAPK1*		*UBE2L3*	*UBE2L3*	*26*	*UBE2L3*
rs887369	X	*CXorf21, GK*	*CXorf21*						*CXorf21*
rs1734787	X	*L1CAM, LCA10, AVPR2, ARHGAP4, NAA10 RENBP, HCFC1, TMEM187, IRAK1, MECP2 OPN1LW, TEX28P2, OPN1MW, TEX28P1 OPN1MW2, TEX28, TKTL1*	*ARHGAP4, NAA10 RENBP, HCFC1 TMEM187, IRAK1 MIR718, MECP2*	*IRAK1*			*IRAK1 MECP2*	*68*	*IRAK1, MECP2*

[a] The LD block is defined as SNPs showing a correlation (r^2) of 0.75 with the associated SNP
[b] The immune phenotype designation is taken from http://www.informatics.jax.org/phenotypes.shtml of genes within +/–200kb of associated SNP
[c] The genes implicated at each locus as potentially causal at each locus
[d] The MHC is not included due to extended LD and gene density at the locus

32. Namjou, B. *et al. PTPN22* association in systemic lupus erythematosus (SLE) with respect to individual ancestry and clinical sub-phenotypes. *PLoS One* **8**, e69404 (2013).
33. Karassa, F.B., Trikalinos, T.A. and Ioannidis, J.P.A. Role of the Fcγ receptor IIa polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: A meta-analysis. *Arthrit. Rheum*. **46**, 1563–71 (2002).
34. Floto, R.A. *et al.* Loss of function of a lupus-associated FcγRIIb polymorphism through exclusion from lipid rafts. *Nat. Med*. **11**, 1056–8 (2005).
35. Fanciulli, M. *et al. FCGR3B* copy number variation is associated with susceptibility to systemic, but not organ-specific, autoimmunity. *Nat. Genet.* **39**, 721–3 (2007).
36. Manku, H. *et al.* Trans-ancestral studies fine map the SLE-susceptibility locus *TNFSF4. PLoS Genet.* **9**, e1003554 (2013).
37. Jacob, C.O. *et al.* Lupus-associated causal mutation in neutrophil cytosolic factor 2 (NCF2) brings unique insights to the structure and function of NADPH oxidase. *P. Natl. Acad. Sci. USA* **109**, E59–67 (2012).
38. Sakurai, D. *et al.* Preferential Binding to Elk-1 by SLE-Associated *IL10* Risk Allele Upregulates *IL10* Expression. PLoS Genet. **9**, e1003870 (2013).
39. Tchernev, V.T. *et al.* The Chediak-Higashi protein interacts with SNARE complex and signal transduction proteins. *Mol Med.* **8**, 56–64 (2002)
40. Molineros, J.E. *et al.* Admixture mapping in lupus identifies multiple functional variants within IFIH1 associated with apoptosis, inflammation, and autoantibody production. *PLoS Genet.* **9**, e1003222 (2013).
41. Namjou, B. *et al.* High-density genotyping of *STAT4* reveals multiple haplotypic associations *with* systemic lupus erythematosus in different racial groups. *Arthritis Rheum.* **60**, 1085–95 (2009).
42. Alexander, T. *et al.* Foxp3+ Helios+ regulatory T cells are expanded in active systemic lupus erythematosus. *Ann. Rheum. Dis.* **72**, 1549–58 (2013).
43. Oparina, N.Y. *et al. PXK* locus in systemic lupus erythematosus: fine mapping and functional analysis reveals novel susceptibility gene *ABHD6. Ann. Rheum. Dis.* ***74***, e14 (2015).
44. Vaughn, S.E. *et al*. Lupus risk variants in the *PXK* locus alter B-cell receptor internalization. *Front. Genet.* **5**, 450 (2014).
45. Castillejo-López C. *et al.* Genetic and physical interaction of the B-cell systemic lupus erythematosus-associated genes *BANK1* and *BLK. Ann. Rheum. Dis.* **71**, 136–42 (2012).
46. Caster, D.J. *et al.* ABIN1 Dysfunction as a Genetic Basis for Lupus Nephritis. *J. Am. Soc. Nephrol.* **24**, 1743–54 (2013).
47. Luo, X. *et al.* A functional variant in *MicroRNA-146a* promoter modulates its expression and confers disease risk for systemic lupus erythematosus. *PLoS Genet*. **7**, e1002128 (2011).
48. Zhang, Y. *et al.* Two missense variants in *UHRF1BP1* are independently associated with systemic lupus erythematosus in Hong Kong Chinese. *Genes Immun.* **12**, 231–4 (2011).
49. Kim, S.J., Gregersen, P.K. and Diamond, B. Regulation of dendritic cell activation by microRNA let-7c and BLIMP1. *J. Clin. Invest.* **123**, 823–33 (2013).
50. Zhou, X. *et al.* Genetic association of *PRDM1-ATG5* intergenic region and autophagy with systemic lupus erythematosus in a Chinese population. *Ann. Rheum. Dis*. **70**, 1330–7 (2011).
51. Adrianto, I. *et al.* Association of a functional variant downstream of *TNFAIP3* with systemic lupus erythematosus. *Nat. Genet.* **43**, 253–8 (2011).

52. Westra, H.-J. *et al.* Systematic identification of *trans* eQTLs as putative drivers of known disease associations. *Nat. Genet.* **45**, 1238–43 (2013).
53. Kottyan, L.C. *et al.* The *IRF5-TNPO3* association with systemic lupus erythematosus (SLE) has two components that other autoimmune disorders variably share. *Hum. Mol. Genet.* **24**, 582–96 (2015).
54. Guthridge, J.M. *et al.* Two functional lupus-associated *BLK* promoter variants control cell-type- and developmental-stage-specific transcription. *Am. J. Hum. Genet.* **94**, 586–98 (2014).
55. Zhao, H. *et al.* An intronic variant associated with systemic lupus erythematosus changes the binding affinity of Yinyang1 to downregulate *WDFY4. Genes Immun.* **13**, 536–42 (2012).
56. Heinig, M. *et al.* A *trans*-acting locus regulates an anti-viral expression network and type 1 diabetes risk. *Nature* **467**, 460–4 (2010).
57. Crispín, J.C. *et al.* Expression of CD44 variant isoforms CD44v3 and CD44v6 is increased on T cells from patients with systemic lupus erythematosus and is correlated with disease activity. *Arthritis Rheum.* **62**, 1431–7 (2010).
58. Zhang, J. *et al.* Epistatic interaction between genetic variants in susceptibility gene *ETS1* correlates with IL-17 Levels in SLE patients. *Ann. Hum. Genet.* **77**, 344–50 (2013).
59. Morris, E.E. *et al.* A GA microsatellite in the *Fli1* promoter modulates gene expression and is associated with systemic lupus erythematosus patients without nephritis. *Arthritis Res. Ther.* **12**, R212 (2010).
60. Mori, T. *et al. Lnk/Sh2b3* controls the production and function of dendritic cells and regulates the induction of IFN-γ–producing T cells. *J. Immunol.* **193**, 1728–36 (2014).
61. Manjarrez-Orduño, N. *et al. CSK* regulatory polymorphism is associated with systemic lupus erythematosus and influences B-cell signaling and activation. *Nat. Genet.* **44**, 1227–30 (2012).
62. Bronson, P.G. *et al.* The rs4774 *CIITA* missense variant is associated with risk of systemic lupus erythematosus. *Genes Immun.* **12**, 667–71 (2011).
63. Fujimoto, M. *et al.* Inadequate induction of suppressor of cytokine signaling-1 causes systemic autoimmune diseases. *Int. Immunol.* **16**, 303–14 (2004).
64. Rhodes, B. *et al.* The *rs1143679* (R77H) lupus associated variant of *ITGAM* (CD11b) impairs complement receptor 3 mediated functions in human monocytes. *Ann. Rheum. Dis.* **71**, 2028–34 (2012).
65. Chrabot, B.S. *et al.* Genetic variation near *IRF8* is associated with serologic and cytokine profiles in systemic lupus erythematosus and multiple sclerosis. *Genes Immun.* **14**, 471–8 (2013).
66. Sun, J., Matthias, G., Mihatsch, M.J., Georgopoulos, K. and Matthias, P. Lack of the transcriptional coactivator OBF-1 prevents the development of systemic lupus erythematosus-like phenotypes in Aiolos mutant mice. *J. Immunol.* **170**, 1699–706 (2003).
67. Shaw, M.H. *et al.* A natural mutation in the Tyk2 pseudokinase domain underlies altered susceptibility of B10.Q/J mice to infection and autoimmunity. *P. Natl. Acad. Sci.* **100**, 11594–9 (2003).
68. Kaufman, K.M. Fine mapping of Xq28: both *MECP2* and *IRAK1* contribute to risk for systemic lupus erythematosus in multiple ancxestral groups. *Ann. Rheum. Dis.* **72**, 437-44 (2013).

ONLINE METHODS

Data: genome-wide association study (GWAS)

We genotyped 4,946 SLE cases and 1,286 healthy controls using the Illumina HumanOmni1-Quad BeadChip (1,140,419 markers). The genotyped controls were mostly from southern Europe, matching our Spanish, Italian and Turkish cases with controls from the same countries. We also used data for 5,727 previously genotyped controls taken from the University of Michigan Health and Retirement Study (HRS). These subjects were genotyped using the Illumina Human2.5M Beadchip (2,443,179 markers).

The clinical features of our GWAS cohort were documented on the basis of standard ACR classification criteria. The experiment was designed to avoid batch effects to the greatest extent possible. All DNA samples were sent to the laboratory at King's College London, UK, where the integrity of the DNA was checked. The GWAS samples were then genotyped at a single laboratory. All data analysis was carried out in the laboratory at King's College.

Genotyping for the GWAS was carried out using 82 plates, processed in 13 batches. Duplicate samples taken from HapMap Phase 3 were added to each plate to check genotyping quality. Case-control status and country of recruitment were randomized across plates as far as possible, in order to avoid artifactual differences in genotyping between plates affecting association statistics.

Our final dataset comprised genotyping of 644,674 SNPs for 4,036 SLE cases and 6,959 controls (1,260 controls of mainly southern European ancestry and 5,699 from the HRS).

Data: Hom *et al.* study

We analyzed data from a previous genome-wide association study of SLE (the Hom *et al.* study), which comprised 1,165 cases following our QC analysis (see Supplementary Text). We used a further 2,107 previously genotyped controls from the NIH CGEMS study, which were genotyped using the Illumina HumanHap550 chip. Owing to the lower density of

genotyping, in some cases data imputed to the density of the 1000 Genomes (1KG) study were used in the analysis of the Hom *et al.* study and the subsequent meta-analysis. Imputed data are identified in tables.

Data: replication study

A cohort of 2,310 cases not included in any previous genetic study of SLE was genotyped using a custom array. The largest group of samples was from the UK, followed by cohorts from France, the USA, Germany and Canada.

The control data for the replication study comprised 3,672 subjects from the HRS cohort (independent of those used in the GWAS), 3,102 subjects from a study of melanoma and 1,202 subjects from a study of blood clotting. These control data were genotyped using the Illumina 2.5M chip. Following QC procedures (Supplementary Text), the final control dataset comprised 6,925 individuals: 3,668 from the HRS, 2,889 from the melanoma study and 368 from the blood clotting study. The final case dataset consisted of 2,018 samples.

In some cases, SNPs identified by our GWAS as genome-wide significant were not present in the replication control data (owing to absent genotyping in one of the three control sets following QC), and so genotypes for those SNPs were imputed (see below). Again, we identify these SNPs in our results tables.

Ethical approval

The UK subjects with SLE in the study were recruited with the study having obtained ethical approval from the London Ethics Committee (MREC/98/2/06 and 06/MRE02/9). Individuals were invited into the study and given information sheets as well as verbal explanations of what the research entailed. For those individuals willing to participate informed written consent was obtained. The recruitment in continental Europe and Canada were subject to local review and ethical approval. Copies of the relevant supporting documentation were sent to the investigators at King's College at the commencement of the study.

Quality control

Initial QC analysis of the genotype data was carried out in accordance with Illumina's Technical Note on Infinium Genotyping Data. *In silico* QC checks were carried out of:

- Individual missingness (3% threshold)
- SNP missingness (3% threshold)
- Identity-by-descent (IBD, 0.125 threshold)
- Population structure
- Minor allele frequency (MAF, 0.002 threshold)
- Autosomal heterozygosity
- X chromosome heterozygosity
- Y chromosome calling and homozygosity
- Hardy-Weinberg equilibrium (control data only)

IBD analysis included checks both within and across cohorts; no subject in the main GWAS or Hom *et al.* study is related to any other subject in either cohort. We calculated principal components for the GWAS data using the EIGENSTRAT algorithm[12], and derived the empirical genomic inflation factor[13,69] for these data. As noted by Price and colleagues[14], the definition of genomic control means that λ_{GC} is proportional to sample size. We therefore report λ_{1000}, the inflation factor for an equivalent study of 1000 cases and 1000 controls[15,70], in the main text, as well as λ_{GC}.

For the replication cohort, population structure was estimated using 46 ancestry informative markers (following QC measures on these SNPs). As described in Supplementary Text, we merged these data with HapMap data to help identify non-European samples. Again, principal components were calculated using the EIGENSTRAT algorithm. 120 subjects that clustered with the non-European HapMap populations were removed from the analysis.

Klinefelter's syndrome

During QC analysis, we identified subjects in our GWAS cohort with abnormal karyotypes, consistent with Klinefelter's syndrome (47, XXY). Three of the 365 male cases in our main GWAS have clinical and genetic data that confirm their status as Klinefelter's sufferers (Supplementary Text). Given that the prevalence of Klinefelter's syndrome in the general population is estimated to be 0.1 – 0.2%[31], this estimate suggests an approximately four- to eight-fold increase in prevalence compared with 46, XY males, consistent with Klinefelter's males and 46, XX females having a similar risk of developing SLE.

Analysis: association

All case-control analysis was carried out using the SNPTEST[71,72] algorithm; we use a standard threshold of $P = 5 \times 10^{-8}$ for reporting genome-wide significance throughout. The inverse variance method was used for meta-analysis. All markers were fully genotyped in the main GWAS (i.e, no imputation was carried out). The imputation carried out for the Hom *et al*. and replication studies, and fine mapping imputation, are described below.

For all SNPs at which we report a novel association with SLE, we compared allele frequencies in the main GWAS controls with those in publically available control cohorts (1KG European samples[18], Wellcome Trust Case Control Consortium (WTCCC) genotypes[73], TwinsUK samples, HapMap CEU population data, and sample genotypes from the Knight laboratory expression data[23]). We tested for a statistically significant ($\alpha = 0.01$) difference in allele frequency between our GWAS and the public controls, using a 1 degree of freedom χ^2 test of allele frequencies. One SNP failed this test (rs1439112, *MGAT5*) and was removed from further analysis. In three further cases, the difference in allele frequency strengthened our observed association. These data are presented in Supplementary Table 7.

Annotation of results

Gene names listed in results tables were identified by overlaying GWAS results onto the UCSC Genome Browser. We adopted a threshold based on linkage disequilibrium: for each

SNP, we noted the set of markers with $R^2 > 0.75$ with respect to the SNP of interest (Table 2).

***Post hoc* QC**

Checks carried out following case-control analysis included examination of plots of raw genotype intensity; this was of particular relevance given the increase in the numbers of relatively rare variants due to the higher density of genotyping (as with imputation, genotype calling is by definition more difficult for rarer variants). We checked that the intensity plots showed clusters of genotypes (i.e., homozygotes or heterozygotes) that were compact and well discriminated. This check was also carried out with stratification by QC group. Plots of intensity were examined for each associated SNP, and for all of the SNPs in the replication study.

Analysis: replication study chip design

We selected SNPs for the replication study based on the results of the meta-analysis of the two GWA studies. At loci with no known association in SLE, we adopted a threshold of $P = 2.5 \times 10^{-05}$, while for loci with previously reported associations the threshold was set at $P = 1 \times 10^{-04}$. This followed the methodology used in Box 1 of the WTCCC study of seven common diseases[73]. This declared SNPs as associated if the posterior odds of association were greater than 10. In that study, the assumption was made that 10 detectable genes were present, so the prior odds of a true association would be in the order of 100,000:1, assuming 1,000,000 independent regions in the genome. Based on the autoimmune genetics literature, we have assumed that there are likely to be as many as 500 genes associated with SLE. We have required posterior odds in favour of a SNP being associated to be >1 (as opposed to >10, which would be advisable if declaring an association rather than choosing SNPs for replication). This gives a *P*-value threshold of 2.5×10^{-05}. For SNPs at loci with previously published SLE associations, we have reduced our threshold for inclusion in the replication study to $P = 1 \times 10^{-04}$. This is because *a priori* we believe these

SNPs are more likely to be at susceptibility loci than those with no evidence of association, increasing the prior odds by at least a factor of 4.

Analysis: 1000 Genomes (1KG) imputation

For imputation, both the main GWAS and the Hom *et al*. data were pre-phased using the SHAPEIT algorithm[74], and then imputed to the density of the 1KG study using IMPUTE[71,72] v2.2.3. Only markers with an IMPUTE INFO score > 0.7 were used in analysis. For SNPs identified in our GWAS as genome-wide significant at which data were absent in the replication study controls, we imputed over a +/– 1Mb region around the SNP of interest.

1KG data were used both to fine map loci and to determine whether multiple signals were present. For this analysis, we carried out a meta-analysis of 1KG imputed GWAS and Hom *et al*. data. Association testing was performed on the 1KG data within a 1 Mb window of the reported SNP. For the MHC, we included the complete 8 Mb region (26–34 Mb) in our analysis. To scan for further independent signals, association tests were performed including the genotype data for the most highly associated SNP as a covariate. If secondary signals were found to be associated by this analysis (with a *P*-value threshold of 5×10^{-08}) and odds ratios were consistent across the single marker and conditional analyses, the secondary signals were reported as independent associations.

In order to address the problem that the most associated (lead SNP, marker with the lowest p-value) variant is not necessarily the best candidate as the true causal variant, we considered markers from the most associated down to a defined cut-off. The cut-off was defined as a Bayes Factor (BF) against the most associated SNP equal to 0.34. This was derived from assuming a prior odds of causality for a non-synonymous SNP equal to 3, taken from an empirical analysis of GWAS annotation[19,75]. Any SNPs above this BF cut-off that were missense variants were declared as more likely candidates than the most associated SNP: assuming that the prior odds of a missense SNP (being causal) against a non-missense SNP to be equal to 3, any missense SNP with a BF > 0.34 will have a

posterior odds > 1 and will therefore have a higher posterior probability than the most associated marker (if the most associated marker is non-missense). Therefore we searched for functional variants within a set of markers where inclusion in this set required a maximum Bayes factor (BF) > 0.34 between the marker and the most associated SNP in the 1KG imputed data. We considered any marker that had a BF > 0.34 with respect to the most associated marker, and noted whether any had functional effects. We calculated an approximate BF following Wakefield[76], using a prior distribution on effect size (odds ratio) that was proportional to MAF (as rare variants are believed to have large effects, while common variants are believed to exert small effects). The BF threshold implies that we believe associations with functional variants, such as missense variants, three times more (say) than intergenic variants that do not correlate with gene expression. We then calculated posterior model probabilities following Maller *et al.*[77], but with prior odds of 3 between missense SNPs and non-missense SNPs; Maller *et al.* use a uniform prior on all model probabilities (all SNPs are considered to have equal weights *a priori*, and therefore the prior odds are 1). We present these results in Supplementary Table 4 where we also, separately, display SNPs with a BF > 0.1 (as a strict threshold of 0.34 does not reflect the uncertainty in prior odds of causality and BF estimates). We also calculated the BF between SNPs presented in Table 1 and the SNPs listed in Supplementary Table 3a and declared that the marker for association had changed if the BF was greater than 10 (equal to "*strong*" evidence on the Jeffreys' scale[78]). These SNPs are annotated in Supplementary Table 3a.

Analysis: the MHC and HLA alleles

We included imputed HLA alleles in analysis of the MHC, allowing us to determine the most likely model of association within this region. HLA imputation was performed using HLA*IMP V2[21] using genotyped SNP data. To determine the best model for association within the HLA alleles alone we ran forward stepwise regression. We then tested the five SNPs listed in Supplementary Tables 6a–c for association, conditional on the HLA alleles. To test whether each of the five SNPs was independent of the HLA alleles (rather than just the alleles in the

best HLA model), we carried out a test conditional on all alleles (i.e., the HLA alleles were used as covariates) in each HLA gene, and for all HLA alleles over all genes. We used a significance threshold at each stage of the stepwise regression of $P = 5 \times 10^{-05}$, which is a Bonferroni adjustment for 204 tests (199 HLA alleles and 5 SNPs), with a familywise Type I error rate of 0.01.

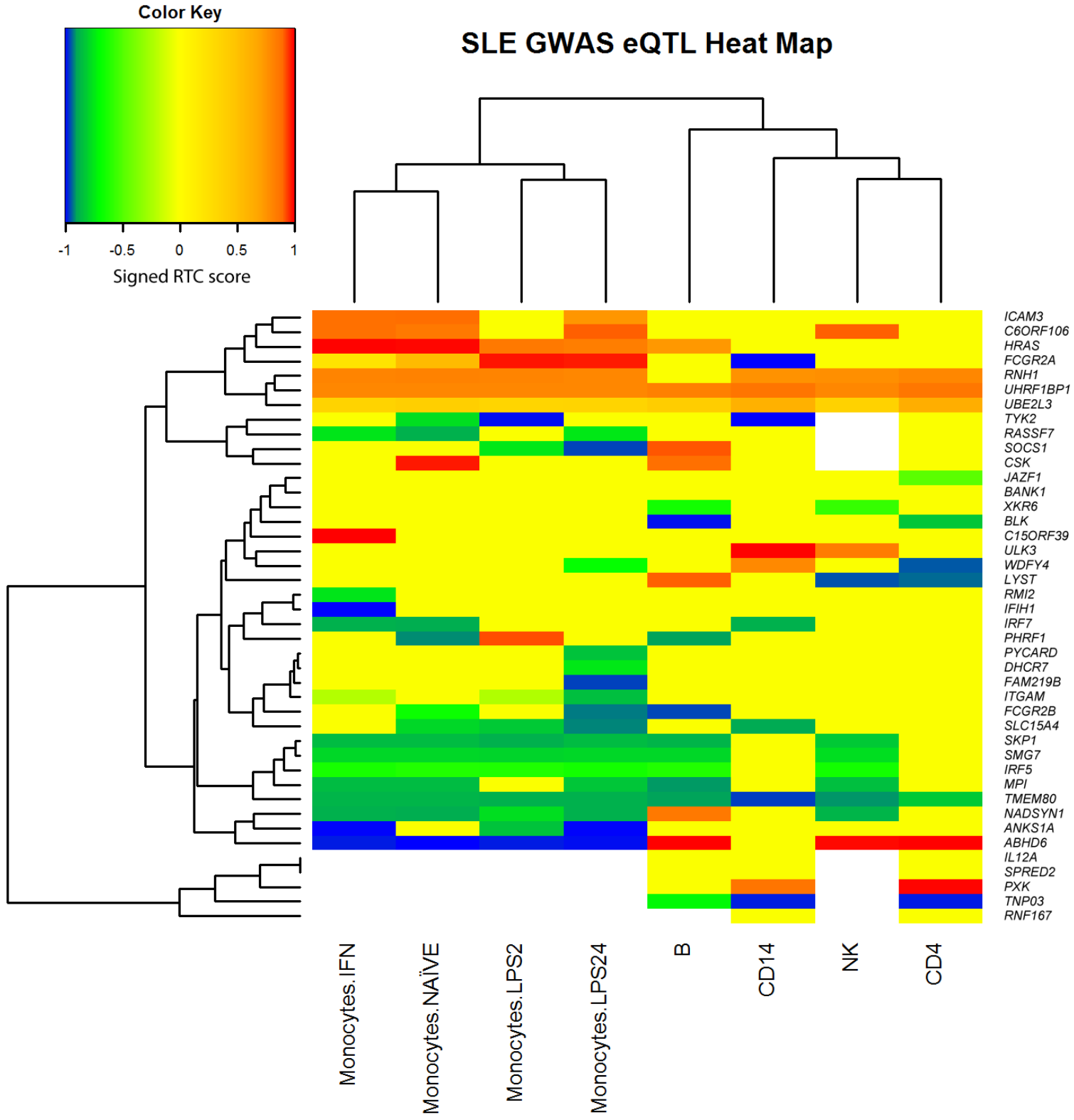
Analysis: gene expression data

Gene expression data were obtained from three sources: firstly, we obtained data from Fairfax *et al.*[22,23] and unpublished data from Fairfax and Knight for NK cells, naïve monocytes, monocytes stimulated by LPS (harvested after 2 hours and 24 hours), IFN and B cells. Secondly, we interrogated the Genevar database for LCL eQTL results, taking results from the MuTHER resource[79]. The CD4 (CD4 T cells) and CD14 (CD14/16 Monocytes) data were obtained from a previous study of gene expression in immune related cells[24]. An adjustment was made for multiple testing using a Bonferroni correction, by counting the number of tests across all loci for genes within +/–1MB of the SLE associated SNP. With a familywise test size of 0.01, the *P*-value threshold was 1.41×10^{-05}.

To test whether observed associations between SNPs and expression levels of *cis*-acting genes were purely due to chance, we calculated the RTC score[25] for all SNP-gene eQTL results displayed in the heat map (Figure 1). This tests the null hypothesis that the GWAS associated SNP and the best eQTL (within a recombination hotspot) are tagging two separate effects, and the observed eQTL is purely due to the LD between the GWAS associated SNP and the "true" eQTL SNP. For our data, we were interested in the distribution of RTC scores, given that eQTL results were generated in multiple cell types. Not all eQTLs were consistently present across all these cells. We therefore plotted the RTC scores against the $-\log_{10}$ *P*-values supporting each *cis* eQTL in all cell types (Supplementary Figures 3a and 3b). Supplementary Figures 3a and 3b show that three genes were outlying: *ITGAM* in two cell types, and *UBE2L3* and *PLD2* in CD4 cells. However, we have strong *a*

priori evidence of a true causal effect on expression by polymorphisms around *UBE2L3*[26]. For *ITGAM*, we note the low RTC scores in Figure 1, which includes all eQTL data for *ITGAM* given that the results are convincing for the eQTL in LPS stimulated monocytes (P = 2.67 x 10^{-19} and RTC = 0.85). We have removed the declaration of an eQTL for *PLD2.* Supplementary Figure 4 displays a heat map for these data using a *t*-statistic.

69. Freedman, M.L. *et al.* Assessing the impact of population stratification on genetic association studies. *Nat. Genet.* **36**, 388–393 (2004).
70. Reich, D.E. & Goldstein, D.B. Detecting association in a case-control study while correcting for population stratification. *Genet. Epidemiol.* **20**, 4–16 (2001).
71. Marchini, J., Howie, B., Myers, S., McVean, G. & Donnelly, P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat. Genet.* **39**, 906–913 (2007).
72. Marchini, J. & Howie, B. Genotype imputation for genome-wide association studies. *Nat. Rev. Genet*. **11**, 499–511 (2010).
73. The Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661–678 (2007).
74. Delaneau, O., Howie, B., Cox, A.J., Zagury, J.-F. & Marchini, J. Haplotype estimation using sequencing reads. *Am. J. Hum. Genet.* **93**, 687–696 (2013).
75. Gagliano, S.A., Barnes, M.R., Weale, M. & Knight, J. A Bayesian method to incorporate hundreds of functional characteristics with association evidence to improve variant Prioritization. *PLoS One* **9**, e98122 (2014).
76. Wakefield, J. Bayes factors for genome-wide association studies: comparison with *P*-values. *Genet. Epidemiol.* **33**, 79–86 (2009).
77. Maller, J.B. *et al.* Bayesian refinement of association signals for 14 loci in 3 common diseases. *Nat. Genet.* **44**, 1294–1301 (2012).
78. Jeffreys, H. Theory of Probability, 3rd ed. (Oxford University Press, Oxford, UK, 1961).
79. Grundberg, E. *et al.* Mapping *cis*- and *trans*-regulatory effects across multiple tissues in twins. *Nat. Genet.* **44**, 1084–1089 (2012).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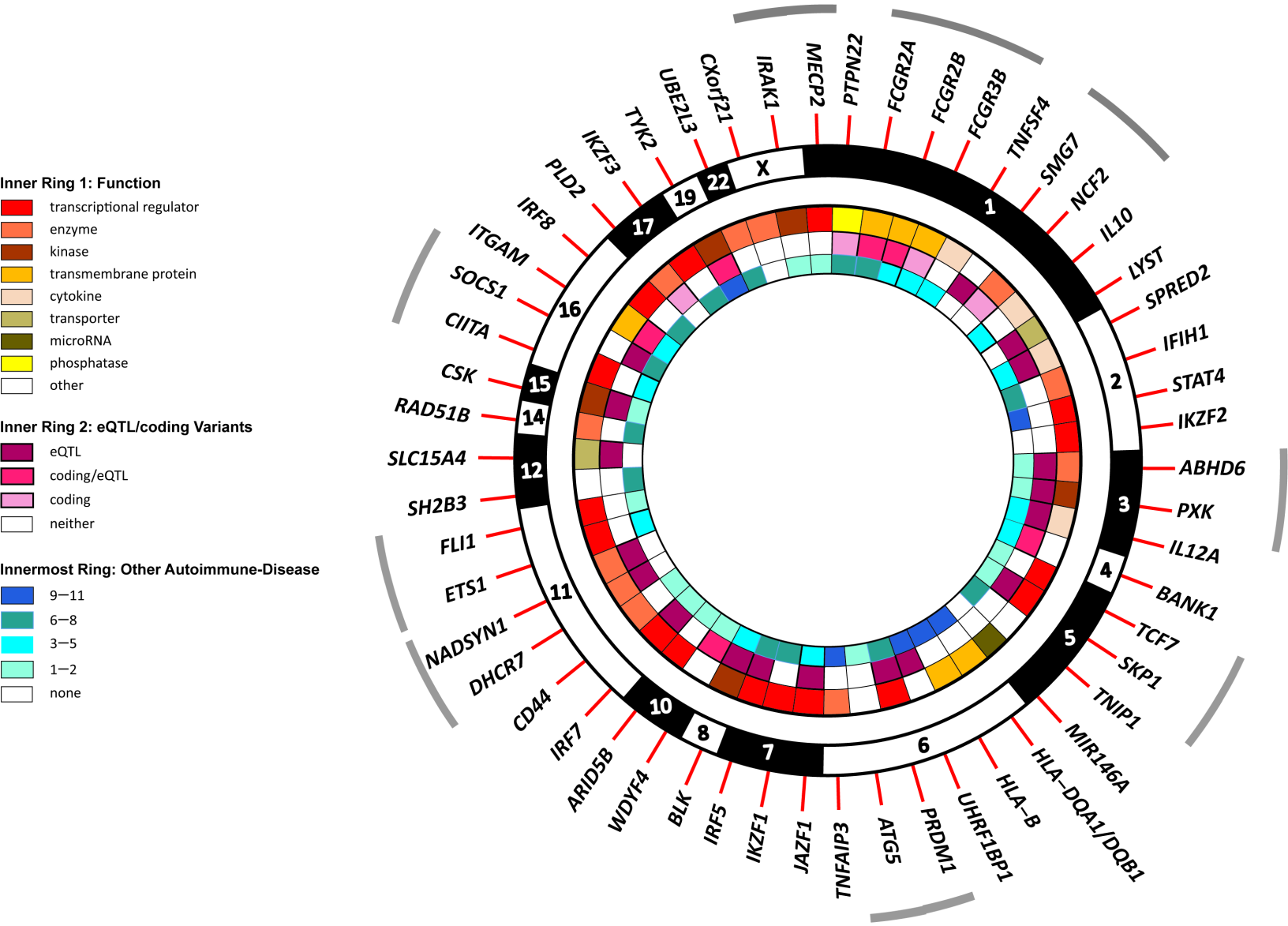
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