EXTENDED REPORT

High-density genotyping of immune loci in Koreans and Europeans identifies eight new rheumatoid arthritis risk loci

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ABSTRACT

Objective A highly polygenic aetiology and high degree of allele-sharing between ancestries have been well elucidated in genetic studies of rheumatoid arthritis. Recently, the high-density genotyping array Immunochip for immune disease loci identified 14 new rheumatoid arthritis risk loci among individuals of European ancestry. Here, we aimed to identify new rheumatoid arthritis risk loci using Korean-specific Immunochip data.

Methods We analysed Korean rheumatoid arthritis case–control samples using the Immunochip and genome-wide association studies (GWAS) array to search for new risk alleles of rheumatoid arthritis with anticitrullinated peptide antibodies. To increase power, we performed a meta-analysis of Korean data with previously published European Immunochip and GWAS data for a total sample size of 9299 Korean and 45 790 European case–control samples.

Results We identified eight new rheumatoid arthritis susceptibility loci (TNFSF4, LBH, EOMES, ET51–FLI1, COG6, RAD51B, UBAH3A and SYNGR1) that passed a genome-wide significance threshold (p<5×10−8), with evidence for three independent risk alleles at 1q25/ TNFSF4. The risk alleles from the seven new loci except TNFSF4 locus (monomorphic in Koreans), together with risk alleles from previously established RA risk loci, exhibited a high correlation of effect sizes between ancestries. Further, we refined the number of single nucleotide polymorphisms (SNPs) that represent potentially causal variants through a trans-ethnic comparison of densely genotyped SNPs.

Conclusions This study demonstrates the advantage of dense-mapping and trans-ancestral analysis for identification of potentially causal SNPs. In addition, our findings support the importance of T cells in the pathogenesis and the fact of frequent overlap of risk loci among diverse autoimmune diseases.

INTRODUCTION

Rheumatoid arthritis (RA; OMIM180300) is a chronic and systemic autoimmune disease affecting up to 1% of the adult population worldwide.1 Total heritability of RA was estimated to be ~65% from a previous twin study that compared the disease discordance in monozygotic twins with dizygotic twins.2 To date, >50 risk loci have been discovered among individuals of European and Asian ancestry,3,4 but only ~16% of the heritability (or ~25% of the genetic heritability) could be explained by the confirmed risk loci.5 Current RA genetic studies have revealed a highly polygenic aetiology by an inferred genetic architecture that hundreds (if not thousands) of common single nucleotide polymorphisms (SNPs) with modest effect and smaller number of rare causal variants account for total genetic heritability of RA.6

A previous study reported the majority of the RA susceptibility alleles are shared among individuals of European and Japanese ancestry (correlation coefficient for effect sizes between ancestries=0.82).3 This observation suggests that there are shared causal variants between the two populations, and further suggests that a large cohort study using multiple ancestries can be powerful to detect new RA risk loci.7 Recently, 14 new RA risk loci were identified by integrating high-density genotype data of immune loci from the Immunochip (iChip) and imputed data from genome-wide association studies (GWAS) among individuals of European ancestry.4 Here, we generate a new iChip+GWAS dataset among individuals of Korean ancestry. We perform a meta-analysis with a previously published European iChip+GWAS dataset,8 as well as new iChip data from individuals of European ancestry (n=2840), for a total sample size of 9299 Korean and 45 790 European case–control samples (see online supplementary table S1).

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METHODS

Korean subjects, genotyping, imputation and quality control
A total of 4689 subjects including 1525 RA cases (average age=52.7 (17–82); female=83.4%) with anticitrullinated peptide antibodies (ACPA) and 3164 healthy controls (average age=39.4 (16–79); female=60.7%) were genotyped by the customised iChip array at multiple centres (SNP Genetics, Inc. Korea and Feinstein Institute for Medical Research for BAE#1; Oklahoma Medical Research Foundation for BAE#2; University of Kansas Diamantina Institute for BAE#3) (see online supplementary table S1). Each subcollection was filtered using standard criteria based on minor allele frequency (MAF), Hardy–Weinberg equilibrium (HWE), call rate per SNP call rate per individual, unique mapping, genetic homogeneity, population stratification and cryptic relatedness (duplicate and cryptic first-degree relative) before and/or after merging the subcollections (see online supplementary table S2).

An independent set of 3700 Korean controls (average age=59.8 (38–89); female=63.0%) was examined by Illumina HumanOmni1-Quad BeadChip GWAS array at the Korea National Institute of Health. A sample was removed if it showed low call rate (<0.95), heterozygosity <0.26 or >0.30, cryptic relatedness (cryptic first-degree relative) or sex inconsistency. The genotype data were merged with a previously reported Korean RA GWAS dataset of 709 ACPA-positive RA cases (average age=52.4 (19–82); female=89.7%) and 201 controls (average age=39.8 (17–76); female=74.6%).

After merging the GWAS datasets, we applied the quality control criteria of MAF≥0.01, p value of HWE<10−4 and call rate > 95% in controls and cases. The quality control-passed control-case GWAS data were pre-phased to construct haplotypes of the autosomal chromosomes by SHAPEIT2 and subsequent imputation was performed by IMPUTE210 using the 1000 Genomes Project phase I reference panel. The imputed data were filtered by the criteria of MAF>1%, maximum probability≥0.9, p value of HWE<10−4 and call rate per SNP≥0.95. A total of 65 014 iChip markers were extracted from the imputed data (see online supplementary table S3).

Principal component analysis was performed by the SNP & Variation Suite 7 software using the SNPs with MAF>5% and linkage disequilibrium (LD) r2<0.2 with other SNPs in a ±250 kb window. Cryptic relatedness with high kinship coefficient (≥0.177) corresponding to the duplicate or first-degree relative was estimated by the KING software.11 Quantile–quantile (Q–Q) plots were generated using the imputed SNPs associated with reading and writing ability to estimate inflation.

In order to examine the third-effect SNP rs2027498 in TNFSF4, an independent Korean cohort including 1254 RA cases (average age=53.1 (17–88); female=87.2%; ACPA(+) =71.1%, ACPA(−)=28.9%) and 1011 healthy controls (average age=54.0 (40–86); female=80.0%) was recruited. The genotyping was performed using Sequenom iPLEX platform at LabGenomics Co. Ltd., showing a genotype call rate of 98.1% and no deviation from HWE.

All patients fulfilled the 1987 criteria of the American College of Rheumatology. The level of ACPA in the Korean RA patients was measured by using the ImmuLisa CCP2 ELISA kit. Anticyclic citrullinated peptide (anti-CCP) >25 units/mL was considered as positive for ACPA.

European subjects, imputation and quality control
The seven European iChip data (ES, NL, SE-E, SE-U, UK, US and i2h2/CORRONA) listed in online supplementary table S1 were reported in two previous studies.4 12 ACPA-negative samples were additionally removed from all data passing the quality control criteria in the previous studies. The ACPA-positive iChip data were further filtered for missingness per SNP/individual (<0.01), MAF (<0.01) and HWE (<0.01).

Each European GWAS data (BRASS, CANADA, NARAC2 and WTCCC) independent of the Immunochip data was pre-phased and imputed by MaCh13 and Minimac14 using the high-density phased reference data from the 1000 Genome Project instead of the reference phase of the HapMap2 data used in the previous study.1 The imputed data were filtered to restrict the analysis to ACPA-positive cases and SNPs with MAF≥1% and imputation r2≥0.5. Q–Q plots were generated for each European collection using the SNPs associated with reading and writing ability. All patients in the reported datasets fulfilled the 1987 criteria of the American College of Rheumatology or were diagnosed by a professional rheumatologist.

RA association test
OR and 95% CI were calculated by PLINK15 with adjustment for top 5 or 10 PCs in the logistic regression to test whether each autosomal SNP was associated with susceptibility to RA. A fixed-effects inverse-variance meta-analysis of the association results from each collection and a heterogeneity test of the SNP effects among the collections were conducted by the GWAMA software.16 Statistical power to detect RA association was calculated using the CaTS Power calculator.

Secondary-effect analysis
The presence of independent effect within the new RA loci with dense iChip markers was examined by conditioning on a lead SNP and/or other independent-effect SNPs and PCs as covariates. The conditional analysis using forward stepwise logistic regression for each collection and subsequent meta-analysis was performed by PLINK15 and GWAMA,16 respectively. When a SNP was significant with p<5×10−5 in the conditional analysis, the SNP was considered to have independent effect.

The genotypes of the independent-effect SNPs (rs61828284, rs4090392, rs2027498) were further phased using PLINK.15 The haplotypes were examined in the European collections that were successfully genotyped or imputed for all three SNPs. In Koreans, rs61828284 and rs4090392 were too rare to infer the haplotype or to perform statistical analysis.

Proxy SNP analysis
The HaploReg v2 software17 was used to search the proxy SNPs of the RA-associated SNPs and to annotate the functional effects at the SNP position. Association of each SNP in the novel RA loci with the expression of the genes within the locus was evaluated using published eQTL data from the lymphoblastoid cell lines of the 856 healthy female twins of the MuTHER resource18 and the HapMap population19 in the Genevar V3.2.0 web-based software.20

RESULTS

Korean-only analysis
We first analysed the Korean iChip+GWAS data from 2234 cases and 7065 controls. A total of 96 952 iChip SNPs passed quality control in the Korean iChip dataset (see online supplementary table S2) and the GWAS-based imputed dataset (see online supplementary table S3 and figure S1). Principal components analysis was used to correct for population stratification, showing no outliers (see online supplementary figure S2). We performed logistic regression analyses to
calculate OR and 95% CI adjusted for the top 10 principal components in the iChip and GWAS datasets independently, followed by an inverse-variance-weighted fixed-modelmeta-analysis. Q–Q plots of p values and inflation factors indicated little evidence of systematic bias ($\lambda_{1000}=1.010$; see online supplementary figure S3).

While we were able to replicate four known RA risk loci (HLA, PADI4, STAT4 and RASGRP1), no new RA risk loci were identified in the Korean-only analysis at a genome-wide level of significance ($p<5\times10^{-8}$; see online supplementary figure S4). However, this analysis was underpowered to achieve the genome-wide significance for alleles with modest effect (see online supplementary figure S5).

**Korean–European meta-analysis: identification of eight new RA risk loci**

Since most known RA risk alleles are shared among individuals of European and Asian ancestry, we performed a meta-analysis with recently published iChip+GWAS data and new iChipdata derived from case-control samples of European ancestry. The GWAS data were imputed to iChip markers using 1000 Genome Project data. A total of 133 816 SNPs were analysed in the Korean–European meta-analysis ($\lambda_{1000}=1.003$) (see online supplementary figure S1 and S3).

In a combined analysis, we found eight new RA susceptibility loci passing a genome-wide significance threshold of $p<5\times10^{-8}$ (figure 1). For seven of the eight loci, the new signal of

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**Figure 1** Manhattan plot from the meta-analysis of the Korean and European datasets. Newly identified and known rheumatoid arthritis risk loci passing the genome-wide significance level ($p<5\times10^{-8}$) are shown with the locus names in red and black, respectively. The dashed gray line indicates the genome-wide significance threshold.
Table 1  Association results for SNPs in novel RA loci

<table>
<thead>
<tr>
<th>rs number</th>
<th>Chr</th>
<th>Position*</th>
<th>Gene</th>
<th>EA/NEA</th>
<th>Korean (n=9299)</th>
<th>European (n=45 790)</th>
<th>Meta-analysis (n=55 089)</th>
<th>LD region</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1893592</td>
<td>21</td>
<td>43 855 067</td>
<td>UBASH3A</td>
<td>C/A</td>
<td>0.25 0.80 (0.74 to 0.87)</td>
<td>0.28 0.91 (0.87 to 0.95)</td>
<td>0.89 (0.86 to 0.92)</td>
<td>8.18×10−11</td>
</tr>
<tr>
<td>rs4936059</td>
<td>11</td>
<td>128 502 496</td>
<td>ETS1-FU1</td>
<td>A/G</td>
<td>0.38 0.90 (0.83 to 0.96)</td>
<td>0.34 0.90 (0.87 to 0.94)</td>
<td>0.90 (0.87 to 0.93)</td>
<td>6.94×10−10</td>
</tr>
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<td>rs61828284</td>
<td>1</td>
<td>173 299 743</td>
<td>TNFSF4</td>
<td>A/G</td>
<td>0.00 NA</td>
<td>0.08 0.81 (0.75 to 0.86)</td>
<td>0.81 (0.75 to 0.86)</td>
<td>2.66×10−9</td>
</tr>
<tr>
<td>rs909685</td>
<td>22</td>
<td>39 747 671</td>
<td>SYNGR1</td>
<td>A/T</td>
<td>0.15 0.82 (0.72 to 0.93)</td>
<td>0.31 0.91 (0.87 to 0.94)</td>
<td>0.90 (0.87 to 0.93)</td>
<td>2.95×10−10</td>
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<tr>
<td>rs7579944</td>
<td>2</td>
<td>30 445 026</td>
<td>LBH</td>
<td>G/A</td>
<td>0.38 1.11 (1.04 to 1.20)</td>
<td>0.36 1.10 (1.06 to 1.14)</td>
<td>1.10 (1.07 to 1.14)</td>
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<td>rs9063518</td>
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<td>40 371 377</td>
<td>COG6</td>
<td>G/A</td>
<td>0.24 0.89 (0.82 to 0.97)</td>
<td>0.27 0.90 (0.87 to 0.94)</td>
<td>0.90 (0.87 to 0.93)</td>
<td>4.53×10−10</td>
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<td>rs9112063</td>
<td>14</td>
<td>68 753 593</td>
<td>RAD51B</td>
<td>G/A</td>
<td>0.14 0.87 (0.78 to 0.96)</td>
<td>0.28 0.91 (0.88 to 0.94)</td>
<td>0.90 (0.87 to 0.94)</td>
<td>3.09×10−8</td>
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<tr>
<td>rs9880772</td>
<td>3</td>
<td>27 777 779</td>
<td>EOMES</td>
<td>G/A</td>
<td>0.22 0.83 (0.75 to 0.92)</td>
<td>0.47 0.92 (0.89 to 0.95)</td>
<td>0.91 (0.88 to 0.94)</td>
<td>3.46×10−8</td>
</tr>
</tbody>
</table>

*Coordinates are based on the hg19 assembly.
†LD region was expanded by the proxy SNPs of independent-effect SNPs in the 1q25/TNFSF4 locus.
Chr, chromosome; EA, effect allele; EAF, effect allele frequency; LD, linkage disequilibrium; NA, not applicable; NEA, non-effect allele; RA, rheumatoid arthritis; SNP, single nucleotide polymorphism.

Three independent risk alleles in 1q25/TNFSF4

For the eight novel loci, we investigated for evidence of independent risk alleles by performing conditional analysis on the lead SNP in the combined Korean–European sample set. We found evidence for two additional risk alleles at the 1q25/TNFSF4 locus: both rs4090392 (pcond=3.82×10−5) and rs2027498 (pcond=1.16×10−5) contributed signals independent of the lead SNP rs61828284 (see online supplementary figure S7, S8 and table S5). However, two of the three 1q25/TNFSF4 SNPs were very rare among Koreans (rs61828284 and rs4090392); the third SNP (rs2027498) was common in Koreans and showed the same direction of effect in both populations (ORKOR=0.90 (0.86−0.94) and ORKOR=0.95 (0.84−1.09). Among Europeans, these three SNPs are in weak LD (r2=0.1, |D′|=0.66). The TAAG haplotype carrying the three protective alleles exhibited the greatest protection against RA (OR=0.67 (0.57−0.77); see online supplementary figure S9).

It was possible that third-effect SNP was associated in Koreans as well as Europeans because the effect size of the SNP was similar between populations. In order to increase power (52%), we attempted additional genotyping of rs2027498 for an independent set of 1254 RA cases and 1011 controls from Korea, but did not find evidence of association (pmeta=0.87; OR=1.01; see online supplementary table S6).

Identification of potentially causal SNPs by trans-ethnic mapping

To find the most likely causal variants in the seven new loci with consistent signals of association in both Koreans and Europeans (excluding 1q25/TNFSF4), we examined local patterns of LD and annotated putative functional variants. The lead SNPs at these seven loci were in LD with 55 and 51 SNPs at r2≥0.9 in the 1000 Genome Project data of East Asian (CHB+JPT) and European (CEU) ancestry, respectively. Considering the overlap between the two populations, we observed only 37 SNPs in LD with the lead SNPs in both populations, none of which was a non-synonymous, nonsense or splicing-site variant (see online supplementary table S7).

When we applied the trans-ethnic mapping to 21 known RA loci and 7 new RA loci showing association in meta-analysis (p<5×10−8) and each of populations (p<0.05), we could narrow down the number of proxy SNPs from 492 SNPs (443 SNPs in Koreans and 231 SNPs in Europeans) to 182 SNPs in the 21 known loci. Among the 28 RA loci, 16 and 19 loci had the decreased number of the proxy SNPs in Koreans and Europeans, respectively (see online supplementary figure S10 and table S8).

An example of the trans-ethnic mapping approach is shown in figure 3. Only two out of eight SNPs were in LD with the lead SNP in both populations: rs909685 (lead SNP) and rs2069235 (r2=0.92 in Asian and r2=1.00 in European). This
Locus contains SYNGR1 (an integral membrane protein associated with presynaptic vesicles in neuronal cells, which is also known as a susceptibility locus for primary biliary cirrhosis). Both variants lie within putative functional sequences (e.g., transcriptional factor-binding motif alteration, histone marks, DNase hypersensitivity, DNA-binding proteins). Furthermore, both SNPs were identical to the most significant eQTL associated with SYNGR1 expression from lymphoblastoid cell lines in previous four studies (see online supplementary figure S11).

**DISCUSSION**

Based on previous Asian–European studies and theoretical estimates of the polygenic architecture of RA, a large number of common genetic variants with modest effect size on risk of RA are expected to be discovered by a trans-ethnic approach. Here, we identified eight new loci with relatively modest OR (0.81 ≤ OR ≤ 0.91 and 1.10 ≤ OR ≤ 1.13) using a large cohort of Korean and European populations, bringing the number of RA loci to >60.

There are several important observations from our study. First, the association of the new loci exhibits a similar trend of ORs between Korean and European populations. Further, there were similar trends of ORs among the 13 data collections and no remarkable deviation between observed and reported MAF, which indicates little possibility of systemic bias or error.

Second, our study continues to emphasise the importance of T cell biology in the pathogenesis of RA. Four of the eight new loci contain genes with established function in CD4+ T cells. TNFSF4, which encodes a cytokine OX40L in the TNF

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**Clinical and epidemiological research**

Figure 3  Overlap of proxy single nucleotide polymorphisms (SNPs) shared in the ancestries and regulatory SNPs in the SYNGR1 locus. (A) Regional association plot for the RPL3–SYNGR1 locus in the chromosome 22. The best hit was found at rs909685 in the intron of SYNGR1. The 13 kb region containing all proxy SNPs of rs909685 is highlighted in pink. Coordinates are based on the hg19 assembly. (B) The proxy SNPs (circle) correlated with the lead SNP rs909685 in Korean and/or European (r² ≥ 0.9). The two proxy SNPs, rs909685 (red) and rs2069235 (orange) were observed in both populations in contrast to the others (grey). (C) The functional annotation of the proxy SNPs. Each proxy SNP was annotated for that it significantly alters the transcription factor binding motifs by the alleles and that it is in the histone mark region, DNase-hypersensitive site (DHS), protein-binding site and eQTL.

lign family, is involved in the regulation of T cell-mediated immune responses. EOMES encodes a transcription factor with a crucial role in differentiation of CD8+ T cells and homeostasis of effector and memory T cells. ETS1 encodes a transcription factor that regulates the differentiation of Th1 cells, regulatory T cells and B cells by affecting the function of other key regulators like T-bet, Foxp3 and Blimp-1. UBASH3A encodes a T-cell ubiquitin ligand that acts as a negative regulator of T-cell receptor (TCR)-mediated signalling.

Third, many of the new RA risk loci are also associated with other complex diseases, especially autoimmune diseases (TNFSF4 with systemic lupus erythematosus (SLE) and Crohn’s disease; EOMES with multiple sclerosis; ETS1 with SLE and coeliac disease; RAD51B with primary biliary cirrhosis and breast cancer; UBASH3A with type 1 diabetes and vitiligo; SYNGR1 with primary biliary cirrhosis). LBH and UBASH3A have been suggested as shared risk loci of RA and coeliac diseases in a meta-analysis of RA and coeliac datasets, but not established in each disease alone. Although functional connection between the new loci and RA pathogenesis is not elucidated yet, the overlap suggests a shared aetiology across autoimmune diseases. All associated genes are known to be highly expressed in immune cells like T cells or broadly expressed across tissues including blood cells (see online supplementary table S9).

Fourth, we found evidence that multiple alleles contribute to risk at one of the newly discovered loci. Using a conditional test among individuals of European ancestry, we found that the lead SNP rs61828284 in 1q23/TNFSF4 could not account for the secondary effect at rs4093092, nor at the third-effect SNP rs2027498. Notably, the association of the secondary-effect SNP but not the third-effect SNP became strengthened by conditioning of the lead SNPs in the meta-analysis. A similar trend was observed among all the European-ancestry collections. The masked or strengthened significance of the secondary SNP before or after conditioning may be the result of Simpson’s paradox, which has been shown in a coeliac locus, SOCS1.

Finally, we used a trans-ethnic approach to narrow the list of putative causal alleles at each of the 28 RA risk loci with association signals in Asians and Europeans. We narrowed down 563 proxy SNPs (in LD with the lead SNP at r² > 0.90 in one or the other population) to 219 putative causal variants (in LD with the lead SNP in both populations). One example is shown at the SYNGR1 locus (figure 3). Similarly, the lead SNP at UBASH3A (rs1893592) among the new loci shared only one proxy SNP in both populations, which is located in 3 bp downstream of the boundary between exon 10 and intron 10 of UBASH3A. The minor allele C of rs1893592 disrupts the consensus sequence R=G or G of the splice donor site in contrast to the major allele A, although biological validation is required for the potential alternative splicing.

A limitation of our study is the coverage of the iChip among individuals of Asian ancestry. The customised iChip array was largely designed to capture variants identified in the CEU cohort of the 1000 Genomes Project pilot study. As a result, we observe that a large portion (42%) of the iChip markers were not polymorphic or rare (MAF < 0.01) in the Korean dataset compared with 22% in the European iChip dataset. Nevertheless, the SNPs with MAF ≥ 0.01 in the Korean population in the iChip target regions were still dense and almost overlapped with the SNP with MAF ≥ 0.01 in the European population (see online supplementary figure S2) so that we
could perform a high-quality meta-analysis, identify new RA risk loci and narrow the list of putative causal variants through a trans-ethnic approach.

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Contributors KK, RMP and S-CB designed the study. KK, S-YB, H-SL, HDS, RMP and S-CB analysed the data. S-YB, HSL, CS-KC, C-BK, Y-KS, T-HK, J-BJ, DHY, YMK, S-KK, C-HS, S-CS, S-LJ, WJ, WTC, J-Y, J-YL, B-GH, SE, MAG-G, LR-R, LA, YO, DD, KPL, EWK, SR, SR-D, JM, JK, LP, PKG, JW, JDG, RM and S-CB recruited, characterised the cases and controls or analysed European genotype data. KK, RMP and S-CB wrote the manuscript. All authors reviewed and approved the manuscript.

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