Cytochrome P450 1A1 and Manganese Superoxide Dismutase Gene Polymorphisms in Behçet's Disease

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ABSTRACT. ***Objective.*** To investigate the association of cytochrome p450 1A1 (CYP1A1) and manganese superoxide dismutase (MnSOD) gene polymorphisms with susceptibility to Behçet's disease (BD) in Taiwan.

Methods. The polymorphisms of CYP1A1 and MnSOD genes were determined in 51 patients with BD and 91 healthy controls by polymerase chain reaction/restriction fragment length polymorphism methods.

Results. The frequencies of CYP1A1 4889G and 4887A were significantly increased in patients with BD. In contrast, there was no significant difference in the frequencies of MnSOD gene polymorphisms between patients with BD and controls. Linkage disequilibrium was found between CYP1A1 4889G and CYP1A1 6235C in controls and patients with BD. However, a similar finding could not be found between CYP1A1 4889G and 4887A. We also found that the association of CYP1A1 4889G with BD was dependent on the presence of CYP1A1 4887A. On the other hand, the association of CYP1A1 4887A with BD was dependent on the presence of CYP1A1 4889G. An additive effect of CYP1A1 4889G and 4887A on the susceptibility to BD could be found.

Conclusion. Simultaneous presence of CYP1A1 4889G and 4887A is associated with development of BD in Taiwan. (J Rheumatol 2004;31:736–40)

Key Indexing Terms:
MANGANESE SUPEROXIDE DISMUTASE CYTOCHROME BEHÇET'S DISEASE

Behçet's disease (BD) is a chronic relapsing inflammatory disease with multiple organ involvement. The most common clinical manifestations are recurrent oral ulcers and genital ulcers. The less common features include central nervous system involvement, arterial aneurysms, mucosal ulceration of intestinal tract, and deep vein phlebitis[1]. BD is common in eastern Asia, Japan, and the Mediterranean Basin[2], but it is relatively uncommon in Taiwan.

The etiology of BD is still unknown. Genetic factors play an important role in pathogenesis of BD[3]. Although the association of HLA-B51 with BD was noted in Japanese[4], no consistent HLA association has been found in other populations[5]. Thus non-HLA genes may also be related to the pathogenesis of BD.

Smoking is a risk factor for vascular involvement in BD[6]. Cytochrome P450 1A1 (CYP1A1) plays an important role in the metabolism of tobacco-derived polycyclic aromatic hydrocarbons (PAH)[7]. CYP1A1 may catalyze activation of PAH to reactive metabolites that initiate damage to DNA[8]. Thus, CYP1A1 may also be related to the pathogenesis of BD. In our previous study, CYP1A1 gene polymorphisms were associated with the development of systemic lupus erythematosus (SLE)[9]. However, the association between CYP1A1 gene polymorphisms and BD is still unknown.

Cytochrome p450 (CYP) is a member of a superfamily of enzymes that catalyze oxidation of various xenobiotics including drugs, toxic chemicals, and carcinogens[10,11]. Most CYP metabolism results in the detoxification of xenobiotics, while some chemicals are activated[12]. The superoxide radical is produced in the detoxification process of CYP[13].

The reactive oxygen species are involved in the pathogenesis of BD[14-16]. Enhanced superoxide generation and decreased superoxide scavenging activity of peripheral blood leukocytes can be found in BD[17]. Serum from patients with BD also enhances superoxide production of normal neutrophils[18]. The decreased superoxide scavenging activity will lead to accumulation of superoxide radical, and this induces tissue damage. Superoxide dismutase (SOD) is a scavenger of reactive oxygen species. There are 3 isoenzymes of SOD including MnSOD, CuZnSOD, and FeSOD. MnSOD is an antioxidant enzyme that protects against free radical-induced cytotoxicity[19]. Thus, MnSOD may also be related to the pathogenesis of BD.

We investigated the roles of CYP1A1 and MnSOD gene polymorphisms in the pathogenesis of BD in Taiwan.

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Submitted January 20, 2003; revision accepted September 26, 2003.

MATERIALS AND METHODS

Fifty-one patients with BD and 91 healthy controls were enrolled in this study. All patients fulfilled the International Study Group criteria for the diagnosis of BD[20]. All patients and healthy controls were Taiwanese.

Polymorphisms of CYP1A1 gene. There are several CYP1A1 gene polymorphisms including 6235 T→C (3' noncoding), 5639 T→C (intron 7), 4889 A→G (exon 7, codon 462 Ile→Val), and 4887 C→A (exon 7, codon 461 Thr→Asn). CYP1A1 polymorphisms were determined by the polymerase chain reaction/restriction fragment length polymorphism (PCR-RFLP) method. The sequences of primers for polymorphisms at nucleotide position 6235 were 5'- GGCTGAGCAATCTGACCCTA -3' and 5'-TAGGAGTCTTGTCTCATGCCT –3'. After PCR, the PCR product was digested with MspI. A sequence with 6235C can be cleaved with MspI. The sequences of primers for polymorphisms at nucleotide positions 4889 and 4887 were 5'-CTGTCTCCCTCTGGTTACAGGAGC -3' and 5'-TTCCACCCGTTGCAGCAG GATAGCC- 3'. After PCR, the product was digested with BsrDI and BsaI for polymorphisms at positions 4889 and 4887, respectively. The sequences with 4889A and 4887C can be cleaved with BsrDI and BsaI, respectively. The sequences of primers for polymorphisms at nucleotide position 5639 were 5'- GGCTGAGCAATCTGACCCTA -3' and 5'-GAAGGGAGACCAATAGAAGG -3'. After PCR, the product was digested with MspI, and a sequence with 5639C can be cleaved with MspI.

Polymorphisms of MnSOD gene. There are 2 polymorphic sites in the MnSOD gene, C1183T (Ala-9 Val) and T5777C (Ile 58 Thr). The C1183T (Ala-9 Val) polymorphisms were determined by PCR/RFLP. The sequences of primers were 5'- AGCCCAGCCTGCGTAGAC -3' and 5'-TACTTCTCCTCGGTGACG -3'. The PCR product was digested with BsawI. A sequence with 1183T, valine at the 9th amino acid of the mitochondrial targeting sequence, can be cleaved with BsawI. T5777C (Ile 58 Thr) polymorphisms were also determined by PCR/RFLP. A set of primers with a mismatched nucleotide (underlined here) was used. The sequence of primers was 5'- CGGATGTTATAGATAAGCTGG -3' and 5'- CAGTGCAGGCTGAAGAGAT –3'. The PCR product was digested with EcoRV. A sequence with 5777T, isoleucine at the 58th amino acid, can be cleaved with EcoRV.

Statistical analysis. The chi-square test with Yates' correction or Fisher's exact test was used for statistical analysis. Delta values were determined for evaluating the possibility of linkage disequilibrium. Interactions of different CYP1A1 gene polymorphisms were analyzed according to Svejgaard and Ryder[21].

RESULTS

The characteristics of patients and controls are given in Table 1. The prevalence of BD was more common in men than in women. Table 2 shows the frequencies of CYP1A1 gene polymorphisms in patients and controls. The genotype frequencies of CYP1A1 4889A/G and 4887C/A were significantly higher in patients than in controls. The allele frequencies of CYP1A1 4889G and 4887A were also significantly increased in patients. A similar finding could also be observed in phenotype frequencies of CYP1A1 4889G and 4887A.

Table 1. Characteristics of patients with Behçet's disease and controls.

	BD, n (%)	Controls, n (%)
	51	91
Age*, mean ± SD, yrs	44 ± 12	42 ± 8
Sex*		
Male	34 (66.7)	63 (69.2)
Female	17 (33.3)	28 (30.8)
Recurrent oral ulcer	51 (100)	
Recurrent genital ulcer	30 (58.8)	
Skin lesion	42 (82.4)	
Uveitis	11 (21.6)	
Pathergy test	4 (7.8)	

* There were no significant differences in age or sex between patients and controls.

There were no significant differences in the genotype and allele frequencies of MnSOD C1183T polymorphisms between patients and controls (Table 3).

Linkage disequilibria among CYP1A1 gene polymorphisms in controls and patients are given in Table 4. Linkage disequilibria were found between CYP1A1 4889G and CYP1A1 6235C in patients and controls. However, there were no linkage disequilibria between CYP1A1 4887A and CYP1A1 4889G.

In the stratification for CYP1A1 4889G, the phenotype frequency of CYP1A1 4887A was significantly higher in CYP1A1 4889G(+) patients than in 4889G(+) controls, but not in 4889G(–) patients and controls (Table 5). In the stratification for CYP1A1 4887A, the phenotype frequency of CYP1A1 4889G was significantly higher in CYP1A1 4887A(+) patients than in 4887A(+) controls, but not in 4887A(–) patients and controls. Thus, the association of CYP1A1 4887A with BD depended on the presence of CYP1A1 4889G. In contrast, the association of CYP1A1 4889G with BD was dependent on the presence of CYP1A1 4887A.

The interactions between CYP1A1 4887A and 4889G in patients and controls are shown in Table 6. The odds ratio was higher in 4887A(+) 4889G(+) than in 4887A(+) 4889G(–) and 4887A(–) 4889G(+) in comparison to 4887A(–) 4889G(–). An additive effect on the susceptibility to BD could be found between 4887A and 4889G.

DISCUSSION

Patients with BD and healthy controls enrolled in this study were ethnically homogenous. The genotype frequencies of CYP1A1 and MnSOD achieved Hardy-Weinberg equilibrium. In this study, men with BD were more common than women with BD, which is compatible with results for the Middle East. The male:female ratio was about 2:1. Vascular involvement is common in BD. In addition to small-vessel vasculitis that accounts for much of the pathology, large-vessel lesions occur in about 25% of Turkish patients[22]. However, we found only 2 patients with deep vein thrombosis, and one patient had superficial thrombophlebitis. Large-vessel lesions were relatively uncommon in our patients.

CYP1A1 gene is located on the long arm of chromosome 15 (q22–24). The polymorphisms of CYP1A1 gene were related to the development of several malignancies[23-27]. To date there is no report about associations of CYP1A1 gene polymorphisms with BD. In this study, the genotype frequencies of CYP1A1 4889A/G and 4887C/A were signif-

Table 2. Frequencies of CYP1A1 gene polymorphisms in patients with Behçet's disease and controls.

CYP1A1 Polymorphisms	BD, n = 51 (%)	Controls, n = 91 (%)	OR (95% CI)	p
Genotype frequencies				
CYP1A1 T6235C				
T/T	18 (35.3)	33 (36.3)	0.9 (0.5–1.9)	NS
T/C	25 (49.0)	46 (50.5)	0.9 (0.5–1.8)	NS
C/C	8 (15.7)	12 (13.2)	1.2 (0.5–3.2)	NS
CYP1A1 A4889G				
A/A	17 (33.3)	51 (56.0)	0.4 (0.2–0.8)	0.007
A/G	31 (60.8)	36 (39.6)	2.4 (1.2–4.8)	0.01
G/G	3 (5.9)	4 (4.4)	1.4 (0.3–6.3)	NS
CYP1A1 C4887A				
C/C	17 (33.3)	58 (63.7)	0.3 (1.1–5.9)	0.004
C/A	33 (64.7)	32 (35.2)	3.4 (1.7–6.9)	0.0006
A/A	1 (2.0)	1 (1.1)	1.8 (0.1–29.4)	NS
Allele frequencies				
CYP1A1 T6235C				
T	61 (59.8)	112 (61.5)	0.9 (0.6–1.5)	NS
C	41 (40.2)	70 (38.5)	1.1 (0.7–1.8)	NS
CYP1A1 A4889G				
A	65 (63.7)	138 (75.8)	0.6 (0.3–0.9)	0.03
G	37 (36.3)	44 (24.2)	1.8 (1.1–3.0)	0.03
CYP1A1 C4887A				
C	67 (65.7)	148 (81.3)	0.4 (0.3–0.8)	0.003
A	35 (34.3)	34 (18.7)	2.3 (1.3–3.9)	0.003

NS: not significant.

Table 3. Frequencies of MnSOD gene polymorphisms in patients with Behçet's disease and controls.

MnSOD C1183T (Ala-9Val)	BD, n = 51 (%)	Controls, n = 91 (%)	OR (95% CI)
Genotype frequencies			
C/C	3 (5.9)	3 (3.3)	1.8 (0.4–9.4)
C/T	16 (31.4)	30 (33.0)	0.9 (0.5–1.9)
T/T	32 (62.7)	58 (63.7)	0.6 (0.3–1.2)
Allele frequencies			
C	22 (21.6)	36 (19.8)	1.1 (0.6–2.0)
T	80 (78.4)	146 (80.2)	0.9 (0.5–1.6)

The differences of MnSOD C1183T polymorphisms between patients with BD and controls were not significant.

icantly higher in patients with BD than in controls. The allele frequencies of CYP1A1 4889G and 4887A were also significantly increased in patients with BD. Therefore, CYP1A1 4889G and 4887A may be precipitating factors for the development of BD. However, our study revealed the association of CYP1A1 4887A with BD was dependent on the presence of CYP1A1 4889G. The association of CYP1A1 4889G with BD was also dependent on the presence of CYP1A1 4887A. Thus, presence of 4887A and 4889G simultaneously is associated with the development of BD. A synergistic effect on the susceptibility to BD can be found between 4887A and 4889G. In our previous study, the increased frequency of CYP1A1 4887A could also be found in patients with SLE[9].

Polymorphisms of CYP1A1 gene at nucleotide positions 6235 and 4889 may lead to higher basal and inducible enzyme activity[28] that will enhance the formation of reactive metabolites and induce cell damage. However, the significance of polymorphisms at nucleotide position 4887 is still unknown. The polymorphism at nucleotide position 4887 may also have a similar effect. The linkage disequilibrium

Table 4. Linkage disequilibria among polymorphisms of CYP1A1 in controls and patients with Behçet's disease.

Allele 1	Allele 2	Δ	p
Controls			
CYP1A1 4889G	CYP1A1 6235C	0.1	< 0.0001
CYP1A1 4887A	CYP1A1 4889G	0.01	NS
BD			
CYP1A1 4889G	CYP1A1 6235C	0.1	0.015
CYP1A1 4887A	CYP1A1 4889G	–0.8	NS

Table 5. Phenotype frequencies of CYP1A1 4887A and 4889G in patients with Behçet's disease and controls stratified by CYP1A1 4889G and 4887A.

	CYP1A1 4889G (+)				CYP1A1 4889G (–)			
	BD	Controls	OR (95% CI)	p	BD	Controls	OR (95% CI)	p
CYP1A1 4887A								
+	23	16	3.1 (1.2–8.2)	0.02	9	17	2.3 (0.7–6.9)	NS
–	11	24			8	34		
	CYP1A1 4887A (+)				CYP1A1 4887A (–)			
	BD	Controls	OR (95% CI)	p	BD	Controls	OR (95% CI)	p
CYP1A1 4889G								
+	23	16	2.7 (1.0–7.6)	0.04	11	24	1.9 (0.7–5.6)	NS
–	9	17			8	34		

Table 6. Interactions between CYP1A1 4887A and 4889G in patients with Behçet's disease and controls.

CYP1A1	BD	Controls	OR (95% CI)	p
4887A (–) 4889G (–)	8	34		
4887A (+) 4889G (–)	9	17	2.3 (0.7–6.9)	NS
4887A (–) 4889G (+)	11	24	1.9 (0.7–5.6)	NS
4887A (+) 4889G (+)	23	16	6.1 (2.3–16.6)	0.0002

between CYP1A1 4889G and 6235C was found in healthy controls and patients with BD, while a similar finding was not found between CYP1A1 4889G and 4887A. The CYP1A1 C4887A and A4889G polymorphisms are in exon 7, known to be related to the enzyme activity of CYP1A1[28]. Therefore, the polymorphisms of exon 7 may play a role in the pathogenesis of BD. Smoking is a risk factor for developing vasculitis in BD, and CYP1A1 plays a role in the metabolism of tobacco-derived PAH. However, only 3 patients had a smoking history among our patients. An investigation of gene-smoking interaction could not be performed due to the small number of cases.

Patients with BD have enhanced superoxide production and decreased superoxide scavenging activity[17]. SOD defends cells against oxidative damage and plays an important role in controlling reactive oxygen and other radical species in cells[29]. MnSOD is tetrameric and inducible, and is located in human mitochondria[30]. MnSOD is also the primary defense against reactive oxygen in mitochondria, and it plays an important role in preventing the development of late-onset diseases[31]. Defects of mitochondria are associated with the degenerative diseases of aging such as Parkinson's disease and Alzheimer's disease[32,33].

MnSOD gene is on the long arm of chromosome 6 (6q25). The MnSOD gene with thymidine at nucleotide position 5777 encodes a native form of MnSOD that has a stable tetrameric interface. However, MnSOD gene with nucleotide sequence 5777C encodes a mutant form, which has increased thermal instability and accelerated thermal inactivation[30,34]. The transport of MnSOD into mitochondria is mediated through interaction of the mitochondrial targeting sequence with receptors on the mitochondrial membrane. The C1183T (Ala-9 Val) polymorphism in the mitochondrial targeting sequence may influence the efficiency of MnSOD transport. The –9 Ala polymorphism results in the formation of α-helix and the –9 Val takes a ß-sheet structure[35]. The α-helix structure is important for the effective transport of precursor proteins into mitochondria[36]. The amino acid substitution (Ala/Val) at position –9 of the mitochondrial targeting sequence may lead to misdirected trafficking, followed by alteration of MnSOD activity in human mitochondria[37]. Polymorphisms of MnSOD gene have been reported to be related to several diseases including Parkinson's disease, diabetes mellitus, and malignancies[35,38-42]. In this study, the MnSOD gene alone was not associated with susceptibility to BD. The MnSOD 5777T polymorphism could not be found in patients with BD or healthy controls in Taiwan. We also found MnSOD and CYP1A1 polymorphisms were not associated with the clinical manifestations of BD (data not shown).

In summary, the simultaneous presence of CYP1A1 4889G and 4887A polymorphisms is associated with susceptibility to Behçet's disease in Taiwan.

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