

# Mutational Spectrum of the *MEFV* Gene in AA Amyloidosis Associated With Familial Mediterranean Fever

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**Introduction.** Familial Mediterranean fever (FMF) is a recessively inherited disease which is characterized by recurrent episodic fever, abdominal pain, and polyserositis. It is caused by mutations in the *MEFV* gene, encoding the pyrin protein. The most important complication of FMF is secondary (AA) amyloidosis that leads to kidney failure. This study aimed to identify the frequency and distribution of *MEFV* mutations in Turkish patients with FMF-associated AA amyloidosis.

**Materials and Methods.** A total of 57 patients with FMF-associated AA amyloidosis and 60 healthy controls were included in this study. We analyzed the *MEFV* gene for E148Q, M694V, M680I, and V726A mutations and R202Q variant by polymerase chain reaction and restriction fragment length polymorphism methods.

**Results.** The male-female ratio was 0.72. The mean age of the patients was  $29.8 \pm 12.8$  years. Among the patients, the rate of the *MEFV* mutations was found to be 77.2%. The most frequently observed genotype was homozygous M694V mutation, which was present in 17 patients (29.8%,  $P < .001$ ), followed by compound heterozygous M680I/M694V (14.3%,  $P = .01$ ). The R202Q allele frequencies were significantly different between patients and control group ( $P = .02$ ; odds ratio, 0.53; 95% confidence interval, 0.30 to 0.94).

**Conclusions.** In this study, mutation analysis of *MEFV* gene confirmed that the most frequent mutation was homozygous M694V genotype. R202Q may be important in patients with FMF-associated AA amyloidosis. Thus, it is suggested that investigation of R202Q should be considered as a genetic test for Turkish FMF patients.

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## INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive inherited auto-inflammatory disorder generally affecting people in areas around the Mediterranean Sea, mainly non-Ashkenazi Jews, Turks, Armenians, and Arabs.<sup>1</sup> It is characterized by recurrent fever crises, accompanied by serositis affecting the peritoneum, the pleura, and the synovia. The disease is caused by mutations in the Mediterranean fever (*MEFV*) gene which encodes

pyrin protein (or marenosttrin). The *MEFV* gene, consisting of 10 exons, is located on chromosome 16p13.3.<sup>2</sup> Currently, more than 300 sequence variants of the *MEFV* have been reported in the Infevers Database.<sup>3</sup> The most frequently seen mutations of *MEFV* gene are the M694V, M680I, E148Q, V726A, and M694I, most of which are located on exon 10.<sup>4-6</sup> The distribution of *MEFV* mutations in FMF patients varies by country and population.<sup>7</sup>

Secondary AA amyloidosis occurs as a result of

the complication of chronic inflammation and is characterized by the accumulation of extracellular amyloid protein in various tissues. The most severe complication of FMF is the development of AA amyloidosis leading to nephrotic syndrome and progressive nephropathy. Sex, ethnicity, and genotype are the main factors that affect the prevalence of FMF-associated amyloidosis. It is more common in North Africa-originated Jewish and Turkish populations.<sup>8</sup> It has often been associated with the M694V mutation, especially at the homozygous state.<sup>1,9</sup> Longtime treatment with colchicine can prevent amyloidosis. The aim of this study was to evaluate the frequency of *MEFV* gene variants in Turkish patients with FMF-associated amyloidosis.

## MATERIALS AND METHODS

### Patients

The study group was composed of 57 FMF-associated AA amyloidosis patients (24 men and 33 women) that were being treated at the Department of Internal Medicine, Faculty of Medicine, at Gaziosmanpasa University and Department of Nephrology at Ordu State Hospital. International criteria were taken into consideration in the diagnosis of FMF. The presence of amyloid depositions was confirmed by tissue biopsies. The control group consisted of 60 healthy volunteers (27 men and 33 women), all aged over 18 years.

All of the participants were of Turkish origin, from the eastern and inner central Black Sea regions of Turkey. Clinical data were collected using a standardized questionnaire which involved questions on age at symptom onset, frequency and duration of FMF attacks, family history, arthritis, fever, peritonitis, pleuritis, synovitis, erysipelas-like rash, pericarditis, and colchicine treatment. Written informed consent was obtained from all of the participants. The study protocol was approved by the ethics committee of Kanuni Education and Research State Hospital in Trabzon.

### *MEFV* Mutation Analysis

Genomic DNA was isolated from the peripheral leukocytes by standard protocols. Screening for *MEFV* gene mutations was performed in the patient and the control group. The most frequently observed 4 mutations (E148Q, M694V, M680I, and V726A) and a variant (R202Q) in the *MEFV* gene were

screened. These *MEFV* mutations were studied with the methods of polymerase chain reaction restriction fragment length polymorphism and restriction fragment length polymorphism. The amplified products were digested with restriction endonuclease enzymes to detect M694V, M680I, V726A, E148Q, and R202Q (HinfI, HphI, AluI, BstNI, and PvuII, respectively). Mutations presented in exon 10 between codons 663 and 771 including M680I, M694V, and V726A, and the mutations E148Q and R202Q in exon 2 were sought for using the procedure previously described.<sup>10,11</sup>

### Statistical Analysis

All statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, IL, USA) and the OpenEpi (version 2.2). Continuous data were reported as mean  $\pm$  standard deviation (range). The chi-square test was used to assess the differences in the allele frequency and genotype distribution between the two study groups. The Hardy-Weinberg equilibrium test was performed for both study groups. Odds ratio and 95% confidence interval were calculated. A *P* value less than .05 was considered significant.

## RESULTS

The patients had a mean age of  $29.77 \pm 12.85$  years, and 57.9 % of them were women. Table 1

**Table 1.** Demographic and Clinical Characteristics of Patients With Familial Mediterranean Fever and Healthy Controls\*

Characteristic	Control Group	Study Group
Sex		
Male	27 (45.0)	24 (42.1)
Female	33 (55.0)	33 (57.9)
Mean age, y	31.1 $\pm$ 113.2	29.8 $\pm$ 12.9
Age at first symptoms, y	...	12.1 $\pm$ 7.7
Age at onset, y	...	21.0 $\pm$ 10.6
Mean number of days with attack episodes	...	28.5 $\pm$ 17.2
Use of colchicine	...	48 (84.2)
Response to colchicine	...	46 (95.8)
Family history	...	34 (59.6)
Fever	...	49 (86.0)
Abdominal pain	...	50 (87.7)
Pleural effusion	...	25 (43.9)
Joint involvement	...	38 (66.7)
Appendicitis	...	11 (19.3)
Erythema	...	9 (15.8)

\*Values in parentheses are percentages.

summarizes the demographic and clinical data related to the patients with AA amyloidosis and the control group.

The mutations found in the patient and control groups and their number and frequencies are shown in Table 2. Among the patients, the rate of the *MEFV* mutations was found to be 82.5%. The most frequently observed genotype was homozygous M694V mutation, which was present in 17 patients (29.8%;  $P < .001$ ), followed by compound heterozygous M680I/M694V (14.3%;  $P = .01$ ). The allele frequencies of the R202Q variant showed a significant difference between the patients and control groups ( $P = .02$ ; odds ratio, 0.53; 95% confidence interval, 0.30 to 0.94). Genotypic and allelic distributions of the R202Q polymorphism are shown in Table 3.

## DISCUSSION

Familial Mediterranean fever is one of the frequently seen diseases in the world with the

prevalence of 1:400 to 1:1000.<sup>12</sup> It is reported that the most frequent mutation in Turkey is M694V, followed by M680I and V726A in the order of frequency.<sup>7,13-20</sup> Although genotype-phenotype correlation has not been established precisely for FMF, many studies put that M694V is associated with early onset of the disease, high frequency of attacks, need for increase in colchicine dose, and amyloidosis.<sup>9,13,21-27</sup> In this study, we have evaluated the distribution of variants of the *MEFV* gene in 57 FMF-associated amyloidosis patients living in the eastern and inner Black Sea regions in Turkey.

Amyloid accumulation may be seen in many organs in AA amyloidosis; however, what frequently causes morbidity and mortality is renal amyloidosis. The most important complication of FMF is the development of AA amyloidosis. Being male was reported to be a nongenetic risk factor in FMF-associated amyloidosis.<sup>28</sup> Although this was confirmed in many studies,<sup>23,29-33</sup> the number of women was greater among the patients in the

**Table 2.** Distribution of *MEFV* Mutations in Patients With Familial Mediterranean Fever and Amyloidosis Compared With Healthy Controls\*

Mutations	Study Group	Control Group	P
No mutations	10 (17.5)	49 (81.7)	< .001
M694V	5 (8.8)	4 (6.7)	.93
M694V homozygote	17 (29.8)	0	< .001
M680I heterozygote	4 (7.0)	2 (3.3)	.63
M680I homozygote	2 (3.5)	0	.72
V726A heterozygote	1 (1.8)	1 (1.7)	>.05
E148Q heterozygote	4 (7.0)	4 (6.7)	>.05
Compound heterozygote mutations			
M680I/M694V	8 (14.0)	0	.01
M680I/V726A	3 (5.3)	0	.39
E148Q/M694V	1 (1.8)	0	>.05
E148Q/M680I	1 (1.8)	0	>.05
E148Q/M694V	1 (1.8)	0	>.05
Total mutations	47 (82.5)	11 (18.3)	< .001

\*Values in parentheses are percentages.

**Table 3.** Genotype and Allele Frequencies of *R202Q* Gene Variation in Patients With Familial Mediterranean Fever and Amyloidosis and Healthy Controls\*

R202Q	Study Group	Control Group	P	Odds Ratio (95% Confidence Interval)
Genotype				
G>G	24 (42.1)	33 (55.0)	.09	...
G>A	23 (40.3)	24 (40.0)		
A>A	10 (17.5)	3 (5.0)		
Alleles				
G	71 (62.2)	90 (75.0)	.02	0.53 (0.30 to 0.94)
A	43 (37.7)	30 (25.0)		

\*Values in parentheses are percentages.

present study (33 versus 24 men). The rate of joint involvement was high, which is a finding consistent with Gershoni-Baruch and colleagues and Kaşifoğlu and colleagues.<sup>31,32</sup> The rate of familial history of FMF was 59.6%. Saatci and coworkers suggested that amyloidosis may be genetic, and patients with a familial history of FMF had 6.04 times higher risk than others.<sup>30</sup> The frequency of amyloidosis in FMF patients was reported to be 2.2% in the Arabic population,<sup>34</sup> 27.6% in Sephardic Jews,<sup>35</sup> and 12.9% to 40.0% in the Turkish population.<sup>13,27,29,31,36</sup>

Colchicine therapy, used to control FMF attacks, is also reported to be effective in preventing the development of amyloidosis.<sup>37</sup> That is why early diagnosis, appropriate treatment strategy, and genetic counseling are important in FMF patients. Many studies indicate that M694V homozygote and heterozygote genotype is the most significant risk factor in the development of amyloidosis.<sup>20,38-41</sup> A study conducted in Turkey suggested that the development of amyloidosis was 6 times higher in homozygote M694V carriers.<sup>31</sup> However, different mutations were also detected in patients that developed amyloidosis.<sup>27,42-44</sup> The most frequent mutation found in the present study was M694V homozygotes (29.8%), which is a finding that supports many studies in the literature.<sup>26,29,31,38,45-48</sup> Touitou and coworkers indicated that M694V homozygosity was a risk factor for amyloidosis for those living in Armenia, Saudi Arabia, and Israel, but it was a borderline factor for the Turkish population.<sup>29</sup> Mimouni and associates found that the rate of M694V homozygosity was 42.8% among patients of Turkish origin.<sup>38</sup> In another study, it was reported that the most common mutation in Turkish patients with FMF-associated amyloidosis was M694V/V726A.<sup>49</sup> Nevertheless, in 3 studies conducted in Turkey, it was reported that there was no correlation between M694V homozygosity and development of amyloidosis.<sup>13,27,50</sup> The difference in results probably derives from the differences in ethnic backgrounds.

Other common genotypes found in this study were, in the order of frequency, M694V/M680I (14.0%), M694V (8.8%), and M680I heterozygote (7.0%). Albayrak and coworkers reported that homozygote genotype (M694V and M680I) was commonly seen in patients with amyloidosis.<sup>51</sup> In the present study, while the rate of M694V

homozygosity was more remarkable, the total rate of M694V homozygote and compound heterozygote was 56.1%. Not confirming the results of Albayrak and coworkers, the rate of M860I homozygosity was quite low (3.5%).<sup>51</sup> Mimouni and associates reported that E148Q mutation was not seen in 4 different ethnic groups, including the Turkish population.<sup>38</sup> E148Q heterozygosity (7.01%) was nevertheless found among our patients (E148Q/M694V; 3.5%).

In addition to the frequently seen mutations in *MEFV* gene (ie, M694V, V726A, M680I, and E148Q), R202Q variant was also added to the spectrum of this study. R202Q in exon 2 was defined as a benign polymorphism by Bernot and colleagues for the first time.<sup>52</sup> It was reported that R202Q carriers have a mild phenotype compared to the carriers of other *MEFV* mutations.<sup>2,53</sup> Yet, it is still considered a variant,<sup>3</sup> and it is commonly seen in FMF patients of Turkish origin.<sup>11,54,55</sup> In the present study, R202Q allele frequency was found to be remarkably significant.

Despite the great number of studies related to FMF-associated amyloidosis, there are still some points that need to be clarified. As far as we know, R202Q variant has not been studied before in Turkish patients with FMF-associated amyloidosis. In the study related to frequent mutations (M694V, M680I, V726A, and E148Q) in FMF-associated amyloidosis, Balcı and colleagues found unidentified alleles at a rate of 47.7%.<sup>46</sup> This indicates that other alleles should not be disregarded in FMF-associated amyloidosis. The data of our study suggests that R202Q variant should be considered a risk factor in the development of amyloidosis.

## CONCLUSIONS

The development of amyloidosis is the most important complication seen in untreated FMF patients. In this study, we evaluated the distribution of *MEFV* mutations in patients with FMF-associated amyloidosis living in the eastern and inner Black Sea regions of Turkey. The correlation between M694V and FMF-associated amyloidosis, found in many studies, was confirmed by the present study. In order to prevent the complication of amyloidosis, there is a need to evaluate R202Q routinely and start the colchicine therapy in early years of the disease. There is also a need for further studies on populations of different ethnic origins.

## CONFLICT OF INTEREST

None declared.

## REFERENCES

- Gershoni-Baruch R, Brik R, Shinawi M, Livneh A. The differential contribution of MEFV mutant alleles to the clinical profile of familial Mediterranean fever. *Eur J Hum Genet.* 2002;10:145-9.
- Cankaya T, Bora E, Bayram Torun M, et al. Clinical significance of R202Q alteration of mefv gene in children with familial mediterranean fever. *Arch Rheumatol.* 2015;30:51-6.
- Infevers [homepage]. *MEFV* (NM\_000243.2) sequence variants. Available from: <http://fmf.igh.cnrs.fr/ISSAID/infevers/search.php?n=1>
- Onen F. Familial Mediterranean fever. *Rheumatol Int.* 2006;26:489-96.
- Yamazaki K, Yamazaki T, Masumoto J, et al. Familial Mediterranean fever as representative autoinflammatory disease. *Rinsho Byori.* 2009;57:371-81.
- Medlej-Hashim M, Delague V, Chouery E, et al. Amyloidosis in familial Mediterranean fever patients: correlation with MEFV genotype and SAA1 and MICA polymorphisms effects. *BMC Med Genet.* 2004;5:1-6
- Caglayan AO, Demiryilmaz F, Ozyazgan I, Gumus H. MEFV gene compound heterozygous mutations in familial Mediterranean fever phenotype: a retrospective clinical and molecular study. *Nephrol Dial Transplant.* 2010;25:2520-23.
- Shohat M, Halpern GJ. Familial Mediterranean fever--a review. *Genet Med.* 2011;13:487-98.
- Dewalle M, Domingo C, Rozenbaum M, et al. Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). *Eur J Hum Genet.* 1998;6:95-7.
- Yigit S, Inanir A, Karakus N, Kesici E, Bozkurt N. Common Mediterranean fever (MEFV) gene mutations associated with ankylosing spondylitis in Turkish population. *Dis Markers.* 2012;33:113-8.
- Yigit S, Karakus N, Tasliyurt T, et al. Significance of MEFV gene R202Q polymorphism in Turkish familial Mediterranean fever patients. *Gene.* 2012;506:43-5.
- Uluca U, Ece A, Sen V, et al. High frequency of E148Q sequence variation in children with familial Mediterranean fever in southeast Turkey. *Arch Argent Pediatr.* 2015;113:133-40.
- 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.
- Ureten K, Gönülalan G, Akbal E, et al. Demographic, clinical and mutational characteristics of Turkish familial Mediterranean fever patients: results of a single center in Central Anatolia. *Rheumatol Int.* 2010;30:911-15.
- Oztuzcu 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.
- Akin H, Onay H, Turker E, Cogulu O, Ozkinay F. MEFV mutations in patients with Familial Mediterranean Fever from the Aegean region of Turkey. *Mol Biol Rep.* 2010;37:93-8.
- Ertekin V, Selimoğlu MA, Pirim I. Familial Mediterranean fever in a childhood population in eastern Turkey. *Pediatr Int.* 2005;47:640-4.
- Solak M, Yildiz H, Koken R, et al. Analysis of familial Mediterranean fever gene mutations in 202 patients with familial Mediterranean fever. *Genet Test.* 2008;12:341-4.
- Keles M, Eyerci N, Uyanik A, et al. The frequency of familial mediterranean Fever related amyloidosis in renal waiting list for transplantation. *Eurasian J Med.* 2010;42:19-20.
- Delibaş A, Oner A, Balci B, et al. Genetic risk factors of amyloidogenesis in familial Mediterranean fever. *Am J Nephrol.* 2005;25:434-40.
- Livneh A, Langevitz P, Shinar Y, et al. MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever. *Amyloid.* 1999;6:1-6.
- Shohat M, Magal N, Shohat T, et al. Phenotype-genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis. *Eur J Hum Genet.* 1999;7:287-92.
- Cazeneuve C, Ajrapetyan H, Papin S, et al. Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever. *Am J Hum Genet.* 2000;67:1136-43.
- Shinar Y, Livneh A, Langevitz P, et al. Genotype-phenotype assessment of common genotypes among patients with familial Mediterranean fever. *J Rheumatol.* 2000;27:1703-7.
- Koksal B, Nur N, Sari M, et al. Clinical and molecular analysis of common MEFV genemutations in familial Mediterranean fever in Sivas population. *Biologia.* 2009;64:388-93.
- Ebrahimi-Fakhari D, Schönland SO, Hegenbart U, et al. Familial Mediterranean fever in Germany: clinical presentation and amyloidosis risk. *Scand J Rheumatol.* 2013;42:52-8.
- Yağcinkaya F, Cakar N, Misirlioğlu M, et al. Genotype-phenotype correlation in a large group of Turkish patients with familial mediterranean fever: evidence for mutation-independent amyloidosis. *Rheumatology (Oxford).* 2000;39:67-72.
- Fonnesu C, Cerquaglia C, Giovinale M, et al. Familial Mediterranean Fever: a review for clinical management. *Joint Bone Spine.* 2009;76:227-33.
- Touitou I, Sarkisian T, Medlej-Hashim M, et al. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. *Arthritis Rheum.* 2007;56:1706-12.
- Saatçi U, Ozen S, Ozdemir S, et al. Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis. *Eur J Pediatr.* 1997;156:619-23.
- Kasifoğlu T, Bilge SY, Sarı İ, Solmaz D, Senel S. Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study. *Rheumatology.* 2014;53:741-5.
- Gershoni-Baruch R, Zacks N, Shinawi M, et al. The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial

- Mediterranean fever. *Arthritis Rheum.* 2003;48:1149-55.
33. Atagunduz MP, Tuglular S, Kantarci G, Akoglu E, Direskeneli H. Association of FMF-related (MEFV) point mutations with secondary and FMF amyloidosis. *Nephron Clin Pract.* 2004;96:131-5.
  34. Majeed HA, Barakat M. Familial Mediterranean fever (recurrent hereditary polyserositis) in children: analysis of 88 cases. *Eur J Pediatr.* 1989;148:636-41.
  35. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med.* 1967;43:227-53.
  36. Odabas AR, Cetinkaya R, Selcuk Y, Bilen H. Familial Mediterranean fever. *South Med J.* 2002;95:1400-3.
  37. Aldea A, Campistol JM, Arostegui JI, et al. A severe autosomal-dominant periodic inflammatory disorder with renal AA amyloidosis and colchicine resistance associated to the MEFV H478Y variant in a Spanish kindred: an unusual familial Mediterranean fever phenotype or another MEFV-associated periodic inflammatory disorder? *Am J Med Genet A.* 2004;124:67-73.
  38. Mimouni A, Magal N, Stoffman N, et al. Familial Mediterranean fever: effects of genotype and ethnicity on inflammatory attacks and amyloidosis. *Pediatrics.* 2000;105:1-7.
  39. Mattit H, Joma M, Al-Cheikh S, et al. Familial Mediterranean fever in the Syrian population: gene mutation frequencies, carrier rates and phenotype-genotype correlation. *Eur J Med Genet.* 2006;49:481-6.
  40. Mansour I, Delague V, Cazeneuve C, et al. Familial Mediterranean fever in Lebanon: mutation spectrum, evidence for cases in Maronites, Greek orthodoxes, Greek catholics, Syrians and Chiites and for an association between amyloidosis and M694V and M694I mutations. *Eur J Hum Genet.* 2001;9:51-5.
  41. Akpolat T, Özkaya O, Özen S. Homozygous M694V as a risk factor for amyloidosis in Turkish FMF patients. *Gene.* 2012;492:285-9.
  42. Booth DR, Gillmore JD, Booth SE, Pepys MB, Hawkins PN. Pyrin/marenostrin mutations in familial Mediterranean fever. *QJM.* 1998;91:603-6.
  43. Dodé C, Hazenberg BP, Pêcheux C, et al. Mutational spectrum in the MEFV and TNFRSF1A genes in patients suffering from AA amyloidosis and recurrent inflammatory attacks. *Nephrol Dial Transplant.* 2002;17:1212-7.
  44. Yalçinkaya F, Akar N, Misirlioglu M. Familial Mediterranean fever--amyloidosis and the Val726Ala mutation. *N Engl J Med.* 1998;338:993-4.
  45. Pasa S, Altintas A, Devecioglu B, et al. Familial Mediterranean fever gene mutations in the Southeastern region of Turkey and their phenotypical features. *Amyloid.* 2008;15:49-53.
  46. Balci B, Tinaztepe K, Yilmaz E, et al. MEFV gene mutations in familial Mediterranean fever phenotype II patients with renal amyloidosis in childhood: a retrospective clinicopathological and molecular study. *Nephrol Dial Transplant.* 2002;17:1921-3.
  47. Duşunsel R, Dursun I, Gündüz Z, et al. Genotype-phenotype correlation in children with familial Mediterranean fever in a Turkish population. *Pediatr Int.* 2008;50:208-12.
  48. Turkcapar N, Tuncali T, Kutlay S, et al. The contribution of genotypes at the MICA gene triplet repeat polymorphisms and MEFV mutations to amyloidosis and course of the disease in the patients with familial Mediterranean fever. *Rheumatol Int.* 2007;27:545-51.
  49. Yalçinkaya F, Tekin M, Cakar N, et al. Familial Mediterranean fever and systemic amyloidosis in untreated Turkish patients. *QJM.* 2000;93:681-4.
  50. Tekin M, Yalçinkaya F, Cakar N, et al. MEFV mutations in multiplex families with familial Mediterranean fever: is a particular genotype necessary for amyloidosis? *Clin Genet.* 2000;57:430-4.
  51. Albayrak F, Selcuk NY, Odabas AR, Cetinkaya R, Pirim I. Genotype-phenotype correlation in patients with familial Mediterranean fever in East Anatolia (Turkey). *Genet Test Mol Biomarkers.* 2010;14:325-8.
  52. Bernot A, da Silva C, Petit JL, et al. Non-founder mutations in the MEFV gene establish this gene as the cause of familial Mediterranean fever (FMF). *Hum Mol Genet.* 1998;7:1317-25.
  53. Comak E, Akman S, Koyun M, et al. Clinical evaluation of R202Q alteration of MEFV genes in Turkish children. *Clin Rheumatol.* 2014;33:1765-71.
  54. Abuhandan M, Kaya C, Guzelcicek A. Evaluation of the MEFV gene mutations and clinical symptoms in 186 patients diagnosed as familial Mediterranean fever. *Dicle Med J.* 2015;42:61-5.
  55. 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.
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