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Association of interleukin 23 receptor gene with sarcoidosis

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Abstract. Interleukin 23 receptor (*IL23R*) gene has been reported as a genetic factor strongly associated with inflammatory bowel disease, psoriasis, and ankylosing spondylitis. We investigated the association between *IL23R* gene single nucleotide polymorphisms (SNPs) and susceptibility to sarcoidosis, including the clinical manifestation of uveitis.

Ninety-one sarcoidosis subjects (58 with and 33 without uveitis) and 104 healthy controls were genotyped for eleven *IL23R* SNPs. DNA was amplified using specific PCR primers and genotyped by denaturing HPLC and/or direct DNA sequencing. Case-control frequency comparisons were analyzed using Chi square test.

Three *IL23R* SNPs, rs7517847 (intron 6), rs11465804 (intron 8), and rs11209026 (exon 9, c.1142G>A, p.Arg381Gln) were associated with sarcoidosis in our population ($p < 0.05$): rs7517847 showed increased frequencies in sarcoidosis compared to controls, but rs11465804 and rs11209026 were decreased. Two of these SNPs were associated with the uveitis subgroup compared to controls: rs11465804 (0.9% vs. 7.2%, OR = 0.11, P = 0.013) and rs11209026 (1.8% vs. 7.3%, OR = 0.23, P = 0.038).

This finding indicates the association of *IL23R* polymorphism with sarcoidosis, especially with sarcoid uveitis. *IL23R* may be a common susceptibility gene shared by several autoimmune disorders including inflammatory bowel disease, psoriasis, and ankylosing spondylitis and sarcoid uveitis.

Keywords: Interleukin 23 receptor, polymorphism, sarcoidosis, uveitis

1. Introduction

Sarcoidosis is a systemic inflammatory disease characterized by non-caseating granulomatous inflammation. It frequently presents with bilateral hilar adenopathy, pulmonary infiltration, ocular and skin lesions, but liver, spleen, lymph node, salivary gland, heart, nervous system, muscles, bones and other organs may also be involved. About 11–83% of patients with sarcoidosis have ocular involvement and uveitis is the most common of all sarcoid eye lesions [1].

The etiology of sarcoidosis still remains unknown. Sarcoidosis is thought to be a complex multifactorial disease resulting from interaction of multiple genes and environmental factors. Familial aggregation and racial differences in incidence suggest the existence of genetic susceptibility to sarcoidosis [2]. Although some HLA genes and other candidate genes such as various cytokine genes, receptor genes and others have been reported to show an association with sarcoidosis, many of the reported associations have not been replicated [3–5].

Interleukin 23 receptor (*IL23R*) gene on chromosome 1p31 was identified as a susceptibility gene for

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Table 1
Demographic data of control and sarcoidosis subjects with and without uveitis

	Sarcoidosis total $n = 91$	Sarcoidosis with uveitis $n = 58$	Sarcoidosis without uveitis $n = 33$	Control $n = 104$
Age (mean ± SD)	58.2 ± 12.2	56.3 ± 6.7	57.5 ± 10.5	48.4 ± 11.9
Sex (% men: women)	30: 70	33: 67	24: 76	42:58
Ethnicity/Race*				
Caucasian	83 (91.2%)	49 (84.5%)	32 (97.0%)	96 (92.3%)
African-American	5	4	1	
Native American				1
Asian	2	2		2
Middle Eastern	1	1		
Mixed racial groups				5
Biopsy proven cases	52 (57.1%)	30 (51.7%)	22 (66.7%)	

*As categorized based on self-report.

inflammatory bowel disease in the North American genome-wide association study [6]. Subsequent studies in several populations revealed the association between these *IL23R* polymorphisms and inflammatory bowel disease (IBD), psoriasis, ankylosing spondylitis, and idiopathic achalasia [7–9]. We have also found an independent association of the *IL23R* gene with acute anterior uveitis (unpublished data). Hence, *IL23R* gene might be a common genetic factor for inflammatory bowel disease and other chronic inflammatory autoimmune diseases.

IL23 is a heterodimeric regulatory cytokine consisting of a p19 and a p40 subunit produced by activated macrophages and dendritic cells. IL23 activity is mediated by binding to the IL23 receptor complex which is composed of an IL-12Rβ1 subunit and a unique cytokine receptor subunit termed IL23R [10]. IL23 binding with IL23R on Th17 cell serves to expand differentiated Th17 cell population and IL23-Th17 interactions are thought to play an important role in the development of autoimmune inflammatory disorders [11].

We investigated the association of *IL23R* polymorphisms with sarcoidosis and especially with sarcoid uveitis. We selected the *IL23R* gene as a candidate gene in sarcoidosis because *IL23R* gene was reported to be a susceptibility gene for Crohn's disease, which is characterized by non-caseating granulomas, a feature also found in sarcoidosis.

2. Materials and methods

2.1. Study subjects

Ninety-one sarcoidosis subjects and 104 healthy controls were included in the study. Written informed consent was obtained from all subjects and the study was performed under a protocol approved by the Institutional Review Boards of Oregon Health & Science University.

The validation of a sarcoidosis diagnosis was made on the basis of the International Consensus Statement on Sarcoidosis [1,12]. All subjects were interviewed about the course of their disease and agreed to release relevant medical records for research review. Three doctors who were blinded from the genetic analysis reports (one ophthalmologist, one pulmonology specialist and one pathologist) reviewed all the subjects' medical records. Fifty two cases (57.1%) were confirmed by tissue biopsy and remaining cases without histological confirmation had radiographic evidence of pulmonary sarcoidosis (bilateral hilar adenopathy, etc) and clinical presentation compatible with sarcoidosis. Among the ninety-one sarcoidosis subjects, 64 (70.3%) were women and 58 (63.7%) presented with uveitis. The majority of the participants in this study were Caucasian (91.2% of cases, 92.3% of controls). The ethnicity of non-Caucasians were 5 African-Americans, 2 Asians, and 1 middle Eastern in sarcoidosis group, whereas 1 native American, 2 Asians, and 5 mixed races in control group. Details of these patients and controls are listed in Table 1.

2.2. Genotyping

The eleven SNPs of *IL23R* gene (rs1004819, rs7517847, rs7530511, rs10489629, rs2201841, rs11465804, rs11209026, rs1343151, rs10889677, rs11209032, and rs1495965) were selected on the basis of their previously reported association with IBD and psoriasis susceptibility [6]. Genomic DNA was extracted from peripheral blood samples of all subjects. Regions of the *IL23R* gene flanking the specific SNP locations were amplified using specific primers and a

Table 2
List of each SNP of *IL23R*, the genotyping methods, and primers used in this study

SNP	Location	Chromosome position	Alleles	Amino acid substitution	Genotyping methods	Primer used (F, forward; R, reverse)
rs1004819	Intron 5	67442801	G/A	–	PCR-dHPLC/sequencing	F: agatctggtggaaatatgtgaaacct R: agttcggcttggccactgttat
rs7517847	Intron 6	67454257	G/T	–	PCR-sequencing	F: acactgttgaccaccttgtcct R: ttcgcaactgggagctcaat
rs7530511	Exon 7	67457975	C/T	Pro310Leu	PCR-dHPLC/sequencing	F: gtctagaagacagcttgg R: agccactgtgctcagcagaaa
rs10489629	Intron 7	67460937	T/C	–	PCR-dHPLC/sequencing	F: aaagtgctgggattacaggcgt R: agtcatgcccagtttccgcttt
rs2201841	Intron 7	67466790	A/G	–	PCR-dHPLC/sequencing	F: acagggtttcaccatgtttgcc R: tttcagcccagtggttgtga
rs11465804	Intron 8	67475114	T/G	–	PCR-sequencing	F: aacaagggaagaaactccgttggg R: ccacctaagccacttcttacattcag
rs11209026	Exon 9	67478546	G/A	Arg381Gln	PCR-dHPLC/sequencing	F: ccacccttctcctttgagacctt R: agctgtgtttggactcagggctta
rs1343151	Intron 9	67491717	G/A	–	PCR- sequencing	F: gattagagttgtttggtgtggcag R: tgccttccttacaagggtattagg
rs10889677	Exon 11	67497708	C/A	3'UTR	PCR-dHPLC/sequencing	F: ggattgctgggccatatgataagc R: tgaggcgtccacataatgct
rs11209032	Intergenic	67512680	G/A	–	PCR-dHPLC/sequencing	F: ctgaaattgggtaggtactacagtgg R: aaggcaatccggtggttctt
rs1495956	Intergenic	67526096	T/C	–	PCR-dHPLC/sequencing	F: tcccatggctctttccagtt R: aactgaggcctagctttgga

Table 3
Minor allele frequencies for *IL23R* SNPs between sarcoidosis subjects and controls

SNP	Allele	Sarcoidosis $n = 91$	Controls $n = 104$	$P-$value	Corrected P- value	Odds ratio (95% CI)	Caucasian (CEU) from HapMap
rs1004819	A	0.280	0.274	0.892	1.000	1.031 (0.661–1.608)	0.289
rs7517847	**T**	**0.615**	**0.471**	**0.004**	**0.048**	**1.800 (1.199–2.690)**	**0.494**
rs7530511	T	0.144	0.107	0.263	1.000	1.412 (0.770–2.590)	0.139
rs10489629	C	0.441	0.490	0.340	1.000	0.820 (0.546–1.232)	0.500
rs2201841	G	0.311	0.272	0.396	1.000	1.210 (0.779–1.879)	0.272
rs11465804	**G**	**0.028**	**0.072**	**0.049**	**0.464**	**0.367 (0.131–1.032)**	**0.078**
rs11209026	**A**	**0.028**	**0.073**	**0.046**	**0.464**	**0.364 (0.130–1.022)**	**0.072**
rs1343151	A	0.379	0.417	0.441	1.000	0.852 (0.567–1.281)	0.378
rs10889677	A	0.300	0.260	0.376	1.000	1.222 (0.784–1.907)	0.287
rs11209032	A	0.294	0.337	0.357	1.000	0.823 (0.535–1.266)	0.306
rs1495956	C	0.456	0.437	0.705	1.000	1.081 (0.724–1.614)	0.414

touch-down polymerase chain reaction (PCR) strategy (Table 2). Amplified products were analyzed using denaturing high-performance liquid chromatography (DHPLC) system (WAVE; Transgenomic, Omaha, NE) and the resultant chromatograms were compared with those of the wild-type DNA and variant DNA. Direct DNA sequencing was performed to confirm the variants.

2.3. Statistical analysis

Allele and genotype frequencies in control and cases were compared by the Chi square test and by the Fisher's exact test when any expected frequency was less than 5.

The tests were considered statistically significant when the p values were smaller than 0.05, and the Holm-Bonferroni correction (Pc) was used to adjust p-values for multiple tests [13]. The odds ratios (ORs) with 95% confidence intervals (CI) were also calculated. R statistical language (http://www.r-project.org) was used for computation. Haplotype frequencies and linkage disequilibrium (LD) were estimated and visualized with the Haploview software (available at http://www.broad.mit.edu/mpg/haploview) [14]. LD plot and R^2 value were obtained from the genotype data of the cases and controls and those of the Caucasian population from the HapMap data (available at http://www.hapmap.org). P-values for haplotype asso-

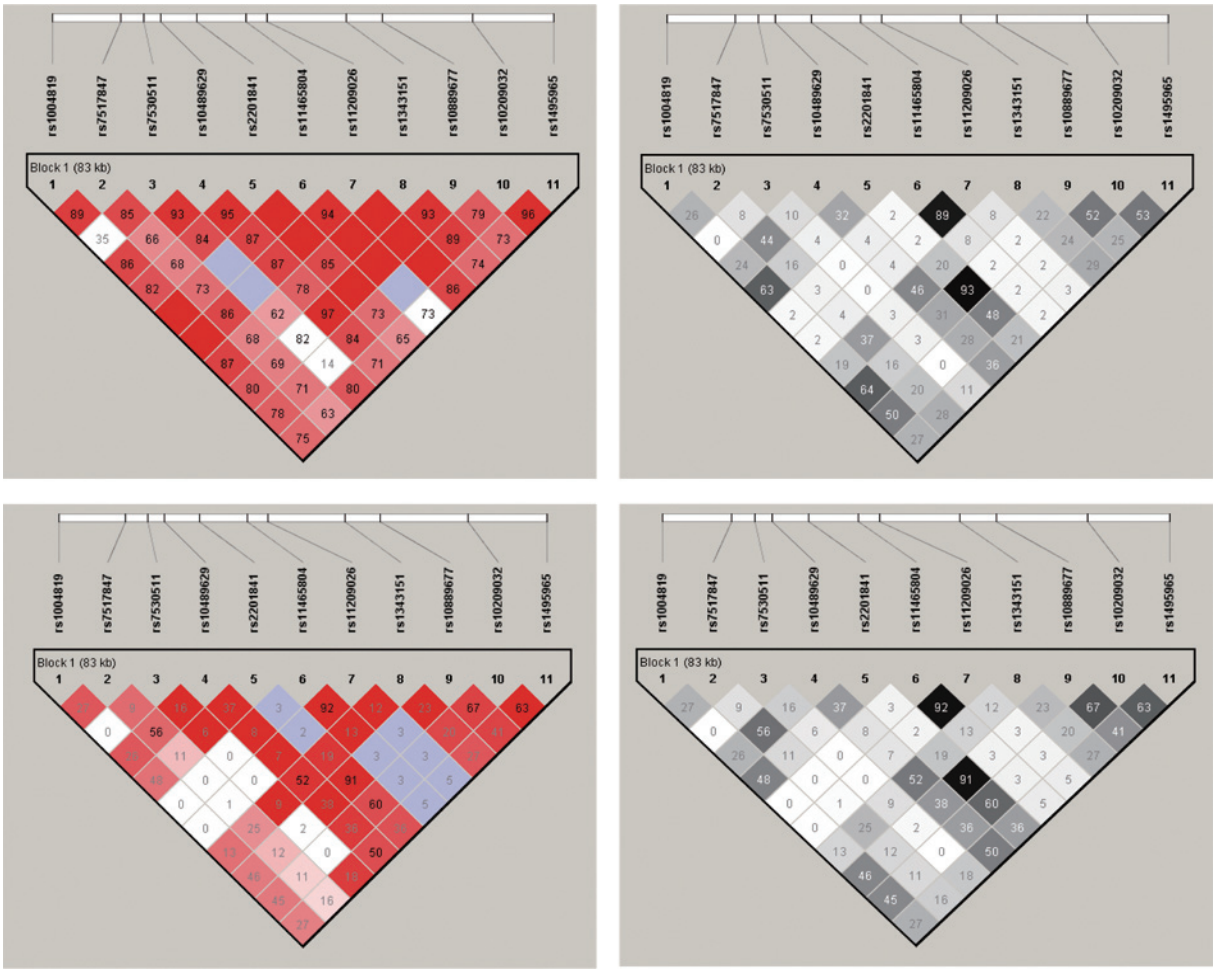

Fig. 1. The structure of linkage disequilibrium between our population (top panels) and Caucasian population from HapMap data (bottom panels) generated by Haploview software. D' (left panels) and r^2 value (right panels) between pairs of SNPs were shown in each box and the intensity of the shading is proportional to D' and r^2 respectively. Red: strong D', white: low D', blue: high D'/low LOD.

ciation analysis were obtained after 1,000 permutation tests using Haploview software.

3. Results

Allele frequencies of 11 *IL23R* SNPs in sarcoidosis cases and healthy controls are shown in Table 3. Genotypes at all loci were in Hardy-Weinberg equilibrium in both sarcoidosis subjects and controls ($p > 0.01$) except for rs1343151 in control group ($P = 0.0004$). Despite this finding, allele frequencies for all SNPs including rs1343151 in our control population were similar to those of Caucasian population (CEU) from HapMap data.

The T allele frequency of rs7517847 was significantly higher in patients than controls (cases 0.615 vs. controls 0.471, $P = 0.004$, OR $= 1.800$). The minor allele frequency (MAF) of SNP rs11209026, previously shown to be protective for Crohn's disease, was decreased in sarcoidosis (patients 0.028 vs. controls 0.073, $P = 0.046$, OR $= 0.364$) and MAF of rs11465804, which showed a strong linkage disequilibrium with rs11209026 ($r^2 > 0.85$, Fig. 1.), was also decreased in sarcoidosis groups. However, these associations lost their significance when Hom-Bonferroni correction was applied for multiple testing correction (corrected $p > 0.05$).

Table 4 shows the allele frequencies of 11 *IL23R* SNPs in two subgroups of sarcoidosis: sarcoidosis with and without uveitis. Minor allele frequencies of rs11209026 and rs11465804 were significantly decreased in the sarcoid uveitis subgroup compared to

Table 4
Minor allele frequencies for *IL23R* SNPs in control and sarcoidosis subjects with and without uveitis

SNP	Allele Genotype	Sarcoidosis with uveitis $n = 58$ [A]	Sarcoidosis without uveitis $n = 31$ [B]	Controls $n = 104$ [C]	P-value OR (95%CI) [A vs. C]	P-value OR (95% CI) [B vs. C]	P-value OR (95% CI) [A vs. B]
rs1004819	A	0.259	0.318	0.274	0.865	0.592	0.491
					0.924 (0.052–1.547)	1.236 (0.678–2.255)	0.748 (0.385–1.452)
rs7517847	**T**	**0.569**	**0.697**	**0.471**	0.116	**0.002**	0.122
					0.675 (0.427–1.066)	**0.387 (0.214–0.700)**	1.742 (0.918–3.307)
rs7530511	**T**	**0.105**	**0.212**	**0.107**	0.883	**0.046**	0.081
					0.984 (0.468–2.070)	**2.252 (1.077–4.707)**	0.437 (0.189–1.013)
rs10489629	C	0.482	0.367	0.490	0.978	0.122	0.199
					0.966 (0.609–1.534)	0.602 (0.333–1.087)	1.606 (0.843–3.060)
rs2201841	G	0.289	0.348	0.272	0.836	0.299	0.511
					1.091 (0.657–1.814)	1.433 (0.793–2.590)	0.762 (0.398–1.456)
rs11465804	**G**	**0.009**	**0.061**	**0.072**	**0.013**	1.000	0.061
					0.114 (0.015–0.874)	0.830 (0.266–2.594)	0.137 (0.015–1.254)
rs11209026	**A**	**0.018**	**0.045**	**0.073**	**0.038**	0.576	0.358
					0.227 (0.051–1.013)	0.606 (0.170–2.163)	0.375 (0.061–2.304)
rs1343151	A	0.422	0.303	0.417	0.975	0.130	0.151
					1.021 (0.644–1.618)	0.607 (0.335–1.098)	1.682 (0.886–3.194)
rs10889677	A	0.281	0.333	0.260	0.782	0.314	0.566
					1.113 (0.666–1.859)	1.426 (0.784–2.594)	0.781 (0.406–1.502)
rs11209032	A	0.281	0.318	0.337	0.366	0.900	0.717
					0.764 (0.463–1.259)	0.913 (0.505–1.652)	0.836 (0.432–1.618)
rs1495956	C	0.414	0.530	0.437	0.776	0.237	0.173
					0.910 (0.574–1.442)	1.455 (0.834–2.538)	0.625 (0.340–1.149)

Table 5
Estimated haplotype frequencies between sarcoidosis and control subjects

Haplotype*	Sarcoidosis+control	Sarcoidosis	Control	P-value	Caucasian (CEU) from HapMap
GGCCATGACGT	0.248	0.230	0.263	0.4553	0.224
ATCTGTGGAAC	0.208	0.231	0.190	0.3210	0.188
GTTTATGGCGC	**0.065**	**0.101**	**0.034**	**0.0078**	**0.071**
GTCTATGGCGT	0.063	0.087	0.041	0.0644	0.076
GGCCATGGCGT	0.056	0.038	0.071	0.1628	0.118
GGCCAGAACGT	0.040	0.022	0.055	0.0961	0.055
GTCCATGACGT	0.030	0.047	0.015	0.0616	0.022
GTCTATGGCAC	0.024	0.011	0.036	0.1220	0.006
GTCCATGGCGT	0.021	0.024	0.019	0.7289	0.018
ATCTGTGGAGT	0.018	0.030	0.008	0.1135	0.017
GGCCATGACGC	0.017	0.029	0.007	0.0900	0.017
GGCTGTGGAAC	0.016	0.014	0.019	0.6822	0.045
GTCTATGGCGC	0.015	0.004	0.024	0.1141	
GGCTGTGGAGT	0.013	0.021	0.006	0.1794	
GGTTATGGCGC	0.012	0.010	0.014	0.7140	0.012
GGCTATGACGT	0.011	0.001	0.020	0.0707	
ATTTATGGCAC	0.011	0.006	0.015	0.3723	0.027
GGCCATGGCAC	0.010	0.012	0.009	0.8046	

* Haplotypes with estimated frequencies > 0.01 are shown.

controls (rs11209026 $P = 0.038$, rs11465804 $P = 0.013$).

Estimated haplotypes whose frequencies were higher than 0.01 were obtained by the Haploview program (Table 5). The frequency of one haplotype GTTTATGGCGC showed significant differences between cases and controls (0.101 vs. 0.034, $P = 0.0078$), which still remained significant ($P = 0.023$) after being corrected by 1,000 random permutation tests for haplotypes. This haplotype included three alleles of three SNP [rs7517847 (T), rs11465804 (T), and rs11209026 (G)] showing significant differences between cases and controls. However, there was no significant difference in frequency of this haplotype between sarcoidosis

Table 6
Reported minor allele frequencies (MAF) of *IL23R* rs11209026 in case control association studies

Disease*	Population	Case MAF(%)	Control MAF(%)	P-value	OR	References
CD	Non-Jewish	1.9	7	5.05E-09	0.26	[6]
CD	Jewish	3.3	7	7.95E-04	0.45	[6]
CD	Spanish white	2	7	0.001	0.3	[9]
IBD	Nethelands	1.2	6.5	5.30E-08	0.19	[19]
CD	UK Caucasian	2.6	5.9	6.58E-06	0.43	[20]
UC	UK Caucasian	3.8	5.9	0.0081	0.63	[20]
CD	German	3	6.8	8.04E-08	0.43	[21]
UC	German	4.9	6.8	0.036	0.7	[21]
CD	Italian	2.1	5.9	0.0067	0.33	[22]
CD	New Zealand	4	7	0.0026	0.54	[23]
UC	New Zealand	4	7	0.037	0.66	[23]
CD	UK Caucasian	2.5	6.2	1.10E-12	0.38	[24]
Psoriasis	UK Caucasian	3.6	7	0.00014	0.49	[25]
Psoriasis	Caucasian	3.5∼5.1	6.0∼7.7	1.89E-04	0.63	[12]
AS	Spanish	3	7	0.001	0.46	[18]
AS	UK Caucasian	4	6	4.00E-06	0.63	[26]
Sarcoidosis	**91.2% Caucasian**	**2.8**	**7.3**	**0.046**	**0.36**	**This study**

*Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; AS ankylosing spondylitis.

uveitis and control group (0.071 vs. 0.034, $P = 0.132$ by Haploview program).

Figure 1 shows the linkage disequilibrium among 11 SNPs. The SNP pairs, rs11465804 with rs11209026, and rs2201841 with rs10889677, showed strong linkage disequilibrium ($r^2 > 0.85$) in our population. The pattern of linkage disequilibrium (r^2) in our population was very similar to that of a Caucasian population (CEU) from HapMap data.

4. Discussion

In this study three *IL23R* SNPs, rs7517847, rs11465804, and rs11209026 (c.1142G>A, p.Arg381 Gln) were nominally significant but did not withstand correction for multiple testing and two of these SNPs, rs11465804 and rs11209026, were associated with the sarcoid uveitis subgroup. It is noteworthy that the coding SNP rs11209026 (p.Arg381Gln), previously identified to be protective for Crohn's disease, was also decreased in sarcoidosis subjects compared to controls and the difference of allele frequencies and odds ratio of the SNP between the two groups in this study were similar to those of other reported studies showing significant associations with several autoimmune diseases (Table 6). These results suggest the possibility of the SNP rs11209026 to show more significant association with sarcoidosis when analyzed in a larger population, whereas our data, with relatively small study groups, show only a weak association of the SNP with sarcoidosis. Recently, the SNP rs11209026 in the *IL23R* gene was reported to be associated with German chronic sarcoidosis [15]. Therefore, our study could be a replication to validate the association of *IL23R* gene with sarcoidosis. We cannot exclude the possibility that this association is due not to sarcoidosis but due to uveitis in our study because rs11209026 showed an association with sarcoid uveitis subgroup only, and not with the sarcoidosis without uveitis subgroup. Further studies will be needed for confirmation.

IL23R SNP rs11209026 has been reported to be associated with IBD, psoriasis, and ankylosing spondylitis, but not with Graves' disease and systemic lupus erythematosus. Multiple sclerosis and rheumatoid arthritis showed different results between studies [7]. This means *IL23R* may be a common susceptible gene only to IBD, psoriasis, and AS, but not to the latter diseases. There have been speculations that *IL23R* may play a more important role in regulating local rather than systemic inflammation [16,17]. Since all of the above diseases are multifactorial in etiology, gene to gene or gene to environmental interactions may act as another cause of the difference. Also, the degree and the variety of associated SNPs may differ among various diseases.

The biological impact and functionality of *IL23R* polymorphism is currently unknown. The site of Arg381Gln polymorphism is located in the initial portion of the IL23R intracytoplasmic region, very close to the first putative tyrosine phosphorylation site at po-

sition 399 [10]. By changing the Arg to Gln at position 381, the interaction between IL23R and its associated Jak-2 kinase may be modified. Lowering of the IL23 signaling pathway by genetic variation of its receptor may protect individuals from severe inflammatory response to environmental factors [18].

In conclusion, this study indicates the association of *IL23R* polymorphism with sarcoidosis, especially with sarcoid uveitis. *IL23R* may be a common susceptibility gene shared by several autoimmune disorders including inflammatory bowel disease, psoriasis, and ankylosing spondylitis and sarcoid uveitis.

4.1. Support statement

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