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Relationship between cytokine single nucleotide polymorphisms and sarcoidosis among Japanese subjects

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Abstract. Several susceptibility genes for sarcoidosis have been identified, but their relationship to the clinical state and prognosis remains to be elucidated. The aim of this study was to elucidate the relationship between sarcoidosis and five single nucleotide polymorphisms (SNPs) of three cytokines expected to play an important role in the inflammatory response. A case-control study was performed with 208 unrelated patients who met the diagnostic criteria for sarcoidosis used in Japan since 2006, and 328 control subjects. Five SNPs were analyzed: interleukin (IL)-*10-819T/C* (rs1800871), *IL-10-592A/C* (rs1800872), *IL-6-634C/G* (rs1800796), tumor necrosis factor-α *(TNF-α)-857C/T* (rs1799724), and *TNF-α -1031T/C* (rs1799964). No significant differences in SNPs were observed between the total sarcoidosis and control groups. However, the prevalence of rs1800871 and rs1800872 polymorphisms differed significantly in the sarcoidosis with eye involvement group compared with the control group [rs1800871 TT (vs. TC + CC): OR = 1.67, *P* = 0.034; rs1800872 AA (vs. AC + CC): OR = 1.66, *P* = 0.036]. Analyzing the cardiac involvement group, the prevalence of the rs1799724 polymorphism was significantly different from that of the control group [rs1799724 TT (vs. CC + CT): OR = 6.01. *P* = 0.006]. We concluded that the rs1799724 C/T polymorphism may affect susceptibility to cardiac sarcoidosis, while the rs1800871 T/C and rs1800872A/C polymorphisms may affect susceptibility to sarcoidosis with eye involvement. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 36-42)*

Key words: sarcoidosis, polymorphism, tumor necrosis factor-α, interleukin

Introduction

Japanese patients with sarcoidosis are at high risk of developing ocular and cardiac lesions (1).

The main cause of sarcoidosis-related death in Japan is cardiac involvement, which accounts for 47–78% of sarcoidosis deaths, whereas lung involvement is the main cause of death in Europe and the United States (2, 3).

We focused on possible SNPs that could influence the inflammatory aspect of sarcoidosis, especially those of cytokines. We selected the cytokine SNPs according to the following characteristics: [1] a distribution of 10% or more of the minor allele among the Japanese population (to achieve statistical power) (4-6) and [2] having the possibility of a functional effect (4, 5, 7).

The granulomatous formation of sarcoidosis is associated with the induction of Th1 cells. The SNPs of various cytokines related to the induction

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of Th1 cells and suppression of Th2 cells have been investigated. There have been several reports on the relationship between sarcoidosis and polymorphisms of tumor necrosis factor alpha (*TNF*-α) (8-13). However, the results have not been consistent and vary among racial groups. Because the manifestation of the disease appears to differ between Japanese patients and those from Europe and the United States, the relationship between *TNF*-α polymorphisms and sarcoidosis needs to be verified in Japan (2, 3). There are fewer reports on the relationship between sarcoidosis and SNPs of interleukin (*IL*) than SNPs of *TNF*-α. To our knowledge, only SNPs of *IL-1β* and *IL-18* have been reported (14 , 15). Therefore, the analysis of additional cytokine SNPs is required.

This study dealt with five SNPs of cytokines with minor alleles that are found at relatively high frequencies (>10%), and we aimed to reveal whether these SNPs are significant predictive factors for the development of sarcoidosis, particularly for sarcoidosis with eye and cardiac involvement.

Materials and Methods

Study Population

We investigated 208 unrelated patients (male/female: 52/156) attending Asahikawa Medical University Hospital and the affiliated hospital between January 2007 and September 2009, who met the diagnostic criteria for sarcoidosis used in Japan since 2006 (16). Of these, 113 (male/female: 24/89) had ocular lesions and 50 (male/female: 11/39) had cardiac involvement.

Ocular involvement was diagnosed essentially according to the above-mentioned criteria (16), but included cases of old iritis and/or uveitis infarction diagnosed by ophthalmologists. Cardiac involvement was evaluated using the criteria of the Japanese Ministry of Health and Welfare (17). The control groups consisted of 328 subjects (male/female: 171/157); 214 (male/female: 165/49) of whom underwent a medical check-up and had no apparent diseases, and 114 (male/female: 6/108) of whom suffered mild chronic lifestyle diseases. None of the control group subjects had any abnormal finding on chest X-ray or electrocardiogram (Table 1). Written informed consent was obtained from all subjects, and the study was approved by the Ethics Committee of Asahikawa Medical University.

Data Collection

Genomic DNA was extracted from peripheral blood of each subject using a kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. We genotyped the following polymorphisms using TaqMan® Genotyping Assays: *IL-10-819T/C* (rs1800871), *IL-10-592A/C* (rs1800872), *IL-6-634C/G* (rs1800796), *TNF*-α *-857C/T* (rs1799724),

Table 1. Age and sex distribution of sarcoidosis and control groups

	Sarcoidosis	Control		
		All	Medical checkup	Chronic disease
	(N = 208) N (%)	(N = 328) N (%)	(N = 214) N (%)	(N=114) N (%)
Sex*				
Males	52 (25.0)	171 (52.1)	165 (77.1)	6 (5.3)
Age**				
20-29	14 (6.7)	11 (3.3)	11 (5.2)	
30-39	19 (9.1)	40 (12.2)	40 (18.7)	
40-49	15 (7.2)	61 (18.6)	60 (28.0)	1 (0.9)
50-59	40 (19.2)	95 (29.0)	70 (32.7)	25 (21.9)
60-69	74 (35.6)	60 (18.3)	24 (11.2)	36 (31.6)
70-79	39 (18.8)	46 (14.0)	6 (2.8)	40 (35.1)
80-	7 (3.4)	15 (4.6)	3 (1.4)	12 (10.5)
Eye involved	113 (54.3)			
Heart involved	50 (24.0)			

* p<0.001 (chi-square test) :sarcoidosis vs. all control group
** p=0.001 (t-test): sarcoidosis vs. all control group

and *TNF*-α *-1031T/C* (rs 1799964). Genotyping was performed in a reaction volume of 10 μL containing approximately 40 ng genomic DNA, 0.25 μL 40X TaqMan® SNP Genotyping Assay Mix, and 5.0 μL of 2X TaqMan® Universal PCR Master Mix. Real-time PCR was performed with the Applied Biosystems StepOne™/StepOnePlus™ real-time PCR system using a protocol consisting of incubation at 50°C for 2 min and 95°C for 10 min, followed by 45 cycles of denaturation at 92°C for 15 s and annealing/extension at 60°C for 1 min.

Statistical Analyses

Age- and sex-adjusted logistic regression analyses were used to obtain the odds ratios (ORs) and 95% confidence intervals (CIs) of each genotype for sarcoidosis. The age- and sex-adjusted ORs for sarcoidosis with eye and cardiac involvement were then analyzed. Analyses were performed using the SPSS package (Dr. SPSS II for Windows). χ^2 tests for deviation from Hardy–Weinberg equilibrium were also calculated. Associations were regarded as significant when they reached $P < 0.05$.

Results

Table 1 shows the characteristics of sarcoidosis and control groups. Age and sex had significant differences. First, age- and sex-adjusted logistic regression analyses were performed among whole sarcoidosis and control groups, but no significant odd ratio of each SNP for development of sarcoidosis was obtained (data not shown). Next, in eye involvement sarcoidosis analyses, there were significant differences in the frequency of rs1800871 T/C and rs1800872 A/C polymorphisms in the sarcoidosis with eye involvement group compared with the control groups in age- and sex-adjusted analyses [rs1800871TT (vs. TC + CC): OR = 1.67, 95% CI = 1.04–2.67]; [rs1800872 AA (vs. AC + CC): OR = 1.66, 95% CI = 1.03–2.66] (Table 2). Finally, in cardiac involvement sarcoidosis analyses, the frequency of the rs1799724 C/T polymorphism in the sarcoidosis with cardiac involvement group was significantly different from that in the control groups [(TT vs. CC): OR = 6.01, 95% CI = 1.66–21.8] (Table 3).

Discussion

To clarify the relationships between these cytokines and sarcoidosis, we selected five cytokine SNPs with minor alleles that are relatively frequent (>10%) in the Japanese. All of these SNPs are located in the promoter regions and probably affect production of each cytokine (4, 7).

TNF-α is a very important cytokine involved in the granuloma formation of sarcoidosis (18, 19). Several studies have reported relationships between sarcoidosis and *TNF*-α SNPs (8-13). In Japan, the minor alleles rs1799724 and rs1799964 were found in 17.7% and 16.0% of 575 controls (4). To our knowledge, the present study is the first to investigate the relationship between these SNPs and sarcoidosis among Japanese subjects.

Several studies have reported findings on the relationship between rs1799724 and sarcoidosis. In England and Netherlands, the minor allele was associated with the development of sarcoidosis (8). In Turkey, more relapses and frequent involvement of three or more organs were found in sarcoidosis patients with this polymorphism, whereas no differences in genotype or allele frequency were found between two subjects (12). In northern India, no relationship has been reported between two subjects (13). In our study, rs1799724 strongly correlated with cardiac sarcoidosis, though it had no association with total sarcoidosis, similary two past studies have reported (8, 13).

TNF-α *-308G/A* (rs1800629) is one of the most investigated SNPs in sarcoidosis(6, 8-11). Although this SNP has been shown to correlate with Löfgren's syndrome, which is extremely rare in Japan (8, 9, 11), there has been no report suggesting a relationship. One Japanese study found a positive result of the association between this polymorphism and cardiac sarcoidosis. (10). However, the number of these subjects was small (N = 26), and there have been no further reports showing a significant relationship between the two subjects after 1999. Because chance may affect the result, and the minor allele is rare in the Japanese (<10%), we did not analyzed the polymorphism.

We found a significant association between the rs1799724T allele and cardiac sarcoidosis. This allele affects TNF-α expression and contributes to the promotion of the inflammatory reaction because or-

Table 2. Age- and sex-adjusted odds ratios of cytokine SNPs for eye involvement in sarcoidosis

Cytokine	SNP		Eye sarcoidosis (N=113) N (%)	Control (N=328) N (%)	*P* value	Age- and sex-adjusted OR (95% CI)
IL10	rs1800871					
Genotypic model		TT	53 (46.9)	129 (39.3)		Reference
		TC	51 (45.1)	165 (50.3)	0.053	0.62 (0.38-1.01)
		CC	9 (8.0)	34 (10.4)	0.142	0.53 (0.22-1.24)
Dominant model		TT	53 (46.9)	129 (39.3)	0.034	1.67 (1.04-2.67)
		TC+CC	60 (53.1)	199 (60.7)		Reference
Recessive model		TT+TC	104 (92.0)	290 (89.6)		Reference
		CC	9 (8.0)	34 (10.4)	0.368	0.69 (0.31-1.55)
IL10	rs1800872					
Genotypic model		AA	53 (46.9)	129 (39.3)		Reference
		AC	51 (45.1)	165 (50.3)	0.055	0.62 (0.38-1.01)
		CC	9 (8.0)	34 (10.4)	0.144	0.53 (0.23-1.24)
Dominant model		AA	53 (46.9)	129 (39.3)	0.036	1.66 (1.03-2.66)
		AC+CC	60 (53.1)	199 (60.7)		Reference
Recessive model		AA+AC	104 (92.0)	290 (89.6)		Reference
		CC	9 (8.0)	34 (10.4)	0.368	0.69 (0.31-1.55)
IL6	rs1800796					
Genotypic model		CC	61 (54.0)	194 (59.1)		Reference
		CG	41 (36.3)	115 (35.1)	0.919	1.03 (0.63-1.68)
		GG	11 (9.7)	19 (5.8)	0.119	2.04 (0.83-4.99)
Dominant model		CC	61 (54.0)	194 (59.1)	0.564	0.87 (0.55-1.39)
		CG+GG	52 (46.0)	134 (40.9)		Reference
Recessive model		CC+CG	102 (90.3)	309 (94.2)		Reference
		GG	11 (9.7)	19 (5.8)	0.116	2.02 (0.84-4.84)
TNFA	rs1799724					
Genotypic model		CC	73 (64.6)	231 (70.4)		Reference
		CT	36 (31.9)	89 (27.2)	0.393	1.25 (0.75-2.07)
		TT	4 (3.5)	8 (2.4)	0.450	1.65 (0.45-6.06)
Dominant model		CC	73 (64.6)	231 (70.4)	0.321	0.78 (0.48-1.27)
		CT+TT	40 (35.4)	97 (29.6)		Reference
Recessive model		CC+CT	109 (96.5)	320 (97.6)		Reference
		TT	4 (3.5)	8 (2.4)	0.507	1.55 (0.43-5.63)
TNFA	rs1799964					
Genotypic model		TT	69 (61.1)	216 (65.9)		Reference
		TC	43 (38.1)	100 (30.4)	0.391	1.24 (0.76-2.01)
		CC	1 (0.8)	12 (3.7)	0.142	0.20 (0.02-1.72)
Dominant model		TT	69 (61.1)	216 (65.9)	0.639	0.89 (0.55-1.44)
		TC+CC	44 (38.9)	112 (34.1)		Reference
Recessive model		TT+TC	112 (99.1)	316 (96.3)		Reference
		CC	1 (0.8)	12 (3.7)	0.124	0.19 (0.02-1.59)

ganic cation transporter 1 is a transcription factor of rs1799724 in the promoter region, suggesting that allele-specific binding is an important factor (4).

Though IL-6 is an important cytokine whose levels increase during the outbreak of sarcoidosis and development of the inflammatory reaction (20), there have been two reports on the relationship between *IL-6* polymorphisms and sarcoidosis (21, 22). The rs1800796 polymorphism is assumed to be a functional SNP (5), and the frequency of the minor allele is relatively high in East Asians compared with Caucasians (5). We found a marginal relationship in

Table 3. Age- and sex-adjusted odds ratios of cytokine SNPs for cardiac sarcoidosis

Cytokine	SNP		Cardiac sarcoidosis (N=50) N (%)	Control (N=328) N (%)	*P* value	Age- and sex-adjusted OR (95% CI)
IL10	rs1800871					
Genotypic model		TT	24 (48.0)	129 (39.3)		Reference
		TC	21 (42.0)	165 (50.3)	0.142	0.61 (0.31-1.18)
		CC	5 (10.0)	34 (10.4)	0.444	0.78 (0.22-1.94)
Dominant model		TT	24 (48.0)	129 (39.3)	0.133	1.62 (0.86-3.06)
		TC+CC	26 (52.0)	199 (60.7)		Reference
Recessive model		TT+TC	45 (90.0)	290 (89.6)		Reference
		CC	5 (10.0)	34 (10.4)	0.766	0.86 (0.30-2.40)
IL10	rs1800872					
Genotypic model		AA	24 (48.0)	129 (39.3)		Reference
		AC	21 (42.0)	165 (50.3)	0.142	0.61 (0.31-1.18)
		CC	5 (10.0)	34 (10.4)	0.444	0.65 (0.22-1.94)
Dominant model		AA	24 (48.0)	129 (39.3)	0.134	1.62 (0.86-3.06)
		AC+CC	26 (52.0)	199 (60.7)		Reference
Recessive model		AA+AC	45 (90.0)	290 (89.6)		Reference
		CC	5 (10.0)	34 (10.4)	0.766	0.86 (0.30-2.40)
IL6	rs1800796					
Genotypic model		CC	29 (58.0)	194 (59.1)		Reference
		CG	16 (32.0)	115 (35.1)	0.621	0.84 (0.42-1.67)
		GG	5 (10.0)	19 (5.8)	0.370	1.68 (0.54-5.25)
Dominant model		CC	29 (58.0)	194 (59.1)	0.887	1.05 (0.55-1.98)
		CG+GG	21 (42.0)	134 (40.9)		Reference
Recessive model		CC+CG	45 (90.0)	309 (94.2)		Reference
		GG	5 (10.0)	19 (5.8)	0.301 1.80	(0.59-5.44)
TNFA	rs1799724					
Genotypic model		CC	27 (54.0)	231 (70.4)		Reference
		CT	18 (36.0)	89 (27.2)	0.091	1.78 (0.91-3.55)
		TT	5 (10.0)	8 (2.4)	0.006	6.01 (1.66-21.80)
		CC	27 (54.0)	231 (70.4)	0.020	0.47 (0.25-0.89)
		CT+TT	23 (46.0)	97 (29.6)		Reference
Recessive model		CC+CT	45 (90.0)	320 (97.6)		Reference
		TT	5 (10.0)	8 (2.4)	0.013	4.95 (1.40-17.45)
TNFA	rs1799964					
Genotypic model		TT	28 (56.0)	216 (65.9)		Reference
		TC	21 (42.0)	100 (30.4)	0.156	1.60 (0.84-3.07)
		CC	1 (2.0)	12 (3.7)	0.510	0.48 (0.05-4.28)
Dominant model		TT	28 (56.0)	216 (65.9)	0.244	0.68 (0.36-1.30)
		TC+CC	22 (44.0)	112 (34.1)		Reference
Recessive model		TT+TC	49 (98.0)	316 (96.3)		Reference
		CC	1 (2.0)	12 (3.7)	0.419	0.41 (0.05-3.59)

the total patient group (P = 0.090, OR = 1.90, 95% CI = 0.91–3.96), but we were unable to find any significant correlation in subclass analysis.

IL-10 plays a suppressive role with respect to inflammatory cytokines (23). While a significant relationship between serum IL-10 level and the activity of cardiac sarcoidosis has been reported (24), there has been no report showing a significant relationship between *IL-10* polymorphisms and sarcoidosis (25). We investigated the relationship between sarcoidosis in Japan and these two SNPs, because significant relationships between these SNPs

and inflammatory and autoimmune diseases have been suggested in chronic viral hepatitis (6), bowel disease (26), and systemic sclerosis (27). We found that the ORs of wild homoalleles of these SNPs were significantly increased in the sarcoidosis with eye involvement group. Because the haplotype with rs1800871T and rs1800872A alleles exhibits reduced IL-10 production in other diseases, a decrease in IL-10 production may conduce remission of T-cell activation and development of the clinical state. In contrast, inverse associations of these SNPs with sarcoidosis have been found in Creuz (28). However, the number of sarcoidosis subjects was small (N = 31), and racial differences may also be responsible for the different result.

Our study has several limitations. First, because the sample size was not large enough, we did not perform any correction for multiple comparisons. However, the result did not seem likely to have happened by chance with a relatively large OR of rs1799724 for cardiac sarcoidosis. In contrast, neither of the IL-10 SNPs had large ORs for sarcoidosis with eye involvement, as patients with ocular sarcoidosis can undergo remission, our criteria included not only present cases but also past cases of ocular disease. Inclusion of sarcoidosis patients whose ocular disease activity disappeared at study period may affect the ORs. Recently, Japanese study has reported no association with these SNPs between sarcoidosis with eye involvement group and whole sarcoidosis group(29). The subjects involved in our study were recruited mainly from the internal medicine department. The characteristics of patients in a recent negative Japanese study were not reported, but many authors of the study were affiliated to the ophthalmology department. Thus, the disease severity and type may be different from our patients. This difference may influence the results concerning IL-10 polymorphisms. Second, the control groups included a medical checkup group and a chronic disease group. If the chronic disease group has the same genetic risk of sarcoidosis, the relationship between SNPs and sarcoidosis would be weakened and may decrease the ORs. Because the disease types of sarcoidosis vary between races, the effect of the SNPs that were found to have significant relationships in this study may be different in other racial groups. Finally, because the rs1799724 polymorphism is located on chromosome 6p21-22 near the human leukocyte antigen (HLA) regions, this result may be affected by linkage disequilibrium with HLA (8, 13). However, the minor allele may stimulate TNF-α production that can affect sarcoidosis activity (4).

In conclusion, the *TNF*-α rs1799724 polymorphism may affect susceptibility to cardiac sarcoidosis. The *IL-10* two polymorphisms may also affect susceptibility to sarcoidosis with eye involvement in Japan. These findings suggest that these three SNPs are valuable predictive factors of the clinical state and prognosis in this poorly understood disease and have wide clinical application.

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