EXTENDED REPORT

Identification of *ST3AGL4*, *MFHAS1*, *CSNK2A2* and *CD226* as loci associated with systemic lupus erythematosus (SLE) and evaluation of SLE genetics in drug repositioning

Yong-Fei Wang,[1] Yan Zhang,[2] Zhengwei Zhu,[3] Ting-You Wang,[1] David L Morris,[4] Jiangshan Jane Shen,[1] Huoru Zhang,[1] Hai-Feng Pan,[5] Jing Yang,[1] Sen Yang,[3] Dong-Qing Ye,[5] Timothy J Vyse,[4] Yong Cui,[6] Xuejun Zhang,[3] Yujun Sheng,[3] Yu Lung Lau,[1] Wanling Yang[1]

Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2018-213093).

For numbered affiliations see end of article.

Correspondence to
Dr Yan Zhang, Guangzhou Women and Children's Medical Center, Guangzhou, China; yannizy@gmail.com, Dr Yujun Sheng, Institute/Department of Dermatology, No.1 Hospital, Anhui Medical University, Hefei, China ; ahmusyj@163.com, Prof Yu Lung Lau, Department of Paediatrics and Adolescent Medicine, The University of Hong Kong; lauylung@hku.hk and Dr Wanling Yang, Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong; yangwl@hku.hk

Y-FW, YZ and ZZ contributed equally.

Received 22 January 2018
Revised 19 March 2018
Accepted 19 March 2018
Published Online First 6 April 2018

To cite: Wang Y-F, Zhang Y, Zhu Z, *et al*. *Ann Rheum Dis* 2018;**77**:1078–1084.

ABSTRACT

Objectives Systemic lupus erythematosus (SLE) is a prototype autoimmune disease with a strong genetic component in its pathogenesis. Through genome-wide association studies (GWAS), we recently identified 10 novel loci associated with SLE and uncovered a number of suggestive loci requiring further validation. This study aimed to validate those loci in independent cohorts and evaluate the role of SLE genetics in drug repositioning.

Methods We conducted GWAS and replication studies involving 12 280 SLE cases and 18 828 controls, and performed fine-mapping analyses to identify likely causal variants within the newly identified loci. We further scanned drug target databases to evaluate the role of SLE genetics in drug repositioning.

Results We identified three novel loci that surpassed genome-wide significance, including *ST3AGL4* (rs13238909, p_{meta}=4.40E-08), *MFHAS1* (rs2428, p_{meta}=1.17E-08) and *CSNK2A2* (rs2731783, p_{meta}=1.08E-09). We also confirmed the association of *CD226* locus with SLE (rs763361, p_{meta}=2.45E-08). Fine-mapping and functional analyses indicated that the putative causal variants in *CSNK2A2* locus reside in an enhancer and are associated with expression of *CSNK2A2* in B-lymphocytes, suggesting a potential mechanism of association. In addition, we demonstrated that SLE risk genes were more likely to be interacting proteins with targets of approved SLE drugs (OR=2.41, p=1.50E-03) which supports the role of genetic studies to repurpose drugs approved for other diseases for the treatment of SLE.

Conclusion This study identified three novel loci associated with SLE and demonstrated the role of SLE GWAS findings in drug repositioning.

INTRODUCTION

Systemic lupus erythematosus (SLE (MIM 152700)) is a prototype autoimmune disease with a strong genetic component in its pathogenesis. To date, genome-wide association studies (GWAS) have identified more than 80 SLE-associated loci.[1–7] However, these susceptibility loci taken together only explained less than 30% of disease heritability,[6 7] suggesting that there are many more loci to be identified.

The current SLE GWAS were mainly performed in European and East Asian populations.[6] Through combining GWAS from the two ethnicities, we recently identified 10 novel loci associated with SLE and uncovered a number of loci with suggestive association signal.[6] In this study, we carried out replication studies for those suggestive loci in three independent cohorts, involving a total of 6585 SLE cases and 8435 healthy controls of Chinese ancestry.

Although GWAS studies have achieved great success in mapping disease loci, the vast majority of GWAS findings have not impacted clinical practice such as disease prognosis or treatment which is an area worth further exploration.[8] To date, a number of studies have demonstrated potential applications for GWAS findings in drug repositioning and new drug development.[9–12] In this study, we evaluated the role of SLE genetics in drug repositioning by scanning drug target databases and protein interactions between these molecular targets and SLE susceptibility genes. The results suggest a potential application of SLE GWAS findings in drug repositioning.

METHODS

Participants

This study was designed in two stages. The GWAS datasets used in discovery stage were from our previous studies.[6] Samples for the three GWAS datasets were collected from Hong Kong (612 cases and 2193 controls, HK_GWAS); Anhui Province, mainland China (1047 cases and 1205 controls, AH_GWAS) and Europe (4036 cases and 6959 controls, EUR_GWAS). For replication studies, one of the replication cohorts was from Hong Kong (1673 cases and 1457 controls, HK_rep), and the other two independent cohorts were both from Anhui Province in mainland China, AH_rep1 (3575 cases and 5730 controls) and AH_rep2 (1337 cases and 1248 controls). All the cases fulfilled the revised criteria of the American College of Rheumatology for diagnosis of SLE.[13] The corresponding controls for replication cohorts were geographically and ethnically matched with the cases. The studies were approved by the respective institutional review boards, and all subjects gave informed consent.

Quality control in the discovery stage

For each GWAS cohort, we performed prephasing using SHAPEIT[14] and conducted imputation using IMPUTE2[15] with 1000 Genomes Project data as reference (phase I integrated set, March 2012, build 37). Single nucleotide polymorphisms (SNPs) with imputation INFO score <0.9 were filtered out. For each GWAS cohort, we removed SNPs with >5% missing data or with minor allele frequency (MAF) <1%, and subjects with >5% missing data. We then tested for Hardy-Weinberg equilibrium (HWE) in each GWAS dataset and removed SNPs with HWE p<1.00E-04 in the controls. We performed association analysis for each of the three studies separately based on an additive model using SNPTEST.[16] To combine association results from different GWAS datasets, we performed meta-analysis based on the inverse variance-based method from METAL.[17]

Candidate loci selection and genotyping in the replication stage

SNPs with meta p value <5E-05 in the discovery stage were selected for further validation. SNPs within 200 kilobase pair (kbp) of known loci for the disease (±200 kbp of the reported SNP)[6] were excluded. Twenty-eight SNPs were chosen for further validation. We first used Sequenom to genotype the selected SNPs in samples from HK_rep and AH_rep1. Twenty-four SNPs were successfully genotyped with a call rate higher than 90%. SNP rs763361 failed HWE test (p<1.00E-04) in the controls of AH_rep1 cohort. SNPs satisfying the following criteria were selected for the second replication stage using samples from AH_rep2: (1) with association p value <0.1 in either HK_rep or AH_rep1 cohort; (2) the direction of association in HK_rep and AH_rep1 cohorts was the same as that in the GWAS. Five SNPs were selected and replicated in AH_rep2 cohort using TaqMan genotyping method. SNP rs13238909 failed to be replicated in AH_rep2 cohort because of low call rate (<70%).

Fine-mapping and functional analyses for variants at the newly identified loci

We extracted all variants that passed quality control in the newly identified loci, with the boundaries determined by recombination rate <10 cM/Mb.[18] A fine-mapping algorithm, PAINTOR V.3.0,[19 20] was used to calculate the posterior probability of causality for each variant in a given locus, based on a multiethnic model. To refine the model, all annotations on DNase-seq peaks were integrated. The credible sets of variants that are 70% likely to contain the causal variants were defined as putative causal variants. To further evaluate the regulatory role of the likely causal variants, epigenomic annotations, such as data on DNase-seq, H3K27ac and H3K4me1 peaks from immune-related cell lines were collected from Encyclopedia of DNA Elements (ENCODE) and ROADMAP Epigenomics projects.[21 22] Expression quantitative trait loci (eQTL) in lymphoblastoid cell lines (LCLs) as well as in naive and stimulated monocytes were also obtained from previous studies.[23 24] To ask whether associations from GWAS and an eQTL are driven by the same underlying genetic effect, we applied COLOC[25] to calculate the posterior probability of a shared causal effect (PP4) between GWAS data and eQTL data, using default prior probability.

Identification of putative SLE susceptibility genes

We tallied genes in the surrounding regions (±200 kb) of reported risk loci for SLE, excluding the major histocompatibility complex (MHC) region. The reported SLE loci were retrieved from Morris *et al*.[6] On average, about five genes in each locus were mapped. To highlight potential genes that are regulated by risk variants, genes in the susceptibility loci supported by any one of the following biological annotations would be defined as putative risk genes: (a) genes with missense variants also being SLE-associated variants or in high linkage disequilibrium (LD) with them (r^2>0.8); (b) genes whose expression is associated with reported SLE variants in cis, the significant eQTLs were collected from immune-related cell types, including T cells,[26 27] B cells,[28] monocytes,[26 28] LCLs[23 27 29] and whole blood[30]; (c) genes that are differentially expressed or methylated in SLE, these data were collected from previous studies[31–34]; (d) genes that are prioritised by DAPPLE[35] or PrixFixe.[36] The tools selected likely risk genes based on commonality in functional annotations from different associated loci. The putative risk genes would be assigned to the ones that are closest to the reported variants if genes within the loci do not have any biological supports for being risk genes.

Drug repositioning for SLE treatment

To evaluate the role of SLE genetics in drug repositioning, we curated the targets of approved drugs for SLE treatment by scanning two databases, the DrugBank V.4.3[37] and the Therapeutic Target Database V.4.3.02.[38] We used protein–protein interaction (PPI) information from InWeb[39] to evaluate the potential relationships between SLE risk genes and drug targets. The graphics of PPI network were generated using Cytoscape V.3.5.1.[40]

RESULTS

Identification of novel SLE susceptibility loci

We selected 28 loci showing suggestive association signals (p<5E-05) from meta-analysis of the three SLE GWAS datasets on both European and Chinese populations (see the Methods section).[6] We then conducted a replication study for those selected loci in 6585 SLE cases and 8435 healthy controls of Chinese ancestry. The selected variants were first genotyped in HK_rep and AH_rep1 cohorts using Sequenom. After that, five variants were further examined using TaqMan assays in the AH_rep2 cohort (see the Methods section).

We then performed meta-analysis on the data from both GWAS and replication cohorts, involving a total of 12 280 cases and 18 828 controls, and identified four loci surpassed genome-wide significance (table 1): rs13238909 (*ST3AGL4*, p_{meta}=4.40E-08, OR=0.85), rs2428 (*MFHAS1*, p_{meta}=1.17E-08, OR=1.13), rs2731783 (*CSNK2A2*, p_{meta}=1.08E-09, OR=1.12) and rs763361 (*CD226*, p_{meta}=2.45E-08, OR=1.12). Among them, the *CD226* locus (rs763361) was recently reported to be associated with SLE in the Korean population.[7]

Fine-mapping and functional implications of newly identified susceptibility loci

To explore functional implications of the four newly identified susceptibility loci, we first performed fine-mapping using PAINTOR[19 20] and identified 9, 1, 2 and 26 putative causal variants at *ST3AGL4*, *MFHAS1*, *CSNK2A2* and *CD226* loci, respectively (see online supplementary table S1). We then integrated these results with annotations on epigenomic markers and cis-regulatory elements, derived from three major immune-related cells including LCLs, T cells and monocytes. These analyses indicated that the putative causal variants in *CSNK2A2* and *CD226* loci might regulate gene expression in a cell type-specific manner (see online supplementary table S2).

The *CSNK2A2* locus presents an illustrative example. We observed that the replicated variant (rs2731783) in the locus

Table 1 Summary statistics for the four newly identified loci that are associated with SLE

SNP	Gene region	Chr	Position (hg19)	Ref/alt allele	Cohorts*	RAF_cases	RAF_controls	OR	SE	P values	P_het
rs13238909	*ST3AGL4*	7	67076373	A/G	Meta (10 943/17 544)	–	–	0.85	0.03	4.40E-08	0.84
					EUR GWAS (4036/6959)	0.151	0.174	0.86	0.04	1.00E-04	
					HK GWAS (612/2193)	0.031	0.042	0.73	0.18	8.42E-02	
					AH_GWAS (1047/1205)	0.062	0.069	0.89	0.12	3.35E-01	
					HK_rep (1673/1457)	0.029	0.033	0.89	0.14	4.35E-01	
					AH_rep1 (3575/5730)	0.054	0.065	0.82	0.06	2.68E-03	
rs2428	*MFHAS1*	8	8641145	T/C	Meta (10 943/17 544)	–	–	1.13	0.02	1.17E-08	0.04
					EUR GWAS (4036/6959)	0.511	0.477	1.15	0.03	1.67E-06	
					HK GWAS (612/2193)	0.866	0.864	1.02	0.09	8.34E-01	
					AH_GWAS (1047/1205)	0.860	0.874	0.88	0.09	1.56E-01	
					HK_rep (1673/1457)	0.880	0.861	1.18	0.07	3.31E-02	
					AH_rep1 (3575/5730)	0.886	0.868	1.17	0.05	4.43E-04	
rs2731783	*CSNK2A2*	16	58253460	A/G	Meta (12 280/18 828)	–	–	1.12	0.02	1.08E-09	0.16
					EUR GWAS (4036/6959)	0.176	0.153	1.17	0.04	3.68E-05	
					HK GWAS (612/2193)	0.327	0.303	1.12	0.07	1.08E-01	
					AH_GWAS (1047/1205)	0.382	0.345	1.17	0.06	1.10E-02	
					HK_rep (1673/1457)	0.327	0.308	1.09	0.06	1.19E-01	
					AH_rep1 (3575/5730)	0.367	0.353	1.06	0.03	5.67E-02	
					AH_rep2 (1337/1248)	0.411	0.362	1.23	0.06	5.64E-04	
rs763361	*CD226*	18	67531642	T/C	Meta (8705/13 062)	–	–	1.12	0.02	2.45E-08	0.30
					EUR GWAS (4036/6959)	0.501	0.474	1.12	0.03	7.52E-05	
					HK GWAS (612/2193)	0.347	0.334	1.06	0.07	3.90E-01	
					AH_GWAS (1047/1205)	0.365	0.354	1.05	0.06	4.39E-01	
					HK_rep (1673/1457)	0.330	0.299	1.15	0.06	2.49E-02	
					AH_rep2 (1337/1248)	0.360	0.313	1.24	0.06	3.33E-04	

*Number of cases/number of controls for each cohort.
AH, Anhui Province; Chr, chromosome; EUR, Europe; GWAS, genome-wide association studies; HK, Hong Kong; P het, p value for heterogeneity test across different cohorts; RAF, frequency of reference allele; Ref/alt, reference/alternative; rep, replication cohort; SLE, systemic lupus erythematosus.

was a shared signal in European (p=3.68E-05) and Asian GWAS (p=3.01E-03), being the peak association signal on meta-analysis of GWAS data from the two ethnicities (p=3.07E-07, figure 1A). In addition to rs2731783, 80 other variants in this region also showed strong association with SLE (p<1.00E-05). We applied fine-mapping algorithm PAINTOR and identified two likely causal variants (rs2550368 and rs2731741) in the region which were located around 17 kbp upstream of *CSNK2A2* and 35 kbp upstream of *CCDC113* (figure 1B). Both variants are in high LD with rs2731783 (r^2>0.95 in both European and Asian populations).

We further examined epigenomic annotations in this region with the aim of dissecting the functional implications of the putative causal variants. Data on DNase hypersensitive peaks suggest that this region is highly active in LCLs, but not in T cells and monocytes. Consistent with the DNase cell type-specific signature, the two putative casual variants seem to reside in an LCL-specific enhancer that is defined by both H3 lysine 27 acetylation (H3K27ac) and H3 lysine 4 monomethylation (H3K4me1) markers (figure 1C).

We then asked which gene(s) is/are potential target(s) for the putative causal variants through examining correlations between the genotypes and expression levels of nine genes within 200 kbp of the putative causal variants. We found that the risk allele (rs2550368-G) was associated with reduced expression of *CSNK2A2* (Spearman p=5.0E-10) and *CCDC113* (Spearman p=5.1E-06) in LCLs, but not in naïve and stimulated monocytes (figure 1D,E). We further used a Bayesian method[25] to test for colocalisation between SLE GWAS and eQTL signals (see the Methods section). The results showed a high posterior probability for a shared causal effect (PP4=96.1%) between SLE association and *CSNK2A2* expression in LCLs (see online supplementary figure S1), suggesting that the signals for SLE GWAS and eQTL were likely driven by the same causal variant. Compared with *CSNK2A2* expression in LCLs, we observed a lower posterior probability for a shared causal effect (PP4=79.4%) between SLE association and *CCDC113* expression (see online supplementary figure S1). The expression level of *CCDC113* was also significantly lower than that of *CSNK2A2* (paired t-test p<2.2E-16, figure 1E) in LCLs. Taken together, these results suggest that the putative causal variants may regulate expression of *CSNK2A2* through affecting enhancer activities in B lymphocytes.

Evaluation of SLE genetics in drug repositioning

To evaluate the role of SLE genetics in drug repositioning, we identified 78 putative SLE risk genes by integrating multiple annotation sources (see online supplementary table S3) and obtained 30 genes targeted by SLE drugs (see online supplementary table S4). Although only *NFKBIA* was mapped as both an SLE risk gene and a pharmacological target for SLE, 18 of the 78 SLE risk genes (23.1%) were found encoding proteins interacting with SLE drug targets (figure 2A). The proportion is significantly greater than that for genes in general within the PPI network (OR=2.41, χ^2 p=1.50E-03). Instead of using putative SLE risk genes, we repeated the analysis using protein-coding genes within the flanking regions (±200 kbp) of SLE-associated SNPs. The result showed similar trend, but was insignificant (OR=1.32, χ^2 p=0.123), probably due to the inclusion of many unrelated genes in the associated loci.

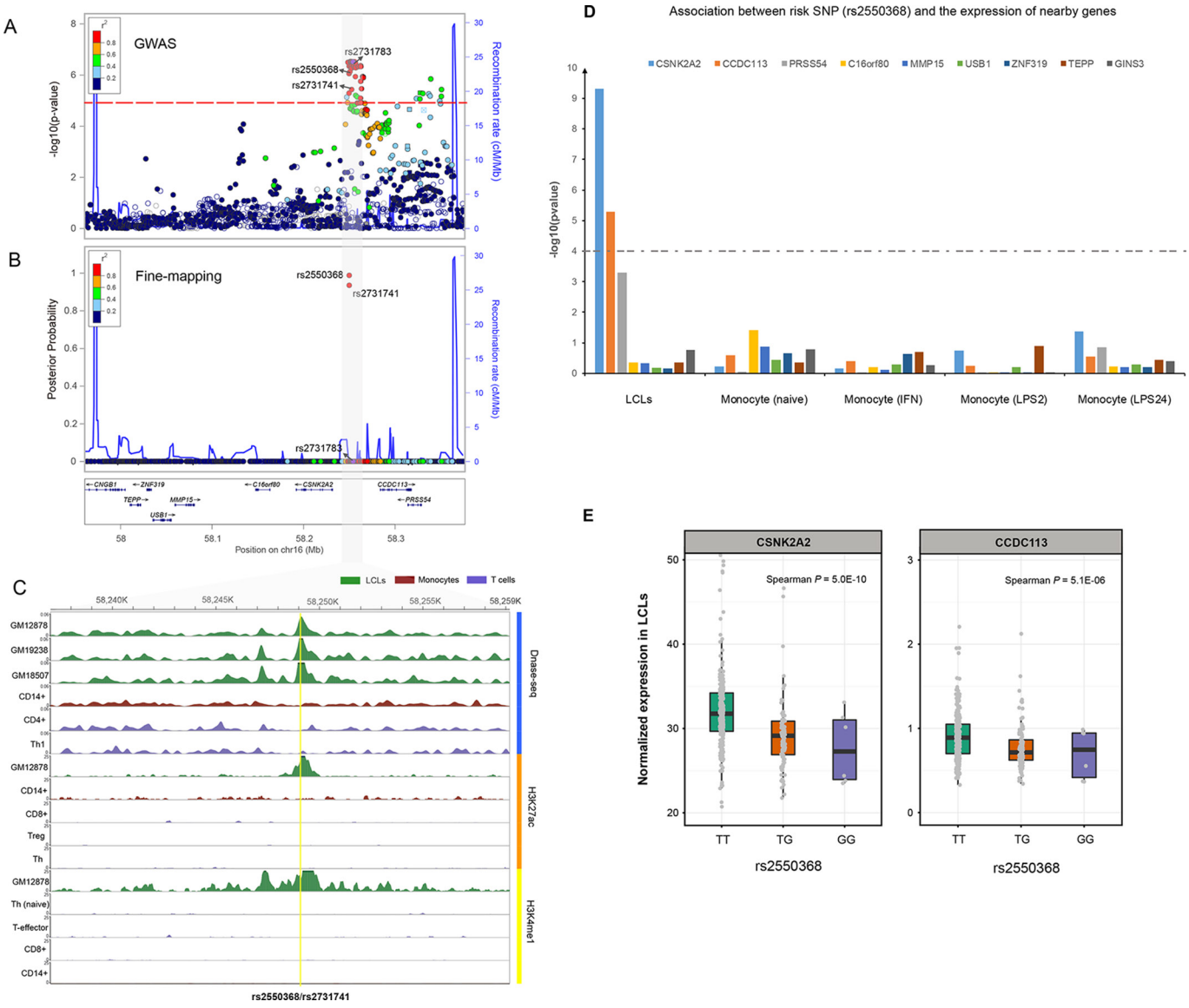

Figure 1 Fine-mapping and functional implications for variants in *CSNK2A2* locus. (A) Regional plot of SLE GWAS associations. (B) Posterior probability of causality for each variant in the region. (C) Overlap between the putative risk variants and functional annotations in LCLs (green), monocytes (red) and T cells (purple). (D) Associations between the risk SNP (rs2550368) and expression of its nearby genes in LCLs, naïve and stimulated monocytes. Y axis indicates –log10(*p values*) for the associations. (E) Expressions of *CSNK2A2* and *CCDC113* in LCLs are associated with the genotype of putative causal variant (rs2550368). GWAS, genome-wide association studies; LCL, lymphoblastoid cell line; SLE, systemic lupus erythematosus.

In contrast, we observed no significant enrichment in interaction between the putative SLE risk genes and targets of drugs not intended for SLE (OR=1.08, χ^2 p=0.849). To further confirm the result, we extended the analyses using drugs intended for unrelated diseases with numbers of targets comparable with that of SLE drugs, namely glaucoma and type 2 diabetes (T2D) which included 25 and 28 drug targets, respectively (see online supplementary tables S5 and S6). We showed that the proportion of putative SLE risk genes interacting with glaucoma drug targets is not significantly different from that expected by chance (OR=1.22, Fisher exact test p=0.682) which was also similar for T2D drugs (OR=1.27, Fisher exact test p=0.562).

DISCUSSION

In this study, we identified three novel loci associated with SLE (*ST3AGL4*, *MFHAS1* and *CSNK2A2*) and also confirmed the association of *CD226* locus with SLE. From the original GWAS datasets, we observed that the statistical power of these newly identified loci was much lower in Asians than that in Europeans. This could be attributed to smaller sample size and lower MAFs (except for rs2731783) in Asian GWAS. For example, the MAF of newly identified SNP rs13238909 in Asians (<7%) is lower than that in Europeans (>15%). We further revisited the data and confirmed that the genotyping quality was good (see online supplementary table S7) and seemed not a factor affecting the association.

We identified putative causal variants at the newly identified loci through fine-mapping algorithms, and further analyses suggested that the putative causal variants in *CSNK2A2* locus may regulate expression of *CSNK2A2* through affecting enhancer activities in B-lymphocytes. *CSNK2A2* encodes an enzyme (CK2) that phosphorylates a number of immune-related TFs and JAK2, playing an important role in JAK-STAT activation.[41] Although the data from public domains are consistent

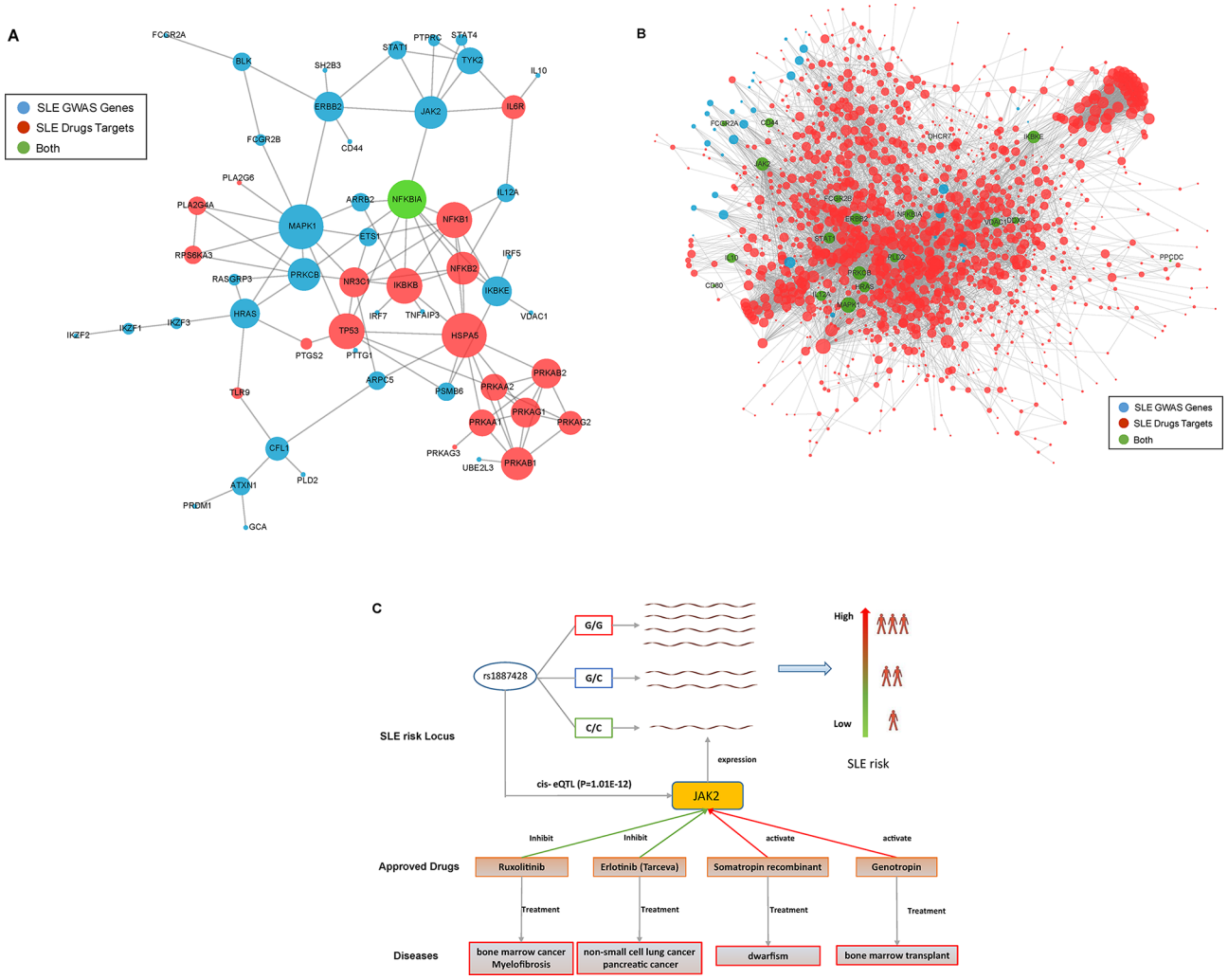

Figure 2 Drug repositioning for the systemic lupus erythematosus (SLE) treatment (A) protein–protein interaction (PPI) network of putative SLE risk genes and genes targeted by SLE drugs. Blue nodes represent SLE risk genes, red nodes indicate genes targeted by SLE drugs. *NFKB1A*, which is considered a risk gene for SLE and a target by SLE drugs, is labelled in green. (B) PPI network of SLE risk genes and genes targeted by all drugs. (C) Illustration of the potential of jakinibs for SLE treatment and the potential side-effect of jak-activators for patients with SLE. GWAS, genome-wide association studies.

here, further molecular assays (eg, CRISPR-Cas9 editing) are needed to confirm the function of these variants and the mechanism of the association.

Understanding the connection between genetic findings and pharmaceutical targets will facilitate translation of GWAS findings to clinical utility in future. Our study demonstrated that SLE risk genes are more likely to be interacting proteins with targets of the approved SLE drugs. We further found 19 SLE risk genes as targets of drugs not intended for SLE (figure 2B), providing a clue to repurposing existing drugs for the SLE treatment. For example, ruxolitinib and erlotinib (Tarceva) are Food and Drug Administration (FDA)-approved drugs indicated for cancers (figure 2C), functioning as *JAK1* and *JAK2* inhibitors (jakinibs). *JAK2* is a risk gene for SLE, encoding a kinase closely involved in JAK/STAT, interferon and cytokine signalling.[42] eQTL data demonstrated that the risk allele (rs1887428-G) was associated with increased expression of *JAK2* (p=1.01E-12).[30] Based on these information, we speculate a potential of jakinibs for the treatment of SLE. Recent studies on mouse model provide certain support for the hypothesis which have demonstrated that ruxolitinib could attenuate cutaneous lupus development in a mouse model.[43] The drug is also now being tested for treatment of other inflammatory diseases (NCT01950780, NCT02809976).[44 45] Similarly, we found an experimental drug, momelotinib (CYT387, NCT01969838) which was designed as an inhibitor for both TBK1/IKBKE and JAK/STAT signalling.[46] Since both *JAK2* and *IKBKE* have been reported as SLE susceptibility loci,[6] we speculate that momelotinib may be an efficacious drug for SLE treatment as it targets more than one SLE-related pathways (see online supplementary figure S2).

In contrast, we speculate that two drugs (somatropin-recombinant and Genotropin), functioning as *JAK2* activators, may accelerate disease progress if given to patients with SLE (figure 2C). A recent survey may support our concern which showed that 12 individuals out of 3745 cases who reported side effects of Genotropin to FDA during the period from 2004 to 2012 developed SLE. The percentage (0.3204%) is nearly nine times greater than any other drugs (0.0362%).[47]

There are a few caveats in these analyses, since both lists of the causal genes for disease associations and targeted genes for treatment options can be incomplete, and inaccurate at times. For example, the ways used to identify SLE risk genes may miss the real causal genes as the real target could be mapped far away from the associated variants.[48] In addition, the validity of drug

repositioning also depends on our knowledge of the targets of existing drugs. Thus, more investigations are necessary to lead to repurposing of existing drugs for SLE treatment, and to gain further insight from genetic findings.

Author affiliations
[1]Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Guangzhou Institute of Paediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China
[3]Institute/Department of Dermatology, No.1 Hospital, Anhui Medical University, Hefei, China
[4]Division of Genetics and Molecular Medicine, King's College London, London, UK
[5]Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, China
[6]Departmentof Dermatology, China-Japan Friendship Hospital, Beijing, China

Acknowledgements The authors thank Hong Kong PhD fellowship scheme (HKPF), HKU Postgraduate Scholarships and the Edward & Yolanda Wong Fund for supporting postgraduate students who participated in this work.

Contributors WY, YLL, YZ, YS and Y-FW designed the association study. Y-FW and YZ wrote the manuscript. WY and JJS revised the manuscript. YZ selected SNPs for validation. YZ, ZZ, YS, HZ, H-FP, JY, SY, D-QY, XZ and YC designed and performed replication studies. Y-FW designed and performed fine-mapping studies. Y-FW and T-YW designed and performed the study of drug repositioning. DLM and TJV shared systemic lupus erythematosus association data in European populations.

Funding WY, YS and Y-FW received grant support from National Key Research and Development Program of China (2017YFC0909001). WY and YLL received support from Research Grant Council of Hong Kong (GRF 17146616, 17125114, HKU783813M). YZ received grant support from National Natural Science Foundation of China (Grant No. 81601423). YS, XZ and YC received grant support from National Key Basic Research Program of China (2014CB541901) and National Natural Science Foundation of China (Grant No.81402590).

Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster and Institutional Ethical Committee of the first affiliated hospital of Anhui Medical University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data request should be sent to yangwl@hku.hk.

REFERENCES

1 Harley JB, Alarcón-Riquelme ME, Criswell LA, *et al*. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. *Nat Genet* 2008;40:204–10.
2 Han JW, Zheng HF, Cui Y, *et al*. Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. *Nat Genet* 2009;41:1234–7.
3 Yang W, Shen N, Ye DQ, *et al*. Genome-wide association study in Asian populations identifies variants in ETS1 and WDFY4 associated with systemic lupus erythematosus. *PLoS Genet* 2010;6:e1000841.
4 Yang W, Tang H, Zhang Y, *et al*. Meta-analysis followed by replication identifies loci in or near CDKN1B, TET3, CD80, DRAM1, and ARID5B as associated with systemic lupus erythematosus in Asians. *Am J Hum Genet* 2013;92:41–51.
5 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* 2015;47:1457–64.
6 Morris DL, Sheng Y, Zhang Y, *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.
7 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.
8 Visscher PM, Brown MA, McCarthy MI, *et al*. Five years of GWAS discovery. *Am J Hum Genet* 2012;90:7–24.
9 Okada Y, Wu D, Trynka G, *et al*. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 2014;506:376–81.
10 Visscher PM, Wray NR, Zhang Q, *et al*. 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am J Hum Genet* 2017;101:5–22.
11 Manolio TA. Bringing genome-wide association findings into clinical use. *Nat Rev Genet* 2013;14:549–58.
12 Nelson MR, Tipney H, Painter JL, *et al*. The support of human genetic evidence for approved drug indications. *Nat Genet* 2015;47:856–60.
13 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
14 Delaneau O, Marchini J. 1000 Genomes Project Consortium. Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. *Nat Commun* 2014;5:3934.
15 Howie B, Fuchsberger C, Stephens M, *et al*. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat Genet* 2012;44:955–9.
16 Marchini J, Howie B, Myers S, *et al*. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet* 2007;39:906–13.
17 Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 2010;26:2190–1.
18 Myers S, Bottolo L, Freeman C, *et al*. A fine-scale map of recombination rates and hotspots across the human genome. *Science* 2005;310:321–4.
19 Kichaev G, Pasaniuc B. Leveraging Functional-Annotation Data in Trans-ethnic Fine-Mapping Studies. *Am J Hum Genet* 2015;97:260–71.
20 Kichaev G, Yang WY, Lindstrom S, *et al*. Integrating functional data to prioritize causal variants in statistical fine-mapping studies. *PLoS Genet* 2014;10:e1004722.
21 Bernstein BE, Birney E. ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012;489:57–74.
22 Kundaje A, Meuleman W, Ernst J, *et al*. Integrative analysis of 111 reference human epigenomes. *Nature* 2015;518:317–30.
23 Lappalainen T, Sammeth M, Friedländer MR, *et al*. Transcriptome and genome sequencing uncovers functional variation in humans. *Nature* 2013;501:506–11.
24 Fairfax BP, Humburg P, Makino S, *et al*. Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. *Science* 2014;343:e1246949.
25 Giambartolomei C, Vukcevic D, Schadt EE, *et al*. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet* 2014;10:e1004383.
26 Raj T, Rothamel K, Mostafavi S, *et al*. Polarization of the effects of autoimmune and neurodegenerative risk alleles in leukocytes. *Science* 2014;344:519–23.
27 Gutierrez-Arcelus M, Lappalainen T, Montgomery SB, *et al*. Passive and active DNA methylation and the interplay with genetic variation in gene regulation. *Elife* 2013;2:e00523.
28 Fairfax BP, Makino S, Radhakrishnan J, *et al*. Genetics of gene expression in primary immune cells identifies cell type-specific master regulators and roles of HLA alleles. *Nat Genet* 2012;44:502–10.
29 Xia K, Shabalin AA, Huang S, *et al*. seeQTL: a searchable database for human eQTLs. *Bioinformatics* 2012;28:451–2.
30 Westra HJ, Peters MJ, Esko T, *et al*. Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat Genet* 2013;45:1238–43.
31 Ko K, Koldobskaya Y, Rosenzweig E, *et al*. Activation of the Interferon Pathway is Dependent Upon Autoantibodies in African-American SLE Patients, but Not in European-American SLE Patients. *Front Immunol* 2013;4:309.
32 Lee HM, Mima T, Sugino H, *et al*. Interactions among type I and type II interferon, tumor necrosis factor, and beta-estradiol in the regulation of immune response-related gene expressions in systemic lupus erythematosus. *Arthritis Res Ther* 2009;11:R1.
33 Lee HM, Sugino H, Aoki C, *et al*. Underexpression of mitochondrial-DNA encoded ATP synthesis-related genes and DNA repair genes in systemic lupus erythematosus. *Arthritis Res Ther* 2011;13:R63.
34 Absher DM, Li X, Waite LL, *et al*. Genome-wide DNA methylation analysis of systemic lupus erythematosus reveals persistent hypomethylation of interferon genes and compositional changes to CD4+ T-cell populations. *PLoS Genet* 2013;9:e1003678.
35 Rossin EJ, Lage K, Raychaudhuri S, *et al*. Proteins encoded in genomic regions associated with immune-mediated disease physically interact and suggest underlying biology. *PLoS Genet* 2011;7:e1001273.
36 Taşan M, Musso G, Hao T, *et al*. Selecting causal genes from genome-wide association studies via functionally coherent subnetworks. *Nat Methods* 2015;12:154–9.
37 Law V, Knox C, Djoumbou Y, *et al*. DrugBank 4.0: shedding new light on drug metabolism. *Nucleic Acids Res* 2014;42:D1091–7.
38 Zhu F, Shi Z, Qin C, *et al*. Therapeutic target database update 2012: a resource for facilitating target-oriented drug discovery. *Nucleic Acids Res* 2012;40:D1128–36.
39 Lage K, Karlberg EO, Størling ZM, *et al*. A human phenome-interactome network of protein complexes implicated in genetic disorders. *Nat Biotechnol* 2007;25:309–16.
40 Shannon P, Markiel A, Ozier O, *et al*. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* 2003;13:2498–504.
41 Zheng Y, Qin H, Frank SJ, *et al*. A CK2-dependent mechanism for activation of the JAK-STAT signaling pathway. *Blood* 2011;118:156–66.
42 Villarino AV, Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak-STAT signaling in the immune system. *Nat Immunol* 2017;18:374–84.
43 Chan ES, Herlitz LC, Jabbari A. Ruxolitinib Attenuates Cutaneous Lupus Development in a Mouse Lupus Model. *J Invest Dermatol* 2015;135:1912–5.
44 Mesa RA. Ruxolitinib, a selective JAK1 and JAK2 inhibitor for the treatment of myeloproliferative neoplasms and psoriasis. *IDrugs* 2010;13:394–403.

45 Mackay-Wiggan J, Jabbari A, Nguyen N, *et al*. Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. *JCI Insight* 2016;1:e89790.
46 Barbie TU, Alexe G, Aref AR, *et al*. Targeting an IKBKE cytokine network impairs triple-negative breast cancer growth. *J Clin Invest* 2014;124:5411–23.
47 MedsFacts. Study of possible correlation between systemic lupus erythematosus and genotropin. 2012 http://factmedcom/report-GENOTROPIN-causing-SYSTEMIC%20LUPUS%20ERYTHEMATOSUSphp.
48 Claussnitzer M, Dankel SN, Kim KH, *et al*. FTO Obesity Variant Circuitry and Adipocyte Browning in Humans. *N Engl J Med* 2015;373:895–907.