The Comparison of Pediatric Patients with Familial Mediterranean Fever Originated from Turkey and Crimea

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What is already known on this topic?

- Familial Mediterranean fever (FMF) is the most frequent monogenic autoinflammatory disease distributed in specific populations such as Turks, Jews, Arabs, Armenians, South Europe, and North Africa.

What this study adds on this topic?

- Herein we describe a new nationality—Crimean Tatars, who had a very high distribution of MEFV mutations and estimated disease prevalence in Turkish population. The first case of FMF was diagnosed in 2016, and patients have some differences in clinical features compared to Turkish children.

ABSTRACT

Objective: We aimed to evaluate the clinical and laboratory features and MEFV allele distribution in Crimean Tatar familial Mediterranean fever patients and to compare them with Turkish familial Mediterranean fever patients and healthy controls.

Materials and Methods: All newly diagnosed familial Mediterranean fever patients with Crimean Tatar nationality (n = 18) in Children’s Regional Hospital in Simferopol were enrolled in the study and were compared to 40 familial Mediterranean fever cases followed up at Hacettepe University, Ankara, Turkey. The distribution of MEFV alleles was assessed in the 127 unrelated healthy Crimean Tatar adults aged 20 years or more from different parts of the Crimea peninsula.

Results: Age and gender distribution, the frequency of colchicine resistance, and colchicine intolerance were similar between Turkish and Crimean Tatar children with familial Mediterranean fever. The duration of familial Mediterranean fever attack was shorter in Turkish patients than in Crimean Tatar (2.0 vs. 3.0 days, P < .001). Chest pain was more frequent in Turkish familial Mediterranean fever patients, whereas arthralgia, arthritis, and erysipelas rash were more common in Crimean Tatar. MEFV allele distribution in Crimean Tatar was M694V-81%, M680I and V726A 9.5% both, and 68.6%, 14.3%, and 12.9% in Turkish, consequently. Homozygous carriers were 11%, compound-heterozygous was 6%, and heterozygous was 83%, compared to Turkish being 45%, 30%, and 25%, respectively. The allele distribution in healthy Crimean Tatar and Turkish was 10.2% and M694V was 7.1%, M680I was 1.6%, and V726A was 1.6%.

Conclusion: The similar MEFV allele prevalence in both populations suggests the high prevalence of familial Mediterranean fever and the high number of undiagnosed patients in the Crimea peninsula. Younger age at onset, shorter duration of attacks, the prevalence of articular involvement, and erysipelas rash were distinctive features of familial Mediterranean fever in Crimean Tatar.

Keywords: Familial Mediterranean fever, periodic fever, autoinflammatory diseases, MEFV, anakinra, canakinumab

INTRODUCTION

Familial Mediterranean fever (FMF) is the most frequent monogenic autoinflammatory disease distributed in specific populations such as Turks, Jews, Arabs, Armenians, South Europe, and North Africa.1 Familial Mediterranean fever is also present in other populations, for example, Japan, Korea, and China.2-4 The disease is characterized by self-limited flares
of fever, serositis, and arthritis. Colchicine is the main treatment agent, and a complete response was observed in more than 60% of patients. An interleukine-1 blockade is a treatment option used when colchicine resistance or intolerance occurs.\(^4\)\(^-\)\(^6\)

Familial Mediterranean fever is caused by mutations in the \textit{MEFV} gene. Most \textit{MEFV} mutations are located in exon 10 (\textit{M694V}, \textit{M680I}, \textit{V624E}, and \textit{V726A}) and exon 2 (\textit{E148Q}). \textit{M694V} distribution ranged from 36.5% (Armenia, Syria) to 65% in Jews population. The second and third place belongs to \textit{M680I} (more in the Armenians and Turks) and \textit{V726A} mutations (in Arabs).\(^1\)\(^-\)\(^3\) The diagnosis of FMF is based on several sets of widely used validated classification criteria. The Yalcinkaya-Ozen and Tel Hashomer criteria include only clinical parameters while the new Eurofever/PRINTO classification criteria which have been published recently combine clinical manifestations and genotype as a base for diagnosis.\(^4\)\(^-\)\(^6\) The disease is diagnosed faster in the countries with high prevalence where physicians are familiar with the disease. However, in countries with a low prevalence of FMF, there are years of delay in disease diagnosis.\(^1\)\(^-\)\(^3\)\(^-\)\(^6\) The first case of FMF among Crimean Tatars was diagnosed in 2016, and increased numbers have been reported since then.\(^2\) Familial Mediterranean fever is a new disease for Crimean aboriginals.\(^7\) How the \textit{MEFV} mutations appeared in Crimean Tatars is still unclear now. There are several theories: Crimean Tatars originated from Turkic-speaking tribes—Pechenegs and Polovtsy, who came to the Crimea Peninsula in X–XI cc after BC and further assimilated with Crimean Greeks, Genoese, Armenians, and further with Ottomans who occupied the Crimean Peninsula in XVI–XIX cc after BC. Near 6 million Crimean Tatars now live in Turkey.\(^8\) Because Crimean Tatars and Turks might have similar genetics, we decided to compare Crimean Tatars with Turkish children for whom FMF is well known and understood. Crimean Tatars, historically, might be related to Turks, so the high prevalence and similar disease severity of Crimean FMF patients were suspected.

We aimed to evaluate the clinical and laboratory features of Crimean Tatar FMF patients, \textit{MEFV} allele distribution in a healthy population, and to compare them with Turkish FMF patients and healthy controls.

**MATERIALS AND METHODS**

This cross-sectional cohort study included all newly diagnosed FMF patients with Crimean Tatar nationality (\(n = 18\)) in the Children’s Regional Hospital in Simferopol from February 2016 to February 2020. The control group consisted of 40 FMF newly diagnosed cases followed up at Hacettepe University, Ankara, Turkey, in an overlapping period. All children were under 18 years of age at the time of inclusion. The diagnosis of FMF was based on the Yalcinkaya-Ozen and Eurofever/PRINTO classification criteria.\(^1\)\(^-\)\(^2\)\(^1\)\(^-\)\(^3\) In each patient, exons 10 and 2 of the \textit{MEFV} gene were sequenced. DNA samples extracted from whole blood were subjected to polymerase chain reaction amplification followed by direct Sanger sequencing. In any doubtful cases, we performed next-generation sequencing panel consisted 302 genes operated in innate immunity (auto-inflammatory diseases and primary immune deficiencies), and we excluded other autoinflammatory diseases.

Colchicine resistance was defined as a patient having a monthly attack during a 6-month period despite the maximal tolerated colchicine doses according to the European Alliance of Associations for Rheumatology (EULAR) definition.\(^3\) Colchicine intolerance means the inability to tolerate the side effects of effective doses of colchicines.\(^3\) Demographics, disease characteristics, and laboratory characteristics were checked at the disease onset and during a disease attack, and treatment options were evaluated for each patient with FMF. For evaluation of the prevalence of FMF in the Crimean Tatars, we check the \textit{MEFV} exon 10 mutations in 127 healthy unrelated adults (>20 years) without signs of FMF or other periodic fever. The healthy population was randomly selected from every 25 regions of the Crimea peninsula. The number of samples was dependent on population size in every region to avoid uneven selection. Blood samples were obtained during the routine check-up program. For comparison analysis between Crimean Tatars and Turkish about \textit{MEFV} genotype distribution, we used the previously published data.\(^1\)\(^6\)

**Statistical Analysis**

Descriptive statistics are reported in terms of medians and interquartile ranges (IQRs) for continuous variables and absolute frequencies and percentages for categorical variables. Missing data were not imputed or included in the analyses. We used a non-parametric statistic because all variables had non-normal distribution. To check whether the distribution was normal or not, we used the Kolmogorov–Smirnov test and distribution graphs. Pearson’s \(\chi^2\) test or the Fisher’s exact test in the expected frequencies <5 was used to compare the categorical variables. A comparison of 2 quantitative variables was carried out using the Mann–Whitney test. The software Statistica (release 10.0, StatSoft Corporation, Tulsa, Okla, USA) was used for data analysis, and \(P\)-value < .05 was considered to indicate a significant difference.

**Ethical Expertise**

Written consent was obtained according to the Declaration of Helsinki. The local Ethics Committee approved the protocol of the trial of Crimean State Federal University (protocol # 7 from May 6, 2020). The study of \textit{MEFV} gene mutations in a healthy population was covered by the grant.

**RESULTS**

**Demographic and Clinical Features**

Age at the time of involvement and gender distribution were similar between Turkish and Crimean Tatars children with FMF (median 12.7 (IQR = 8.5-16.4) vs. 11.3 (IQR = 6.8-14.9) years, \(P = .326\) and 57.5% for the female gender vs. 33.3% for the male gender, \(P = .089\), respectively). In Crimean Tatars, the diagnosis of FMF was established later than in Turkish patients (\(P < .001\)), although the first fever attack was reported to be earlier by parents (\(P = .04\)). Half (\(n = 9\)) of Crimean Tatars and 33% (\(n = 13\)) of Turks had the first episode before 2 years old (\(P = .204\)) and 78% (\(n = 14\)) and 75% (\(n = 30\)) before 5 years old, consequently (\(P = .820\)). There were no differences between 2 two groups regarding the positive family history of FMF, the consanguinity rates, and the spectrum of the FMF-associated comorbidities. The duration of the FMF attack was shorter in Turkish patients than in Crimean Tatars (2.0 days vs. 3.0 days, \(P < .001\)). All Crimean Tatars had fever during attacks, while it was present in...
only 82.5% of Turkish FMF patients \( (P = .058) \). As for attack characteristics, chest pain was more frequently observed in Turkish FMF patients, whereas arthralgia, arthritis, and erysipeloid rash were more common in Crimean Tatars \( (P = .039 \) for chest pain and \( P < .001 \) for arthralgia, arthritis, and erysipeloid rash) (Table 1). The duration of the chest and abdominal pain attacks was shorter in Crimean Tatars than in Turks \( (P < .001 \) and \( P = .043 \), respectively). Crimean Tatars had lower hemoglobin \( (104.0 \, (98.0; 110.0)) \) than Turkish \( (115.0 \, (109.0; 123.0; \ P < .001 \) for all)). Joint involvement (arthralgia and arthralgia) was documented in the majority of Crimean Tatars. Oligoarthritis had 5/16 (31.2%) of patients leading. Turkish patients often had comorbid disease \( (n = 4, 10\%) \): immunoglobulin A (IgA) vasculitis \( (n = 1, 2.5\%) \), sacroiliitis \( (n = 1, 2.5\%) \), autoimmune hepatitis \( (n = 1, 2.5\%) \), and inflammatory bowel disease (IBD) \( (n=1, 2.5\%) \), compared to Crimean Tatars \( (n = 5, 27.8\%) \): IgA vasculitis \( (n = 2, 11.1\%) \), sacroiliitis \( (n = 2, 11.1\%) \), and juvenile idiopathic arthritis (JIA) \( (n = 1, 11.1\%) \).

### Table 1. Comparative Data of FMF Patients of Turkish and Crimean Tatar Origin

| FMF Features          | Turkish FMF Patients (n = 40) | Crimean Tatars FMF Patients (n = 18) | \( P \) |
|-----------------------|------------------------------|--------------------------------------|--------|
| Gender, males, n (%)  | 23 (57.5)                    | 6 (33.3)                             | .089*  |
| Age of inclusion, years | 12.7 (8.5; 16.4)             | 11.3 (6.8; 14.9)                     | .326** |
| The age of onset, years, (IQR) | 3.3 (1.9; 5.0)           | 1.3 (0.2; 3.9)                       | .040** |
| Age of FMF diagnosis, years, (IQR) | 4.7 (2.5; 8.2)          | 9.6 (4.1; 14.3)                      | .005** |
| Diagnosis delay, years, (IQR) | 0.9 (0.2; 2.1)            | 5.5 (2.1; 9.5)                       | <.001  |
| Family history of FMF, n (%) | 16 (40.0)                  | 9 (50.0)                             | .477*  |
| Familial consanguinity, n (%) | 8 (20.0)                  | 6 (33.3)                             | .272*  |
| **Initial features**   |                             |                                      |        |
| Fever, n (%)           | 33 (82.5)                    | 18 (100.0)                           | .058*  |
| Episode duration, days, (IQR) | 2.0 (2.0; 3.0)           | 3.0 (3.0; 6.0)                       | <.001**|
| Fever duration, hours, (IQR) | 48.0 (48.0; 72.0)       | 72.0 (72.0; 120.0)                   | <.001**|
| Chest pain, n (%)      | 12 (30.0)                    | 5 (6)                                | .039*  |
| Chest pain duration, hours, (IQR) | 48.0 (24.0; 72.0)     | 0.0 (0.0; 0.0)                       | <.001**|
| Abdominal pain, n (%)  | 30 (75.0)                    | 9 (50.0)                             | .061*  |
| Abdominal pain duration, hours, (IQR) | 48.0 (24.0; 48.0)    | 24.0 (24.0; 24.0)                    | .043** |
| Arthritis, n (%)       | 10 (25.0)                    | 16 (88.9)                            | <.001* |
| Joints with arthritis, n (%) |                           |                                      |        |
| Knee                  | 8 (80.0)                     | 15 (68.2)                            | .082*  |
| Ankle                 | 2 (20.0)                     | 0 (0.0)                              |        |
| Hip                   | 0 (0.0)                      | 5 (22.7)                             |        |
| Pubic symphysis       | 0 (0.0)                      | 2 (9.1)                              |        |
| Wrist                 | 0 (0.0)                      | 1 (5.5)                              |        |
| Monoarthritis, n (%)  | 9 (90.0)                     | 11 (68.8)                            | .033*  |
| Two joints with arthritis, n (%) | 1 (10.0)            | 5 (31.2)                             |        |
| Arthralgia, n (%)     | 19 (47.5)                    | 17 (94.4)                            | <.001* |
| Erysipeloid rash, n (%) | 0 (0.0)                     | 9 (50.0)                             | <.001* |
| **Genotype distribution** |                           |                                      |        |
| MEFV genotypes, n (%)  |                             |                                      |        |
| M694V/M694V           | 17 (42.5)                    | 2 (11.0)                             | .01*   |
| M694V/M680I           | 2 (5.0)                      | 0 (0)                                |        |
| M694V/V726A           | 3 (7.5)                      | 0 (0)                                |        |
| M694V/R202Q           | 1 (2.5)                      | 0 (0)                                |        |
| M694V/-               | 7 (17.5)                     | 13 (72.2)                            |        |
| M694V/R761H           | 1 (2.5)                      | 0 (0)                                |        |
| M680I/M680I           | 1 (2.5)                      | 0 (0)                                |        |
| M680I/V726A           | 5 (12.5)                     | 1 (5.6)                              |        |
| M680I/-               | 1 (2.5)                      | 1 (5.6)                              |        |
| V726A/-               | 1 (2.5)                      | 1 (5.6)                              |        |
| R761H/-               | 1 (2.5)                      | 0 (0)                                |        |
| Homozygous, n (%)     | 18 (45.0)                    | 2 (11.1)                             | .001*  |
| Compound-heterozygous, n (%) | 12 (30.0)              | 1 (5.6)                              |        |
| Heterozygous, n (%)   | 10 (25.0)                    | 15 (83.3)                            |        |

\*\*\** test/Fisher's exact test, **Mann–Whitney U test.

ESR, erythrocyte sedimentation rate; IQR, interquartile range; FMF, familial Mediterranean fever; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis.
Mediterranean Fever Patients
The genotypes and alleles distribution differed between the 2 groups: the M694V allele was more distributed in the Crimean Tatar patients than in Turkish patients but did not reach statistical significance (68.6% and 81.0%, \( P = .271 \)). While the majority of Crimean Tatar patients had heterozygous mutations, Turkish children predominantly had homozygous or compound heterozygous mutations \( (P = .001) \).

Mediterranean Fever Patients
The frequency of alleles in healthy unrelated Crimean Tatars adults (>20 years) without signs of FMF was 13/127 (10.2%): M694V was in 9 adults, among them 8 were heterozygous and 1 homozygous without clinical signs of FMF (7.1%); V726A was in 2 adults (1.6%) and M680I in 2 adults (1.6%). Healthy Crimean Tatar adults had a similar distribution of MEFV variants as healthy Turkish adults.\(^9\) There were no differences between MEFV alleles frequency between FMF children of both nationalities (table 3).

### TREATMENT OPTIONS

Colchicine was the main initial treatment, and the doses were similar in both groups. There was no significant difference between Crimean Tatar FMF patients and Turkish FMF patients regarding the frequency of colchicine resistance (25.0% vs. 27.8%) and colchicine intolerance (2.5% vs. 11.1%) \( (P = .824 \) and \( P = .181 \), respectively). Colchicine-related adverse effects also did not differ between the 2 groups \( (P = .348) \). However, the biological agent preferences of groups were different. Two Crimean Tatar children with sacroiliitis and JIA received tumor necrosis factor alpha (TNF-\( \alpha \)) inhibitors (adalimumab and etanercept), and 1 Turkish patient with sacroiliitis received etanercept. In the Crimean Tatars, 2 children with FMF received tocilizumab due to the impossibility of accessing interleukin-1 (IL) blockers. However, canakinumab was the most commonly used biological agent in both groups. A comprehensive comparative analysis is in table 2.

### DISCUSSION

Our study shows the first information about the FMF cohort in the Crimea peninsula and gives information about demography, clinical course, laboratory features, MEFV allele distribution, and treatment in FMF patients and healthy controls. Some similarities and differences compared to Turkish FMF children were observed.

There was no significant difference in MEFV mutation distribution between Crimean Tatar children and Turkish FMF patients in our study. The first Crimean Tatar FMF patient was diagnosed in 2016.\(^10\) Lack of awareness about FMF in Crimean Tatars, the lack of knowledge about FMF in local physicians, and low estimated disease prevalence in the Crimea peninsula might lead to greater difficulty in FMF diagnosis. The diagnostic delay in

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### Table 2. Treatment of Turkish and Crimean Tatar Patients with FMF

| Treatment* | Turkish FMF Patients (\( n = 40 \)) | Crimean Tatars FMF Patients (\( n = 18 \)) | \( P \) |
|------------|-------------------------------------|----------------------------------|------|
| Colchicine, mg/ kg, (IQR)* | 0.035 (0.027; 0.04) | 0.033 (0.021; 0.05) | .887** |
| Colchicine, mg/day, (IQR)* | 1.0 (1.0; 1.5) | 1.5 (1.0; 1.5) | .329** |
| Biologics for colchicine resistant/intolerant FMF patients, n (%)* | 8 (20.0) | 6 (33.3) | .273* |
| Anakinra | 1 (12.5) | 0 (0.0) | .165* |
| Canakinumab | 7 (87.5) | 4 (66.7) | |
| Tocilizumab | 0 (0.0) | 2 (33.3) | |
| Biologics for FMF-associated JIA\(^a\): | 1 (2.5) | 2 (11.1) | .171* |
| Adalimumab | 0 (0.0) | 1 (12.5) | .266* |
| Etanercept | 1 (11.1) | 1 (12.5) | |
| Colchicine resistance, n (%)* | 10 (25.0) | 5 (27.8) | .824* |
| Colchicine intolerance, n (%)* | 1 (2.5) | 2 (11.1) | .171* |
| Colchicine adverse events, n (%)* | | | |
| Gastrointestinal side effects | 0 (0.0) | 2 (11.1) | .133* |
| Hematological side effects | 1 (2.5) | 1 (5.6) | .555* |
| Hypertransaminasemia | 3 (7.5) | 2 (11.1) | .651* |

\*Chi-square test/ Fisher’s exact test; **Mann–Whitney test; *last observation.

FMF, familial Mediterranean fever; IQR, interquartile range.

### Table 3. MEFV Mutation Distribution in FMF Patients and Healthy Population Between Turkish \(^7\) and Crimean Tatars

| Alleles | Turkish Mediterranean Fever (\( n = 40 \)) | Crimean Tatars (\( n = 18 \)) | \( P \) | Turkish (\( n = 100 \))** | Crimean Tatars (\( n = 127 \)) | \( P \) |
|---------|-------------------------------------|--------------|------|-----------------|-----------------|------|
| M694V | 48 (71.6) | 17 (81.0) | .796 | 3/200 (3.0) | 9 (7.1) | .267 |
| M680I | 10 (15.0) | 2 (9.5) | | 5 (5.0) | 2 (1.6) | |
| V726A | 8 (13.4) | 2 (9.5) | | 2 (2.0) | 2 (1.6) | |
| R761H | 2 (2.9) | 0 (0.0) | | | | |
| R202Q | 1 (1.6) | 0 (0.0) | | | | |

FMF, familial Mediterranean fever.

*This analysis included only data about exon 10 MEFV gene variants (E148Q was excluded from the analysis); **data adopted from.
Crimean Tatar FMF patients was 5.5 years, and similar to FMF studies in Germany, there is also a lack of awareness about FMF and a low prevalence of FMF. The delay in FMF diagnosis in Turks and Armenians in Germany was 8 years, but in Turkey, it was 2.5 years.14,15

Healthy Crimean Tatars have a similar MEFV mutation prevalence (10.2%) and distribution of exon 10 pathogenic alleles of the MEFV gene compared to Turkish (10.0%). The frequency of MEFV alleles ranges from 20% in Armenians and Ashkenazi Jew to 39% in Iraqi Jews.19,20 The allele distribution in Turkey is 10% and the prevalence of FMF is near 1: 1075.21 In the Crimea peninsula, the number of Crimean Tatars is 232,000 people, so we can expect near 200 patients undiagnosed with FMF according to the allele distribution. Genotype distribution of the MEFV gene in FMF patients is similar to non-Ashkenazi Jews: M694V was 76.8%, V726A was 11.7%, and M680I was 0.4%.22

There are several distinct clinical features of FMF in Crimean Tatars compared to Turks. Crimean Tatar patients were younger at the time of the first FMF attack; 50% of them and 33% of Turks had the first episode before 2 years old and 78% and 75% before 5 years old. In the literature, in populations with a high prevalence of FMF, the disease onset was reported in only 15% of the children before the age of 2 and in 58%-65% of the children before the age of 5.23 Crimean Tatars have a different course of FMF flares. Crimean Tatars rarely had chest pain and abdominal pain despite the prolonged fever but more often had arthritis, arthralgia, and erysipelas rash. Abdominal pain was reported in 82%-96% of FMF patients. Less number of patients with abdominal pain might be explained by the lower rate of homozgyous careers in Crimean Tatars because the severe course of FMF and abdominal pain are usually associated with the presence of homozgyous mutations, and heterozygous carriers usually have a milder course.22,23 Chest pain related to pleuritis was detected only in 5.6% of Crimean Tatars. Chest pain is diagnosed more often in adults (21%-84%) and is strongly correlated to the patient’s age.24,25 The younger age and the prevalence of heterozygous patients may explain the low incidence of chest pain.

Arthritis was a hallmark of FMF flares in Crimean Tatars. In Turks, the most frequently affected joints were the knee and ankle with predominant monoarticular involvement. However, Crimean Tatars also had hip, wrist, and pubic symphysis involvement, and one-third of the patients had oligoarticular involvement, which initially leads to misdiagnosis of JIA and wrong treatment. Arthritis was described in 26%-37% of Arabs, 47% of Turks, and 77.4% of Sephardic Jews with FMF. Generally, arthritis has been highly associated with M694V mutation.26,27,28

Sacroiliitis was one of the frequent comorbid diseases related to the FMF course. In our study, patients with sacroiliitis had no peripheral joint involvement, no enthesitis, and no back involvement. They were Human leucocyte antigen (HLA) B27 negative and had no family history of spondyloarthritis. A similar pattern was shown before in several studies.28-31

Erysipelas-like erythema (ELE) was a common finding observed in half of the Crimean Tatar FMF patients. In previous studies, the rate of erysipelas rash ranged from 3% to 46%.32,33 The frequency of ELE was reported to be higher in patients with M694V homozygous mutation which might explain the increased rate of ELE in our study.

Colchicine was used as monotherapy in 55.6% of Crimean Tatar FMF patients and 77.5% of Turkish FMF patients. In the literature, colchicine was found to be effective in 51%-68% of patients, and colchicine resistance was reported in 2.7%-10% of patients.33,34 In our study, the frequency of colchicine resistance was much higher in both groups, resulting in increased use of biological treatment. On the other hand, the colchicine resistance was associated with M694V genotype and more severe disease course.22,29,35

The higher frequency of the M694V genotype might have caused the increased rate of colchicine resistance in our study. The main indications for biologics were persisted flare episodes and increased C-reactive protein (CRP) between FMF episodes, despite using the maximally tolerated colchicine dose.35

The differences in frequency used biologics used between the 2 populations were observed. While anakinra was used in Turkish FMF patients, Crimean Tatar FMF patients received canakinumab due to the lack of anakinra approval for FMF in our country before finishing the trial. The most commonly used biological treatment in both groups was canakinumab, whose effectiveness was confirmed in the Canakinumab Pivotal Umbrella Study in Three Hereditary Periodic Fevers (CLUSTER) trial and real-life data.36,37 Other options are possible too which include IL-6, TNF-a, and JAK-inhibitors and could be suggested in the cases of colchicine and anti-IL-1 treatment resistance.38-39

The study limitations included the small sample size, especially in the Crimean subgroup, the retrospective type of the study, and impossibility to make a whole sequence of MEFV gene in some patients.

**CONCLUSION**

The similar MEFV allele prevalence in both populations suggests the high prevalence of FMF and the high number of undiagnosed patients in the Crimea peninsula. Younger age at onset, shorter duration of attacks, the prevalence of articular involvement, and erysipelas rash were distinctive features of FMF in Crimean Tatars.

**Ethics Committee Approval:** This study was approved by Ethics committee of Crimean Federal University, (Approval No: 7, May 6, 2020).

**Informed Consent:** Written Informed consent was obtained from all parents/guardians of minors participating in the study according to the Declaration of Helsinki.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – M.M.K., U.A.K., E.S., S.O.; Design – M.M.K., U.A.K., E.S., S.O.; Supervision – S.O., Y.B.; Funding – E.N.S.; Materials: M.M.K., U.A.K., O.V.Z., E.S., E.N.S., V.I.N., A.V.T., S.I.V., N.V.L., Y.B.; Data collection and/or Processing: U.A.K., O.V.Z., E.S., E.N.S., V.I.N., A.V.T., S.I.V., N.V.L.; Analysis and/or Interpretation – M.M.K., OVZ, UAK, ES, SO.; Literature Review – M.M.K., S.O.; Writing – M.M.K., S.O., Critical Review – M.M.K., Y.B., S.O.
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