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Intercellular Adhesion Molecule-1 Polymorphisms in Korean Patients with Behçet's Disease

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Intercellular adhesion molecule-1 (ICAM-1) is expressed on vascular endothelial cells and its expression increases during the inflammatory response in patients with active Behçet's disease (BD). The *ICAM1* gene mutations are associated with BD in Caucasians, but clinical features of the mutation phenotype are unknown. We analyzed *ICAM1* polymorphisms in Korean BD patients to determine if there was an association between particular mutations and clinical symptoms. The prevalence of *ICAM1R241G* and *ICAM1K469E* polymorphisms was determined among 197 patients with BD and 248 healthy controls using *Bsr*G1 and *Bst*U1 PCR-RFLP. The frequency of both genotypes *ICAM1469*K/*E* and *ICAM-1469*E/*E* was significantly higher in BD patients compared with controls (66.0% vs 52.4%, p=0.004, OR=1.28, 95% CI 1.08-1.50) and the allele frequency of *ICAM1469*E* was higher in patients with skin lesions (0.41), genital ulcers (0.41), vasculitis (0.43), ocular lesions (0.41) and arthritis (0.39) than in controls (0.31). Only one heterozygote, *ICAM1241G/R*, was detected in BD patients but the *ICAM1241*R* mutation was not found in any of the 248 healthy controls. These results show that the *ICAM1* mutation is associated with BD susceptibility, and is another genetic risk factor for BD among the Korean population.

Key Words : *Intercellular Adhesion Molecule-1; Behçet Syndrome; Polymorphism, Restriction Fragment Length*

INTRODUCTION

Behçet's disease (BD) is a chronic and multisystemic inflammatory disease of multifactorial etiology, involving both infectious and genetic factors (1). The clinical major symptoms of BD in Korean patients are oral ulcers (98.8%), skin lesions (84.3%), genital ulcers (83.2%), ocular lesions (50.9%), and minor symptoms including articular symptoms (38.4%), gastrointestinal symptoms (7.3%), neurological symptoms (4.6%), epididymitis (0.6%), and vascular symptoms (1.8%) (2). This wide range of clinical symptoms of BD probably reflects different genetic backgrounds.

Intercellular adhesion molecule-1 (ICAM-1, CD54) is expressed on endothelial cells and various other cells and its expression is increased during inflammation. ICAM-1 is a member of the immunoglobulin superfamily and is a ligand of macrophage-1 antigen (Mac-1; $\alpha_M\beta_2$, CD11b/CD18) and lymphocyte function associated antigen-1 (LFA-1; $\alpha_L\beta_2$, CD11a/CD18) (3). It is also involved in leukocyte migration into sites of inflammation and T-cell receptor-mediated activation of resting T cells (4).

ICAM1 gene (OMIM 147840) is located on chromosome 19p13.3-13.2 with polymorphisms of K29M, G241R, K469E, A496T, and G1838A in the 3′UTR (5, 6). Single base polymorphisms causing amino acid substitutions were identified for *ICAM1* at codon 241 in exon 4 (GGG→AGG; Gly→Arg) for the Ig-like domain 3, the binding site of Mac-1, and at codon 469 in exon 6 (AAG→GAG; Lys→Glu), which codes for the Ig-like domain 5 (7). BD patients were evaluated for the levels of both soluble and tissue ICAM-1 and it has been hypothesized that the two mutations, G241R and K469E, result in more effective binding of ICAM1 to Mac-1 and LFA-1, thereby enhancing the inflammatory response (8). Both Mac-1 and LFA-1 binding site mutations might be involved in some of the inflammation events responsible for BD. While the pathogenic role of these polymorphisms is unknown, an association has been found with inflammatory diseases such as Behçet's disease in Jordanian or Palestinian populations (9), giant cell arteritis (10), rheumatoid arthritis (11), inflammatory bowel disease (12), and chronic renal allograft failure (13).

In this study, we investigated whether *ICAM1* gene polymorphisms in Korean BD patients are associated with different clinical subsets of BD.

MATERIALS AND METHODS

Patients with BD were recruited from the Behçet's Disease specialty clinic of Severance Hospital, Yonsei Universi-

ty College of Medicine (Table 1). A total of 197 patients with BD and 248 healthy controls without BD were enrolled. The diagnosis of BD was made according to the established clinical criteria of the International Study Group Behçet's Disease (14) and the revised Shimizu's classification (15). After obtaining informed consent, blood samples were collected and genomic DNA was extracted from peripheral blood leukocytes with a QiaAmp Blood kit (Qiagen, Valencia, CA, U.S.A.).

The *ICAM1G241R* polymorphism was detected by *Bsr*GI PCR-RFLP (New England Biolabs, Beverly, MA, U.S.A.) (16, 17). The *ICAM1K469E* polymorphism was analyzed by *Bst*UI PCR-RFLP (New England Biolabs, Beverly, MA, U.S.A.) (17, 18).

For statistical analysis of the data, the SAS program (v 8.0e) was used.

Table 1. Demographic and clinical features of Korean patients with BD

	Female/Male No.	No. (%)
Female/Male		96/101 (49/51)
Mean age ±SD		40 ±10 yr
Mean disease duration ±SD		11 ±7 yr
Major symptoms		
Oral ulcers	96/101	197 (100.0)
Skin lesions	88/98	186 (94.4)
Genital ulcers	87/80	167 (84.8)
Ocular lesions	74/77	151 (76.6)
Minor symptoms		
Arthritis	57/57	114 (57.9)
Vasculitis	4/40	44 (22.3)
Central nervous system	7/4	11 (5.6)
Gastrointestinal lesions	4/7	11 (5.6)

RESULTS

The distribution of the *ICAM1469*E* polymorphism differed significantly between patients and healthy controls. The frequency of both genotypes *ICAM1469*K/*E* and *ICAM1469*E/*E* was significantly higher in BD patients than in controls (66.0% vs 52.4%, p=0.004, OR=1.28, 95% CI 1.08-1.50). The genotype and allele frequencies of *ICAMK469E* in patients and in controls are shown in Table 2. The frequency of *ICAM1469*E* was higher in patients with skin lesions (0.41), genital ulcers (0.41), vasculitis (0.43), ocular lesions (0.41), and arthritis (0.39) than in controls (0.31). The disease duration, age at onset of BD, sex distribution, duration of follow-up, and the use of drugs did not differ between both genotypes of patients carrying *ICAM1469E*. Only one heterozygote *ICAM1241G/R* was detected in BD patients and the *ICAM1241*R* mutation was not found among healthy Korean controls. The heterozygote was found in a 56-yr old man with a 12-yr history of the disease who presented with ocular lesions and had a genotype of *ICAM-1469*E/*E.* Our results show that the *ICAM1469*E* polymorphism is associated with BD, whilst the *ICAM1241*R* polymorphism is rare among Koreans.

DISCUSSION

Association between *ICAM1* gene mutations and BD depends on ethnic origins (Table 3). The frequency of *ICAM-1469*E* was higher in Korean patients with BD than in controls, Palestinians, and Jordanians, while the frequency of *ICAM1241*R* was higher in Italians (9, 19). The *ICAM1* gene has also been associated with rheumatoid arthritis (RA) in Italian patients. *ICAM1241R* was associated with RA

Table 2. Genotype and allele frequencies of *ICAM1K469E* in Korean patients with BD and in controls

	No.	*K/*K (%)	*K/*E (%)	*E/*E (%)	*E	*p* value	OR	95% CI
Controls	248	118 (47.6)	107 (43.1)	23 (9.3)	0.31			
All patients	197	67 (34.0)	100 (50.8)	30 (15.2)	0.41	0.004	1.28	1.08-1.50
skin lesions	186	61 (32.8)	96 (51.6)	29 (15.6)	0.41	0.002	1.29	1.10-1.52
without	11	6 (54.5)	4 (36.4)	1 (9.1)	0.32	ns		
genital ulcers	167	56 (33.5)	84 (50.3)	27 (16.2)	0.41	0.004	1.26	1.08-1.47
without	30	11 (36.7)	16 (53.3)	3 (10.0)	0.35	0.002	1.89	1.26-2.86
ocular lesions	151	50 (33.1)	78 (51.6)	23 (15.2)	0.41	0.001	1.30	1.12-1.52
without	46	17 (34.8)	22 (50.0)	7 (15.2)	0.40	ns		
vasculitis	44	14 (31.8)	22 (50.0)	8 (18.2)	0.43	0.053	1.10	1.00-1.21
without	153	53 (34.6)	78 (51.0)	22 (14.4)	0.40	0.011	1.22	1.05-1.42
arthritis	114	38 (33.3)	63 (55.3)	13 (11.4)	0.39	0.011	1.20	1.05-1.38
without	83	29 (34.9)	37 (44.6)	17 (20.5)	0.43	0.045	1.14	1.01-1.29
CNS	11	6 (54.5)	4 (36.4)	1 (9.1)	0.27	ns		
without	186	61 (32.8)	96 (51.6)	29 (15.6)	0.41	0.002	1.29	1.10-1.52
gastrointestinal	11	2 (18.2)	7 (63.6)	2 (18.2)	0.50	ns		
without	186	65 (34.9)	93 (50.5)	28 (15.1)	0.40	0.008	1.25	1.06-1.46

CNS, central nervous system.
p value, patients with *ICAM1469*E* positive vs controls with *ICAM1469*E* positive; OR, odds ratio; CI, confidence interval; ns, not significant.

Table 3. Allele frequencies of *ICAM1241*R* and *ICAM1469*E* among BD patients from different populations

		Allele frequency		*p* value	Reference
		Patients with BD	Controls		
Korean	No.	197	248		the present study
	*241*R*	0.003	0.000	ns	
	*469*E*	0.410	0.310	0.003	
Jordanian or Palestinian	No.	83	103		9
	*241*R*	0.012	0.015	ns	
	*469*E*	0.476	0.383	0.046	
Italian	No.	74	228		19
	*241*R*	0.115	0.031	0.0001	
	*469*E*	0.439	0.439	ns	

p value, patients vs controls; ns, not significant.

but the allele and phenotype frequencies of *ICAM1469E* did not differ significantly between RA patients and the control group in the Italian study (11). The different results might be due to different genetic backgrounds. The frequency of *ICAM1241*R* showed a population variation in contrast to the frequency of *ICAM1469*E.* The frequency of *ICAM1469*E* is high in various countries (0.310-0.510). While *ICAM1241*R* is quite rare in most populations, the frequency of *ICAM1241*R* is higher in Europeans (0.031-0.180) (10, 13, 16, 20) compared to in Koreans and Japanese (0.000) (21) and Palestinians and Jordanians (0.015) (9). In line with a previous report that suggested *ICAM1469*E* is associated with inflammatory disease (22), our study shows that the frequency of *ICAM1469*E* is higher in Korean BD patients than in controls. We cannot draw any conclusion on the association of *ICAM1G241R* with BD, as described in Italian patients, because there was no case with *ICAM1-G241R* among the Korean BD patients in this study. *ICAM1* mutations, especially *ICAM1469*E*, might act as another genetic susceptibility factor for BD in the Korean population as well as the recently described *MICA A6* allele and HLA-B51 (23).

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