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Demographic, clinic, and genetic characteristics in 149 children diagnosed with familial mediterranean fever

Elif Guler Kazanci[1], Muhammet Furkan Korkmaz[2], Vefik Arica[3], Ahmet Ibrahim Kurtoglu[3]

[1]Yuksek Ihtisas Training and Research Hospital, University of Health Sciences, Department of Pediatric Hematology, Bursa, Turkey
[2]Yuksek Ihtisas Training and Research Hospital, University of Health Sciences,Department of Pediatrics, Bursa, Turkey
[3]Mustafa Kemal University, Faculty of Medicine, Department of Pediatrics, Hatay, Turkey

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Abstract

Familial Mediterranean fever (FMF) is a hereditary disease characterized by recurrent attacks of fever, peritonitis, pleuritis and/or synovitis. In this study, we retrospectively evaluated demographic, clinical findings, and genetic features in 149 children (63 male/86 female) with FMF. The mean age of the patients at the time of diagnosis was 6.44 ± 3.21 years. A positive family history for FMF was present in 26%, and 8% of the patients had consanguinity between the parents. The frequency of family history of FMF was found to be higher in patients diagnosed under 10 years of age (p=0.038). Frequencies of the most frequent symptoms observed in cases during episodes were abdominal pain (95%), fever (68%), and arthralgia/arthritis (23%). Genetic analysis revealed that 16% of the patients had homozygous mutations, 32% had heterozygous mutations, and 38% had compound heterozygous mutations, while no mutations were detected in 21 (14%). There were mutant genes in 218 alleles, the most frequently observed were R202Q (48%), M694V (24%), and E148Q (17%). Patients with non-R202Q compound heterozygous mutation had higher frequency of high fever, CRP (C-reactive protein) levels, and fibrinogen levels during the episodes (p=0.006, p=0.001, and p=0.042, respectively). Thus, our study showed that R202Q mutation appeared to have no significant disease-causing and clinical effects, while mutations at exon 10 were associated with increased severity of symptoms as well as elevated levels of acute phase reactants. Further studies with larger FMF populations may shed more light on the role of these mutations in the pathogenesis of FMF.

Keywords: Familial Mediterranean fever, MEFV gene mutation, children, clinical manifestations

Introduction

Familial Mediterranean Fever (FMF) is a chronic periodic inflammatory disease characterized by recurrent fever and polyserositis episodes. Although the etiology and pathogenesis of FMF are uncertain, immune mechanisms are thought to play a major role. The most important feature that distinguishes FMF from other chronic inflammatory diseases is the complete normalization of the patient between inflammatory episodes [1,2] However, in some studies conducted in recent years, elevated levels of cytokines and inflammatory markers during episode-free periods suggest that subclinical inflammation continues. [3-5].

***Coresponding Author:** Muhammet Furkan Korkmaz, Yuksek Ihtisas Training and Research Hospital, University of Health Sciences,Department of Pediatrics, Bursa, Turkey, E-mail: korkmazmfurkan@gmail.com

This disease occurs mainly in Turkish, Arab, Armenian, Jewish and other Mediterranean ethnic groups. Based on the data provided by the Turkish FMF Study Group, the incidence of the disease is 1/1000 and the carrier rate is as high as 1/5 [6]. In the studies, M694V mutation was found most frequently in Turkish populations as in other races [7,8]. It is stated that more than 160 mutations in the MEFV gene cause this disease. However, M694V, V726A, M680I, M694I and E148Q mutations account for 74% of all FMF-related mutations. [9]. In the studies, it was found that there was a relationship between the type of mutation and the age of onset of clinical findings and the severity of the disease. Clinical findings were more severe in patients with homozygous MEFV gene mutation [10]. Furthermore, although some studies have reported correlations between genetic characteristics and the severity, course, and prognosis of FMF, the data on this issue are not clear.

In this study, the demographic, clinic, and genetic characteristics as well as the treatment response in 149 Turkish pediatric patients diagnosed with FMF in two different centers are presented.

Materials and Methods

In this study, medical records of 149 FMF patients between 0 and 18 years of age followed up at two tertiary centers between January 2018 and June 2019, i.e. Department of Pediatrics, Bursa Yüksek İhtisas Training and Research Hospital and Department of Pediatrics, Research and Application Hospital, Medical Faculty of Hatay Mustafa Kemal University were retrospectively analyzed after obtaining the approval of local ethics committee, (2011-KAEK-25-2019/09-11).

Demographic data, family history, use of medication, and gene mutations were recorded in all patients, as well as the age at disease onset, episode frequency, accompanying symptoms, complete blood count, CRP (C-reactive protein), ESR (Erythrocyte sedimentation rate), and fibrinogen levels.

Venous blood samples of 2 to 5 mL obtained from each patient were transferred to medical genetic laboratory in EDTA tubes at 18-24 ℃ for genetic analysis.

MEFV gene-related mutations were screened at the Medical Genetics Center of both hospitals using the next generation sequencing method (Illumina device).

For data analysis SPSS (Statistical Package for Science Studies) version 21.0 statistic software pack was used. Categorical variables were expressed with n (%), while mean ± standard deviation and median (min-max) values were used for continuous variables with or without normal distribution, respectively.

The chi-square test or Fisher's exact test were used to compare the frequency of qualitative variables. In cases where the prerequisites of parametric tests could not be fulfilled for some variables, Mann-Whitney U test was used for two-group comparisons and Kruskal Wallis tests for multiple group comparisons. In all tests, $p < 0.05$ was considered statistically significant.

Results

The mean age of 149 patients included in the study was 8.12 ± 3.48 years (range: 1-16 y). Of these, 63 (42%) were male and 86 (58%) were female. The mean age of the patients at the time of diagnosis was 6.44 ± 3.21 years, with 75% of the patients having a disease onset earlier than 10 years of age (Table 1).

Table 1. Demographic and clinical data of Familial Mediterranean fever cases

Parameters	FMF* cases n=149	Age ≤10 n=111	Age >10 n=38	P-value
Sex (M/F), n (%)	63/86 (42/58)	44/67	19/19	0,6
Age (years), mean ± SD**	8,12 ± 3,48	6,46 ± 2,15	12,94 ± 1,62	0,02
Age at diagnosis, mean ± SD	6,44 ± 3,21	4,96 ± 2,04	10,73 ± 1,82	<0.001
Number of attacks in the last year, median (min-max)	3 (0-10)	3 (0-9)	3 (0-10)	0,9
FMF in family history, n (%)	39 (26)	34 (23)	5 (3)	0,038
Consanguineous marriage, n (%)	12 (8)	10 (7)	2 (1)	0,6
Colchicine usage time (months), median (min-max)	12 (0-84)	12 (0-84)	24 (0-60)	0,054

*: Familial Mediterranean fever, **: standard deviation

The median value for the frequency of episodes in the last year was 3 days (0-10 days). A positive family history for FMF was present in 26%, and 8% of the patients had parents with consanguineous marriage.

The median duration of colchicine use was 12 months (0-84 months), with a median dosage of 1 mg/day (0-4 mg/day). When the demographic and clinical data of the patients were analyzed statistically, the frequency of family history of FMF was found to be higher in patients diagnosed under 10 years of age (p=0.038).

Abdominal pain (95%), fever (68%) and arthralgia / arthritis (23%) were frequently observed when the patients were evaluated for accompanying symptoms during the episode (Table 2).

When mutation analysis results of our patients were examined, 24 (16%) patients had homozygous, 48 (32%) patients had heterozygote and 56 (38%) patients had compound heterozygous mutations, while no mutations were detected in 21 (14%) patients. As a result of this study, mutant genes were detected in 218 alleles. The most common alleles were R202Q (48%), M694V (24%), and E148Q (17%). The mutation analysis results of the cases are shown in Table 3.

In order to examine the effect of R202Q, which is the most common mutation in our study, on clinical and laboratory results, the data of patients were compared in three groups as R202Q homozygote, R202Q / M694V and non-R202Q compound heterozygote (Table 4). The frequency of fever, CRP and fibrinogen levels during the episode was higher in patients with non-R202Q compound heterozygous mutations (p=0.006, p=0.001, p=0.042, respectively).

Table 2. Clinical symptoms of the patients during an episode

Symptoms	n (%)
Abdominal pain	141 (95)
Fever	101 (68)
Arthralgia/arthritis	34 (23)
Nausea and vomiting	32 (21)
Chest pain	18 (12)
Myalgia	12 (8)

Table 3. Distribution of Mediterranean fever gene

Genotype	Mutation	n (%)
Heterozygous for one mutation	R202Q/-	21 (14)
	E148Q/-	9 (6)
	M694V/-	8 (5)
	V726A	3 (2)
	P369S/-	3 (2)
	A744S/-	2 (1)
	M680I (G/C)/-	1 (1)
	R761H/-	1 (1)
Homozygous for one mutation	R202Q/R202Q	16 (10)
	E148Q/E148Q	5 (3)
	M694V/M694V	3 (2)
Compound heterozygous	R202Q/M694V	31 (21)
	R202Q/E148Q	10 (7)
	M680I (G/C)/V726A	3 (2)
	E148Q/M694V	3 (2)
	E148Q/P369S	3 (2)
	M694V/V726A	2 (1)
	E148Q/V726A	1 (1)
	E148Q/R202Q/M694V	1 (1)
	E148Q/M694V/V726A	1 (1)
	M694V/M680I (G/C)	1 (1)
Mutation (+)		128 (86)
Mutation (-)		21 (14)
Total		149 (100)

Discussion

In this study, patients followed up at two tertiary care centers with a diagnosis of FMF were retrospectively analyzed in terms of demographic, clinic, and genetic characteristics.

FMF is an autosomal recessive systemic inflammatory disorder commonly occurring in our geographical area that is associated with diagnostic challenges [11]. There is no specific laboratory test for diagnosis, and currently, clinical and family history are the most important tools for diagnosis [12].

FMF is mainly childhood disease, and is usually diagnosed within the first 10 years of life. In a study by Sohar et al. [13], the age of onset of clinical findings was before 10 years of age in 65% of the patients and before 20 years of age in 90% of the patients. Ben-Chetrit et al. [11] reported first occurrence of symptoms within the first 10 years of life in approximately 50% of patients with FMF, while only 2% of the patients had a disease onset after 30 years of age. In the current study, the mean age of the patients at the time of diagnosis was 6.44 ± 3.21 years, with 75% of the cases having a disease onset before 10 years of age.

In most published reports, FMF has been reported to affect both genders at similar rates. In a multi-center study conducted in our country, the female / male ratio was reported as 1.2 to 1 [6]. Similarly in our study, the female / male ratio was found to be 1.3 / 1.

As with all autosomal recessive diseases, consanguineous marriages are associated with an increased likelihood of mutant alleles in FMF [14]. Eight percent of our patients had parents with consanguineous marriage, while 26% had a positive family history for FMF. In our study, the incidence of family history of FMF was found to be higher in patients diagnosed under 10 years of age.

Table 4. Relationship between genotype, clinical and laboratory findings in patients

Parameters	R202Q Homozygous N=16	R202Q/M694V N=31	Non R202Q CH N=13	P-value
Sex (M/F), n	7/9	9/22	4/9	0,5
Age (years)*	7,8 ± 2,8	8,5 ± 3,6	6,8 ± 3,6	0,3
Age at diagnosis*	5,7 ± 3,1	6,9 ± 3,5	5,8 ± 2,9	0,5
Number of attacks in the last year**	3 (1-8)	3 (0-9)	3 (2-10)	0,7
FMF in family history, n	8	8	3	0,5
Consanguineous marriage, n	0	1	2	0,1
Colchicine usage time (months)**	12 (0-36)	12 (0-60)	12 (0-48)	0,06
Abdominal pain, n	16	29	10	0,07
Fever, n	7	20	13	0,006
Arthralgia/arthritis, n	2	5	4	0,4
Hb (g/dL)*	12,8 ± 1,7	12,5 ± 1,4	12,5 ± 1,5	0,7
WBC (x109)*	7,6 ± 2,5	8,8 ± 2,8	8,2 ± 2,6	0,5
Platelet count (/µL)*	303000 ± 88000	313000 ± 98000	320000 ± 83000	0,9
CRP (mg/L)**	3,3 (0-3,3)	3,3 (0-54,9)	35 (3,3-100)	0,001
ESR (mm/saat)**	5 (2-20)	5(0-69)	17 (3-52)	0,064
Fibrinojen (mg/dL)**	203 (0-342)	318 (0-681)	350 (126-2228)	0,042

Abbreviations: CH: Compound heterozygous, Hb: Hemoglobin, WBC: White blood count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate
*: mean ± standard deviation, **: median (min-max)

Recurrent abdominal pain with fever is the most common symptom in FMF disease. Although these typical findings are seen in different populations and races in different frequencies, arthralgia/arthritis, chest pain, joint pain and erysipelas-like rash may also be observed in patients [15]. Based on the data from the Turkish FMF Study Group, the most common symptoms included abdominal pain (93%) and fever (92%). Also, in our study, abdominal pain (95%) and fever (68%) were the most common symptoms in accordance with the literature.

In recent years, significant advances have been achieved in understanding the molecular basis of FMF and supporting diagnosis through emerging molecular genetic methods. The number and type of mutations in the MEFV gene that play a role in the etiology of FMF cases vary among populations. Among the most common mutations, M694V, M680I, V726A and M694I are located on exon 10, while E148Q mutation, which is frequently observed, is located on exon 2. No mutation is detected in approximately 20% of patients [16,17]. The most frequently identified mutant alleles in our study were R202Q (48%), M694V (24%), and E148Q (17%), with 14% of the patients having no mutations.

The most frequently detected mutation in FMF patients is known to be the M694V mutation [17]. Until now, the mutations most frequently identified in Turkish patients include M694V, M680I, V726A and M694I [14]. These mutations at exon 10 may co-exist with amyloidosis and may lead to a more severe clinical presentation, while the mutations of M148Q and R202Q in exon 2 have a controversial role in the etiology of FMF [18,19]. While Ozturk et al. [20] found no association between heterozygous R202Q mutations and FMF, they also showed that the clinical manifestations may emerge when it co-occurs with other disease-causing mutations. On the other hand, Yiğit et al. [21] recommended routine examination of R202Q mutations, as these mutations may lead to FMF when they are in the homozygous form. Again, Çankaya et al. [22] showed that the presence of R202Q mutations may lead to clinical FMF.

The most frequently detected mutation in FMF patients is known to be the M694V mutation [17]. M694V, M680I, V726A and M694I are the most common mutations reported in AAA patients in our country so far [14]. It is thought that these mutations caused by exon 10 may cause a more severe clinical presentation with amylodosis. It is controversial that mutations such as E148Q and R202Q caused by exon 2 cause disease [18,19]. While Ozturk et al. [20] found no association between heterozygous R202Q mutations and FMF, they also showed that the clinical manifestations may occur in association with other disease-causing mutations. However, Yigit et al. [21] suggested that R202Q may also cause disease in homozygous forms and should be included in routine molecular examination. Similarly, Çankaya et al. [22] showed that FMF disease may occur in some patients in the presence of R202Q mutation.

Giaglis et al. [23] reported a 9.2% R202Q homozygous polymorphism in FMF patients in the Greek population and 0.7% in healthy subjects. Yiğit et al. [21] observed heterozygous and homozygous R202Q polymorphism in 59.6% and 14.7% of Turkish patients, respectively. In the current study, R202Q mutation was detected as 14% heterozygous, 21% homozygous and 29% compound heterozygous. When comparing the data of patients to examine the effect of R202Q on clinical and laboratory results, the frequency of fever, CRP and fibrinogen levels during episode was higher in patients with non-R202Q compound heterozygote mutation than patients with R202Q. Accordingly, our study supports the hypothesis that R202Q does not have disease-causing effects as suggested by some previous studies.

The most important limitations of this study are the limited number of patients and the small number of mutations that can be examined and the retrospective nature of the study.

Conclusion

In conclusion, although M694V gene mutation was reported to be the most common mutation in previous studies in our country, R202Q mutation was the most common type of mutation in our study. However, our study showed that R202Q had no significant effect on disease-causing and clinical effects, whereas mutations at exon 10 could increase the frequency of symptoms and elevate acute phase reactant levels during episode. We believe that the effects of mutations on FMF patients will be further elucidated in future studies with larger series.

Competing interests
The authors declare that they have no competing interest.

Financial Disclosure
The financial support for this study was provided by the investigators themselves.

Ethical approval
Research and Application Hospital, Medical Faculty of Hatay Mustafa Kemal University were retrospectively analyzed after obtaining the approval of local ethics committee, (2011-KAEK-25-2019/09-11).

Elif Guler Kazanci ORCID: 0000-0003-0910-1142
Muhammet Furkan Korkmaz ORCID: 0000-0001-5440-7955
Vefik Arica ORCID: 0000-0002-2080-4677
Ahmet Ibrahim Kurtoglu ORCID: 0000-0001-8581-5652

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