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MEFV gene is a probable susceptibility gene for Behçet's disease

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Objective: Behçet's disease (BD) is a rare, chronic, multisystem inflammatory disorder. The prevalence of BD is higher in the Middle Eastern and Mediterranean populations. Another chronic inflammatory disease, familial Mediterranean fever (FMF), is also known to be highly prevalent in these populations. The prevalence of BD is higher in the FMF patient population than in populations known to be rich in BD . Both BD and FMF have some pathophysiological features in common and they result from inappropriate activation of neutrophils. Clinical manifestations of both diseases can mimic each other and the coexistence of both diseases in the same patient has been reported. Given that BD and FMF have similar pathophysiological, epidemiological, and clinical features, we hypothesized that the gene responsible for FMF, *MEFV*, may also play a role in the pathogenesis of BD.
Methods: Forty-two BD patients who had no symptoms and family history for FMF and 66 healthy controls were screened for common *MEFV* gene mutations (E148Q, M680I, M694V, and V726A).
Results: Fifteen patients (36%) displayed *MEFV* mutations (nine M694V, five E148Q, and one M680I) and mutation rates were significantly elevated compared to 66 (11%) healthy controls ($p=0.0034$).
Conclusion: The occurrence of frequent *MEFV* mutations in BD patients suggests that the *MEFV* gene is involved in the pathogenesis of Behçet's disease.

Behçet's disease (BD) is a recurrent inflammatory condition characterized by oral and genital ulceration, uveitis, skin lesions, increased risk of developing thrombosis, and central nervous system involvement. Familial Mediterranean fever (FMF) is an autosomal recessive and is also known as an autoinflammatory disease characterized by recurrent episodes of apparently unprovoked inflammation. However, unlike other autoimmune disorders, FMF lacks the production of high-titre autoantibodies or antigen-specific T-cells (1). Both BD and FMF are known to be highly prevalent in Middle Eastern and Mediterranean populations (2, 3). The gene responsible for FMF, designated *MEFV*, was identified in 1997 by positional cloning (4). *MEFV* encodes a 781 amino acid protein, pyrin, that is predominantly expressed in polymorphonuclear leukocytes (PMNs) and cytokine-activated monocytes (5). Pyrin consists of four functional domains, a B-box zinc-finger domain, a coiled-coil domain, a C-terminal B30.2 domain, and a 92 amino acid N-terminal PYRIN domain that is shared by a number of other proteins involved in apoptosis and inflammation (6). The antiinflammatory role of pyrin is further evidenced by identification of mutations in CD2 binding protein 1 (CD2BP1) and its interaction with pyrin (7).

In BD, the underlying pathology is believed to be vasculitis with immune complex deposition. This inflammation may relate to other autoinflammatory conditions and their suggested mechanisms. BD is not a Mendelian disorder; however, considering its occasional familial presentation and its close association with genes of major histocompatibility complexes, BD is under some sort of genetic control (8).

Therefore, this study was designed to investigate whether there is any correlation between BD and pyrin gene mutations.

Material and methods

Forty-two patients with BD and 66 controls who were all Turkish were included in this study. Patients with BD were clinically and serologically diagnosed by the Department of Dermatology, Gulhane Military Medical Academy, and all fulfilled three or more International Study Group (ISG) criteria for BD (9). They were not symptomatic for FMF and did not have a family history of FMF. Eleven out of 42 patients were female and the mean age of the patients was 32 years. The 66 controls were all healthy and had no symptoms for either FMF or BD.

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Fourteen of the 66 controls were female and the mean age of the controls was 34 years. Informed consent was obtained from all patients and controls that participated in this study.

Blood samples from patients and controls were taken at the Medical Genetics Department, Gulhane Military Medical Academy. DNA extraction was undertaken using the QIAamp® DNA Mini Kit (QIAGEN Cat. No. 51306) according to the manufacturer's instructions. Four pyrin gene mutations (E148Q, M680I, M694V, and V726A) were detected from patients and controls by using the PRONTO™ FMF Basic Kit (Sayvon Diagnostic Ltd. Cat. No. 9904) according to the manufacturer's instructions.

Allele frequencies were compared with the χ^2-test and Fisher's exact χ^2-test (SPSS for Windows 11.0). Significance was assigned to p values < 0.05.

Results

Pyrin gene mutations were found in 15 (three female and 12 male) patients and seven (two female and five male) controls (36% and 11%, respectively). Mutation V726A was not found in any of the groups. In the patients with BD, nine out of 42 (21%) had an M694V mutation (three homozygotes), five (12%) had an E148Q mutation and one (2%) had an M680I mutation. In the control group, four out of 66 (6%) had an M694V mutation, one (2%) had an E148Q mutation and two (3%) had M680I mutation (Table 1). The difference in mutation frequency for the pyrin gene between the patient group and the control group was statistically significant (p=0.0034). When distribution was compared between patients and controls, the frequency of the M694V mutation was significantly higher in the patient group than the controls (p=0.0367). In addition, mutation E148Q frequency was also significantly higher in the patient group than the controls (p=0.0321). The frequency of the M680I mutation was not statistically significant.

Table 1. Distribution and p value of mutations in control and patient groups. p values were calculated by the χ^2-test and Fisher's exact χ^2-test (SPSS for Windows 11.0).

	Patient group	Control group	p value
Mutation frequency	15/27	7/59	0.0034
M694V	9(3*)/33	4/62	0.0367
E148Q	5/37	1/65	0.0321
M680I	1/41	2/64	0.9999

*Homozygous.

Discussion

BD is a chronic, inflammatory, multisystemic disorder with unknown aetiology. Because the pathognomonic clinical features and tools are absent, the diagnosis of BD relies mainly on its characteristic clinical features and the judgement of the experienced physician. Recent advances in molecular genetics and identification of disease genes have made it possible to correlate disease pathogenesis with genotype.

Studies concerning the relationship between autoinflammatory disease and suspected genes may help to explain the pathogenesis. An autoinflammatory disease characterized by recurrent episodes of apparently unprovoked inflammation, but unlike other autoimmune disorders, lacks the production of high-titre autoantibodies or antigen-specific T-cells, may have a different inflammatory mechanism. The gene pyrin is predominantly expressed in PMNs and cytokine-activated monocytes (5). Recent advances showed that pyrin consists of four functional domains (the PYRIN domain, a B-box zinc-finger domain, a coiled-coil domain, and a C-terminal B30.2 domain), and the PYRIN domain is shared by a number of proteins involved in apoptosis and inflammation and is a member of the six-helix bundle, death-domain super family that includes death domains, death effector domains, and caspase recruitment domains (CARDs) (10). Like other members of this super family, the PYRIN domain appears to allow for the interaction, or assembly, of macromolecular complexes by PYRIN–PYRIN interactions (11, 12). The antiinflammatory role of pyrin has been further evidenced by the identification of mutations in CD2BP1 (also referred to as proline, serine, threonine phosphatase interacting protein, PSTPIP1) (7). Mutations in CD2BP1 result in the autosomal dominant PAPA syndrome, which is characterized by severe, destructive, early-onset inflammation of the joints, skin, and muscle (8, 13). In addition, mutations in another pyrin-related protein, cryopyrin, are associated with Muckle–Wells/familial cold urticaria and chronic infantile neurological cutaneous and articular syndrome (14).

Touitou et al have previously investigated the relationship between the *MEFV* gene and BD (15). In their study, 15 of 38 patients with BD were from ancestry with a high risk for FMF disease and three mutations on the pyrin gene (M694V, V726A, and E148Q) were detected in the patient group with a frequency of 2.6%, 2.6%, and 5.2%, respectively. In comparison to this study, frequencies in our findings are much higher. This could be explained by the differences in patient population and methodology chosen in the two studies. In addition, two other studies concerning BD and the *MEVF* gene mutation reported a clinical and genetic correlation (16, 17). Atagunduz et al also reported that 26% of BD

patients were found to carry one single *MEFV* mutation, compared to 9.1% in the control group (17).

We propose that *MEFV* gene mutations have a role in inflammation in general and could be an additional susceptibility genetic factor in BD. In our study, four mutations (E148Q, M680I, M694V, and V726A) were screened and the statistical findings may be further supported by sequencing all coding regions of the pyrin gene for newer mutations, especially the PYRIN domain, which is located at the second to 92nd amino acids of the pyrin gene.

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