The Turkish Journal of Pediatrics 2024; 66: 465-472
https://doi.org/10.24953/turkjpediatr.2024.4580

Original Article

Cost-saving approach with screening of selected variants in genetic diagnosis in Turkish pediatric familial Mediterranean fever patients: a single center longitudinal study

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ABSTRACT

Background. The aim of this study was to investigate whether a short exon screening consisting of selected variants could confirm the diagnosis in patients with a preliminary diagnosis of familial Mediterranean fever (FMF), thus providing a cost-saving alternative to a comprehensive MEditerranean FeVer (*MEFV*) gene sequence analysis test.

Methods. This observational study on pediatric patients focused on clinically suspected FMF cases without prior genetic analysis. Participants met the Turkish pediatric FMF criteria. They underwent short exon screening for M694V, M680I, V726A, and E148Q variants. Those who were heterozygous or negative on short exon screening received further *MEFV* gene sequence analysis.

Results. The study involved 1557 patients. Pathogenic variants in both alleles of the *MEFV* gene were found in 611 patients (39.2%), and a high-penetrance variant in heterozygosity or an E148Q variant on the other allele was found in 643 patients (41.3%). A further 189 patients (12.1%) had one or two E148Q variants. Short-exon screening was negative in 114 patients (7.6%). Of the 876 patients who underwent *MEFV* gene sequence analysis, additional variants were found in 72 of the 762 initially heterozygous patients. Of the 114 initially negative patients, 34 had homozygous or compound heterozygous variants, and 74 had heterozygous variants. Ultimately, only 6 patients yielded negative results in the *MEFV* gene sequence analysis.

Conclusion. The short exon screening for common *MEFV* mutations offers a practical and cost-saving alternative to comprehensive *MEFV* gene sequence analysis in populations with a high prevalence of FMF.

Key words: Familial Mediterranean fever, genetics, diagnosis, cost-saving.

The most common autoinflammatory disease in the world is familial Mediterranean fever (FMF), which is particularly prevalent in populations originating from the Eastern Mediterranean region.[1] The prevalence of FMF has been reported to be 1:1000 worldwide, displaying significant regional variations, and Türkiye is most likely the nation with the highest prevalence.[2,3]

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Received 31st Mar 2024, revised 25th Jun 2024, 20th Aug 2024, accepted 26th Aug 2024.

Recurrent episodes of fever, sterile peritonitis, arthritis, pleuritis, and erysipelas-like erythema (ELE) are its defining features. The disease can present with many different clinical phenotypes and the diagnosis is primarily based on clinical symptoms.[4] The Tel Hashomer criteria was developed as the first diagnostic criteria for the adult population.[5] Later, Livneh et al.[6] developed a criteria set, and this criterion was found to have low specificity for pediatric cases. For this reason, new FMF criteria were formulated for the pediatric group in 2009, known as the Turkish FMF Pediatric criteria.[4] Although the validity of these criteria remains

limited for other ethnic groups, they are highly relevant among the Turkish population, which is considered an endemic community. In Turkish children, these criteria have demonstrated a sensitivity and specificity of 93.4% and 84.1%, respectively.[7]

FMF is known to be inherited in an autosomal recessive manner, but a substantial number of heterozygous individuals who express phenotypic characteristics are present.[8] It results from gain-of-function mutations located on the MEditerranean FeVer (*MEFV*) gene. The *MEFV* gene, comprising 10 exons, is located on chromosome 16 (16p13.3) and encodes a 781 amino acid protein called pyrin.[9,10] Multiple sequence variants in the *MEFV* gene have been associated with FMF, with 397 sequence variants identified in the *MEFV* gene according to the INFEVERS database (http://fmf.igh.cnrs.fr/infevers/) since its initial definition in 1997.[9] These variants based on current evidence are categorized according to their potential association with the disease phenotype as benign, likely benign, likely pathogenic, or pathogenic.[11] Additionally, there exist a considerable number of variants whose clinical associations remain unclear, and these are termed variants of uncertain significance (VUS).[11,12]

Identifying the correct patient solely based on diagnostic criteria may not always be possible. A study conducted by Ben-Chetrit E. and colleagues[13], which involved the analysis of 446 patients for *MEFV* mutations, found that only 43% of patients referred by a general practitioner were genetically confirmed, while 76.4% of patients referred by specialists received genetic confirmation. However, even in countries with a high prevalence of FMF, the diagnosis can still be missed, delayed, or misdiagnosed. In addition, some patients may present with atypical symptoms. In these groups of patients or in those who may carry pathogenic or sequence variants but remain asymptomatic, genetic testing is crucial for accurate guidance on prophylaxis and treatment.

Predominantly, mutations in exon 10 of the *MEFV* gene, including M694V, M680I, V726A, and M694I, have the highest allele frequencies among different ethnic groups and are considered pathogenic variants.[14] However, the classification of the E148Q variant, which is frequently observed in certain populations, as a disease-causing mutation remains controversial.[15]

The aim of this study was to investigate whether a short exon screening consisting of selected variants could confirm the diagnosis in patients with a preliminary diagnosis of FMF based on clinical findings, thus providing a cost-saving alternative to a comprehensive *MEFV* gene sequence analysis test.

Patients and methods

This is a longitudinal observational study conducted on pediatric patients with clinically suspected FMF at the University of Health Sciences, Umraniye Training and Research Hospital, Department of Pediatric Rheumatology, Türkiye, from June 2019 to October 2023. A total of 1557 patients with clinically suspected FMF who had not yet undergone genetic analysis were included. All participants who were referred to our tertiary care pediatric rheumatology center were of Turkish descent and met the criteria outlined in the Turkish pediatric FMF criteria.[4] We excluded patients with any other associated autoinflammatory diseases and rheumatic disease. A comprehensive approach was taken, including detailed medical histories, physical examinations, and analysis of laboratory tests performed during both symptomatic and asymptomatic periods. Our team then implemented a short exon screening protocol created by us, targeting the M694V, M680I, V726A, and E148Q variants. All patients included in the study underwent initial screening with the short exon test. Patients identified as heterozygous or negative based on the screening were subjected to a *MEFV* gene sequence analysis.

During the course of the study, it was determined that the *MEFV* gene sequence analysis cost was 4.2 times higher than that of the short exon screening kit.

The study protocol was reviewed and approved by the Ethics Committee of University of Health Sciences, Umraniye Training and Research Hospital (Approval No:B.10.1.TKH.4.34.H.GP.0.01/46, Approval Date: 20/03/2019) in line with the ethical principles stated in the Declaration of Helsinki. Written informed consent was obtained from legal guardians.

Statistical analysis

The statistical analyses were conducted using SPSS version 25.0. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov - Smirnov test) to determine whether or not they were normally distributed. In the descriptive analysis, normally distributed variables were presented as mean, +/- standard deviation (SD), and non-normally distributed variables were presented as median and interquartile range (Q1-Q3). Categorical variables were compared with the chi square test. The Mann–Whitney U test was used to compare the non-normally distributed variables between two independent groups. One-way ANOVA was used to compare the parameters between the groups. An overall p-value of less than 0.05 was considered to show a statistically significant difference.

Results

In this study, a total of 1557 patients were involved. Among these patients, 793 (50.9%) were female, and 764 (49.1%) were male. The median age of the patients at diagnosis was 6 years (interquartile range, IQR: 4-9). The median age at onset of symptoms was 4 years (IQR: 2-7.5). The median number of annual attacks experienced by the patients was 12 (IQR: 6–24), and the mean duration of the episode was 3 ± 1.7 days. There was consanguinity in 331 patients (21.2%).

The most common symptom observed in the study was abdominal pain, in 1400 patients (89.9%). After abdominal pain, the most common symptoms in the study were fever (88%), and musculoskeletal involvement, in the form of arthralgia (59%), myalgia (52.7%), and arthritis (23%). Additionally, amyloidosis was reported in three patients. The demographic characteristics of the patients, clinical manifestation and characteristics of attack episodes are presented in Table I.

In the short exon screening analysis, we identified two pathogenic variants in both alleles of the *MEFV* gene in 611 patients (39.2%). Meanwhile, 643 patients (41.3%)

Table I. Demographic characteristics, clinical manifestations, and characteristics of attack episodes in patients with familial Mediterranean fever (N=1557).

Gender (F / M)	793 / 764
Age at diagnosis (years), median (IQR)	6 (4-9)
Age at onset of symptoms (years), median (IQR)	4 (2-7.5)
Number of annual attacks, median (IQR)	12 (6-24)
Duration of the episode (days), mean ± SD	3 ± 1.7
Clinical characteristics	
Abdominal pain, n (%)	1400 (89.9%)
Fever, n (%)	1370 (88%)
Arthralgia, n (%)	932 (59.9%)
Myalgia, n (%)	821(52.7%)
Arthritis, n (%)	358 (23%)
Exertional leg pain, n (%)	402 (25.8%)
Chest pain, n (%)	285 (18.3%)
Diarrhea, n (%)	268 (17.2%)
Vomiting, n (%)	226 (14.5%)
Headache, n (%)	197 (12.7%)
Erysipelas-like erythema, n (%)	175 (11.2%)
Constipation, n (%)	94 (6%)
Protracted febrile myalgia	15 (1%)
Orchitis, n (%)	7 (0.4%)
Amyloidosis, n (%)	3 (0.2%)

IQR, interquartile range; SD, standard deviation.

possessed either one high-penetrance variant in heterozygosity or E148Q variant in the other allele. Furthermore, 189 patients (12.1%) had either one or two E148Q variants, as detailed in Table II. A total of 114 patients (7.6%) yielded negative results in the genetic tests.

MEFV gene sequence analysis was conducted in a total of 876 patients (56.2%) who either showed no mutation or had heterozygous variants as identified in the short-exon screening. Out of a total of 762 patients who initially presented with heterozygous variants, 72 were found to have additional variants in the other allele. In the remaining 690 patients, no mutations were observed in the second allele. The most frequently detected variants in the second allele were R761H and P369S variants. Detailed results of the variant analysis for these patients are presented in Table III. In the group of 114 patients where no mutation was initially detected in the short-exon screening, 34 patients were subsequently found to have either homozygous or compound heterozygous variants. Furthermore, heterozygous variants were detected in 74 patients. As a result of this analysis, the *MEFV* gene sequence analysis yielded a negative result in the case of 6 patients. The distribution of patients according to short exon screening and *MEFV* gene sequence analysis results is shown in Fig. 1. The genotype results of patients whom no mutation was detected in the short-exon screening are reported in Table IV.

In terms of allele frequencies, M694V was the most common variant (42.8%), followed by M680I (9.1%), E148Q (8.3%), V726A (7.9%), R761H (2.4%), and P369S (1.4%).

Table II. Most Common mutations identified with short exon screening analysis.

Mutations	n (%)
M694V / M694V	340 (21.8)
M680I / M680I	29 (1.9)
V726A / V726A	13 (0.8)
E148Q / E148Q	13 (0.8)
M694V / M680I	111 (7.1)
M694V / V726A	90 (5.8)
M680I / V726A	28 (1.8)
M694V / E148Q	44 (2.8)
M680I / E148Q	7 (0.4)
V726A / E148Q	6 (0.4)
M694V / -	409 (26.3)
M680I / -	80 (5.1)
V726A / -	97 (6.2)
E148Q / -	176 (11.2)
No mutation	114 (7.4)

Table III. Variants detected in second allele from MEFV gene analysis in patients with heterozygous variants identified by short-exon screening.

Mutations	n (%)
R761H	32 (4.1)
P369S	14 (1.8)
H478Y	1 (0.1)
A744S	3 (0.4)
M694I	6 (0.8)
I591T	5 (0.6)
F479L	1 (0.1)
R653H	1 (0.1)
K695R	2 (0.2)
L110P	5 (0.6)
T267I	1 (0.1)
R408Q	1 (0.1)

Discussion

This study makes a significant contribution to the field of diagnosis, especially in a population like Türkiye, where FMF is common. We aimed to provide an innovative approach that reduces cost without disrupting diagnosis, by implementing a short exon screening protocol focusing on common *MEFV* gene mutations. Our findings provide favorable insight into the practicality and effectiveness of this short exon screening method in the real world. This longitudinal study was designed to be limited to a single center, primarily due to the challenges of conducting affordable genetic evaluation in populations where FMF is commonly suspected.

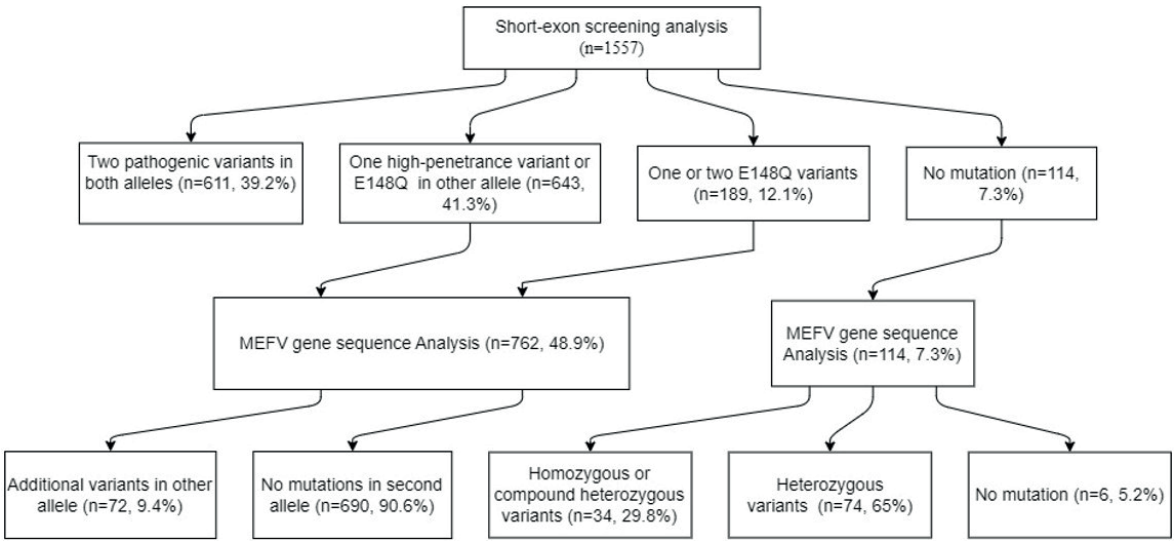

Fig. 1. Flowchart of *MEFV* gene analysis: Short exon screening and sequence analysis results.
MEFV, MEditerranean FeVer

In Türkiye, the diagnosis of FMF is often considered in pediatric patients with recurrent fever, leading to an increase in the frequency of genetic testing. However, the high costs associated with genetic testing place a significant economic burden on the country. Since FMF is an autosomal recessive disease, its definitive genetic diagnosis is made by identifying two pathogenic variants in the *MEFV* gene. However, the presence of at least one pathogenic variant is regarded as corroborative for accurately classifying FMF patients exhibiting a consistent phenotypic presentation.[16,17]

Table IV. The genotype results of patients with no mutation detected in short exon screening.

Mutations	n (%)
R761H / -	27 (23.7)
P369S / R408Q	18 (15.8)
A744S / -	15 (13.1)
P369S / -	8 (7)
K695R / -	7 (6.1)
R761H / R761H	7 (6.1)
I591T / -	5 (4.4)
F469L / -	3 (2.6)
T267I / -	3 (2.6)
E230K / -	3 (2.6)
P369S / P369S	2 (1.7)
K695R / R761H	2 (1.7)
R653H / A289E	1 (0.8)
Y471X / -	1 (0.8)
R354W / -	1 (0.8)
F479L / F479L	1 (0.8)
I641F / I641F	1 (0.8)
R761H / M694I	1 (0.8)
F479L / M694I	1 (0.8)
V487M / -	1 (0.8)
No mutation	6 (5.2)

Most pathogenic or likely pathogenic variants in FMF are located on exon 10. In regions where FMF is endemic, the M694V variant is the most common. Other common exon 10 variants, such as M694I, V726A and M680I, account for approximately 75% of all FMF cases.[18,19] In the present study, the frequency of these variants was found to be 80%, consistent with the literature.

Despite the classification of the E148Q variant as non-pathogenic, it has been included in the short exon screening kit. This decision was based on its notable prevalence in the Turkish population and in some other populations, as well as its documented association with clinical findings in several studies.[15,20,21]

Familial Mediterranean fever is typically inherited in an autosomal recessive pattern,

yet approximately 30% of patients present with a monoallelic disease harboring a single pathogenic variant.[17] In our cohort, a single variant was identified in 762 patients (48.9%). Upon conducting a comprehensive gene analysis in these patients, the frequency of identifying an additional variant was found to be 9.4%. The low incidence of detecting a second variant indicates that, in endemic populations, short-exon screening may yield sufficiently accurate results.

In the study by Kilim et al.[22], a short screening kit targeting five main mutations (E148Q, M680I, M694I, M694V and V726A) was used in a cohort of 1637 patients suspected of having FMF. The results showed that 812 patients (49.6%) had no detectable mutations, 581 patients (35.5%) had one mutation, 241 patients (14.7%) had two mutations (including 122 homozygous and 119 compound heterozygous), and 3 patients (0.2%) had three mutations. Subsequently, genetic testing was conducted on the patients, including R761H, A744S, K695R, M680I(c/t), and P369S, and additional mutations were identified in 68 patients (%4.3).

Moradian et al.[23] performed a study on 1299 FMF patients, employing a short screening kit for 12 *MEFV* mutations (E148Q, P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H). A subset comprising 23 heterozygous, 20 homozygous, and 20 asymptomatic individuals (63 in total) underwent *MEFV* gene sequence analysis. The analysis revealed that 4.3% of the heterozygous patients exhibited additional mutations undetectable by the initial sequencing.

Mattit et al.[24] included a total of 83 patients diagnosed with FMF and 242 healthy Syrian controls in their study. All participants were screened for the five most common *MEFV* mutations (M694V, M694I, M680I, V726A, and E148Q). In 25 patients (30%) who exhibited only one or no mutations, sequencing of exon 10 was performed, and in three patients additional mutations were identified (12%).

In the aforementioned studies, the frequency of additional mutations ranged from 4.3% to 12%, which is consistent with our findings. Generally, studies have shown that short exon screening kits offer high accuracy rates in diagnosing FMF. This is particularly beneficial in regions such as Türkiye, where the economic burden is significant.

In countries with a high prevalence of FMF and a significant rate of consanguineous marriages, the accumulation of affected individuals across consecutive generations may give the impression of dominant inheritance. However, this phenomenon is, in reality, a form of pseudo-dominant transmission. The frequency of consanguineous marriages within our country is 24%, which was comparable with our study.[25] This may explain the clinical manifestation observed in 48.9 % of our patients who possess a heterozygous mutation. Nevertheless, several *MEFV* variants exhibiting true dominant inheritance patterns have also been identified.[8,26]

Although this study makes significant contributions, it has limitations, primarily due to its focus on a specific ethnic group. This may limit the generalizability of the findings to other populations. Future research could aim to validate these findings in diverse ethnic backgrounds. As our study focused on common *MEFV* gene mutations, it may limit the comprehensiveness of our diagnostic approach, especially in cases with atypical genetic profiles. Furthermore, our reliance on Turkish pediatric FMF criteria may not cover all phenotypic variations of the disease.

In conclusion, the short exon screening for common *MEFV* mutations offers a practical and 4-fold lower cost alternative to comprehensive genetic testing in populations with a high prevalence of FMF. This approach can facilitate early diagnosis and the timely initiation of treatment, improving patient outcomes. As FMF is a complex and variable condition, an integrated approach that combines clinical assessment with targeted genetic testing is essential for optimal patient management.

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of the University of Health Sciences, Umraniye Training and Research Hospital (Approval No:B.10.1.TKH.4.34.H.GP.0.01/46).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BS, ŞÇ, and TC; data collection: ŞÇ, and TC; analysis and interpretation of results: BS, YKD, and ŞÇ; draft manuscript preparation: BS and ŞÇ. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Ben-Chetrit E, Touitou I. Familial Mediterranean fever in the world. Arthritis Rheum 2009; 61: 1447-1453. https://doi.org/10.1002/art.24458
2. Ozalkaya 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: 779-784. https://doi.org/10.1007/s00296-010-1383-8
3. Ozen S, Karaaslan Y, Ozdemir O, et al. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study. J Rheumatol 1998; 25: 2445-2449.
4. Yalçinkaya F, Ozen S, Ozçakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) 2009; 48: 395-398. https://doi.org/10.1093/rheumatology/ken509
5. Sohar E, Gafni G, Pras M. Tel Hashomer criteria for the diagnosis of FMF. In: Sohar E, Gafni G, Pras M, editors. Proceedings of the First International Conference on FMF. London and Tel Aviv: Freund Publishing House; 1997: 207.
6. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40: 1879-1885. https://doi.org/10.1002/art.1780401023
7. Sag E, Demirel D, Demir S, et al. Performance of the new 'Eurofever/PRINTO classification criteria' in FMF patients. Semin Arthritis Rheum 2020; 50: 172-175. https://doi.org/10.1016/j.semarthrit.2019.08.004
8. Stoffels M, Szperl A, Simon A, et al. MEFV mutations affecting pyrin amino acid 577 cause autosomal dominant autoinflammatory disease. Ann Rheum Dis 2014; 73: 455-461. https://doi.org/10.1136/annrheumdis-2012-202580
9. The International FMF 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. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet 1997; 17: 25-31. https://doi.org/10.1038/ng0997-25
11. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015; 17: 405-424. https://doi.org/10.1038/gim.2015.30
12. Van Gijn ME, Ceccherini I, Shinar Y, et al. New workflow for classification of genetic variants' pathogenicity applied to hereditary recurrent fevers by the International Study Group for Systemic Autoinflammatory Diseases (INSAID). J Med Genet 2018; 55: 530-537. https://doi.org/10.1136/jmedgenet-2017-105216
13. Ben-Chetrit E, Urieli-Shoval S, Calko S, Abeliovich D, Matzner Y. Molecular diagnosis of FMF: lessons from a study of 446 unrelated individuals. Clin Exp Rheumatol 2002; 20: S25-S29.
14. Tufan A, Lachmann HJ. Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review. Turk J Med Sci 2020; 50: 1591-1610. https://doi.org/10.3906/sag-2008-11
15. Öztürk K, Coşkuner T, Baglan E, et al. Real-life data from the largest pediatric familial Mediterranean fever cohort. Front Pediatr 2022; 9: 805919. https://doi.org/10.3389/fped.2021.805919

16. Booth DR, Gillmore JD, Lachmann HJ, et al. The genetic basis of autosomal dominant familial Mediterranean fever. QJM 2000; 93: 217-221. https://doi.org/10.1093/qjmed/93.4.217

17. Booty MG, Chae JJ, Masters SL, et al. Familial Mediterranean fever with a single MEFV mutation: where is the second hit? Arthritis Rheum 2009; 60: 1851-1861. https://doi.org/10.1002/art.24569

18. Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. Eur J Hum Genet 2001; 9: 473-483. https://doi.org/10.1038/sj.ejhg.5200658

19. Yaşar Bilge Ş, Sarı İ, Solmaz D, et al. The distribution of MEFV mutations in Turkish FMF patients: multicenter study representing results of Anatolia. Turk J Med Sci 2019; 49: 472-477. https://doi.org/10.3906/sag-1809-100

20. Dundar M, Kiraz A, Emirogullari EF, et al. A molecular analysis of familial Mediterranean fever disease in a cohort of Turkish patients. Ann Saudi Med 2012; 32: 343-348. https://doi.org/10.5144/0256-4947.2012.343

21. Kırnaz B, Gezgin Y, Berdeli A. MEFV gene allele frequency and genotype distribution in 3230 patients' analyses by next generation sequencing methods. Gene 2022; 827: 146447. https://doi.org/10.1016/j.gene.2022.146447

22. Kilim Y, Magal N, Shohat M. Expanding the panel of MEFV mutations for routine testing of patients with a clinical diagnosis of familial Mediterranean fever. Isr Med Assoc J 2011; 13: 206-208.

23. Moradian MM, Sarkisian T, Ajrapetyan H, Avanesian N. Genotype-phenotype studies in a large cohort of Armenian patients with familial Mediterranean fever suggest clinical disease with heterozygous MEFV mutations. J Hum Genet 2010; 55: 389-393. https://doi.org/10.1038/jhg.2010.52

24. 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: 481-486. https://doi.org/10.1016/j.ejmg.2006.03.002

25. Koç İ. Türkiye'de akraba evliliklerinin yaygınlığının değişimi ve dirençli grupların belirlenmesi: 2018 Türkiye Nüfus ve Sağlık Araştırması'ndan evlilik kuşaklarına göre analizler. Turkish Journal of Public Health 2022; 20: 423-438. https://doi.org/10.20518/tjph.1114922

26. Rowczenio DM, Youngstein T, Trojer H, et al. British kindred with dominant FMF associated with high incidence of AA amyloidosis caused by novel MEFV variant, and a review of the literature. Rheumatology (Oxford) 2020; 59: 554-558. https://doi.org/10.1093/rheumatology/kez334