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Association of *MICA* Polymorphism with HLA-B51 and Disease Severity in Korean Patients with Behçet's Disease

The HLA-B51 allele is known to be associated with Behçet's disease (BD) in many ethnic group. However, it has not yet been clarified whether the HLA-B51 gene itself is the pathogenic gene related to BD or whether it is some other gene in linkage disequlibrium with HLA-B51. Recently, the Triplet repeat (GCT/AGC) polymorphism in transmembrane region of the MHC class I chain-related A (*MICA*) gene was identified. To investigate the association of *MICA* with BD, we studied the *MICA* polymorphism in 108 Korean BD patients and 204 healthy controls in relation to the presence of HLA-B51 and clinical manifestations. The triplet repeat polymorphism was determined by polymerase chain reaction (PCR)-denaturing polyacrylamide gel electrophoresis (PAGE). The phenotype frequency of the MICA*A6 allele (relative risk, RR=2.15, p=0.002) and HLA-B51(RR=1.87, p=0.022) were significantly increased in the Korean patients with BD. A strong linkage disequilibrium was observed between the MICA*A6 and HLA-B51 in both the patients with BD and control subjects. Stratification analysis showed that MICA*A6 homozygosity was strongly associated with BD in the HLA-B51-negative population, and HLA-B51 was also associated with MICA*A6-negative population. In conclusion, MICA*A6 rather than HLA-B51 was strongly associated with Korean patients with BD, and the MICA*A6 allele is a useful susceptibility marker of BD, especially in the HLA-B5-negative subjects.

Key Words : *MICA Polymorphism; Behçet's Disease; HLA-B51*

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INTRODUCTION

Behçet's disease (BD) is a multisystemic inflammatory disorder characterized by recurrent oral and genital ulcers, and ocular, joint, and skin lesions. Involvement of the gastrointestinal tract, central nervous system, or pulmonary vasculature is less common, but accounts for the majority of mortality associated with the disease (1, 2). BD has a worldwide distribution but its prevalence and severity are geographically variable. Although its etiology and pathogenesis remains unclear, its onset is believed to be triggered by the involvement of some external factors in individuals with a particular genetic background (1, 3-7).

BD is known to be associated with HLA-B51 in many different ethnic groups. MHC class I chain-related genes A (MICA) located only 46 kb centromeric of the HLA-B gene, has been identified within the class I region (3-9). Expression of *MICA* has been detected in fibroblast and epithelial cell lines, gastrointestinal epithelium, keratinocytes, endothelial cells, and monocytes (10, 11). The *MICA* gene is regulated by promoter heat shock elements similar to those of the *hsp70* genes (9). An association with *MICA* and BD has been reported with a triplet repeat microsatellite polymorphism (GCT/AGC)n in the transmembrane (TM) region of the *MICA* gene (3-6, 8). The six (GCT) repetition (MICA*A6) was present in significantly more BD patients than controls in the Japanese, Middle Eastern, and Greek populations (1, 3, 4, 12, 13). On the other hand, there was a lack of association between the *MICA* TM region polymorphism and BD in the Spanish and Italian populations (14, 15). The *MICA* microsatellite polymorphism exhibit a strong linkage disequilibrium with the HLA-B locus. Therefore, the roles (primary versus secondary) of polymorphism of the MICA molecule in the susceptibility and the severity of BD are still unclear.

We investigated the microsatellite polymorphism of the MICA gene in Korean patients with BD and analyzed the relationship between these polymorphisms and HLA-B51 and the clinical manifestations.

MATERIALS AND METHODS

Patients and controls

One-hundred and eight Korean patients with BD and 204 ethnically matched healthy controls were enrolled in this study.

BD was diagnosed and classified according to the criteria proposed by the International Behçet's disease study group (16). The mean age of the patients was 41.2 yr (range, 21-62 yr) and the mean duration of the disease was 3.8 yr (range, 0.4-25.5 yr). This study was performed in accordance with the Declaration of Helsinki.

DNA extraction

DNA was prepared from peripheral blood cells of patients and controls by salting out of cellular proteins and alcohol precipitation.

HLA-B typing

HLA-B typing was performed using the ARMS (amplification-refractory mutation system)-PCR (polymerase chain reaction) method (17). Each tube contained a primer mix consisting of the allele- or group-specific primer pairs and a positive control primer, which matched the non-allelic sequences. HLA-B typing included 39 sets of primer mixtures. PCR reactions were performed in a volume of 13 μL as modified in the class I ARMS-PCR reference manual of the 12th International Histocompatibility Workshop. The PCR product size was defined on 1.5% agarose gel pre-stained with ethidium bromide.

MICA transmembrane region analysis

For analysis of the microsatellite repeat polymorphism in the TM region of the *MICA* gene, PCR primers flanking the TM region (MIC-A5F, 5′-CCTTTTTTTCAGGGAAAGTGC-3′; MIC-A5R, 5′-CCTTACCATCTCCAGAAACTGC-3′) were designed. The MIC-A5R primer corresponds to the intron 4 and exon 5 boundary region and MIC-A5F is located in the intron 5. PCR conditions and purification were performed as described by Mizuki et al. (6).

PCR was carried out in a Perkin Elmer 9600 Thermal Cycler with mixtures consisting of 40 ng of genomic DNA, 10 × PCR buffer (10 mM Tris-HCl, pH 8.3, 40 mM KCl, and 15 mM $MgCl_2$, Bioneer, Korea), 250 μM dNTPs (Bioneer), 10 pmole of each primer (Bioneer), and 1 U of *Taq* polymerase (Bioneer). Amplified products were mixed with equal volumes of denaturing solution (95% formamide, 20 mM EDTA, 0.05% bromophenol blue, and 0.05% xylene cyanol FF). The mixtures were denatured at 95℃ for 2 min. Five microliters of each of the mixtures was loaded onto a 6% denaturing polyacrylamide gel. Polymorphic fragments in the gel were visualized by silver staining. Single-strand conformational polymorphism analysis was applied to determine the one-or two-base differences in the MICA alleles (MICA 5, MICA 5.1, and MICA 6) as described by Choi et al. (18).

Statistical analysis

The gene and phenotype frequencies were estimated by direct counting. The significance of the distribution of alleles between the patients with BD and healthy controls was examined using the chi-square (χ^2) and Fisher's exact probability tests. Relative risk (RR) were calculated using Woolf's method (19). The relative (primary vs secondary) importance of the *MICA* and *HLA-B51* alleles in terms of the susceptibility to BD was determined using the methods described by Svejgaard and Ryder (20).

RESULTS

Analysis of the data demonstrated that the gene frequency of the MICA*A6 allele was significantly increased in BD patients, as compared with healthy controls (45.8% vs 26.5%, RR=2.35, p<0.001), and that the MICA*A5.1 allele was significantly decreased in BD patients (4.2% vs 19.1%, RR=0.18, p<0.001) (Table 1). The phenotype frequency of the MICA*A6 allele was significantly higher in BD than in control (63.9% vs 45.1%, RR=2.15, p=0.002). Furthermore, the phenotype frequency of those homozygous for the MICA*A6 allele was more strongly associated with BD (27.8% vs 4.8%, RR=4.52, p<0.001) than that of those heterozygous for MICA*A6 allele (Table 2). Thirty-eight of the 108 BD patients were HLA-B*51 positive (35.2%), as compared with

Table 1. Gene frequencies of the microsatellite polymorphism in the transmembrane region of the *MICA* gene in patients with Behçet's disease

Microsatellite allele	BD n=216 (%)	Control n=408 (%)	*p* value	RR
A4	19 (8.8)	53 (13.0)	NS*	
A5	60 (27.7)	107 (26.2)	NS	
A5.1	9 (4.2)	78 (19.1)	< 0.001	0.18
A6	99 (45.8)	108 (26.5)	< 0.001	2.35
A9	29 (13.4)	62 (15.2)	NS	

BD, Behçet's disease ; RR, relative risk; *NS, not significant.

Table 2. Phenotype frequencies of the microsatellite polymorphism in the TM region of the *MICA* gene in patients with Behçet's disease

Microsatellite allele	BD n=108 (%)	Control n=204 (%)	*p* value	RR
A4	14 (13.0)	49 (24.0)	0.026	0.47
A5	51 (47.2)	91 (44.6)	NS*	
A5.1	7 (6.5)	64 (31.4)	< 0.001	0.15
A6	69 (63.9)	92 (45.1)	0.002	2.15
A6/A6	30 (27.8)	16 (4.8)	< 0.001	4.52
A9	29 (26.9)	57 (27.9)	NS	
HLA-B51	38 (35.2)	46 (22.5)	0.022	1.87

BD, Behçet's disease ; RR, relative risk; *NS, not significant.

Table 3. Association of MICA*A6 allele and HLA-B51 with susceptibility to Behçet's disease

A. Association between BD and MICA*A6 allele in the presence or absence of HLA-B51

	HLA-B51 positive		HLA-B51 negative*	
MICA*A6	+	–	+	–
BD	34	4	35	35
Control	44	2	48	110

B. Association between BD and HLA-B51 in the presence or absence of MICA*A6 allele

	MICA*A6 allele positive		MICA*A6 allele negative†	
HLA-B51	+	–	+	–
BD	34	35	4	35
Control	44	48	2	110

*p=0.007, RR=2.29 ; †p=0.039, RR=6.29. BD, Behçet's disease ; RR, relative risk.

Table 5. Clinical association of MICA*A6 and MICA*A9 allele in Behçet's disease

Clinical manifestations	MICA*A6		MICA*A9	
	positive n=69 (%)	negative n=39 (%)	positive n=69 (%)	negative n=39 (%)
Oral ulcer	69 (100)	39 (100)	29 (100)	79 (100)
Genital ulcer	40 (58.0)	25 (64.1)	18 (62.1)	47 (59.5)
Skin lesion	41 (59.4)	26 (66.7)	19 (65.5)	48 (60.8)
Arthritis	37 (53.6)	25 (64.1)	16 (55.2)	46 (58.2)
Uveitis	28 (40.6)	11 (28.2)	8 (27.6)	31 (39.2)
GI lesion	6 (8.7)	1 (2.6)	0 (0.0)	7 (8.9)
CNS lesion	3 (4.3)	2 (5.1)	1 (3.4)	4 (5.1)
Thrombosis	4 (5.8)	2 (5.1)	1 (3.4)	5 (6.3)
Complicated form*	31 (44.9)	14 (35.9)	8 (27.6)†	45 (53.2)

*uveitis/CNS/GI/thrombosis; †p=0.018. GI lesion, gastrointestinal lesion; CNS lesion, central nervous system lesion.

46 of 204 controls (22.5%) (RR=1.87, p=0.022) (Table 2).

The MICA*A6 allele was present in most (89.5%) of the HLA B51-positive patients and in additional 35 (50.0%) B51-negative patients. Thirty-four of the 69 MICA*A6-positive patients had HLA-B*51 and 4 of the 39 MICA*A6-negative patients had HLA- B*51 (Table 3).

Therefore, to elucidate which allele, MICA*A6 or HLA-B*51, has the stronger association with BD, the association of the MICA*A6 allele with BD, after stratification for the effect of HLA-B51, was estimated. The MICA*A6 allele was significantly associated with BD (RR=2.29, p=0.007). On the other hand, when we estimated the association of HLA-B51 with BD after stratification for the effect of MICA*A6 allele, a significant association between B51 and BD was observed (RR=6.29, p=0.039) (Table 3). The susceptibility risk of the MICA*A6 homozygosity for BD was elevated in the HLA-B51-negative patients (RR=21.27, p<0.001) (Table 4). Our results suggest that the MICA*A6 allele, rather than HLA-B51, is strongly associated with BD in Korea and an useful susceptibility marker for BD, especially in the HLA-B51-negative Korean population.

Table 4. Association of MICA*A6 homozygote and HLA-B51 with susceptibility to Behçet's disease

A. Association between BD and MICA*A6/A6 in the presence or absence of HLA-B51

	HLA-B51 positive		HLA-B51 negative*	
MICA*A6/A6	+	–	+	–
BD	15	23	15	55
Control	14	32	2	156

B. Association between BD and HLA-B51 in the presence or absence of MICA*A6/A6

	MICA*A6/A6 positive†		MICA*A6/A6 negative‡	
HLA-B51	+	–	+	–
BD	15	15	23	55
Control	14	2	32	156

*p<0.001, RR=21.27; †p=0.023, RR=0.143; ‡p=0.030, RR=2.04. BD, Behçet's disease; RR, relative risk.

Table 6. Association of MICA TM region polymorphisms and Behçet's disease in the different populations

Populations	Microsatellite alleles	RR	p value	References
Korean	A6	2.35	< 0.001	Park et al. (Persent study)
Japanese	A6	2.70	0.00041	Mizuki et al. (13)
Jordanian	A6	4.39	0.005	Mizuki et al. (12)
Greek	A6	2.93	0.013	Yabuki et al. (5)
Italian	A6		NS	Salvarani et al. (15)
Spanish	A6		NS	Gonzalez-Escribano et al. (14)

RR, relative risk.

However, most of the B51-positive patients (89.5%) and B51-positive healthy controls (95.7%) possessed the MICA *A6 allele, demonstrating a strong linkage disequilibrium of MICA*A6 and HLA-B51.

We analyzed clinical manifestations according to the MICA gene polymorphism and the presence of HLA-B51. As is summarized in Table 5, patients with MICA*A6 tended to show intestinal and ocular involvement more frequently, but this was not statistically significant.

Involvement of the gastrointestinal tract, central nervous system (CNS), ocular and vascular systems is related with poor prognosis of BD. Therefore, the clinical manifestations with the involvement of those systems were considered to be severe complications of BD.

The frequency of the MICA*A9 allele was no different between BD and the controls, whereas patients with MICA *A9 had less severe BD complications, in terms of uveitis, thrombosis, and intestinal involvement, than those without (Table 5). However, no associations were observed between the clinical features and HLA-B*51 (data not shown).

DISCUSSION

It is well established that BD is associated with the HLA-B51 molecule that has a relatively high incidence, which ranges from 36.3% to 76.9% in many ethnic groups including the Asian and Eurasians (1, 12, 21). In our study, the prevalence of HLA-B51 was found to be significantly increased in patients with BD (35.2% vs 22.5%).

In the present study, we demonstrate that the MICA*A6 allele is significantly associated with the susceptibility to BD, as was shown by the previous data on Japanese population (6). However, the MICA*A6 allele is not associated with BD in some ethinic groups (Table 6).

Mizuki et al. suggested that a genetic predisposition to BD appears to play an important role with a strong association with the *MICA* gene rather than HLA B51 (6), but a recent report has suggested that the real pathogenic gene for BD is the HLA-B gene itself and the HLA-B*51 allele is the major susceptibility gene responsible for the development of BD (4, 13, 15, 22). Therefore, we cannot be certain whether HLA-B51 itself or a closely linked gene is responsible for the susceptibility to BD.

In the present study, an association was observed between the MICA*A6 allele and BD, and also observed between HLA-B51 and BD. After stratification for the effect of HLA-B51, the MICA*A6 allele was significantly associated with BD. After stratification for the effect of the MICA*A6 allele, the association between HLA-B51 and BD was observed in the MICA*A6 allele-negative patients. We observed a strong linkage disequilibrium of MICA*A6 and HLA-B51. Our results suggest that the MICA-A6 allele rather than the HLA-B51 allele is strongly associated with Korean BD and an useful susceptibility marker for BD, especially in the HLA-B51-negative Korean population.

The etiologic role of the polymorphism in the MICA molecules is still unknown. Enhanced T cell proliferative response to the mycobacterial 65-kDa heat shock protein (hsp) peptides and their homologous peptides derived from human 60-kDa hsp have been demonstrated in patients with BD (23). An increased number of $\gamma\delta$ T cells preferentially respond to hsp65 in the peripheral blood and the involved tissues from patients with BD, and a phenotypically distinct subset of the $\gamma\delta$ T cells, CD45RA+CD45RO-Vgamma9+Vdelta2+, may contribute to the immunological abnormalities, which in turn, probably lead to the complex pathophysiology of Behçet's disease (24-27). T cells expressing the $V_\delta 1$ receptor form 70-90% of $\gamma\delta$ T cells in the intestinal epithelium, where MICA is also expressed (1). It has also been reported that MICA*A6 may tend to activate $V_\delta 1$ $\gamma\delta$ T cells more effectively via specific interaction with $\gamma\delta$ T cells, because of either the presence of specific amino acids in the a1/a2 domains linked to MICA*A6 or that of a particular $V_\delta 1$ $\gamma\delta$ T-cell repertoire that can recognize the MICA molecule with MICA*A6 in an efficient way (5, 27).

In our study, the MICA*A6 allele was present in six of the seven patients with intestinal involvement, more specifically those that had experienced episodes of intestinal hemorrhage or ulcer. This result could be explained by the more effective activation of $\gamma\delta$ T cells of the intestinal epithelium by MICA*A6 than by other *MICA* alleles. Patients with the MICA*A6 allele tended to show intestinal and ocular involvement more frequently, whereas patients with MICA*A9 had less severe BD complications, in terms of uveitis, thrombosis, neurological, and intestinal involvement, than those without MICA*A9. Although the prevalence of severe complications associated with BD was low in our study group, it seems that the polymorphism of the MICA-TM allele is related with the clinical manifestations and severity of Korean patients with BD.

Recently, a *MICA* genotyping study showed a strong association between the MICA009 allele and BD in the Japanese population. In this study, the *MICA* gene was found not to be directly involved in the pathogenesis of BD (4). Further study is required to elucidate the role of the *MICA* gene in the development and severity of BD.

In summary, the MICA*A6 allele is a useful susceptibility marker for BD, especially in the HLA-B51- negative Korean population, and that the *MICA* gene polymorphism rather than that of HLA-B51 is strongly associated with the susceptibility to BD in the Korean population. Moreover, it is believed that the *MICA* gene polymorphism may play an important role in the severity of BD in the Korean population.

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