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Paroxonase 1-L55M gene polymorphism in Behcet's disease

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Objective
The aim of this work was to study paroxonase 1-L55M gene polymorphisms in Behcet's disease (BD) and its relation to clinical manifestations.

Background
BD is a type of vasculitis characterized by recurrent orogenital ulcers, relapsing uveitis, and skin, articular, vascular, neurologic, and gastrointestinal manifestations. Genetic, environmental, and immunological factors are involved in its pathogenesis. Paraoxonase is thought to play an important role in the protection of low-density lipoprotein and high-density lipoprotein particles from oxidation. Lipid peroxidation and free oxygen radicals are believed to play a role in BD pathogenesis.

Patients and methods
In the current study, we examined 40 BD patients (group II). The diagnosis of BD was made according to the International Study Group Criteria of Behcet's Disease. We included 40 healthy adults as controls (group I). All participants were subjected to thorough history taking, physical examination, and laboratory investigations, including serum lipid profile (total cholesterol, triglycerides, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol) and paroxonase 1-L55M gene study using PCR.

Results
BD shows male predominance with a male:female ratio of 2.1:1. Oral and genital ulcers were the most common presentation and were present in almost all patients, followed by vascular, skin, central nervous system, and articular manifestations. There were no significant statistical differences between BD patients and the control group as regards *PON1* genotype and allele frequencies.

Conclusion
PON1 L55M gene polymorphism is not associated with an increased risk for BD or its clinical manifestations.

Keywords:
atherosclerosis, Behcet's disease, paroxonase 1

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Introduction

Behcet's disease (BD) is a chronic inflammatory vasculitis characterized by recurrent oral and genital ulcerations, ocular manifestations, and arthritis. In addition, neurological and large-vessel involvement can occur in some cases [1].

A Turkish dermatologist, Hulusi Behcet, described BD in 1937. The causes and pathogenesis of BD have not been fully understood yet. However, it is now considered as an immunoinflammatory, multisystemic disorder affecting blood vessels of all sizes [2].

Cases of BD cluster along the ancient silk road. The prevalence of BD is 80–370 cases per 100 000 population in Turkey, 0.6/100 000 in Yorkshire, and 10/100 000 in Japan. The most important genetic factor associated with BD is HLA-B5101 [3]. The leading causes of morbidity in BD are neurologic involvement and uveitis (threat of visual loss). Major vessel disease (43.9%), central nervous system (CNS) involvement and sepsis (12.2%), and cancer (14.6%) are the main causes of death [3].

Paraoxonase 1 (*PON1*) is an enzyme exclusively located on high-density lipoprotein (HDL) in the serum. *PON1* causes hydrolysis of organophosphate substrates and also metabolizes lipid peroxides leading to protection against accumulation of low-density lipoprotein (LDL) [4].

The paraoxonases are basically lactonases with one of the broadest known substrate specificities. All three

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PONs metabolize 5-hydroxy cicosatetraeomic acid 1,5 lactone and 4-hydroxy docosahexaenoic acid. Organophosphates are exclusively hydrolyzed by PON1, which has additional esterase activity [5].

Paraoxonases are believed to play an important role in the protection of LDL and HDL particles from oxidation. It is thought that lipid peroxidation and free oxygen radicals play an important role in the pathogenesis of BD [4].

The aim of this work was to study paroxonase 1-L55M gene polymorphisms in BD and its relation to clinical manifestations of BD.

Patients and methods

We examined 40 BD patients (group II). These patients were selected from the outpatient clinics of rheumatology, ophthalmology, dermatology, and neurology, Menoufia University Hospital, Shebeen El-Kom, Egypt, during the period from June 2015 to January 2017. Informed consent from all participants was obtained in accordance with the local ethical committee. The diagnosis of BD was made according to the International Study Group Criteria of Behcet's Disease. We included 40 healthy adult individuals as controls (group I).

All controls and patients were subjected to medical history taking and complete physical examination. Investigations were carried out for all patients and controls, including complete blood count, fasting blood glucose, lipid profile (cholesterol, triglycerides, LDL, and HDL), glycosylated hemoglobin, and paroxonase 1-L55M gene study using PCR.

Ten milliliters of fasting (12–14 h) venous blood was drawn from the cubital vein of every patient. Four milliliter was transferred slowly into an evacuated EDTA tube for DNA extraction for genotyping. Two milliliter was transferred slowly into an evacuated EDTA tube for measuring glycated hemoglobin (HbA1c). Two milliliter was transferred slowly into an evacuated EDTA tube and centrifuged for 5 min at 4000 rpm; the plasma obtained for determination of plasma glucose was frozen at −20°C until analysis.

Two milliliter was transferred slowly into a plain tube for determination of total cholesterol, triglycerides, and HDL-cholesterol. It was left for 30 min for clotting and then centrifuged for 10 min at 4000 rpm. After that, the serum obtained was frozen at −20°C until analysis.

Serum cholesterol, serum triglycerides, and serum HDL-cholesterol were determined using enzymatic colorimetric test, using kits supplied by Spinreact (Girona, Spain) [6]. LDL cholesterol was estimated using Friedewald's formula [7]. Glycosylated hemoglobin was estimated using enzymatic colorimetric test, using kits supplied by Teco Diagnostics (Anaheim, California, USA).

Genotyping for paroxonase 1-L55M gene [4]: Blood DNA extraction was performed using GF-1 Blood DNA extraction kit (Vivantis, Selangor, Malaysia). PCRs were performed in a final volume of 25 µl consisting of 10 µl of DNA template and 12.5 µl of master mix [2.5 µl of 10× PCR buffer, 1.5 µl of $MgCl_2$ 25 mmol/l, 0.5 µl of dNTPs 10 mmol/l, 0.5 µl of Taq polymerase 5 U/µl, 1 µl of forward primer 50 mmol/l (5'-CCT GCA ATA ATA TGA AACAAC-3'), 1 µl of reverse primer 50 mmol/l (5'-TGA AAG ACT TAAACT GCC AGTC-3')], and 0.5 µl of distilled water.

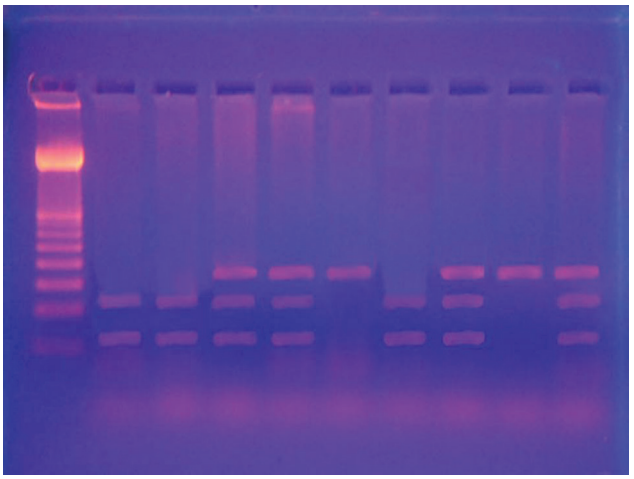
Applied Biosystem 2720 thermal cycler (Foster city, California) was used for PCR amplification. PCR condition included initial denaturation at 94°C for 6 min followed by 32 cycles as follows: denaturation at 94°C for 1 min, annealing at 60°C for 1 min, and extension at 72°C for 1 min). Thereafter, final extension step was carried out at 72°C for 4 min.

The PCR product was then digested with NlaIII (New England Biolabs, Ipswich, Massachusetts, USA) at 37°C for 1 h (2.5 µl of 10× NE buffer 4, 1 µl of NlaIII, 6.5 µl of distilled water, and 10 µl of PCR product). The NlaIII digestive products were run using 4% agarose gel electrophoresis for 30 min. It was stained with ethidium bromide. Ultraviolet light was used for band visualization. Digested PCR products were 172 bp for the L allele and 106 and 66 bp for the M allele (Fig. 1).

Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 19.0 for Windows (SPSS Inc.,

Figure 1



PON1 genotyping using restriction enzyme NlaIII.

Chicago, Illinois, USA) and MedCalc 13 for windows (MedCalc Software BVBA, Ostend, Belgium).

Quantitative data were expressed as mean ± SD. It was analyzed by applying *t*-test for comparison between two groups of normally distributed variables. For the qualitative data, it was expressed in the form of number and percentage and then it was analyzed by applying χ^2 for comparison between two or more independent qualitative variables normally distributed.

Calculation of allelic frequency for both patients and controls was performed. The χ^2-test was used to compare allele frequency of the *PON55* gene polymorphism between BD patients and controls. Odds ratio and 95% confidence interval (CI) were calculated to compare BD risk around genotypes and alleles. A *P* value less than 0.05 was considered as statistically significant.

Results

There was no significant statistical difference between the studied groups as regards age and sex. Age range in the control group was 18–45 years with a mean age 29 ± 6.85 years. Age range in BD patients was 18–48 years with a mean age of 28.65 ± 6.46 years. The number of male participants was nearly similar in both groups: 28 (70%) in the control group and 27 (67.5%) in the BD group. The number of female participants was nearly similar in both groups: 12 (30%) in the control group and 13 (32.5%) in the BD group. BD patients showed male predominance with a male:female ratio of 2.1:1 (Table 1).

Distribution of diagnostic features of BD among studied patients revealed that oral ulcers were present in 40 (100%) patients. Genital ulcers were present in 40 (100%) patients. Eye lesions were present in 27 (67.5%) patients in the form of anterior and posterior uveitis [22 (55%) and 7 (17.5%), respectively]. Skin lesions were present in 16 (40%) patients in the form of EN and pseudofolliculitis [4 (10%) and 12 (30%), respectively]. The Pethargy test was positive in 12 (30%) patients. Vascular involvement was present in 17 (42.5%) patients in the form of arterial and venous thrombosis [7 (17.5%) and 10 (25%), respectively]. Neuro-Behcet manifestations were present in nine (22.5%) patients. Articular manifestations were present in seven (17.5%) patients. Renal affection was present only in one (2.5%) patient in the form of proteinuria. There were no gastrointestinal, cardiac, or pulmonary involvements in studied patients (Table 2).

There was no significant statistical difference between the studied groups as regards genotype and allele frequency of *PON1*. The distribution of *PON1* genotype LL genotype was present in 75% of controls and 72.5% of cases. LM genotype was present in 20% in the control group and 22.5% in the case group. MM genotype was equal in both cases and controls; it was 5%. The frequencies of L and M alleles were 85 and 15% in cases and 83.75 and 16.25% in controls, respectively (Table 3).

There was no significant statistical difference between *PON1* genotype as regards clinical manifestations of BD. The distribution of *PON1* genotype in BD patients was 72.5% LL, 22.5% LM, and 5% MM among patients with oral ulcers. It was 72.5% LL, 22.5% LM, and 5% MM among patients with genital ulcers. It was 66.6% LL, 25% LM, and 8.4% for MM among patients with positive pathergy test. It was 63.6% LL, 31.8% LM, and 4.6% MM among patients with anterior uveitis. It was 85.7% LL and 14.3% LM among patients with posterior uveitis. It was 71.4% LL and 22.3% LM among patients with articular manifestations. It was 77.7% LL and 22.3% LM among patients with CNS disease. It was 100% LL among patients with venous thrombosis. It was 71.4% LL and 28.6% LM among patients with arterial thrombosis. It was 100% LM among patients with renal disease. It was 50% LL, 25% LM, and 25% MM among patients with EN. It was 75% LL, 16.6% LM, and 8.4% MM among patients with pseudofolliculitis (Table 4).

There was no significant statistical difference in the distribution of *PON1* L55M allele frequency between healthy controls and BD patients according to clinical manifestations. The frequencies of L allele and M alleles were 85 and 15% in the control group,

Table 1 Demographic data of the studied groups

	Controls (Group I) (*n*=40)	Patients with BD (Group II) (*n*=40)	Test of significance	*P*
Age (years)				
Mean±SD	29±6.85	28.65±6.46	*t*-Test=0.23	0.81 (NS)
Range	18-45	18-48		
Sex (*n* [%])				
Male	28 (70)	27 (67.5)	χ^2=0.58	0.8 (NS)
Female	12 (30)	13 (32.5)		
BD patients (male/female ratio)		2.1/1		

BD, Behcet's disease.

Table 2 Distribution of clinical criteria of Behcet's disease in studied Behcet's disease patients

	Group II (BD) (*n*=40) (*n* [%])	
	Present	Absent
Oral ulcers	40 (100)	0 (0)
Genital ulcers	40 (100)	0 (0)
Eye lesions	27 (67.5)	13 (22.5)
Anterior uveitis	22 (55)	18 (45)
Posterior uveitis	7 (17.5)	33 (82.5)
Skin	16 (40)	24 (60)
EN	4 (10)	36 (90)
Psuedofolliculitis	12 (30)	28 (60)
Pathergy test	12 (30)	28 (60)
Vascular involvement	17 (42.5)	23 (57.5)
Arterial thrombosis	7 (17.5)	33 (82.5)
Venous thrombosis	10 (25)	30 (75)
Neuro-Behcet	9 (22.5)	31 (77.5)
Articular involvement	7 (17.5)	33 (82.5)
Renal involvement	1 (2.5)	39 (97.5)
GIT involvement	0 (0)	40 (100)
Cardiac involvement	0 (0)	40 (100)
Pulmonary involvement	0 (0)	40 (100)

BD, Behcet's disease; EN, erythema nodosum; GIT, gastrointestinal tract.

Table 3 Genotype and allele frequency of PON1 gene and risk of developing Behcet's disease

Variables	Group I (*n*=40) (*n* [%])	Group II (*n*=40) (*n* [%])	OR	95% CI	*P*
Genotype					
LL	30 (75)	29 (72.5)	1.12	0.4-2.85	0.8 (NS)
LM	8 (20)	9 (22.5)	0.86	0.3-0.78	0.7 (NS)
MM	2 (5)	2 (5)	1	0.13-7.5	1.0 (NS)
Allele					
L	68 (85)	67 (83.75)	1.1	0.46-2.58	0.8 (NS)
M	12 (15)	13 (16.25)	0.9	0.4-2.1	0.8 (NS)

CI, confidence interval; L, leucine; LL, leucine leucine; LM, leucine methionine; M, methionine; MM, methionine methionine; OR, odds ratio.

Table 4 The distribution of *PON1* L55M genotype in Behcet's disease patients according to clinical manifestations

	PON1 L55M genotype (*n* [%])			*P*
	LL	LM	MM	
Control	30 (75)	8 (20)	2 (5)	-
Oral ulcers	29 (72.5)	9 (22.5)	2 (5)	1 (NS)
Genital ulcers	29 (72.5)	9 (22.5)	2 (5)	1 (NS)
Positive pathergy test	8 (66.6)	3 (25)	1 (8.4)	0.66 (NS)
Ocular				
Anterior uveitis	14 (63.6)	7 (31.8)	1 (4.6)	0.9 (NS)
Posterior uveitis	6 (85.7)	1 (14.3)	0 (0)	0.9 (NS)
Articular	5 (71.4)	2 (28.6)	0 (0)	0.9 (NS)
Neuro-Behcet	7 (77.7)	2 (22.3)	0 (0)	0.8 (NS)
Venous thrombosis	10 (100)	0 (0)	0 (0)	0.8 (NS)
Arterial thrombosis	5 (71.4)	2 (28.6)	0 (0)	0.9 (NS)
Renal	0 (0)	1 (100)	0 (0)	0.3 (NS)
Erythema nodosum	2 (50)	1 (25)	1 (25)	0.17 (NS)
Pseudofolliculitis	9 (75)	2 (16.6)	1 (8.4)	0.66 (NS)

L, leucine; LL, leucine leucine; LM, leucine methionine; M, methionine; MM, methionine methionine.

respectively. The frequencies of L allele and M allele were 83.75 and 16.25% in patients with oral ulcers, respectively. The frequencies of L allele and M allele were 83.75 and 16.25% in patients with genital ulcers, respectively. The frequencies of L allele and M allele were 79.2 and 20.8% in patients with positive pathergy test, respectively. The frequencies of L allele and M allele were 83.3 and 16.7% in patients with ocular manifestations, respectively. The frequencies of L allele and M allele were 79.54 and 20.46% in patients with anterior uveitis, respectively. The frequencies of L allele and M allele were 93 and 7% in patients with posterior uveitis, respectively. The frequencies of L allele and M allele were 85.7 and 14.3% in patients with articular manifestations, respectively. The frequencies of L allele and M allele were 88.8 and 11.2% in patients with CNS manifestations, respectively. The frequency of L allele was 100% in patients with venous thrombosis. The frequencies of L allele and M allele were 85.7 and 14.3% in patients with arterial thrombosis, respectively. The frequencies of L allele and M allele were 50 and 50% in patients with renal manifestations, respectively. The frequencies of L allele and M allele were 62.5 and 37.5% in patients with EN, respectively. The frequencies of L allele and M allele were 83.3 and 16.7% in patients with psuedofolliculitis, respectively (Table 5).

Discussion

BD is a chronic systemic vasculitis, characterized by recurrent oral and genital ulcers and uveitis. It also affects many systems, including the heart, lung, CNS, blood vessels, and gastrointestinal tract [8]. The mechanism of atherosclerosis in BD may be due to lipid abnormalities. Peroxidation of lipids and lipoprotein is thought to be important in the pathogenesis of atherosclerosis. Their profiles and relation with atherogenesis were detected in patients with BD [4].

PON1 is an enzyme exclusively located on HDL. It hydrolyzes organophosphate substrates and metabolizes lipid peroxides leading to protection against accumulation of LDL [9]. In the current study, we aimed to study paroxonase 1-L55M gene polymorphisms and its relation to clinical manifestations of BD. Paroxonase 1-L55M gene study was performed using PCR. We examined 40 BD patients (group II). All patients with BD fulfilled the International Study Group Criteria of Behcet's Disease. Forty healthy adults were examined as the control group (group I).

As regards the demographic data of the studied groups, our study showed that there was no significant statistical difference between the studied groups as regards age and sex. BD patients showed male predominance with a male:female ratio of 2.1:1. El-Najjar *et al.* [10] reported that male-to-female

Table 5 Distribution of *PON1* L55M allele frequency in healthy controls and Behcet's disease patients according to clinical manifestations

	PON1 (*n* [%])		*P*	OR (95% CI)
	L allele	M allele		
Control	68 (85)	12 (15)	-	-
Oral ulcers	67 (83.75)	13 (16.25)	0.82 (NS)	1.09 (0.46-2.58)
Genital ulcers	67 (83.75)	13 (16.25)	0.82 (NS)	1.09 (0.46-2.58)
Positive pathergy test	19 (79.2)	5 (20.8)	0.49 (NS)	1.49 (0.46-4.7)
Ocular	45 (83.3)	9 (16.7)	0.79 (NS)	1.13 (0.44-2.9)
Anterior uveitis	35 (79.54)	9 (20.46)	0.44 (NS)	1.5 (0.5-3.7)
Posterior uveitis	13 (93)	1 (7)	0.44 (NS)	0.4 (0.05-3.5)
Articular	12 (85.7)	2 (14.3)	0.92 (NS)	0.9 (0.18-4.7)
Neuro-Behcet	16 (88.8)	2 (11.2)	0.61 (NS)	0.7 (0.14-3.4)
Venous thrombosis	20 (100)	0 (0)	0.16 (NS)	0.13 (0.007-2.3)
Arterial thrombosis	12 (85.7)	2 (14.3)	0.9 (NS)	0.9 (0.18-4.7)
Renal	1 (50)	1 (50)	0.23 (NS)	5.6 (0.3-96.8)
EN	5 (62.5)	3 (37.5)	0.12 (NS)	3.4 (0.7-16.1)
Pseudofolliculitis	20 (83.3)	4 (16.7)	0.84 (NS)	1.13 (0.32-3.9)

CI, confidence interval; EN, erythema nodosum; L, leucine; M, methionine; OR, odds ratio.

ratio was 1.7: 1 in Zagazig, Egypt. Davatchi [11] showed that the male-to-female ratio was 5.37 in Egypt, 0.63 in Korea, 0.98 to 1 in Japan, 1.14 in Iran, 1.78 in Turkey, and 2.45 in Morocco.

According to the distribution of clinical criteria of BD in studied BD patients, this study showed that oral and genital ulcers were predominant features in all patients. Eye lesions were present in 67.5% in the form of anterior (55%) and posterior uveitis (17.5%). Skin lesions were present in 40% in the form of EN (10%) and peudofolliculitis (30%). The Pethargy test was positive in 30%. Vascular involvement was present in 42.5% in the form of arterial and venous thrombosis (17.5 and 25%, respectively). Neuro-Behcet manifestations were present in 22.5%. Articular manifestations were present in 17.5%. Renal affection was present in 2.5%. There was no GIT, cardiac, or pulmonary involvement in studied patients. El-Najjar *et al.* [10] concluded that oral ulcers were present in 84.2%, genital ulcers in 78.2%, ocular involvement in 73.7%, arthritis in 5.3%, arthralgia in 26.3%, neurological involvement in 26.3%, pulmonary manifestations in 26.3%, gastrointestinal manifestations in 10.5%, and cutaneous manifestations in 10.5%; no patient had peripheral vascular disease. Sula *et al.* [12] reported that the prevalence of BD manifestations was as follows: oral ulcer, 100%; genital ulcers, 94%; pathergy positivity, 75%; erythema nodosum, 43.2%; papulopustular lesions, 74.2%; and vascular involvement, 6.8%. Systemic involvement was present in the form of articular involvement in 79.5%, ocular involvement in 28.8%, pulmonary involvement in 2.3%, vascular involvement in 9.8%, neurologic involvement in 2.3%, and genitourinary system involvement in 0.8%. Calamia *et al.* [13] showed that dermatologic lesions included oral ulcers (100%), genital ulcers (62%), erythema nodosum (46%), and papulopustular lesions (54%). Ocular lesions were present in eight patients, vascular complications in three patients, and CNS involvement was present in only three participants, in the study on 13 participants. Alpsoy *et al.* [14] revealed that oral ulcers were the most common manifestation (100%), and other manifestations were present as follows: genital ulcers, 85.3%; erythema nodosum, 44.2%; papulopustular lesions, 55.4%; skin pathergy reaction, 37.8%; joint involvement, 29.2%; and ocular articular, 33.4%.

There was no significant statistical difference between the studied groups as regards genotype and allele frequency of *PON1*. *PON 1* LL genotype was present in 75% in the control group and in 72.5% in the case group. LM genotype was present in 20% in the control group and 22.5% in the case group. MM genotype was present in 5% in both groups. The frequencies of L and M alleles were 85 and 15% in cases and 83.75 and 16.25% in controls, respectively. According to these results, *PON1* L55M gene polymorphism is not associated with increased risk for BD. In contrast Dursun *et al.* [4] revealed that the frequencies of L and M alleles were 75.0 and 25.0% in cases and 87.0 and 13.0% in controls, respectively, and the relative risk for BD patients was more than 2.23 times higher in individuals with the *PON*55 M allele.

There was no significant statistical difference in allele frequencies and clinical manifestations of BD, but Dursun *et al.* [4] showed that the frequency of the *PON*55 M allele in the ocular, articular, and CNS manifestations of BD patients was higher in comparison with that of the control group and the statistical difference was significant. Moreover, the M allele was associated with greater than 3.5-fold increased relative risk for ocular, 3.1-fold for CNS, and 2.4-fold articular manifestation of BD. This difference

may be due to genetic differences between Egyptian and Turkish.

Conclusion

PON1 L55M gene polymorphism is not associated with increased risk for BD or its clinical manifestations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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