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ORIGINAL ARTICLE

Clinical and Demographic Evaluation According to MEFV Genes in Patients with Familial Mediterranean Fever

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Abstract

The present study examined the relationship between clinical findings and mutation analyses in children with Familial Mediterranean Fever (FMF) in the inner Black Sea region of Turkey. This retrospective, cross-sectional study included patients with FMF who were evaluated between 2007 and 2015. FMF was diagnosed according to the Tel Hashomer criteria. FMF mutations were analyzed using a Real-time PCR System (Roche Diagnostics, Mannheim, Germany), and patients were classified into three groups according to allele status. The most common symptom was abdominal pain (99%, $n=197$). The most frequent mutations were M694V and R202Q. Chest pain was reported more often in patients homozygous for M694V (61.4%). Although fever, abdominal pain, and arthritis were more commonly observed with the M694V mutation, chest pain was the most common symptom in R202Q carriers ($n=10$, 32.3%). Proteinuria was observed in 42 (21.2%) patients, frequently accompanied by the M694V mutation (28.6%). The most common mutations in children with FMF in Turkey were M694V and R202Q. Recurrent abdominal pain and arthritis/arthralgia were commonly observed in patients with M694V and R202Q mutations. Moreover, chest pain was commonly seen with the R202Q mutation. Thus, R202Q might be a disease-causing mutation in FMF patients.

Keywords Clinical features · Familial Mediterranean Fever · MEFV gene · R202Q

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Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammtory disease characterized by self-limiting recurrent short-term attacks of fever and serosal inflammation (Bakkaloglu 2003). Although it is observed around the world, FMF is more common among Turkish, Armenian, Arabic, and Sephardic Jewish peoples residing in the eastern Mediterranean zone (Ben-Chetrit and Levy 1998). In Turkey, the estimated prevalence of FMF is 1/1000, and the carrier rate is approximately 1:5 (Tunca et al. 2005). Clinical manifestations or symptoms of FMF usually begin during the first decade of life (Berkun et al. 2012); therefore, FMF is usually diagnosed in childhood.

The primary signs and symptoms of the disease in many patients are fever, abdominal pain, chest pain, and arthritis/arthralgia. Serum amyloid A (SAA), an acute-phase reactant produced in the liver, is quite elevated, especially during attacks. The diagnosis of FMF relies on clinical criteria; Tel Hashomer criteria are widely used for this purpose (Livneh et al. 1997). Genetic analyses may support the clinical diagnosis in suspicious cases (Shohat and Halpern 2011).

The Mediterranean fever (MEFV) gene, which is responsible for FMF, is located on chromosome 16p13.3. This gene has ten exons and encodes the pyrin protein, which regulates neutrophil activity. The most common mutations have been identified in exons 2 and 10 (Aksentijevich et al. 1997). A total of 314 gene mutations have thus far been identified in the MEFV gene. The most common mutations, located in exon 10 of the MEFV gene, are M694V, M680I, E148Q, V726A, and M694I; these account for 85% of disease cases (The International F. M. F. C. 1997, Yalcinkaya et al. 2000, Touitou 2001). These mutations are seen at different frequencies among the affected ethnic groups and in the population at large (Caglayan et al. 2010). Many studies have been conducted in recent years investigating the effects of MEFV gene mutations on clinical findings.

In this study, we investigated the relationship between genetic mutations accompanying symptoms and clinical findings in 199 pediatric patients who were admitted with complaints of recurrent fever, abdominal pain, and arthritis/arthralgia and who were diagnosed with FMF. In addition, the relationship between proteinuria rate and genetic mutations, as well as the effect of colchicine treatment on SAA, were investigated.

Methods

This study was conducted as a retrospective, cross-sectional study. The data were transferred from the file records of 199 FMF patients who were followed between January 2009 and December 2015 in the Department of Pediatrics at Gaziosmanpaşa University Faculty of Medicine. All of the patients were of Turkish origin, from the inner Black Sea region of Turkey. Only one individual from each family was included in the study. All patients with FMF were under treatment with colchicines.

The clinical and demographic data of the patients (e.g., fever, abdominal pain, arthritis, erysipelas-like rash, family history, age at disease onset, and age at diagnosis) were obtained from patient files and individual interviews with the patients' parents. FMF was diagnosed according to the Tel Hashomer criteria, and mutations in the MEFV gene were identified (Shohat and Halpern 2011). Using the Tel Hashomer criteria, two major criteria or one major and two minor criteria are required for a definitive diagnosis, and one major and one minor criteria for a likely diagnosis (Table 1). The severity of the disease was determined according to previously published criteria (Pras et al. 1998). MEFV gene analysis was performed on all patients; the results are summarized in Table 2. Patients were divided into three groups based on MEFV genotypes: homozygous, compound heterozygous, and heterozygous.

Gene/mutation Analysis

Blood specimens were drawn into EDTA-containing tubes, and genomic DNA samples were extracted from the peripheral leukocytes of the collected venous blood using a High Pure PCR Template Preparation Kit (Roche Molecular Biochemicals, Mannheim, Germany) according to the manufacturer's instructions. For MEFV single nucleotide polymorphisms (SNPs), genotyping was performed using commercial kits (TIB MOLBIOL GmbH, Berlin, Germany) and the LightCycler 480 II Real-Time PCR System (Roche Diagnostics, Mannheim, Germany) according to the manufacturers' protocols.

Investigated mutations included p.E148Q (c.442G>C) and p.R202Q (c.605G>A) in exon 2; p.P369S (c.1105C>T) in exon 3; p.F479L (c.1437C>G) in exon 5; and p.M680I (c.2040G>C), p.M680I (c.2040G>A), I692del (c.2076>2078del), p.M694V (c.2080A>G), p.M694I (c.2082G>A), p.K695R (c.2084A>G), p.V726A (c.2177T>C), p.A744S (c.2230G>T), and p.R761H (c.2282G>A) in exon 10.

Table 1 Tel-Hashomer diagnosis criteria for FMF

Major criteria:
1. Recurrent febrile episodes accompanied by peritonitis, pleuritis or synovitis
2. Amyloidosis of AA-type without a predisposing disease
3. Favorable response to colchicine therapy
Minor criteria:
4. Recurrent febrile episodes
5. Erysipelas-like erythema
6. Familial Mediterranean Fever in first degree relative
Definitive diagnosis: 2 major or 1 major and 2 minor
Probable diadnosis:1 major and 1 minor

Table 2 Genotype distribution of the patients

	n (%)
M694V	46 (23)
R202Q	26 (13)
E148Q	17 (8.5)
V726A	6 (3)
M680I	6 (3)
K695R	3 (1.5)
A744S	3 (1.5)
P369S	1 (0,5)
R761H	1 (0.5)
M694V-R202Q	34 (14)
E148Q-R202Q	9 (4.5)
M680I-M694V	8 (4)
E148Q-V726A	6 (3)
E148Q-M694V	5 (2.5)
M694V-V726A	5 (2.5)
R202Q-V726A	2 (1)
M680I-V726A	2 (1)
P369S-M694V	2 (1)
T681I-M680I	1 (0.5)
M694V-R761H	1 (0.5)
No detected mutation	15 (7.5)

Statistical Analysis

Chi-square tests were used to evaluate categorical variables; the results are expressed as numbers and percentages. Continuous variables are expressed as the mean (*M*) and standard deviation (SD). Pearson correlation coefficients were calculated to determine correlations between variables. P values < 0.05 were considered to indicate statistically significant results. Calculations were performed with available statistics software (SPSS Statistics 19; IBM Corp., Armonk, NY). The Ethics Committee for Clinical Research of the Gaziosmanpasa University School of Medicine approved this study. All procedures were conducted in accordance with the declaration of Helsinki principles after obtaining informed consent from patients and/or their parents.

Results

The study population consisted of 199 patients diagnosed with FMF (103 males, 96 females; male/female ratio 1.07/1) whose average age at diagnosis was 11.69 ± 4.12 years (range: 4–17years). The average age at disease onset was 8 ± 3.0 years. The average period between disease onset and diagnosis was

42 months. Yearly attacks prior to treatment decreased significantly with colchicine treatment. Detailed clinical and demographic data are shown in Table 3.

The correlations of genetic mutations with symptoms were as follows. Common symptoms in our patients were, in order, abdominal pain (99%, $n=17$), fever (72.9%, $n=145$), arthritis (30.7%, $n=61$), chest pain (15.6%, $n=31$), and erysipelas-like rash (6%, $n=12$). These symptoms were most commonly accompanied by the M694V mutation (43.7%). Other mutations commonly seen with clinical signs were the compound heterozygous mutation M694V–R202Q (23.3%) and R202Q (13.3%).

While fever, abdominal pain, and arthritis were more commonly observed with the M694V mutation, chest pain was the most common symptom associated with the R202Q mutation ($n=10$, 32.3%). Although chest pain was more common in compound heterozygotes, there was no statistically significant difference in the frequency of chest pain among MEFV genotypes ($p=0.064$). Erysipelas-like rash was the most prominent symptom associated with the M694V–R202Q ($n=3$, 25%) compound heterozygous mutation.

Table 3 Demographic, clinical and mutation characters of FMF patients

Variables	Statistics
Age at onset (years)	8.15 ± 3.50
Age at diagnosis (years)	11.69 ± 4.12
Sex	
Male	96 (48.2)
Female	103 (51.8)
Medical history	
FMF in familial history	102 (51.5)
Apendectomy history	32 (16.1)
Clinical findings	
Fever	145 (72.9)
Severity score	6.3 ± 2.3
Abdominal pain	197 (99)
Artrhralgia/arthritis	61 (30.7)
Chest pain	31 (15.6)
Skin eruption	12 (6)
Proteinuria	42 (21.2)
Response to Colchicine	
Complete	187 (94)
Non-response	12 (6)
Type of mutation	
Heterozygote	81 (40.75)
Homozygote	28 (14.07)
Compound heterozygote	75 (37.68)
Wild type	15 (7.53)

Data are shown as mean ± standard deviation *n* (%)

Proteinuria was observed in 42 (21.2%) patients and was frequently accompanied by the M694V mutation (28.6%). Among compound heterozygotes, proteinuria was most commonly observed with the M694V–R202Q mutation (21.5%). Two patients in whom amyloidosis was detected histopathologically had the M694V homozygous mutation. Proteinuria was seen at a rate of 35.7% ($n=15$) in patients with a compound heterozygous mutation. There was no statistically significant difference among MEFV genotypes ($p=0.39$).

Thirty-two (16.1%) patients had had an appendectomy prior to diagnosis. Among allele groups, the compound heterozygote group showed the highest rate (49.2%, $n=16$) of appendectomy ($p<0.05$). Appendectomy was commonly seen in M694V–R202Q compound heterozygotes and M694V homozygotes (18.8% and 15.6%, respectively).

According to disease severity scores, 5% ($n=10$) of cases had severe illness. The disease severity score was higher in those who had had an appendectomy than in those who had not ($p=0.035$), and the average colchicine dose was higher among these patients ($p<0.001$).

The response to colchicine was better in heterozygotes (41.7%). The best response to colchicine was in the M694V–R202Q and homozygous M694V mutation carriers (17.4%/33 and 13.4%/25, respectively). Furthermore, the response to colchicine was better in those who were young at the time of diagnosis ($p<0.001$).

A family history of FMF was present in 102 (51.1%) patients, although there was no statistically significant difference in the distribution of MEFV genotypes between those with and without such a history. Statistically significant differences in the age at diagnosis and age at disease onset were found in those with a family history compared to those without ($p=0.022$ and 0.002, respectively). Complaints of chest pain were less frequent in those with a family history ($p<0.001$).

12 (6%) were unresponsive. Three patients developed diarrhea during colchicine treatment. Detailed clinical findings and mutation analysis information are shown in Table 4.

Discussion

In this study, the relationships among MEFV gene mutations, clinical symptoms, and genotypes/phenotypes were investigated in 199 pediatric patients diagnosed with FMF in the inner Black Sea region of Turkey. In addition, the relationships between mutations in the MEFV gene and accompanying clinical symptoms were evaluated.

FMF is a prototype of the periodic fever syndrome, with fever accompanied by abdominal pain, chest pain, joint pain, and erythema-like skin lesions. Mutations in the MEFV gene, located mostly in exons 2 and 10, may vary among peoples and ethnic groups. Thus, whereas M694V is more common among Jews, Turks, and Armenians, M680I is commonly seen in Armenians, M694I in Arabs, and E148Q in European peoples (Ben-Chetrit et al. 2002; Papadopoulos et al. 2010).

Various studies have been carried out in Turkey, and the overall frequencies of mutations have been reported in the respective regions. These findings have

Table 4 The correlation of clinical findings and mutation types in patients with FMF

Mutation type	Fever, *n* (%)	Abdominal pain, *n* (%)	Artritis/ Atralgia, *n* (%)	Chest pain, *n* (%)	Skin eruption, *n* (%)	Appendectomy, *n* (%)	Response to colchicine, *n* (%)	Familial history, *n* (%)	Proteinuria, *n* (%)
M694V	21 (21.4)	46 (23.4)	13 (21.4)	6 (19.3)	1 (8.3)	9 (28.1)	42 (22.5)	25 (24.5)	12 (28.6)
R202Q	18 (12.5)	26 (13.2)	11 (18)	10 (32.3)	2 (16.7)	3 (9.4)	23 (12.3)	13 (12.8)	5 (11.9)
E148Q	13 (9)	17 (8.6)	6 (9.8)	–	–	1 (3.1)	17 (9.1)	10 (9.8)	–
V726A	6 (4.1)	6 (3)	1 (1.6)	3 (9.27)	–	1 (3.1)	6 (3.2)	3 (2.9)	1 (2.4)
M680I	6 (4.2)	6 (3)	–	–	–	–	6 (3.2)	4 (3.9)	3 (7.6)
K695R	3 (2.1)	3 (1.5)	–	–	–	–	3 (1.6)	1 (1)	1 (2.4)
A744S	3 (2.1)	3 (1.5)	1 (1.6)	–	–	–	3 (1.6)	2 (2)	–
P369S	–	1 (0.5)	–	–	–	–	1 (0.5)	–	–
R761H	–	1 (0.5)	–	–	–	–	–	–	–
M694V-202Q	25 (17.2)	8 (17.2)	10 (16.4)	7 (22.6)	3 (25)	6 (18.8)	33 (17.7)	15 (14.8)	9 (21.5)
E148Q -R202Q	5 (5)	9 (4.6)	3 (4.9)	1 (3.2)	1 (8.3)	3 (9.4)	8 (4.3)	5 (4.9)	3 (7.2)
M680I (g/c)-M694V	6 (4.1)	7 (3.6)	1 (1.6	–	–	3 (9.4)	8 (4.3)	3 (2.9)	–
E148Q-M694V	4 (2.8)	5 (2.5)	3 (4.9)	–	2 (16.7)	1 (3.1)	3 (1.6)	2 (2)	1 (2.4)
E148Q-V726A	4 (2.8)	6 (3)	1 (1.6)	–	–	1 (3.1)	6 (3.2)	4 (3.9)	–
M694V- V726A	3 (2.1)	5 (2.5)	1 (1.6)	1 (3.2)	1 (8.3)	1 (3.1)	5 (2.7)	1 (1)	1 (2.4)
R202Q-V726A	1 (0.7)	2 (1)	1 (1.6)	–	–	–	2 (1.1)	1 (1)	–
M680I (g/c)-V726A	1 (0.7)	2 (1)	1 (1.6)	–	–	1 (3.1)	2 (1.1)	2 (2)	1 (2.4)
P369S-694V	2 (1.4)	2 (1)	–	–	–	–	2 (1.1)	2 (2)	–
T681I-M680I (g/c)	1 (0.7)	1 (0.5)	1 (1.6)	1 (3.2)	–	–	1 (0.5)	–	
M694V -V 761H	–	–	–	–	–	–	1 (0.5)	–	

demonstrated regional differences and similarities in the frequencies of MEFV mutations. According to the Turkish FMF study group, the most common MEFV mutations were M694V (51.4%), M680I (14.4%), and V726A (8.6%) (Tunca et al. 2005). In a study that showed the carrier rate in the healthy Turkish population to be 20%, the frequencies of mutations in the diseased group were M694V, 51.55%; M680I, 9.22%; and V726A, 2.88% (Yilmaz et al. 2001). The most common mutations in 147 pediatric patients in the southeastern region of Turkey were E148Q (30.7%), M694V (26.0%), R761H (13.5%), M680I (13.0%), V726A (10.5%), and P369S (6.3%) (Ece et al. 2014). In another study, the most common mutations in 1058 FMF patients from the eastern region of Turkey were M694V (36.50%), E148Q (32.77%), V726A (14.09), and M694I (4.41%) (Coskun et al. 2015). The most common mutations in 1330 Iranian FMF patients were M594V, E148Q, V726A, M680I, and M694I (42%, 21%, 19%, 14%, and 2%, respectively). In a recent study, the distribution of MEFV mutations M694V, M680I, V726A, K695R, and E148Q was 32.7%, 13.7%, 6%, 6.3%, and 3.4%, respectively. In addition, the G138G and A165A polymorphisms were found to be more common in the FMF group than in the control group (Oksuz et al. 2017).

In our study, M694V (23.3%), R202Q (13.1%), and E148Q (8.5%) were the most common mutations. Thus, the R202Q mutation was the second most common mutation found in our study.

It has been noted that the vast majorty of FMF-associated mutations are clustered around the pyrin B30.2 domain (Arakelov et al. 2018). To date, 28 disease-causing mutations have been identified in the B30.2 region of the human pyrin crystal structure (Weinert et al. 2009). In our study, MEFV SNP genotyping was performed using commercial kits.

The main symptoms of FMF are fever (96%), peritonitis (91%), pleurisy (57%), arthritis/arthralgia (45%), and erysipelas-like erythema (1.3%) (Samuels et al. 1998). The form of these clinical symptoms may vary among ethnic groups and communities (Dusunsel et al. 2008). Recent studies of the Turkish population have shown abdominal pain to be the most prominent symptom, followed by fever, arthritis, pleuritis, and erysipelas-like erythema (Ureten et al. 2010; Ozalkaya et al. 2011). In the present study, the most common symptom was abdominal pain (99%). Other common symptoms, in order of the rate of incidence, were fever (72.9%), arthritis/arthralgia (30.7%), chest pain (15.6%), and erysipelas-like rash (6%). Similar to other studies, clinical signs in our patients were most commonly accompanied by the M694V mutation. In contrast to our results, another study found that fever (97.3%) was the most common symptom; other symptoms were abdominal pain (96.6%), arthritis (43.2%), and chest pain (40.7%) (Kilic et al. 2015). As in the present study, these clinical signs have been shown to be most often accompanied by the M694V mutation (Ozalkaya et al. 2011; Kilic et al. 2015; Kilinc et al. 2016). In our study, unlike in other studies, the R202Q mutation was the second most common mutation accompanying fever, abdominal pain, and arthritis symptoms.

The R202Q polymorphism, which is quite common, is not regarded as a pathogenic mutation (Bernot et al. 1998; Öztürk et al. 2008). Nonetheless, the R202Q mutation was the second most common mutation (13.1%) and had a high prevalence in clinically diagnosed FMF patients in our study. Our knowledge of the

clinical features of the R202Q mutation in previous studies is limited. The R202Q mutation was first identified in exon 2 of the MEFV gene (Bernot et al. 1998). In the Greek population, R202Q homozygosity and heterozygosity were detected in 14/152 (9.2%) and 48/152 (31.6%) patients, respectively. Other researchers have emphasized that the presence of the R202Q mutation in its homozygous form can pose a risk for FMF, particularly in cases where MEFV gene mutations are not present (Giaglis et al. 2007). A homozygous R202Q genetic change was detected in 4 of 26 patients diagnosed with FMF who were negative for other mutations in the MEFV gene, and it was emphasized that R202Q gene changes may be mutations instead of polymorphisms (Ritis et al. 2004). In addition, R202Q was found at a higher rate in FMF patients compared to the healthy control group in recent studies, suggesting that R202Q is a disease-causing mutation. In a previous study in our region, the R202Q mutation showed a high rate of occurrence in patients diagnosed with clinical FMF (Yigit et al. 2012). In a study conducted using sequence analysis in the southeastern Mediterranean region of Turkey, R202Q (21.35%) was reported to be the most common mutation. The mutations commonly seen in the Turkish population were seen less often [E148Q (8.85%), M694V (7.95%), M680I (2.40%), and V726A (1.85%)] (Gunesacar et al. 2014). In a study conducted in the southwestern Mediterranean region of Turkey, the most common mutation was R202Q (39.13%). In the present study, the M694V–R202Q compound heterozygous mutation was seen at a significantly higher rate and frequently accompanied symptoms of fever, abdominal pain, arthritis, and chest pain (Kilinc et al. 2016). In a comprehensive MEFV gene analysis carried out using 1000 genomic databases, a homozygous p.R202Q mutation was present in five major populations, providing further evidence that these mutations are significantly more common than disease-causing mutations in all populations (Moradian et al. 2017). In recent studies conducted in Turkey, the R202Q mutation has been reported to be associated with clinical signs. In these studies, the complex homozygous R202Q–M694V gene mutation was associated with an increase in the risk of chronic periodontitis and FMF-associated secondary amyloidosis (Fentoglu et al. 2017). In the present study, the R202Q mutation was the second most common mutation accompanying these symptoms. While fever, abdominal pain, and arthritis were more commonly observed with the M694V mutation, chest pain was the most commonly observed symptom with the R202Q mutation. In addition, the incidence of chest pain accompanying the M694V mutation and the compound heterozygous mutation M694V–R202Q was noteworthy. Consistent with our study, another study conducted in our country found that the frequency of the compound heterozygous mutation M694V–R202Q was 24% and that of the R202Q allele was 24.6% (Gumus 2018).

In our study, E148Q was the third most common mutation, but chest pain and an erysipelas-like rash were not observed with this mutation. M680I and K695R, with which only fever and abdominal pain were observed, were rare mutations. The least common mutations were P369S and R761H, which were only accompanied by abdominal pain. There was no family history of these two mutations. Both of our patients who were diagnosed with FMF after Henoch-Schonlein purpura had the M694V mutation.

Proteinuria is commonly reported with the M694V mutation and less commonly with the E148Q mutation (Dundar et al. 2012). Consistent with the literature, proteinuria was most commonly observed with the M694V mutation in our patients. Proteinuria was not detected with the E148Q mutation, which was present entirely in the heterozygous form. In several studies showing a genotype–phenotype correlation in FMF, the M694V mutation has been associated with a worse prognosis and has been shown to be a risk factor for amyloidosis (Brik et al. 1999; Gershoni-Baruch et al. 2002; Yilmaz et al. 2009). In the present study, the M694V and compound heterozygous M694V–R202Q mutations were associated with a higher likelihood of appendectomy. In addition, the disease severity score was higher in those who had had an appendectomy compared to those who had not.

Some authors have stated that the frequency of family history was lower in MEFV mutation-negative FMF patients (Ben-Zvi et al. 2015). In one study, the family history associated with FMF was reported as 4% (Yilmaz et al. 2009); in another, it was 28.7% (Ozturk et al. 2012). In our study, family history of FMF was relatively high. Although there was no statistically significant difference in the distribution of MEFV genotypes between those with and without such a history.

The major limitation of this retrospective study was the use of commercial kits for MEFV gene analysis. In addition, the study group was small. Nonetheless, our genotype–phenotype correlation results will contribute to the mutation profile of Turkish FMF patients.

In summary, this was a comprehensive study showing the types and rates of mutations accompanying the demographic and clinical features of children with FMF in our study region. The most common mutation was M694V, which was also the mutation most commonly seen together with clinical symptoms. The high rate of incidence of the R202Q mutation in this study is remarkable. Chest pain and an erysipelas-like rash were more common with heterozygous mutations and compound heterozygous mutations accompanied by R202Q, particularly in clinically diagnosed FMF patients. The high incidence of the R202Q mutation in our region and its frequent association with clinical symptoms indicate a risk for FMF disease.

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