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.
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. 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. 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).

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. 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 carriers 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
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                 |

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. In various recent studies, it has been reported that 70% to 80% of the total FMF cases consisted of these five mutations. 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. 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 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. 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>0.05) (Tables 3 and 4). Nevertheless, as seen in Tables 3 and 4, the
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%). 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. 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. 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. 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

### 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)       |
| **Total**           | **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)         |
| **Total**           | **218**|       |       |       |                 |

P=.419.

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

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

P=.234.
93% to 100% of Turks, Arabs, Jews, and Armenians. Although in some studies, arthritis was reported as a common symptom, followed by fever and abdominal pain. In 2009, Inal and colleagues reported that fever was the most common symptom, and it was followed by abdominal pain or peritonitis. 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. 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. Clinical manifestations were different between the different mutation profiles. In Table 6, mutational profiles and application criteria of patients are compared.

Sayarlioglu and colleagues 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.

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.

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

| 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 = 0.04**
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