original article

A molecular analysis of familial Mediterranean fever disease in a cohort of Turkish patients

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Ann Saudi Med 2012; 32(4): 343-348

DOI: 10.5144/0256-4947.2012.343

BACKGROUND AND OBJECTIVES: Familial Mediterranean fever (FMF) is an autosomal recessive disorder caused by mutations in *MEFV* gene, which encodes pyrin. FMF is especially prevalent among Turks, Armenians, non-Ashkenazi Jews, and Arabs. The aim of this study was to determine the frequency and spectrum of 12 *MEFV* mutations of these patients and any genotype-phenotype correlation in this large Turkish group.

DESIGN AND SETTING: A retrospective study at Erciyes University Medical Faculty, from January 2007 to June 2009.

PATIENTS AND METHODS: We enrolled 446 Turkish FMF patients and identified the known 12 MEFV mutations with clinical investigations. DNA was amplified by PCR and subjected to reverse hybridization for the detection of MEFV gene mutations.

RESULTS: Among the 446 patients, 103 (46.6%) had a heterozygous genotype, 44 (19.9%) had a homozygous-genotype, and 74 (33.49%) had a compound heterozygous genotype. The most common mutation detected was heterozygote M694V (46/221). Of the included 446 patients, 218 (48.87%) were male and 228 (51.12%) were female. High parental consanguinity rates affect FMF development. The clinical spectrum varied with different mutation profiles.

CONCLUSIONS: This study plays an important role in detecting the distribution of *MEFV* mutations and determining clinical approaches among Turk FMF patients. Also, we seemed to detect a distinctive clinical picture, specifically a lower frequency of amyloidosis.

Familial Mediterranean fever (FMF) is an autosomal recessive, systemic inflammatory disorder characterized by unprovoked recurrent, self-limited episodes of fever; and serosal, synovial, or cutaneous inflammation attacks with abdominal pain, pleuritis, and arthritis.[1,2] FMF is a disease that is especially seen in several eastern Mediterranean populations, like Turks, Sephardic Jews, Armenians, and Arabs.[3] The carrier frequency of the disease is approximately 1 per 8-16 individuals. The estimated prevalence of FMF in Turkey is 1/1000, and carrier rate is 1/5.[4] Peritoneal and pleural inflammation, arthritis, erysipelas-like erythema, and arthralgia are well-known features of FMF and may vary in different populations.[5] Arthritis occurs more frequently in Jews than in Turks, Arabs, and Armenians.[6]

The gene is located on chromosome 16p13.3 and includes 10 exons and encodes a 781-amino acid protein named pyrin or marenostrin.[7] The pyrin protein is associated with the interleukin-1 (IL-1)-related inflammatory reactions and is involved in the regulation of apoptosis and inflammation. The *MEFV* transcript, which plays an essential role in the inflammatory response, is expressed in granulocytes. Recently obtained data revealed over 70 different mutations in FMF patients. These are grouped as missense, nonsense, and deletion mutations. Most of the mutations are localized in a small part of exon 10.[8,9] Four common mutations in exon 10 (M694V, M694I, V726A, and M680I) and onemutation in exon 2 constitute 85% of the known mutations in geographical areas where FMF is frequent.[10] In recent studies, it was seen that the severity of the disease is affected by environmental factors, and *MEFV* mutations are not the only cause of the disease.[6,11]

In the clinical approach, the FMF patients are di-

vided into two subgroups: phenotype 1 and phenotype 2. In phenotype 1, only attacks of serosal inflammation are reported. In phenotype 2, only amyloidosis is present and no other clinical manifestations are reported.[12] Reactive or secondary AA amyloidosis is seen in FMF patients as a severe complication. The amyloid slowly accumulates in various organs and tissues; organ dysfunction follows this period. Renal amyloidosis is especially common in Turks.[13] Colchicine has been used for the prevention of the disease and has been shown to markedly change the clinical course of the disease (especially the development of amyloidosis).[14] The objective of this study was twofold: (1) to determine the frequency of the 12 mutations of the *MEFV* gene in a large FMF cohort, medical treatment, treatment response, and association with the family history; and (2) to determine the genotype-phenotype correlation between the mutation types and clinical course of the disease in the Turkish population around middle Anatolia.

PATIENTS AND METHODS

The study group comprised 446 unrelated patients (age range, 1-70 years; 218 male and 228 female) who were diagnosed as having FMF by Fonnesu and colleagues.[15] They were referred to our clinic for FMF mutation analysis between January 2007 and June 2009. This retrospective study was approved by the Erciyes University Medical Faculty, and informed consent was obtained from all the participants. The study was performed in Middle Anatolia, Turkey, with the collaboration of the Department of Medical Genetics and the Department of Gastroenterology of Erciyes University Medical Faculty. Molecular test results of each and every patient were obtained; 2 mL of peripheral blood sample of each patient with EDTA was used for DNA extraction. A commercially available strip test assay (FMF strip assay; ViennaLab, www.viennalab.com) was used in the diagnosis of FMF and determination of its 12 common mutations. According to the FMF strip test method, multiplex PCR was performed using biotinylated primers for the amplification of exons 2, 3, 5, and 10. Investigated mutations were as follows: E148Q in exon 2; P369S in exon 3; F479L in exon 5; and M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H in exon 10. Hybridization of PCR products to the strip absorbed immobilized wild type and mutated oligonucleotide probes. Hybridization was performed in an automated incubator (AutoLIPA; Innogenetics, Belgium). Hybridizations were illuminated by the reaction of streptavidin-alkaline phosphatase and color substrate.

Mutation results are given in percentages. Categorical variables were compared using the chi-square test. Also, the Fisher exact test was used to compare the values. $P<.05$ was considered statistically significant.

RESULTS

In the study group, comprising patients referred to our clinic for FMF testing, 225 had no definable mutations. One hundred three (46.6%) of the subjects were carrying at least 1 mutated *MEFV* allele. The frequencies of M694V, E148Q, M680I (G/C), and V726A mutation carriages were 20.81%, 9.5%, 7.23%, and 4.97%, respectively. Forty-four (19.9%) subjects had the homozygous genotype and 74 (33.49%) had the compound heterozygous genotype. All the homozygous patients were from consanguineous families. Heterozygous M694V (46/221), compound heterozygous M694V/M680I (G/C) (27/221), homozygous M694V (25/221), and heterozygous E148Q (21/221) mutations were significantly common in the mutation carrier group (**Table 1**). The allele frequencies of the most common mutations were M694V, 15.8%; M680I (G/C), 8.85%; E148Q, 5.15%; and V726A, 4.14% (**Table 2**).

Of the 446 patients, 48.87% were male (n=218) and 51.1% were female (n=228) (female-to-male ratio, 1.04:1). The main clinical characteristics were as follows: abdominal pain was observed in 353 (79.1%) patients; fever, in 230 (51.6%) patients; arthritis, in 138 (30.9%) patients; and erysipelas-like erythema, in 24 (5.4%) patients. The clinical characteristics, such as abdominal pain, arthritis, and fever, were more prevalent in females than in males , and the female-to-male ratio was, respectively, 55/45, 61/38, and 59/41.

FMF patients were divided into two groups, female and male (see **Tables 3 and 4**), and these groups were compared according to ages and mutation types. Genotype distribution according to gender was as follows: the non-carrier group was more prevalent among females (female-to-male ratio: 49.56/45.41), compound heterozygotes were more prevalent among males (21.10%), and the *MEFV*-mutated allele–carrying rate was higher among males as compared to females (males, 54.59%; females, 50.44%). When the groups were compared, significant regional differences were observed in mutation-carrying profile in Kayseri and other cities. Especially, heterozygous mutation-carrying rates were higher in Kayseri than other mutational forms.

As a complication, amyloidosis developed in 17 (3.81%) patients. Appendectomy was performed in 47 (10.5%) patients, mostly for compound heterozygous mutations; and cholecystectomy was performed in 11 (2.5%) patients, mostly for compound heterozygous mutations. Of the included cases, 29 patients had an

operation history without any mutation profile; in addition, 19 patients had a history of inoperable appendix pain.

Colchicine therapy was administered to 125 patients; 41 (32.8%) of them responded to the therapy, while 10 (8%) did not. Seventy-four (59.2%) of these 125 patients used both colchicine and medical supportive therapy. Colchicine treatment response and mutational comparisons are summarized in **Table 5**. M694V homozygous (n=3; 12.5%) and compound heterozygous (n=3; 12.5%) states were also found in patients with erysipelas.

DISCUSSION

In this study, we investigated 446 patients suffering from FMF. Demographic and clinical characteristics of the FMF mutations, as well as colchicine treatment responses and the phenotype-genotype correlations, were compared in the FMF patients. The results of our study were similar to those of the other researchers, with the observation that M694V homozygous patients had a more severe clinical course of the disease, and the M694V mutation had a higher frequency when compared with other mutational forms. The study also confirms the mutational heterogeneity of FMF in Anatolia.

Some differences have been reported in gene mutations of FMF in the various Mediterranean populations. The five most common mutations were M694V, M680I, M694I, E148Q, and V726A.[16,17] In various recent studies, it has been reported that 70% to 80% of the total FMF cases consisted of these five mutations.[4,18,19] In our study group, the most common mutation was M694V heterozygosity (20.81%), followed by M694V-M680I (G/C) compound heterozygosity, M694V homozygosity, E148Q heterozygosity, and M680I (G/C) heterozygosity with 12.21%, 11.3%, 9.5%, and 7.23%, respectively. We could not identify the M694I mutation in our patient group. In 2008, Solak and colleagues studied 202 FMF patients and found M694V to be the most frequent mutation among them. Other mutations such as E148Q, M680I, V726A, and M694V were described based on their frequencies.[20] Our observation of M694V as the most common mutation is in agreement with that of Solak and colleagues (2008). The M694V heterozygous form constituted 20.81% and M694V homozygous form, 11.3%. Demirkaya and colleagues[21] studied 330 patients. They reported the R761H mutation compound heterozygote form in 23 patients and also found R761H as a frequent mutation for all the Mediterranean populations. Nevertheless, Touitou did not report R761H as a frequent mutation, which is a finding similar to that reported by Demirkaya and colleagues.[18] In the present study, the R761H mutation was found in 4 patients in the heterozygous form, which is in agreement with the findings by Touitou regarding the frequency of the R761H mutation (1.8%), as seen in **Table 1**. Also, we found rates similar to those in their report. No significant differences were reported in age and mutation types between genders ($P>.05$) (**Tables 3 and 4**). Nevertheless, as seen in **Tables 3 and 4**, the

Table 1. Distribution of the MEFV gene mutations.

Mutation	Genotype	Number (n=221)	%
Heterozygotes (n=103) (46.6%)	M694V	46	20.81
	E148Q	21	9.5
	M680I (G/C)	16	7.23
	V726A	11	4.97
	R761H	4	1.8
	K695R	3	1.3
	P369S	1	0.45
	A744S	1	0.45
Homozygotes (n=44) (19.9%)	M694V	25	11.3
	M680I (G/C)	12	5.42
	E148Q	5	2.26
	V726A	2	0.9
Compound heterozygotes (n=74) (33.49%)	M694V/M680I (G/C)	27	12.21
	M694V/V726A	11	4.97
	M680I (G/C)/V726A	9	4.07
	M694V/E148Q	7	3.16
	M680I (G/C)/E148Q	3	1.3
	E148Q/P369S	3	1.3
	E148Q/V726A	2	0.9
	OTHERS	12	5.42

Table 2. Common MEFV mutations among the FMF-affected cohort of patients.

Mutation (221 patients)	Number of alleles	Allele frequency (%)
M694V	141	15.8
M680I (G/C)	79	8.85
E148Q	46	5.15
V726A	37	4.14

Table 3. Frequency of *MEFV* gene mutations according to age and gender among females.

Age (years) (n=228)	0-20	21-40	41-60	61-80	Total (number %)
No detected mutation	80	21	10	2	113 (49.6)
Heterozygote	26	16	2	-	44 (19.3)
Homozygote	25	3	2	-	30 (13.2)
Compound heterozygote	26	11	4	-	41 (18.0)
					228

P=.216.

Table 4. Frequency of MEFV gene mutations according to age and gender among males.

Age (years) (n=218)	0-20	21-40	41-60	61-80	Total (number %)
No detected mutation	68	27	2	2	99 (45.4)
Heterozygote	35	13	4	-	52 (23.9)
Homozygote	13	6	-	-	19 (8.7)
Compound heterozygote	30	9	5	2	46 (21.1)
Other	2	-	-	-	2 (0.9)
					218

P=.419.

Table 5. Response to colchicine therapy according to mutation forms.

	Response to colchicine therapy	
Mutation	+	-
No mutation	10	5
Heterozygote	10	-
Homozygote	6	2
Compound heterozygote	15	3
	41	10

P=.234.

main diagnostic age was approximately between 0 and 20 years. The difference in carrier rate was also not statistically significant between genders ($P>.05$), but the carrier rate was higher in males than in females.

In the research by Inal et al, the consanguinity rate was higher in families of FMF patients. Our study reveals a positive family history in 25% (111/446) of patients; 16% (70/446) of all patients had parental consanguinity, and this ratio was not as high as that found by Inal and colleagues (40%).[2] However, the consanguinity rate in parents who had a positive family history might be a factor affecting the development of FMF disease in some of our patients.

An increased risk of amyloidosis (12%) among M694V homozygotes was reported by different Turkish groups.[2] The relationship between FMF and amyloidosis is still obscure. Some reports demonstrated no association between genotype and phenotype and/or development of amyloidosis. In the studies by Tunca et al and Tekin et al, which were performed in the Turkish population, no relationship was shown between amyloidosis and the presence of the homozygous M694V mutation.[4,22] On the contrary, in the study by Yalcinkaya et al., the M694V mutation was found to be more frequent in Turkish FMF patients with amyloidosis.[23] In some other studies, a positive correlation was found between the M694V mutation and amyloidosis.[20,24,25] According to Pasa and colleagues,[1] amyloidosis was found in 4 of 17 patients who were homozygous for the M694V mutation (in group 1); 3 of 34 patients had compound heterozygosity with M694V/other forms (in group 2). In our study, we detected 17 patients with amyloidosis, and development of amyloidosis was not found to correlate with disease severity; however, we found a higher prevalence of amyloidosis development in patients with the M694V mutation. Five patients with amyloidosis had M694V heterozygosity (23.53%); M694V homozygosity was detected only in 3 (17.65 %) of them. E148Q heterozygosity was found only in 1 (5.8%) patient with amyloidosis. In addition, we found 8 patients without the mutation. We concluded that non-identification of mutations in these patients may be due to many factors, including the presence of other rare mutations, unknown mutations, or genetic heterogeneity and also some mutations that were not found in our strip assay. Consequently, the most common mutation was M694V, with 3 homozygous and 5 heterozygous forms. In conclusion, the most common mutation form was M694V heterozygosity (20.8%).

Colchicine treatment was used in some patients. Forty-one (32.8%) of 125 patients used only colchicine, and their response to the treatment was complete. Ten (8%) did not respond to colchicine treatment. Seventy-four also exhibited an incomplete response to colchicine and used a supportive treatment with the colchicine therapy for a significant effect. As a result, there was no significant difference in response to colchicine treatment between patients with various mutational distributions.

Clinical features varied in different populations. Fever was the most common symptom, occurring in about

93% to 100% of Turks, Arabs, Jews, and Armenians.[3] Although in some studies, arthritis was reported as a common symptom, followed by fever and abdominal pain. In 2009, Inal and colleagues[2] reported that fever was the most common symptom, and it was followed by abdominal pain or peritonitis.[4,26] In our study group, the most common symptoms were abdominal pain (79.1%) and fever (51.6%), which is similar to the findings by Inal and colleagues.[2] Arthritis was observed in 30.9% of patients. Diarrhea (6.7%, 30/446), vomiting (7.6%, 34/446), and constipation (3.6%, 16/446) were the other symptoms. Kone Paut et al reported diarrhea in 4% of the patients in their study group; nevertheless, our rate was higher than in their report.[27] Clinical manifestations were different between the different mutation profiles. In **Table 6**, mutational profiles and application criteria of patients are compared.

Sayarlioglu and colleagues[28] reported that only 14% (57/401) of patients had adult-onset FMF (disease onset at age over 20 years), and only 5 (1.3%) had the first attack after 40 years of age (late-onset FMF). Our study group consisted of patients with a large age range, and 68% (305/446) of our patients had ages in the range 0-20 years at the onset of FMF, 23.7% (106/446) had the adult-onset (21-40 years) FMF, and 7.8% had the late-onset (41-80) FMF. There might be some clinical and molecular differences in the onset of the disease.

Our study group included heterozygous (46.6%) and compound heterozygous (33.49%) mutations with the clinical manifestations of FMF disease. To date, it has been pointed out that FMF is an autoinflammatory disorder generally caused by recessively inherited mutations in the *MEFV* gene. FMF is quite prevalent in the Armenian population, in which majority of the patients have two mutated alleles; yet in 18% of symptomatic patients, just 1 mutation has been detected. To explain this finding, in 2010, Moradian and colleagues analyzed the symptoms and genotypes of 1299 patients, including 236 affected heterozygous patients with a definite diagnosis of FMF. They selected a subset of 63 heterozygous, homozygous, and asymptomatic normal individuals and completely sequenced their *MEFV* genes (exons) to discover any other mutations potentially missed by currently used screening methods. Besides four synonymous polymorphisms in exons 2 and 5, they found a T267I mutation in 1 heterozygous patient with a severe case of FMF who should have been designated as a compound heterozygote; yet the other genotypes were all accurate. They used a binomial probability distribution of symptoms in homozygous FMF patients to estimate the likelihood of their occurrences in heterozygous patients and demonstrated the assemblage of patients into groups with similar clinical criteria using statistical clustering. They found extremely high probabilities for the presence of FMF symptoms in heterozygous individuals and determined that symptoms were equally likely to occur in both genotypes analyzed. Therefore, their study supports the rising evidence that a single *MEFV* mutation could be associated with mild FMF symptoms. However, heterozygous patients presenting with a severe phenotype should be further analyzed for the less common second *MEFV* mutation using gene sequencing.[29]

Table 6. Mutation profiles and application criteria reported to the clinics.

	Number of patients (n)		
Mutation profile	**Fever**	**Abdominal pain**	**Arthritis**
Normal	100	172	50
Mutation group	130	181	88
Mutational distribution of the application criteria			
M694V heterozygote	23	34	20
M694V homozygote	15	20	16
E148Q heterozygote	14	20	9
E148Q homozygote	4	7	3
M680 (G/C) homozygote	12	14	7
M680 (G/C) heterozygote	7	12	5
Compound heterozygote	55	74	28

P=.04

This study established the spectrum of the *MEFV* mutations among Turk FMF patients. There seems to be a distinctive clinical picture, specifically a lower frequency of amyloidosis. The range and distribution of *MEFV* mutations in Turk patients are similar to those noted in other ethnic groups (M694V) often affected by FMF. However, the proportion of unidentified disease-causing *MEFV* mutations is higher in Turk patients. There is a need for further investigations for finding new etiologic factors or new undefined molecular techniques to identify new parameters. In conclusion, because of the genetic heterogeneity in Anatolia, larger serial country-based analyses are required to investigate the rate of these mutations, the association between the mutations on one hand and a family history of consanguinity and clinical manifestations on the other hand. Also, the high incidence of *MEFV* gene mutations in the Turkish population indicates that newborn screening may be required in the future.

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