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Matrix Metalloproteinase-9 rs17576 Gene Polymorphism and Behçet's Disease: Is There an Association?

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ABSTRACT

Background: Clinical studies have reported a significant association between matrix metalloproteinases (MMP), particularly (MMP-9), and inflammatory diseases including Behçet's disease (BD).

Purpose: To study the relationship between *MMP-9 rs17576* gene polymorphism and the development of BD, and its relation to disease activity among Egyptian patients.

Methods: A total of 100 BD patients and 100 healthy control volunteers were genotyped for *MMP-9 rs17576* polymorphism with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), followed by the confirmation of our results in random subgroups using direct DNA sequencing technique.

Results: The frequency of the GG genotype and G allele was significantly higher in BD patients as compared to the normal controls ($p = 0.011$, OR 8.61; $p = 0.03$, OR 1.65, respectively). There was no significant association between the *MMP-9 rs17576* polymorphism and the clinical outcomes of BD.

Conclusion: our study suggests a significant association of the *MMP-9 rs17576* A/G polymorphism with increased risk of BD development in Egyptian patients.

KEYWORDS

Behçet's disease; gene polymorphism; matrix metalloproteinase; *MMP-9 rs17576*

Introduction

Behçet's disease (BD) is a multisystemic autoimmune inflammatory disorder (Aksoy et al., 2011). The main pathogenic elements are caused by genetic predisposition, especially those which are HLA-dependent, and environmental factors, for example, infection (Cantarini et al., 2015). Both genetic and environmental factors cause immune dysregulation involving T and B cells with hyperactive neutrophils (Durrani et al., 2011).

Classically, BD is characterized by recurrent oral and genital ulcers, uveitis and characteristic skin lesions, but they can also present with arthritis, gastrointestinal lesions, central nervous symptoms and vascular lesions (Sakane et al., 1999).

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BD is characterized by an increased proteolytic activity and a chronic degradation of the extracellular matrix components like collagen, fibronectin, elastin and laminin (Choke et al., 2006).

The matrixins, or in another word matrix metalloproteinases (MMPs), are members of the large metzincin superfamily (Lo¨ffek et al., 2011). MMPs are capable of degradation of all extracellular matrix (ECM) components and basement membrane. In addition, MMPs regulate the release or activation of chemokines, cytokines, and other bioactive molecules, thus participating in physiological processes such as both innate and adaptive immunity, inflammation and angiogenesis (Fanjul-Fernandez et al., 2010).

The human Matrix metalloproteinases (MMPs) are synthesized as zymogens and activated by a variety of factors (Campbell et al., 1999; Zhang et al., 1999). The largest member of this family, MMP-9, is expressed by macrophages at the site of tissue damage and plays an important role in aneurysm formation and seems to be involved in leukocyte trafficking cells (Elmore et al. 1998). It acts as a pro-inflammatory factor (Renckens et al., 2006) and plays distinct roles under both physiological and pathological conditions (Johnson et al., 1998). Gene polymorphisms of *MMP-9* alter its expression at the transcriptional level (Zhang et al., 1999) resulting in inflammatory diseases, including BD (Lee et al., 2010).

The *MMP-9* gene is located on chromosome 20q11-q13, with various functional polymorphisms identified in its promoter and coding regions. The *MMP-9* 836A/G (rs17576, Gln279Arg, Q279R) polymorphism is one of these functional variants, which resides in exon 6 of the *MMP-9* gene. This polymorphism alters the MMP-9 protein conformation through substitution of the uncharged amino acid (glutamine) by the positively charged amino acid (arginine) resulting in a change in the MMP-9 substrate-binding and enzyme activity (Zhang et al., 1999). Belo et al. (2012) study reported that the absence of the G allele of the 836A/G polymorphism was associated with lower MMP-9 levels in obese children in Brazil. However, both Chiang et al. (2012) study on Community-acquired pneumonia patients and Naouali et al. (2015) study on BD patients found no effect of the 836A/G polymorphism on MMP-9 gene expression.

A recent study on the Tunisian population reported a significant association of *MMP-9* rs17576 polymorphism with Behçet's disease (Naouali et al., 2015)

The aim of this work was to study the relationship between *MMP-9 rs17576* gene polymorphism and development of Behçet's disease, and its relation to disease activity among Egyptian patients.

Patients and methods

This study included 100 BD patients (81 males and 19 females) with a mean age of 33.1 ± 9.8 years and 100 healthy subjects (76 males and 24 females) as a control group with a mean age of 33.8 ± 9.1 years. Patients were recruited from the Department of Rheumatology and Rehabilitation and Internal medicine Departement (Kasr Al Aini hospitals, Cairo University, Egypt). All patients met the Criteria of International Study Group for BD (Davatchi et al., 2014). BD patients were subjected to complete clinical evaluation and routine laboratory investigations. Individual characteristics of patients with BD and controls were summarized in Table 1.

Table 1. Descriptive data of BD patients.

	BD patients (n = 100)	Controls (n = 100)	p-value
Age (years)	33.1 ± 9.8	33.8 ± 9.1	0.62
Male sex, %	81.0	76.0	0.39
Disease duration (years)	6.0 (4.0–11.0)		
Clinical manifestations, %			
Oral ulcers	94.0		
Genital ulcers	83.0		
Skin lesions	43.0		
Arthritis	22.0		
Uveitis	69.0		
Vascular involvement	31.0		
Neurological involvement	22.0		
Chest involvement	15.0		
GIT involvement	15.0		
Laboratory findings			
AST (U/L)	20.0 (16.0–25.0)		
ALT (U/L)	24.0 (17.0–32.8)		
ESR (mm/hr)	12.0 (9.0–23.8)		

BD, Behçet's disease; GIT, gastrointestinal tract; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate. Variables with normal distribution are presented as mean ± standard deviation. Skewed variables are presented as median (interquartile range).

MMP-9 rs17576 genotype determination

Genomic DNA was extracted from 2 ml EDTA anticoagulated whole blood samples using a TINAamp DNA extraction kit (Tangen Biotech, China). *MMP-9* rs17576 polymorphism was analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) according to the protocol proposed by Wu et al. (2013) using the following primers: TCACCCTCCCGCACTCTGG (forward); CGGTCGTAGTTGGCGGTGG (reverse). PCR conditions were as follows: denaturation at 95°C for 5 min, 30 cycles of 94°C for 30 s, annealing at 66°C for 1 min, and extension at 72°C for 1 min, and a final extension at 72°C for 10 min. The amplicon size was 300 bp, and three genotypes were generated after digestion by MspI (Thermo), GG homozygosity (170 bp, 130 bp), AG heterozygosity (300 bp, 170 bp, 130 bp) and uncut AA homozygosity (300 bp) (Figure 1).

Sequencing

Random samples from each genotype were confirmed by direct sequencing (Figure 2). The amplified PCR products were purified using the QIAquick PCR purification kit (Qiagen,

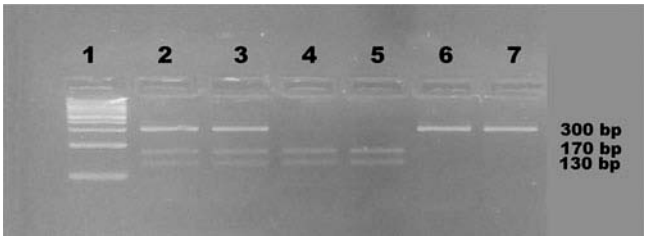

Figure 1. Agarose gel showing RFLP analysis of the *MMP-9 rs17576* polymorphism. Lane 1 shows 100 bp DNA ladder. Lanes 2 and 3 show the heterozygous AG genotype; lanes 4 and 5 show the homozygous GG genotype; and lanes 6 and 7 show the homozygous AA genotype.

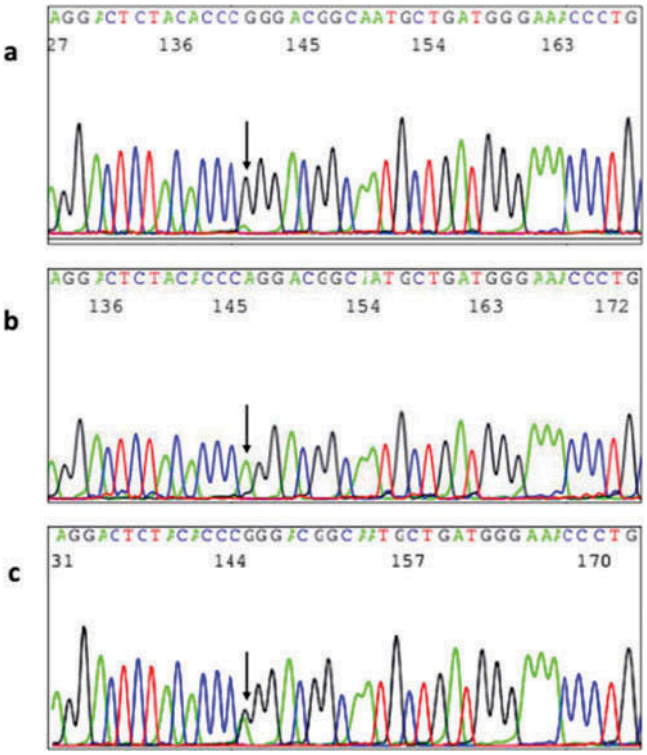

Figure 2. The sequencing results of *the MMP-9 rs17576* polymorphism. a) The arrow indicates the presence of the minor allele G at the polymorphic site instead of A. b) The arrow indicates the presence of the major allele A. c) The arrow indicates the presence of the heterozygous A/G genotype.

Germany), and this was followed by cycle sequencing using the BigDye terminator cycle sequencing kit, version 3.1 (Applied Biosystems, USA). The reactions were cleaned from the excess BigDye terminator by using CentriSep columns (Princeton separations, USA). The cleaned-up products were directly sequenced to detect the polymorphic site by ABI 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

Data were analyzed using the SPSS (Statistical Package for Social Science) version 16.0 statistical software. Parametric data were presented as mean ± SD, while nonparametric data were presented as median and percentiles for quantitative variables, whereas frequency and percentages were used for qualitative variables. Differences were calculated by chi-square and Fisher exact tests (for categorical variables) or the Student *t*-test, Mann–Whitney U test and Kruskal–Wallis test (for continuous variables). Hardy–Weinberg equilibrium (HWE) was assessed using a $\chi 2$ test in each group. Haploview, a web-based calculator Snpstats (Sole´ et al., 2006) was used to assess the differences in genotype and allele frequencies between the BD patients and the control groups by calculation of odds ratios with 95% confidence intervals (CI). A p value less than 0.05 was considered significant.

Table 2. The genotype and allele frequencies of *MMP-9 rs17576* gene polymorphism in the BD and healthy control groups.

	Healthy controls (n = 100)	BD patients (n = 100)	OR (95% CI)	p value
	n (%)	n (%)		
A/A	59 (59%)	47 (47%)	1.00	
A/G	40 (40%)	45 (45%)	1.41 (0.80–2.50)	0.237
G/G	1 (1%)	8 (8%)	10.04 (1.21–83.15)	0.013
A/A	59 (59%)	47 (47%)	1.00	0.089
A/G–G/G	41 (41%)	53 (53%)	1.62 (0.93–2.84)	
A/A–A/G	99 (99%)	92 (92%)	1.00	0.011
G/G	1 (1%)	8 (8%)	8.61 (1.06–70.17)	
A allele (major)	158 (79.0)	139 (70.0)	1.00	0.03
G allele (minor)	42 (21.0)	61 (30.0)	1.65 (1.05–2.60)	

BD, Behçet's disease.

Table 3. Distribution of *MMP-9 rs17576* genotypes in BD patients as regards different clinical data.

	MMP-9 genotype, n (%)			
	A/G–G/G	A/A	OR (95% CI)	p value
Oral ulcers	49 (92.5)	45 (95.7)	0.54 (0.09–3.12)	0.489
Genital ulcers	46 (86.8)	37 (78.7)	1.78 (0.62–5.2)	0.284
Skin lesions	25 (47.2)	18 (38.3)	1.44 (0.65–3.2)	0.371
Arthritis	14 (26.4)	8 (17.0)	1.75 (0.66–4.6)	0.258
Uveitis	32 (60.4)	37 (78.7)	0.42 (0.17–1.0)	0.05
Vascular involvement	14 (26.4)	17 (36.2)	0.63 (0.27–1.5)	0.292
Neurological involvement	8 (15.1)	14 (29.8)	0.42 (0.16–1.1)	0.077
Chest involvement	6 (11.3)	9 (19.1)	0.54 (0.18–1.6)	0.274
GIT involvement	9 (17.0)	6 (12.8)	1.4 (0.46–4.3)	0.556

GIT, Gastrointestinal tract.

Results

The *MMP-9 rs17576* SNP was genotyped in 100 BD patients and 100 normal controls. The genotypes and allele distribution did not deviate from HWE in both the BD patients and the control groups. Our results showed that a significant difference was found between BD patients and normal controls concerning that the *MMP-9 rs17576* genotypes frequency, the frequency of the GG genotype and G allele in BD patients were significantly higher than that in normal controls (p = 0.011, OR 8.61; p = 0.03, OR 1.65, respectively) (Table 2) . We further studied the association of *MMP-9 rs17576* SNP with the clinical findings of BD including genital ulcers, skin lesions, arthritis, ocular, vascular and neurological manifestations. Our study did not find a significant association with any of these disease parameters (Table 3).

Discussion

Behçet's disease (BD) is an inflammatory disorder with multiple organs involvement. Its exact etiology is unknown, but an autoimmune pathogenesis has been strongly suggested. Genetic predisposition and immune dysregulation involving T and B cells contribute to BD pathogenesis (Durrani et al., 2011).

Metalloprotease family is zinc-dependent endoproteinases that are categorized into multiple groups according to their substrate specificity. This family includes gelatinase A (72-kDa gelatinase; MMP-2), gelatinase B (92-kDa gelatinase; (MMP-9) (The largest member of this family) and macrophage elastase (MMP-12) (Corbel et al., 2002).

The MMP family proteins contribute in degradation of the extracellular matrix in both normal physiological processes like embryonic development, tissue remodeling and reproduction as well as in pathological conditions like arthritis and metastasis (Nagase et al., 1999).

MMP-9 appears to be a regulatory factor in neutrophil migration across the basement membrane (Delclaux et al., 1996) and involved in leukocyte trafficking cells in BD (Campbell et al., 1999). In addition to neutrophil migration, MMP-9 has several important functions, such as extracellular matrix degradation, cleavage of several chemokines and activation of IL-1β (Opdenakker et al., 2001).

Human MMP-9 plays a role in many inflammatory diseases, including BD (Park et al., 2012); it was found to be expressed by macrophages located at the site of tissue damage in BD like in aortic aneurysms (Pyo et al., 2000) and in cerebrospinal fluids of neuro-BD patients (Hamzaoui et al., 2009). After declaring its role in pathogenesis, MMP-9 was found to be an activity indicator in BD (Pay et al., 2007).

A study on Egyptian patients reported that MMP-9 serum level was significantly higher in BD patients with vascular, skin, neurological and ocular lesions. Also, the authors reported a significant positive correlation between MMP-9 serum level and BD activity (Ganeb et al., 2012)

MMP-9 activity is regulated at its gene expression level and post-transcriptionally (Vandooren et al., 2013). The postulation that MMP-9 gene variations could be involved in BD development has led to exploring a number of *MMP-9* gene polymorphisms in BD. *MMP-9 rs17576* A/G polymorphism was found to be associated with variable diseases like cancer (Hu et al., 2005), Henoch-Schonlein purpura (Park et al., 2006), and internal carotid artery bulb (Abilleira et al., 2007).

Although several studies have suggested the significant role of MMP-9 in inflammatory conditions, yet there is a paucity of data and published studies regarding the role of *MMP-9 rs17576* A/G SNP with respect to BD. Only one Tunisian study, according to our knowledge, has investigated the association of *MMP-9 rs17576* A/G gene polymorphisms with BD (Naouali et al., 2015). So, confirmation studies conducted in other populations are required to explore such an association.

In our work, the *MMP-9 rs17576* SNP was genotyped in 100 Egyptian BD patients and in another 100 concordant normal controls. To our knowledge, it is the first study investigating *MMP-9* gene polymorphism in Egyptian BD patients

In our study, we found a significant difference between BD patients and normal controls as regards the MMP-9 rs17576 genotypes and allele frequency. The *MMP-9 rs17576* GG genotype and G allele were more frequent in BD patients ($p = 0.011$, $p = 0.03$, respectively) than in the involved normal personnel.

In our examined subjects, the mere presence of the *MMP-9 rs17576* G allele carried a 1.65-fold risk of development of BD. Furthermore; the *MMP-9 rs17576* G/G genotype carriers had 8.61 times risk of BD development than A/G, and A/A genotypes.

A near similar result was reported for the *MMP-9 rs17576* A/G polymorphism in a group of Arabic BD patients in Tunisia (Naouali et al., 2015) where, the authors found a significant association between the G allele and increased BD risk ($OR = 6.24$, $p < 0.0001$).

In this study, we further analyzed the association of the *MMP-9 rs17576* gene polymorphism with the clinical features of BD. However, we did not find a significant association with any of them. This goes hand in hand with the results of Naouali et al. (2015) study on Tunisian patients.

The MMP-9 enzyme consists of three common domains: the pro-peptide domain, hemopexin-like c-terminal domain and the catalytic domain (Active site) (Massova et al., 1997). The *MMP-9 rs17576* A/G polymorphism was reported to be located in the catalytic domain which enhances substrate binding (Allan et al., 1995; O'Farrell et al., 2000). The presence of this polymorphism at that active location might explain its association with an increased risk of development of BD, and its presumed role in the pathogenesis process in BD by enhancing substrate binding leading to excess matrix degradation and neutrophil migration to the damaged tissues.

Conclusion

The *MMP-9 rs17576* GG genotype and G allele were more significantly frequent in our BD patients than controls. The *MMP-9 rs17576* GG genotype carriers had 8.61 times risk of BD development than A/G, A/A genotypes. However, *MMP-9 rs17576* polymorphism had no specific association with any of the clinical findings of BD. Further larger studies are needed to confirm such results and to validate the association between *MMP-9 rs17576* polymorphism and risk of BD development.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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