Meta-analysis of 208370 East Asians identifies 113 susceptibility loci for systemic lupus erythematosus

ABSTRACT

Objective Systemic lupus erythematosus (SLE), an autoimmune disorder, has been associated with nearly 100 susceptibility loci. Nevertheless, these loci only partially explain SLE heritability and their putative causal variants are rarely prioritised, which make challenging to elucidate disease biology. To detect new SLE loci and causal variants, we performed the largest genome-wide meta-analysis for SLE in East Asian populations.

Methods We newly genotyped 10,029 SLE cases and 180,167 controls and subsequently meta-analysed them jointly with 33,488 SLE cases and 14,826 controls from published studies in East Asians. We further applied a Bayesian statistical approach to localise the putative causal variants for SLE associations.

Results We identified 113 genetic regions including 46 novel loci at genome-wide significance (p<5×10^{-8}). Conditional analysis detected 233 association signals within these loci, which suggest widespread allelic heterogeneity. We detected genome-wide associations at six new missense variants. Bayesian statistical fine-mapping analysis prioritised the putative causal variants to a small set of variants (95% credible set size ≤10) for 28 association signals. We identified 110 putative causal variants including 10 putative causal variants with high confidence (posterior probability ≥0.8).

Key messages

What is already known about this subject?

► Genome-wide association studies have identified nearly 100 susceptibility loci for systemic lupus erythematosus (SLE) risk.

► The known SLE loci explain partially the disease heritability.

What does this study add?

► This study identified 113 genomic regions including 46 novel loci for SLE risk.

► The study prioritised 110 putative causal variants including 10 putative causal variants with high confidence (posterior probability ≥0.8).

How might this impact on clinical practice or future developments?

► These findings revealed new genetic basis for SLE and generated molecular mechanisms hypotheses for further investigations.
causal variants with posterior probabilities ≥0.1 for 57 SLE loci, among which we prioritised 10 most likely putative causal variants (posterior probability ≥0.8). Linkage disequilibrium score regression detected genetic correlations for SLE with albumin/globulin ratio ($r_g=-0.242$) and non-albumin protein ($r_p=0.238$).

**Conclusion** This study reiterates the power of large-scale genome-wide meta-analysis for novel genetic discovery. These findings shed light on genetic and biological understandings of SLE.

**INTRODUCTION**

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterised by the production of autoantibodies that damage multiple organs. Considerable genetic predisposition contributes to SLE aetiology. To date, nearly 100 susceptibility loci have been identified for SLE, mainly through genome-wide association studies (GWASs). However, these loci collectively only explain ~30% of SLE heritability and their biology, in terms of causal variants, effector genes and cell types and pathological pathways that mediate genetic effects, has not yet been fully characterised.

Genome-wide association meta-analyses have been performed to uncover new genetic associations for SLE in Asians, Europeans and trans-ancestral populations. However, the study sample sizes were relatively modest, which limits their ability for genetic discovery. GWASs have successfully linked genetic variants with human common diseases and traits. Nonetheless, only ~8% of GWAS participants are East Asians. East Asians have a unique population genetic history and may have ethnicity-specific genetic architecture involved in the development of disease and manifestations. For example, SLE has a remarkably higher prevalence and younger age of onset in Asians. Genetic heterogeneity may explain, at least partly, a remarkably higher prevalence and younger age of onset in development of disease and manifestations. For example, SLE has an opportunity to identify unique genetic associations even for the same diseases and traits that have already been well studied in Europeans.

**METHODS**

**Study participants**

We recruited a total of 10,029 SLE cases and 180,167 healthy controls in three independent case–control cohorts from mainland China, Korea and Japan. We analysed additionally 3,348 SLE cases and 14,826 controls that were published in our previous East Asian SLE GWAS to increase statistical power. All the cases fulfilled the revised American College of Rheumatology SLE classification criteria or were diagnosed by collagen disease physicians (online supplemental table 1). Each participant provided written informed consent.

** Genome-wide association analyses**

We newly genotyped 10,029 SLE cases and 180,167 controls, and revisited raw genome-wide genotype data in 3,348 SLE cases and 14,826 controls from the five published studies. Quality controls were conducted for each of the eight data sets. Genotype imputation was accomplished using reference panels from the 1000 Genomes Project (1KGP) phase 3 and population-specific reference panels in IMPUTE2/4 and MINIMAC4. Within each data set, we filtered out association results based on imputation quality (IMPUTE info ≤0.3), minor allele frequency (MAF) ≤0.5% or Hardy-Weinberg equilibrium test $p<1.0 \times 10^{-6}$ in controls. For each cohort, the association analysis for the X chromosome was conducted separately by sex and then meta-analysed across both men and women. For data sets analysed using a linear mixed model (online supplemental table 1), allelic effects and standard errors were converted to a log-odds scale to correct for case–control imbalance.

**FIXED-EFFECTS META-ANALYSIS**

We aggregated the association summary statistics from the eight data sets using a fixed-effects inverse-variance meta-analysis in METAL. We applied a genomic control correction to each association summary statistic. Heterogeneity

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**Figure 1** Summary of meta-analysis association results and comparison of MAFs for lead variants within the 46 novel loci between East Asians and Europeans. (A) Manhattan plot of genome-wide association meta-analysis results from 208,370 SLE East Asians including 133,778 SLE cases and 194,993 controls. Minus log10-transformed association $p$ values (y-axis) are plotted along chromosomal positions (x-axis). Known and novel loci are highlighted in light blue and pink, respectively. The red dashed line denotes the genome-wide association significance threshold of $p=5 \times 10^{-8}$. The grey dashed line represents $p=10^{-30}$, at which the $y$-axis breaks. (B) Comparison of MAFs of lead variants within the 46 novel loci between East Asians (y-axis) and non-Finnish Europeans (x-axis) in the Genome Aggregation Database (gnomAD) v3. Variants with more than 10 times higher MAFs in East Asians are coloured purple above a red dashed line. MAF, minor allele frequency.
in allelic effect sizes among data sets was assessed using Cochran’s Q statistic. We excluded genetic variants available in only a single data set. We defined SLE susceptibility loci by merging ±250 kilobases (kb) windows around genomewide associated variants to ensure that lead single nucleotide polymorphisms (SNPs) were at least 500 kb apart. We defined lead variants as the most significant SLE-associating variant within each locus. A locus was considered novel if the lead SNP was at least 500 kb away from any previously reported SLE-associated variants.

### Approximate conditional association analysis

To dissect distinct association signals at each SLE locus, we performed an approximate conditional analysis using GCTA COJO with genome-wide meta-analysis summary statistics based on linkage disequilibrium (LD) estimated from 7021 unrelated Chinese controls. The Chinese reference individuals for LD calculation were retrieved from the Chinese using the Illumina Infinium Global Screening Array data (online supplemental table 1), excluding first-degree and second-degree relatives.

### Table 1: Association results for the 46 novel susceptibility loci for systemic lupus erythematosus

| Region | CHR | Position | Variant | EA | NEA | EAF | OR | SE | P value | I² | PHet | N | Nearest gene |
|--------|-----|----------|---------|----|-----|-----|----|----|----------|----|-------|---|---------------|
| 1      | 1   | 117043302| rs9651076| A  | G   | 0.431| 1.117| 0.015| 3.26E–13| 10.7| 0.347| 208| 370 | CD59       |
| 2      | 1   | 157108159| rs11678537| C | G   | 0.107| 1.211| 0.024| 6.68E–16| 43.7| 0.114| 208| 370 | ETV9       |
| 3      | 1   | 201979455| rs3086357 | A  | G   | 0.251| 1.106| 0.017| 4.25E–09| 0.0 | 0.672| 208| 370 | ELF3       |
| 4      | 2   | 7537079  | T       | T  | G   | 0.321| 0.887| 0.017| 8.40E–13| 68.3| 0.007| 208| 370 | LOC10056274|
| 5      | 2   | 111877174| rs37954925| C | G   | 0.878| 1.169| 0.024| 5.11E–11| 56.4| 0.043| 208| 370 | BCL2L11    |
| 6      | 2   | 198929086| rs5752733| T  | C   | 0.260| 1.143| 0.017| 1.25E–14| 0.0 | 0.647| 208| 370 | PLCL1      |
| 7      | 3   | 280720886| rs438613  | T  | C   | 0.588| 0.920| 0.014| 7.52E–09| 69.4| 0.006| 208| 370 | LINC01980  |
| 8      | 3   | 72225916 | rs7637448 | A | C   | 0.871| 0.877| 0.023| 1.28E–08| 0.0 | 0.906| 208| 370 | LINC00870  |
| 9      | 4   | 200048424| rs213694  | T  | A   | 0.280| 0.975| 0.015| 1.11E–09| 55.0| 0.061| 208| 370 | TLR4       |

**Values for the χ² test of genetic heterogeneity;** Region, unique ID for genomic region; SE, Standard error of odds ratio. **P**-values for the χ² test of genetic heterogeneity; Region, unique ID for genomic region; SE, Standard error of odds ratio.
Bayesian statistical fine-mapping analysis

To prioritise causal variants in SLE susceptibility loci, a statistical fine-mapping analysis was performed using FINEMAP v1.4 software, with meta-analysis z-scores and LD matrices estimated from the 7021 Chinese reference individuals. We used default priors and parameters in FINEMAP, assuming at most five causal signals in the ±250 kb region around a lead variant at each SLE locus. FINEMAP computed a posterior probability (PP) for each genetic variant being the true putative causal variant. For each association signal, we ranked the candidate putative causal variants in a descending order of their PPs, and then built a 95% credible set of causal variants by including the ordered variants until their cumulative PP reached 0.95.

Heritability estimation by LD score regression

Overall SLE heritability \( h^2 \) explained by genome-wide variants was estimated using the LD score regression model with LD scores from the 1KGP East Asian descendants, based on an SLE population prevalence of 0.03% in East Asian populations. SLE heritability estimation was further partitioned according to known and novel SLE loci using stratified LD score regression. The boundary of each SLE locus was arbitrarily defined as ±500 kb flanking the lead SLE-risk variant.

Genetic correlation between SLE and other traits by LD score regression

We calculated genetic correlations between 98 traits (39 diseases and 59 quantitative traits) and SLE by using bivariate LD score regression. We used the LD scores from the 1KGP East Asian descendants, limited the genetic variants to the HapMap3 SNPs and removed the variants with extended human leucocyte antigen (HLA) region (chromosome 6: 25 to 34 megabases (Mb)).

Patient and public involvement

Patients and the public were not involved in the design or analysis of this study.

RESULTS

Identification of 46 novel SLE susceptibility loci

We performed a large genome-wide association meta-analysis in 13 377 SLE cases and 194 993 controls of East Asians (online supplemental table 1). To the best of our knowledge, this is the largest genetic association study of SLE to date. The effective sample size \( N_{eff} = 50 072 \) is three-fold and four-fold larger than...
that test statistics were well-calibrated, with a genomic-control inflation factor $\lambda_{GC}=1.06$ (indicating that ancestry effects had been well controlled; online supplemental figure 1). LD score regression\(^9\) showed that polygenic effects (89.4%), rather than biases, primarily caused the inflation residual (estimated mean $\chi^2 = 1.32$ and LD-score intercept $= 1.03$).

We detected 26,379 genetic variants associated with SLE at $p<5 \times 10^{-8}$ within 113 loci (figure 1A and online supplemental table 2), of which 46 were novel (table 1). The pairwise LD between lead variants was low ($LD r^2 < 0.002$). For seven novel loci, MAFs of the lead SNPs were 10-fold higher in East Asians than in Europeans (figure 1B). Two of them and their LD neighbours ($r^2 \geq 0.2$ in either East Asians or Europeans) would be undetectable in Europeans with the same effective sample size and risk magnitude due to low statistical power ($<10\%$; online supplemental table 3).

**Associations at exonic variants**

The meta-analysis identified lead missense variants in two novel loci (CHD23 and LRKK1; figure 2A,B and online supplemental table 2). In addition, we detected three new exonic variants (including two missense variants) within the reported SLE loci including CSK (rs11535760), IKKKB (rs2272736) and TYK2 (rs5882956) genes (figure 2C–E and online supplemental table 2). They were not correlated with previously reported exonic variants within the same genes ($LD r^2 < 0.02$ in East Asians or Europeans; online supplemental table 4), suggesting possible allelic heterogeneity of these genes. We replicated four known associations for missense variants at AHNK2 (rs2819426),\(^{33}\) IRAK1 (rs1059702),\(^{34}\) NCF2 (rs13306575) and WDFY4 (rs7097397; online supplemental table 2).\(^{35,36}\)

**Secondary association signals within SLE loci**

To dissect the source of association signals at each locus, we conducted an approximate conditional analysis using GCTA\(^{27}\) with meta-analysis summary statistics and LD estimates from 7021 unrelated Chinese controls. We acknowledge the limitations of using LD estimation from a single population for a meta-analysis of diverse East Asians. We identified a total of 233 independent association signals with conditional $p<5 \times 10^{-8}$, 169 of which arose from non-HLA regions (online supplemental table 5). We observed from two to four signals at each of 28 non-HLA loci (including seven novel loci). For example, we discovered two distinct association signals within the known STAT4 locus, including the previously reported SNP rs11889341\(^{12}\) and the new insert-deletion variant (indel) rs71403211 (figure 3A). For the 46 novel loci, we discovered 55 distinct signals (online supplemental table 5 and figure 2). We noticed that most of the signal index variants ($n=190$, 82%) are common (MAF $\geq 5\%$) with modest effects (online supplemental table 5).

Approximate conditional analysis detected two novel missense variants at WDFY4 and OAS1 genes. We detected two distinct signals within WDFY4, including the known (rs7097397)\(^{37}\) and a new (rs7072606) missense variant ($LD r^2=0.02$ between two variants in East Asians), which suggests allelic heterogeneity at this locus (figure 3B). We provided for the first time genome-wide association evidence at a missense variant within OAS1 (rs1131476, LD $r^2=0.78$ with rs1051042, which is a known missense variant but only exhibited suggestive significance with SLE in previous study\(^{35}\); figure 3C and online supplemental table 5).
We identified 11 exonic variants including two missense variants within known loci IKKB,9 TYK2,4 WDFY47 and OAS1,21 and three known missense variants within known AHNAK2,45 IRAK145 and NCF2.45 36 These findings suggested allelic heterogeneity within several of these loci and highlighted the disease-risk effects of genes AHNAK2, CSK, IKKB, IRAK1, NCF2, OAS1, TYK2 and WDFY4 within eight known loci, and CHD23 and LRRK1 within two novel loci which potentially alter gene product activity in an allele-specific manner. The novel gene CHD23 plays a role in cell migration40 while LRRK1 encodes a multiple-domain leucine-rich repeat kinase. A previous study observed that LRRK1-deficient mice exhibited a profound defect in B-cell proliferation and survival and impaired B-cell receptor-mediated NF-κB activation,41 which suggested that the association within this region might confer the risk of SLE through modulating the NF-κB pathway and the activities of B cells.

We noted that the Bayesian statistical fine-mapping analysis prioritised the lead missense variant rs35983016 as the most likely putative and 59 quantitative traits in Biobank Japan participants using bivariate LD score regression12 (online supplemental table 7). As expected, we detected significant positive genetic correlations between SLE and two other autoimmune diseases: rheumatoid arthritis (r=0.437) and Graves’ disease (r=0.318). In addition, we found unreported genetic correlations (FDR<0.05) with albumin/globulin ratio (r=−0.242) and non-albumin protein (r=0.238).

**DISCUSSION**

Here, we carried out the largest-ever genome-wide association meta-analysis for SLE and identified 113 risk loci including 46 novel regions for SLE in 208 370 East Asians including 13 377 SLE cases and 194 993 controls. This study revealed new genetic predispositions for SLE and generated hypotheses for further studies to investigate diseases functional mechanisms.

Epidemiological studies have found the higher prevalence of SLE in East Asians and heterogeneous disease manifestations across ethnicities.15 16 Previous investigations suggested genetics might explain the phenotypic heterogeneity.9 We observed that the MAFs of the index variants for several novel genetic associations were much higher in East Asians than in Europeans. Specifically, we suggested two novel loci were more likely specific to East Asians. These findings might help explain the genetic basis of SLE phenotypic heterogeneity between East Asians and Europeans. The results reinforce the power of large-scale genetic association for genetic discovery of SLE in relatively less studied populations.

We identified 11 exonic variants including two missense variants within novel loci CHD23 and LRRK1, four novel missense variants within known SLE loci IKKB,9 TYK2,4 WDFY47 and OAS1,21 and three known missense variants within known AHNAK2,45 IRAK145 and NCF2.45 36 These findings suggested allelic heterogeneity within several of these loci and highlighted the disease-risk effects of genes AHNAK2, CSK, IKKB, IRAK1, NCF2, OAS1, TYK2 and WDFY4 within eight known loci, and CHD23 and LRRK1 within two novel loci which potentially alter gene product activity in an allele-specific manner. The novel gene CHD23 plays a role in cell migration40 while LRRK1 encodes a multiple-domain leucine-rich repeat kinase. A previous study observed that LRRK1-deficient mice exhibited a profound defect in B-cell proliferation and survival and impaired B-cell receptor-mediated NF-κB activation,41 which suggested that the association within this region might confer the risk of SLE through modulating the NF-κB pathway and the activities of B cells. We noted that the Bayesian statistical fine-mapping analysis prioritised the lead missense variant rs35983016 as the most likely putative
causal variant for this association. This variant is highly frequent in our study individuals but is rare in Europeans. The molecular mechanisms in SLE risk worthy further investigations.

In the present study, we localised the putative causal variants for SLE genetic association in high resolution. Our findings indicated that the putative causal variants for the majority of SLE associations were non-coding variants. We provided targets of candidate putative causal variants with high confidence for several SLE loci. These findings are worthy for further exploration in functional experiments. We showed the regulatory effect of one of the putative causal variants in an accompanied paper. We acknowledged the limitation of a small LD reference panel from single population in the Bayesian statistical fine-mapping analysis.

We found for the first time the significant genetic correlations between SLE, albumin/globulin ratio and non-albumin protein. These findings might reflect the renal complications commonly developed in SLE patients who have been reported to have significantly lower albumin/globulin ratio and higher serum globulin than healthy controls in epidemiological studies. These shared genetic basis findings might suggest a common pathway underlying the SLE risk and kidney function in addition to the direct damage of SLE autoantibodies on kidney.

In summary, we detected 46 novel loci for SLE risk in the largest meta-analysis and prioritised putative causal variants for 65 causal signals. This study highlights the power of large-scale genetic association study in East Asian populations. The findings reveal the genetic predispositions for SLE and provide clues for further the investigation of disease mechanisms.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The meta-analysis summary association statistics in the current study are available from the corresponding author on reasonable request.

Ethics approval The study protocol was approved by the Institutional Review Board at each participating institute and the meta-analysis study was additionally approved by the Institutional Review Board at Anhui Medical University, Hangzhou Hospital of Anhui Medical University, and the Ibaraki University Hospital of Rheumatic Diseases, and RIKEN Center for Medical Sciences.

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REFERENCES

1 Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. Nat Rev Rheumatol 2016;12:605–20.
2 Guerra SG, Vyse TJ, Cunningham Graham DS. The genetics of lupus: a functional perspective. Arthritis Res Ther 2012;14:211.
3 Getaeva V, Sandling JK, Hom G, et al. A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and LL1 as risk loci for systemic lupus erythematosus. Nat Genet 2009;41:1234–7.
4 Cunningham Graham DS, Morris DL, Bhanage BR, et al. Association of FCN2, IKZF1, IRF8, IFH1, and TYK2 with systemic lupus erythematosus. PLoS Genet 2011;7:e1002341.
5 Kasaoka Y, Shimane K, Kochi Y, et al. Genome-wide association study identifies AFF1 as a susceptibility locus for systemic lupus erythematosus in Japanese. PLoS Genet 2012;8:e1002455.
6 Kim K, Bang SY, Lee H-S, et al. The HLA-DRB1 amino acid positions 11-13-26 explain the majority of SLE-MHC associations. Nat Commun 2014;5:5902.
7 Ikazaki S, Ishigaki K, Kochi Y, et al. PD4A is a genetic determinant to systemic lupus erythematosus and involved in murine autoimmune phenotypes. Ann Rheum Dis 2019;78:509–18.
8 Morris DL, Sheng Z, Yang Z, et al. Genome-wide association meta-analysis in Chinese and European individuals identifies ten new loci associated with systemic lupus erythematosus. Nat Genet 2016;48:940–6.
9 Catalina MD, Owen KA, Labonte AC, et al. The pathogenesis of systemic lupus erythematosus: harnessing big data to understand the molecular basis of lupus. J Autoimmun 2020;110:102359.
10 Sun C, Molineros JE, Looger LL, et al. High-Density genotyping of immune-related loci identifies new SLE risk variants in individuals with Asian ancestry. Nat Genet 2016;48:323–30.
11 Bentham J, Morris DL, Graham DSC, et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. Nat Genet 2014;47:1457–64.
12 Buniello A, MacArthur JAL, Cerezo M, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. Nucleic Acids Res 2019;47:D1005–12.
13 Sinau G, Williams SM, Tishkoff SA. The missing diversity in human genetic studies. Cell 2019;177:26–31.
14 Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006;15:308–18.
15 Morris SA, Isenberg DA. A study of the influence of ethnology on serology and clinical features in lupus. Lupus 2017;26:17–26.
16 Ishigaki K, Akiyama M, Kanai M, et al. Large-Scale genome-wide association study in a Japanese population identifies novel susceptibility loci across different diseases. Nat Genet 2020;52:669–79.
17 Auton A, Brooks LD, et al. 1000 Genomes Project Consortium. A global reference for human genetic variation. Nature 2015;526:68–74.
18 Kim Y, Kim B, Han B. The Korean reference genome Project: construction of the reference panel for imputation analysis. Presented at the 6th Annual Meeting of The American Society of Human Genetics; October 6, 2015, Baltimore, MD, 2015.
19 Byszcz C, Freeman C, Peitova D, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562:203–9.
20 Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet 2009;5:e1000529.
21 Das S, Forer L, Schönherr S, et al. Next-Generation genotype imputation service and methods. Nat Genet 2016;48:1284–7.
22 Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–75.
23 Marchini J, Howie B. Genotype imputation for genome-wide association studies. Nat Rev Genet 2010;11:499–511.
Systemic lupus erythematosus

25 Cook JP, Mahajan A, Morris AP. Guidance for the utility of linear models in meta-analysis of genetic association studies of binary phenotypes. European Journal of Human Genetics 2017;25:240–5.

26 Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26:2190–1.

27 Yang J, Ferreira T, Morris AP, et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. Nat Genet 2012;44:369–75.

28 Benner C, Spencer CCA, Havulinna AS, et al. FINEMAP: efficient variable selection using summary data from genome-wide association studies. Bioinformatics 2016;32:1493–501.

29 Bulik-Sullivan BK, Loh P-R, Finucane HK, et al. LD Score regression distinguishes confounding from polygenicity in genomewide association studies. Nat Genet 2015;47:1236–41.

30 Chen P-W, Luo R, Jian X, et al. The ARF6 GTPase-activating proteins ARAP2 and ACAP1 define distinct endosomal compartments that regulate integrin α5β1 traffic. J Biol Chem 2014;289:30237–48.

31 Morimoto K, Baba Y, Shinoara H, et al. LRRK1 is critical in the regulation of B-cell responses and CARMA1-dependent NF-κB activation. Sci Rep 2016;6:25738.

32 Zhang Y, Zhang J, Yang J, et al. Meta-Analysis of GWAS on two Chinese populations followed by replication identifies novel genetic variants on the X chromosome associated with systemic lupus erythematosus. Hum Mol Genet 2015;24:274–84.

33 Armstrong DL, Eisenstein M, Zidovetzki R, et al. Systemic lupus erythematosus-associated neutrophil cytosolic factor 2 mutation affects the structure of NADPH oxidase complex. J Biol Chem 2015;290:12595–602.

34 Armstrong DL, Eisenstein M, Zidovetzki R, et al. Systemic lupus erythematosus-associated neutrophil cytosolic factor 2 mutation affects the structure of NADPH oxidase complex. J Biol Chem 2015;290:12595–602.

35 Kim-Howard X, Sun C, Molineros JE, et al. Allelic heterogeneity in NCF2 associated with systemic lupus erythematosus (SLE) susceptibility across four ethnic populations. Hum Mol Genet 2014;23:1656–68.

36 Yang J, Ferreira T, Morris AP, et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. Nat Genet 2012;44:369–75.

37 Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26:2190–1.

38 Wang L, Zhu C, Zhu Z, et al. Exome-wide association study identifies four novel loci for systemic lupus erythematosus in Han Chinese population. Ann Rheum Dis 2018;77:417.

39 Zhang Y, Zhang J, Yang J, et al. Meta-Analysis of GWAS on two Chinese populations followed by replication identifies novel genetic variants on the X chromosome associated with systemic lupus erythematosus. Hum Mol Genet 2015;24:274–84.

40 Zhang Y, Zhang J, Yang J, et al. Meta-Analysis of GWAS on two Chinese populations followed by replication identifies novel genetic variants on the X chromosome associated with systemic lupus erythematosus. Hum Mol Genet 2015;24:274–84.

41 Kwon OC, Lee JS, Ghang B, et al. Predicting eventual development of lupus nephritis at the time of diagnosis of systemic lupus erythematosus. Semin Arthritis Rheum 2018;48:462–6.