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

Xianyong Yin [1,2,3,4,5,6], Kwangwoo Kim [7], Hiroyuki Suetsugu,[8,9,10] So-Young Bang,[11,12] Leilei Wen,[1,2,3] Masaru Koido,[9,13] Eunji Ha,[7] Lu Liu,[1,2,3] Yuma Sakamoto,[14] Sungsin Jo,[12] Rui-Xue Leng [15], Nao Otomo,[8,9,16] Viktoryia Laurynenka,[17] Young-Chang Kwon,[12] Yujun Sheng,[1,2,3] Nobuhiko Sugano [18], Mi Yeong Hwang,[19] Weiran Li,[1,2,3] Masaya Mukai,[20] Kyungheon Yoon,[19] Minglong Cai,[1,2,3] Kazuyoshi Ishigaki,[9,21,22,23] Won Tae Chung,[24] He Huang,[1,2,3] Daisuke Takahashi,[25] Shin-Seok Lee,[26] Mengwei Wang,[1,2,3] Kohei Karino,[27] Seung-Cheol Shim,[28] Xiaodong Zheng,[1,2,3] Tomoya Miyamura,[29] Young Mo Kang,[30] Dongqing Ye [15], Junichi Nakamura,[31] Chang-Hee Suh,[32] Yuanjia Tang,[33] Goro Motomura,[10] Yong-Beom Park,[34] Huihua Ding,[33] Takeshi Kuroda,[35] Jung-Yoon Choe,[36] Chengxu Li,[5] Hiroaki Niiro,[37] Youngho Park,[12] Changbing Shen,[38,39] Takeshi Miyamoto,[40] Ga-Young Ahn,[11] Wenmin Fei,[5] Tsutomu Takeuchi,[41] Jung-Min Shin,[11] Keke Li,[5] Yasushi Kawaguchi,[42] Yeon-Kyung Lee,[11] Yongfei Wang [43], Koichi Amano,[44] Dae Jin Park,[11] Wanling Yang [43], Yoshifumi Tada,[45] Ken Yamaji,[46] Masato Shimizu,[47] Takashi Atsumi,[48] Akari Suzuki,[49] Takayuki Sumida,[50] Yukinori Okada [51,52], Koichi Matsuda,[53,54] Keitaro Matsuo,[55,56] Yuta Kochi,[57] Japanese Research Committee on Idiopathic Osteonecrosis of the Femoral Head, Leah C Kottyan [17,58], Matthew T Weirauch,[17,58] Sreeja Parameswaran,[17] Shruti Eswar,[17] Hanan Salim,[17] Xiaoting Chen,[17] Kazuhiko Yamamoto [49], John B Harley,[17,58,59] Koichiro Ohmura,[60] Tae-Hwan Kim [11,12], Sen Yang,[1,2,3] Takuaki Yamamoto,[61] Bong-Jo Kim,[19] Nan Shen [17,33,62], Shiro Ikegawa,[8] Hye-Soon Lee,[11,12] Xuejun Zhang,[1,2,3,63] Chikashi Terao [9,64,65], Yong Cui,[5] Sang-Cheol Bae [11,12]

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For numbered affiliations see end of article.

Correspondence to
Dr Chikashi Terao, Laboratory for Statistical and Translational Genetics Analysis, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan; chikashi.terao@riken.jp, Professor Yong Cui, Department of Dermatology, China-Japan Friendship Hospital, Beijing, China; wuhucuiyong@vip.163.com and Professor Sang-Cheol Bae, Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, The Republic of Korea; scbae@hanyang.ac.kr

XY, KKim and HS contributed equally.

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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 3348 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 ($p<5\times10^{-8}$). 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

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_g=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.[1] Considerable genetic predisposition contributes to SLE aetiology.[2] To date, nearly 100 susceptibility loci have been identified for SLE, mainly through genome-wide association studies (GWASs).[3–8] However, these loci collectively only explain ~30% of SLE heritability[9] 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.[10]

Genome-wide association meta-analyses have been performed to uncover new genetic associations for SLE in Asians,[11] Europeans[12] and trans-ancestral populations.[9] 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.[13] Nonetheless, only ~8% of GWAS participants are East Asians.[14] 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.[15 16] Genetic heterogeneity may explain, at least partly, the phenotypic diversity of SLE between East Asians and Europeans.[9] Hence, large-scale East Asian investigations may provide an opportunity to identify unique genetic associations even for the same diseases and traits that have already been well studied in Europeans.[17]

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 3348 SLE cases and 14 826 controls that were published in our previous East Asian SLE GWASs[4 6–9] 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 3348 SLE cases and 14 826 controls from the five published studies.[4 6–9] 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 v5[18] and population-specific reference panels[19] in IMPUTE2/4[20 21] or MINIMAC4.[22]

We tested association between SLE risk and genotype dosages in each data set using a logistic regression or linear mixed model in PLINK,[23] SNPTEST[24] or EPACTS (https://genome.sph.umich.edu/wiki/EPACTS) (online supplemental table 1). Within each data set, we filtered out association results based on imputation quality (IMPUTE info or MINIMAC r^2 ≤0.3), minor allele frequency (MAF) ≤0.5% or Hardy-Weinberg equilibrium test $p<1.0\times10^{-6}$ 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.[25]

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.[26] We applied a genomic control correction to each association summary statistic. Heterogeneity

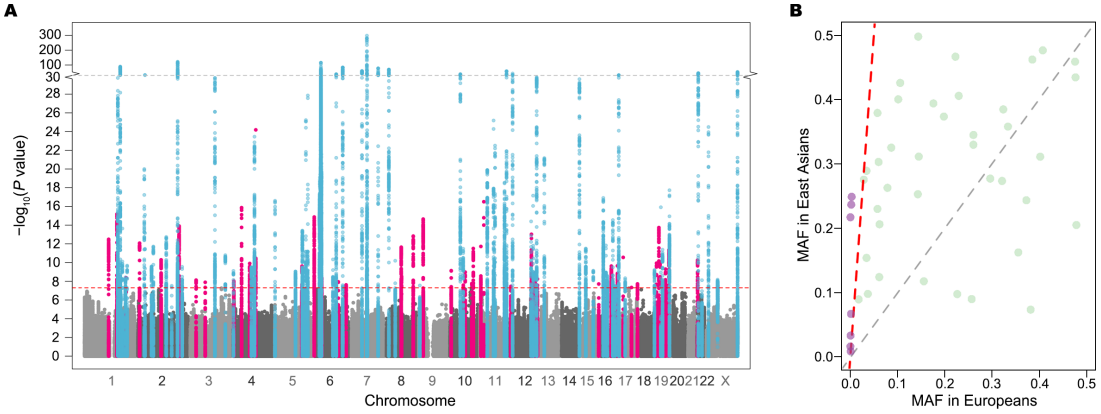

Figure 1 Summary of meta-analysis association results and comparison of MAFs for lead variants within the 46 novel loci between East Asians and Europeans. (A) Manhattan plot of genome-wide association meta-analysis results from 208 370 SLE East Asians including 13 377 SLE cases and 194 993 controls. 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 $p=5\times10^{-8}$. 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.

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	I^2	P_{Het}	N	Nearest gene
1	1	117 043 302	rs9651076	A	G	0.431	1.117	0.015	3.26E−13	10.7	0.347	208 370	*CD58*
2	1	157 108 159	rs116785379	C	G	0.107	1.211	0.024	6.68E−16	43.7	0.114	208 370	*ETV3*
7	1	201 979 455	rs3806357	A	G	0.251	1.106	0.017	4.25E−09	0.0	0.672	208 370	*ELF3*
9	2	7 573 079	rs75362385	T	G	0.321	0.887	0.017	8.40E−13	68.3	0.007	208 370	*LOC100506274*
14	2	111 877 174	rs73954925	C	G	0.878	1.169	0.024	5.11E−11	56.4	0.043	208 370	*BCL2L11*
18	2	198 929 806	rs7572733	T	C	0.260	1.143	0.017	1.25E−14	0.0	0.647	208 370	*PLCL1*
20	3	28 072 086	rs438613	T	C	0.588	0.920	0.014	7.52E−09	69.4	0.006	208 370	*LINC01980*
21	3	72 225 916	rs7637844	A	C	0.871	0.877	0.023	1.28E−08	0.0	0.906	208 370	*LINC00870*
25	4	2 700 844	rs231694	T	C	0.380	1.111	0.018	9.71E−09	23.7	0.269	57 253	*FAM193A*
26	4	40 307 587	rs113284964	G	GCTTC	0.371	1.134	0.015	1.35E−16	67.2	0.009	208 370	*LINC02265*
27	4	79 644 279	rs6533951	A	G	0.350	1.111	0.016	1.25E−10	61.4	0.024	208 370	*LINC01094*
28	4	84 146 996	rs6841907	T	C	0.729	0.906	0.016	1.10E−09	43.5	0.115	208 370	*COQ2*
31	4	109 061 618	rs58107865	C	G	0.227	0.802	0.021	6.57E−25	1.1	0.409	208 370	*LEF1*
34	5	131 120 338	rs370449198	A	AC	0.922	0.721	0.060	4.41E−08	0.0	0.408	187 562	*FNIP1*
35	5	131 829 578	rs2549002	A	C	0.682	0.905	0.016	2.40E−10	20.6	0.279	208 370	*IRF1*
40	6	243 302	rs9503037	A	G	0.693	0.881	0.016	1.36E−15	42.3	0.123	208 370	*LOC285766*
43	6	36 715 031	rs34868004	CA	C	0.225	1.104	0.017	4.46E−09	40.7	0.134	208 370	*CPNE5*
46	6	116 690 849	rs9488914	T	C	0.920	0.862	0.026	1.14E−08	65.3	0.013	208 370	*DSE*
48	6	154 570 651	rs9322454	A	G	0.659	1.090	0.015	2.42E−08	0.0	0.430	208 370	*IPCEF1*
54	8	71 330 166	rs142937720	A	AAGTGGCC	0.383	0.894	0.016	2.27E−12	67.9	0.008	208 370	*NCOA2*
55	8	72 894 959	rs17374162	A	G	0.411	0.917	0.015	3.02E−09	35.7	0.169	208 370	*MSC-AS1*
56	8	129 425 593	rs16902895	A	G	0.678	1.122	0.016	1.48E−13	0.0	0.801	208 370	*LINC00824*
58	9	21 267 087	rs7858766	T	C	0.538	1.139	0.016	2.25E−15	0.0	0.825	208 370	*IFNA22P*
59	10	5 910 746	rs77448389	A	G	0.913	0.855	0.025	7.30E−10	0.0	0.584	208 370	*ANKRD16*
62	10	64 411 288	rs10995261	T	C	0.240	0.909	0.017	2.57E−08	43.9	0.113	208 370	*ZNF365*
63	10	73 466 709	rs10823829	T	C	0.718	0.910	0.016	1.05E−09	0.0	0.771	208 370	*CDH23*
64	10	105 677 911	rs111447985	A	C	0.073	1.172	0.028	1.72E−08	0.0	0.526	208 370	*STN1*
65	10	112 664 114	rs58164562	T	C	0.748	0.892	0.016	3.14E−12	33.3	0.186	208 370	*BBIP1*
66	11	4 113 200	rs3750996	A	G	0.834	1.167	0.022	1.89E−12	0.0	0.522	208 370	*STIM1*
67	11	18 362 382	rs77885959	T	G	0.978	1.694	0.062	3.16E−17	0.0	0.511	204 433	*GTF2H1*
74	12	4 140 876	rs2540119	T	C	0.544	1.086	0.015	3.51E−08	44.9	0.106	208 370	*PARP11*
77	12	103 916 080	rs6539078	T	C	0.591	0.894	0.015	9.49E−14	0.0	0.916	208 370	*LOC105369945*
79	12	121 368 518	rs3999421	A	T	0.506	0.910	0.016	1.29E−09	47.3	0.091	208 370	*XLOC_009911*
81	12	133 040 182	rs200521476	G	GCATCAC	0.812	0.875	0.023	5.66E−09	26.7	0.235	208 370	*FBRSL1*
86	15	101 529 012	rs35985016	A	G	0.930	0.843	0.030	1.95E−08	0.0	0.897	204 433	*LRRK1*
90	16	50 089 207	rs11288784	G	GT	0.365	0.902	0.016	2.38E−10	0.0	0.664	208 370	*HEATR3*
93	16	79 745 672	rs11376510	G	GT	0.737	0.898	0.017	2.23E−10	0.0	0.719	208 370	*MAFTRR*
95	17	7 240 391	rs61759532	T	C	0.076	1.235	0.032	2.79E−11	24.9	0.247	208 370	*ACAP1*
97	17	47 468 020	rs2671655	T	C	0.651	1.087	0.015	4.60E−08	0.0	0.756	208 370	*LOC10272459*
98	17	76 373 179	rs113417153	T	C	0.193	0.893	0.020	1.90E−08	2.1	0.403	208 370	*PGS1*
100	18	77 386 912	rs118075465	A	G	0.147	1.140	0.020	1.16E−10	0.0	0.543	208 370	*LOC284241*
101	19	948 532	rs2238577	T	C	0.455	0.885	0.016	1.83E−14	60.8	0.026	208 370	*ARID3A*
102	19	6 697 088	rs5826945	A	T	0.929	0.836	0.028	9.67E−11	50.0	0.075	208 370	*C3*
105	19	33 072 768	rs12461589	T	C	0.248	0.898	0.017	5.00E−10	0.0	0.510	208 370	*PDCD5*
106	19	49 851 746	rs33974425	CCAGCTGCAT	C	0.702	1.120	0.016	4.40E−12	42.6	0.121	208 370	*TEAD2*
108	22	18 649 356	rs4819670	T	C	0.210	1.151	0.022	5.53E−11	0.0	0.650	208 370	*USP18*

CHR, chromosome; EA, effect allele; EAF, effect allele frequency; I^2, genetic heterogeneity I^2 statistics at scale of 0% to 100%; N, study sample size; NEA, non-effect allele; OR, Odds ratio; P_{Het}, P-values for the χ^2 test of genetic heterogeneity; Region, unique ID for genomic region; ;SE, Standard error of odds ratio.

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 genome-wide 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-associated 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[27] 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 study using the Illumina Infinium Global Screening Array data (online supplemental table 1), excluding first-degree and second-degree relatives.

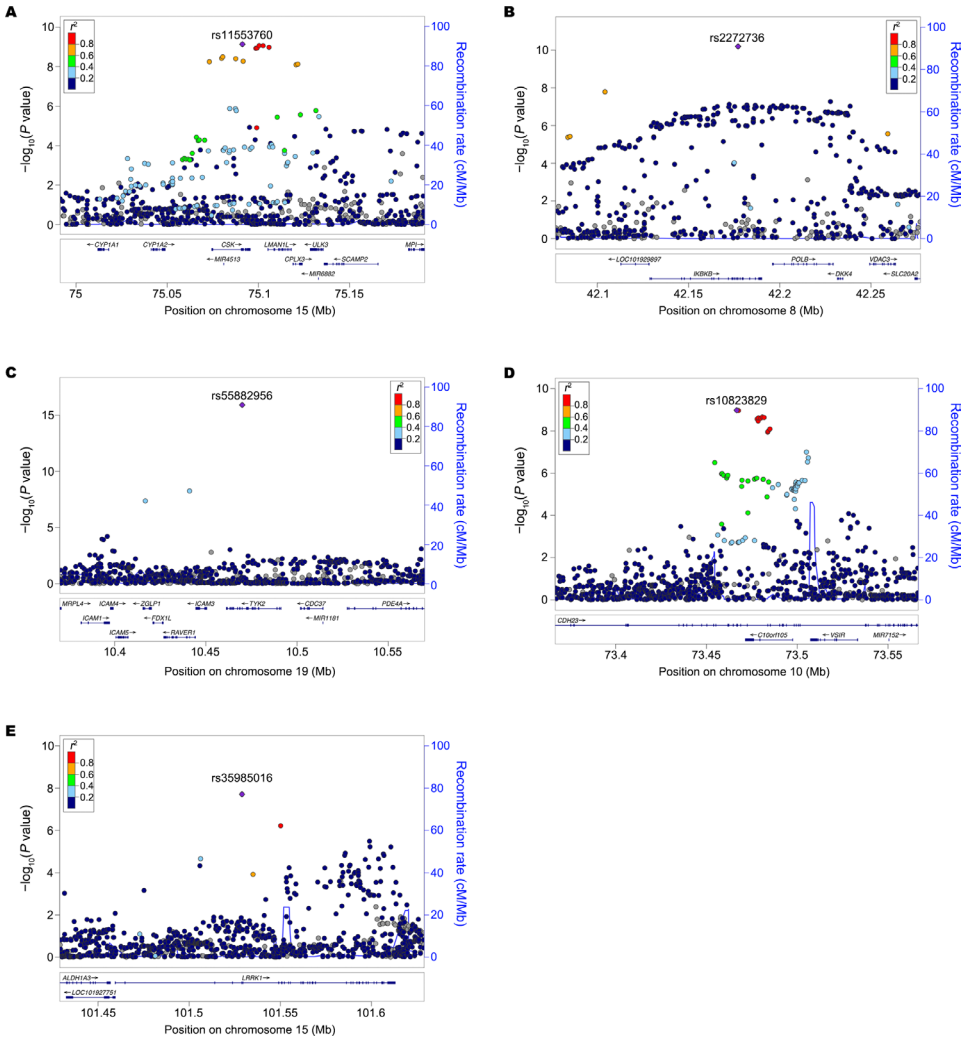

Figure 2 New lead exonic variants identified at three known (*CSK*, *IKBKB* and *TYK2*) and two novel (*CHD23* and *LRRK1*) loci. (A) rs11553760 (synonymous variant) at *CSK*. (B) rs2272736 (p.Arg303Gln, missense variant) at *IKBKB*. (C) rs55882956 (p.Arg703Trp, missense variant) at *TYK2*. (D) rs10823829 (synonymous variant) at *CHD23*. (E) rs35985016 (p.Lys203Glu, missense variant) at *LRRK1*. The lead SNP is labelled as purple diamond. The LD is estimated from 7021 Chinese samples. LD, linkage disequilibrium; Mb, megabases; SNP, single nucleotide polymorphism.

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,[28] 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[29] with LD scores[18] from the 1KGP East Asian descendants, based on an SLE population prevalence of 0.03% in East Asian populations.[1] SLE heritability estimate was further partitioned according to known and novel SLE loci using stratified LD score regression.[30] 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[17] and 59 quantitative traits[31] and SLE by using bivariate LD score regression.[32] We used the LD scores[18] 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

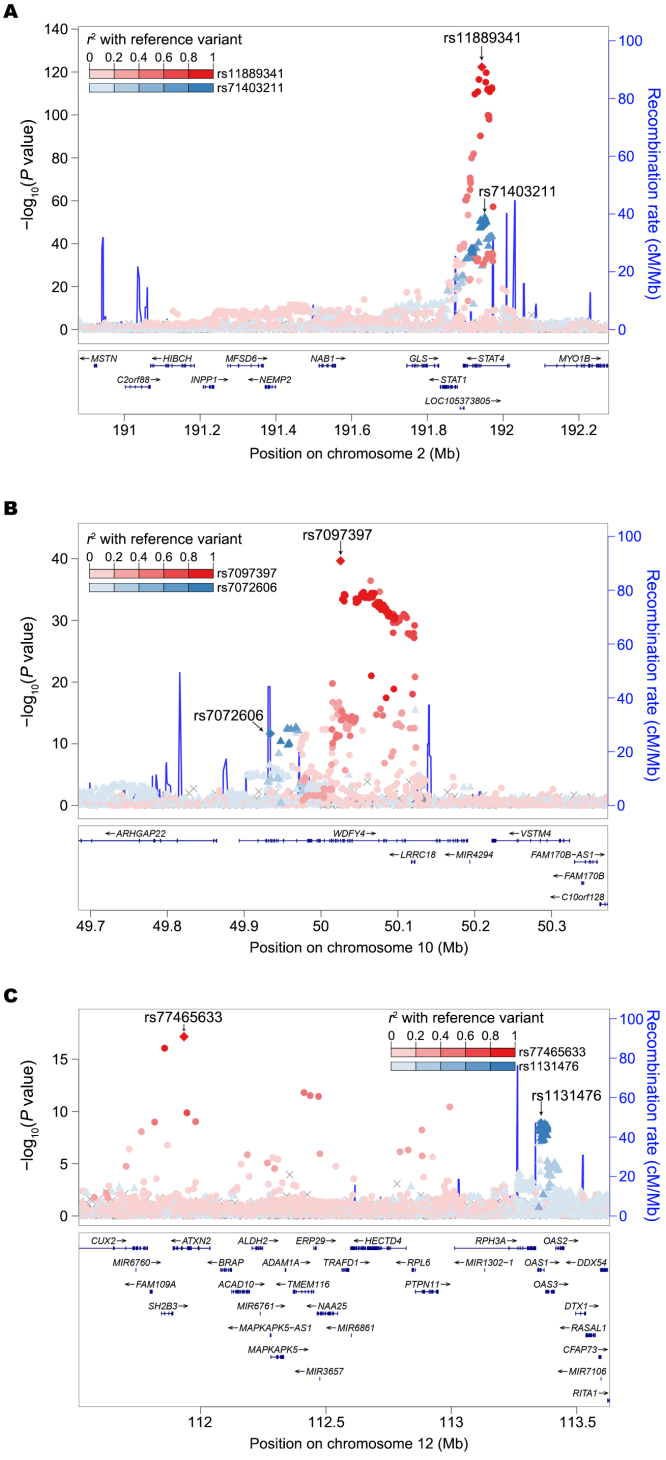

Figure 3 Two independent association signals identified. (A) At two intronic variants within known *STAT4* locus. (B) At known (rs7097397, p.Arg1816Gln) and new (rs7072606, p.Ser214Pro) missense variants within *WDFY4* locus. (C) A known intronic variant within *ATXN2* gene and a new (rs1131476, p.Ala352Thr) missense variant within *OAS1* gene. The lead and secondary index variants are labelled in diamond. The lead variant and its LD proxies are in red while the secondary signal index variant and its LD proxies are in blue. The LD is estimated from 7021 Chinese samples. LD, linkage disequilibrium; Mb, megabases.

that of the largest published trans-ancestry[9] and East Asian[11] meta-analyses, respectively.

We tested associations for 11 270 530 genetic variants in a fixed-effects meta-analysis. A quantile–quantile plot showed 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[29] showed that polygenic effects (89.4%), rather than biasses, 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 $p<5\times10^{-8}$ 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 ≥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 *LRRK1*; 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* (rs11553760), *IKBKB* (rs2272736) and *TYK2* (rs55882956) 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 *AHNAK2* (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 $p<5\times10^{-8}$, 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 ≥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,[33] figure 3C and online supplemental table 5).

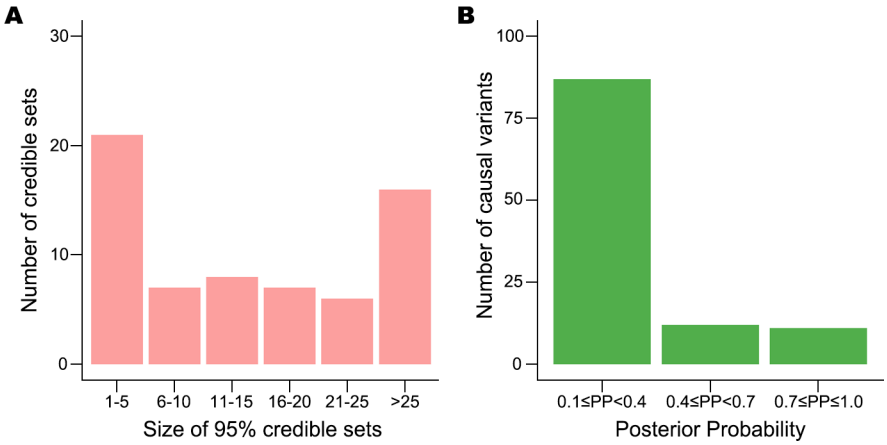

Figure 4 Results of statistical fine-mapping analysis. (A) Number of 95% credible sets of putative causal variants, binned by their sizes. (B) Number of potential causal variants with posterior probabilities (PP) ≥0.1, which are considered to be the true causal variants.

Prioritisation of causal variants

To prioritise putative causal variants, we conducted a Bayesian statistical fine-mapping analysis for 111 loci using FINEMAP[28] after excluding complex associations involving the *HLA* and 7q11.23. We found exactly the same number of association signals in 57 loci between FINEMAP causal configuration with the highest posterior probability and the GCTA approximate conditional test. To be conservative, we only summarised the statistical fine-mapping results for these 57 regions, which contained 65 association signals (online supplemental table 6).

For each signal, we built a credible set of putative causal variants with a 95% probability of including the true causal variants. The size of 28 credible sets was small (size ≤10; figure 4A). Among the 110 putative causal variants with posterior probability ≥0.1 (figure 4B), we found four coding variants (3.6%), which implies that most of these associations are probably induced by non-coding causal variants. The prioritised variants are available to be tested as potential targets in perturbation experiments. For example, the allele-specific regulatory activity of the intronic variant (rs10036748) with the highest posterior probability (0.387) in the *TNIP1* locus was recently experimentally characterised in SLE.[38]

We pinpointed a single most likely causal variant with high confidence (posterior probability ≥0.8) for four known (*ATXN2*, *BACH2*, *DRAM1*/*WASHC3* and *NCF2*) and six novel (17p13.1, *ELF3*, *GTF2H1*, *LRRK1*, *LOC102724596*/*PHB* and *STIM1*) loci (online supplemental table 6). For example, we prioritised rs61759532 as a putative causal variant at the novel 17p13.1 locus (PP=0.999). This variant is located in an intron of *ACAP1*, which encodes a key regulator of integrin traffic for cell adhesion and migration.[39]

SNP-BASED HERITABILITY

To assess the proportion of phenotypic variance explained by common variants, we applied LD score regression[29] to the meta-analysis results. Assuming a population prevalence of 0.03% for SLE,[1] we estimated the liability-scale SNP-based heritability from all non-*HLA* variants as h^2_{SNP} = 7.24% (SE=0.78%). The 66 known and 46 novel non-*HLA* loci explained 62.6% (SE=4.9%) and 22.1% (SE=2.6%) of this overall SNP-based heritability, respectively.

Genetic correlation with other diseases/traits

To explore shared genetics between SLE and various traits, we calculated genetic correlations of SLE with 39 complex diseases and 59 quantitative traits in Biobank Japan participants using bivariate LD score regression[32] (online supplemental table 7). As expected, we detected significant positive genetic correlations between SLE and two other autoimmune diseases: rheumatoid arthritis (r_g=0.437) and Graves' disease (r_g=0.318). In addition, we found unreported genetic correlations (FDR<0.05) with albumin/globulin ratio (r_g=−0.242) and non-albumin protein (r_g=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 *IKBKB*,[9] *TYK2*,[9] *WDFY4*[37] and *OAS1*,[33] and three known missense variants within known *AHNAK2*,[33] *IRAK1*[34] and *NCF2*.[35 36] These findings suggested allelic heterogeneity within several of these loci and highlighted the disease-risk effects of genes *AHNAK2*, *CSK*, *IKBKB*, *IRAK1*, *NCF2*, *OAS1*, *TYK2* and *WDFY4* within eight known loci, and *CDH23* 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 migration[40] 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 rs35985016 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.[42] 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.

Author affiliations
[1]Department of Dermatology, First Affiliated Hospital, Anhui Medical University, Hefei, Anhui, China
[2]Institute of Dermatology, Anhui Medical University, Hefei, Anhui, China
[3]Key Lab of Dermatology, Ministry of Education (Anhui Medical University), Hefei, Anhui, China
[4]Inflammation and Immune Mediated Diseases Laboratory of Anhui Province, Hefei, Anhui, China
[5]Department of Dermatology, China-Japan Friendship Hospital, Beijing, China
[6]Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA
[7]Department of Biology and Department of Life and Nanopharmaceutical Sciences, Kyung Hee University, Seoul, Korea
[8]Laboratory for Bone and Joint Diseases, RIKEN Center for Medical Sciences, Kanagawa, Japan
[9]Laboratory for Statistical and Translational Genetics Analysis, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan
[10]Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[11]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea
[12]Hanyang University Institute for Rheumatology Research, Seoul, Korea
[13]Division of Molecular Pathology, Department of Cancer Biology, Institute of Medical Science, The University of Tokyo, Tokyo, Japan
[14]Koga Hospital 21, Fukuoka, Japan
[15]Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, Anhui, China
[16]Department of Orthopedic Surgery, Keio University School of Medicine, Tokyo, Japan
[17]Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[18]Department of Orthopaedic Medical Engineering, Osaka University Graduate School of Medicine, Osaka, Japan
[19]Division of Genome Research, Center for Genome Science, National Institute of Health, Osong Health Technology Administration Complex, Cheongju, Korea
[20]Department of Rheumatology & Clinical Immunology, Sapporo City General Hospital, Hokkaido, Japan
[21]Divisions of Genetics and Rheumatology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[22]Center for Data Sciences, Harvard Medical School, Boston, Massachusetts, USA
[23]Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
[24]Department of Internal Medicine, Dong-A University Hospital, Busan, Korea
[25]Department of Orthopaedic Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Hokkaido, Japan
[26]Division of Rheumatology, Department of Internal Medicine, Chonnam National University Medical School and Hospital, Gwangju, Korea
[27]Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Hokkaido, Japan
[28]Division of Rheumatology, Department of Internal Medicine, Chungnam National University Hospital, Daejeon, Korea
[29]Department of Internal Medicine and Rheumatology, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan
[30]Division of Rheumatology, Department of Internal medicine, Kyungpook National University Hospital, Daegu, Korea
[31]Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan
[32]Department of Rheumatology, Ajou University School of Medicine, Suwon, Korea
[33]Shanghai Institute of Rheumatology, Renji Hospital, Shanghai Jiao Tong University, School of Medicine (SJTUSM), Shanghai, China
[34]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[35]Niigata University Health Administration Center, Niigata, Japan
[36]Department of Rheumatology, Catholic University of Daegu School of Medicine, Daegu, Korea
[37]Department of Medical Education, Kyushu University Graduate School of Medical Sciences, Fukuoka City, Japan
[38]Department of Dermatology, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China
[39]Shenzhen Key Laboratory for Translational Medicine of Dermatology, Shenzhen Peking University - The Hong Kong University of Science and Technology Medical Center, Shenzhen, Guangdong, China
[40]Department of Orthopaedic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan
[41]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan
[42]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan
[43]Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Pok Fu Lam, Hong Kong, China
[44]Department of Rheumatology & Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan
[45]Department of Rheumatology, Faculty of Medicine, Saga University, Saga, Japan
[46]Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan
[47]Hokkaido Medical Center for Rheumatic Disease, Hokkaido, Japan
[48]Department of Orthopaedic Surgery, Showa University School of Medicine, Tokyo, Japan
[49]Laboratory for Autoimmune Diseases, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan
[50]Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
[51]Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan
[52]Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPi-iFReC), Osaka University, Osaka, Japan
[53]Laboratory of Genome Technology, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan
[54]Laboratory of Clinical Genome Sequencing, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan
[55]Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan
[56]Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[57]Department of Genomic Function and Diversity, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan
[58]Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio, USA
[59]US Department of Veterans Affairs Medical Center, Cincinnati, Ohio, USA
[60]Department of Rheumatology and Clinical immunology, Kyoto University Graduate school of Medicine, Kyoto, Japan
[61]Department of Orthopaedic Surgery, Faculty of Medicine, Fukuoka University, Fukuoka, Japan
[62]State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine (SJTUSM), Shanghai, China
[63]Department of Dermatology, Institute of Dermatology, Huashan Hospital, Fudan University, Shanghai, China
[64]Clinical Research Center, Shizuoka General Hospital, Shizuoka, Japan
[65]The Department of Applied Genetics, The School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan

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Contributors XY, KKim and HS contributed equally to this work, and either has the right to list himself first in bibliographical documents. SCB, YC, CT, XZhang, XY, KKim and HS conceived the study design. SCB, YC, XZhang, SY, KKim and CT acquainted the financial support. XY, KKim, HS, CT, YC and SCB wrote the manuscript. XY, KKim, HS, EH, XZheng, VL and YW conducted all of the analyses with the help of JBH, LCK, MTW, SP, SE, HS, KT, NO, MK, KI and C Terao. KKim, SYB, LW, LL, RXL, YSheng, MYH, WL, KYoon, MC, HH, MW, YTang, HD, CL, CS, WF, KL, BJK, HSL, SCB, SH, YSakamoto, NSugano, MM, DT, KKarino, TMiyamura, JN, GM, TKuroda, HN, TMiyamoto, TT, YKawaguchi, KA, YTada, KYamaji, MS, TA, AS, TSumida, YOkada, KMatsuda, KMatsuo, YKochi, TSeki, YTanaka, TKubo, RH, TYoshioka, MY, TKabata, YA, YOhta, TO, YN, AK, YY, KOhzono, KYamamoto, KOhmura, TYamamoto and SI generated genetic data. SYB, SJ, YCK, WTC, SSL, SCS, YMK, DY, CHS, YBP, JYC, YP, GYA, JMS, YKL, DJP, WY, THK, SY, BJK, NShen, HSL, XZhang, CT and SCB managed the cohort data. All authors reviewed and approved the manuscript.

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ORCID iDs
Xianyong Yin http://orcid.org/0000-0001-6454-2384
Kwangwoo Kim http://orcid.org/0000-0001-8926-6216
Rui-Xue Leng http://orcid.org/0000-0002-2453-5865
Nobuhiko Sugano http://orcid.org/0000-0003-4035-3989
Dongqing Ye http://orcid.org/0000-0001-6604-9614
Yongfei Wang http://orcid.org/0000-0002-1260-6291
Wanling Yang http://orcid.org/0000-0003-0063-6327
Yukinori Okada http://orcid.org/0000-0002-0311-8472
Leah C Kottyan http://orcid.org/0000-0003-3979-2220
Kazuhiko Yamamoto http://orcid.org/0000-0001-9037-3625
Tae-Hwan Kim http://orcid.org/0000-0002-3542-2276
Nan Shen http://orcid.org/0000-0002-5875-4417
Chikashi Terao http://orcid.org/0000-0002-6452-4095
Sang-Cheol Bae http://orcid.org/0000-0003-4658-1093

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