

The Spectrum of MEFV Gene Mutations and Genotypes in the Middle Northern Region of Turkey

Gokce Celep¹, Zeynep Hulya Durmaz² , Yalciner Erdogan¹ , Seviye Akpınar¹ , Saban Abdullah Kaya³ ,
Rıdvan Guckan⁴ 



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ORCID IDs of the authors:
Z.H.D. 0000-0002-3260-0030
Y.E. 0000-0002-3476-7395
S.A. 0000-0002-5970-4518
S.A.K. 0000-0003-1595-5793
R.G. 0000-0002-8125-7195

¹Department of Paediatrics, Amasya University School of Medicine, Sabuncuoğlu Şerefeddin Training and Research Hospital, Amasya, Turkey

²Department Biochemistry, Amasya University School of Medicine, Sabuncuoğlu Şerefeddin Training and Research Hospital, Amasya, Turkey

³Department of Paediatric Surgery, Amasya University School of Medicine, Sabuncuoğlu Şerefeddin Training and Research Hospital, Amasya, Turkey

⁴Department of Microbiology, Amasya University School of Medicine, Sabuncuoğlu Şerefeddin Training and Research Hospital, Amasya, Turkey

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Correspondence to: Gokce Celep
E-mail: gokce4celep@yahoo.com

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is a common, inherited, autosomal recessive inflammatory disease in children. The diagnosis of FMF is based on clinical features and positive family history supported with genetic testing. This study aimed to determine the frequency and distribution of Mediterranean fever (MEFV) gene alterations of a city in Northern Anatolia.

Materials and Methods: We evaluated MEFV gene mutations in 374 children preliminary diagnosed as FMF by a commercial kit based on real-time polymerase chain reaction technique in a one-year period, and screened 12 mutations.

Results: At least one mutation was detected in 213 patients (57%) and 38 genotypes with 11 distinct mutations. A total of 137 (64.3%) of mutation-positive children were heterozygous, 45 (21.1%) were compound heterozygous, and 2 (0.9%) were complex heterozygous; and 14 (6.4%) patients were homozygous, 6 (2.8%) were compound homozygous, and 3 (1.4%) were complex homozygous. With a frequency of 50.1%, R202Q was the most common mutation. Also, R202Q/M694V was the most common compound heterozygous genotype. In 43 alleles, R202Q-M694V mutations were found to be in linkage disequilibrium. In our cohort, M694V, E148Q, V726A, and M680I (G/C) were other common mutations; whereas F479L, A744S, K695R, P369S, M694I, and R761H were the rare mutations. None of our patients had M680I (G/A) mutation.

Conclusion: We determined the most common MEFV alteration prevalence in children of our region for the first time. The high R202Q mutation and linkage disequilibrium (LD) rates were the remarkable results of this study.

Keywords: MEFV mutations, FMF, R202Q, Northern Anatolia

Introduction

Familial Mediterranean fever (FMF) is a common, hereditary auto inflammatory disease in children. It is a monogenic disorder inherited in the autosomal recessive manner [1]. FMF, also named as “recurrent polyserositis,” is characterized by spontaneously resolving, self-limited recurrent paroxysms of fever; polyserosal, synovial sterile inflammation, rash, family history, and favorable response to colchicine treatment. It is one of the important reasons of fever of unknown origin in children [1, 2]. The most severe complication of this disease is renal amyloidosis, which leads to renal failure [1]. The diagnosis of FMF is based on clinical features and positive family history. Genetic testing is used to support the clinical diagnosis, especially in small children with a family history as they cannot localize pain and cannot express themselves correctly [1, 2].

FMF is the result of mutations in the MEditerraneanFeVer (MEFV) gene located on chromosome 16p13.3 and mainly expressed in granulocytes. It consists of 10 exons and encodes pyrin (marennin) protein [1, 3]. Pyrin is the key of caspase-1 and interleukin-1 β pathways, leading to inflammation. The role of pyrin in the pathogenesis of FMF is not well known [1, 2]. It may have a regulatory role in either suppressing or exacerbating the inflammatory response [2, 4]. Mutations in MEFV are also related with polyarteritis nodosa, Henoch-Schönlein purpura (HSP), and juvenile idiopathic arthritis (JIA)

FMF is common in Armenians, Turks, Sephardic Jews, and Arabs, groups that comprise the populations of the Eastern Mediterranean and Middle East regions, also in France, Germany,

Italy, Spain, Japan, and United States; in fact it common worldwide, which is thought to be the result of migrations in our century [1, 2]. The ethnic diversity in Turkey causes a high rate of heterozygosity and homozygosity. The prevalence of FMF in Turkey is 1:1000, and its frequency is similar in girls and boys. The carrier frequency is 1:5 among Turks [5]. 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 populations with high carrier rates and high rate of consanguineous marriages, it is possible that one or both parents have pathogenic variants or may be mildly affected [1]. Pseudo dominant transmission is also considered as one of the reasons [2]. Heterozygous people usually have a later age of onset (mean age 18 years) and milder disease with fever and abdominal symptoms without frank peritonitis [1, 2].

To date, 329 sequence variants for MEFV have been defined. The mutations responsible for the disease may be missense, nonsense, or deletion type [6]. The four missense mutations in exon 10 (M694V, M680I, M694I, V726A) are responsible for approximately 85% of MEFV gene mutations. The E148Q and R202Q mutations are often determined in geographic areas where FMF is common, but the clinical outcome of these alterations is not well defined [6]. Mutation causing R202Q (c.605G>A) change was described as a frequent polymorphism, and G allele was found in linkage disequilibrium (LD) with M694V [6]. LD is a way of genetic diversity so that certain alleles of each gene are inherited together more often than that would be expected by chance [6]. Although clinical symptoms and the course of the illness are still the cornerstones of diagnosing FMF, molecular confirmation can help make the diagnosis earlier in suspected cases [5].

In this retrospective study, 374 pediatric patients with suspicious FMF were evaluated by analyzing MEFV gene mutations in one-year period. Our aim was to determine the frequency and spectrum of MEFV gene mutation alterations in our province to contribute the MEFV mutation data of Turkey. We focused on only genetic tests and ignored clinical findings.

Materials and Methods

In this retrospective study, molecular genetic testing of 374 children admitted to the pediatrics, pediatric surgery, and pediatric emergency outpatient clinics of a tertiary medical center in the middle Black Sea region, north of Turkey, with the clinical signs of FMF between January 1, 2016, and

December 31, 2016, were investigated. FMF-referring symptoms were defined as three or more paroxysmal episodes of abdominal pain, pleuritic chest pain, fever, fever of unknown origin, mono-oligoarthritis; all lasting for 6-72 hours and erysipelas like erythema (Livneh and Yalçınkaya criteria [2, 7]). Patients suffering from at least two clinical signs of FMF and confirmed family history underwent mutation analyses after three or more attacks. All patients were referred from clinics of our hospital, the only medical center in our city which is small, located in the middle northern region of Turkey, and does not have a high immigration rate. The results of our study represent the prevalence of MEFV mutations in patients with suspicious FMF in one-year period. Peripheral venous blood samples were collected in tubes with ethylenediaminetetraacetic acid (EDTA), and sent to an external laboratory for analysis. Genomic deoxyribonucleic acid (DNA) was extracted from blood samples as per the standard procedures. After DNA isolation, a commercially available kit based on real-time polymerase chain reaction technique with Montania 4896 instrument (Anatolia Geneworks, Istanbul, Turkey) was applied to detect MEFV mutations. E148Q, R202Q (exon 2), P369S (exon 3), F479L (exon 5), M680I (G/C), M680I (G/A), M694V, M694I, A744S, R761H, V726A, and K695R (exon 10) mutations were screened.

Statistical Analysis

The results were presented with descriptive features. All the descriptive analyses were performed using the The Statistical Package for the Social Sciences (SPSS) computer software version 15.0 (SPSS Inc.; Chicago, IL, USA) with presentation as mean \pm SD or percentages for normally distributed variables, and medians with minimum-maximum values for not normally distributed variables when indicated.

Our study was approved by the local committee of education and research hospital with decision no: 62949364-000-6221.

Results

Demographic and genetic features of the participants

Among 374 patients, 216 were girls (56.8%) and 158 were boys (41.6%), with the mean age 7.20 \pm 4.49 years. A total of 161 patients (43%) had no mutations, whereas at least one mutation was detected in 213 patients (57%). A total of 38 different genotypes and 11 distinct mutations were detected in 213 patients. Of these mutation-positive children, 137 (64.3%) were heterozygous, 45 (21.1%) were compound heterozygous, and 2 (0.9%) were com-

plex heterozygous; whereas 14 (6.4%) patients were homozygous, 6 (2.8%) were compound homozygous, and 3 (1.4%) were complex homozygous.

MEFV Gene Mutation Analyses

Mutant genes were detected in 341 alleles in our cohort; and R202Q was the most common mutation with a frequency of 50.1%. The frequencies of heterozygous, compound heterozygous, homozygous, compound homozygous, and complex genotypes of the R202Q mutation were 21.8% (n=83), 10.1% (n=38), 2.1% (n=8), 0.5% (n=2), and 3% (n=11), respectively. Five patients were heterozygous with M694V and homozygous with R202Q. One patient had another complex genotype with R202Q/M680I (G/C)/M694V/M694V (Table 1). R202Q/wt heterozygosity, found in 83 patients, was the most common genotype (21.8%). R202Q/M694V was the most common compound heterozygous genotype (6.6%). We found R202Q and M694V were in LD in 43 alleles. Also, R202Q/R202Q was the most frequent homozygous genotype with a frequency of 2.1% (Table 1). M694V (16.7%), E148Q (11.1%), V726A (9.9%), and M680I (G/C) (6.4%) were other commonly detected mutations. F479L, A744S, K695R, P369S, M694I, and R761H were the rare mutations in our cohort. None of our patients had M680I (G/A) mutation (Table 2).

Discussion

Here, we reported the frequency of MEFV mutations of 374 pediatric patients with preliminary diagnosis of FMF living in our province. Genotypes of 213 mutation-positive patients were also included. Eleven different mutations with 38 distinct genotypes were determined. The major finding of this study was that the most common alteration detected in our province was R202Q mutation with an allele frequency of 50.1% (n=171). The most common five mutations and their frequencies in our study were as follows: R202Q (50.1%), M694V (16.7%), E148Q (11.1%), V726A (9.9%), M680I (G/C) (6.4%). In previous studies from Turkey, M694V, M680I, V726A, M694I, and E148Q were reported as common mutations (Table 3). These are also the most frequent mutations among the population of countries where FMF prevalence is high [1]. F479L, A744S, K695R, P369S, M694I, and R761H were the rare mutations of our cohort. None of our patients had M680I (G/A) mutation. The data of rare mutations differ between different regions of Turkey [8, 9].

In our study, R202Q mutation was determined as the most frequent mutation. R202Q alteration has been known since 1998 [6]. It is de-

Table 1. Genotype distribution of our patients

Mutation (n; %)	Genotype	Patients (total)	
		n	%
Heterozygous genotypes (n=137, 64.3%)			
	A744S/ wt	2	0.5
	E148Q/ wt	24	6.3
	F479L/ wt	1	0.3
	K695R/ wt	1	0.3
	M680I(G/C)/ wt	9	2.4
	P369S/ wt	1	0.3
	R202Q/ wt	83	21.8
	V726A /wt	14	3.7
	M694V/ wt	2	0.5
Compound heterozygous genotypes (n=45; 21.1%)			
	E148Q/M680I(G/C)	2	0.5
	E148Q/V726A	1	0.3
	F479L/ M680I(G/C)	1	0.3
	M694V/V726A	2	0.5
	P369S/E148Q	1	0.3
	R202Q/A744S	2	0.5
	R202Q/E148Q	3	0.8
	R202Q/K695R	1	0.3
	R202Q/M680I(G/C)	1	0.3
	R202Q/M694V	25	6.6
	R202Q/P369S	2	0.5
	R202Q/V726A	3	0.8
	M694I/R202Q	1	0.3
Complex heterozygous genotypes (n=2; 0.9%)			
	E148Q/M694V/R202Q	1	0.3
	R202Q/M694V/M680I(G/C)	1	0.3
Homozygous genotypes (n=14; 6.5%)			
	E148Q/E148Q	1	0.3
	M680I(G/C)/M680I(G/C)	2	0.5
	R202Q/R202Q	8	2.1
	R761H/R761H	1	0.3
	V726A/V726A	2	0.5
Compound homozygous (n=6; 2.8%)			
	E148Q/M694V	1	0.3
	E148Q/V726A	1	0.3
	F479L/V726A	1	0.3
	R202Q/M694V	2	0.5
	V726A/M680I(G/C)	1	0.3
Complex homozygous (n=3; 1.4%)			
	R202Q/M694V/K695R	2	0.5
	R202Q/V726A/M694V	1	0.3
Others (n=6; 2.8%)			
	M694V/R202Q/R202Q	5	1.3
	R202Q/M680I(G/C)/M694V/M694V	1	0.3
Subtotal			
Patients with mutation	213	56.9	
No mutation	Patients without mutation	161	43.1

defined as a variation observed in symptomatic patients [6]. R202Q (c. 605G>A) is described as a frequent polymorphism, and the G allele is found to be in LD with M694V in Infevers Database [6]. There are few studies addressing the R202Q mutation in the literature. Studies in Greek and Turkish patients suggest that R202Q is associated with an FMF phenotype, but limited data are available about the clinical significance of R202Q alteration. Ritis et al. reported R202Q homozygosity in 4 of 26 Greek patients with FMF, compared to 60 healthy controls having no mutation; and they suggested that R202Q gene alteration may be a mutation more than a polymorphism [10]. Also, they detected homozygosity of the R202Q polymorphism in 9.2% of patients with FMF compared to 0.7% healthy controls in a Greek population [11]. The clinical significance of R202Q alteration in Turkish patients has been published in independent studies. Öztürk et al. reported that R202Q homozygosity might be associated with the disease in some patients with FMF; although there was no R202Q homozygosity in their control group, but a high frequency of heterozygosity in the control group, concluding that it has no effect when it is in a heterozygous state [12]. Also Yigit et al. found that although the heterozygosity of R202Q was similar in patients with FMF and healthy controls, the homozygosity was higher in patients with FMF when compared with healthy controls (14.7%-2.7%) [13]. The authors claimed that R202Q polymorphism can be the cause of illness only in the homozygous form [12, 13]. Another study by Çomak et al. showed that 7 patients with R202Q alterations in a cohort of 225 R202Q (+) patients had typical episodes of FMF of which 2 (3.6 %) had heterozygous R202Q alterations. The authors suggested that R202Q alteration is associated with an inflammatory phenotype and has clinical significance for FMF [14]. Güneşçar et al. reported that R202Q was the most frequently observed mutation in 427 (21.35%) of 2000 alleles in Hatay province, in the Mediterranean region of Turkey [15]. In a recent study from İstanbul, reflecting whole Turkey, Barut et al. reported R202Q mutation prevalence as 6.9% in children diagnosed with FMF [16]. Coşkun et al. reported 452 (42.6%) R202Q variation in 1058 individuals suspected with FMF from Van, but they had no healthy control group, either [17]. The absence of a healthy control group is a limitation of our study too. Because of that, we failed to determine the frequency of R202Q homozygosity or heterozygosity among healthy individuals to compare our data in the preliminary FMF diagnosed group. However, all patients with homozygous or heterozygous R202Q mutation had at least one or more clinical features of FMF with family history.

We also found that in 43 alleles, R202Q and M694V were in LD. Unknown genetic alterations may cause phenotypical features by LD [6]. The study by Sayın Kocakap from Turkey showed high LD between R202Q and M694V [9]. Kılınc et al. from Southeastern Mediterranean region (Kahramanmaraş) of Turkey reported R202Q mutation frequency as 39.13% in 260 heterozygous subjects of their study group consisting of 831 patients with FMF. They attracted attention to frequent M694V/R202Q togetherness in their cohort concluding that clinical investigations must be conducted to identify its role in phenotype [18].

In our study, the second most commonly seen mutation was M694V with an allele frequency of 16.7% (n=57). In nearly all regions of Turkey, the most common mutation is M694V. The overall frequency of M694V mutation in patients

suspected and diagnosed with FMF is reported as 23.5% within 16693 individuals from different parts of Turkey [9]. It is also the most frequent mutation in the populations where FMF is common and related with renal amyloidosis, the worst complication of the disease [1]. Ece et al., from the southeast of Turkey, reported M964V mutation with a frequency of 26% as the second common mutation in their study group consisting of 147 patients and 192 independent alleles [19].

In our study, E148Q was determined as the third most frequent mutation with a frequency of 11.1% (n=38). E148Q was also detected as the third common mutation in all Turkish patients with a frequency of 6.8% [9]. However, Evliyaoğlu et al. reported this mutation as the most common one in the southern part of Turkey [20]. This mutation is considered a functional polymorphism, and is usually related with atypi-

cal FMF presenting a mild clinical phenotype. It is also related with other recurrent fever and inflammation syndromes [6].

In this study, the frequency of V726A mutation was found as 9.9% (n=32). In previous studies from Turkey, the allele frequency of the V726A mutation was 1.9% [15]. It was reported as the fourth most common mutation in many studies from Turkey [9, 15]. It is also one of the most common mutations in Middle East populations and related with classical FMF phenotype [6, 21].

The fifth common mutation in our cohort was M680I (G/C), and its frequency was 6.4% (n=22). It is one of the common mutations in the Turkish population [8, 9]. The frequency was reported as 15.9% in a different study and one of the symptomatic mutations of MEFV [20]. It is also common in Middle East countries and Armenia [6].

In this study group, K695R, A744S, F479L, P369S, R761H, and M694I were determined as the rare mutations. The frequencies of these rare mutations ranged from 1.1% to 1.9%. The distribution of rare mutations was compatible with the data of other Turkish population studies [15].

In conclusion, our study is the first from our region to reflect the MEFV mutation data of child population suspicious of FMF in just one year. The most common five mutations in decreasing order were R202Q (50.1%), M694V (16.7%), E148Q (11.1%), V726A (9.9%), and M680I (G/C) (6.4%), respectively. There are many ethnic groups in Turkey; our study group also confirms the mutational heterogeneity of FMF in our region (Table 3; [22-29]). FMF is frequent in the central Anatolia and Black Sea region of Turkey [30]. To our knowl-

Table 2. Allele and mutation frequencies of MEFV mutations among mutant patients (n=213)

Allele	Number of alleles	Allele frequency (%)	Number of mutations	Mutation frequency (%)
R202Q	171	50.1	142	50.5
M694V	57	16.7	43	15.3
E148Q	38	11.1	35	12.4
A744S	4	1.1	4	1.4
F479L	4	1.1	3	1.0
K695R	6	1.7	4	1.4
M680I(G/C)	22	6.4	18	6.4
P369S	4	1.1	4	1.4
V726A	32	9.9	26	9.2
M694I	1	0.3	1	0.3
R761H	2	0.6	1	0.3
Total	341/100	281	100	

Table 3. Common MEFV alteration frequencies in patients suspected with FMF in pediatric population from different regions of Turkey (%)

Reference	R202Q	M694V	E148Q	V726A	M680I(G/C)	Number of patients	Age of patients (years)	Region
Şahin S et al. [22].		15	4.9	2.7	5.1	929	----	Northern Anatolia
Günel Özcan A. et al. [23]		6.8	8.3	4.4	4.4	136	9±3, 27±9	Central Anatolia
Ceylan et al. [24]		14.2	4.4	5.4	3.9	802	3-75 (range)	Central Anatolia
Dündar et al. [25]		14.7	5.5	4.8	7.6	2067	0-80 (range)	Central Anatolia
Sayın KD et al. [9]	23.7	14.8	6.9	3.9	4.1	351	21±14.3	Central Anatolia
Özalkaya E et al. [26]		24.4	6.7	5	8.1	308	9.6±3.9	Western Anatolia
Battal F et al. [27]	11.7	20	13.3	6.7	11.7	60	3-18 (range)	Western Anatolia
Coşkun S et al. [16]	42.6	36.5	32.7	14	3.9	1058	8.2±3.5	Eastern Anatolia
Doğan H et al. [28]		42.8	14.7	16.3	14.1	1620	1-72 (range)	Eastern Anatolia
Öztuzcu S. et al. [29]		41.7	26.8	8.3	8.9	3341	1-80	Southeastern Anatolia
Evliyaoğlu O et al. [19]		3.2	9.6	1.9	1.4	332	1-15 (range)	Southeastern Anatolia
Güneşçar R et al. [15]	21.3	7.9	8.8	1.8	2.4	1000	1-70 (range)	Southern Anatolia
Barut K et al. [16]	6.9	41.1	5.7	4.8	5.6	708/617	12.3±4.4	İstanbul (North-western, reflecting Turkey)

edge, our data are one of the highest R202Q mutation frequency rates from Turkey. It has not been identified yet whether R202Q is a mutation or a polymorphism; more studies referring clinical features are needed for this identification. We had no healthy control group; this limited us to conclude that this is either a polymorphism or a mutation significant for clinical phenotype. Other limitation of our study is that according to the study design, we did not mention the clinical features of our cohort, and reported just one year's data. This is an important shortcoming; and we only focused on genetic variations in this study. More time is needed for clinical follow-up and certain diagnosis. The discrepancies between this study and the previous ones carried out in populations in different regions of Turkey might have resulted from the number of participants, genetic heterogeneity, methods, and available kits used to detect the MEFV mutations. These techniques are not sufficient to detect rare or undefined alterations; direct sequencing of MEFV gene may be useful to identify unknown mutations in regions where FMF is prevalent. We need further studies with large patient series to define the mutation table of Turkey.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Amasya University, Sabuncuoğlu Şerefeddin Training and Research Hospital with the decision number: 62949364-000-6221.

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References

- Shohat M. Familial Mediterranean fever. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mefford HC, Stephens K, Amemiya A, Ledbetter N (eds). GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; updated 2016 Dec 15.
- Aydın F, Özçakar ZB, Yalçinkaya F. Familial Mediterranean fever: Diagnosis and treatment in children. *Türkiye Klinikleri J Rheumatol-Special Topics* 2017; 10: 46-54
- Consortium FF. A candidate gene for familial Mediterranean fever. *Nat Genet* 1997; 17: 25-31. [\[CrossRef\]](#)
- Manukan G, Rustam A. Update on Pyrin functions and mechanisms of Familial Mediterranean Fever. *Front Microbiol* 2016; 7: 456. [\[CrossRef\]](#)
- 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: 553-5. [\[CrossRef\]](#)
- Touitou, I., ed. (<http://fmf.igh.cnrs.fr/infevers>). 2017. Infevers: an evolving mutation database for autoinflammatory syndromes.
- Yalçinkaya F, Ozen S, Ozçakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. *Rheumatology* 2009; 48: 395-8. [\[CrossRef\]](#)
- Turkish FMF Study Group. Familial Mediterranean fever (FMF) in Turkey Results of a Nationwide Multi-center Study. *Medicine* 2005;84: 1-11. [\[CrossRef\]](#)
- Sayin Kocakap DB, Gunel-Ozcan, A, Cabuk, F, Ensari, C. The frequency of familial Mediterranean fever gene mutations and genotypes at Kirikkale and comparison with the mean of regional MEFV mutation frequency of Turkey. *Mol Biol Rep* 2014; 41: 1419-26. [\[CrossRef\]](#)
- Ritis K, Giaglis S, Spathari N, et al. Non-isotopic RNAase cleavage assay for mutation detection in MEFV, the gene responsible for familial Mediterranean fever, in a cohort of Greek patients. *Ann Rheum Dis* 2004; 63: 438-43. [\[CrossRef\]](#)
- Giaglis S, Papadopoulos V, Kambas K, et al. MEFV alterations and population genetics analysis in a large cohort of Greek patients with familial Mediterranean fever. *Clin Genet* 2007; 71: 458-67. [\[CrossRef\]](#)
- Öztürk A, Ozçakar B, Ekim M, Akar N. Is MEFV gene Arg202Gln (605G > A) A disease-causing mutation? *Turk J Med Sci* 2008; 38: 205-8.
- Yigit S, Karakus N, Tasliyurt T, Kaya SU, Bozkurt N, Kisacik B. Significance of MEFV gene R202Q polymorphism in Turkish familial Mediterranean fever patients. *Gene* 2012; 506: 43-5. [\[CrossRef\]](#)
- Çomak E, Akman S, Koyun M, et al. Clinical evaluation of R202Q alteration of MEFV genes in Turkish children. *Clin Rheumatol* 2014; 33: 1765- 71. [\[CrossRef\]](#)
- Gunesacar R, Celik MM, Arica V, Elmacioglu, S, Ozturk OH. Frequency of MEFV gene mutations in Hatay province, Mediterranean region of Turkey and report of a novel missense mutation (I247V). *Gene* 2014; 546: 195-9. [\[CrossRef\]](#)
- Barut K, Şahin S, Adroviç A, Sinoplu AB, Yücel G, Pamuk G. Familial Mediterranean fever in childhood: a single center experience. *RheumatolInt* 2018; 38: 67-74. [\[CrossRef\]](#)
- Coşkun S, Ustul 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: 128-31. [\[CrossRef\]](#)
- Kilinc M, Ganiyusufoglu E, Sager H, et al. The report of sequence analysis on familial Mediterranean fever gene (MEFV) in South-eastern Mediterranean region (Kahramanmaraş) of Turkey. *Rheumatol Int* 2016; 36: 25-31. [\[CrossRef\]](#)
- Ece A, Çakmak E, Uluca Ü, et al. The MEFV mutations and their clinical correlations in children with familial Mediterranean fever in southeast Turkey. *Rheumatol Int* 2014; 34: 207-12. [\[CrossRef\]](#)
- Evliyaoglu O, Bilici S, Yolbas I, Kelekci S, Sen V. Common MEFV gene mutations in children with FMF in Diyarbakir, Turkey. *Dicle Tıp Dergisi (Dicle Medical Journal)* 2009; 36: 80-4. [\[CrossRef\]](#)
- Majeed H, El-Khateeb M, El-Shanti H, Abu Rabaiha Z, Tayeh M, Najib D. The Spectrum of Familial Mediterranean Fever Gene Mutations in Arabs: Report of a Large Series. *Semin Arthritis Rheum* 2005; 34: 813-8. [\[CrossRef\]](#)
- Sahin S, Ozyurt H, Akbas A, et al. Frequently seen mutations in MEFV gene in the FMF diseases in Tokat Region. *Turk Klinik Biyokimya Derg (Journal of Turkish Clinical Biochemistry)* 2009; 7: 81-6.
- Gunel-Ozcan A, Sayin DB, Misirlioglu ED, Güllter S, Yakaryilmaz F, Ensari C. The spectrum of FMF mutations and genotypes in the referrals to molecular genetics laboratory at Kirikkale University in Turkey. *Mol Biol Rep* 2009; 36: 757-60. [\[CrossRef\]](#)
- Ceylan GG, Ceylan C, Ozturk E. Frequency of alterations in the MEFV gene and clinical signs in familial Mediterranean fever in Central Anatolia, Turkey. *Genet Mol Res* 2012; 11: 1185-94. [\[CrossRef\]](#)
- 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: 5065-69. [\[CrossRef\]](#)
- Özalkaya E, Mir S, Sozeri B, Berdeli A, Mutlubas F, Cura A. Familial Mediterranean Fever gene mutation frequencies and genotype-phenotype correlations in the Aegean region of Turkey. *Rheumatol Int* 2011; 31: 779-84. [\[CrossRef\]](#)
- Battal F, Silan F, Topaloglu N, et al. The MEFV gene pathogenic variants and phenotype-genotype correlation in children with familial Mediterranean fever in the Çanakkale population. *Balkan J Med Genet* 2017; 19: 23-8. [\[CrossRef\]](#)
- Dogan H, Faruk Bayrak O, et al. Familial Mediterranean fever gene mutations in north-eastern part of Anatolia with special respect to rare mutations. *Gene* 2015; 568: 170-5. [\[CrossRef\]](#)
- Öztuzcu S, Ulaşlı 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: 2601-7. [\[CrossRef\]](#)
- Barut K, Pamuk G, Adroviç A, et al. Comparison of Familial Mediterranean Fever and juvenile idiopathic arthritis patients according to family origin. *Turk Pediatri Ars* 2018; 53: 31-6. [\[CrossRef\]](#)