Research Article

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1255344

Evaluation of the frequency of MEFV gene variants in patients with a pre-diagnosis of Familial Mediterranean Fever (FMF) in southeast Türkiye

Türkiye'nin güneydoğusunda Ailevi Akdeniz Ateşi (AAA) ön tanısı alan hastalardaki MEFV gen varyantlarının sıklığının değerlendirilmesi

Derya Karaer, Bahtiyar Şahinoğlu, Abdullah İhsan Gürler, Kadri Karaer

Posted date:23.02.2023 Acceptance date:15.03.2023

Abstract

Purpose: Familial Mediterranean Fever (FMF) is a hereditary auto inflammatory disease (MIM#249100). The most common symptoms are abdominal pain, high fever, and arthralgia. FMF is the result of variants in the MEditerraneanFeVer (MEFV) gene located on chromosome 16p13.3, which contains 10 exons and encodes the pyrin (marenostrin) protein. The frequency of MEFV gene variants that cause FMF varies according to ethnic groups, countries and even different regions in the same country. In our study, we aimed to determine the frequency and distribution of MEFV gene changes that cause Familial Mediterranean fever in southeast Türkiye.

Materials and methods: A total of 6.660 patients with a pre-diagnosis of FMF, including 3.495 women and 3.165 men, were included in the study. Fragment analysis was performed to investigate the MEFV gene variants of the patients and the 19 most common variants in the Turkish population were examined.

Results: We found at least one variant in 50.17% (3.341) of our 6.660 patients. In our patients, 108 different genotypes; in Exon 2, 3, 5 and 10 and we identified 16 different variants. We found 2.120 (63.21%) patients were heterozygous, 693 (20.74%) were compound heterozygotes, 275 (8.23%) were homozygous and 261 (7.81%) were complex genotypes. The five variants with the highest allele frequency are; R202Q (27.84%), M694V (22.83%), E148Q (21.98%), V726A (7.42%), and M680I (G>C) (6.39%).

Conclusion: We identified the most common prevalence of MEFV gene alteration in a large patient group in our region. High R202Q mutation rates were among the remarkable results of this study.

Key words: FMF, MEFV gene variants, fragment analysis.

Karaer D, Sahinoglu B, Gurler AI, Karaer K. Evaluation of the frequency of MEFV gene variants in patients with a pre-diagnosis of Familial Mediterranean Fever (FMF) in southeast Türkiye. Pam Med J 2023;16:456-464.

Öz

Amaç: Ailevi Akdeniz Ateşi (AAA) kalıtsal bir otoinflamatuar hastalıktır (MIM#249100). En sık görülen semptomlar yüksek ateş, karın ağrısı ve artraljidir. AAA, 16p13.3 kromozomu üzerinde yer alan, 10 ekzondan oluşan ve pirin (marenostrin) proteinini kodlayan MEditerraneanFeVer (MEFV) genindeki varyantların sonucudur. AAA'ya neden olan MEFV gen varyantlarının sıklığı etnik gruplara, ülkelere ve hatta aynı ülke içindeki farklı bölgelere göre değişmektedir. Bu çalışmada, Türkiye'nin güneydoğusunda Ailesel Akdeniz ateşine neden olan MEFV gen değişikliklerinin sıklığını ve dağılımını belirlemeyi amaçladık.

Gereç ve yöntem: Çalışmaya Ailevi Akdeniz Ateşi ön tanısı almış olan 3,495 kadın ve 3,165 erkek olmak üzere toplam 6.660 hasta dahil edildi. Hastaların MEFV gen varyantlarını araştırmak için fragman analizi yapıldı ve Türk popülasyonunda en sık görülen 19 varyant incelendi.

Bulgular: Çalışmaya dahil edilen 6,660 hastamızın %50,17'sinde (3,341) en az bir varyant tespit edildi. Hastalarımızda 108 farklı genotip; Exon 2, 3, 5 ve 10'da olmak üzere 16 farklı varyant belirledik. Hastaların 2,120'sinde (%63,21) heterozigot, 693'ünde (%20,74) bileşik heterozigot, 275'inde (%8,23) homozigot ve 261'inde (%7,81) kompleks genotip bulundu. Alel frekansı en yüksek olan 5 varyant sırasıyla; R202Q (%27,84), M694V (%22,83), E148Q (%21,98), V726A (%7,42) ve M680I (G>C) (%6,39) olarak belirlendi.

Sonuç: Bölgemizde geniş bir hasta grubunda yaptığımız bu çalışma ile FMF ön tanısı almış olan hastalarda en sık görülen MEFV gen değişikliklerinin sıklığını ve dağılımını belirledik. Yüksek R202Q mutasyon oranları bu çalışmanın dikkat çekici sonuçları arasında yer almaktadır.

Anahtar kelimeler: FMF, MEFV gen varyantları, fragman analizi.

Karaer D, Şahinoğlu B, Gürler Aİ, Karaer K. Türkiye'nin güneydoğusunda Ailevi Akdeniz Ateşi (AAA) ön tanısı alan hastalardaki MEFV gen varyantlarının sıklığının değerlendirilmesi. Pam Tıp Derg 2023;16:456-464.

Derya Karaer, Asist. Prof. Pamukkale University Faculty of Medicine, Department of Medical Genetic, Denizli, Türkiye, e-mail: dkaraer@pau.edu.tr (https://orcid.org/0000-0002-1874-0109) (Corresponding Author)

Bahtiyar Şahinoğlu, M.D. Dr. Ersin Arslan Training and Research Hospital, Genetic Diseases Diagnosis Center, Gaziantep, Türkiye, e-mail: mem_baxtiyar@yahoo.com (https://orcid.org/0000-0002-2208-540X)

Abdullah İhsan Gürler, M.D. Dr. Ersin Arslan Training and Research Hospital, Genetic Diseases Diagnosis Center, Gaziantep, Türkiye, e-mail: aihsangurler@hotmail.com (https://orcid.org/0000-0002-9034-715X)

Kadri Karaer, Assoc. Prof. Pamukkale University Faculty of Medicine, Department of Medical Genetic, Denizli, Türkiye, e-mail: kkaraer@pau.edu.tr (https://orcid.org/0000-0003-1415-9103)

Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disorder (MIM# 249100) and is characterized by recurrent attacks of fever, inflammation of the serous membranes [1]. The most common symptoms are abdominal pain, joint pain and swelling, chest pain, self-limiting fever and erysipelas-like erythema. The frequency of attacks can vary from once a week to once a year. Between attacks, patients are completely normal and this feature is important for diagnosis [2]. Although FMF is an autosomal recessive disease, heterozygous individuals have also been reported to show symptoms associated with the disease [3]. This disease is common in the generation that includes our country. The incidence in Turks, Armenians, Arabs and Jews is much higher than in other societies. It can also be found less frequently in Greece, Italy and Spain, but with increasing immigrations, FMF is a disease seen all over the world today [4-6]. The carrier rate of FMF in Türkiye is 1/5 and its estimated prevalence is 1/1000 [7].

The *MEFV* gene responsible for FMF is located on chromosome 16p13.3, consists of 10 exons and encodes a 781 amino acid protein called marenostrin or pyrin (OMIM Protein Accession Number: NP_000234.1) [8, 9]. Mutations in the *MEFV* gene disrupt the role of the pyrin region, resulting in an uninterrupted inflammatory response. To date, 391 variants in the *MEFV* gene have been reported according to the Infevers database [10]. The most common variants in the *MEFV* gene have been identified in exon 10 and exon 2, but the spectrum of *MEFV* variants in FMF patients differs between populations and ethnic groups [11].

The diagnosis of the disease can be made by clinical signs according to TelHashomer criteria. However, identification of disease-causing *MEFV* gene mutations is useful for establishing or confirming the diagnosis of FMF [12, 13].

Here, we aim to contribute to Türkiye's *MEFV* variant spectrum data by presenting *MEFV* gene variant data in a large group of 6.660 patients referred to our laboratory due to FMF findings.

Materials and methods

The study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee with the decision dated 08 February 2023 and numbered E-60116787-020-328733. A total of 6.660 patients (3.165 men, 3.495 women) referred from different clinics to our center (Gaziantep Dr. Ersin Arslan Training and Research Hospital Genetic Diagnosis Center) between 2016 and 2022 were included in the study. The *MEFV* gene variant analysis results of these patients who presented with a pre-diagnosis of FMF were evaluated.

Genomic DNA extraction

For variant analysis, genomic DNA isolation was performed from the peripheral venous blood sample collected in EDTA (ethylenediaminetetraacetic acid) tubes by using the "Maxwell RSC" DNA isolation kit (Promega/ USA) from the blood with an automated system (Maxwell RSC Promega/ USA). Spectrophotometric measurements were made for the obtained DNAs (Nano-drop/USA). 10-50 ng/µL DNA was used for the study.

Molecular analysis

In the fragment analysis method, PCR was performed with specific primers (GML SNP DEtective *MEFV* kit) for DNA material obtained from peripheral blood samples taken from patients. The obtained PCR product was evaluated by applying fragment analysis in ABI 3500 DNA Sequencer. Nineteen variants of *MEFV* gene were analyzed by fragment analysis method. These variants are; located in Exon 2: p.R202Q, p.S179I, p.E167D, p.E148Q; Exon 3: p.P369S, p.P350R; Exon 5: p.F479L, p.Y471X and Exon 10: p.R761H, p.A744S, p.V726A, p.K695R, p.K695N, p.M694I, p.M694V, p.I692del, p.M680I (G>A), p.M680I (G>C), p.G632A.

Results

Of the 6.660 patients with a pre-diagnosis of FMF, whose age range was between newborn and 80, 3.495 (52.48%) were female and 3.165 (47.52%) were male. No variant was detected in 3.319 patients (49.83%). At least one variant was found in 3.341 (50.17%) patients. Of the 3.341 patients with variants, 49% (n=1.638) were male and 51% (n=1.703) were female. 108 different genotypes and 16 different variants (4/16 with exon 2, 2/16 with exon 3, 1/16 with exon 5 and 9/16 with exon 10) were detected in these patients.

Heterozygous genotype was determined in two thousand one hundred twelve (63.21%) patients, compound heterozygous in six hundred ninety-three (20.74%) patients, homozygous in two hundred seventy-five (8.23%) patients, and complex genotype in two hundred and sixty-one (7.81%) patients (Table1). The most common variants as heterozygous were E148Q, R202Q and M694V, respectively and the most common homozygous variant we saw was M694V.

Table 1. Genotype distribution and frequencies of patients

Variant (n, %)	Genotype	Patients	
		n	%
Heterozygous	E148Q/wt	609	18.22
(n=2112, 63.21%)	R202Q/wt	580	17.36
	M694V/wt	322	9.63
	V726A/wt	175	5.24
	M680I (G>C)/wt	120	3.60
	P369S/wt	91	2.72
	R761H/wt	75	2.24
	A744S/wt	68	2.04
	K695R/wt	33	0.99
	M694I/wt	32	0.96
	I692del/wt	3	0.09
	M680I (G>A)/wt	2	0.06
	F479L/wt	1	0.03
	E167D/wt	1	0.03
	Subtotal	2.112	63.21
Compound heterozygous	R202Q/ M694V	178	5.33
(n=693, 20.74%)	E148Q/ R202Q	64	1.91
	E148Q/ M694V	58	1.74
	M680I (G>C)/ M694V	43	1.29
	E148Q/ P369S	38	1.13
	M694V/ V726A	38	1.13
	M680I (G>C)/ V726A	27	0.80
	M694V/ R761H	24	0.72
	E148Q/ M680I (G>C)	22	0.66
	E148Q/ V726A	21	0.63
	E148Q/ M694I	18	0.54
	R202Q/ V726A	18	0.54
	R202Q/ P369S	17	0.50
	R202Q/ M680I (G>C)	14	0.42
	R202Q/ R761H	13	0.39
	P369S/ R408Q	12	0.36
	M680I (G>C)/ R761H	9	0.27
	E148Q/ A744S	9	0.27
	R202Q/ A744S	8	0.24
	V726A/ A744S	7	0.20
	F479L/ E167D	7	0.20
	M694I/ M694V	6	0.18
	E148Q/ R761H	6	0.18
	M694I/ R761H	5	0.15
	M694V/ A744S	4	0.12
	V726A/ R761H	4	0.12
	M694I/ V726A	3	0.09
	E148Q/ K695R	2	0.06
	R202Q/ M694I	2	0.06

Table 1. Genotype distribution and frequencies of patients (continued-1)

Variant (n, %)	Complex genotype	Patients	
		n	%
Compound heterezygous (n=693, 20.74%) (continued)	P369S/ M694V	2	0.06
	M680I (G>C)/ K695R	2	0.06
	V726A/ K695R	2	0.06
	E148Q/ M680I (G>A)	1	0.03
	R202Q/ S179I	1	0.03
	R202Q/ K695R	1	0.03
	P369S/ V726A	1	0.03
	P369S/ A744S	1	0.03
	M680I (G>C)/ M680I (G>A)	1	0.03
	M680I (G>C)/ M694I	1	0.03
	M680I (G>A)/ R761H	1	0.03
	M694I/ A744S	1	0.03
	A744S/ R761H	1	0.03
	Subtotal	693	20.74
Homozygous (n=275, 8.23%)	M694V	81	2.40
	R202Q	70	2.09
	M680I (G>C)	37	1.11
	E148Q	34	1.02
	V726A	23	0.69
	R761H	15	0.45
	M694I	8	0.24
	A744S	5	0.15
	P369S	2	0.06
	Subtotal	275	8.23
Complex (total) (n=261, 7.81%)			
Homozygous/ Homozygous (n=81, 2.42%)	R202Q/ M694V	78	2.33
	E148Q/ P369S	1	0.03
	F479L/ E167D	1	0.03
	E148Q/ M694I	1	0.03
	Subtotal	81	2.42
Homozygous/ Homozygous/ Homozygous (n=1, 0.03%)	E148Q/ R408Q/ P369S	1	0.03
Homozygous/ Heterozygous (n=65, 1.94%)	R202Q/ M694V	45	1.35
	M694V/ R202Q	8	0.24
	E148Q/ P369S	3	0.09
	R202Q/ P369S	3	0.09
	E167D/ E148Q	1	0.03
	E148Q/ M694I	1	0.03
	R202Q/ K695R	1	0.03
	P350R/ R202Q	1	0.03
	M694I/ R761H	1	0.03
	M694I/ V726A	1	0.03
	Subtotal	65	
Homozygous/ Heterozygous/ Heterozygous (n=1, 0.03%)	M694I/ M694V/ V726A	1	0.03

Table 1. Genotype distribution and frequencies of patients (continued-2)

Variant (n, %)	Complex genotype	Patients	
		n	%
Heterozygous/ Heterozygous/ Heterozygous (n=107, 3.20%)	E148Q/ R202Q/ M694V	32	0.96
	R202Q/ M694V/ V726A	21	0.63
	R202Q/ M694V/ R761H	12	0.36
	R202Q/ M694V/ M680I (G>C)	6	0.18
	E148Q/ M694V/ R202Q	5	0.15
	E148Q/ P369S/ R202Q	5	0.15
	E148Q/ P369S/ R408Q	3	0.09
	E148Q/ P369S/ V726A	3	0.09
	E167D/ G/ V726A	2	0.06
	E167D/ F479L/ M694V	2	0.06
	E148Q/ P369S/ M694V	2	0.06
	R202Q/ M694V/ A744S	2	0.06
	A744S/ P369S/ R202Q	1	0.03
	E167D/ F479L/ R202Q	1	0.03
	E167D/ E148Q/ F479L	1	0.03
	E148Q/ R202Q/ M680I (G>C)	1	0.03
	E148Q/ P369S/ M680I (G>C)	1	0.03
	E148Q/ M694I/ M680I (G>C)	1	0.03
	P369S/ R408Q/ M694I	1	0.03
	R202Q/ M694V/ V726A	1	0.03
	R202Q/ P369S/ A744S	1	0.03
	E148Q/R202Q/ M694I	1	0.03
	R202Q/P369S/ V726A	1	0.03
	P369S/ R408Q/ V761H	1	0.03
	Subtotal	107	
Heterozygous/ Heterozygous/ Heterozygous/ Heterozygous (n=6, 0.18%)	E148Q/ R202Q/ M694V/ M694I	3	0.09
	E148Q/ R202Q/ P369S/ M694V	2	0.06
	E167D/ R202Q/ F479L/ M694V	1	0.03
	Subtotal	6	0.18
Patients with MEFV variants (total)		3.341	50.17
Patients without MEFV variants		3.319	49.83
Total number of patients		6660	

Of the 19 variants studied, R202Q had the highest allele frequency of 27.84%. The second variant with the highest allele frequency was M694V (22.83%) and the third variant was E148Q (21.98%). The other variants identified, in order of allele frequency, were as follows: V726A, M680I (G>C), P369S, R761H, A744S, M694I, K695R, E167D, F479L, I692del, M680I (G>A), P350R, S179I (Table 2).

Of the 19 variants examined by fragment analysis in the *MEFV* gene, 3 were not detected in any of our cases. These were the F471X, G632A and K695N.

The number of patients, distribution and frequency of *MEFV* variants detected in this study are given in Table 2.

Table 2. Allele frequencies of MEFV variants among 3341 patients

Exon number	Variant	Nucleotid change	Aminoacid change	rs number	Number of patients	Number of alleles	Variated allele frequency (%)
2	R202Q	c.605G>A	p.Arg202Gln	rs224222	1198	1395	27.84
10	M694V	c.2080A>G	p.Met694Val	rs61752717	977	1144	22.83
2	E148Q	c.442G>C	p.Glu148Gln	rs3743930	950	1101	21.98
10	V726A	c.2177T>C	p.Val726Ala	rs28940579	349	372	7.42
10	M680I (G>C)	c.2040G>C	p.Met680Ile	rs28940580	283	320	6.39
3	P369S	c.1105C>T	p.Pro369Ser	rs11466023	193	197	3.93
10	R761H	c.2282G>A	p.Arg761His	rs104895097	166	181	3.62
10	A744S	c.2230G>T	p.Ala744Ser	rs61732874	108	113	2.25
10	M694I	c.2082G>A	p.Met694Ile	rs28940578	87	99	1.98
10	K695R	c.2084A>G	p.Lys695Arg	rs104895094	41	41	0.82
2	E167D	c.501G>C	p.Glu167Asp	rs104895079	17	19	0.38
5	F479L	c.1437C>G	p.Phe479Leu	rs104895083	16	17	0.34
10	I692del	c.2076_2078del	p.Ile692del	rs104895093	4	4	0.08
10	M680I (G>A)	c.2040G>A	p.Met680Ile	rs28940580	4	4	0.08
3	P350R	c.1049C>G	p.Pro350Arg	-	1	2	0.04
2	S179I	c.536G>T	p.Ser179Ile	rs104895125	1	1	0.02
						Total:5010	

Discussion

FMF is an autoinflammatory disease [6, 14]. Defined as a Mediterranean Basin disease, FMF was first observed in Jewish and Armenian patients, then spread among Turks and Arabs through migration routes [15]. Türkiye is one of the countries with the highest prevalence of the disease (1:1000) and many studies have shown that the carrier rate is around 20-25% [16].

FMF disease is more common in males (male: female ratio of 1.2:1), the mean age of onset is 9.6, and the mean age at diagnosis is 16.4 [7]. When we look at the male-female ratio in our patients, the number of female patients is higher with a difference of 2%, and it differs from this situation.

The number and variety of variants in the *MEFV* gene involved in the etiology of FMF vary between populations [17]. In our study, 19 variants, which were reported to be frequently observed in cases sent to our laboratory with a pre-diagnosis of FMF, were screened. At least one change was detected in 50.17% of the cases. The changes in the first five that we found the highest frequency were R202Q, M694V, E148Q, V726A, M680I (G>C). It has been reported in the literature that these variants constitute approximately 85% of the variants in the Mediterranean region [5, 6]. We determined the frequency of these five variants in exon 10 (M694V, M680IG>C and V726A) and exon 2 (E148Q and R202Q) to be 86.5% in our study population. This rate is very similar to previously reported rates.

We found complex genotype in 7.81%, homozygous in 8.23%, compound heterozygous in 20.74% and heterozygous genotype in 63.21% of our patients. 25-33% of people diagnosed with FMF carry only one variant in the *MEFV* gene. These heterozygous carriers with a single variant may display the FMF phenotype [18]. We identified only one heterozygous variant in 2.112 (31%) of 6.660 patients who were clinically evaluated as FMF, but *MEFV* whole gene analysis is required in this group to make a clear interpretation of this issue for our patients.

The rate of complex genotype in our country varies between 0.7% and 1.3% [19, 20]. In a study conducted with Syrian patients, this rate was found to be 6.7% [21]. We determined 7.81% complex genotypes in our patients. This can be explained by the increase in the Syrian patient population and its effect on the genotype distribution, since our region is a region that receives heavy Syrian immigration.

R202Q is generally considered to be a benign variant, but there are also publications emphasizing its increased frequency in FMF patients compared to healthy individuals and contributing to the FMF phenotype, some studies highlighting that homozygous or compound heterozygous R202Q mutation types can cause FMF and amyloidosis. The incidence of R202Q in the Turkish population varies between 5 and 34% [22, 23]. R202Q was the most common variant that we identified first with a frequency of 27.84%. 580 patients were heterozygous and 81 patients were homozygous. R202Q and M694V compound heterozygosity was the most common compound heterozygosity.

M694V was reported as the most common first or second variant with a frequency ranging from 15.6% to 67.2% in studies conducted in different regions of Türkiye [24]. In our study, M694V was the second most common variant with a frequency of 22.83%. As in two studies, one with a cohort of more than 2.800 (frequency of M694V is 18.86%) patients and the other with more than 27.000 (frequency of M694V is 29.47%) patients, our study also shows that the M694V is the leading pathogenic variant in Turks [7, 25].

E148Q is a variant with conflicting pathogenicity, also seen in the healthy population. It is classified as a Variant of Indeterminate Significance (VUS) [26]. It has been reported that the frequency of E148Q mutations in Türkiye has changed from 3.5% to 30.8% [27]. In a comprehensive study conducted by the National Genetics Consortium, the frequency of E148Q was found to be 18.27% [25]. We found the E148Q frequency as 21.98% and this result was similar.

Oztuzcu et al. [28], in their study with 3.341 patients in the same region as us, between 2009 and 2013; they found the most common *MEFV* gene variant and allele frequencies as follows: M694I (1.62%), A744S (2.45%), R761H (4.96), V726A (8.31%), M680I (G>C) (8.98%), E148Q (26.88%), M694V (41.77%). They did not report R202Q. While the top five variants are similar, especially the allele frequency of the M694V variant (22.83% in our study) differs considerably. In another study conducted in Sanliurfa, which is very close to the region we study, the frequency of common MEFV gene variants is as follows; V726A (6.5%), R761H (8), M680I (10%), E148Q (16%), M694V (17%), R202Q (24%) [29]. Although the first five variants in the article are similar, especially the allele frequency of the M694V variant (22.83% in our study) is quite different from ours. While the most common variants in Gumus's [29] study were similar, the incidence of R761H variants was different from ours.

In our patients, among the variants we examined; We did not find three variants, the F471X, G632A and K695N.

No variant was detected in 49.83% (3.319) of the 6.660 patients in the study population. This high rate of unidentified variant in these patients may be due to many factors other than the regions we looked at, such as the presence of other rare variants, unknown mutations, or genetic heterogeneity.

Our study, with the number of 6.660 patients, is the study with the largest number of patients performed by a single center in the southeast region.

In FMF, the distribution of variants in the *MEFV* gene can vary greatly from one population to another, even within the same population. Various variants may have a characteristic distribution in certain regions. Molecular diagnosis of MEFV is a clinically useful tool and is valuable for molecular diagnosis in determining variant frequencies and distributions of regions. This study, which was conducted with 6.660 patients, is a study showing the distribution of *MEFV* gene variants in southeastern Türkiye.

Conflict of interest: No conflict of interest was declared by the authors.

References

1. Sohar E, Gafni J, PrasM Heller J. Familial Mediterranean fever: a survey of 470 cases and review of the literature. Am J Med 1967;43:227-253. https://doi.org/10.1016/0002-9343(67)90167-2
2. Akyol Önder EN, Ertan P. Familial Mediterranean fever. CBU-SBED 2020;7:413-417. http://doi.org/10.34087/cbusbed.696594
3. Fragouli E, Eliopoulos E, Petraki E, et al. Familial Mediterranean fever in crete: a genetic and structural biologicalapproach in a population of "intermediate risk". Clin Genet 2007;73:152-159. https://doi.org/10.1111/j.1399-0004.2007.00948.x

4. Akar N, Misiroğlu M, Yalcinkaya F, et al. MEFV mutations in Turkish patients suffering from Familial Mediterranean fever. Hum Mut 2000;15:118-119. https://doi.org/10.1002/(sici)1098-1004(200001)15:1%3C118::aid-humu29%3E3.0.co;2-5
5. Alghamdi M. Familial Mediterranean fever, review of the literature. Clin Rheumatol 2017;36:1707-1713. https://doi.org/10.1007/s10067-017-3715-5
6. Soriano A, Manna R. Familial Mediterranean fever: new phenotypes. Autoimmun Rev 2012;12:31-37. https://doi.org/10.1016/j.autrev.2012.07.019
7. Tunca M, Akar S, Onen F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 2005;84:1-11. https://doi.org/10.1097/01.md.0000152370.84628.0c
8. FMF French Consortium, Bernot A, Clepet C, Dasilva C. A candidate gene for Familial Mediterranean fever. Nat Genet 1997;17:25-31. https://doi.org/10.1038/ng0997-25
9. FMF International Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause Familial Mediterranean fever. Cell 1997;90:797-807. https://doi.org/10.1016/s0092-8674(00)80539-5
10. Infevers: an online database for autoinflammatory mutations. Copyright. Available at: https://infevers.umai-montpellier.fr/web/. Accessed September 01, 2022
11. Dundar M, Emirogullari EF, Kiraz A, Taheri S, Baskol M. Common Familial Mediterranean fever gene mutations in a Turkish cohort. Mol Biol Rep 2011;38:5065-5069. https://doi.org/10.1007/s11033-010-0652-7
12. Dode C, Pecheux C, Cazeneuve C, et al. Mutations in the *MEFV* gene in a large series of patients with a clinical diagnosis of Familial Mediterranean fever. Am J Med Genet 2000;92:241-246. https://doi.org/10.1002/(SICI)1096-8628(20000605)92:4%3C241::AID-AJMG3%3E3.0.CO;2-G
13. Eisenberg S, Aksentijevich I, Deng Z, Kastner DL, Matzner Y. Diagnosis of Familial Mediterranean fever by a molecular genetics method. Ann Intern Med 1998;129:539-542. https://doi.org/10.7326/0003-4819-129-7-199810010-00005
14. Ozdogan H, Ugurlu S. Familial Mediterranean fever. Presse Med 2019;48:61-76. https://doi.org/10.1016/j.lpm.2018.08.014
15. San A. Familial Mediterranean fever cases in Turkey. Int J Nephrol Kidney Fail 2020;6:1-8. http://dx.doi.org/10.16966/2380-5498.200
16. Yılmaz E, Ozen S, Balci B, et al. Mutation frequency of familial Mediterranean fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet 2001;9:553-555. https://doi.org/10.1038/sj.ejhg.5200674
17. Ozen S, Batu ED. The myths we believed in Familial Mediterranean fever: what have we learned in the past years? Semin Immunopathol 2015;37:363-369. https://doi.org/10.1007/s00281-015-0484-6
18. Shohat M. Familial Mediterranean fever. University of Washington, Seattle.1993
19. Cekin N, Akyurek ME, Pinarbasi E, Ozen F. *MEFV* mutations and their relation to major clinical symptoms of Familial Mediterranean fever. Gene 2017;626:9-13. https://doi.org/10.1016/j.gene.2017.05.013
20. Coskun S, Ustyol L, Bayram Y, et al. The spectrum of *MEFV* gene mutations and genotypes in Van province, the eastern region of Turkey, and report of a novel mutation (R361T). Gene 2015;562:128-131. https://doi.org/10.1016/j.gene.2015.02.059
21. Jarjour RA, Al Berrawi S. Familial Mediterranean fever in Syrian children: phenotype–genotype correlation. Rheumatol Int 2015;35:629-634. https://doi.org/10.1007/s00296-014-3116-x
22. Milenković J, Vojinović J, Debeljak M, et al. Distribution of *MEFV* gene mutations and R202Q polymorphism in the Serbian population and their influence on oxidative stress and clinical manifestations of inflammation. Pediatr Rheumatol 2016;14:1-9. https://doi.org/10.1186/s12969-016-0097-1
23. Yigit S, Karakus N, Tasliyurt T, Uzun Kaya S, Bozkurt N, Kisacik B. Significance of *MEFV* gene R202Q polymorphism in Turkish Familial Mediterranean fever patients. Gene 2012;506:43-45. https://doi.org/10.1016/j.gene.2012.06.074
24. Onalan Etem E, Deveci SD, Erol D, Yuce H, Elyas H. Familial Mediterranean fever: a retrospective clinical and molecular study in the East of Anatolia region of Turkey. Open Rheumatol J 2010;4:1-6. https://doi.org/10.2174/1874312901004010001
25. Dundar M, Fahrioglu U, Yildiz SH, et al. Clinical and molecular evaluation of *MEFV* gene variants in the Turkish population: a study by the National Genetics Consortium. Funct Integr Genomics 2022;22:291-315. https://doi.org/10.1007/s10142-021-00819-3
26. Eyal O, Shinar Y, Pras M, Pras E. Familial Mediterranean fever: penetrance of the p.[Met694Val];[Glu148Gln] and p.[Met694Val];[=] genotypes. Hum Mutat 2020;41:1866-1870. https://doi.org/10.1002/humu.24090
27. Aydın E, Cakmak E, Uluca U, et al. The *MEFV* mutations and their clinical correlations in children with Familial Mediterranean fever in southeast Turkey. Rheumatol Int 2014;34:207-212. http://dx.doi.org/10.1007/s00296-013-2858-1
28. Oztuzcu S, Ulaslı M, Ergun S, et al. Screening of common and novel Familial Mediterranean fever mutations in south-east part of Turkey. Mol Biol Rep 2014;41:2601-2607 http://dx.doi.org/10.1007/s11033-014-3118-5
29. Gumus E. The Frequency of *MEFV* gene mutations and genotypes in Sanliurfa province, south-eastern region of Turkey, after the Syrian civil war by using next generation sequencing and report of a novel exon 4 mutation (I423T). J Clin Med 2018;7:105-111. https://doi.org/10.3390/jcm7050105

Acknowledgments: We thank the Bio. Ömer Şimşek of the Dr. Ersin Arslan Training and Research Hospital, Genetic Diseases Diagnosis Center in Gaziantep, for his help.

Ethics committee approval: Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study (the registry number: E-60116787-020-328733, date: 08 February 2023).

Author contribution

K.K. and A.I.G. responsible for medical examination and planning of the study. B.S. and D.K. performed data collection, analysis and calculations. D.K. wrote the draft with the contributions of all the authors. K.K. and D.K. discussed the results, reviewed and commented on the article.