Lack of association between IL10 polymorphisms and sarcoidosis in Japanese patients

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Purpose: To investigate whether interleukin 10 (IL10) gene polymorphisms are associated with the development of sarcoidosis in Japanese patients.

Methods: Two hundred and eighty-eight Japanese sarcoidosis patients and 310 Japanese healthy controls were recruited. We genotyped 9 single-nucleotide polymorphisms in IL10 and assessed the allelic diversity between cases and controls.

Results: No significant differences in the frequency of IL10 alleles, genotypes, and haplotypes in the sarcoidosis cases compared to the controls were detected.

Conclusions: Our results suggest that IL10 polymorphisms are not significantly related to the pathogenesis of sarcoidosis in the Japanese population.

Sarcoidosis is a systemic inflammatory disorder characterized by non-caseating granuloma formation in many organs, such as: lung, skin, eye, lymph nodes, central and peripheral nervous system, and heart [1-3].

In Japan, the reported incidence rate of the disease is 1.01 per 100,000 inhabitants [4]. On a global scale, this incidence rate is low. African Americans incidence rate of the disease is 35.5 per 100,000. That of Caucasian Americans is 10.9 per 100,000 [5]. Japanese patients have a higher likelihood of ocular involvement compared with other ethnic groups [4,6]. According to a recent epidemiological study of sarcoidosis in Japan, patients with ocular involvement was 54.8% of cases and impaired vision was the most frequent symptom (28.8%) [4]. In European patients, erythema nodosum of skin lesions is commonly seen. It is rare in Japanese patients [7]. This way, the frequency and course of sarcoidosis varies widely among racial groups. It supports the assumption that some predisposing genetic factors play roles in the development of the disease. There is also evidence supporting a possibility of association with genetic factors. Some familial sarcoidosis cases [8], and associations between the disease and human leukocyte antigen (HLA) systems were reported [9,10]. The exact cause of the disease remains undetermined, but it is currently thought that genetic factors may be the basis of disease susceptibility.

It is also thought that environmental factors associate with the disease progression. By using polymerase-chain-reaction (PCR) techniques, Mycobacterium tuberculosis and Propionibacterium acnes DNA have been detected in sarcoid lesions [11-14]. Recent studies have shown that serum samples from sarcoidosis patients contain antibodies against mycobacterium antigens [15]. These studies suggest that immune responses to bacterial infections can affect the development of sarcoidosis.

The inflammatory response in sarcoidosis is characterized by the increased production of several inflammatory cytokines produced by type 1 helper T (Th1) cells and macrophages, such as interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor alpha.
(TNF-α) [16-18]. These cytokines seem to play a roll leading to the formation of granuloma [3]. In some of sarcoidosis patients, the granulomatous response resolves, and the remaining patients have chronic disease include fibrosis. Interleukin-10 (IL-10) produced by type 2 helper T (Th2) cells is associated with the resolution [3]. IL-10 is a potent suppressor of these inflammatory cytokines [19]. Several studies reported that changes in cytokine production might have been caused by a genetic polymorphisms and some of them might be involved in disease susceptibility and progression. Recent studies have reported that IL10 polymorphisms were associated with several inflammatory diseases [20-22]. In the present study, we evaluated the association of multiple SNPs in IL10 in Japanese sarcoidosis patients.

METHODS
Subjects: Two hundred and eighty-eight unrelated patients with a diagnosis of sarcoidosis and 310 healthy controls were recruited from Yokohama City University, Hokkaido University, Fujita Health University, Tokyo University, Keio University, Kumamoto City hospital and Yuasa eye clinic. All patients and control participants were of Japanese ethnicity. Sarcoidosis patients were diagnosed according to the diagnostic criteria developed by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (JSSOG) previously described [23]. Uveitis with sarcoidosis was assessed based on the “Guidelines for Diagnosis of Ocular Lesions in Sarcoidosis” prepared by the JSSOG. The ocular features of sarcoidosis were defined as granulomatous uveitis plus two or more of the following: infiltration of the anterior chamber (mutton-fat keratic precipitates/iris nodules), trabecular meshwork nodules and/or tent-shaped peripheral anterior synchiae, masses of vitreous opacities (snowball-like or string of pearls-like appearance), periphlebitis with perivascular nodules; multiple candle-wax type chorioretinal exudates and nodules, and/or laser photocoagulation spot-like chorioretinal atrophy. All subjects had a similar social background and resided in the same urban area. The research methods were in compliance with the guidelines of the Declaration of Helsinki. Details of the study were explained to all patients and controls, and valid consent for genetic screening was obtained.

IL10 genotyping: Peripheral blood lymphocytes were collected, and genomic DNA was extracted from peripheral blood cells using the QIAamp DNA Blood Maxi Kit (Qiagen, Tokyo, Japan). We selected IL10 SNPs which previously showed a significant association with Japanese Behcet’s disease [22]: rs1878672, rs1554286, rs1518111, rs3021094, rs3790622, rs3024490, rs1800872, rs1800871, and rs1800896 (Figure 1, Table 1). Genotyping of all SNPs was performed using the TaqMan 5’exonuclease assay using primers supplied by Applied Biosystems (Foster City, CA).
| rsID   | Position Build 37.1 | Location | Allele | 1>2 | Cases n=288 | Controls n=310 | p     | OR (95% CI)         |
|--------|---------------------|----------|--------|-----|-------------|----------------|-------|---------------------|
| rs1878672 | chr1: 206,943,713  | Intron 3 | C>G    | 31  | 31 (5.4)    | 41 (6.7)       | 0.356 | 0.80 (0.49–1.29)   |
| rs1554286  | chr1: 206,944,233  | Intron 3 | T>C    | 181 | 180 (31.4)  | 210 (34.0)     | 0.347 | 0.89 (0.70–1.13)   |
| rs1518111  | chr1: 206,944,645  | Intron 2 | A>G    | 224 | 220 (39.1)  | 235 (37.5)     | 0.296 | 0.88 (0.69–1.12)   |
| rs3021094  | chr1: 206,944,952  | Intron 1 | A>C    | 224 | 220 (39.1)  | 235 (37.5)     | 0.296 | 0.88 (0.69–1.12)   |
| rs3790622  | chr1: 206,945,163  | Intron 1 | C>T    | 36  | 36 (6.3)    | 30 (4.9)       | 0.298 | 0.29 (0.16–0.54)   |
| rs3024490  | chr1: 206,945,311  | Intron 1 | T>G    | 191 | 180 (31.2)  | 210 (34.0)     | 0.286 | 0.86 (0.68–1.11)   |
| rs1800872  | chr1: 206,946,407  | 5′ UTR   | A>C    | 31  | 31 (5.4)    | 41 (6.7)       | 0.420 | 0.87 (0.68–1.12)   |
| rs1800871  | chr1: 206,946,634  | 5′ UTR   | T>C    | 179 | 180 (31.2)  | 210 (34.0)     | 0.286 | 0.86 (0.68–1.11)   |

1: major allele; 2: minor allele.

Table 1. Allele frequencies of SNPs of the *IL10* gene among cases and controls.
### Table 2. Genotype frequencies of SNPs of the IL10 gene among cases (n=288) and controls (n=310).

| rsID     | Allele | Status | Genotype Frequency, n (%) | 1/1 | 1/2 | 2/2 | p   | 1/1+1/2 | 2/2 | p   | 1/1 | 1/2+2/2 | p   |
|----------|--------|--------|----------------------------|-----|-----|-----|-----|---------|-----|-----|-----|---------|-----|
| rs1878672 | C>G    | Cases  | 258 (89.6)                 | 29  | (10.1) | 1   | (0.3) | 0.650  | 287 | (99.7) | 1   | (0.3) | 0.602 |
|          |        | Controls | 269 (87.3)               | 37  | (12.0) | 2   | (0.7) | 0.602  | 306 | (99.4) | 2   | (0.7) | 0.524 |
| rs1554286 | T>C    | Cases  | 135 (46.9)                 | 125 | (43.4) | 28  | (9.7) | 0.640  | 260 | (90.3) | 28  | (9.7) | 0.452 |
|          |        | Controls | 134 (43.4)            | 140 | (45.5) | 35  | (11.3) | 0.452  | 274 | (88.7) | 35  | (11.3) | 0.315 |
| rs1518111 | A>G    | Cases  | 136 (47.2)                 | 124 | (43.1) | 28  | (9.7) | 0.574  | 260 | (90.3) | 28  | (9.7) | 0.515 |
|          |        | Controls | 133 (43.2)            | 140 | (45.5) | 35  | (11.4) | 0.515  | 273 | (88.6) | 35  | (11.4) | 0.343 |
| rs3021094 | A>C    | Cases  | 105 (36.5)                 | 142 | (49.3) | 41  | (14.2) | 0.5023 | 247 | (85.8) | 41  | (14.2) | 0.236 |
|          |        | Controls | 132 (42.7)            | 122 | (39.5) | 55  | (17.8) | 0.236  | 254 | (82.2) | 55  | (17.8) | 0.118 |
| rs3790622 | C>T    | Cases  | 254 (88.2)                 | 32  | (11.1) | 2   | (0.7) | 0.576  | 286 | (99.3) | 2   | (0.7) | 0.524 |
|          |        | Controls | 279 (90.6)            | 28  | (9.1)  | 1   | (0.3) | 0.524  | 307 | (99.7) | 1   | (0.3) | 0.389 |
| rs3024490 | T>G    | Cases  | 129 (44.8)                 | 127 | (44.1) | 32  | (11.1) | 0.466  | 256 | (88.9) | 32  | (11.1) | 0.343 |
|          |        | Controls | 125 (40.7)            | 140 | (45.5) | 42  | (13.7) | 0.343  | 265 | (86.3) | 42  | (13.7) | 0.284 |
| rs1800872 | A>C    | Cases  | 136 (47.2)                 | 124 | (43.1) | 28  | (9.7) | 0.507  | 260 | (90.3) | 28  | (9.7) | 0.438 |
|          |        | Controls | 132 (42.9)            | 140 | (45.5) | 36  | (11.7) | 0.438  | 272 | (88.3) | 36  | (11.7) | 0.284 |
| rs1800871 | T>C    | Cases  | 136 (47.4)                 | 123 | (42.9) | 28  | (9.8) | 0.557  | 259 | (90.2) | 28  | (9.8) | 0.524 |
|          |        | Controls | 133 (43.2)            | 140 | (45.5) | 35  | (11.4) | 0.524  | 273 | (88.6) | 35  | (11.4) | 0.303 |
| rs1800966 | A>G    | Cases  | 258 (89.6)                 | 29  | (10.1) | 1   | (0.3) | 0.701  | 287 | (99.7) | 1   | (0.3) | 0.601 |
|          |        | Controls | 269 (87.6)            | 36  | (11.7) | 2   | (0.7) | 0.601  | 305 | (99.3) | 2   | (0.7) | 0.452 |

1: major allele; 2: minor allele.
Probe fluorescence signals were detected by TaqMan Assay for real-time PCR (7500 Real Time PCR System; Applied Biosystems) following the manufacturer’s instructions.

**Statistical analysis:** Hardy–Weinberg equilibrium was tested for each SNP among the controls. Differences in allele and genotype frequencies between cases and controls were assessed by the χ² test. The Haploview 4.1 program was used to compute pair-wise linkage disequilibrium (LD) statistics [24]. Standardized disequilibrium D' value and r² value were plotted, and LD blocks were defined according to the criteria [25]. Haplotype frequencies were estimated with an accelerated expectation-maximization algorithm, similar to the partition-ligation-expectation-maximization method described previously [26]. P values <0.05 were considered statistically significant.

### RESULTS

We genotyped nine common SNPs in **IL10**: rs1878672, rs1554286, rs1518111, rs3021094, rs3790622, rs3024490, rs1800872, rs1800871, and rs1800896. All SNPs were in Hardy–Weinberg equilibrium in the controls (data not shown). All 9 SNPs were located in 1 haplotype block, and the magnitude of LD between each SNP was extremely high, with pair-wise D'≥0.83 (Figure 1). The allele and genotype frequencies of the 9 SNPs in both the cases and controls are listed in Table 1 and Table 2, respectively. No statistically significant association was observed for any of the SNPs between the cases and controls. Furthermore, there were no significant differences in the haplotype frequencies of all 9 SNPs between the cases and controls (Table 3). We analyzed clinical features according to 9 SNPs. In a stratified analysis according to lesion location, which included the eye, lungs, skin heart, and nerves, none of these clinical features were found to be significantly associated with 9 SNPs (data not shown).

**DISCUSSION**

The aim of the current study was to investigate whether **IL10** polymorphisms affect the development of Japanese patients with sarcoidosis. Our results showed that all the **IL10** polymorphisms were not significantly associated with any clinical subtype of sarcoidosis including ocular involvement in Japanese patients. Here we report a lack of association between **IL10** variants and Japanese sarcoidosis patients, suggesting that the possibility of attributing the pathogenesis of sarcoidosis to **IL10** genetic variations is low.

**IL-10** produced by Th2 cells suppresses inflammatory cytokines produced by Th1 cells. Although the mechanism of **IL-10** in sarcoidosis is unclear, it is thought to be associated with granuloma resolution [2,3]. Some studies have reported that serum levels of **IL-10** were increased in several inflammatory diseases, such as; Crohn’s disease, diffuse cutaneous systemic sclerosis and active Behçet's disease [27-29]. In addition, increased serum levels of **IL-10** in sarcoidosis patients have been reported [30,31].

Recent studies have also reported that **IL10** gene polymorphisms were associated with several inflammatory diseases. Wang et al. [20] reported **IL-10** concentration was significantly higher in Crohn’s disease patients than in the controls and **IL10** polymorphisms were associated with increased patient serum **IL-10** levels. Hudson et al. [21] reported that **IL10** genotypes were associated with systemic sclerosis-related autoantibodies and contribute to the etiology of systemic sclerosis. Recently, Mizuki et al. [22] performed a genome-wide association study for Behçet’s disease and identified **IL10** as a disease susceptibility gene. Muraközy et al. [32] investigated an association of **IL10** polymorphisms with sarcoidosis, however they could not find any significant differences. As with the previous report, we could not find any association between **IL10** gene polymorphisms and sarcoidosis. On the other hand, Vasakova et al. [33] have recently shown that there are significant differences in the frequencies of **IL10** polymorphisms between sarcoidosis and healthy controls in the Czech Caucasian population, whereas they suggested that their findings cannot be generalized since the sample size in the study was small.

In summary, the **IL10** polymorphisms do not appear to be significantly relevant to Japanese sarcoidosis patients. However, further genetic studies in other ethnic populations are needed to confirm our findings.

### Table 3. Haplotype Frequencies of SNPs of the **IL10** Gene Among Cases and Controls.

| Haplotype     | Cases n=288       | Controls n=310 | p     | OR (95%CI)          |
|---------------|------------------|----------------|-------|---------------------|
| CTACCTATA     | 32.6             | 32.4           | 0.934 | 1.01 (0.79–1.29)    |
| CTAACTATA     | 28.0             | 26.1           | 0.461 | 1.10 (0.85–1.42)    |
| CCGACGCCA     | 26.0             | 27.3           | 0.605 | 0.93 (0.72–1.21)    |
| CGGACGCCG     | 5.4              | 6.5            | 0.410 | 1.10 (0.85–1.42)    |
| CTACTTATA     | 6.3              | 4.9            | 0.304 | 1.30 (0.79–2.14)    |
| CTAACGATA     | 1.7              | 2.5            | 0.396 | 0.71 (0.31–1.58)    |

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are required to elucidate the association between IL10 polymorphisms and sarcoidosis.

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