ARTHRITIS & RHEUMATISM
Vol. 60, No. 2, February 2009, pp 364–371
DOI 10.1002/art.24245

Genetic Risk Factors for Rheumatoid Arthritis Differ in Caucasian and Korean Populations

Hye-Soon Lee,[1] Benjamin D. Korman,[2] Julie M. Le,[2] Daniel L. Kastner,[2] Elaine F. Remmers,[2] Peter K. Gregersen,[3] and Sang-Cheol Bae[4]

Objective. **Recent studies have identified a number of novel rheumatoid arthritis (RA) susceptibility loci in Caucasian populations. The aim of this study was to determine whether the genetic variants at 4q27, 6q23, *CCL21*, *TRAF1*/*C5*, and *CD40* identified in Caucasians are also associated with RA in a Korean case–control collection. We also comprehensively evaluated the genetic variation within *PTPN22*, a well-established autoimmune disease–associated gene.**

Methods. **We designed an experiment to thoroughly evaluate the *PTPN22* linkage disequilibrium region, using tag single-nucleotide polymorphisms (SNPs) and disease-associated SNPs at 5 RA-associated loci recently identified in Caucasians, in 1,128 Korean patients with RA and 1,022 ethnically matched control subjects. We also resequenced the *PTPN22* gene to seek novel coding variants that might be contributing to disease in this population.**

Results. **None of the susceptibility loci identified in Caucasian patients with RA contributed significantly to disease in Koreans. Although tag SNPs covering the *PTPN22* linkage disequilibrium block were polymorphic, they did not reveal any disease association, and resequencing did not identify any new common coding region variants in this population. The 6q23 and 4q27 SNPs assayed were nonpolymorphic in this population, and the *TRAF1*/*C5*, *CD40*, and *CCL21* SNPs did not show any evidence for association with RA in this population of Korean patients.**

Conclusion. **The genetic risk factors for RA are different in Caucasian and Korean patients. Although patients of different ethnic groups share the HLA region as a major genetic risk locus, most other genes shown to be significantly associated with disease in Caucasians appear not to play a role in Korean patients with RA.**

Rheumatoid arthritis (RA) is a chronic autoimmune arthritis characterized by progressive joint destruction. Both genetic and environmental factors have been shown to play a role in the development of RA. Although the largest genetic risk factor predisposing to RA, a common set of alleles at HLA–DRB1, has been associated with RA in populations of both Caucasian and Asian ancestry (1,2), many other risk loci have been shown to confer RA susceptibility in only 1 ethnic group. For example, although *PTPN22* has been consistently shown to be associated with RA in Caucasians, the 620W risk allele in this gene is not found and thus is not disease-associated in Asian populations (3–7). In contrast, *PADI4*, *SLC22A4*, and *FCRL3* have been associated with RA in studies of Asian patients, but the associations were weak or negative in populations of European ancestry (6,8–14). Although these results suggest that the genetic risk alleles that confer susceptibility to RA are heterogeneous across major ethnic groups, recent reports have identified a common *STAT4* haplo-

Supported in part by the Korea Health 21 R&D Project (grant 01-PJ3-PG6-01GN11-0002) and by the NIH (Intramural Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases). Mr. Korman's work was supported by the NIH Clinical Research Training Program. Dr. Gregersen's work was supported by grants from the NIH (R01-AR-44422 and N01-AI-95386).

[1]Hye-Soon Lee, MD, PhD: Hanyang University College of Medicine and the Hospital for Rheumatic Diseases, Seoul, South Korea, and The Feinstein Institute for Medical Research, Manhasset, New York; [2]Benjamin D. Korman, BS, Julie M. Le, BS, Daniel L. Kastner, MD, PhD, Elaine F. Remmers, PhD: National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland; [3]Peter K. Gregersen, MD: Feinstein Institute for Medical Research, Manhasset, New York; [4]Sang-Cheol Bae, MD, PhD, MPH: Hanyang University College of Medicine and the Hospital for Rheumatic Diseases, Seoul, South Korea.

Dr. Gregersen has received consulting fees, speaking fees, and/or honoraria from Roche Pharmaceuticals (less than $10,000).

Address correspondence and reprint requests to Elaine F. Remmers, PhD, National Institutes of Health, 9 Memorial Drive, 9/1W108, MSC 0908, Bethesda, MD 20892-0908. E-mail: remmerse@mail.nih.gov.

Submitted for publication June 10, 2008; accepted in revised form October 13, 2008.

type that confers a similar degree of risk of RA in both Asian and Caucasian populations (15,16).

Outside of the HLA region, the R620W variant of the *PTPN22* gene is the most consistently and most strongly disease-associated variant identified in RA association studies performed in Caucasian populations. Although this variant is not found in Asians, it is possible that other variants within this important candidate gene could contribute to genetic susceptibility to RA in Asian populations. In addition to *PTPN22*, new RA susceptibility loci in Caucasian populations have been identified in several recent genetic studies. The *TRAF1*/*C5* locus has been identified both by a genome-wide association study and as a candidate gene (7,17). Two independent followup genome-wide association studies identified a susceptibility locus on 6q23 near *TNFAIP3* (18,19). A large meta-analysis using genome-wide association and replication collections identified the *CD40* and *CCL21* loci (20), and a 4q27 region including *IL2*/*IL21* has been identified through a candidate gene approach after being shown to be associated with other autoimmune diseases (21). To date, there has been no study in an Asian population of SNPs in these new regions associated with RA. Therefore, the aim of this study was to determine whether *PTPN22* variants or any of 5 disease-associated SNPs recently identified in Caucasians also contribute to RA in Koreans.

PATIENTS AND METHODS

Study population. The study group comprised 1,128 Korean patients with RA who were enrolled consecutively from the outpatient clinic of the Hospital for Rheumatic Diseases, Hanyang University, Seoul, South Korea and 1,022 ethnically matched control subjects for whom no history of RA or other autoimmune diseases was noted in the self-reported questionnaire at the time of enrollment. All patients with RA met the American College of Rheumatology (formerly, the American Rheumatism Association) 1987 revised criteria for the classification of RA (22). The study was approved by the institutional review board of Hanyang University Hospital. Written informed consent was obtained from all participants.

All subjects were typed for HLA–DRB1 subtypes, using polymerase chain reaction (PCR) and sequence-specific oligonucleotide probe hybridization. Because the second most significant risk allele for RA in the Korean population was DRB1*0901, we regarded DRB1*0901 as a member of the shared epitope (SE) group, in addition to the following alleles: DRB1*0101, *0102, *0401, *0404, *0405, *0408, *0413, *1001, and *1402. Among 1,128 patients with RA, cyclic citrullinated peptide (CCP) antibody data were available for 807 patients. These data were based on quantitative duplicate measurements by enzyme-linked immunosorbent assay, using the DIASTAT anti-CCP kit (FCCP 200; Axis-Shield, Dundee, Scotland, UK) according to the manufacturer's instructions. The staging system proposed by Steinbrocker et al (23) was used as a measure of the radiographic severity of RA.

***PTPN22* resequencing.** Genomic DNAs from 48 rheumatoid factor–positive Korean patients with RA were sequenced over the regions representing the promoter region (up to −2,000 bp), all 21 exons including exon–intron boundaries, and the 3′–untranslated region of *PTPN22*, using standard dideoxy DNA sequencing techniques (Polymorphic DNA Technologies, Alameda, CA).

SNP selection and assay design. We used the Tagger method (ref. 24, and http://www.broad.mit.edu/mpg/tagger/) to select SNPs polymorphic in the HapMap combined Han Chinese in Beijing (CHB) and Japanese in Tokyo (JPT) database (25) across the 400-kb linkage disequilibrium block that includes *PTPN22*. In addition, all variants identified from the *PTPN22* exon resequencing were selected. A total of 34 SNPs/variants were selected from the *PTPN22* linkage disequilibrium block. Last, we identified SNPs that have been reported as associated with RA in either a Caucasian (*TRAF1*/*C5*, 6q23, 4q27, *CD40*, and *CCL21* loci) or Asian (*PADI4*) population and selected 1 disease-associated SNP per region (a total of 6 SNPs were selected). The 40 selected SNPs were used to design multiplex genotyping assays using Sequenom RealSNP (www.realsnp.com) and eXTEND applications (Sequenom, San Diego, CA).

Genotyping. Multiplex PCR was used to amplify DNA products containing up to 25 SNPs in a single reaction from 5 ng genomic DNA. Synthetic oligonucleotides that bind adjacent to the SNP site were then hybridized and extended with nucleotides complementary to the template SNP site, using modified nucleotides that terminate the extension reaction at the interrogated SNP and generate alternate products of mass sufficiently different to be separated by mass spectrometry. The extended products were separated by matrix-assisted laser desorption ionization−time-of-flight mass spectrometry, and the genotypes were determined by SpectroTyper software (Sequenom). Calls were evaluated and edited by cluster analysis, which was performed with SpectroTyper software, version 4.0.

Statistical analysis. Association tests for SNPs and haplotypes in patients and control subjects and the regional linkage disequilibrium structure for analyzed SNPs were determined using Haploview software, version 4.0 (26). We excluded SNPs with significant deviation from Hardy-Weinberg equilibrium ($P < 0.005$) and SNPs with a minor allele frequency in controls of <0.01. We reanalyzed the association of all SNPs with specific subgroups of RA (CCP antibody–positive RA, severe erosive RA, or SE-positive RA) using multivariate logistic regression with adjustments for age and sex. These subgroup analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the patients and control subjects. Among the patients with RA, the mean ± SD age was 52.4 ± 11.9 years, the mean ± SD age at disease onset was 39.9 ± 11.5 years, 89.7% were female, 81.4% were positive for the SE, 17.0% showed no erosive

Table 1. Association tests of SNPs in the *PTPN22* region in 1,128 Korean patients with rheumatoid arthritis and 1,022 control subjects*

No.	SNP	Chromosome 1 position	Major allele: minor allele	Minor allele frequency		χ^2	*P*
				Cases	Controls		
1	rs7554019	113887246		Assay failed			
2	rs17359281	113987482	A:G	0.186	0.180	0.22	0.64
3	rs1230673	113996036	T:C	0.091	0.099	0.69	0.41
4	rs6537792	114021124	G:C	0.340	0.346	0.15	0.70
5	rs3789597	114057662	C:T	0.066	0.073	0.89	0.35
6	rs6668829	114131976	C:T	0.066	0.068	0.11	0.74
7	rs6537798	114153229	C:A	0.122	0.131	0.62	0.43
8	rs3789604	114156465	T:G	0.209	0.204	0.15	0.70
9	rs3811021	114158186	T:C	0.211	0.203	0.37	0.54
10	rs1217412	114158734	G:A	0.347	0.353	0.16	0.69
11	rs1217413	114159273	G:A	0.354	0.366	0.58	0.45
12	rs3761935	114174051	T:G	0.214	0.202	1.00	0.32
13	rs2797415	114178616	T:C	0.347	0.357	0.43	0.51
14	rs2476601†	114179091	G:A	0.000	0.000		
15	Novel var. 6	114182653	T:C	0.002	0.001		
16	rs1746853	114184620	T:G	0.280	0.287	0.25	0.62
17	rs3827734	114192648	A:C	0.014	0.009		
18	Novel var. 5	114192772	G:T	0.002	0.002		
19	rs1217407	114195271	A:G	0.355	0.356	0.02	0.90
20	rs3765598	114195986	C:T	0.212	0.203	0.49	0.48
21	Novel var. 4	114202742	G:A	0.000	0.000		
22	rs1217418	114202754	A:G	0.138	0.153	1.83	0.18
23	Novel var. 3	114203459	C:A	0.000	0.000		
24	Novel var. 2	114203467	C:G	0.001	0.001		
25	rs2488457	114216891	C:G	0.356	0.367	0.52	0.47
26	Novel var. 1	114216892	C:T	0.000	0.000		
27	rs1235005	114218960	G:C	0.144	0.154	0.83	0.36
28	rs12566340	114221851	T:C	0.360	0.361	0.01	0.94
29	rs2358994	114230984	A:G	0.373	0.382	0.37	0.54
30	rs1018592	114232141		H-W‡			
31	rs1217393	114235469		Assay failed			
32	rs10776775	114238005	A:G	0.214	0.217	0.09	0.77
33	rs1217401	114240474	A:G	0.070	0.080	1.58	0.21
34	rs1217398	114249299	C:G	0.145	0.138	0.50	0.48

* SNP = single-nucleotide polymorphism; var. = variant.
† R620W variant.
‡ Hardy-Weinberg disequilibrium.

changes (Steinbrocker stage I), and 83.0% demonstrated erosions (Steinbrocker stages II, III, and IV). Among RA patients with CCP antibody data (n = 807), 681 (84.4%) were anti-CCP positive. The mean ± SD age of control subjects was 36.8 ± 12.5 years, and 86.3% were female.

***PTPN22* sequence variants identified by resequencing.** Nineteen sequence variants (i.e., variants identified in 1 or more resequenced DNAs) were identified in the exonic (exons and intronic splice junction regions) and the promoter regions of *PTPN22* in the resequenced Korean DNA samples. Of these, 13 had previously been identified, and 6 were novel. The novel variants were submitted to the Database of Single-Nucleotide Polymorphisms (dbSNP; http://www.ncbi.nlm.nih.gov/SNP/) (the ss numbers are as follows: ss103510562, ss103510564, ss103510567, ss103510570, ss103510573, and ss103510576). Although all of the novel variants were rare (i.e., found in only a single DNA of the 48 resequenced), they were included in the case–control genotyping. One of the novel variants was found in the promoter region, 4 were intronic, and 1 was a splice junction variant.

Genotype assay results. Of the 40 SNPs included in the assay design, assays for 2 SNPs failed (Table 1) (additional information is presented in Supplementary Table 1, available on the *Arthritis & Rheumatism* Web site at http://www3.interscience.wiley.com/journal/76509746/home). The genotype call rate was >95% for the remaining markers, with the exception of rs6537798,

Table 2. No association of genetic variants at 4q27, 6q23, *CCL21, TRAF1/C5,* and *CD40* with disease in Korean patients with rheumatoid arthritis and control subjects*

Gene or region	SNP	Major allele: minor allele	Allelic association				Genotypic association						
			Major allele count: minor allele count (minor allele frequency)				Case genotypes			Control genotypes			
			Cases	Controls	P†	OR (95% CI)	11, count (freq)	12, count (freq)	22, count (freq)	11, count (freq)	12, count (freq)	22, count (freq)	P‡
4q27	rs6822844	G:T	2,229:1 (0.00)	1,987:1 (0.00)	–	–	0 (0.00)	1 (0.00)	1,114 (1.00)	0 (0.00)	1 (0.00)	993 (1.00)	–
6q23	rs6920220	G:A	2,223:3 (0.00)	1,973:1 (0.00)	–	–	0 (0.00)	3 (0.00)	1,110 (1.00)	0 (0.00)	0 (0.00)	986 (1.00)	–
CCL21	rs2812378	T:C	2,070:158 (0.07)	1,856:120 (0.06)	0.18	1.18 (0.92–1.51)	8 (0.01)	142 (0.13)	964 (0.87)	7 (0.01)	106 (0.11)	875 (0.89)	0.358
TRAF1/C5	rs3761847	G:A	1,139:1,087 (0.51)	974:976 (0.50)	0.43	1.05 (0.93–1.19)	256 (0.23)	575 (0.52)	282 (0.25)	233 (0.24)	508 (0.52)	234 (0.24)	0.751
CD40	rs4810485	G:T	1,483:743 (0.34)	1,341:635 (0.32)	0.39	1.06 (0.93–1.20)	122 (0.11)	499 (0.45)	492 (0.44)	106 (0.11)	423 (0.43)	459 (0.46)	0.577
PADI4§	rs2240340	G:A	1,168:1,056 (0.48)	1,207:763 (0.39)	1.15×10^{-8}	1.43 (1.26–1.62)	254 (0.23)	548 (0.49)	310 (0.28)	158 (0.16)	447 (0.45)	380 (0.39)	1.10×10^{-7}

* SNP = single-nucleotide polymorphism; OR = odds ratio; 95% CI = 95% confidence interval; 11 = homozygous, minor allele; 12 = heterozygous; 22 = homozygous, major allele; freq = frequency.
† For alleles, by chi-square test.
‡ For genotypes, by chi-square test.
§ Association reported in Asian populations.

Table 3. *PTPN22*-region haplotypes and frequencies in HapMap populations*

	Allele present on the haplotype												Frequency	
Haplotype	rs666829	rs6537798	rs3789604	rs3811021	rs1217413	rs2797415	rs1746853	rs2476601†	rs2127407	rs3765598	rs1217418	rs2488457	CHB + JPT	CEU
1A	C	C	T	T	G	T	T	A	A	C	A	C	0	0.142
1B	C	C	T	T	G	T	T	G	A	C	A	C	0.579	0.092
2	C	C	G	C	A	C	G	G	G	T	A	G	0.206	0.198
3	C	A	T	T	A	C	G	G	G	C	G	G	0.112	0.200
4	T	A	T	T	A	C	T	G	G	C	G	G	0.055	0.283

* CHB = Han Chinese in Beijing; JPT = Japanese in Tokyo.
† R620W variant.

Table 4. *PTPN22* haplotype association analysis in Korean patients with rheumatoid arthritis and control subjects*

Haplotype	Estimated haplotype frequency		*P*	OR (95% CI)
	Patients	Controls		
1B	0.633	0.624	0.548	1.04 (0.92–1.18)
2	0.198	0.192	0.609	1.04 (0.89–1.22)
3	0.070	0.082	0.141	0.84 (0.67–1.06)
4	0.066	0.068	0.820	0.97 (0.76–1.24)

* Haplotypes are those identified in Table 2, with the addition of 2 single-nucleotide polymorphisms, rs1217412 and rs3761935. The A allele of rs1217412 was found only on haplotype 1B, and the G allele of rs3761935 was found only on haplotype 2. OR = odds ratio; 95% CI = 95% confidence interval.

which had a 77.7% call rate. No patients or control subjects were polymorphic at rs2476601 (R620W), while 1–9 minor alleles (of 4,300 alleles) were present in the 6 novel *PTPN22* variants, the 6q23 SNP rs6920220, and the 4q27 SNP rs6822844 (Supplementary Table 1 and Table 2). Additionally, the *PTPN22* tag SNP rs1018592 was not analyzed, because of significant deviation from Hardy-Weinberg equilibrium.

RA association tests. No statistically significant association ($P < 0.05$) with RA was detected between any of the 24 polymorphic *PTPN22* tag SNPs (Table 1 and Supplementary Table 1) from the linkage disequilibrium block covering the *AP4B1*, *C1orf178*, *PTPN22*, *RSBN1*, *PTHF1*, and *MAG13* genes. In addition, Caucasian RA–associated SNPs at *TRAF1/C5*, *CD40*, and *CCL21* were found to be polymorphic in the Korean population but not to be associated with disease (Table 2). As noted above, the 4q27 and 6q23 variants were too rare in this population to be evaluated for association (Table 2). The *PADI4* SNP rs2240340 was noted to be strongly disease-associated, with a *P* value of 1.15×10^{-8} and an odds ratio of 1.43 (95% confidence interval 1.26–1.62) for the presence of the disease-associated T allele on patient chromosomes compared with control chromosomes (Table 2). In the subgroup analyses, there were no significant genotypic or allelic associations of any of these SNPs in subgroups of patients classified according to radiographic severity (Steinbrocker stage I and stages II–IV), SE status (SE positive and SE negative), and the CCP status (CCP antibody positive and CCP antibody negative) compared with control subjects, except for *PADI4* SNP rs2240310, which was significantly associated with RA irrespective of SE status ($P < 0.01$) or CCP antibody positivity ($P < 0.0001$).

***PTPN22* linkage disequilibrium.** The linkage disequilibrium structure of the broad genomic region containing the *PTPN22* gene was similar in individuals in the HapMap Centre d'Etude du Polymorphisme Humain Utah residents with ancestry from northern and Western Europe (CEU) and the combined CHB and JPT populations, with a 400-kb region of strong linkage disequilibrium containing 6 genes (*MAGI3, PHTF1, RSBN1, PTPN22, C1orf178, AP4B1*) identified in both populations (see Supplementary Figure 1, available on the *Arthritis & Rheumatism* Web site at http://www3.interscience.wiley.com/journal/76509746/home). The 24 *PTPN22* tag SNPs that passed quality control captured ($r^2 > 0.8$) 90% of the 185 HapMap variants within the 400-kb region that had a minor allele frequency of >5% in the CHB + JPT population. Although the linkage disequilibrium structure of the *PTPN22* gene region was similar in individuals in the HapMap CEU and CHB + JPT populations, the frequencies of the common haplotypes in these 2 populations were very different. Eleven of the 13 tag SNPs used for the haplotype association analysis of the 85-kb *PTPN22* gene region (see below) were genotyped in the HapMap CHB + JPT and CEU samples. These 11 SNPs defined only 4 common haplotypes (those with >5% frequency) in both populations. All 4 common haplotypes found in the Asian samples were also common haplotypes in the CEU samples, but the haplotype frequencies were strikingly different between the 2 populations (Table 3). Interestingly, the 620W autoimmune disease–associated variant was found only on a portion (approximately half) of the copies of haplotype 1 in the CEU samples, but was not found on any of the haplotype 1 copies in the CHB + JPT samples (Table 3).

Haplotype analysis. *PTPN22* haplotypes were constructed using the SNPs from Table 1, numbers 6 through 25, including only those with a minor allele frequency >0.05, using Haploview software. These 13 SNPs covered the entire 85-kb *PTPN22* gene region. The 4 common haplotypes (each with a frequency >5%) together accounted for 96.6% of the chromosomes of the individuals genotyped. Association tests were performed for each of these 4 haplotypes, and none were found to be associated with disease (Table 4).

DISCUSSION

Recent whole-genome association studies in European ancestry case–control collections have shown that after HLA variants, SNPs within the *PTPN22* genetic region are consistently the second most significantly disease-associated variants in the genome (3,7).

However, the proposed causative variant, an SNP encoding a structural variant (R620W) of the *PTPN22* protein, is not present in the Asian population. We therefore sought to determine whether other *PTPN22* alleles are associated with RA in Asian patients. We also evaluated variants in 5 other loci that have strong evidence for association in Caucasians with RA in a large Korean RA case–control series.

SNP variants within the *PTPN22* linkage disequilibrium block were evaluated using a tag SNP approach to interrogate the known common variants in the region. None of the 24 polymorphic SNPs covering the genomic region including *PTPN22* were associated with susceptibility to RA in this Korean population. Of note, we have confirmed that the R620W variant is nonpolymorphic in this population and have shown that a promoter SNP, rs2488457, which has been reported to be associated with RA in Caucasians and with type 1 diabetes mellitus in Japanese (27), had no evidence for association in Korean patients with RA. The genotyped SNPs cover 90% of the known polymorphic SNPs in the 400-kb *PTPN22* linkage disequilibrium block ($r^2 > 0.8$), and none were associated with disease. Furthermore, none of the 4 common *PTPN22* haplotypes were associated with disease. Coupled with the fact that no common *PTPN22* structural variants were identified by resequencing, these data provide strong evidence that common *PTPN22*-region genetic variants are not associated with RA in this population. This is in stark contrast to the very strong association signals seen in multiple case–control studies in Caucasians with RA.

Although none of the common *PTPN22* variants were associated with disease, the novel rare variants are more difficult to evaluate. Interestingly, 3 of the novel variants identified (1 promoter and 2 intronic) were found in a single patient with RA but in no control subjects. Further work will be required to determine whether any of the rare variants of *PTPN22* might be private mutations that contribute to disease susceptibility.

This study also demonstrated that SNPs in 5 additional regions (*TRAF1*/*C5*, 6q23, 4q27, *CD40*, and *CCL21*) that are strongly associated with RA in Caucasians are either nonpolymorphic (6q23 and 4q27) or are not associated with RA in Korean patients (*TRAF1*/*C5*, *CD40*, and *CCL21*). For these SNPs, we can say with certainty only that the SNP associated with disease in Caucasians is not associated with disease in Koreans. Further investigation and fine mapping similar to what we have done with *PTPN22* would be needed to determine whether other polymorphic SNPs in these regions are associated with RA in Koreans. In comparison, we genotyped the *PADI4* SNP rs2240340, for which we previously reported an association in a subset (545 patients and 392 control subjects) of this case–control series (9), and found a striking association, with a *P* value for association of 1.15×10^{-8}, in this larger collection.

These data provide convincing evidence that the genetic risk factors for RA differ substantially between Asian and Caucasian populations. Although the HLA region has been clearly demonstrated to be the most substantial genetic risk factor in populations of both ancestries, the other genetic contributions seem to be very different. *PTPN22* consistently has the second strongest genetic effect in whole-genome association studies in Caucasians, yet our data indicate that not only is the R620W variant not present in Koreans, but also that no other common polymorphisms in the region are significant risk alleles in Koreans. The other loci associated with RA in Caucasians for which we assayed SNPs (*TRAF1*/*C5*, 6q23, 4q27, *CD40*, *CCL21*) were derived from rigorously interpreted and well-replicated studies and probably represent many of the next tier of susceptibility loci in populations of European ancestry. The fact that none of these SNPs demonstrated association in this large Korean study reveals a large degree of genetic heterogeneity of RA across continental ancestry differences, especially when juxtaposed with the *PADI4* locus, which has been strongly associated with RA in this and other Asian populations but which has shown little evidence for association in Caucasians (14).

In conclusion, we observed no association between RA in Koreans and tag SNPs covering the entire *PTPN22* region or with individual SNPs shown to be strongly associated with disease in Caucasians at the *TRAF1*/*C5*, 6q23, 4q27, *CD40*, and *CCL21* loci. When contrasted with other loci such as *PADI4*, *FCRL3*, and *SLC22A4*, which have been shown to be associated with RA in Asian but not Caucasian populations, these data indicate that most of the disease-associated variants have arisen independently in different continental populations, and that different points in disease-associated pathways are influenced by genetic risk factors in the different populations. Therefore, one would expect that whole-genome association studies in Asian populations would reveal more and different susceptibility loci than those that have been described in Caucasian patients with RA. The identification of such loci should expand our understanding of the processes that lead to the development of RA.

AUTHOR CONTRIBUTIONS

Dr. Remmers had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Lee, Korman, Kastner, Remmers, Gregersen, Bae.

Acquisition of data. Lee, Korman, Le, Kastner, Remmers, Gregersen, Bae.

Analysis and interpretation of data. Lee, Korman, Le, Kastner, Remmers, Gregersen, Bae.

Manuscript preparation. Lee, Korman, Kastner, Remmers, Gregersen, Bae.

Statistical analysis. Lee, Korman, Remmers.

REFERENCES

1. Jun KR, Choi SE, Cha CH, Oh HB, Heo YS, Ahn HY, et al. Meta-analysis of the association between HLA-DRB1 allele and rheumatoid arthritis susceptibility in Asian populations. J Korean Med Sci 2007;22:973–80.
2. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 2002;4 Suppl 3:S265–72.
3. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–78.
4. Begovich AB, Carlton VE, Honigberg LA, Schrodi SJ, Chokkalingam AP, Alexander HC, et al. A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. Am J Hum Genet 2004;75:330–7.
5. Gregersen PK, Lee HS, Batliwalla F, Begovich AB. PTPN22: setting thresholds for autoimmunity. Semin Immunol 2006;18: 214–23.
6. Mori M, Yamada R, Kobayashi K, Kawaida R, Yamamoto K. Ethnic differences in allele frequency of autoimmune-disease-associated SNPs. J Hum Genet 2005;50:264–6.
7. Plenge RM, Seielstad M, Padyukov L, Lee AT, Remmers EF, Ding B, et al. TRAF1-C5 as a risk locus for rheumatoid arthritis: a genomewide study. N Engl J Med 2007;357:1199–209.
8. Hu X, Chang M, Saiki RK, Cargill MA, Begovich AB, Ardlie KG, et al. The functional 169T→C single-nucleotide polymorphism in FCRL3 is not associated with rheumatoid arthritis in white North Americans. Arthritis Rheum 2006;54:1022–4.
9. Kang CP, Lee HS, Ju H, Cho H, Kang C, Bae SC. A functional haplotype of the PADI4 gene associated with increased rheumatoid arthritis susceptibility in Koreans. Arthritis Rheum 2006;54: 90–6.
10. Kochi Y, Yamada R, Suzuki A, Harley JB, Shirasawa S, Sawada T, et al. A functional variant in FCRL3, encoding Fc receptor-like 3, is associated with rheumatoid arthritis and several autoimmunities. Nat Genet 2005;37:478–85.
11. Plenge RM, Padyukov L, Remmers EF, Purcell S, Lee AT, Karlson EW, et al. Replication of putative candidate-gene associations with rheumatoid arthritis in >4,000 samples from North America and Sweden: association of susceptibility with PTPN22, CTLA4, and PADI4. Am J Hum Genet 2005;77:1044–60.
12. Suzuki A, Yamada R, Chang X, Tokuhiro S, Sawada T, Suzuki M, et al. Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. Nat Genet 2003;34:395–402.
13. Tokuhiro S, Yamada R, Chang X, Suzuki A, Kochi Y, Sawada T, et al. An intronic SNP in a RUNX1 binding site of SLC22A4, encoding an organic cation transporter, is associated with rheumatoid arthritis. Nat Genet 2003;35:341–8.
14. Lee YH, Rho YH, Choi SJ, Ji JD, Song GG. PADI4 polymorphisms and rheumatoid arthritis susceptibility: a meta-analysis. Rheumatol Int 2007;27:827–33.
15. Lee HS, Remmers EF, Le JM, Kastner DL, Bae SC, Gregersen PK. Association of STAT4 with rheumatoid arthritis in the Korean population. Mol Med 2007;13:455–60.
16. Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. N Engl J Med 2007;357:977–86.
17. Kurreeman FA, Padyukov L, Marques RB, Schrodi SJ, Seddighzadeh M, Stoeken-Rijsbergen G, et al. A candidate gene approach identifies the TRAF1/C5 region as a risk factor for rheumatoid arthritis. PLoS Med 2007;4:e278.
18. Plenge RM, Cotsapas C, Davies L, Price AL, de Bakker PI, Maller J, et al. Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. Nat Genet 2007;39:1477–82.
19. Thomson W, Barton A, Ke X, Eyre S, Hinks A, Bowes J, et al. Rheumatoid arthritis association at 6q23. Nat Genet 2007;39: 1431–3.
20. Raychudhuri S, Remmers EF, Lee AT, Hackett R, Guiducci C, Burtt NP, et al. Common variants at CD40 and other loci confer risk of rheumatoid arthritis. Nat Genet 2008;40:1216–23.
21. Zhernakova A, Alizadeh BZ, Bevova M, van Leeuwen MA, Coenen MJ, Franke B, et al. Novel association in chromosome 4q27 region with rheumatoid arthritis and confirmation of type 1 diabetes point to a general risk locus for autoimmune diseases. Am J Hum Genet 2007;81:1284–8.
22. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
23. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659–62.
24. De Bakker PI, Yelensky R, Pe'er I, Gabriel SB, Daly MJ, Altshuler D. Efficiency and power in genetic association studies. Nat Genet 2005;37:1217–23.
25. The International HapMap Consortium. The International HapMap Project. Nature 2003;426:789–96.
26. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005;21: 263–5.
27. Kawasaki E, Awata T, Ikegami H, Kobayashi T, Maruyama T, Nakanishi K, et al. Systematic search for single nucleotide polymorphisms in a lymphoid tyrosine phosphatase gene (PTPN22): association between a promoter polymorphism and type 1 diabetes in Asian populations. Am J Med Genet A 2006;140:586–93.