The Turkish Journal of Pediatrics 2024; 66: 180-190
https://doi.org/10.24953/turkjpediatr.2024.4589

**Original Article**

# Health conditions of first-degree relatives of children with familial Mediterranean fever

Sema Yıldırım[1], Fatih Haşlak[2], Mehmet Yıldız[2], Amra Adrovic[2], Ayten Aliyeva[2], Aybüke Günalp[2], Esma Aslan[2], Elif Kılıç Könte[2], Ümit Gül[2], Sezgin Şahin[2], Kenan Barut[2], Özgür Kasapçopur[2]

*[1]Department of Pediatrics, İstanbul Medeniyet University, Goztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul; [2]Department of Pediatric Rheumatology, İstanbul University-Cerrahpaşa, Cerrahpaşa Medical School, İstanbul, Türkiye.*

## ABSTRACT

**Background.** Given the strong genetic background of familial Mediterranean fever (FMF), the frequently reported co-existing diseases in children with FMF should also be investigated in other family members. Therefore, we aimed to examine the medical conditions of first-degree relatives (FDRs) of our pediatric patients with FMF in the present study.

**Methods.** Chronic diseases of FDRs of pediatric 449 FMF, 147 juvenile idiopathic arthritis (JIA) patients and 93 healthy controls (HC) were questioned during their routine clinical visits for 9 consecutive months.

**Results.** A total of 1975 FDRs of 449 FMF, 690 FDRs of 147 JIA patients, and 406 FDRs of 93 HC were included into the study. The most common medical conditions were non-atopic asthma (n=71, 3.6%), type 2 DM (n=14, 2%), and tonsillectomy history (n=12, 2.95%) in the FMF, JIA, and HC groups, respectively. Atopic diseases (FMF vs. JIA: p=0.013; FMF vs. HC: p=0.014), rheumatic diseases (FMF vs. JIA: p=0.030; FMF vs. HC: p=0.017), and surgical histories (FMF vs. JIA: p<0.01; FMF vs. HC: p=0.026), including adenoidectomy, tonsillectomy, and appendectomy, were significantly more common in the FMF group than in other groups.

**Conclusions.** Our novel findings may contribute to understanding the hereditary burden of co-existing diseases in children with FMF and encourage further studies involving genetic screenings.

**Key words:** familial Mediterranean fever, arthritis, juvenile, parents.

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease, characterized by attacks of recurrent fever, abdominal pain, chest pain, arthritis, arthralgia, myalgia and/or rashes.[1] First attacks of overall 90% of patients are seen before 20 years of age.[2] Therefore, the diagnostic process of FMF mainly concerns general pediatricians and pediatric rheumatologists. Although this autosomal recessive inherited disease was firstly described in patients with certain ethnicities living around the Mediterranean region, patients from all over the world have also been reported since.[3]

✉ Fatih Haşlak
drfatihhaslak@gmail.com

Received 13th Dec 2023, revised 30th Jan 2024, 18th Mar 2024, accepted 1st Apr 2024.

Considering the chronic pro-inflammatory process and immune-disturbed conditions caused by FMF, co-existing diseases have been widely discussed. It was recently shown that the most common comorbidities were juvenile idiopathic arthritis (JIA) and immunoglobulin A vasculitis (IgAV).[1,4] Furthermore, it was demonstrated in the studies involving all age groups that the frequencies of spondyloarthropathies, Behçet disease, Sjögren disease, polyarteritis nodosa (PAN), inflammatory bowel diseases, multiple sclerosis (MS), and psoriasis were higher in patients with FMF.[5,6]

It is well-documented that mutations in a gene called *MEFV*, which is composed of 10 exons and encodes pyrin protein are responsible

for the disease.[3] Although over 310 sequence variants in this gene have been reported and listed in an online registry named *Infevers* so far, M694V, M680I, V726A, M694I and E148Q mutations have been found to be responsible for more than 85% of the cases.[5,6] In addition, the genotype-phenotype correlation is well-established. For instance, M694V mutations were found to be significant indicators of a more severe disease course, earlier disease onset, colchicine resistance and amyloidosis.[7,8]

Although there are several studies evaluating the diseases of relatives of patients with JIA and systemic lupus erythematosus (SLE), there is no such data regarding FMF.[9-11] Given the strong genetic background of FMF, the diseases that have been previously demonstrated as co-existing in children with FMF should also be investigated in other family members. Therefore, we aimed to examine the diseases of first-degree relatives (FDRs) of our pediatric patients with FMF in the present study.

## Methods

### *Study population*

For nine consecutive months, medical conditions, and surgical histories of mothers, fathers, and siblings of healthy children, children with FMF, and children with JIA were evaluated during their regular outpatient visits. There was no disease list that may limit and divert the answers of the families. After all the participants were informed about the study in detail and informed consent was taken, they were questioned as to whether they had any chronic disease and operation history at their face-to-face appointments. The data were collected by the relevant physicians and confirmed via checking national health registries.

The FDRs of children with JIA and FMF who are being followed up by our department for at least six months were included in the study. The control group was established by the FDRs of healthy children admitted to the pediatric department for routine child-health monitoring and vaccination procedures. Among the FDRs of index cases, those with FMF were excluded from the study (n=422).

The diagnosis of FMF was established by Yalçınkaya et al. criteria[2] and the diagnosis of JIA was done according to the International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis.[12]

### *Selected disease groups*

Autoimmune diseases, atopic diseases, rheumatic diseases, malignancies, and surgical histories were thought to be closely linked to FMF or its treatment for various reasons, which will be discussed in detail further. Thus, classification was performed for further analysis.

Those with at least one of the following were regarded to have the rheumatic disease: acute rheumatic fever (ARF), ankylosing spondylitis (AS), Behçet's disease (BD), gout disease, IgAV, JIA, periodic fever - aphthous stomatitis - pharyngitis - cervical adenitis (PFAPA) syndrome, rheumatoid arthritis (RA), sarcoidosis, scleroderma, Sjogren disease (SD), SLE, and uveitis.

Those with any autoimmune disease rather than the rheumatic ones, such as adrenal insufficiency, autoimmune haemolytic anemia, autoimmune hepatitis, celiac disease (CD), Graves' disease (GD), Hashimoto thyroiditis, MS, psoriasis, type 1 diabetes mellitus (DM), and vitiligo was considered to have autoimmune diseases.

Allergic urticaria, allergic rhinitis, atopic dermatitis, atopic asthma, drug allergy, and food allergy were classified as atopic diseases. While patients with acute myeloid leukemia (AML), brain tumor, breast cancer, Hodgkin lymphoma (HL), or neuroblastoma were regarded to have malignancy, those with a history of adenoidectomy, appendectomy, or

tonsillectomy were considered to have surgical history.

### *Ethical approval*

This study was approved by the Institutional Review Board of İstanbul University-Cerrahpaşa, Cerrahpaşa Medical School (04/04/2018-127814). All the patients or their parents gave us written informed consents, and we adhered to the guidelines of the Declaration of Helsinki throughout the research. The authors declare no conflict of interest.

### *Statistical analysis*

All of the statistical analyses were performed by using IBM SPSS 21.0 program (SPSS Inc., Chicago, IL, USA). Categorical variables were reported as numbers and percentages. Chi square or Fisher's exact test were used to compare the frequencies of the diseases between groups. The statistical significance was defined as p value<0.05. We employed Prism 8 software (GraphPad Software, San Diego, California) to illustrate data in graphs.

## Results

### *Demographic findings*

First-degree relatives of 449 patients with FMF (female: 255), 147 patients with JIA (female: 95), and 93 healthy children (female: 55) were included in the study. The mean age of healthy children, patients with FMF and JIA were 7.7 ± 4.6 years, 12.6 ± 4.8 years, and 11.6 ± 5.2 years, respectively. A total of 3071 participants (1975 first degree relatives of FMF patients, 690 of JIA patients and 406 of healthy children) were included in the study.

### *The most common medical conditions*

While the most common conditions reported among the FDRs of the patients with FMF were non-atopic asthma (n=71, 3.6%), tonsillectomy history (n=66, 3.3%) and type 2 DM (n=55, 2.8%), the most common conditions detected among the relatives of patients with JIA were type 2 DM (n=14, 2%), Hashimoto thyroiditis (n=13, 1.8%), non-atopic asthma (n=13, 1.8%), and tonsillectomy history (n=13, 1.8%). Among relatives of the healthy children, tonsillectomy history (n=12, 2.95%), non-atopic asthma (n=10, 2.5%) and Hashimoto thyroiditis (n=6, 1.47%) were the most common ones (Table I).

### *Selected disease groups*

The most common medical condition in the study group was surgical history (n=194, 6.3%). The others were as follows: atopic diseases (n=132, 4.3%), autoimmune diseases (n=121, 3.9%), rheumatic diseases (n=101, 3.3%), and malignancies (n=6, 0.2%). At least one medical condition was detected in 23.73% of the participants (n=729). Surgery history was the most common medical condition in all groups (FMF group: 149, 7.5%; JIA group: 27, 3.9%; HC group: 18, 4.4%). While autoimmune diseases were the most common disease group in both JIA (n=25, 3.6%) and HC groups (n=13, 3.2%), it was atopic diseases in FMF group (n=103, 5.2%).

### *Comparisons between groups*

Comparing the frequencies of the medical conditions among the patients' FDRs revealed that ARF was significantly more common in the FMF group than in the JIA group (p=0.01). Besides, allergic rhinitis (p=0.008) and appendectomy history (p<0.001) were significantly more common in the FMF group than both in the JIA and HC groups (Table I).

While there was no significant difference between the JIA and HC group in terms of disease group frequencies, surgery history (FMF vs. JIA: p<0.01; FMF vs. HC: p=0.026), atopic diseases (FMF vs. JIA: p=0.013; FMF vs. HC: p=0.014), and rheumatic diseases (FMF vs. JIA: p=0.030; FMF vs. HC: p=0.017) were significantly more common in the FMF group than in JIA and HC groups (Table II).

**Table I.** The comparison of the disease frequencies reported among the first-degree relatives of the participants between groups, n (%).

| | FMF group (n=1975) | JIA group (n=690) | HC group (n=406) | p value |
|---|---|---|---|---|
| Acute myeloid leukemia | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.35 |
| Acute rheumatic fever | 22 (1.1%) | 1 (0.14%) | 1 (0.24%) | **0.01**[a] |
| Adenoidectomy history | 34 (1.7%) | 12 (1.7%) | 5 (1.23%) | 0.76 |
| Adrenal insufficiency | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.35 |
| Allergic urticaria | 2 (0.1%) | 1 (0.14%) | 0 (0%) | 1.00 |
| Allergic rhinitis | 35 (1.7%) | 4 (0.5%) | 1 (0.24%) | **0.008**[b] |
| Amyloidosis | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Ankylosing spondylitis | 5 (0.25%) | 4 (0.5%) | 2 (0.49%) | 0.41 |
| Appendectomy history | 50 (2.5%) | 3 (0.4%) | 1 (0.24%) | **<0.001**[c] |
| Atopic dermatitis | 43 (2.1%) | 12 (1.7%) | 3 (0.73%) | 0.14 |
| Autoimmune haemolytic anaemia | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.35 |
| Autoimmune hepatitis | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.17 |
| Atopic asthma | 19 (1%) | 2 (0.3%) | 5 (1.2%) | 0.16 |
| Behçet's disease | 11 (0.5%) | 0 (0%) | 2 (0.49%) | 0.11 |
| Brain tumor | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Breast cancer | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.35 |
| Cataract | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.35 |
| Celiac disease | 1 (0.05%) | 0 (0%) | 1 (0.24%) | 0.27 |
| Colonic polyps | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Crohn disease | 1 (0.05%) | 0 (0%) | 0 (0%) | 0.75 |
| Cystic fibrosis | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Drug allergy | 2 (0.1%) | 0 (0%) | 0 (0%) | 0.71 |
| Ectodermal dysplasia | 1 (0.05%) | 0 (0%) | 0 (0%) | 0.75 |
| Epilepsy | 3 (0.15%) | 1 (0.14%) | 0 (0%) | 0.85 |
| Fibromyalgia | 2 (0.1%) | 0 (0%) | 0 (0%) | 0.71 |
| Food allergy | 1 (0.05%) | 1 (0.14%) | 0 (0%) | 0.58 |
| Gastritis | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Gout disease | 1 (0.05%) | 0 (0%) | 1 (0.24%) | 0.29 |
| Graves' disease | 11 (0.5%) | 4 (0.5%) | 1 (0.24%) | 0.86 |
| Hashimoto thyroiditis | 50 (2.5%) | 13 (1.8%) | 6 (1.47%) | 0.32 |
| Immunoglobulin a vasculitis | 1 (0.05%) | 1 (0.14%) | 0 (0%) | 0.98 |
| Hirschsprung disease | 0 (0%) | 0 (0%) | 1 (0.24%) | 0.13 |
| Hodgkin lymphoma | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.35 |
| Juvenile ıdiopathic arthritis | 5 (0.25%) | 1 (0.14%) | 0 (0%) | 0.54 |
| Lymphedema | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Migraine | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Multiple sclerosis | 2 (0.1%) | 1 (0.14%) | 1 (0.24%) | 0.59 |

FMF: Familial Mediterranean Fever; HC: Healthy control; JIA: Juvenile Idiopathic Arthritis; PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, adenitis.

[a] Significantly more common in FMF group than in JIA group (p=0.018)

[b] Significantly more common in FMF group than in both JIA group (p=0.025) and HC group (p=0.022)

[c] Significantly more common in FMF group than in both JIA group (p=0.001) and HC group (p=0.003)

**Table I.** Continued.

| | FMF group (n=1975) | JIA group (n=690) | HC group (n=406) | p value |
|---|---|---|---|---|
| Myocarditis | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.35 |
| Nephrolithiasis | 0 (0%) | 0 (0%) | 1 (0.24%) | 0.13 |
| Neuroblastoma | 0 (0%) | 0 (0%) | 2 (0.49%) | 0.13 |
| Non-atopic asthma | 71 (3.6%) | 13 (1.9%) | 10 (2.5%) | 0.06 |
| Osteogenesis ımperfecta | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.35 |
| Pfapa syndrome | 2 (0.1%) | 0 (0%) | 0 (0%) | 0.57 |
| Precocious puberty | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Primary hypertension | 0 (0%) | 0 (0%) | 1 (0.24%) | 0.13 |
| Psoriasis | 14 (0.7%) | 1 (0.14%) | 2 (0.49%) | 0.22 |
| Rheumatoid arthritis | 23 (1.1%) | 7 (1%) | 0 (0%) | 0.09 |
| Sarcoidosis | 1 (0.05%) | 1 (0.14%) | 0 (0%) | 0.58 |
| Scleroderma | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Sjogren disease | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Spastic paraplegia | 1 (0.05%) | 0 (0%) | 0 (0%) | 1.00 |
| Systemic lupus erythematosus | 1 (0.05%) | 0 (0%) | 0 (0%) | 0.64 |
| Thalassemia | 2 (0.1%) | 2 (0.28%) | 0 (0%) | 0.30 |
| Thrombophilia | 2 (0.1%) | 0 (0%) | 0 (0%) | 1.00 |
| Tonsillectomy history | 66 (3.3%) | 13 (1.8%) | 12 (2.95%) | 0.15 |
| Trisomy 18 | 0 (0%) | 1 (0.14%) | 0 (0%) | 0.35 |
| Type 1 diabetes mellitus | 4 (0.2%) | 3 (0.4%) | 1 (0.2%) | 0.50 |
| Type 2 diabetes mellitus | 55 (2.8%) | 14 (2%) | 5 (1.2%) | 0.13 |
| Ulcerative colitis | 2 (0.1%) | 0 (0%) | 1 (0.24%) | 0.45 |
| Uveitis | 7 (0.35%) | 0 (0%) | 0 (0%) | 0.20 |
| Vitiligo | 0 (0%) | 0 (0%) | 1 (0.24%) | 0.132 |

FMF: Familial Mediterranean Fever; HC: Healthy control; JIA: Juvenile Idiopathic Arthritis; PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, adenitis.
[a] Significantly more common in FMF group than in JIA group (p=0.018)
[b] Significantly more common in FMF group than in both JIA group (p=0.025) and HC group (p=0.022)
[c] Significantly more common in FMF group than in both JIA group (p=0.001) and HC group (p=0.003)

**Table II.** The comparison of the frequencies of certain disease groups among the first-degree relatives of the participants between groups , n (%).

| | Study groups (n=3071) | | | p value | | |
|---|---|---|---|---|---|---|
| | FMF group (n=1975) | JIA group (n=690) | HC group (n=406) | FMF vs. JIA | FMF vs. HC | JIA vs. HC |
| Any medical condition | 541 (27.4%) | 123 (17.8%) | 65 (16%) | <0.01 | <0.01 | 0.441 |
| Rheumatic diseases | 80 (4%) | 15 (2.2%) | 6 (1.5%) | 0.030 | 0.017 | 0.559 |
| Atopic diseases | 103 (5.2%) | 20 (2.9%) | 9 (2.2%) | 0.013 | 0.014 | 0.628 |
| Autoimmune diseases | 83 (4.2%) | 25 (3.6%) | 13 (3.2%) | 0.508 | 0.428 | 0.844 |
| Malignancies | 1 (0.05%) | 3 (0.4%) | 2 (0.5%) | 0.056 | 0.077 | 1 |
| Surgery history | 149 (7.5%) | 27 (3.9%) | 18 (4.4%) | <0.01 | 0.026 | 0.794 |

FMF: Familial Mediterranean Fever; HC: Healthy control; JIA: Juvenile Idiopathic Arthritis.

## Discussion

In the present study, the diseases of the FDRs of healthy children, patients with FMF, and patients with JIA were evaluated, and compared with each other. Nearly a quarter of the participants had at least one medical condition. Non-atopic asthma, type 2 DM, and tonsillectomy history were the most common medical conditions in the FMF, JIA, and HC groups, respectively. Allergic rhinitis, ARF, and appendectomy history were significantly more common in the FMF group. While the most common group of medical conditions in all participants was surgical history, the most common group of disorders was atopic diseases. Atopic diseases, surgical history, and rheumatic diseases were significantly more common in the FMF group than in the others.

It was previously shown that while T helper-2 lymphocytes are the key elements in allergic diseases, T helper-1 lymphocyte-dependent inflammation has a pivotal role in the pathogenesis of FMF.[13,14] Therefore, a relatively low frequency of atopic diseases in patients with FMF is an expected finding. Consistently, children with FMF were shown to have a decreased frequency of atopic diseases than the general population.[15] However, more recent papers have provided contradictory findings with the previous ones. Two different studies showed a similar atopy frequency between children with FMF and their healthy peers.[16,17] Moreover, it was suggested that atopy is not only a frequent condition in FMF patients but also one of the components of the disease.[18] It was elucidated with the aid of recent increasing immunological knowledge that FMF pathogenesis is not as simple as T-helper 1 lymphocyte-driven inflammation. It also includes a large number of other immune elements, including innate immune cell-related cytokines, T-helper 17 lymphocytes, and T regulatory cells.[19,20] Besides, in addition to the T-helper-2 response, there is a significant T-helper 17 effect, mutual in both FMF and atopy, in the pathogenesis of atopic diseases.[20,21] Thus, the relationship between FMF and atopy remains unclear, considering the recent clinical and immunological findings. We found that allergic rhinitis and atopic diseases in general, were significantly more common in the FDRs of patients with FMF. Although close relatives of FMF patients probably share these complex immune mechanisms, it should be kept in mind that environmental circumstances, such as exposure to allergens rather than genetic susceptibility, play a pivotal role in allergic disorder development.

It is well-known that acute appendicitis is the most common indication of urgent abdominal surgery.[22] Abdominal signs caused by peritoneal irritation in FMF attacks are easily confused with acute appendicitis.[23] Therefore, as has been previously shown in several studies, appendectomy history might be more frequent in patients with FMF compared to the general population.[24-26] However, up to this study, FDRs of patients with FMF were not evaluated regarding their appendectomy histories. Although we excluded those diagnosed with FMF from the FDRs, appendectomy history in FDRs of FMF patients was significantly more common than in FDRs of healthy children and FDRs of patients with JIA. They might have FMF, however, *MEFV* gene mutations are not routinely performed in FDRs of patients with FMF unless they experience symptoms suggestive of FMF. Acute phase measurements have shown that healthy relatives of FMF patients tend to have subclinical inflammation, which is the main reason for several complications caused by FMF-related tissue damage.[27,28] Therefore, subclinical inflammation in these milder and undiagnosed cases may have a pivotal role for this novel finding. One of our participants in the group of FDRs of FMF patients had developed amyloidosis. This is consistent with the idea that FDRs of FMF patients may experience subclinical inflammation even if they are not diagnosed with FMF. We suggest that *MEFV* mutations should also be performed in FDRs of FMF patients who experienced acute appendicitis. On the other hand, we showed that overall surgical history was significantly

more common in the FMF group than the others, not only the appendectomy history. Adenoidectomy and tonsillectomy were the other surgical histories detected in our study population. PFAPA was previously shown to be highly related with FMF genetically and shares many common features with FMF which may cause a diagnostic challenge.[29-31] Tonsillectomy and adenoidectomy seem to be curative treatment options in most patients with PFAPA.[32] Although there were only 2 FDRs with PFAPA in the FMF group, we hypothesize that a significant amount of them were undiagnosed in the past, due to the newly growing and currently insufficient awareness of PFAPA among clinicians in our country.

In a study supported by anti-streptolysin O titters measurement, the relationship between FMF and ARF was investigated, and FMF patients were found to be more prone to develop ARF than the general population.[33] Parents of children with and without FMF were questioned regarding certain diseases previously, and it was revealed that ARF was significantly more common among family members of children with FMF.[34] Similarly, the frequency of ARF was significantly higher in FDRs of patients with FMF than FDRs of patients with JIA and healthy children in our study. Considering that arthritis is one of the cardinal signs in both ARF and FMF, the high prevalence of ARF among the FDRs of patients with FMF may be attributed to the possible misdiagnosis. On the other hand, since uncontrolled inflammatory response is a primary mechanism in both ARF and FMF, a pathogenetic similarity may be a reasonable explanation for the relationship between ARF and FMF.[35,36] It has been recently demonstrated that JIA is the most common accompanying disease in children with FMF.[1,4] Furthermore, sacroiliitis is thought to be more frequent in FMF patients.[37-39] However, in our study, the frequencies of chronic arthritis such as JIA, rheumatoid arthritis, and sacroiliitis did not differ among the FDRs of the groups. The association of vasculitis and FMF was widely investigated, and it has been showed that certain types such as IgAV, PAN and Behçet disease are more frequent in patients with FMF.[40] However, none of our participants had PAN. Besides, the frequency of vasculitis did not differ between the FDRs of FMF patients, JIA patients and healthy children in the present study. Our study revealed that not only ARF, but overall rheumatic disease was also significantly more common in the FMF group than in other groups. Although we excluded those with FMF from the FDRs of children with FMF, this novel finding which is entirely in line with the highly hereditary nature of FMF, makes us consider the possible accumulation of genetic rheumatic conditions whose inheritance pattern is yet to be unknown in this group.

Inflammatory bowel diseases (IBDs) are another investigated disease in several studies as to whether they accompany FMF, and they have been found to be more common in children with FMF.[41,42] In our study, only four participants had IBDs (ulcerative colitis:3; Crohn disease:1), and the frequency of IBDs was not found to be significantly different between groups. Similarly, neither spondyloarthropathy nor IBD were found to be significantly more common in a study comparing *MEFV* carriers and healthy controls.[34] Although the most common skin finding of FMF is erysipeloid erythema, psoriasis was also found to be associated with FMF.[35,43] Besides, a previous study reported an increased frequency of psoriasis in family members and close relatives of patients with FMF.[44] Although psoriasis was more common in FDRs of patients with FMF in the present study, there was no significant difference between the groups. While we only included the FDRs in this study, Barut et al.[44] also questioned second-and third-degree relatives in their study which found a high prevalence of psoriasis among families of FMF patients. This extended questioning may be responsible for the difference between the findings of these two studies.

Multiple sclerosis (MS), an autoimmune condition, is one of the most investigated co-morbid diseases in patients with FMF, and it was found to be significantly more frequent

compared to the general population.[45-50] Moreover, E148Q mutation has been suggested as a novel risk factor for developing MS.[50] However, only two of the FDRs of FMF patients had MS in our study, and there was no significant difference regarding the frequency between the groups. It may be related with the rarity of E148Q mutation among our index cases. However, as a limitation of this study, we did not evaluate the genetic results of our FMF patients. Beyond MS, the frequency of all detected non-rheumatic autoimmune diseases among the participants as a group of disorders was similar between FMF, JIA, and HC groups in our study. Similarly, a recent paper showed autoimmune diseases not to be increased in genetically confirmed FMF patients.[6] We evaluated this finding in accordance with the fact that the pathogenesis of FMF involves a mix of mainly innate and, to a lesser extent, adaptive immune system dysregulations.[35]

There are three main limitations to our study. Firstly, we compared the FMF, JIA, and healthy control groups regardless of the disease subtypes of the patients with JIA. Secondly, age and gender distribution of FDRs and their effects on the disease frequencies could not be assessed due to the nonavailability of data. Thirdly, we did not evaluate the genetic results either of our index FMF cases nor of their FDRs, which could be useful for a better understanding of the health condition distribution among participants. On the other hand, the main strength of the present study is that this is the first study evaluating the medical conditions with all aspects of the FDRs of patients with FMF in quite a large cohort.

In conclusion, although the co-existing diseases in children with FMF have previously been widely discussed, all medical conditions of FDRs of these patients have not been evaluated thus far. Given the strong genetic background of the disease it is necessary that fathers, mothers, and siblings of the patients with FMF are also investigated. This is a first attempt at doing this with a quite large cohort. We revealed that atopic diseases, rheumatic diseases, and surgical history were significantly more common in FDRs of children with FMF than in FDRs of children with JIA and FDRs of healthy children. This novel finding may contribute to understanding the hereditary burden of co-existing diseases in children with FMF.

## Ethical approval

The study was approved by Institutional Review Board (04/04/2018-127814) of İstanbul University-Cerrahpaşa, Cerrahpaşa Medical School.

## Author contribution

Study conception and design: SY, ÖK; data collection: FH, MY, AAdrovic, AAliyeva, AG, EA, EKK, ÜG, SŞ, KB; analysis and interpretation of results: SY, FH, MY; draft manuscript preparation: SY, FH, MY. All authors reviewed the results and approved the final version of the article.

## 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. 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
2. Yalçınkaya F, Özen S, Özçakar 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
3. Padeh S, Berkun Y. Familial Mediterranean fever. Curr Opin Rheumatol 2016; 28: 523-529. https://doi.org/10.1097/BOR.0000000000000315

4. 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

5. Ozdogan H, Ugurlu S. Familial Mediterranean fever. Presse Med 2019; 48: e61-e76. https://doi.org/10.1016/j.lpm.2018.08.014

6. 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

7. Sönmez HE, Esmeray P, Batu ED, et al. Is age associated with disease severity and compliance to treatment in children with familial Mediterranean fever? Rheumatol Int 2019; 39: 83-87. https://doi.org/10.1007/s00296-018-4123-0

8. Akpolat T, Özkaya O, Özen S. Homozygous M694V as a risk factor for amyloidosis in Turkish FMF patients. Gene 2012; 492: 285-289. https://doi.org/10.1016/j.gene.2011.10.012

9. Ganapati A, Arunachal G, Arya S, et al. Study of familial aggregation of autoimmune rheumatic diseases in Asian Indian patients with systemic lupus erythematosus. Rheumatol Int 2019; 39: 2053-2060. https://doi.org/10.1007/s00296-019-04355-z

10. James JA, Chen H, Young KA, et al. Latent autoimmunity across disease-specific boundaries in at-risk first-degree relatives of SLE and RA patients. EBioMedicine 2019; 42: 76-85. https://doi.org/10.1016/j.ebiom.2019.03.063

11. Pohjankoski H, Kautiainen H, Kotaniemi K, Korppi M, Savolainen A. Diabetes, coeliac disease, multiple sclerosis and chronic arthritis in first-degree relatives of patients with juvenile idiopathic arthritis. Acta Paediatr 2012; 101: 767-771. https://doi.org/10.1111/j.1651-2227.2012.02658.x

12. 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.

13. Aypar E, Ozen S, Okur H, Kutluk T, Besbas N, Bakkaloglu A. Th1 polarization in familial Mediterranean fever. J Rheumatol 2003; 30: 2011-2013.

14. Umetsu DT, DeKruyff RH. Th1 and Th2 CD4+ cells in the pathogenesis of allergic diseases. Proc Soc Exp Biol Med 1997; 215: 11-20. https://doi.org/10.3181/00379727-215-44109

15. Sackesen C, Bakkaloglu A, Sekerel BE, et al. Decreased prevalence of atopy in paediatric patients with familial Mediterranean fever. Ann Rheum Dis 2004; 63: 187-190. https://doi.org/10.1136/ard.2003.007013

16. Aydoğmuş Ç, Ayaz NA, Çakan M, et al. Is there any difference regarding atopy between children with familial Mediterranean fever and healthy controls? Allergol Immunopathol (Madr) 2017; 45: 549-552. https://doi.org/10.1016/j.aller.2016.12.006

17. Amet C, Selçuk Duru N, Elevli M, Çivilibal M. Atopy in children and adolescents with familial Mediterranean fever. J Pediatr Res 2015; 2: 118-121. https://doi.org/10.4274/jpr.41636

18. Celiksoy MH, Dogan C, Erturk B, Keskin E, Ada BS. The MEFV gene and its association with familial Mediterranean fever, severe atopy, and recurrent respiratory tract infections. Allergol Immunopathol (Madr) 2020; 48: 430-440. https://doi.org/10.1016/j.aller.2019.12.010

19. Ibrahim JN, Jounblat R, Delwail A, et al. Ex vivo PBMC cytokine profile in familial Mediterranean fever patients: Involvement of IL-1β, IL-1α and Th17-associated cytokines and decrease of Th1 and Th2 cytokines. Cytokine 2014; 69: 248-254. https://doi.org/10.1016/j.cyto.2014.06.012

20. Ovadia A, Livneh A, Feld O, et al. T helper 17 polarization in familial Mediterranean fever. Genes Immun 2013; 14: 212-216. https://doi.org/10.1038/gene.2013.6

21. Wang YH, Wills-Karp M. The potential role of interleukin-17 in severe asthma. Curr Allergy Asthma Rep 2011; 11: 388-394. https://doi.org/10.1007/s11882-011-0210-y

22. Prystowsky JB, Pugh CM, Nagle AP. Current problems in surgery. Appendicitis. Curr Probl Surg 2005; 42: 688-742. https://doi.org/10.1067/j.cpsurg.2005.07.005

23. Simon A, van der Meer JW, Drenth JP. Familial Mediterranean fever-a not so unusual cause of abdominal pain. Best Pract Res Clin Gastroenterol 2005; 19: 199-213. https://doi.org/10.1016/j.bpg.2004.11.009

24. Ben-Chetrit E, Levy M. Colchicine prophylaxis in familial Mediterranean fever: reappraisal after 15 years. Semin Arthritis Rheum 1991; 20: 241-246. https://doi.org/10.1016/0049-0172(91)90019-v

25. Lidar M, Doron A, Kedem R, Yosepovich A, Langevitz P, Livneh A. Appendectomy in familial Mediterranean fever: clinical, genetic and pathological findings. Clin Exp Rheumatol 2008; 26: 568-573.

26. Kaşifoğlu T, Cansu DU, Korkmaz C. Frequency of abdominal surgery in patients with familial Mediterranean fever. Intern Med 2009; 48: 523-526. https://doi.org/10.2169/internalmedicine.48.1602

27. Lachmann HJ, Sengül B, Yavuzşen TU, et al. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford) 2006; 45: 746-750. https://doi.org/10.1093/rheumatology/kei279

28. Özer S, Yılmaz R, Sönmezgöz E, et al. Simple markers for subclinical inflammation in patients with familial Mediterranean fever. Med Sci Monit 2015; 21: 298-303. https://doi.org/10.12659/MSM.892289

29. Veres T, Amarilyo G, Abu Ahmad S, et al. Familial periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome; is it a separate disease? Front Pediatr 2022; 9: 800656. https://doi.org/10.3389/fped.2021.800656

30. 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

31. Yamagami K, Nakamura T, Nakamura R, et al. Familial Mediterranean fever with P369S/R408Q exon3 variant in pyrin presenting as symptoms of PFAPA. Mod Rheumatol 2017; 27: 356-359. https://doi.org/10.1080/14397595.2017.1267173

32. Gozen ED, Yildiz M, Kara S, et al. Long-term efficacy of tonsillectomy/adenotonsillectomy in patients with periodic fever aphthous stomatitis pharyngitis adenitis syndrome with special emphasis on co-existence of familial Mediterranean fever. Rheumatol Int 2023; 43: 137-145. https://doi.org/10.1007/s00296-022-05210-4

33. Tekin M, Yalçinkaya F, Tümer N, Cakar N, Koçak H. Familial Mediterranean fever and acute rheumatic fever: a pathogenetic relationship? Clin Rheumatol 1999; 18: 446-449. https://doi.org/10.1007/s100670050136

34. Kalyoncu M, Acar BC, Cakar N, et al. Are carriers for MEFV mutations "healthy"? Clin Exp Rheumatol 2006; 24: S120-S122.

35. Yıldız M, Haşlak F, Adrovic A, Barut K, Kasapçopur Ö. Autoinflammatory diseases in childhood. Balkan Med J 2020; 37: 236-246. https://doi.org/10.4274/balkanmedj.galenos.2020.2020.4.82

36. Castro SA, Dorfmueller HC. A brief review on group A streptococcus pathogenesis and vaccine development. R Soc Open Sci 2021; 8: 201991. https://doi.org/10.1098/rsos.201991

37. Borman P, Gökoğlu F, Taşbaş O, Yilmaz M, Yorgancioğlu ZR. Familial Mediterranean fever-related spondyloarthropathy. Singapore Med J 2009; 50: e116-e119.

38. Langevitz P, Livneh A, Zemer D, Shemer J, Pras M. Seronegative spondyloarthropathy in familial Mediterranean fever. Semin Arthritis Rheum 1997; 27: 67-72. https://doi.org/10.1016/s0049-0172(97)80007-8

39. 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.

40. Ozdogan H, Arisoy N, Kasapçapur O, et al. Vasculitis in familial Mediterranean fever. J Rheumatol 1997; 24: 323-327.

41. Beşer OF, Kasapçopur O, Cokuğraş FC, Kutlu T, Arsoy N, Erkan T. Association of inflammatory bowel disease with familial Mediterranean fever in Turkish children. J Pediatr Gastroenterol Nutr 2013; 56: 498-502. https://doi.org/10.1097/MPG.0b013e31827dd763

42. 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

43. Erden A, Batu ED, Seyhoğlu E, et al. Increased psoriasis frequency in patients with familial Mediterranean fever. Ups J Med Sci 2018; 123: 57-61. https://doi.org/10.1080/03009734.2017.1423425

44. Barut K, Guler M, Sezen M, Kasapçopur O. Inceased frequency of psoriasis in the families of the children with familial Mediterranean fever. Clin Exp Rheumatol 2016; 34: S137.

45. Ozdogan H, Ugurlu S, Uygunoglu U, et al. The efficacy of anti- IL-1 treatment in three patients with coexisting familial Mediterranean fever and multiple sclerosis. Mult Scler Relat Disord 2020; 45: 102332. https://doi.org/10.1016/j.msard.2020.102332

46. Salehzadeh F, Enteshari Moghaddam A. Coexisting diseases in patients with familial Mediterranean fever. Open Access Rheumatol 2020; 12: 65-71. https://doi.org/10.2147/OARRR.S252071

47. Yahalom G, Kivity S, Lidar M, et al. Familial Mediterranean fever (FMF) and multiple sclerosis: an association study in one of the world's largest FMF cohorts. Eur J Neurol 2011; 18: 1146-1150. https://doi.org/10.1111/j.1468-1331.2011.03356.x

48. Elhani I, Dumont A, Vergneault H, et al. Association between familial Mediterranean fever and multiple sclerosis: a case series from the JIR cohort and systematic literature review. Mult Scler Relat Disord 2021; 50: 102834. https://doi.org/10.1016/j.msard.2021.102834

49. Ceylan G, Erten S, Ercan K. Co-existence of familial Mediterranean fever and multiple sclerosis in two patients. Acta Reumatol Port 2014; 39: 342-344.

50. Kümpfel T, Gerdes LA, Wacker T, et al. Familial Mediterranean fever-associated mutation pyrin E148Q as a potential risk factor for multiple sclerosis. Mult Scler 2012; 18: 1229-1238. https://doi.org/10.1177/1352458512437813