



Molecular analyses of MEFV gene mutation variants in Turkish population

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Abstract

Background Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease primarily affecting individuals of Turkish, Armenian, Arab, and non-Ashkenazi Jewish descent, caused by mutations in the MEFV gene. The aim of this study was to review the common genotype distributions of MEFV variants and mutations in the Turkish population and evaluate rare mutations.

Methods and results The study included 2984 patients who applied to Ankara University İbni Sina Hospital Immunology Laboratory with clinical suspicion of FMF between 2004 and 2014. The data of patients from different regions of the country who were followed up in the immunology-rheumatology clinic with clinical suspicion and presumptive diagnosis of FMF were evaluated retrospectively. Patients were tested for all mutations in Exon 2 and Exon 10, including M694V, M680I, M694I, V726A, E148Q and R202Q. There were 2504 patients with FMF variant. According to genotyping, R202Q ($n = 1567$, 39.2%) was the most common mutation. The most common co-variant was the R202Q/M694V genotype ($n = 507$, 16.98%). Allele frequencies for MEFV mutations were as follows: R202Q ($n = 1567$, 39.2%), M694V ($n = 1004$, 25.1%), E148Q ($n = 463$, 11.5%), M680I ($n = 354$, 8.8%), V726A ($n = 319$, 7.9%), A744S ($n = 51$, 1.2%), R761H ($N = 41$, 1.0%), P706P ($N = 25$, 0.6%), E167D ($N = 23$, 0.5%), M694I ($N = 23$, 0.5%), and K695R ($N = 20$, 0.5%).

Conclusion This research revealed the prevalence of both common and rare MEFV gene mutations in Turkish FMF patients in various age groups. R202Q was the most prevalent mutation.

Keywords Familial Mediterranean Fever · MEFV gene mutations · R202Q · Türkiye

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Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive inflammatory disorder caused by mutations in the MEFV gene [1–3]. The term “Familial Mediterranean Fever” is derived from its genetic inheritance and its high occurrence in Mediterranean areas, particularly notable in Armenian, Arab, Jewish, and Turkish populations. Although FMF is not common in Spain, Italy, Iran, and Greece, it has acquired worldwide awareness because of increasing immigration in recent decades [1, 4–6]. Advancements in molecular biology and genetics has led to a more detailed understanding of FMF, including aspects such as penetrance, pathogenesis, mutation types (gain-of-function or loss-of-function), and heredity [7, 8].

The responsible gene, MEFV, located on the short arm of chromosome 16p13.3, was identified three decades ago [9] and comprises 10 exons and 781 codons [2, 10]. Mutations within this gene lead to the synthesis of a dysfunctional

protein known as “pyrin,” which plays a crucial role in both the innate immune system and the regulation of inflammation [7, 11]. Consequently, these mutations can result in uncontrolled and excessive inflammation through the synthesis of interleukin-1 (IL-1) [2, 4, 7].

MEFV mutations predominantly occur in exons 2 and 10, with 390 different variants identified, of which approximately 59% are located in these exons [6, 7, 12]. Among the various mutations identified in the MEFV gene, M694V is the most common and pathogenic worldwide, particularly among the Mediterranean regions. Other commonly observed pathogenic mutations include M680I, V726A, M694I, and E148Q. Collectively, these five mutations account for approximately 80% of genotypes in FMF patients from Mediterranean populations [7, 13, 14]. Out of the reported 29 MEFV mutations, 26 are missense mutations, one is a nonsense mutation (Y688X), and two are minor deletions (I692del, M694del) [2, 15].

FMF patients often have recurrent attacks characterized by fever and serositis with intense chest, abdominal, or joint pain, as well as accompanying symptoms like abdominal discomfort, pleuritis, arthritis, and skin manifestations [3, 5]. The unpredictable nature of these episodes poses clinical challenges, necessitating a comprehensive understanding of the disease spectrum for accurate diagnosis [16]. Despite the availability of genetic testing for FMF, challenges persist due to the diversity of mutations and the potential for atypical presentations in clinical practice [7, 17]. In this context, Türkiye stands out as a focal point for FMF research. With a population of approximately 82 million, Türkiye carries a considerable burden of FMF, estimated at 1 in 1000 individuals in [7, 17]. This places Türkiye among the countries most affected globally, highlighting the urgent necessity for thorough genetic investigations and improved diagnostic methodologies [7, 18].

In this study, our aim was to investigate the genotype distribution of common and rare FMF variants in the Turkish population.

Materials and methods

Patient groups

Over a ten years period (between January 2004 and December 2014), patient’s histories were retrospectively investigated. This research included a total of 2984 patients who were suspected of having FMF. All patients exhibited one or more symptoms typically associated with FMF, predominantly including abdominal pain, fever, arthralgia, and erysipelas-like erythema. Diagnosis was based on the Tel-Hashomer criteria or a detailed clinical assessment.

Informed consent was obtained from all patients or their parents before undergoing genetic testing. This work was approved by the Ankara University Human Research Ethics Committee. (decision no: I06-356-22).

Sanger sequencing

DNA sequence analysis was conducted using two different instruments. Blood samples were collected in vacuum tubes containing ethylenediaminetetraacetic acid (EDTA) according to the manufacturer’s instructions for the Blood Genomic DNA Isolation Kit (Norgen Biotek, Canada), enabling DNA extraction from peripheral blood. PCR amplification of the MEFV gene was performed using forward and reverse primers targeting exons 2 and 10. The PCR conditions were as follows: initial denaturation at 94 °C for 5 min, followed by 30 cycles of denaturation at 94 °C for 30 s, annealing at 58 °C for 45 s, extension at 72 °C for 1 min, and a final extension at 72 °C for 5 min. The PCR products were observed on a 2% agarose gel through electrophoresis.

For the first instrument, the amplification products were purified using the Genomic DNA Purification Kit (Fermentas, USA) before sequence analysis with an automated fluorescence-based sequencer system (Beckman Coulter CEQ 8000). For the second instrument, the PCR products underwent sequencing using the ABI Prism BigDye Terminator Cycle Sequencing Ready Reaction Kit according to the manufacturer’s instructions (Applied Biosystems, Foster City, USA). Sequence analysis was conducted with an automated fluorescence-based sequencer system (ABI PRISM 3130, Applied Biosystems).

Statistical analysis

Descriptive statistics were presented as mean \pm standard deviation for the variables whereas they were presented as number and percentage (%) for nominal variables. Categorical variables were evaluated using Pearson’s chi-square test or Fisher’s exact test as appropriate. A *p* value of less than 0.05 was considered statistically significant and the analyses were conducted using the Statistical Package for Social Sciences (SPSS, Version 15.0, Chicago, IL).

Results

MEFV variations (one or more MEFV mutations per patient) located in Exon 2 and Exon 10 were detected in 2504 of the 2984 patients (83.9%). 480 of the 2984 patients (16.1%) had no detected variant despite clinical symptoms. A total of 44 different FMF variants were identified in 2504 patients included in the study, with 28 variants were found

in the exon 2 region and 16 in exon 10. The study group comprised 1499 (59.9%) female and 1005 (40.1%) male patients, with an average age of 31.91 (± 14.34) years.

The most common FMF variants/mutations are R202Q ($n=1567$, %39,2), M694V ($n=1004$, %25,1), E148Q ($n=463$, %11,5), M680I ($n=354$, %8,8), V726A ($n=319$, by 7.9%), A744S ($n=51$, %1,2), R761H ($N=41$, %1,0), P706P ($n=25$, by 0.6%), E167D ($N=23$ 0.5%), M694I

($N=23$ 0.5%) K695R ($N=20$, 0.5), respectively. Gender-specific distributions of mutation prevalence is shown in Table 1, while Fig. 1 demonstrates the distribution of the most common mutations observed in our study population. This common mutation constitutes 92,5% of the entire patient population. Eighteen variants are present in only one patient. Among the 14 consensus variants, our patient group did not have the pathogenic variant I692del in exon 10.

Table 1 The allele frequencies of MEFV mutations

Mutation	Total alleles $n(\%)$	Mutation	Female $n(\%)$	Mutation	Male $n(\%)$
R202Q	1567 (39.22)	R202Q	944 (40.62)	R202Q	623 (37.28)
M694V	1004 (25.13)	M694V	543 (23.36)	M694V	461 (27.59)
E148Q	463 (11.59)	E148Q	273 (11.75)	E148Q	190 (11.37)
M680I	354 (8.86)	M680I	197 (8.48)	M680I	157 (9.4)
V726A	319 (7.98)	V726A	195 (8.39)	V726A	124 (7.42)
A744S	51 (1.28)	A744S	31 (1.33)	A744S	20 (1.2)
R761H	41 (1.03)	R761H	22 (0.95)	R761H	19 (1.14)
P706P	25 (0.63)	L110P	16 (0.69)	P706P	12 (0.72)
E167D	23(0.58)	E167D	14 (0.6)	M694I	11 (0.66)
M694I	23 (0.58)	P706P	13 (0.56)	K695R	10 (0.60)
L110P	21 (0.53)	M694I	12 (0.52)	E167D	9 (0.54)
K695R	20 (0.50)	T267I	11 (0.47)	E230K	7 (0.42)
T267I	14 (0.35)	K695R	10 (0.43)	L110P	5 (0.30)
E230K	12 (0.30)	E230K	5 (0.22)	T267I	3 (0.18)
P180L	5 (0.13)	P180L	5 (0.22)	G219G	2 (0.12)
G219G	5 (0.13)	G219G	3 (0.13)	S242S	2 (0.12)
P124P	3 (0.08)	P124P	2 (0.09)	R653H	2 (0.12)
S104C	3 (0.08)	S104C	2 (0.09)	P124P	1 (0.06)
S683S	3 (0.08)	E148V	2 (0.09)	A279E	1 (0.06)
P646P	3 (0.08)	S683S	2 (0.09)	S104C	1 (0.06)
R653H	3 (0.08)	P646P	2 (0.09)	S108R	1 (0.06)
I640M	3 (0.08)	I640M	2 (0.09)	S154P	1 (0.06)
S675N	3 (0.08)	S675N	2 (0.09)	N130N	1 (0.06)
S154P	2 (0.05)	G111G	2 (0.09)	E251K	1 (0.06)
S242S	2 (0.05)	R178W	1 (0.04)	T262T	1 (0.06)
E148V	2 (0.05)	P180P	1 (0.04)	V704I	1 (0.06)
V704I	2 (0.05)	P188P	1 (0.04)	S683S	1 (0.06)
G632S	2 (0.05)	A217A	1 (0.04)	P646P	1 (0.06)
G111G	2 (0.05)	S154P	1 (0.04)	G632S	1 (0.06)
R178W	1(0.03)	R151S	1 (0.04)	I640M	1 (0.06)
A279E	1(0.03)	P132P	1 (0.04)	S675N	1 (0.06)
S108R	1(0.03)	S117G	1 (0.04)		
P180P	1(0.03)	I259V	1 (0.04)		
P188P	1(0.03)	G196R	1 (0.04)		
A217A	1(0.03)	V704I	1 (0.04)		
R151S	1(0.03)	R653H	1 (0.04)		
P132P	1(0.03)	G632S	1 (0.04)		
S117G	1(0.03)	L649V	1 (0.04)		
N130N	1(0.03)				
I259V	1(0.03)				
G196R	1(0.03)				
E251K	1(0.03)				
T262T	1(0.03)				
L649V	1(0.03)				
TOTAL	3995 (100)		2324(100)		1671(100)

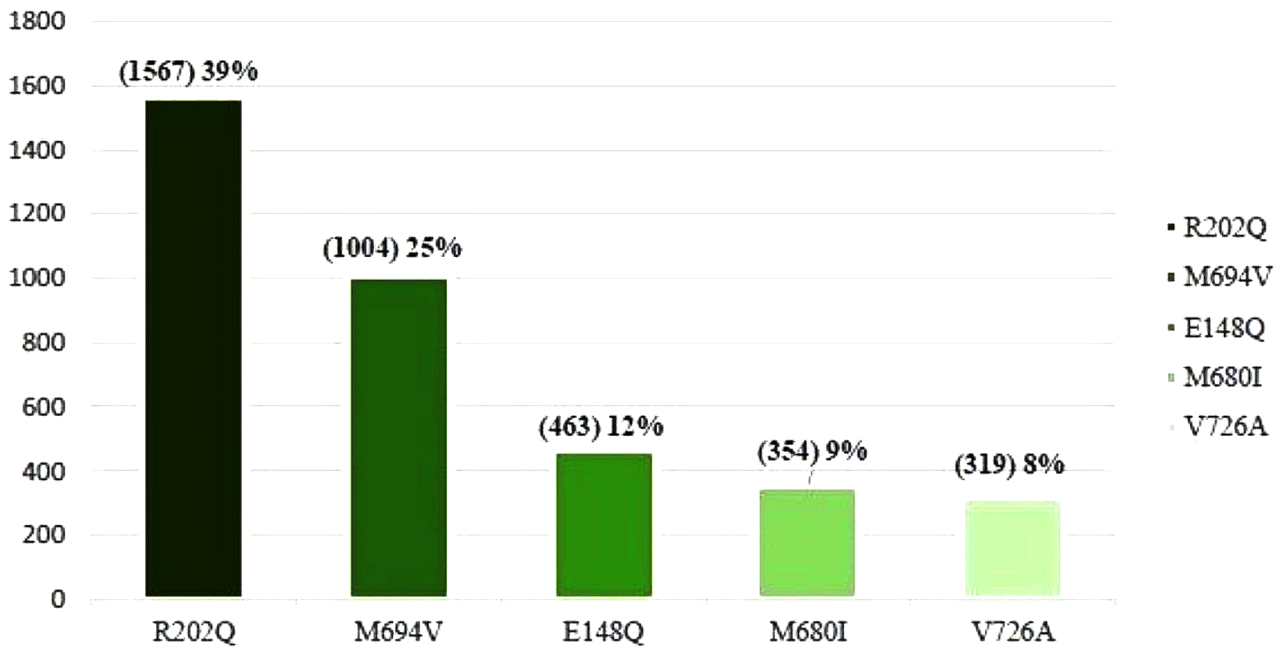


Fig. 1 Most common mutations in the study group

According to zygosity, patients were classified as heterozygous ($n=1172$), homozygous ($n=157$), compound heterozygous ($n=591$), compound homozygous ($n=174$), or compound heterozygous/homozygous (complex) ($n=410$). The three most common homozygous mutations found in patients are as follows: in Exon 2 R202Q ($n=334$, 93.8%), E148Q ($n=17$, 4.7%), and E167D ($n=7$, 0.23%). In Exon 10, the most common variations are M694V ($n=111$, 3.72%), V726A ($n=100$, 3.35%), and M680I ($n=94$, 3.15%). Combined mutations found in patients; Heterozygous/Heterozygous: R202Q/M694V ($n=243$, 8.14%), R202Q/E148Q ($n=56$, 1.88%), M680I/V726A ($n=46$, 1.54%), M694V/E148Q ($n=38$, 1.27%) Homozygous/Homozygous: R202Q/M694V ($n=169$, 5.66%). Homozygous/Heterozygous: R202Q/M694V ($n=71$, 2.38%), Heterozygous/Homozygous: R202Q/M694V ($n=24$, 0.8%). The complex genotype was R202Q/M694V/M680I ($n=108$, 3.62%). The distribution of MEFV genotypes found in patients is given in Table 2.

The ranking of the three most prevalent mutations in different age groups is as follows: for individuals aged 12 and under, M680I ($n=205$, 47.0%), R202Q ($n=111$, 25.4%), and M694V ($n=58$, 13.3%). In the age group of 13–19 years old, R202Q ($n=189$, %39,7), M694V ($n=106$, %22,2), E148Q ($n=71$, %14,9). For individuals aged 20 and above, the top three mutations were R202Q ($n=1254$, 38.8%), M694V ($n=828$, 25.6%), E148Q ($n=358$, 11.0%). Notably, in individuals aged 12 and under, the most frequent mutation observed was M680I, distinguishing this

group from others. Furthermore, the incidence of mutation is significantly greater in individuals above the age of 20 compared to other age groups ($p<0.001$). Figure 2 shows the frequency of the first 10 mutations according to age groups. In the patient group in our study women more than men mutations has been identified. Our study also revealed a higher prevalence of mutations in females compared to males within the patient group. Specifically, R202Q ($n=944$, 40.62%), M694V ($n=543$, 23.36%), and E148Q ($n=271$, 11.75%) mutations were more frequently observed in females. Conversely, in males, the mutation frequencies were R202Q ($n=623$, 37.28%), M694V ($n=461$, 27.59%), and E148Q ($n=190$, 11.37%). Our analysis found a higher prevalence of mutations in women compared to males within the patient group. However, there was no statistically significant difference between the frequency of mutations in males and females ($p<0.076$). Figure 3 shows the distribution of the top 10 mutations in men and women.

Discussion

FMF, a hereditary autoinflammatory disease prevalent in Turkish, Arab, Jewish, and Armenian populations, is characterized by recurrent episodes of abdominal pain, serositis, and fever [6]. Approximately 1 in 1000 individuals in the Turkish population are estimated to be affected by FMF, with around 20% of the population carrying the disease [19]. While clinical diagnosis is sufficient to identify FMF,

Table 2 Distribution of MEFV mutations in patients

Mutation	<i>n</i>	%
Homozygous		
R202Q Homozygous	84	2.81
M680I Homozygous	29	0.97
V726A Homozygous	18	0.60
E148Q Homozygous	11	0.37
M694V Homozygous	10	0.34
R761H Homozygous	3	0.10
E167D Homozygous	2	0.07
Total	157	5.26
Heterozygous		
R202Q Heterozygous	561	18,80
E148Q Heterozygous	198	6,63
M694V Heterozygous	111	3,72
V726A Heterozygous	100	3,35
M680I Heterozygous	94	3,15
A744S Heterozygous	34	1,14
R761H Heterozygous	13	0,44
P706P Heterozygous	13	0,44
K695R Heterozygous	11	0,37
M694I Heterozygous	8	0,27
E167D Heterozygous	7	0,23
E230K Heterozygous	3	0,10
P124P Heterozygous	2	0,07
T267I Heterozygous	2	0,07
S104C Heterozygous	2	0,07
I640M Heterozygous	2	0,07
G111G Heterozygous	1	0,03
A279E Heterozygous	1	0,03
S154P Heterozygous	1	0,03
P132P Heterozygous	1	0,03
E148V Heterozygous	1	0,03
N130N Heterozygous	1	0,03
I259V Heterozygous	1	0,03
T262T Heterozygous	1	0,03
S683S Heterozygous	1	0,03
P646P Heterozygous	1	0,03
G632S Heterozygous	1	0,03
Total	1172	39.27
Compound Heterozygous		
R202Q Heterozygous/M694V Heterozygous	243	8,14
E148Q Heterozygous/R202Q Heterozygous	56	1,88
M680I Heterozygous/V726A Heterozygous	46	1,54
E148Q Heterozygous/M694V Heterozygous	38	1,27
R202Q Heterozygous/M680I Heterozygous	22	0,74
R202Q Heterozygous/V726A Heterozygous	21	0,70
E148Q Heterozygous/V726A Heterozygous	19	0,64
E148Q Heterozygous/M680I Heterozygous	18	0,60
M694V Heterozygous/V726A Heterozygous	17	0,57
M694V Heterozygous/M680I Heterozygous	13	0,44
E148Q Heterozygous/L110P Heterozygous	9	0,30
M680I Heterozygous/R761H Heterozygous	7	0,23
E148Q Heterozygous/A744S Heterozygous	6	0,20
R202Q Heterozygous/P706P Heterozygous	6	0,20
E167D Heterozygous/V726A Heterozygous	6	0,20
T267I Heterozygous/V726A Heterozygous	6	0,20

Table 2 (continued)

Mutation	<i>n</i>	%
R202Q Heterozygous/K695R Heterozygous	4	0,13
V726A Heterozygous/R761H Heterozygous	4	0,13
R202Q Heterozygous/A744S Heterozygous	3	0,10
E230KHeterozygous/M680I Heterozygous	3	0,10
E148Q Heterozygous/S683S Heterozygous	2	0,07
R202Q Heterozygous/E167D Heterozygous	2	0,07
R202Q Heterozygous/G219G Heterozygous	2	0,07
R202Q Heterozygous/M694I Heterozygous	2	0,07
R202Q Heterozygous/S675N Heterozygous	2	0,07
M694V Heterozygous/A744S Heterozygous	2	0,07
V726A Heterozygous/K695R Heterozygous	2	0,07
P124P Heterozygous/R202Q Heterozygous	1	0,03
G111G Heterozygous/M680I Heterozygous	1	0,03
E148Q Heterozygous/E148V Heterozygous	1	0,03
E148Q Heterozygous/S242S Heterozygous	1	0,03
E148Q Heterozygous/R151S Heterozygous	1	0,03
E148Q Heterozygous/S154P Heterozygous	1	0,03
E148Q Heterozygous/P646P Heterozygous	1	0,03
E148Q Heterozygous/R653H Heterozygous	1	0,03
E148Q Heterozygous/P706P Heterozygous	1	0,03
E148Q Heterozygous/S675N Heterozygous	1	0,03
R202Q Heterozygous/L110P Heterozygous	1	0,03
R202Q Heterozygous/P188P Heterozygous	1	0,03
R202Q Heterozygous/S117G Heterozygous	1	0,03
R202Q Heterozygous/V704I Heterozygous	1	0,03
R202Q Heterozygous/R761H Heterozygous	1	0,03
R202Q Heterozygous/L649V Heterozygous	1	0,03
E167D Heterozygous/M694V Heterozygous	1	0,03
P180L Heterozygous/M694V Heterozygous	1	0,03
S104C Heterozygous/V726A Heterozygous	1	0,03
E251K Heterozygous/M694V Heterozygous	1	0,03
M694V Heterozygous/M694I Heterozygous	1	0,03
M694V Heterozygous/R761H Heterozygous	1	0,03
M680I Heterozygous/A744S Heterozygous	1	0,03
M680I Heterozygous/M694I Heterozygous	1	0,03
M680I Heterozygous/G632S Heterozygous	1	0,03
M680I Heterozygous/P646P Heterozygous	1	0,03
M680I Heterozygous/K695R Heterozygous	1	0,03
V726A Heterozygous/P706P Heterozygous	1	0,03
A744S Heterozygous/R761H Heterozygous	1	0,03
M694I Heterozygous/R761H Heterozygous	1	0,03
Total	591	19.8
Complex alleles		
R202Q Homozygous/M694V Homozygous	169	5,66
R202Q Heterozygous/M694V Heterozygous/M680I Heterozygous	108	3,62
R202Q Homozygous/M694V Heterozygous	71	2,38
E148Q Heterozygous/R202Q Heterozygous/M694V Heterozygous	68	2,28
R202Q Heterozygous/M694V Heterozygous/V726A Heterozygous	64	2,14
R202Q Heterozygous/M694V Homozygous	24	0,80
R202Q Heterozygous/M694V Heterozygous/R761H Heterozygous	8	0,27
R202Q Heterozygous/E230K Heterozygous/M694V Heterozygous	6	0,20
E148Q Heterozygous/M694V Heterozygous/V726A Heterozygous	5	0,17
E148Q Heterozygous/R202Q Heterozygous/L110P Heterozygous	4	0,13
R202Q Heterozygous/P180L Heterozygous/M694V Heterozygous	4	0,13

Table 2 (continued)

Mutation	<i>n</i>	%
R202Q Heterozygous/M694V Heterozygous/A744S Heterozygous	4	0,13
E148Q Heterozygous/L110P Heterozygous/M694V Heterozygous	3	0,10
R202Q Heterozygous/T267I Heterozygous/M694V Heterozygous	3	0,10
R202Q Heterozygous/E167D Heterozygous/M694V Heterozygous	3	0,10
R202Q Heterozygous/M694V Heterozygous/M694I Heterozygous	3	0,10
R202Q Heterozygous/M680I Heterozygous/P706P Heterozygous	2	0,07
R202Q Homozygous/G219G Heterozygous	2	0,07
E148Q Heterozygous/R202Q Homozygous	1	0,03
E148Q Heterozygous/M694V Homozygous	1	0,03
E148Q Homozygous/V726A Heterozygous	1	0,03
E148Q Homozygous/V726A Homozygous	1	0,03
E148Q Homozygous/R761H Homozygous	1	0,03
E148Q Homozygous/M694I Heterozygous	1	0,03
E148Q Homozygous/L110P Homozygous	1	0,03
R202Q Homozygous/R178W Heterozygous	1	0,03
R202Q Homozygous/V726A Homozygous	1	0,03
R202Q Homozygous/P706P Heterozygous	1	0,03
E167D Homozygous/M680I Heterozygous	1	0,03
T267I Homozygous/V726A Homozygous	1	0,03
E148Q Heterozygous/L110P Heterozygous/M680I Heterozygous	1	0,03
E148Q Heterozygous/S242S Heterozygous/M694V Heterozygous	1	0,03
E148Q Heterozygous/M694V Heterozygous/M680I Heterozygous	1	0,03
E148Q Heterozygous/M694V Heterozygous/M694I Heterozygous	1	0,03
E148Q Heterozygous/V726A Heterozygous/R653H Heterozygous	1	0,03
R202Q Heterozygous/A217A Heterozygous/M694V Heterozygous	1	0,03
R202Q Heterozygous/M694V Heterozygous/R761H Heterozygous	1	0,03
R202RQ Heterozygous/M694V Heterozygous/V704I Heterozygous	1	0,03
R202Q Heterozygous/M694V Heterozygous/K695R Heterozygous	1	0,03
R202Q Heterozygous/M694V Heterozygous/I640M Heterozygous	1	0,03
R202Q Heterozygous/M694V Heterozygous/R653H Heterozygous	1	0,03
E167D Heterozygous/G196R Heterozygous/P706P Heterozygous	1	0,03
T267I Heterozygous/M694V Heterozygous/V726A Heterozygous	1	0,03
T267I Heterozygous/M680I Heterozygous/V726A Heterozygous	1	0,03
E148Q Heterozygous/R202Q Homozygous/M694V Heterozygous	1	0,03
E148Q Homozygous/L110P Heterozygous/M694V Heterozygous	1	0,03
R202Q Homozygous/G219G Heterozygous/M694V Heterozygous	1	0,03
E148Q Heterozygous/R202Q Heterozygous/L110P Heterozygous/M694V Heterozygous	1	0,03
E148Q Heterozygous/R202Q Heterozygous/P180P Heterozygous/M694V Heterozygous	1	0,03
E148Q Heterozygous/R202Q Heterozygous/M694V Heterozygous/M680I Heterozygous	1	0,03
R202Q Heterozygous/S108R Heterozygous/M694V Heterozygous/V726A Heterozygous	1	0,03
Total	584	19.57
Number of patients with any mutation	2504	83.91
Number of patients with no mutation	480	16.09
Total number of patients	2984	100

nearly 80% of diagnosed patients exhibit MEFV gene mutations [3, 20]. However, genetic analysis is not mandatory, but it is important for confirming or excluding the diagnosis, particularly in cases with atypical clinical phenotypes [17, 21]. Early diagnosis and treatment of FMF are necessary to prevent amyloidosis, the most common and worse complication of the disease, and to improve patients' quality of

life [3, 22, 23]. Detection of MEFV gene variants provides benefits for the diagnosis and treatment of FMF. Shinar et al. recommended screening for 14 selected MEFV gene variants, of which 9 are classified as known pathogenic variants (M694V, M680I, V726A, M694I, A744S, R761H, I692del, E167D, T267I), while 5 are categorized as variants of uncertain significance (K695R, E148Q, P369S, F479L, I591T) [24].

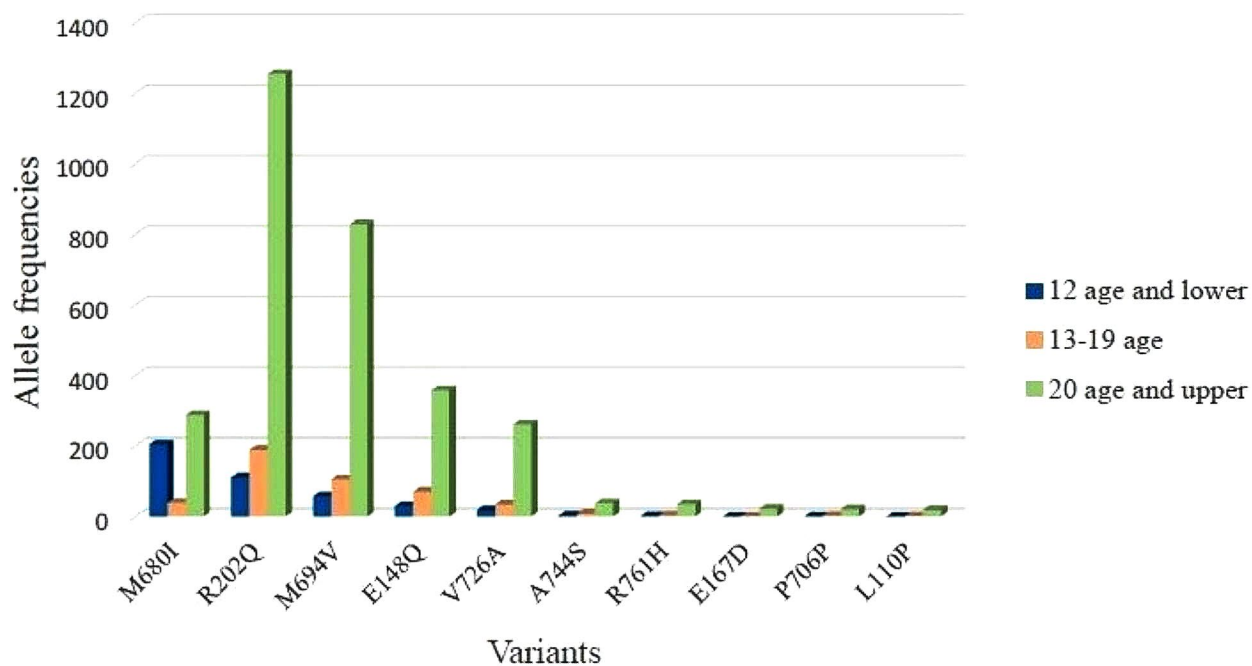


Fig. 2 Most common variants in the study population according to age groups

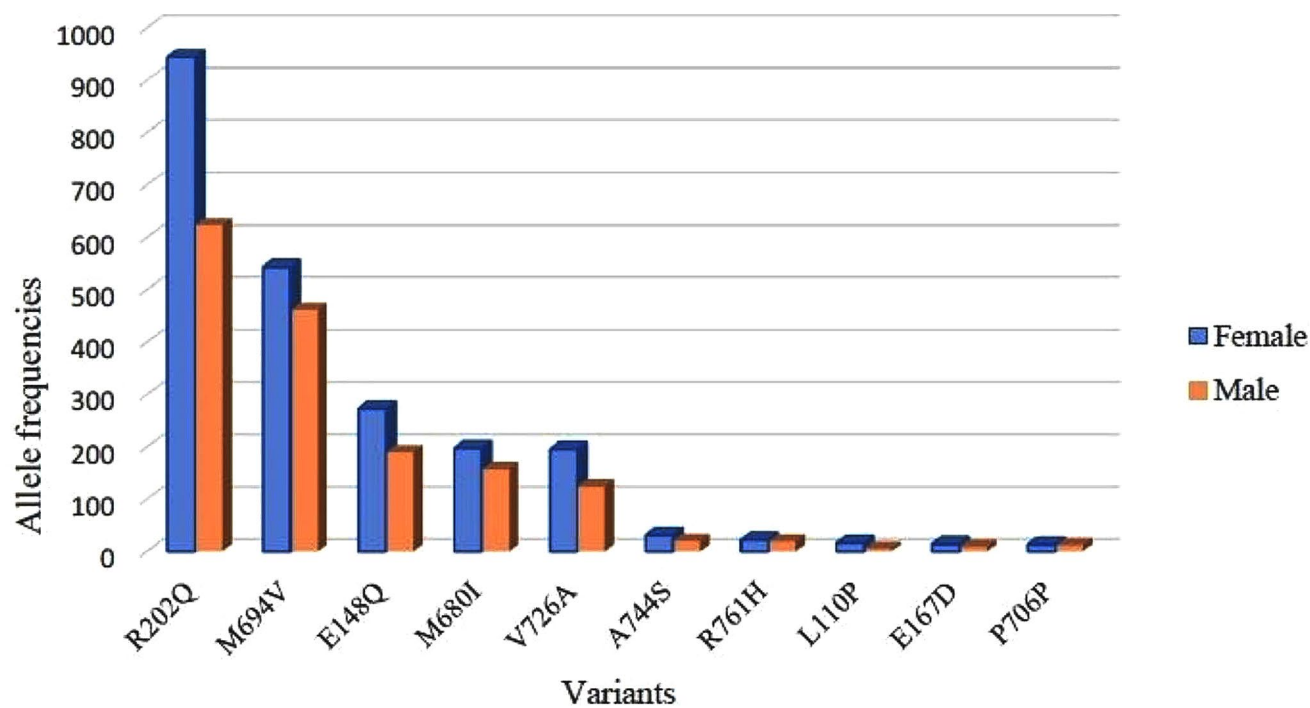


Fig. 3 Most common variants in both males and female

Regarding polymorphisms associated with FMF, we identified single nucleotide changes with allele frequencies of A165A 2406 (21.8%), G138G 2383 (21.5%), and D102D 2255 (20.4%) in our patient population. These synonymous nucleotide changes in the Exon 2 region of the MEFV gene do not alter amino acid structure but modify the codon specifying an amino acid [25]. Akar et al. noted a significant difference in the ala138gly polymorphism between patients diagnosed with amyloidosis and FMF and those without amyloidosis, suggesting an association between the g138g polymorphic allele and amyloidosis development [26]. However, Öksüz et al. found no significant association between these polymorphisms and clinical features in FMF patients [27]. Consequently, these polymorphisms were excluded from our study's evaluation. Further research is warranted to explore all variations in the MEFV gene and evaluate the impact of these genetic variants on linkage disequilibrium.

In our study, Table 1 demonstrates that the most prevalent variant is R202Q, accounting for 1567 cases (39.22%). Among these, 84 cases (2.81%) were homozygous for the R202Q variant, while 561 cases (18.80%) were heterozygous. Arpacı et al. conducted a study in the Hatay region involving 2639 patients, reporting the R202Q mutation as the most common, with 1319 cases (19.55%) being homozygous [13]. They found that clinical findings among patients with homozygous and heterozygous R202Q mutations were similar, and all patients responded to colchicine treatment.

In a study by Kırnaz et al. involving 3230 patients and using NGS, the most frequent mutation identified was R202Q, with 1097 cases (37.48%) reported [12]. Sönmezgöz et al. highlighted the prevalence of M694V and R202Q mutations in children with FMF in the Black Sea region [28]. They observed that patients with M694V and R202Q mutations commonly presented with recurrent abdominal pain and arthritis/arthritis. Additionally, they stated that the R202Q mutation commonly causes chest pain [28]. Kandur et al. reported that R202Q mutation was associated with the inflammatory phenotype of FMF, and typical clinical findings of arthritis were observed in patients with M694V/R202Q heterozygous mutation [29].

Furthermore, Dunder et al. found that 85.8% of patients diagnosed with amyloidosis carried the R202Q mutation [7]. Recent investigations have highlighted the prevalence of the R202Q variant among FMF patients within the Turkish population [7, 12, 13, 29]. The lack of recognition of the R202Q mutation in prior studies may have resulted from its exclusion in analyses focusing on the 14 accepted variants considered as mutations. This omission could be the cause of why the R202Q variant was overlooked in previous analyses. Taken together, these findings, in conjunction with our study, suggest that the R202Q mutation may play a significant role in the pathogenesis of the disease.

In a study comprising 1719 FMF patients in Turkey, researchers noted the most frequently observed pathogenic variants among Turkish FMF patients from 15 rheumatology clinics across various regions to be M694V, M680I, V726A, E148Q, and M694I, respectively. Notably, the study did not report the presence of the R202Q mutation within this patient cohort [20]. Additionally, Balta et al. reported in a study involving 1028 patients that the first three homozygous variants M694V, R202Q, E148Q, as well as the most common M694V/R202Q genotype, were identified among their patients [19].

In a study involving 3230 patients, Kırnaz et al. reported that the most common mutations in sequence were R202Q, E148Q, M694V, V726A, and M680I, collectively constituting 80% of the patient group [12]. According to research conducted by a comprehensive national genetic consortium, including over 27,000 patients, indicated that the dominant MEFV gene variants in Turkish society are M694V, E148Q, R202Q, M680I, and V726A, respectively [7]. In our study with 2984 patients, the most common mutations observed, in sequence, were R202Q, M694V, E148Q, M680I, and V726A. Notably, most of our patient population are from the Central Anatolia region. The variance observed in the research conducted by the National Genetic Consortium may be attributed to the inclusion of patients from all regions of Turkey, including the Turkish Republic of Northern Cyprus. Additionally, this discrepancy could be associated with the genetic diversity within our nation, stemming from prolonged interactions among various ethnic groups residing in geographically distinct areas.

The major complication of FMF is renal amyloidosis, present in 12% of patients. In populations where the disease is common, such as in our country, it is essential to diagnose and treat the condition early to prevent amyloidosis and enhance quality of life [3, 7, 22, 23]. Homozygous M694V is associated with renal amyloidosis, which is considered the most important genotype [7, 20, 30–32]. Studies by Dunder et al. reported the prevalence of M694V as 29.47%, while Yaşar bilge et al. reported it as 24%, Sari et al. reported it as 54.9%, and Yildirim et al. reported it as 39%, making it the most common mutation in Turkish patients [7, 20, 33, 34].

In our investigation, we found that the M694V mutation ranks as the second most prevalent mutation, with an allele frequency of 25.13% ($n=1004$). Homozygous M694V was found in 0.34% ($n=10$) of individuals, while heterozygous M694V was found in 3.72% ($n=111$) of individuals. The most common co-variant reported in studies is the R202Q/M694V genotype [13, 14, 21, 32]. The INFEVERS genetic database reported that the G allele of the R202Q (c.605G>A) mutation was in linkage disequilibrium with M694V (<http://fmf.igh.cnrs.fr/ISSAID/infevers/search.php>) [35]. Sayın Kocakap et al. showed that M694V mutation (55.8%) was in

LD with R202Q mutation [17]. Kandur et al. have shown that the R202Q/M694V mutation association causes an increase in disease symptoms [29]. Additionally, both M694V and R202Q have been reported as mutations associated with amyloidosis in studies [7, 13]. In our study, the heterozygous R202Q/M694V mutation was observed in 8.14% ($n=243$) of individuals, while the homozygous R202Q/M694V mutation was observed in 5.66% ($n=169$) of individuals. Our findings are in accord with previous research, highlighting the prevalence of the R202Q/M694V co-variant.

Regarding the E148Q mutation, classified as a mutation of unknown significance in FMF diagnosis, it emerged as the third most common mutation in our study. It exhibited an allele frequency of 11.59% ($n=463$), with 0.37% ($n=11$) homozygous and 6.63% ($n=198$) heterozygous occurrences. Notably, E148Q has been identified as the most frequent mutation in certain ethnic populations, such as Japanese and Egyptian patients [36, 37]. Research indicates that both homozygous and heterozygous E148Q variants are associated with a mild FMF phenotype [13, 38, 39]. It is among the most common mutations in studies conducted in different regions of Türkiye [12, 13, 17, 20, 38]. In our study, it was found to be the 3rd most common mutation. The observed regional disparities in mutation frequencies may stem from differences in study methodologies or ethnic compositions.

Despite clinical presentations, no variants were observed in 480 individuals (16.1%). This frequency contrasts with the 4.5% reported by Balta et al., 26.3% by Dundar et al., and 9% by Yaşar bilge et al. [7, 19, 20]. Studies have indicated that some FMF patients exhibit no detectable mutations. It is possible that our patients belong to this subset without mutations. Notably, our study only screened mutations in the Exon2 and Exon10 regions, potentially overlooking mutations in Exon 1, 3, and 5. In our study, we identified nucleotide changes not described in INFEVERS [36]. Although some of the patients in whom these changes were detected received a diagnosis and treatment for FMF, they could not be classified as new genotypes because they may have pathogenic mutations in other exons (e.g. A279E, P132P, T262T). Additionally, no patients in our study exhibited the I692del mutation, which is occasionally observed in other Mediterranean populations.

Numerous studies have consistently reported a higher proportion of female FMF patients compared to male patients [7, 12, 17, 19, 20]. In our study, the rate of female patients was 59.9%, indicating a potential epigenetic effect in FMF. Figure 3 demonstrates that there was no statistically significant difference in the most common mutations observed between men and women.

Regarding different age groups, the highest mutation rate of 78% was observed in individuals over 20 years of age ($p<0.001$). Mutations were identified in 11.5% of individuals aged 13–19 years and 10.5% of individuals under 12 years of

age. It is established that the initial onset of FMF symptoms occurs before the age of 10 in approximately 60% of patients, before the age of 20 in 90%, and before the age of 40 in most of the remaining cases. Gursoy et al. reported the mean age at diagnosis as 29.05 ± 13.59 years [40]. Yaşar bilge et al. reported a similar age at diagnosis of 26.6 ± 13.59 years [20]. DüNDAR et al. noted that 50% of the variants were detected in patients older than 20 years [7]. In our study, 78% of the variants were observed in individuals over 20 years of age. Moreover, the M680I mutation was more frequently detected in individuals aged 12 years and younger compared to other age groups in our study. This finding suggests a potential for early-onset disease mutation in children. The M680I mutation has been associated with abdominal and chest pain in previous studies [7, 18, 38]. Therefore, it is crucial to request genetic testing at the onset of symptoms and promptly confirm the diagnosis to avoid delays in diagnosing FMF in patients.

Routine blood tests to diagnose FMF are non-specific and limited. In addition, they cannot eliminate the need for genetic testing. It is accepted that we need genetic test results for a definitive diagnosis of FMF, and only clinical criteria can be considered for a possible diagnosis and trial of colchicine treatment. Currently, MEFV gene testing plays a critical role in the diagnosis of FMF to confirm the presence of the disease and determine the appropriate treatment plan [41]. Many of the known mutations in the MEFV gene are associated with different symptom profiles and disease severity [42]. Therefore, determining the genotype allows the development of personalised treatment approaches in the management of the disease. The use of genetic testing appears to be an essential element in improving patients' quality of life and minimising disease-related complications.

Our study has several limitations. Firstly, due to the retrospective nature of the data analysis spanning a period of ten years, clinical information for most patients was unavailable. Consequently, the relationship between patient genotypes and phenotypes could not be fully elucidated. Additionally, the sequence analysis of all exons in the MEFV gene is crucial for accurately diagnosing and treating patients. This comprehensive analysis may offer additional insights into diagnosing patients with varying phenotypes. Understanding which MEFV variant corresponds to specific phenotypes or ameliorates certain symptoms could facilitate early treatment initiation and prevent life-threatening complications.

Conclusion

In conclusion, variants/mutations in the MEFV gene were evaluated in 2984 patients. In our study group, the genotype distributions of both common and rare mutations in the exon 2 and exon 10 regions were revealed. Currently, the most

common mutation in exon 2 in the Turkish population is known as E148Q. Compared to large studies from Turkey, our study shows that the R202Q mutation is found in about 40% of patients and is more common in our society. In addition, the M680I variant was found to be the most common variant in patients aged 12 years and younger. The clinical symptoms of FMF are diverse and vary in severity. As it is not a disease with simple genotype-phenotype characteristics, it is important to know all possible genotypes in the community. For this reason, our study also shows the distribution of MEFV mutations found in patients in our community. The data from our study will contribute to future genotype-phenotype studies of FMF disease.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval Informed consent was obtained from all patients or their parents before undergoing genetic. This work was approved by the Ankara University Human Research Ethics Committee. (decision no: 106-356-22).

Consent for publication The final content of this paper was read and approved by all of the authors.

Competing interests The authors declare no competing interests.

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