Association of MEFV mutations and vascular involvement in Behçet’s disease: a study from Hatay, Turkey

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Abstract

Introduction: In this study, we aimed to determine the frequency of MEFV mutations in Behçet’s disease (BD) and to investigate the relationship between clinical findings of the disease and the MEFV mutations.

Material and methods: A total of 66 participants (30 BD patients, 36 healthy subjects) were included in this study. The MEFV gene was analyzed by using DNA sequence analysis.

Results: The distribution of MEFV mutations was not significantly different between the patients and the control group (p = 0.373). However, individuals with R202Q mutation had a risk of OR 4 times (95% CI: 1.1–14.5) higher than those without the mutation (p = 0.035). The rate of vascular involvement was statistically significantly higher in patients with the mutation than in patients without the mutation (p = 0.005).

Conclusions: MEFV mutation was associated with vascular involvement in patients with BD. This is also the first study to indicate that the R202Q mutation may have a role in BD. However large series from different regions are required to compare these results.

Key words: vascular, Behçet’s disease, MEFV mutation.

Introduction

Behçet’s disease (BD) is a multi-system variable vasculitis, and the disease is common in regions along the ancient Silk Road, extending from Japan to the Mediterranean countries. Increasing prevalence of the disease along the Silk Road, familial aggregation, and association with genes within and outside the major histocompatibility complex (MHC) region are the main evidence of the genetic influence and a complex inheritance pattern of the disease [1].

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterized by self-limiting serositis and fever attacks, and the disease is caused by the mutations in the Mediterranean fever (MEFV) gene. The disease is mainly found in people of Mediterranean descent and especially in certain ethnic groups such as Jews, Turks, Armenians, and Arabs [2]. The carrier rate of MEFV mutations has been reported as 20% in the Turkish population [3].

The relationship between FMF and BD has been described and both diseases include recurrent febrile attacks, abdominal and arthritic findings due to serosity [4, 5]. Clinical similarity of these two diseases may reflect different manifestations of a common disease spectrum [6].

In this study, we aimed to determine the frequency of MEFV mutations in BD in the Hatay region located in the south of Turkey and to investigate the relationship between clinical findings of the disease and the MEFV mutations.
Material and methods

A total of 66 participants (30 patients, 36 healthy subjects) were included in this prospective study. Patients and healthy subjects at least 18 years old participated in the study. All patients fulfilled the diagnostic criteria of the International Study Group for BD [7].

Disease duration was defined as duration since diagnosis of BD. Genomic DNA was isolated from the whole blood sample with EDTA using the isolation High Pure PCR template preparation kit. Exons 2, 3, 5, and exon 10 of the MEFV gene were analyzed by using DNA sequence analysis.

The mean ages of the patient and control groups were analyzed by Student’s t-test. The relationship of variables at the categorical measurement level was examined using the Fisher’s exact test and χ² test and 2 × 2 odds ratio coefficients.

The software SPSS for Windows version 24.0 was used for statistical analysis and p < 0.05 was considered as statistically significant.

Bioethical standards

The study was approved by the Ethics Committee of Mustafa Kemal University Faculty of Medicine (approval number 2019/35). The informed consent was obtained from all studied patients.

Results

Thirty patients with BD were included in the study: 25 male (83.3%), 5 female (16.7%), mean age 41.03 ±10.48 years, range 19–61. The disease duration was 8.56 ±8.25 years (range 0.04–30). Thirty-six gender- and age-matched healthy subjects: 28 male (77.8%), 8 female (22.2%), mean age 41.17 ±9.31 years, range 19–61, served as controls. While HLA-B*51 positivity was 56.66% (n = 17; 16 male, 1 female) in patients with BD, it was 11.1% (n = 4; 2 male, 2 female) in the control group (p < 0.001). MEFV mutations were present in 50% (n = 15) of the patients with BD and 38.9% (n = 14) of the healthy controls (p = 0.365).

MEFV mutations of the patients were as follows: R202Q (66.7%, n = 10), E148Q (6.7%, n = 1), V726A (6.7%, n = 1), E148Q/V726A (6.7%, n = 1), R202Q/M694V (6.7%, n = 1), and P369S (6.7%, n = 1). Only one of these patients had in the homozygous genotype of R202Q.

MEFV mutations of the control group were as follows: E148Q (28.6%, n = 4), R202Q (28.6%, n = 4), R202Q/P369S (7.1%, n = 1), E148Q/R202Q/P369S (7.1%, n = 1), R202Q/M694V (7.1%, n = 1), M694I (7.1%, n = 1), P369S (7.1%, n = 1), and V726A (7.1%, n = 1).

The distribution of MEFV mutations was not significantly different between the patients and the control group (p = 0.373). However, according to the odds ratio calculation, it was found that individuals with R202Q mutation had a risk of OR 4 times (95% CI: 1.10–14.50) higher than those without the mutation (p = 0.035).

Table I shows the distribution of FMF-related MEFV mutations in the patients with BD and the control subjects.

Table I. MEFV mutation distribution of the patients and the control group

| Parameters         | Patients [n (%)] | Controls [n (%)] | p-value* (OR; CI 95%) | p-value** |
|--------------------|-----------------|-----------------|----------------------|-----------|
| R202Q              | 10 (66.7)       | 4 (28.6)        | **0.035 (4; 1.10–14.50)** |           |
| E148Q              | 1 (6.7)         | 4 (28.6)        | 0.261 (0.28; 0.03–2.62) |           |
| P369S              | 1 (6.7)         | 1 (7.1)         | 0.895 (1.21; 0.07–20.15) |           |
| R202Q/M694V        | 1 (6.7)         | 1 (7.1)         | 0.895 (1.21; 0.07–20.15) |           |
| V726A              | 1 (6.7)         | 1 (7.1)         | 0.895 (1.21; 0.07–20.15) |           |
| R202Q/P369S        | 0 (0)           | 1 (7.1)         | 0.566 (0.39; 0.02–9.88)  |           |
| E148Q/R202Q/P369S  | 0 (0)           | 1 (7.1)         | 0.566 (0.39; 0.02–9.88)  |           |
| E148Q/V726A        | 1 (6.7)         | 0 (0)           | 0.428 (3.72; 0.15–94.52) |           |
| M694I              | 0 (0)           | 1 (7.1)         | 0.566 (0.39; 0.02–9.88)  |           |
| Total              | 30 (50)         | 36 (38.9)       | **0.373**             |           |

* p-value was obtained from 2 × 2 odds ratio, ** p-value was obtained from Fisher’s exact test and χ² test.
CI – confidence interval, OR – odds ratio.
significantly higher in patients with a mutation (53.3%) was statistically significantly higher compared that in patients without mutation (6.7%; \( p = 0.005 \)).

All patients with vascular involvement (\( n = 9 \)) were male and one of them had deep vein thrombosis, one of them had deep vein thrombosis and pulmonary embolism, and the others had superficial thrombophlebitis.

The incidence of arthritis in patients with mutation (13.3%) was found to be statistically significantly lower than that in patients without mutation (53.3%) \( (p = 0.020) \). No statistically significant relationship was found between the clinical findings of patients with mutations and HLA-B*51 \( (p > 0.05) \).

Table II shows the presence of MEFV mutation and HLA-B*51 positivity according to the clinical characteristics of the disease.

### Discussion

The prevalence and distribution of MEFV mutations in the control subjects were not significantly different from those in patients with BD in our study. However, the most common mutation in BD was R202Q and the individuals with R202Q mutation were found to have a higher risk than those without mutation.

Imirzalioglu et al. [8] performed MEFV mutation analysis in BD and detected it in 36% of the patients. In several other studies conducted in Turkish population, it was reported that M694V was detected as a dominant mutation [9, 10]. In the study conducted by Baruch et al. [11], MEFV mutations were analyzed and it was reported that there was no difference in the frequency and distribution in the mutated alleles between the patient and control groups.

Ben-Chetrit et al. [12] reported the MEFV mutation carrier rate as 1 : 3.2 in a study conducted on BD patients, consisting of Palestinian Arabs and Jews. Various results have been reported in terms of the frequency and distribution of MEFV mutations in BD patients, including the studies mentioned above and our study, which may be the consequence of regional and racial differences. In addition, the difference of our study from other studies is that, to the best of our knowledge, R202Q mutation has not been analyzed in BD patients before and we have identified R202Q mutation carriage as a risk factor for BD. There are no data to compare these results, as the R202Q mutation has not been analyzed in BD before.

Vascular involvement was statistically significantly higher in patients with a mutation than in patients without a mutation in our study. In addition, the incidence of arthritis was statistically significantly lower in the patients with a mutation than the patients without a mutation. MEFV mutation was detected in 64.7% of HLA-B*51 positive patients in our study. Burillo-Sanz et al. [13] reported that there is an epistatic interaction between B51 and MEFV and suggested that the association of MEFV with BD could be modulated by the HLA molecules.

### Conclusions

Vascular involvement is observed more frequently in patients with MEFV mutation and these patients may need to be followed more carefully. MEFV mutations were also found in half of the BD patients.

However, in order to reach a more definite conclusion, studies with participation of larger groups of patients are required in regions where BD is common.
The authors declare no conflict of interest.
This work was supported by the Scientific Research Project Fund of Mustafa Kemal University Faculty of Medicine under the project number 19.M.031.

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