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Frequency of rheumatic diseases in patients with familial Mediterranean fever

Ailesel Akdeniz ateşi hastalarında romatizmal hastalıkların sıklığı

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Abstract

Purpose: Mutations in the Mediterranean FeVer (MEFV) gene, which causes familial Mediterranean fever (FMF), may also cause the emergence of other specific rheumatic diseases. This study aims to determine the frequency of other rheumatologic diseases in paediatric FMF patients, evaluate whether there are clinical and genetic differences between those with and without concomitant rheumatologic diseases, and compare the data with previous studies.

Materials and methods: The files of FMF patients who were followed up at the paediatric rheumatology department were reviewed retrospectively. Demographic data, MEFV mutations, treatment, disease severity scores, and concomitant rheumatic diseases were recorded from the files.

Results: There were 303 FMF patients (154 female/149 male). The mean age at diagnosis was 7.04±3.9 years. The mean disease duration was 5.33±3.13 years. In the cohort, 41 FMF patients (13.5%) were diagnosed with another rheumatic disease. There were 22 cases of juvenile idiopathic arthritis (53.6%), seven cases of vasculitis (17%), six cases of periodic fever aphthous stomatitis and adenitis syndrome (14.6%), three cases of Behçet's disease (7.3%), two cases of acute rheumatic fever (4.8%), and one case of systemic lupus erythematosus (2.4%). Thirty-two of these of these 41 FMF patients (78%) had the *M694V* mutation (homozygous in 11, heterozygous in 21). Disease activity scores Pras and ISSF scores were higher in FMF patients with rheumatic diseases (p=0.002 and p<0.001, respectively).

Conclusion: Other rheumatologic diseases should be evaluated in FMF patients. Regarding other accompanying rheumatic diseases, the *M694V* mutation and disease severity scores are notable factors.

Key words: Familial Mediterranean fever, rheumatic disease, MEFV mutation.

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Öz

Amaç: Ailesel Akdeniz ateşine (FMF) neden olan Mediterranean FeVer (MEFV) genindeki mutasyonlar başka spesifik romatizmal hastalıkların da ortaya çıkmasına neden olabilir. Bu çalışmanın amacı pediatrik FMF hastalarında diğer romatizmal hastalıkların sıklığını belirlemek, eşlik eden romatizmal hastalığı olan ve olmayanlar arasında klinik ve genetik farklılık olup olmadığını değerlendirmek ve verileri önceki çalışmalarla karşılaştırmaktır.

Gereç ve yöntem: Çocuk romatoloji bölümünde takip edilen FMF hastalarının dosyaları retrospektif olarak incelendi. Dosyalardan demografik veriler, MEFV mutasyonları, tedavi, hastalık şiddet skorları ve eşlik eden romatizmal hastalıkları kaydedildi.

Bulgular: 303 FMF hastası (154 kadın/149 erkek) vardı. Ortalama tanı yaşı 7,04±3,9 idi. Ortalama hastalık süresi 5,33±3,13 yıldı. Kohortta 41 FMF hastasına (%13,5) başka bir romatizma hastalığı teşhisi kondu. 22 juvenil idiyopatik artrit (%53,6), yedi vaskülit (%17), altı periyodik ateş aftöz stomatit ve adenit sendromu (%14,6), üç Behçet hastalığı (%7,3), iki akut romatizmal ateş (%4,8) ve bir sistemik lupus eritematozus (%2,4) olgusu vardı. Bu 41 FMF hastasının 32'sinde (%78) *M694V* mutasyonu vardı (11'i homozigot, 21'i heterozigot). Hastalık şiddet skorları Pras ve ISSF skorları romatizmal hastalığı olan FMF hastalarında daha yüksekti (sırasıyla p=0.002 ve p<0.001).

Sonuç: FMF hastalarında diğer romatolojik hastalıklar da değerlendirilmelidir. Eşlik eden diğer romatizmal hastalıklarda ise *M694V* mutasyonu ve hastalık şiddet skorları önemli faktörlerdir.

Anahtar kelimeler: Ailesel Akdeniz ateşi, romatizmal hastalık, MEFV mutasyonu.

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Introduction

Familial Mediterranean fever (FMF) is a monogenic autoinflammatory disease. It is characterised by recurrent episodes of fever and polyserositis. Turkish, Jewish, Armenian, and Arab populations are the most affected by FMF [1]. Clinical findings are used to diagnose and the diagnosis is supported by the ethnicity, family history, and genetic testing. FMF is an autosomal recessive disease caused by mutations in the *MEFV* gene. The *MEFV* gene encodes pyrin (also known as marenostrin), and mutations in the *MEFV* gene can result in an inability to control inflammation [2]. Gain-of-function mutations in the *MEFV* gene lead to increased levels of the most potent pro-inflammatory cytokine, interleukin (IL)-1 beta [3]. Furthermore, cytokine levels, such as TNF-α, IL-6, and sIL-2r, were higher during an acute FMF attack than during the silent period and in healthy controls [4]. In addition, studies have shown that colchicine, the primary treatment for FMF patients, decreases serum inflammatory cytokine levels, such as IL-6, IL-8, and TNF- α in FMF patients [5]. These cytokine interactions may increase the frequency and severity of other rheumatologic diseases in FMF, particularly juvenile idiopathic arthritis, vasculitis, and other autoimmune diseases.

Few studies have focused on the relationship between FMF and concomitant diseases in children [6-11]. Recent studies have found that the frequency of associated diseases ranged from 12.8% to 18.9% among FMF patients, but in these studies, some of the concomitant diseases were non-rheumatic, such as asthma, migraine, etc. [6-11]. The primary objective of this study was to determine the prevalence of other rheumatic diseases in paediatric FMF patients. The secondary goal was to determine whether clinical and genetic differences between those with and without concomitant rheumatic diseases.

Materials and methods

The medical files of paediatric patients with FMF diagnosed and followed up at the paediatric rheumatology unit in a university hospital in the last ten years (2010-2020) were retrospectively reviewed. To be included in the study, the patient had to have completed at least one year of follow-up and regularly come to the control visits (generally every 3-6 months). Data, including demographic information (age, gender, and disease duration), clinical features, *MEFV* gene mutations, medications, and co-occurring rheumatic diseases, were recorded from the files.

The diagnosis of FMF was made according to Turkish paediatric FMF criteria [12]. The criteria included at least three attacks with 6-72 hours duration of fever, abdominal pain, chest pain, arthritis, and family history. At least two criteria are required for the diagnosis of FMF. Patients with FMF and concomitant rheumatic diseases were included in the study and divided into two main groups. The diagnosis of concomitant rheumatic diseases, such as juvenile idiopathic arthritis (JIA), vasculitis, periodic fever aphthous stomatitis and adenitis (PFAPA) syndrome, Behçet's disease, acute rheumatic fever, and systemic lupus erythematosus were evaluated by the previously defined criteria for those diseases [13-18]. Sanger sequencing was used to analyse *MEFV* gene variants in exons 2, 3, 5, and 10. The severity of the disease was determined by the Pras score, which was adjusted based on the colchicine dose and the international severity score system for familial Mediterranean fever (ISSF) score [19-21].

Despite getting the maximum permissible dose for 6 months, one episode per month was defined as resistance to colchicine treatment.

The study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study and this research was in compliance with the declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using SPSS software, version 21.0. Variables were investigated using analytic methods (Kolmogorov-Smirnov) to determine whether they were normally distributed. The descriptive analysis data were expressed as mean-standard deviation (SD) or median, minimum-maximum, where appropriate. Fisher's exact and Pearson's chi-square tests were used for differences between categorical parameters. Continuous data were analysed by Student's t-test or Mann-Whitney U test, as appropriate. A p-value <0.05 was considered statistically significant.

Results

The study included a total of 303 patients (154 female/149 male). The mean age at diagnosis was 7.04±3.9 years. The mean disease duration was 5.33±3.13 years. FMF history in relatives was 52.1% (158 patients). Clinical features at diagnosis were abdominal pain in 201 patients (66.3%), chest pain in 12 patients (3.9%), arthritis in 25 patients (8.2%), and orchitis in 1 patient (0.3%). Forty-one (13.5%) of the 303 FMF patients were diagnosed with FMF and an accompanying rheumatic disease (20 females, 21 males).

There were 22 cases of JIA (53.6%), seven cases of vasculitis (17%), six cases of periodic fever aphthous stomatitis and adenitis (PFAPA) syndrome (14.6%), three cases of Behçet's disease (7.3%), two cases of acute rheumatic fever (4.8%), and one case of systemic lupus erythematosus (2.4%). There were 11 enthesitis-related arthritis patients, eight oligoarticular arthritis patients, and three rheumatoid factor negative polyarticular arthritis patients among the 22 JIA patients. There were seven patients with vasculitis, six with IgA vasculitis, and one with polyarteritis nodosa (PAN). There was no difference between the FMF groups with and without rheumatic disease in terms of age, gender, family history, disease duration, or colchicine dosage (Table 1).

Figure 1 shows the *MEFV* mutation analyses of the cohort. Table 2 shows the

Table 1. Demographic features of familial Mediterranean fever patients

	All patients (n=303)	Without rheumatic diseases (n=262)	With rheumatic diseases (n=41)	*p*
Mean age (years)	12.24±4.93	12.32±4.91	11.74±5.09	0.48
Female/male n/n	154/149	134/128	20/21	0.77
Family history n (%)	158 (52.1%)	136 (51.9%)	22 (53.7%)	0.83
Mean age at diagnosis of FMF (years)	7.04±3.9	7.04±3.81	7.02±4.46	0.96
Disease duration (years) (mean)	5.33±3.13	5.42±3.11	4.76±3.28	0.21
Colchicine dosage (mg/day) (median)	1 (0.5-1.5)	1 (0.5-1.5)	1 (0.5-1.5)	0.21

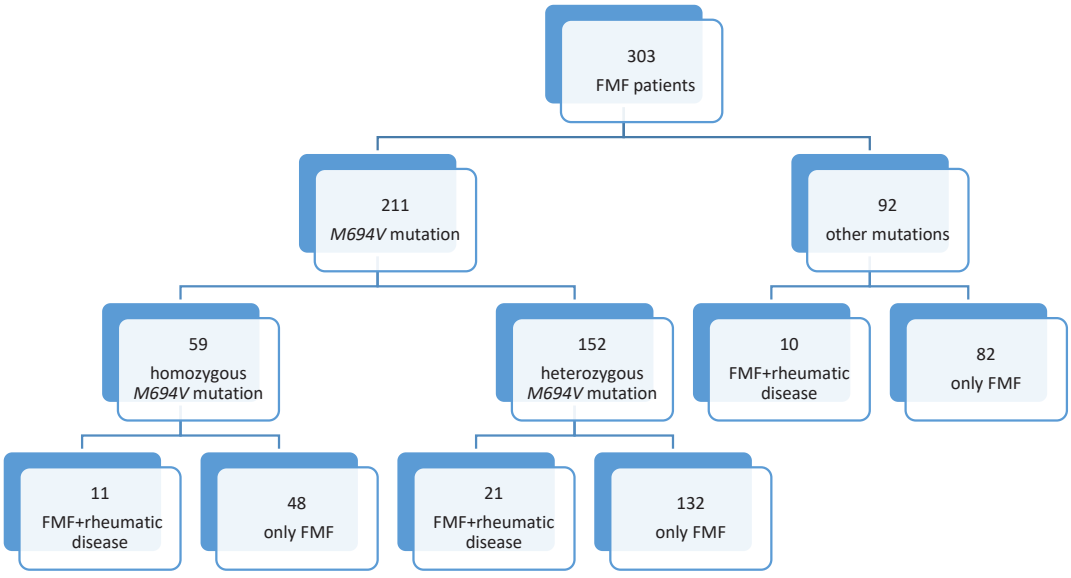

Figure 1. *MEFV* mutation of patients

Table 2. Mutations of familial Mediterranean fever patients

	All patients (n=303)	Without rheumatic diseases (n=262)	With rheumatic diseases (n=41)	*p*
M694V positivity n (%)	211 (69.6%)	180 (68.7%)	32 (78%)	0.37
M694V homozygosity n (%)	59 (19.4%)	48 (18.3%)	11 (26.8%)	0.2
M680I positivity n (%)	50 (16.5%)	45 (17.1%)	5 (12.1%)	0.42
V726A positivity n (%)	34 (11.2%)	31 (11.8%)	3 (7.3%)	0.59
E148Q positivity n (%)	39 (12.9%)	34 (12.9%)	5 (12.1%)	0.88

MEFV mutations of all cohorts. Table 3 depicts the *MEFV* mutation analyses of patients with coexisting rheumatic diseases. The *M694V* mutation in the *MEFV* gene was found in 32 of 41 FMF patients with rheumatic disease, which was significantly greater than the prevalence in FMF patients without rheumatic disease (78% *vs.* 68.7%). Similarly, the percentage of *M694V* homozygous mutations was higher in the group with an associated rheumatic disease (26.8% *vs.* 18.3%).

Colchicine was administered to all patients. Due to concomitant disorders, methotrexate, etanercept, tocilizumab, and sulfasalazine were additionally given to six, five, two, and two

Table 3. Mutations of familial Mediterranean fever patients with rheumatic diseases

Mutations	Disease	n=41
Homozygous		**12**
M694V/M694V	Enthesitis-related arthritis	4
	Polyarticular JIA RF negative	2
	IgA vasculitis	2
	Oligoarticular JIA	2
	Polyarteritis nodosa	1
M680I/M680I	Behçet's disease	1
Heterozygous		**24**
M694V/-	PFAPA	5
	Enthesitis related arthritis	4
	Oligoarticular JIA	3
	IgA vasculitis	2
	Behçet's disease	1
V726A/-	IgA vasculitis	1
	Acute rheumatic fever	1
E148Q/-	Enthesitis-related arthritis	2
	Polyarticular JIA	1
	Oligoarticular JIA	1
	PFAPA	1
K695R/-	Acute rheumatic fever	1
	Behçet's disease	1
Compound heterozygous		**5**
M694V/M680I	Enthesitis related arthritis	1
	Oligoarticular JIA	1
	Systemic lupus erythematosus	1
	IgA vasculitis	1
M694V/V726A	Oligoarticular JIA	1

PFAPA: Periodic fever aphthous stomatitis and adenitis syndrome
JIA: Juvenile idiopathic arthritis
IgA: Immunoglobulin A

patients, respectively, in addition to colchicine. Two colchicine-resistant FMF patients with *M694V* homozygous mutations received anti-IL1B treatment.

There was a statistically significant difference in terms of Pras scores between the FMF groups with and without rheumatic disease (median 6 *vs*. 5, p=0.002). The ISSF scores of the groups were also significantly different (median 2 *vs*. 3, p<0.001) (Table 4).

Table 4. Severity scores of familial Mediterranean fever patients with and without a rheumatic disease

	All patients (N=303)	Without rheumatic diseases (n=262)	With rheumatic diseases (N=41)	*p*
Pras severity score median (min-max)	5 (4-9)	5 (4-9)	6 (4-9)	0.002*
Pras severity score category, mild, n (%)	194 (64%)	175 (66.8%)	19 (46.3%)	0.01*
Pras severity score category, moderate, n (%)	101 (33.3%)	82 (%31.3%)	19 (46.3%)	0.057
Pras severity score category, severe, n (%)	8 (2.6%)	5 (1.9%)	3 (7.3%)	0.079
ISSF severity score median (min-max)	2 (0-7)	2 (0-5)	3 (0-7)	<0.001*
ISSF severity score category, mild, n (%)	215 (71%)	199 (76%)	16 (39%)	<0.001*
ISSF severity score category, moderate, n (%)	86 (28.4%)	63 (%24)	23 (56.1%)	<0.001*
ISSF severity score category, severe, n (%)	1 (%0.3)	0 (%0)	1(%2.4)	0.01*

ISSF: International severity score system for familial Mediterranean fever
*p<0.05 significant

Discussion

Concurrent diseases in FMF have been explored, and recent studies have indicated that 12.8%-18.9% of FMF patients have an associated disease; however, some of the concomitant diseases in these investigations include asthma, migraines, and other conditions [6-11]. The prevalence of other rheumatic diseases in children with FMF was 13.5% in our study, which is similar to the literature from Turkey (Table 5). The presence of the *M694V* mutation and disease severity scores can all be regarded as relevant risk factors for rheumatic disorders associated with FMF.

The FMF severity score (Pras) was initially established for adults and subsequently adapted for children [19, 20]. This was carried out by adjusting the dosage of colchicine for children. Recently, ISSF scoring criteria have been created and verified for both children and adults [21]. Disease-related sequelae, acute phase measurements, attack traits, and exertional leg pain are all included in this score. As a result, it is the most sensitive and specific. In this study, the ISSF scores were considerably higher in FMF patients with concomitant diseases. We noticed that the severity of the disease was linked to a higher prevalence of comorbidities in our FMF patient population. As a result, clinicians should be aware of the elevated risk of comorbidities in patients with more severe FMF and manage these comorbidities as soon as possible.

Patients with FMF frequently complain of musculoskeletal symptoms [22]. FMF arthritis is characterized by acute attacks of pain and swelling that usually affect large joints in the lower extremities and heal without treatment within 2-3 days. Exertional leg pain is one of the ISSF score's characteristics, and it can be separated from JIA. In our study, 22 patients with FMF (7.2%) had JIA. In other studies, JIA was observed in 1.5-6.1% of FMF patients [7, 8]. Rozenbaum et al. [23] reported three patients with FMF and JIA, all of whom had the *M694V* mutation and had an exceptionally poor prognosis, implying that more aggressive treatment, such as the early use of biologic agents, is required when JIA and FMF coexist.

Table 5. Comparison of the study and the other paediatric studies

	Our cohort	Ozcakar et al. [7]	Kisla Ekinci et al. [8]	Yildiz et al. [9]	Balcı-Peynircioglu et al. [10]	Ayaz et al. [11]
Patient (n)	303	600	494	686	2000	1687
FMF and concomitant disease n (%)	41 (13.5%)	77 (12.8%)	85(17.2%)	130 (18.9%)	94 (4.7%)	118 (7%)
JIA n (%)	22 (7.2%)	21 (3.5%)	27 (5.5%)	42 (6.1%)	31 (1.5%)	63 (3.7%)
IgA vasculitis n (%)	6 (1.9%)	19 (3.1%)	12 (2.4%)	20 (2.9%)	25 (1.2%)	35 (2%)
Polyarteritis nodosa n (%)	1 (0.3%)	9 (1.5%)	NA	3 (0.4%)	1 (0.3%)	1 (0.05%)
PFAPA n (%)	6 (1.9%)	NA	6 (1.2%)	7 (1%)	NA	NA
Acute rheumatic fever n (%)	2 (0.6%)	3 (0.5%)	NA	6 (0.8%)	16 (0.8%)	NA
Behçet's disease n (%)	3 (1%)	1 (0.1%)	NA	1 (0.1)	3 (0.1%)	1 (0.05%)
Systemic lupus erythematosus (nephritis) n (%)	1 (0.3%)	1 (0.1%)	NA	3 (0.4%)	1 (0.05%)	2 (0.1%)

FMF: Familial Mediterranean fever, JIA: Juvenile idiopathic arthritis
PFAPA: Periodic fever aphthous stomatitis and adenitis syndrome
IgA: Immunoglobulin A, NA: Not Available

Etanercept was administered to five patients with JIA and FMF in our cohort. Tocilizumab was used in two individuals with rheumatoid factor-negative polyarticular JIA.

Only a few studies on FMF and paediatric sacroiliitis are currently available [24-26]. In paediatric FMF patients with sacroiliitis, the prevalence of the *M694V* mutation was higher than in adult research [27]. In our analysis, the most common mutations in patients with sacroiliitis were *M694V* mutations (8 of 11 sacroiliitis). In one of the paediatric studies, patients with FMF related sacroiliitis had significantly higher levels of inflammation than those with juvenile spondyloarthropathy [24]. In addition, individuals with juvenile spondyloarthropathy had higher spinal and enthesitis involvement, as well as HLA-B27-positivity, than patients with FMF related sacroiliitis [24]. In the diagnosis of enthesitis-related arthritis, Gulhan et al. [27] found that being HLA B27 negative increases the prevalence of *MEFV* mutation, which could be one of the genetic factors. Since 11 patients with sacroiliitis also had enthesitis in our study, all diagnoses were enthesitis-related arthritis according to ILAR criteria, with only one patient having HLA-B27 positive.

The most prevalent type of vasculitis in children is IgA vasculitis (Henoch-Schönlein purpura). According to several recent studies, vasculitis, particularly IgA vasculitis, is more common among FMF patients than in the general population, with the *M694V* mutation being the most common [28, 29]. Ozdogan et al. [30] reported that IgA vasculitis was present in 7% of FMF patients, and nine patients were diagnosed with FMF after the emergence of IgA vasculitis. According to the Turkish FMF study group, 2.7% of patients with IgA vasculitis [6]. In other studies, IgA vasculitis rates were 1.2-2.9% [7-9]. The prevalence of FMF and IgA vasculitis was 1.9% in this study, and all patients were diagnosed with FMF after IgA vasculitis disease. We investigate FMF clinical findings and *MEFV* mutations in patients with vasculitis on a routine basis in our clinic.

The most common autoinflammatory disorders in childhood are FMF and PFAPA. *MEFV* mutations may be found in

PFAPA patients [31, 32]. According to the literature, PFAPA patients with FMF are more resistant to adenotonsillectomy than patients without FMF [33]. Furthermore, prophylactic colchicine treatment reduces attack frequency and extends episode intervals in PFAPA patients with *MEFV* mutations [34, 35]. Previous studies' rates were 1-1.2% [8, 9]. Six patients (1.9%) with FMF had PFAPA in our study. All of them used colchicine, and five carried the *M694V* mutation.

MEFV mutation carriers may have increased inflammation and suffer from other rheumatic diseases [36]. In a Turkish multicentric FMF study, the homozygous *M694V* mutation was 28%, and the *M694V* allele frequency was 51.4% [6]. In our study, the frequency of the homozygous *M694V* mutation was 19.4%, and the frequency of the *M694V* allele was 69.6%. According to recent investigations, the *M694V* mutation may represent a sensitivity component for concurrent disorders [6]. *MEFV* mutations, according to Ozen et al. [37], may predispose patients to inflammation. In childhood FMF patients, the *M694V* mutation may be a risk factor for rheumatic disorders. *M64V* was the most common mutation in our study. However, there was no difference between the two groups because *M694V* is a prevalent and important mutation in our region.

The first limitation of this study was that it was a retrospective study. The second limitation was the small number of patients because the study was conducted in a single centre.

In conclusion, our study and other studies have shown that other rheumatic diseases are common in FMF patients so, routine rheumatic disease evaluation may be beneficial in FMF patients. Having higher disease severity scores and the presence of the *M694V* mutation are key risk factors for having FMF-related rheumatic disorder.

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

References

1. Ben Chetrit E, Levy M. Familial Mediterranean fever. Lancet 1998;351:659-664. https://doi.org/10.1016/S0140-6736(97)09408-7
2. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet 1997;17:25-31. https://doi.org/10.1038/ng0997-25
3. Chae JJ, Cho YH, Lee GS, et al. Gain-of-function Pyrin mutations induce NLRP3 protein-independent interleukin-1β activation and severe autoinflammation in mice. Immunity 2011;34:755-768. https://doi.org/10.1016/j.immuni.2011.02.020
4. Baykal Y, Saglam K, Yilmaz MI, Taslipinar A, Akinci SB, Inal A. Serum sIL-2r, IL-6, IL-10 and TNF-alpha level in familial Mediterranean fever patients. Clin Rheumatol 2003;22:99-101. https://doi.org/10.1007/s10067-002-0682-1
5. Kiraz S, Ertenli I, Arici M, et al. Effects of colchicine on inflammatory cytokines and selectins in familial Mediterranean fever. Clin Exp Rheumatol 1998;16:721-724.
6. 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
7. Özçakar ZB, Çakar N, Uncu N, Çelikel BA, Yalçinkaya F. Familial Mediterranean fever-associated diseases in children. QJM 2017;110:287-290. https://doi.org/10.1093/qjmed/hcw230
8. Kişla Ekinci RM, Balci S, Ufuk Altintaş D, Yilmaz M. The influence of concomitant disorders on disease severity of familial mediterranean fever in children. Arch Rheumatol 2017;33:282-287. https://doi.org/10.5606/ArchRheumatol.2018.6488
9. Yildiz M, Adrovic A, Tasdemir E, et al. Evaluation of co-existing diseases in children with familial Mediterranean fever. Rheumatol Int 2020;40:57-64. https://doi.org/10.1007/s00296-019-04391-9
10. Balcı Peynircioğlu B, Kaya Akça Ü, Arıcı ZS, et al. Comorbidities in familial Mediterranean fever: analysis of 2000 genetically confirmed patients. Rheumatology (Oxford) 2020;59:1372-1380. https://doi.org/10.1093/rheumatology/kez410
11. Ayaz NA, Tanatar A, Karadağ ŞG, Çakan M, Keskindemirci G, Sönmez HE. Comorbidities and phenotype-genotype correlation in children with familial Mediterranean fever. Rheumatol Int 2021;41:113-120. https://doi.org/10.1007/s00296-020-04592-7
12. 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
13. Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis. 2006;65:936-941. https://doi.org/10.1136/ard.2005.046300
14. Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. JAMA 1992;268:2069-2073.

15. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-392.
16. Thomas KT, Feder HM Jr, Lawton AR, Edwards KM. Periodic fever syndrome in children. J Pediatr 1999;135:15-21. https://doi.org/10.1016/s0022-3476(99)70321-5
17. Koné Paut I, Shahram F, Darce Bello M, et al. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. Ann Rheum Dis 2016;75:958-964. https://doi.org/10.1136/annrheumdis-2015-208491
18. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677-2686. https://doi.org/10.1002/art.34473
19. Pras E, Livneh A, Balow JE Jr, et al. Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet 1998;75:216-219. https://doi.org/10.1002/(sici)1096-8628(19980113)75:2<216::aid-ajmg20>3.0.co;2-r
20. Ozen S, Aktay N, Lainka E, Duzova A, Bakkaloglu A, Kallinich T. Disease severity in children and adolescents with familial Mediterranean fever: a comparative study to explore environmental effects on a monogenic disease. Ann Rheum Dis 2009;68:246-248. https://doi.org/10.1136/ard.2008.092031
21. Demirkaya E, Acikel C, Hashkes P, et al. Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF). Ann Rheum Dis 2016;75:1051-1056. https://doi.org/10.1136/annrheumdis-2015-208671
22. Brik R, Shinawi M, Kasinetz L, Gershoni-Baruch R. The musculoskeletal manifestations of familial Mediterranean fever in children genetically diagnosed with the disease. Arthritis Rheum 2001;44:1416-1419. https://doi.org/10.1002/1529-0131(200106)44:6<1416::AID-ART236>3.0.CO;2-6
23. Rozenbaum M, Rosner I. Severe outcome of juvenile idiopathic arthritis (JIA) associated with familial Mediterranean fever (FMF). Clin Exp Rheumatol 2004;22:75-78.
24. Sönmez HE, Batu ED, Demir S, Bilginer Y, Özen S. Comparison of patients with familial Mediterranean fever accompanied with sacroiliitis and patients with juvenile spondyloarthropathy. Clin Exp Rheumatol 2017;108:124-127.
25. Aydin F, Özçakar ZB, Çakar N, et al. Sacroiliitis in children with familial mediterranean fever. J Clin Rheumatol 2019;25:69-73. https://doi.org/10.1097/RHU.0000000000000770
26. Ozer E, Seker D, Taner E, et al. The frequency of juvenile spondyloarthropathies in childhood familial Mediterranean fever. Clin Exp Rheumatol 2018;36:141-145.
27. Gülhan B, Akkuş A, Ozçakar L, Beşbaş N, Ozen S. Are MEFV mutations susceptibility factors in enthesitis-related arthritis patients in the eastern Mediterranean?. Clin Exp Rheumatol 2014;32:160-164.
28. Bayram C, Demircin G, Erdoğan O, Bülbül M, Caltik A, Akyüz SG. Prevalence of MEFV gene mutations and their clinical correlations in Turkish children with Henoch-Schönlein purpura. Acta Paediatr 2011;100:745-749. https://doi.org/10.1111/j.1651-2227.2011.02143.x
29. Ozçakar ZB, Yalçinkaya F, Cakar N, et al. MEFV mutations modify the clinical presentation of Henoch-Schönlein purpura. J Rheumatol 2008;35:2427-2429. https://doi.org/10.3899/jrheum.080405
30. Ozdogan H, Arisoy N, Kasapçapur O, et al. Vasculitis in familial Mediterranean fever. J Rheumatol 1997;24:323-327.
31. Adrovic A, Sahin S, Barut K, Kasapcopur O. Familial Mediterranean fever and periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: shared features and main differences. Rheumatol Int 2019;39:29-36. https://doi.org/10.1007/s00296-018-4105-2
32. Dagan E, Gershoni Baruch R, Khatib I, Mori A, Brik R. MEFV, TNF1rA, CARD15 and NLRP3 mutation analysis in PFAPA. Rheumatol Int 2010;30:633-636. https://doi.org/10.1007/s00296-009-1037-x
33. Pehlivan E, Adrovic A, Sahin S, Barut K, Kul Cınar O, Kasapcopur O. PFAPA syndrome in a population with endemic familial mediterranean fever. J Pediatr 2018;192:253-255. https://doi.org/10.1016/j.jpeds.2017.08.078
34. Gunes M, Cekic S, Kilic SS. Is colchicine more effective to prevent periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis episodes in Mediterranean fever gene variants?. Pediatr Int 2017;59:655-660. https://doi.org/10.1111/ped.13265
35. Butbul Aviel Y, Tatour S, Gershoni Baruch R, Brik R. Colchicine as a therapeutic option in periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome. Semin Arthritis Rheum 2016;45:471-474. https://doi.org/10.1016/j.semarthrit.2015.07.005
36. Kalyoncu M, Acar BC, Cakar N, et al. Are carriers for MEFV mutations "healthy"? Clin Exp Rheumatol 2006;24:120-122.
37. Ozen S, Bakkaloglu A, Yilmaz E, et al. Mutations in the gene for familial Mediterranean fever: do they predispose to inflammation?. J Rheumatol 2003;30:2014-2018.

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Authors' contributions to the article

G.O.Y., S.Y., Z.E.T. and H.T. constructed the main idea and hypothesis of the study. G.O.Y., S.Y., Z.E.T. and H.T. developed the theory and arranged/edited the material and method section. G.O.Y. and S.Y. evaluated the data in the results section. G.O.Y. and S.Y., reviewed, corrected, and approved the discussion section of the article. In addition, all authors discussed the entire study and approved the final version.