RESEARCH ARTICLE

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The Spectrum of *MEFV* Gene Mutations and Genotypes in Patients with Familial Mediterranean Fever in Black Sea Region of Turkey

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Objective: Familial Mediterranean Fever (FMF) is the most common hereditary autoinflammatory disease characterized by recurrent, febrile episodes accompanied by peritonitis, pleuritis, and arthritis. The present study aims to evaluate the distribution of *MEFV* gene mutations in a large patient group from a single center and compares with other studies from different regions of Turkey.

Materials and Methods: In this study, demographic and clinical informations, *MEFV* mutation reports, and molecular testing methods of 1113 patients admitted to pediatric genetic and medical genetic outpatient clinics of a city-state hospital with the suspicion of FMF were investigated retrospectively.

Results: 854 patients (76.7%) had at least one mutation in *MEFV,* whereas 259 patients (23.3%) had no mutation. Among 854 patients, 394 (46.1%) were heterozygous, 63 (7.4%) were homozygous, 240 (28.1%) were compound heterozygous and 157 (18.4%) had complex genotype. 31 different mutations and total 1507 mutations were detected. The most common five mutations were R202Q, M694V, E148Q, M608I, and P369S. 777 patients (91%) underwent *MEFV* sequencing and 77 patients (9%) were analyzed with strip assay technique. The most common mutation in the patients underwent strips assay was M694V (45.9%), whereas in the exon 2,3,5,10 of *MEFV* sequenced patients R202Q (38.3%) was detected as the most common mutation.

Conclusion: In conclusion, our study revealed different results from the previous studies from Turkey. We had a high mutation detection rate and P369S was the one of the commonest mutation in our study. According to the method used to detect *MEFV* variants, the mutation frequencies may vary in between the studies.

Key Words: *Familial Mediterranean Fever, MEFV mutations, molecular testing*

Türkiye'nin Karadeniz Bölgesi'nde Ailesel Akdeniz Ateşi Hastalarında *MEFV* Geni Mutasyon ve Genotip Dağılımı

Amaç: Ailesel Akdeniz Ateşi (AAA), peritonit, plörit ve artritin eşlik ettiği tekrarlayan ateşli ataklarla karakterize en sık kalıtsal otoenflamatuar hastalıktır. Bu çalışma, tek bir merkezden büyük bir hasta grubundaki *MEFV* gen mutasyonlarının dağılımını değerlendirmeyi ve Türkiye'nin farklı bölgelerindeki diğer çalışmalarla karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmada, FMF şüphesi ile şehir devlet hastanesinin pediatrik genetik ve tıbbi genetik polikliniklerine başvuran 1113 hastanın demografik ve klinik bilgileri, *MEFV* mutasyon raporları ve moleküler test yöntemleri retrospektif olarak incelendi.

Bulgular: 854 hastada (% 76.7) *MEFV*'de en az bir mutasyon bulunurken, 259 hastada (% 23.3) mutasyon saptanmadı. 854 hastadan 394'ü (% 46.1) heterozigot, 63'ü (% 7.4) homozigot, 240'ı (% 28.1) bileşik heterozigot ve 157'si (% 18.4) kompleks genotipe sahipti. 31 farklı mutasyon ve toplam 1507 mutasyon tespit edildi. En yaygın beş mutasyon R202Q, M694V, E148Q, M608I ve P369S idi. 777 hastaya (% 91) *MEFV* dizi analizi uygulanırken, 77 hasta (% 9) strip yöntemi ile analiz edildi. Strip testi yapılan hastalarda en sık görülen mutasyon M694V (% 45.9) iken, *MEFV* ekzon 2,3,5, ve 10 dizi analizi yapılan hastalarda en sık görülen mutasyon R202Q (% 38.3) olarak saptandı.

Sonuç: Çalışmamızda Türkiye'de yapılmış olan önceki çalışmalardan farklı sonuçlar ortaya çıkmıştır. Çalışmamızda mutasyon tespit oranı yüksekti ve P369S en yaygın mutasyonlardan biriydi. *MEFV* varyantlarını tespit etmek için kullanılan yönteme göre, mutasyon frekansları çalışmalar arasında farklılık gösterebilmektedir.

Anahtar Kelimeler: *Ailesel Akdeniz Ateşi, MEFV mutasyonları, moleküler test*

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Introduction

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent, febrile episodes accompanied by peritonitis, pleuritis, arthritis, and/or erysipelas-like erythema (1). The frequency of attacks varies from once every week to several times a year. A typical attack of FMF lasts 0.5–3 days, and between attacks patients are generally asymptomatic (2). One of the devastating outcomes of FMF is the development of AA amyloidosis, which mostly affects the kidneys but may involve other organs (3). Life-long prophylactic colchicine is the main

treatment of FMF, which reduces the number of acute attacks and prevents the development of amyloidosis (4, 5).

FMF is the most common hereditary autoinflammatory disease worldwide and affects about 70 million people (6, 7). FMF is prevalent among populations surrounding the Mediterranean Sea, most commonly affects Jews, Turks, Armenians, and Arabs, however, in recent years, more cases have been reported in countries not related or close to this region. Turkey is one of the countries with the highest number of FMF patients, and a prevalence of about 1:1000. The carrier frequency among Turks is 1:5 (8, 9).

FMF is an autosomal recessive disease caused by mutations in the *MEFV* gene encoding the pyrin protein (1). Pyrin is expressed in neutrophils, monocytes, dendritic cells and in peritoneal, pleural, synovial, and dermal fibroblasts. Mutated pyrin protein causes an exaggerated inflammatory response as a result of uncontrolled production of interleukin (IL)-1ß (10). *MEFV* has 10 exons and the majority of the disease-associated variants are encoded by exon 10. To date, more than 333 sequence variants have been defined, nearly all of which are missense substitutions (11). Although many variants are considered to be associated with the FMF phenotype, the majority of cases are caused by M694V, M608I, V726A, and M694I mutations clustered on exon 10, the prevalence of which varies according to the population studied (6).

Several sets of diagnostic criteria have been proposed. Diagnosis of FMF is based on Tel-Hashomer criteria which depends on clinical manifestations (12). In atypical clinical cases, genetic analysis of *MEFV* is needed for confirming the FMF diagnosis.

The present study aims to evaluate the distribution of *MEFV* gene mutations in a large patient group from a single center in the Black Sea Region of Turkey and compares with other studies from different regions of Turkey.

Materials and Methods

Research and Publication Ethics: The Non-Invasive Clinical Research Ethics Committee of our hospital approved the study (protocol code: GOKA/2019/3/9).

The molecular genetic testing of 1113 patients admitted to pediatric genetic and medical genetic outpatient clinics of a tertiary medical center in the Middle Black Sea Region, north of Turkey, with the suspicion of FMF according to Tel-Hashomer criteria between January 1, 2015, and December 31, 2019, were investigated retrospectively. Demographic and clinical informations, *MEFV* mutation reports, and molecular testing methods were evaluated from patients' clinical genetic files retrospectively. The patients at least one mutation detected in the FMF genetic testing were included.

Results

From all 1113 patients, 854 patients (76.7%) had at least one mutation in *MEFV*, whereas 259 patients (23.3%) had no mutation. Among 854 patients, 510 were female (59.7%) and 344 were male (40.3%), with the mean age 22.3±16.7 years (min:1 years, max:85 years). The mean age of the complaint onset was 11.6±9.4 years. Among the mutation positive patients, 674 (78.9%) had abdominal pain, 495 (58%) had a fever, 514(63.6%) had arthralgia/arthritis and 93 (10.8%) had chest pain. The consanguinity rate was 31%. A family history of FMF was present in 425 (49.8%) patients. Of those 854 patients, 394 (46.1%) were heterozygous, 63 (7.4%) were homozygous, 240 (28.1%) were compound heterozygous and 157 (18.4%) had complex genotype. 31 different mutations and total 1507 mutations were detected in the patient group. The most common nine mutations were R202Q, M694V, E148Q, M608I, P369S, V726A, R408Q, A744S, and F479L respectively (Table 1).

Table 1. *MEFV* gene mutations frequencies among 854 patients

Mutation	Number of mutation	Mutation frequency (%)
R202Q	520	34.5
M694V	366	24.3
E148Q	175	11.6
M608I	142	9.4
P369S	60	4.0
V726A	57	3.8
R408Q	51	3.4
A744S	33	2.2
F479L	21	1.4
R761H	10	0.7
E167D	9	0.6
T267I	9	0.6
K695R	8	0.5
S166L	8	0.5
G304R	7	0.5
E148V	6	0.4
L110P	6	0.4
A287T	3	0.2
T177I	3	0.2
c.2223_2224del	2	0.2
G394R	1	0.07
P283R	1	0.07
Q198R	1	0.07
R148Q	1	0.07
R652C	1	0.07
R653H	1	0.07
R439H	1	0.07
V338L	1	0.07
V415*	1	0.07
S339F	1	0.07
R329H	1	0.07
Total	1507	100.0

These nine mutations were 94.6% (1425/1507) of total mutations. The most common six heterozygous mutations were R202Q, M694V, E148Q, M608I, V726A, A744S (Table 2). The most common homozygous genotypes were R202Q, M694V, M608I, E148Q, and V726A, respectively (Table 2). The three most common compound heterozygous genotypes were M694V/R202Q, E148Q/R202Q, and M608I/V726A (Table 3). Among 157 patients with complex genotype, 124 (79%) had three, 30 (19.1%) had four and 3 (1.9%) had five mutations. The most common complex genotype was M694V/R202Q/R202Q (Table 4). 777 (91%) patients underwent *MEFV* sequencing and the remaining 77 patients (9%) were analyzed for common known *MEFV* mutations (M694V, M694I, M608I(G/C), M608I(G/A), E148Q, P369S, V726A, A744S, I692del, K695R, R761H, and F479L) with strip assay technique. Exon 2,3,5 and 10 of the *MEFV* sequencing was the most common molecular testing method in the patient group (716 patients, 83.8%). Exon 10 and whole gene sequenced in 27 (3.2%) and 34 (4%) of the patients respectively. The most common mutation was M694V in the patients underwent strips assay and exon 10 of *MEFV* sequencing (45.9% and 48.6% respectively), whereas in the exon 2,3,5,10 of *MEFV* and whole *MEFV* sequenced patients the most common mutation was R202Q (38.3% and 35.1% respectively) (Table 5).

Table 2. Distribution of heterozygous and homozygous genotypes

Genotype	Heterozygous n (%)	Homozygous n (%)
R202Q	144 (36.5)	27 (42.9)
M694V	78 (19.8)	15 (23.9)
E148Q	58 (14.7)	8 (12.7)
M608I	52 (13.2)	12 (19.0)
V726A	20 (5.1)	1 (1.6)
A744S	14 (3.6)	-
Others	28 (7.1)	-
Total	394 (100)	63 (100)

Table 3. Distribution of compound heterozygous genotypes

Genotype	Compound Heterozygous n (%)
M694V/R202Q	95 (39.6)
E148Q/R202	20 (8.3)
M608I/V726A	10 (4.2)
M694V/V726A	9 (3.7)
M608I/E148Q	9 (3.7)
M608I/R202Q	9 (3.7)
P369S/R408Q	9 (3.7)
M608I/A744S	7 (2.9)
M694V/M608I	6 (2.5)
A744S/R202Q	6 (2.5)
M694V/E148Q	5 (2.1)
E148Q/L110P	4 (1.7)
M694V/F479L	4 (1.7)
E167D/F479L	4 (1.7)
F479L/R202Q	4 (1.7)
Others	39 (16.3)
Total	240 (100)

Table 4. Distribution of complex genotypes

Genotype	Complex genotype n (%)
M694V/R202Q/R202Q	30 (19.1)
E148Q/P6369S/R408Q	18 (11.5)
M694V/M694V/R202Q/R202Q	16 (10.2)
M694V/M608I/R202Q	14 (8.9)
M694V/E148Q/R202Q	11 (7.0)
P6369S/R408Q/R202Q	10 (6.4)
M694V/V726A/R202Q	7 (4.5)
M694V/M694V/R202Q	6 (3.8)
M608I/M608I/E148Q/E148Q	1 (0.6)
Others	44 (28.0)
Total	157 (100)

Table 5. Comparison of methods used for mutation analysis

	Strip assay for common *MEFV* mutations	**Exon 10 of *MEFV* sequencing**	**Whole *MEFV* sequencing**	**Exon 2,3,5,10 of *MEFV* sequencing**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Number of the patients (n=854)	77(9.0)	27(3.2)	34(4.0)	716(83.8)
Total number of mutations (n=1507)	109(7.2)	37(2.4)	74(4.9)	1288(85.5)
Detected mutations	M694V,E148Q M608I,V726A F479L,P369S A744S,R761H	M694V,M608I V726A,A744S	R202Q,M694V E148Q,M608I P369S,V726A R408Q,A744S F479L,R761H E167D, E148V T177I	R202Q,M694V E148Q,M608I P369S,V726A R408Q,A744S F479L,R761H E167D,T267I K695R,S166L G304R,E148V L110P,A287T T177I, G394R c.2223_2224del P283R,Q198R R148Q,R652C R653H,R439H V338L,V415* S339F,R329H
Heterozygous	49(63.6)	17(63.0)	10(29.4)	318(44.4)
Homozygous	13(16.9)	3(11.1)	1(2.9)	46(6.4)
Compound heterozygous	11(14.3)	7(25.9)	11(32.4)	211(29.5)
Complex genotype	4(5.2)	-	12(35.3)	141(19.7)
Most common mutations	M694V(45.9) E148Q(24.8) M608I(15.6) V726A(5.5)	M694V(48.6) M608I(27.0) V726A(13.5) A744S(10.8)	R202Q(35.1) M694V(28.4) E148Q(6.8) V726A(6.8) M608I(5.4)	R202Q(38.3) M694V(21.5) E148Q(11.1) M608I(8.6) P369S(4.3)
Most common genotypes	M694V/-(29.9) E148Q/-(16.9) M694V/M694*V* (13.0)	M694V/- (44.4) M694V/V726A (14.8)	M694V/R202Q (17.6) R202Q/- (14.7)	M694V/R202Q (12.4) M694V/R202Q/R202Q (4) E148Q/R202Q (2.8)

Discussion

Here, we reported the *MEFV* mutations reports of 1113 patients with clinical suspicion of FMF living in the northern Anatolia. We detected at least one mutation in 854 (76.7%) patients, and 31 different mutations were detected. 259 patients (23.3%) had no mutation. In other studies from Turkey, the prevalence of patients without mutations was in the range of 38.2-65.9% (11, 13, 14). The lower number of the patients without mutation in our study may be due to the high rate of consanguinity (31%) and we conducted a regional study from a single center.

FMF is a monogenic disorder inherited in the autosomal recessive manner. Although FMF is inherited autosomal recessively, some recent studies suggested that heterozygous people might manifest a spectrum of clinical features of mild and late-onset FMF. In several studies, as many as 30% of patients with FMF have only a single mutation in *MEFV*, even after whole exons sequencing. Partial penetrance and variable expressivity were suggested to explain the clinical features of FMF in heterozygous subjects (15,16). 46.1% of our patients with the clinical signs of FMF had heterozygous *MEFV* mutation.

In previous regional and country-wide studies from Turkey, R202Q, M694V, E148Q, M608I, V726A, and M694I were reported as the most common mutations (17, 18). In this study, the most frequently observed mutations were R202Q, M694V, E148Q, M608I, P369S, and V726A. None of our patients had M694I mutation.

R202Q was the most common mutation (34.5%) in our study. R202Q was found in 5-34% of the Turkish population. Sayin et al. (19), Coskun et al. (20), Gumus et al. (11), Celep et al. (21) found the R202Q as the most common mutation. In some reports, it is still listed as a polymorphism and the clinical outcome of this alteration is not well defined. However, there were other studies accepted R202Q as a mutation with clinical significance. It was emphasized that homozygous or compound heterozygous R202Q mutations could cause the FMF phenotype (22). Arpacı et al. reported that R202Q, the clinical findings of the patients with R202Q mutation were similar to the diagnostic clinical findings of FMF reported in the literature, and all patients responded to colchicine treatment. They stated that R202Q may be a mutation rather than polymorphism

and R202Q may be a risk factor in the development of the FMF clinic (23).

The G allele of R202Q was found in linkage disequilibrium (LD) with M694V, it means that certain alleles of each gene are inherited together more often than that would be accepted by chance (24). We found that in 179 alleles M694V and R202Q were in LD. Celep et. al showed LD between M694V and R202Q in 43 alleles (21). Kılınç et al. emphasized the frequent accompanying presence of M694V with R202Q and its' clinical impact in their study (17).

M694V was the second most common mutation (24.3%) in our study. In the majority of the reports from Turkey, M694V was the most common mutation. Dogan et al. (25) Oztuzcu et al. (26), Barut et al. (27) reported M694V as a first common mutation with the frequency of 42.8%, 41.7%, and 41.1% respectively, whereas, in the study of Evliyaoglu et al. (28) M694V frequency was 3.2%.

In our study, E148Q was the third most common mutation (11.6%). It was reported as a third common mutation in Turkey with a frequency of 6.8% (8, 19). It is found in 3-18% of the major ethnicities where FMF is common (2). The clinical significance of E148Q mutation is not well defined. It is considered as a polymorphism, and usually related with mild FMF phenotype (24).

P369S was the fifth common mutation (4%) in our patient group. This was the one of the major difference of our study from previous ones. Celep et al. (21) reported the allele frequency of P369S as 1.1% from the northern Anatolia. The allele frequency of P369S was 2.5% in the study of Gumus et al. (11).

M608I and V726A mutations were two of the common mutations in Turkish population (11). M608I frequency was reported in the range of 14.1-2.4% from previous studies (21). We found M608I as a fourth common mutation (9.4%). V726A frequency was reported in the range of 16.3-1.8 % from previous studies (21). V726A was the sixth common mutation (3.8%) in our study.

The majority of *MEFV* gene mutations responsible for the disease are missense mutations, whereas nonsense or deletion type mutations are rare (2). 29 (93.5%) of total 31 different mutations were missense mutations. Only 1 mutation was deletion type and 1 was a nonsense mutation.

When interpreting the mutation results of the patients, it is important to consider the method used for mutation detection. A number of methods are used in the diagnosis of FMF (17). In some studies, the patients were screened for the most common known mutations responsible for the majority of FMF, whereas some used sequencing of the gene. Some centers prefer sequencing only the exons coding the majority of disease-causing mutations, some others perform whole gene sequencing. Although the patient number was not homogenous, we saw that the method of exon 2,3,5 and 10 sequencing and whole gene sequencing revealed a more different number of mutations, more compound heterozygous and complex genotypes than the strip assay method. We also noticed that the most common mutations varied according to the method used to identify mutations. Gene sequencing either by the Sanger method or next-generation sequencing has the advantage to identify rare or novel variants, whereas interpreting the complex genotypes and novel variants may be difficult, and segregation analysis of the family is needed often.

In conclusion, our study revealed different results from the previous studies from Turkey. We had a high mutation detection rate in patients. P369S was the one of the commonest mutation in our study. According to the method used to detect *MEFV* gene variants, the frequencies of the mutations may vary in between the studies. The method should be in consider when giving genetic counseling to the families. We believe that our study may add some contribution to the mutational data of FMF.

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