Research letter

Genome-wide association study identifies three novel susceptibility loci for systemic lupus erythematosus in Han Chinese

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Dear Editor, Systemic lupus erythematosus (SLE) is a common prototypic autoimmune disease with substantial genetic predispositions. It is more prevalent in Asian than in White people. Genome-wide association studies (GWASs) have discovered more than 80 genetic loci for the risk of SLE,[1] which improves the understanding of SLE aetiology and provides potential therapeutic targets. However, each GWAS finding only confers a relatively small effect, and in total cannot fully explain SLE heritability, suggesting more genetic variants are yet to be discovered.

To detect novel susceptibility loci for SLE, we conducted a two-stage GWAS in a Han Chinese population. All patients met the revised American College of Rheumatology SLE classification criteria.[2] The age-matched controls were recruited without SLE, family history of SLE or any other autoimmune diseases. Each participant provided written informed consent. The study was approved by the institutional review board of Anhui Medical University, China and was conducted according to the Declaration of Helsinki.

In the discovery stage, we performed strict quality control on variants and samples in the SLE GWAS dataset, which have been described before.[2] After quality control, the genotype data of 493 955 autosomal single-nucleotide polymorphisms (SNPs) in 1047 individuals with SLE and 1205 controls were imputed using IMPUTE 2 (http://mathgen.stats.ox.ac.uk/impute/impute_v2.html) together with the 1000 Genomes Project reference data (phase 1 integrated set, March 2012, build 37). The SNPs with imputation INFO scores of $> 0{\cdot}9$ were included in further analyses. A logistic regression model (additive model) was used for single-variant association analysis with sex as a covariate.

In the replication stage, we genotyped 82 top SNPs in an independent cohort of 3509 patients and 8246 controls using the Sequenom MassARRAY (Agena Bioscience, San Diego, CA, U.S.A.) system. The SNPs were chosen if they satisfied several criteria: (i) beyond 500 kilobase (kb) from any SLE locus; (ii) not within the major histocompatibility complex region; (iii) with $P < 5{\cdot}00 \times 10^{-4}$ in the discovery stage; (iv) Hardy–Weinberg equilibrium $P \geq 10^{-4}$ in both controls and cases; (v) minor allele frequency > 1%; (vi) within known susceptibility genes/loci for autoimmune disorders. We tested their association for the risk of SLE in Plink 1·07 (http://zzz.bwh.harvard.edu/plink/) using logistic regression (additive model) with sex as a covariate.

We aggregated the association evidence through a meta-analysis using METAL (http://csg.sph.umich.edu/abecasis/metal/index.html) and evaluated the heterogeneity between the two stages via I^2 and Q statistics. There were 17 SNPs that met the threshold of genome-wide significance but 14 of them failed a Hardy–Weinberg equilibrium test at $P < 10^{-4}$ or with $I^2 > 30\%$. We identified three novel loci associated with disease: *KIT* (rs2855772_C, odds ratio (OR) = 1·40, $P_{meta} = 1{\cdot}21 \times 10^{-15}$), *GPR78* (rs13116227_T, OR = 1·34, $P_{meta} = 3{\cdot}05 \times 10^{-11}$) and *TRAPPC11* (rs10018951_T, OR = 1·31, $P_{meta} = 1{\cdot}18 \times 10^{-14}$) (Table 1).

Rs2855772 is resided in an intron of *KIT*, which is a tyrosine kinase receptor and plays a key role in cell differentiation and survival of immune cells. The *KIT* ligand-binding can promote the activation of signal transducer and activator of transcription (STAT) family members in Janus kinase (JAK)/STAT signalling that is critical in SLE.[3] Moreover, the soluble *KIT* (s*KIT*) level is significantly lower in patients with SLE and is correlated with titre of anti-DNA antibody and SLE Activity Index score. It is also negatively affected by high doses of corticosteroid for SLE therapy.[4]

Rs13116227 locates ~2·2 kb 5′-upstream of *GPR78*, which is a member of G protein–coupled receptor and coupled to stimulatory (Gs) protein resulting in increased cyclic adenosine monophosphate, which then inhibits nuclear factor kappa B activation.[5]

Rs10018951 locates in an intron of the *TRAPPC11* gene and encodes the enhancer regulatory function for *TRAPPC11* in CD14 + monocytes and skin.[6] *TRAPPC11* encodes a component of the transport protein particle (TRAPP) complex. Depletion of *TRAPPC11* will cause a stressed unfolded protein response (UPR). Persistent UPR results in endoplasmic reticulum stress, which in turn is associated with cell dysfunction and apoptosis.[7] Apoptosis-related genes have been found to have more than twofold higher expression levels in patients with SLE with active disease compared with those with inactive disease.[8]

We conducted real-time polymerase chain reaction and expression quantitative trait loci analysis to determine gene expression differences and regulatory effect of SNPs, respectively. We also analysed the correlation between genes' mRNA expression levels and clinical parameters of SLE. Unfortunately, the results were statistically insignificant after correcting for multiple testing.

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Table 1 Three novel genome-wide significant systemic lupus erythematosus single-nucleotide polymorphisms (SNPs) identified in this study

					GWAS				Replication				Meta		
					1047 cases, 1205 controls				3509 cases, 8246 controls				4556 cases, 9451 controls		
					MAF				MAF						
SNP	Chr	Position (hg19)	Gene[a]	Allele[b]	Case	Control	OR (95% CI)	P[c]	Case	Control	OR (95% CI)	P[c]	P_{hwe}	OR	P_{meta}[d]	I^2, %
rs2855772	4	55548475	*KIT*	C/T	0·1433	0·1041	1·44 (1·20–1·72)	$6·44 \times 10^{-5}$	0·1312	0·09772	1·39 (1·27–1·53)	$2·95 \times 10^{-12}$	0·04074	1·40	$1·21 \times 10^{-15}$	0
rs13116227	4	8558266	2·2 kb 5′ of *GPR78*	T/C	0·1299	0·09253	1·46 (1·21–1·77)	$6·37 \times 10^{-5}$	0·1211	0·09561	1·30 (1·18–1·44)	$5·57 \times 10^{-8}$	0·3896	1·34	$3·05 \times 10^{-11}$	13·71
rs10018951	4	184609373	*TRAPPC11*	T/C	0·2101	0·1622	1·37 (1·81–1·60)	$3·60 \times 10^{-5}$	0·193	0·1555	1·30 (1·20–1·41)	$4·86 \times 10^{-11}$	0·5372	1·31	$1·18 \times 10^{-14}$	0

The details of other SNPs selected for the replication study are available from the authors on request. GWAS, genome-wide association studies; MAF, minor allele frequency; CI, confidence interval. [a]Annotated by Haploreg v4·1 (http://archive.broadinstitute.org/mammals/haploreg/haploreg.php); [b]minor allele/major allele; [c]association statistic adjusted for sex; [d]association statistic adjusted for sex and study.

In conclusion, we identified three novel susceptibility regions at *KIT*, *GPR78* and *TRAPPC11* for SLE. These discoveries provide new insights into the genetic and biological basis of SLE.

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Conflicts of interest: none to declare.

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