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Original Article

The importance of Mediterranean fever gene in familial Mediterranean fever

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Abstract

Objective: Familial Mediterranean fever (FMF) is the most common autoinflammatory disease characterized by recurrent serositis attacks and fever. The discovery of the Mediterranean fever (*MEFV*) gene has been a milestone in FMF etiopathogenesis. Our knowledge about the relationship between the *MEFV* gene and FMF phenotype increases each day. This study aims to investigate the relationship between *MEFV* gene mutations and the FMF clinical findings of a single-center FMF cohort.

Methods: Gender, age, age at symptom onset, age at diagnosis, clinical characteristics, and *MEFV* gene analysis of the patients were recorded.

Results: A total of 837 FMF patients were included in this study. There were 515 females and 322 males. The age at symptom onset was 18.3±10.9 years, while the age at diagnosis was 24.4±10.9 years. The most common symptom that accompanied fever was peritonitis (91.1%), while the other common clinical findings were pleuritis (45%), myalgia (44%), and arthritis (36%). A total of 47 patients developed amyloidosis. A total of 553 (66%) FMF patients had M694V mutation, 221 (26%) of which were homozygous, while 332 (40%) were heterozygous. Exon 10 mutation frequency was 759 (91%), while the non-exon 10 mutation frequency was 78 (9%). There was no wild type among the patients.

Conclusion: In conclusion, the fact that a vast majority of the disease burden was constituted by the exon 10, especially M694V mutations and that none of the 837 patients from our cohort had a wild-type FMF proved the significance of *MEFV* gene mutation analysis. Therefore, we speculate that it is necessary to examine the *MEFV* gene mutations in each FMF suspected case. It seems plausible to re-evaluate the FMF diagnosis for cases in which a wild type *MEFV* gene mutation occurs.

Keywords: Familial Mediterranean fever, genes, genotype, phenotype

Introduction

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease characterized by recurrent serositis attacks accompanied by fever (1, 2). Attacks are self-limiting, usually last 12-96 hours, and have the following clinical symptoms: abdominal pain; joint pain; chest pain; myalgia; and skin rash, which typically presents on the dorsum of the feet (3, 4). FMF is a monogenic disease that frequently affects individuals of Eastern Mediterranean origin (Turks, Arabs, Armenians, and Jews) (1). Clinical characteristics, duration of the attacks, and severity of the disease may differ among ethnic groups (5).

Heller et al. (6) first described the detailed manifestation of the FMF in 1955. The discovery of colchicine in 1972 was a revolutionary step in FMF treatment (7). The discovery of the Mediterranean fever (*MEFV*) gene localized in the short arm of the 16th chromosome (16p13.3) in 1997 was the milestone for understanding the etiopathogenesis of the disease (8, 9). The *MEFV* gene encodes the protein called "pyrin" (marenostrin), which consists of 781 amino acids and is responsible for FMF (8, 9). Pyrin is a component of the nucleotide-binding oligomerization domain-containing-like receptor family pyrin domain-containing 3 inflammasome complex and is released from mononuclear cells. It leads to interleukin (IL)-1β expression and the activation of caspase-1 that is responsible for the onset of inflammation (10). Pyrin, which is mutated in FMF, leads to an uncontrolled expression of IL-1β and, thus, to an exaggerated inflammatory response (11). Specific microtubule combination inhibitors used in FMF therapy prevent pyrin-induced caspase-1 activation in mononuclear cells and, thus, IL-1 secretion (12).

After the *MEFV* gene was identified, it was found that not all mutations in the *MEFV* gene cause an FMF phenotype of the same severity (13). It was observed that especially the M694V mutation in exon 10 leads to more severe manifestations; more frequent colchicine resistance; and FMF-related complications such as amyloidosis, arthritis, erysipelas-like erythema (EBE), sacroiliitis, and so on (14, 15). In contrast, there is still

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no consensus about the clinical significance of variants other than M694V, M694I, M680I, and V726A mutations that constitute the main burden of FMF etiopathogenesis (16). The fact that the decreased frequency of wild-type FMF prevalence in recent studies and including the *MEFV* mutations in recently developed diagnosis criteria raised questions about the wild-type FMF (17,18).

Increased knowledge about the relationship between FMF and *MEFV* gene has inevitable consequences for the clinic. Therefore, further studies investigating the contribution of the *MEFV* gene to the FMF clinical findings are required. In this study, we aimed to investigate the relationship between FMF and *MEFV* gene mutations in our cohort from a single center.

Methods

FMF patients admitted to our rheumatology department between February 1, 2013, and December 31, 2019, were included in this study. Livneh and Tel-Hashomer classification criteria were used as diagnostic criteria. The Ethical Committee of Ondokuz Mayıs University approved this study (Approval Number: 2020/353). All the patients' data were collected from our hospital's database. Gender, age, age at symptom onset, age at diagnosis, comorbidities, family history, symptom causes, clinical symptoms (such as fever, peritonitis, pleuritis, pericarditis, arthritis, myalgia, EBE, vasculitis, and amyloidosis), *MEFV* gene analysis, laboratory results, and treatments of the patients were recorded.

Statistical analysis

Statistical analyses were performed with IBM Statistical Package for the Social Sciences software version 21.0 (IBM SPSS Corp.; Armonk, NY, USA). Mean value, standard deviation, and percentages were calculated for each clinical findings as descriptive statistics. The Spearman Chi-square test was used for the evaluation of categorical data, while the Student-t test was used for binary comparisons of linear data. The statistically significant threshold was $p<0.05$.

Main Points

- Vast majority of the disease burden was constituted by exon 10, especially M694V mutations.
- The procedure of FMF diagnosis should include *MEFV* gene mutations.
- The presence of wild-type FMF should be questioned.

Results

This study included 837 FMF patients. Demographics and clinical characteristics of patients were presented in Table 1. There were 515 females and 322 males. The age at symptom onset was 18.3±10.9 years, while the age at diagnosis was 24.4±10.9 years. The most common symptom that accompanied fever was peritonitis (91.1%), while the other common clinical symptoms were pleuritis (45%), myalgia (44%), and arthritis (36%). We detected that 47 patients developed amyloidosis. Ten patients had a vasculitis diagnosis along with FMF.

A total of 63 patients were receiving anti-IL-1 treatment, 46 patients were using anakinra, and 17 patients were receiving canakinumab treatment. Anti-IL-1 treatment was initiated in 32 patients because of unresponsiveness to colchicine, in 17 patients because of amyloidosis, in 9 patients because of elevated liver enzymes, and in 5 patients because of diarrhea. Menstruation triggers the FMF attacks in 45 patients, while exposure to cold in 10 patients, and working out in 6 patients.

The genetic results of the patients can be found in Table 2. M694V mutation was present in 553 (66%) FMF patients, 221 (26%) of which were homozygous and 332 (40%) were heterozygous. The exon 10 mutation frequency was 759 (91%), while the non-exon 10 mutation frequency was 78 (9%). No wild type was detected in this study.

The acute phase values of the patients were significantly decreased compared with pre-treatment (Table 3). Of liver enzymes, alanine aminotransferase level increased after treatment. None of the patients had elevated muscle enzymes after colchicine treatment. Besides, patients did not develop leukopenia, which requires the termination of drug therapy.

Table 1. Demographic and clinical features of familial Mediterranean fever patients.

Clinical Feature	Result
Age (year)	33.2±12.5
Gender (F/M)	515/322
Age at onset of symptoms (year)	18.3±10.9
Age at diagnosis (year)	24.0±13.8
Family history (n)	478
Fever (n)	820
Peritonitis (n)	763
Pleuritis (n)	375
Pericarditis (n)	69
Arthritis (n)	303
Erysipelas-like erythema (n)	88
Myalgia (n)	365

F: female; M: male.

Discussion

In this study, we investigated the clinical and laboratory characteristics of FMF patients from a single center. 62% of 837 patients were females, and their age at diagnosis was 24. Peritonitis (91%) was the most common symptom in FMF attacks, while the rates of incidence for pleuritis and arthritis were 45% and 36%, respectively. Exon 10 mutations were present in 91% of FMF patients, among which M694V (66%) mutation was the most common cause for FMF. Non-exon 10 mutations were only present in approximately 9% of patients. In

Table 2. *MEFV* gene mutations of familial Mediterranean fever patients.

Clinical Feature	Result
With Exon 10 Mutations	
M694V homozygous	221
M694V heterozygous	172
M694V heterozygous, M680I heterozygous	98
M694V heterozygous, V726A heterozygous	31
M694V heterozygous, E148Q heterozygous	31
M680I homozygous	88
M680I heterozygous	42
M680I heterozygous, V726A heterozygous	34
M680I heterozygous, E148Q heterozygous	13
M694I heterozygous	3
V726A heterozygous	26
Without Exon 10 Mutations	
E148Q homozygous	21
E148Q heterozygous, P369S heterozygous, R408C heterozygous	12
R202Q homozygous	4
R202Q heterozygous	30
P369S heterozygous	8
A744S heterozygous	3

Table 3. Pretreatment and current laboratory data in familial Mediterranean fever patients.

Parameter	Before treatment	Actual	p
Sedimentation (mm/h)	36±23	17±15	<0.001
C-reactive protein (mg/L)	29±43	5±11	<0.001
Fibrinogen (mg/dL)	4.4±1.6	3.3±2.4	<0.001
AST (U/L)	21±17	22±13	0.338
ALT (U/L)	21±23	23±19	0.017
Proteinuria (mg/day)	73±410	69±500	0.782

AST: alanine aminotransferase; ALT: aspartate aminotransferase.

contrast, none of the 837 patients from our cohort had a wild type. In 63 patients, anti-IL-1 therapy was initiated owing to colchicine resistance or intolerance.

Sohar et al. (4) examined the 470 FMF cases and found that 60% of the disease started in the first decade and 90% in the first 2 decades. This study is still used as a reference in important medical sources. Tunca et al. (19) examined 2,838 cases and found that the age at diagnosis was 9.6 years. We found that the age at diagnosis for FMF was 24.0 years, which contradicts the previous results. In contrast, a recent study carried out in Turkey with 979 FMF patients found that the age at diagnosis was 28 years (20). Furthermore, another multicenter *MEFV* gene mutation study involving 1,719 cases found that the age at diagnosis for FMF was 26.6 years (17). A study from Japan showed that the age at the disease onset was equal to or more than 28 years for 205 out of a 395 FMF patients (21). Although recent studies support our findings, younger age at diagnosis reported by previous studies can be explained by the inclusion of *MEFV* gene mutation analysis in FMF diagnosis procedures, increased awareness about the effect of *MEFV* gene mutation on the etiopathogenesis of FMF, and diagnosis of patients with late-onset and mild clinical findings.

In our cohort of 837 FMF cases, there were no wild-type patients. Yaşar Bilge et al. (17) carried out a multicenter genetic analysis of 1,719 cases and found that 46% were wild-type patients, while Sag et al. (18) reported 5% for the wild-type FMF. Including only genetically confirmed patients into a 2,000-case study, where the comorbidity of FMF patients was investigated in Turkey (22), predicts the significance of the positivity of *MEFV* gene mutation in the diagnosis and clinical findings of the disease.

In this study, 66% of FMF patients had M694V mutation, and 91% had an exon 10 mutation. Similarly, exon 10 mutations were responsible for 89.4% of all FMF patients in the work of Sag et al. (18). These results show that the exon 10 mutation in the *MEFV* gene is the greatest contributor to the FMF phenotype formation. Moreover, Balcı-Peynircioğlu et al. (22) found that the comorbidities were mostly seen in those who have an M694V mutation located in exon 10. In our study, the fact that exon 10 and M694V mutations constitute the majority of the genetic burden emphasizes the significance of exon 10 and M694V mutations for the FMF (23).

As a result, the data of 837 FMF patients from our cohort revealed the significance of *MEFV* gene. We claim that older FMF diagnosis age found in the present and other recent studies, when compared with previous studies, is due to the contribution of *MEFV* gene analysis to the diagnosis stage. Thus, FMF patients who have an older age of disease onset and milder clinical findings can be diagnosed. Moreover, current studies and our study show that exon 10 mutations make the biggest contribution to the formation of FMF clinical findings. These results suggest that *MEFV* gene mutations should be examined in each patient suspected with FMF, and that the FMF diagnosis should be re-evaluated in cases where *MEFV* gene mutation was not present.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethical Committee of Ondokuz Mayıs University (Approval Number: 2020/353).

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