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ORIGINAL ARTICLE

The *MEFV* mutations and their clinical correlations in children with familial Mediterranean fever in southeast Turkey

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Abstract The aim of this study was to determine the Mediterranean fever (*MEFV*) gene mutations and their clinical correlations in children with familial Mediterranean fever (FMF) in southeast Turkey. Clinical and laboratory characteristics of 147 (65 males, 82 females) consecutive children with FMF having a positive *MEFV* gene mutation were prospectively investigated. Patients with negative *MEFV* gene mutations or atypical FMF presentations and those from other regions of the country were excluded. Clinical manifestations and disease severity scores were recorded. The six most frequent *MEFV* mutations including M694V, V726A, R726H, P369S, E148Q and P369S were investigated by a reverse hybridization test method. The median age of study group was 9.0 years, median age at diagnosis was 7.8 years, median age at disease onset was 5.0 years, and median follow-up duration was 4.0 years. A positive family history of FMF and parent-to-offspring transmission was found in 58.5 and 42.2 % of families, respectively. The frequencies of independent alleles, with decreasing order, were E148Q (30.7 %), M694V (26.0 %), R761H (13.5 %), V726A (13.0 %), P369S (10.5 %) and M680I (6.3 %) in FMF patients. The M694V subgroup had higher mean disease severity score and longer attack duration compared with E148Q and other mutations subgroups ($p < 0.05$). Two patients with amyloidosis had the M694V homozygote genotype. In conclusion contrast to other regions and many other ethnicities of the world, the most frequent *MEFV* gene mutation was E148Q in southeast Turkey. The M694V mutation frequency was lower, and disease severity was relatively mild in FMF children of this region.

Keywords Familial Mediterranean fever · *MEFV* gene · Mutations · Clinical findings · Southeast Turkey

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessively inherited inflammatory disease that characterized by recurrent episodes of peritonitis, fever, rashes and arthritis [1]. FMF is caused by mutations in the Mediterranean fever (*MEFV*) gene, which is located on the short (p) arm of chromosome 16 at position 13.3. The gene encodes a protein called pyrin/maronestrin that regulates neutrophil activity [1].

The disease onset is usually under 10 years of age in 60 % and under 20 years in 90 % of patients [2]. Therefore, it is imperative to diagnose and treat FMF in childhood, in order to prevent the development of its most serious complication, amyloidosis.

Although FMF is mainly prevalent among the population inhabited around the Mediterranean Sea (Jews, Armenians, Turks and Arabs), it can be seen all around the world due to immigration and increased transportation [3].

Phenotype–genotype correlations have not been completely determined in patients with FMF. However, several investigators have reported increased disease severity and development of renal amyloidosis in patients having specific *MEFV* gene mutations such as homozygous M694V

mutation [3–5]. The phenotypic variations in the clinical course of the disease are largely attributed to genetic heterogeneity. Studies comparing disease phenotype related to *MEFV* genotype suggested that some mutations are more pathogenic than others, yet clinical expression of the disease can vary among patients having the same mutations [2, 6]. Types of *MEFV* mutations and clinical picture of FMF change in different geographic regions and ethnic groups. There are limited data regarding the features of FMF patients in southeast Turkey [7].

The aim of this study was to investigate the frequency of *MEFV* gene mutations and their clinical correlations in FMF children in the southeast region of Turkey.

Methods

The study group included 147 consecutive FMF children with a positive *MEFV* gene mutation. Patients aged 17 years or younger and attending to the Pediatric Outpatient Clinics of the Dicle University Hospital were included. The *MEFV* gene mutations of parents and sibling, who had a medical history or clinical finding suggested the possibility of FMF, were also screened. Our main inclusion criteria were diagnosis of FMF based on Livneh criteria [8], having a positive *MEFV* mutation and being inhabitant of southeast Turkey. Therefore, those with negative mutations or inhabitants of other regions of Turkey were excluded from the study.

The clinical and demographical characteristics, results of *MEFV* gene mutation analysis and response to colchicine treatment were recorded and analyzed. Baseline characteristics including age, sex, information regarding parental consanguinity, presence of other affected family members, date of disease onset and date of diagnosis were all determined. Clinical manifestations, including features such as duration and frequency of fever episodes, presence of arthritis, arthralgia, abdominal pain, erysipelas-like erythema, peritonitis, pleurisy, amyloidosis and urinary abnormalities, were also determined for the study. Acute phase reactants including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell count (WBC) were measured.

Complete response to colchicine treatment was defined as complete control of the clinical manifestations and acute phase reactants within normal limits; incomplete response was defined as persistence of some clinical manifestations and/or some elevated test results of acute phase reactants, and no response as no improvement in attack frequency and/or severity of disease despite colchicine treatment [9]. We used a disease severity score adapted by Ozen et al. [10] and included the following features: (a) age at onset [11–20 years (2 points), 6–10 years (3 points) and <6 years (4 points)], (b) number of attacks per month [<1 (1 point), 1–2 (2 points), >2 (3 points)], (c) acute or protracted arthritis (2 and 3 points, respectively), (d) presence of erysipelas-like erythema (2 points), (e) dose of colchicine [less than appropriate dose (0 point), appropriate dose (1 point) and more than appropriate dose (2 points)], and (f) development of amyloidosis (3 points). The severity score is the sum of each parameter. A score of 3–5 is accepted as mild, 6–9 moderate and >9 is severe disease.

The study protocol was approved by the Ethical Committee of our Institution, and informed consents were obtained from the parents of all participating subjects.

The *MEFV* gene mutation analysis

Molecular diagnosis of FMF was carried out in Dicle University Hospital Laboratories. Peripheral blood samples of the patients were obtained for DNA extraction. A reverse hybridization test method by FMF strip assay (ViennaLab labordiagnostika Gmbh, Vienna, Austria) was performed. Six mutations located in exon 2 (E148Q), exon 3 (P369S) and exon 10 (M680I, M694V, V726A and R761H) were investigated. The assay includes four successive steps for which reagents are provided: (a) DNA isolation from blood samples, (b) in vitro multiple amplification reaction, (c) hybridization of amplification products and (d) detection of bound biotinylated sequences. Amplifications were conducted on an Applied Biosynthesis Thermocycler 9700 using the protocol supplied by the manufacturer.

Statistical analysis

Descriptive statistics for continuous numerical variables were used. Distribution pattern of continuous variables was examined by Kolmogorov–Smirnov test. Differences between two groups were assessed by Chi-square test or Fisher's exact test for categorical variables, and Student's *t* test or Mann–Whitney *U* test according to distribution pattern of data. Kruskal–Wallis test was used for the multiple group comparisons. A p value of less than 0.05 was accepted as significant. SPSS version 12 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

The study group consisted of 147 patients (65 males, 82 females; male/female ratio 1.0/1.3) with FMF with a mean age of 8.7 ± 3.0 years (median 9.0, range 2.0–16.0). The mean age at disease onset was 5.4 years (range 0.5–12.0) and mean age at diagnosis was 7.6 years (range 2–13.0).

The mean duration for delay in diagnosis was 2.1 years (median 1.5; range 0.2–7.0). The main demographic and clinical characteristics are shown in Table 1. The mean follow-up period was 4.5 years (range 0.5–7). Fever and abdominal pain were observed in over 95 % of our study group. Arthralgia was observed in approximately 60 %, arthritis in 20 % and chest pain in 18 % of patients (Table 1). Most patients had attack duration of 12–72 h (in 81.9 %), and attack frequency was one or 2 attacks per month in 56.5 % of the patients (Table 1). The mean disease severity score was 6.5 ± 1.5 points (median 6, range 3–10). The distribution of disease severity score was as follows: mild disease (a score of 3–5) in 43 (29.3 %), moderate (a score of 6–9) in 99 (67.3 %) and severe (a score >9) disease in 5 (3.4 %).

Parental consanguinity was found in 64 (43.5 %) families. Family history of FMF was found in a relative of patients in 86 (58.5 %) families, and FMF was detected in 40 % of siblings, in 4.8 % of mothers, in 3.8 % of fathers and in 11.6 % of other relatives. Although FMF mutation analyses of parents and/or siblings were not performed in 46 families, a parent-to-offspring transmission of the *MEFV* gene mutations was documented in 62 (42.2 %) families. Forty-two (28.6 %) were from a single parent, and 20 (13.6 %) had the mutations in both parents.

Table 1 The clinical characteristics of 147 children with familial Mediterranean fever

Characteristics	*n* (%) or Mean ± SD
Male/Female	65/82
Age at onset (years)	5.4 ± 3.2
Age at diagnosis (years)	7.6 ± 3.0
Delay in diagnosis (years)	2.1 ± 1.6
Follow-up period (years)	4.2 ± 2.3
Disease severity score	6.5 ± 1.5
Attack duration (h)	
<12	17 (11.6)
12–24	23 (15.6)
24–48	54 (37.7)
48–72	42 (28.6)
>72	11 (7.5)
Attack frequency before treatment	
Irregular	34 (23.2)
1–4/month	93 (63.3)
>4/month	20 (13.6)
Fever	144 (97.9)
Abdominal pain	145 (98.6)
Arthralgia	88 (59.9)
Arthritis	30 (20.4)
Myalgia	27 (18.4)
Chest pain	26 (17.7)
Erythema	23 (15.6)
Response to colchicine	
Complete response	32 (21.8)
Incomplete response	111 (75.5)
No response	4 (2.7)

FMF familial Mediterranean fever, *SD* standard deviation

Various preliminary diagnoses had been made prior to an FMF diagnosis, including urinary tract infections (53.1 %), intestinal parasitosis (31.4 %), constipation (30.5 %), gastritis or gastroenteritis (21.0 %), acute appendicitis (5.4 %), acute nephritis (6.8 %) and nephrolithiasis (4.1 %) in our patients. All patients had normal renal functions (data not shown), and urinalysis revealed mild proteinuria in 13 (8.8 %), mild hematuria in 7 (4.8 %), microscopic hematuria plus mild proteinuria in 6 (4.1 %) and nephrotic proteinuria in 2 (1.4 %) patients. Patients with nephrotic proteinuria had renal amyloidosis at presentation. Hematuria was evaluated, nephrolithiasis was found in 5 patients, and 8 described a history of previous acute glomerulonephritis (AGN) attack. Acute nephritis and other causes of hematuria such as hypercalciuria, Alport's syndrome and urinary tract abnormalities or infections were excluded with appropriate investigations, including urinary calcium excretion, ultrasound examination, urine culture and hearing test. Mild proteinuria disappeared during follow-up period; however, severe proteinuria continued in two children with nephrotic proteinuria.

Colchicine was prescribed as 0.5 mg daily in 27 (18.4 %) children (<5 years of age), 1 mg daily in 104 (70.4 %), 1.5 mg daily in 12 (8.2 %) and 2 mg daily in 4 (2.7) children with FMF. Colchicine use was reported as regular in 93.2 %, irregular in 4.1 % and only during attacks in 3 % of patients. Colchicine was not discontinued in any patients. Complete or incomplete response to colchicine treatment was observed in 97.3 % of children with FMF.

The numbers and frequencies of detected 192 independent alleles (102 alleles were null) with decreasing order were the following: E148Q in 59 (30.7 %) patients, M694V in 50 (26.0 %), R761H in 26 (13.5 %), M680I in 25 (13.0 %), V726A in 20 (10.5 %) and P369S in 12 (6.3 %) in children with FMF. The three most frequent single-allele *MEFV* genotypes were E148Q/Null, V726A/Null and R761H/Null, and the two most frequent homozygous genotypes were M694V/M694V and E148Q/P369S in patients (Table 2). Heterozygous mutations were detected in 104 (70.7 %), homozygous mutations in 28 (19.1 %) and compound heterozygous mutations in 15 (10.2 %) patients. Two patients with amyloidosis had the M694V homozygote genotype.

In parents and siblings of FMF patients, the three most frequent independent alleles were E148Q (28.1 %), M694V (21.9 %) and R761H (17.3 %). The frequencies of other *MEFV* gene mutations in siblings and parents of FMF

Table 2 The distribution of *MEFV* genotypes in children with familial Mediterranean fever ($n = 147$)

One allele	*n* (%)	Two alleles	*n* (%)
E148Q/–	39 (26.5)	M694V/M694V	15 (10.2)
V726A/–	23 (15.7)	E148Q/P369S	8 (5.5)
R761H/–	16 (10.9)	E148Q/E148Q	4 (2.7)
M694V/–	14 (9.5)	R761H/R761H	4 (2.7)
P369S/–	9 (6.1)	M680I/M680I	3 (2.0)
M680I/–	3 (2.0)	Others/Others	9 (6.2)

children were M680I in 35 (13.5 %), V726A in 25 (9.6 %) and P369S in 25 (9.6 %). We found 15 (17.2 %) homozygous, 10 (11.5 %) compound heterozygous and 62 (71.3 %) heterozygous mutations among 87 relatives who had also clinical findings similar to FMF. There were 8 (6.3 %) compound heterozygotes and 9 (7.1 %) homozygotes and 109 (86.5 %) heterozygotes among the 126 apparently healthy relatives of the FMF patients.

While patients were divided into three subgroups according to genotypes with one or two mutations of E148Q, M694V and others (other mutations), no significant differences were found in gender ratio, age at onset and most of other clinical findings ($p > 0.05$). However, erythema was found to be more frequent in the M694V subgroup compared with the E148Q subgroup as well as others subgroups ($p = 0.012$). The M694V subgroup had higher disease severity scores and longer attack durations compared with E148Q and others subgroups ($p < 0.05$) (Table 3).

Discussion

The study was performed in a tertiary university hospital in southeast Turkey that nearly all FMF suspected children were referred. Totally, 147 FMF children having a positive *MEFV* mutation were included. The patients were evaluated regarding demographic, clinical and mutational characteristics. Because FMF patients from other parts of Turkey are never referred to our hospital and we excluded the patients originating from other regions, the results of our study represent the population living in southeast Turkey. Our study is the first exclusively examine FMF children with positive *MEFV* mutation in southeast Turkey, in combination with *MEFV* mutations of parents and siblings whose medical history and/or clinical findings cause suspicion of FMF.

We investigated the most frequent six *MEFV* gene mutations. Five missense *MEFV* gene mutations (M694V, M680I, M694I, V726A and E148Q) account for the most frequent *MEFV* gene mutations in peoples originating around the eastern Mediterranean region [2, 10]. The most distinctive finding of the present study was the highest frequency of E148Q mutation, which has been reported as associated with relatively mild disease course [1, 2, 11].

Most of the studies reported that FMF affect both sexes equally; however, male or female predominance was also reported in different series [11, 12]. In our study, we found a slight female predominance (1.3/1) (Table 1).

The mean age at disease onset (5.4 years), age of FMF diagnosis (7.6 years) and delay in diagnosis (2.1 years) in

Table 3 Clinical findings in children with familial Mediterranean fever according to different genotypes

	E148Q* ($n = 55$)	M694V** ($n = 35$)	Others*** ($n = 57$)	*p*
Male/Female	24/31	18/17	23/34	NS
Age at onset	6.4 ± 3.7	4.7 ± 2.4	5.0 ± 2.8	NS
Disease severity score	6.06 ± 1.45	7.15 ± 1.73	6.50 ± 1.37	**0.003**[¶], **NS**[§], NS[†], **0.005**[‡]
Attack duration				
<12 or 12–24 h	20 (36.4)	8 (22.8)	9 (15.8)	**0.031**[¥]
24–48 h	20 (36.4)	10 (28.6)	29 (50.9)	
<48 h	15 (27.2)	17 (48.6)	19 (33.3)	
Fever	54 (98.2)	32 (91.4)	55 (96.4)	NS
Abdominal pain	52 (94.5)	34 (97.1)	56 (98.2)	NS
Arthritis	11 (20.0)	9 (25.7)	8 (14.0)	NS
Chest pain	6 (10.9)	7 (20.0)	11 (19.3)	NS
Erythema	4 (7.3)	11 (31.4)	10 (17.5)	**0.012**[¥]

* E148Q/E148Q, E148Q/Other or E148Q/–

** M694V/M694V, M694V/Other or M694V/–

*** Others/Others

Differences; [¶] E148Q versus M694V subgroups, [§] M694V versus others, [†] E148Q versus others subgroups; [‡] Difference between three subgroups by Kruskal–Wallis test, *NS* not significant, [¥] Difference between three groups

Table 4 The most common MEFV mutations reported in different studies from the various regions of Turkey and some ethnic origins of other nationalities

References	Regions of Turkey	Number of patients	Median age (range) (years)	Mutations (%)					
				M694V	V726A	M680I	E148Q	R761H	P369S
Tunca et al. [3]	All over the Turkey	1,090	23 (2–87)	51.5	8.1	14.4	NR	NR	NR
Yalcinkaya et al. [12]	Central	167	6 (0.1–40)	43.5	11.1	13.0	NR	NR	NR
Öztürk et al. [13]	West	369	12.5 (2–30)	51.9	10.8	10.4	15.5	1.0	5.5
Evliyaoglu et al. [7]	Southeast	104	11.5 (5–15)	18.3	8.6	6.7	30.8	2.9	10.6
Our study	Southeast	147	9.0 (2–16)	26.0	13.0	6.3	30.7	13.5	10.5

Summary of other nationalities with mean ratios of MEFV mutations [14]

Ethnic origin	Number of patients	Mutations (%)					
		M694V	V726A	M680I	E148Q	Others	Unknown
Jews	1,301	65.0	3.0	1.0	5.0	6.0	20.0
Arabs	706	20.0	14.0	7.0	6.0	3.0	38.0
Armenians	378	37.0	19.0	21.0	3.0	4.0	16.0

NR not reported

our patients were comparable to previous studies. A study from western Turkey reported the mean age at FMF onset as 5.3 years, age at diagnosis 8.4 years and delay in diagnosis as 2 years similar to our results [13]. A study by Ozen et al. [10] found lower mean age at disease onset (3.6 vs. 4.6 years), age at diagnosis (6.4 vs. 11.9 years) and delay of diagnosis (2.8 vs. 7.2 years) in FMF patients from eastern Mediterranean compared with Europeans. It has been suggested that late onset and longer delay in diagnosis in European countries might be result from milder phenotypic manifestations due to environmental factors and extremely low incidence of the disease in Europe [10].

Frequencies of FMF manifestations in previous studies from Turkey, Armenia, Israel, Arab countries and Italy have been reported as follows: fever 92–100 %, abdominal pain 91–96 %, chest pain 31–84 %, arthritis 33–70 % and skin rash 3–40 % [14]. Arthritis, chest pain and erythema frequencies of our patients were found to be lower than those of previous reports (Table 1). According to disease severity scores, only 3.4 % of our patients had severe disease, while 29 % of them had mild and 67 % had a moderate disease course. The milder disease course may be related to more frequent E148Q and less frequent M694V mutations of our study group compared with other reports. The M694V homozygous and the compound heterozygous mutations have been reported together with severe disease activity and development of renal amyloidosis. Mean severity scores were found highest in homozygous and compound heterozygous M694V mutations [14]. A recent study also suggested that having a M694V mutation (for homozygosity or heterozygosity) increased the disease severity significantly in FMF children [10]. Another study suggested that the only genetic variable associated with FMF disease severity was the M694V mutation that in contrast with some previous studies [15]. In accordance with these studies, our study demonstrated that M694V subgroup had a higher disease severity score, longer attack duration and more frequent erysipelas-like erythema compared with E148Q subgroup (Table 3).

The rate of parental consanguinity has been reported as 20–25 % for the last 25 years in Turkey [12]. Parental consanguinity of our patients was higher (43.5 %) compared to general population of our country, and we detected parent-to-offspring transmission of FMF in 42.2 % of our families. More frequent parental consanguinity may be responsible for the higher ratio of parent-to-offspring transmission.

Although mild proteinuria may be seen in FMF, hematuria is not a usual finding in FMF. Some of our patients had transient microscopic hematuria. We investigated the cause of hematuria and found that hematuria of our patients was related to urolithiasis or a previous AGN attack.

Studies on FMF genotype in different regions of Turkey have reported the most frequent mutation as M694V with the frequency from 42.1 to 51.9 % [12, 16]. It has been reported that the frequency of E148Q mutations in Turkey changes from 3.5 to 19.3 % [17]; however, in our study, we found E148Q frequency as 30.7 % and M694V as 26.0 %. Another study from our region reported E148Q frequency as 30.2 % and M694V as 18.3 %, approximate to our results [7] (Table 4).

In conclusion, the genotype distribution of children with FMF in southeast Turkey was found as different from other parts of Turkey. In southeast Turkey, E148Q was the most frequent mutation and the frequency of the M694V mutation was lower compared to other regions of Turkey.

Disease severity was relatively mild in FMF children in southeast Turkey. Further prospective studies with more patients are necessary to verify our results.

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