Interleukin 1 Polymorphisms in Patients with Ankylosing Spondylitis in Korea

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ABSTRACT. ***Objective.*** Studies in ankylosing spondylitis (AS) and psoriatic arthritis (PsA) cohorts have demonstrated that the interleukin 1 (IL-1) gene cluster contains a major susceptibility locus for AS and PsA. We examined the association between the IL-1 gene cluster and susceptibility to AS in Korea.

Methods. In total, 451 patients with AS and 402 ethnically matched healthy controls were genotyped with 51 single-nucleotide polymorphisms (SNP) within the IL-1 gene cluster (specifically located within the IL1A, IL1B, IL1RN, and IL1F5-10 genes based on findings of previous association studies). Samples were genotyped by MALDI-TOF mass spectrometry using standard Sequenom iPLEX conditions. Genotyping assays were designed using AssayDESIGNER 2.0 and all SNP designed as 4 multiplex reactions. The resulting product was analyzed using the MassArray Compact Analyzer, and genotype results were determined. Univariate SNP marker distributions in case-control populations were tested by chi-square tests.

Results. No SNP showed association with p value < 0.05. Haplotype analysis revealed an association with the 6 markers (empirical $p \leq 2 \times 10^{-4}$, corresponding to Bonferroni corrected p = 0.05). Analysis of each 2, 3, 4, 5-marker sliding window revealed association with the IL1A locus (especially haplotype rs12622683-rs11123148-rs10165537).

Conclusion. Single SNP associations noted in outbred Caucasian populations were not found in the Korean AS cohort. Haplotype analysis revealed associations with IL1 locus. These results support the notion that the IL1 locus is associated with susceptibility to AS. (First Release May 15 2008; J Rheumatol 2008;35:1603–8)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS INTERLEUKIN 1 POLYMORPHISMS KOREA

Ankylosing spondylitis (AS) is one of the most common causes of inflammatory arthritis after rheumatoid arthritis[1,2]. AS is characterized by inflammation of axial skeleton, sacroiliac joints, and to a lesser degree, peripheral joints and certain extraarticular organs, including the eyes, skin, and cardiovascular system. Over time, chronic spinal inflammation (spondylitis) can lead to complete fusion of the vertebrae, a process referred to as ankylosis, and is associated with loss of mobility of the spine.

The pathogenesis of AS is unknown, but it is well established that genetic factors play a major role in susceptibility. Twin study results estimate the heritability of AS to be over 90%[3]. There is an established association between development of AS and HLA-B27[4]. Although HLA-B27 is recognized to be the major gene associated with AS, only 1%–5% of B27-positive individuals develop disease, and the contribution of B27 to the overall genetic predisposition has been estimated at only 20%–30%[3]. Therefore, there is increasing evidence to suggest that genes outside the MHC region play a substantial role in disease susceptibility and expression of AS[5].

With respect to the pathogenesis of AS, proinflammatory cytokines such as interleukin 1 (IL-1) could be implicated in sacroiliitis. The original members of the IL-1 superfamily are IL-1α, IL-1ß, and the IL-1 receptor antagonist (IL-1RA). These are encoded by the genes IL-1A, IL-1B, and the IL-1RN, respectively[6]. IL-1α and Il-1ß are proinflammatory cytokines involved in inflammation and immunity. The IL-1RA competes for receptor binding with IL-1α and IL-1ß, blocking their role in immune activation.

Association of members of the IL-1 gene cluster with AS has been reported by several groups[7-11]. Recent studies in

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multiple AS and psoriatic arthritis (PsA) cohorts have demonstrated that the IL-1 gene cluster contains a major susceptibility locus for AS and PsA[8,12,13].

Although our previous analysis of single-nucleotide polymorphisms (SNP) in IL-1 complex genes did not support a major role for them in AS susceptibility in populations in Seoul and Toronto[14], it was important to extend our research by examining additional SNP and haplotypes. This would provide a more rigorous examination of the role of genetic variants within the IL-1 gene cluster in the etiology of AS patients of Korean descent.

MATERIALS AND METHODS

Patient selection. A total of 451 patients with AS (423 men) and 402 ethnically matched healthy controls (380 men) were enrolled for study. All patients were native Koreans with AS satisfying the modified New York criteria[15]. Informed consent was obtained from all patients. Clinical information was collected systematically. Controls were volunteers from Seoul who participated as a result of a local advertising campaign seeking controls for genetic studies. Healthy volunteers were screened by questionnaire to exclude those with a personal or family history of arthritis.

This study was approved by the local ethics committee of Hanyang University.

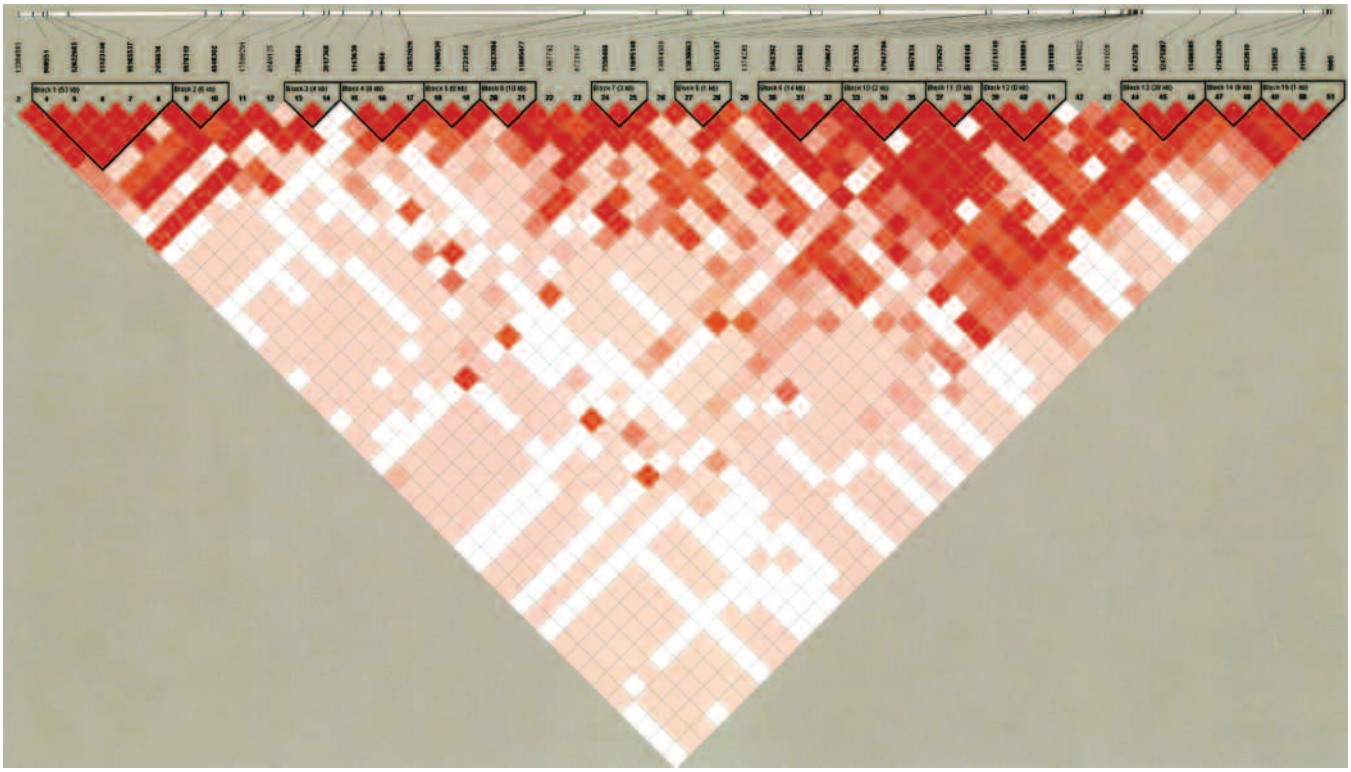
Genotype analysis. Samples of whole blood were obtained from AS patients and controls. DNA was extracted using the Wizard Genomic DNA purification kit (Promega, Madison, WI, USA). In total, 51 SNP (Table 1) within the IL–1 gene cluster (specifically located within the IL–1A, IL–1B, IL–1RN, and IL–1F5-10 genes) were genotyped in 451 AS patients and 402 controls. Reactions were multiplexed where possible. Detection of SNP was performed using the chip-based matrix-assisted laser desorption ionization time-of-flight mass spectrometry platform (Sequenom, San Diego, CA, USA). Briefly, polymerase chain reaction (PCR) and extension reactions were designed using MassArray Design software (Sequenom). Primers were obtained from Integrated DNA Technologies (Coralville, IA, USA). PCR primers were used to amplify 5 ng of genomic DNA using standard conditions for MassArray genotyping. Unincorporated nucleotides in the PCR product were deactivated using shrimp alkaline phosphatase. Amplification of the SNP site was carried out using MassExtend primer and involved the use of a mass-modified specific termination mix. The primer extension products were then cleaned and spotted onto a SpectroChip (Sequenom). The chip was scanned using a mass spectrometry workstation (Sequenom), and the resulting spectra were analyzed using SpectroTyper-RT software (Sequenom).

Statistical analysis. Tests of Hardy-Weinberg equilibrium were performed for all polymorphic IL–1 SNP on controls only. Single-marker case-control differences were evaluated for all polymorphic IL–1 SNP, using chi-square tests with 2 degrees of freedom (df), comparing the 3 genotypes in cases versus controls. Cochrane-Armitage test for trend[16] across the 3 genotypes (1 df), and genotypic chi-square tests for association between each marker and trait using the qtscore function in the GenAbel R package[17] were performed, and a logistic model was performed to estimate odds ratios under the log-additive model. When 1 allele was rare, we grouped the rare allele with the heterozygotes and performed a 1-df Fisher exact test. Haploview was used to examine linkage disequilibrium patterns across the markers[18].

In haplotype-based association analysis, we used the algorithm proposed by Schaid, *et al*[19] to test the association between (ambiguous) haplotypes and the trait. The algorithm was implemented in the haplo.stats R package (haplo.score.slide function. Note we modified the function in order to get haplotypes and their frequencies). The algorithm can be summarized as follows: an EM algorithm was used to compute the maximum likelihood estimates of the haplotype frequencies and the posterior probabilities of the pairs of haplotypes for each subject. The algorithm starts with known haplotypes from a subset of the loci and progressively discards those with low frequencies before inserting more loci. The process is repeated until haplotypes for all loci are established. The posterior probabilities are then used to compute the score statistics for the association of (ambiguous) haplotypes with traits. Permutation tests were performed for each haplotype to obtain empirical significance levels. P values < 0.05 were considered significant. We used sliding windows of 2, 3, 4, or 5 consecutive markers when

Table 1. Odds ratios for disease association of 51 single-nucleotide polymorphisms (SNP) in the IL1 gene cluster in a Korean AS case-control cohort.

Marker	Allele	OR (95% CI)	p
rs13384583	T	1.07 (0.83–1.38)	0.59
rs2138606	T	1.03 (0.82–1.30)	0.80
rs908551	T	1.12 (0.91–1.37)	0.28
rs12622683	T	1.08 (0.88–1.32)	0.49
rs11123148	A	1.05 (0.85–1.31)	0.64
rs10165537	T	1.10 (0.89–1.35)	0.39
rs2856838	T	1.05 (0.84–1.33)	0.67
rs1878319	C	1.36 (0.98–1.90)	0.07
rs4848302	T	1.09 (0.89–1.35)	0.40
rs17598291	T	1.06 (0.84–1.35)	0.63
rs4849125	A	1.25 (0.92–1.69)	0.16
rs7596684	C	1.41 (0.97–2.04)	0.07
rs3917368	A	1.11 (0.91–1.34)	0.30
rs1143630	C	1.11 (0.87–1.43)	0.41
rs16944	G	1.19 (0.99–1.44)	0.06
rs13032029	T	1.07 (0.89–1.30)	0.47
rs11690539	C	1.19 (0.97–1.46)	0.10
rs2723154	A	1.10 (0.86–1.40)	0.44
rs13023984	A	1.18 (0.91–1.54)	0.22
rs11695077	T	1.01 (0.82–1.24)	0.97
rs4387792	T	1.07 (0.88–1.30)	0.49
rs6723197	G	1.01 (0.82–1.24)	0.91
rs7559466	G	1.15 (0.95–1.40)	0.16
rs11695148	G	1.08 (0.87–1.34)	0.50
rs10864909	A	1.33 (0.99–1.79)	0.06
rs13030063	C	1.18 (0.96–1.45)	0.11
rs12711747	G	1.01 (0.74–1.36)	0.98
rs1374280	C	1.03 (0.79–1.33)	0.85
rs1562302	G	1.02 (0.84–1.24)	0.83
rs2515402	C	1.10 (0.89–1.35)	0.40
rs7558672	A	1.15 (0.92–1.44)	0.22
rs6755354	G	1.09 (0.88–1.34)	0.42
rs17042786	T	1.06 (0.85–1.33)	0.59
rs1867834	T	1.02 (0.78–1.34)	0.88
rs10165797	C	1.01 (0.82–1.23)	0.96
rs7570267	A	1.11 (0.80–1.53)	0.53
rs4849148	C	1.01 (0.84–1.22)	0.91
rs12711749	A	1.06 (0.87–1.29)	0.59
rs13019891	T	1.01 (0.77–1.33)	0.93
rs3811050	C	1.01 (0.82–1.24)	0.96
rs12469822	G	1.02 (0.80–1.30)	0.90
rs3811058	C	1.05 (0.87–1.28)	0.62
rs6743376	C	1.02 (0.82–1.26)	0.89
rs12475887	C	1.06 (0.87–1.29)	0.56
rs13406085	A	1.00 (0.81–1.24)	0.99
rs17042939	G	1.07 (0.79–1.43)	0.67
rs4252019	T	1.04 (0.86–1.27)	0.68
rs315952	C	1.14 (0.94–1.38)	0.20
rs315951	C	1.03 (0.85–1.26)	0.74
rs9005	A	1.05 (0.85–1.29)	0.68



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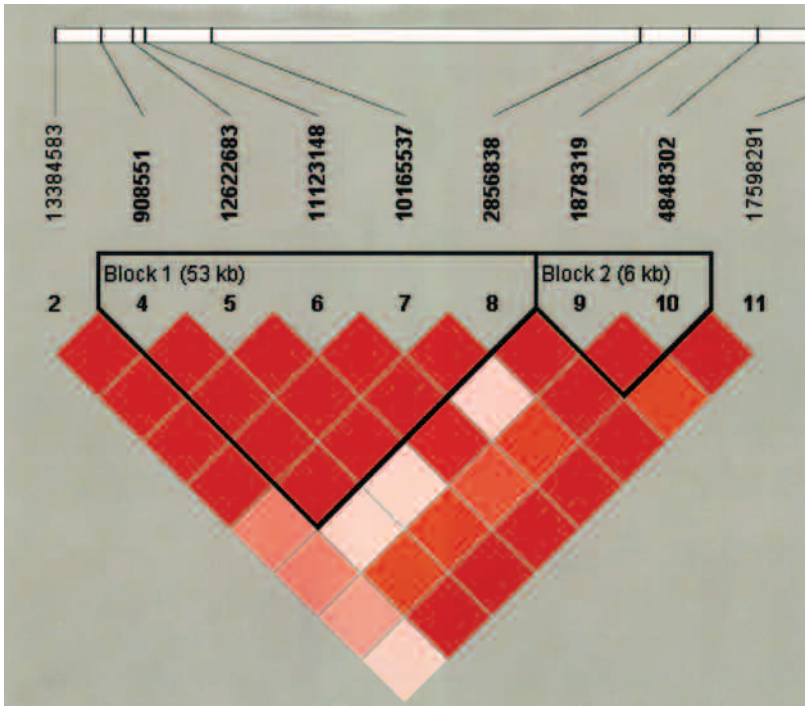

B

Figure 1. A. Haplotype structure of all markers. B. Haplotype structure of a selected subset of markers.

evaluating haplotype associations. Thus, we performed a total of 51 univariate tests and 194 haplotype tests. Using a Bonferroni correction for the number of tests, we might therefore consider p values < 0.0002 as significant; however, this adjustment is known to be overly conservative, especially when tests are correlated.

RESULTS

In total, 853 subjects were genotyped (451 patients with AS, 402 controls) with IL–1 gene cluster polymorphisms; 93.8% (423/451) of the AS patients were male. The mean age of the

AS patients was 34 years. HLA-B27 was present in 97.1% (438/451).

In the control group, only one marker displayed evidence of a departure from Hardy-Weinberg equilibrium (*rs13386452*; p = 0.0005). Although there was statistically marginal association with the Korean AS population in *rs16944* (p = 0.06), no SNP were strongly associated with disease (Table 1). Using Haploview, 15 blocks were identified (Figure 1A). In some specific regions, such as the region with markers rs908551-rs12622683-rs11123148-rs10165537-rs2856838, strong linkage disequilibrium was observed (Figure 1B). We tested the associations between haplotypes constructed based on 2, 3, 4, and 5 consecutive loci (near the IL–1A region) with the trait and used simulation to determine empirical p value (the maximum number of simulations was set to 200,000). Using a Bonferroni correction for the 245 tests performed, the significant haplotype results were as follows: The markers rs12622683-rs11123148 ($p = 1 \times 10^{-4}$) were associated on a combination of 2 consecutive loci. The markers rs908551-rs12622683-rs11123148 ($p = 1 \times 10^{-5}$) and rs12622683-rs11123148-rs10165537 ($p = 1.5 \times 10^{-5}$) were associated on combinations of 3 consecutive loci. The markers rs2138606-rs908551-rs12622683-rs11123148 (p = 0), rs908551-rs12622683-rs11123148-rs10165537 (p = 0), and rs12622683-rs11123148-rs10165537-rs2856838 ($p = 2.5 \times 10^{-5}$) were associated on combinations of 4 consecutive loci. The markers rs2138606-rs908551-rs12622683-rs11123148-rs10165537 ($p = 2.1 \times 10^{-8}$) and rs908551-rs12622683-rs11123148-rs10165537-rs2856838 ($p = 1.3 \times 10^{-7}$) were also associated on combinations of 5 consecutive loci (Table 2). It should be noted that since the haplotype tests included sliding overlapping windows, many of the tests will be highly correlated and this p value correction is likely to be far too conservative.

DISCUSSION

Chromosome 2q13, a region containing the IL-1 family gene cluster, was linked to AS in whole-genome screens[5]. Association of allele 2 of a variable number of tandem repeats (VNTR) in intron 2 of the IL1RN gene with AS, but not with polymorphisms in IL–1A or IL-1B, has been reported in 2 European populations[7,9]. IL-1RA production has been reported to be increased in association with this allele[20]. A Canadian study analyzed SNP of IL–1RN instead of VNTR allele 2 of IL–1RN. This study showed global association of *rs315952* and *rs315951* alleles (in exon 6 of the gene) with AS (p = 0.001 and 0.04, respectively), and with *rs419598* genotypes (in exon 4) globally (p = 0.03) — this was not found in our study, mostly due to underrepresentation of homozygosity for the minor "C" allele among AS cases (p = 0.01, odds ratio 0.5)[10]. Consistent with results reported by Maksymowych, *et al*[10], IL–1 gene family members (alleles and genotypes of the markers such as IL–1F10.3, IL–1RN.4, and IL–1RN.VNTR) were found to be important determinants of susceptibility to AS in a Taiwanese study[11]. Timms, *et al*[8] reported no associations with markers in IL1RN, but found a highly significant association with markers in IL1B and IL1F10, confirmed in a family-based association study. Recently, the Spondyloarthritis Research Consortium of Canada (SPARCC) study concluded that IL–1 locus, or a locus close to IL–1, is associated with susceptibility to AS, showing a total of 14 SNP (most significant at *rs3783526* and *rs1143627*) and haplotypes of IL–1A and IL–1B (especially haplotypes such as *rs1143634/rs1143630/rs3917356* and *rs1143630/rs3917356/rs3917354*) in an analysis of 3 Canadian populations.

However, some family-based association studies have found that there was no association between IL-1 gene and AS. Jin, *et al*[21] demonstrated that IL–1RN was not associated with AS, investigating the 5 most informative SNP (*rs1794065*, *rs419598*, *rs315952*, *rs315951*, *and rs895495*) and microsatellite markers (*D2S 2216*, *D2S 373*, *D2s 340*, *D2S121*, and *D2S 347*).

Within a family-based association study in which it was concluded that the *rs16944* and *rs3811058* polymorphisms were primarily associated with disease, haplotypes of these 2 markers were strongly associated with disease both within-family (p = 0.0002 in the fully typed parent-case trio and affected sib-pair families; $p = 1.7 \times 10^{-18}$ among all families) and by case-control analysis (p = 0.04)[8]. In various studies, *rs16944* polymorphisms have been found to be associated with several diseases, such as systemic sclerosis[22], gastric cancer, and schizophrenia in Caucasians[23,24]. In Korean studies, IL1B-511 (*rs16944*) C/C genotypes were significantly associated with a decreased risk of cervical cancer[25] and IL1B-511 (*rs16944*) C/T was implicated in an increased risk of endstage kidney failure[26]. The *rs16944* was significantly associated with AS in certain Canadian cohorts[12]; however, this marker has marginal but not statistically significant association with AS in Korea. Although our analysis found that no SNP showed strong association in a Korean AS population, there were some impressive haplotype associations. One reason the haplotypic findings are stronger than individual SNP associations could be because reported markers may not be causally associated with disease or may encode only part of the susceptibility effect. In addition, a well known problem with large-scale association studies is the presence of undetected population structures, which can lead not only to false-positive results but also to failures to detect genuine haplotypic associations[27]. With only a few markers in a candidate gene, we cannot use genotype-based methods to test for population substructure; however, we feel that our controls were well matched to our cases because Koreans are a homogeneous ethnic group, and we also compared control subjects matched for age and sex.

Power calculation is an important step in planning a genetic association study to identify candidate genes for dis-

Table 2. Selected disease haplotype sliding-window associations. Only associations with $p \leq 2 \times 10^{-4}$, corresponding to Bonferroni corrected $p \leq 0.05$, are shown.

Combinations of Markers	Haplotype Frequencies		Empirical
	Cases	Controls	p*
rs12622683-rs11123148	TG (0.692)	TG (0.663)	1×10-4
	CA (0.265)	CA (0.245)	
	CG (0.043)	CG (0.081)	
	Rare (0)	Rare (0)	
rs908551-rs12622683-rs11123148	TTG (0.693)	TTG (0.654)	1×10-5
	CCA (0.265)	CCA (0.246)	
	CCG (0.042)	CCG (0.078)	
	Rare (0)	Rare (0.022)	
rs12622683-rs11123148-rs10165537	TGT (0.693)	TGT (0.658)	1.5×10-5
	CAG (0.264)	CAG (0.245)	
	CGG (0.043)	CGG (0.077)	
	Rare (0)	Rare (0.020)	
rs2138606-rs908551-rs12622683-rs11123148	TTTG (0.688)	TTTG (0.653)	0
	GCCA (0.236)	GCCA (0.232)	
	TCCG (0.042)	TCCG (0.079)	
	Rare (0.034)	Rare (0.036)	
rs908551-rs12622683-rs11123148-rs10165537	TTGT (0.693)	TTGT (0.651)	0
	CCAG (0.265)	CCAG (0.245)	
	CCGG (0.042)	CCGG (0.075)	
	Rare (0)	Rare (0.029)	
rs12622683-rs11123148-rs10165537-rs2856838	TGTC (0.688)	TGTC (0.645)	2.5×10-5
	CAGT (0.219)	CAGT (0.200)	
	CAGC (0.045)	CAGC (0.045)	
	Rare (0.048)	Rare (0.110)	
rs2138606-rs908551-rs12622683-rs11123148-rs10165537	TTTGT (0.688)	TTTGT (0.649)	2.1×10-8
	GCCAG (0.236)	GCCAG (0.231)	
	TCCGG (0.042)	TCCGG (0.076)	
	Rare (0.034)	Rare (0.044)	
rs908551-rs12622683-rs11123148-rs10165537-rs2856838	TTGTC (0.688)	TTGTC (0.641)	1.3×10-7
	CCAGT (0.219)	CCAGT (0.200)	
	CCAGC (0.045)	CCAGC (0.045)	
	Rare (0)	Rare (0.114)	

* Based on 200,000 permutations.

ease susceptibility. If we assume that there is a 5% difference in the allelic frequency between patients with AS and controls, the power of our study[28,29] varied from 74% to 94% as the odds ratios increased from 1.7 to 2.0. Previously, we analyzed a relatively small sample, which limited the interpretation of findings[14]. To enhance the confidence of the analysis, we expanded our sample size and included linkage analysis, where the number of identical-by-descent alleles shared by siblings is random. Therefore our haplotype analyses of consecutive loci in the IL–1 gene cluster support that there is an AS disease susceptibility locus near the IL–1A region.

Other SNP and haplotype associations noted in outbred Caucasian populations were not found in the Korean AS cohort. Variable patterns of association across populations may be attributable to geographic separation and ethnic disparity. Moreover, these discrepancies may reflect the clinical differences in the patient populations studied. Our analysis did not include stratification by disease severity. Future studies might address this aspect.

Haplotype analysis revealed association with AS in Korean subjects in the IL-1 locus. Our results support the concept that there is a disease susceptibility locus in the IL–1 gene cluster.

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