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Lack of association of the −463 G/A myeloperoxidase promoter polymorphism with Behçet's disease in Italian patients

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Objective. To investigate potential associations between the −463 G/A myeloperoxidase (MPO) promoter polymorphism and susceptibility to, and clinical expression of, Behçet's disease (BD).
Methods. One hundred and seventy-five Italian patients who satisfied the International Study Group criteria for BD and 235 healthy age- and sex-matched blood donors were genotyped for the −463 G/A promoter polymorphism of the MPO gene by molecular methods. The patients were subgrouped according to the presence or absence of clinical manifestations.
Results. The distribution of allele and genotype frequencies of the MPO −463A/G polymorphism did not differ significantly between the BD patients and the healthy controls. Carriers of the −463 A allele (A/A or A/G) [odds ratio (OR) 0.7, 95% confidence interval (CI) 0.5–1.1] and homozygosity for A allele (OR 0.3, 95% CI 0.1–1.3) were less frequent among BD patients than among the controls, but the difference was not statistically significant. No significant associations were found when BD patients with and those without clinical manifestations were compared.
Conclusion. Our data suggest that the −463 G/A promoter polymorphism of the MPO gene is not associated with susceptibility to, and clinical expression of, BD in Italian patients.

Key words: Behçet's disease, Myeloperoxidase gene polymorphism, Myeloperoxidase, Disease manifestation.

Behçet's disease (BD) is a multi-systemic inflammatory disorder, which preferentially affects oral and genital mucous membranes, skin and eyes [1–3]. Arthritis, gastrointestinal, vascular and central nervous system (CNS) involvement may also be present. Vasculitis is the pathological lesion underlying most clinical manifestations of BD. BD has a distinctive geographical distribution, with the highest prevalence in countries along the ancient 'Silk Route', including Italy, Turkey, Iran, China and Japan [1–3]. The aetiology of BD is largely unknown, but genetic and environmental factors are probably involved [1–3].

Myeloperoxidase (MPO) is a haeme-containing peroxidase expressed and stored in neutrophils and monocytes, which, during cellular activation and degranulation, is released into phagocytic vacuoles as well as into the extracellular space [4, 5]. MPO catalyses a reaction between hydrogen peroxide and chloride to generate hypochlorous acid (HOCl), a potent oxidant and chlorinating agent that can cause vascular damage when released by activated cells at inflammatory sites [6, 7]. Investigations have shown that various functions of neutrophils in peripheral blood, such as chemotaxis, phagocytosis and generation of reactive oxygen species (ROS) are enhanced in BD [8–12]. High levels of MPO have been found in both plasma and supernatants of neutrophil cultures from patients with active BD [13–15]. Therefore, activated neutrophils and MPO may play a central role in the pathophysiology of BD.

The promoter region of the MPO gene has a single G-to-A base substitution at position −463, which has been reported to be functionally important since it influences MPO expression [16–18]. The GG genotype is associated with higher levels of MPO mRNA expression and higher levels of MPO protein than GA/AA genotypes [16–18]. Several diseases have been reported to be associated with the −463 G/A MPO promoter polymorphism [19–24]. Recently, MPO-antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis was found to be associated with GG genotype in females but not in males [22]. Moreover, GA/AA genotype was associated with an increased incidence of relapse and an earlier age at diagnosis. These results suggest that a genetically determined regulation of MPO expression may be implicated in the pathogenesis and clinical expression of vasculitis.

The aim of our study was to assess the role of this MPO promoter polymorphism in the susceptibility to and clinical expression of BD in a cohort of Italian patients.

Materials and methods

Study population

Case patients were 175 consecutive patients with BD who were followed in nine different Italian referral centers [25] over a 7-yr period (1999–2005). All patients fulfilled the criteria developed by the International Study Group for BD (ISG) [26]. The control group consisted of 235 gender- and age-matched healthy subjects who were unrelated volunteer blood donors. The median age of the controls was 34 yrs (range 19–44), 50% of whom were males. All study subjects were Caucasians who had been residing in Italy for at least one generation. No ethnic differences were present between patients and controls. Written informed consent was obtained from patients and controls before inclusion in the study. The study was approved by the Ethics Committees of the participating centres.

HLA class I typing

Serological HLA class I typing was performed by a standard microlymphocytotoxicity technique, using peripheral blood

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TABLE 1. Demographic and clinical features of 175 Italian patients with Behçet's disease

	Number	Percentage
Female/Male	80/95	45.7/54.3
Mean age at disease onset ± S.D. (yrs)	30 ± 12	
Mean disease duration (yrs)	11 ± 8	
Oral ulcers	175	100
Cutaneous lesions	146	83.4
Papulopustular lesions	94	53.7
Erythema nodosum	75	42.9
Genital ulcers	109	62.3
Epididymitis	12	6.9
Eye lesions	98	56.0
Anterior uveitis	54	30.9
Posterior uveitis and retinal vasculitis	77	44.0
Arthritis	75	42.9
Central nervous system involvement	30	17.1
Venous thrombosis[a]	48	27.4
Deep venous thrombosis	33	18.9
Positive pathergy test[b]	41/102	40.2
HLA-B51[c]	95/151	62.9

[a]Subcutaneous thrombophlebitis + deep vein thrombosis.
[b]Pathergy test was performed on 102 patients.
[c]HLA-B51 was performed on 151 patients.

lymphocytes [27]. Out of the 175 Italian patients with BD, 151 were typed for HLA-B51 allele.

DNA extraction and genotyping

DNA was extracted from peripheral blood leucocytes using phenol/chloroform method, according to standard procedures [28]. Polymorphisms were detected by using RFLP-PCR analysis as described by London *et al.* [21]. A 350-bp DNA fragment was amplified using forward primer MPOF (5′-CGG TAT AGG CAC ACA ATG GTG AG-3′) and reverse primer MPOR (5′-GCA ATG GTT CAA GCGATT CTT C-3′).

PCR amplification was performed in 25 μl reaction containing 100 μM of each dNTP, 20 pmol each primer, 1 unit Taq polymerase. Amplification profile was as follows:

- initial denaturation 95°C for 2 min;
- 35 cycles of: 94°C for 30 s, 62°C for 30 s, 72°C for 30 s;
- final extension at 72°C for 3 min.

PCR products were digested with the restriction enzyme AciI. This enzyme can reveal the presence of an A or G nucleotide at the −463 position. Electrophoresis analysis of digested PCR products was performed in 2% agarose gel stained with ethidium bromide (0.5 μg/ml) to show patterns for the three genotypes: 169, 120 and 61 bp fragments for the homozygous wild-type (−463GG); 289, 169, 120 and 61 bp fragments for the heterozygous type (−463AG); and 289 and 61 bp fragments for the homozygous mutant type.

Statistical analysis

Statistical analysis was performed using SPSS statistical package (SPSS Inc., Chicago, IL, USA). The frequencies of the alleles and genotypes among the case patients and control group were compared by chi-squared test. Odds ratios (ORs) were calculated together with their 95% confidence intervals (95% CIs). We performed a power calculation for an unmatched case-control study and estimated relative risk using Power and Sample Size Calculation version 2.1.31 software.

Results

The demographic and clinical characteristics of the 175 Italian patients with BD are reported in Table 1.

The allele and genotype frequencies of the −463GA MPO promoter polymorphism in BD patients and in the control group are shown in Table 2. The distribution of the MPO-G/A genotype did not differ significantly between BD patients and the controls, although the GG genotype was more frequent in BD patients as compared with the controls (61.1 *vs* 53.6%, respectively).

TABLE 2. Frequencies of alleles, genotypes and carriage rates of MPO polymorphism in patients with Behçet's disease and controls

	Behçet's disease ($n=175$)	Controls ($n=235$)	P	OR (95% CI)
Allele				
A	71/350 (20.3)	120/470 (25.5)	0.08	0.7 (0.5–1.0)
G	279/350 (79.7)	350/470 (74.5)		
Genotypes				
A/A	3/175 (1.7)	11/235 (4.7)		
A/G	65/175 (37.1)	98/235 (41.7)	0.128	
G/G	107/175 (61.1)	126/235 (53.6)		
Carriage rate				
A/A + A/G	68/175 (38.9)	109/235 (46.4)	0.13	0.7 (0.5–1.1)
G/G	107/175 (61.1)	126/235 (53.6)		
A/G + G/G	172/175 (98.3)	224/235 (95.3)	0.17	0.3 (0.1–1.3)
A/A	3/175 (1.7)	11/235 (4.7)		

Allele G frequency was similar in BD patients and controls (79.7 *vs* 74.5%, respectively). Carriers of the A allele (AA or AG) were less frequent among the BD patients than among the controls (OR 0.7, 95% CI 0.5–1.1). Homozygosity for the A allele was also less frequent in BD patients than in controls (OR 0.3, 95% CI 0.1–1.3). However, these differences were not statistically significant.

Given the sample sizes (175 patients with BD and 235 controls) and the allele frequencies of the polymorphism examined, we can conclude with 80% certainty that there is a genetic relative risk of 1.53 for BD in carriers of the −463GA MPO promoter polymorphism.

Since a study [22] has shown that the influence of the MPO-G/A polymorphism could be gender-specific, we compared the influence of MPO genotype in BD females and BD males. No influence of gender was observed (data not shown). We confirmed that in either BD females and BD males there was no association with the MPO-G/A polymorphism.

The associations between the −463GA MPO polymorphism and the clinical manifestations of BD defined in Table 1 were evaluated in the 175 BD patients, comparing patients with and without manifestations. No significant associations were found (data not shown). Carriers of the A allele (AA or AG) were less frequent in BD patients with anterior uveitis than in those without (29.6 *vs* 43.0%), but the difference was not statistically significant.

Discussion

BD is a polygenic disease in which multiple genetic factors, in combination with environmental risk factors such as infectious agents, are probably of importance in determining disease susceptibility and clinical expression [1–3]. Although the strongest genetic association identified in BD has been with HLA-B51 and MICA-A6 alleles [1–3, 29], recent studies have found that R/G 241 polymorphism of ICAM-1 gene [30], Glu/Asp 298 polymorphism of eNOS gene [31] and −634 C/G polymorphism of VEGF gene [32] are associated with BD susceptibility in the Italian population.

Vasculitis is the pathological lesion underlying most of the clinical findings of BD. In one immunopathological study, Kobayashi *et al.* [33] showed that the predominant lesion in vasculo-Behçet's is a neutrophilic vasculitis involving the vasa vasorum. Further, these authors showed that neutrophils and endothelial cells of the vasa vasorum are activated. Several studies have found that patients with BD have increased plasma MPO activity, reflecting neutrophil activation [13–15]. Yazici *et al.* [13]

found strong positive correlations between MPO, erythrocyte sedimentation rate and C-reactive protein levels in patients with BD, suggesting the presence of a relationship between the extent of inflammation and neutrophil activation. Several investigations have shown in BD patients an increased ROS production by neutrophils [9–12] and a decreased superoxide scavenging activity in both neutrophils and plasma [34–38]. Therefore, a disrupted oxidant/antioxidant equilibrium may play an important role in tissue injury and in the inflammatory reaction in BD. Recently, Yazici *et al*. [13] showed that the neutrophil–MPO–HOCL system oxidizes plasma proteins in patients with BD. Further, these authors showed that patients with active disease had significantly higher plasma levels of MPO and advanced oxidation protein products (AOPP), which is one of the products of MPO-mediated protein oxidation, compared with patients with inactive disease and healthy controls [13]. MPO may determine vascular damage by several mechanisms. MPO has been shown to activate metalloproteinase and catalytically consume endothelium-derived NO by reducing its bioavailability and impairing its vasodilatory and anti-inflammatory functions [6]. Endothelial dysfunction evaluated by endothelium-dependent vasodilation occurs in BD patients [39]. Furthermore, NO production was found to be decreased in patients with active disease compared with the inactive period and the control group [39]. Taken together, these observations indicate that neutrophil activation and MPO may have an important role in the pathogenesis of vascular lesions in BD.

A functional promoter polymorphism has been identified in the promoter region of the MPO gene, consisting of a G to A substitution. The −463 G/A polymorphism is situated within an Alu-encoded hormone response element and creates a SP1 site in the G allele promoter, and an oestrogen receptor-α binding site in the A promoter. The GG genotype is associated with a 2- to 3-fold higher expression of MPO messenger RNA and protein expression than GA/AA genotypes [16–18].

The high-expression GG genotype has been associated with an increased risk of Alzheimer's disease [19], multiple sclerosis [40], while the low-expression genotypes (AG and AA) have a protective role in coronary artery disease [23, 41, 42].

A genetically determined regulation of MPO expression may be implicated in the pathogenesis and clinical expression of vasculitis. The studies that have evaluated the association between MPO promoter polymorphism and vasculitis have reported discordant results. Reynolds *et al*. [22] observed that MPO-ANCA-associated vasculitis was associated with GG genotype in females but not in males. Moreover, GA/AA genotype was associated with an increased incidence of relapse and an earlier age at diagnosis. We recently found that subjects homozygous for the allele G have an increased risk of developing GCA [43]. The results of these two studies suggest that a genetically determined up-regulation of MPO expression may predispose to the development of vasculitis. However, in contrast to the findings of Reynolds *et al*. [22], no associations were observed in the study of Fiebeler *et al*. [44] between the MPO promoter polymorphism and MPO-ANCA-associated vasculitis.

One of the most important causes of failure to replicate findings in genetic association studies of vasculitis is the inadequacy of sample sizes. The number of patients with MPO-ANCA-associated vasculitis studied by Reynolds *et al*. [22] and by Fiebeler *et al*. [44] were 50 and 48 patients, respectively.

In this study, we evaluated the −463 G/A polymorphism in an ethnically homogeneous and large group of Italian patients with BD. Although carriers of, and homyoygosity for, the A allele were less frequent among the BD patients than among the controls, suggesting that a genetically determined reduced activity of MPO might be protective against the development of BD, the differences were not statistically significant. However, multicentre collaborations to recruit an adequate number of patients are required.

A second aim of this study was to determine whether this MPO polymorphism might be associated with the clinical expression of BD in our cohort of Italian patients.

However, when patients with and without manifestations were compared, no associations were found, although our study is probably not sufficiently powered to detect significant associations between this MPO polymorphism and clinical manifestations.

In conclusion, we did not find any association between the −463 G/A MPO promoter polymorphism and susceptibility to, and clinical expression of, BD. These results do not support the hypothesis that a genetically determined regulation of MPO expression may predispose to the development and clinical expression of this vasculitis in Italian patients. Further, larger studies are required to confirm our findings in other populations.

The authors have declared no conflicts of interest.

Rheumatology key message

- −463 G/A promoter polymorphism of the MPO gene may not predispose to the development and clinical expression of Behçet's disease in Italian patients.

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