The Turkish Journal of Pediatrics 2026; 68: 627-638
https://doi.org/10.24953/turkjpediatr.2026.8444

**Original Article**

# Genotype–phenotype divergence in pediatric familial Mediterranean fever across two closely related populations: a Türkiye–Azerbaijan comparison

Vafa Guliyeva[1], Selen Duygu Arık[2], Pınar Prencuva Akyürek[2], Bengisu Menentoğlu[2], Govhar Verdiyeva[3], Leyla Sahratova[4], Fatma Gül Demirkan[5], Özlem Akgün[2], Nuray Aktay Ayaz[2]

*[1]Department of Pediatric Rheumatology, Liv Bona Dea Hospital, Baku, Azerbaijan; [2]Department of Pediatric Rheumatology, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Türkiye; [3]Department of Pediatrics, Educational Therapeutic Clinic, Azerbaijan Medical University, Baku, Azerbaijan; [4]Department of Pediatrics, Republican Diagnostic Center, Baku, Azerbaijan; [5]Department of Pediatric Rheumatology, Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences, İstanbul, Türkiye.*

## ABSTRACT

**Background.** Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease and has a high prevalence in Türkiye. Despite shared ethnic ties, pediatric FMF in Azerbaijan remains poorly characterized. This study aimed to systematically compare the clinical, laboratory, and genetic characteristics of pediatric FMF patients from Türkiye and Azerbaijan to determine whether common ancestral origins result in uniform disease expression.

**Methods.** This retrospective bicentric study enrolled pediatric FMF patients aged 0–18 years who met the Eurofever/PRINTO criteria and had ≥12 months of follow-up at specialized centers in Türkiye and Azerbaijan. Demographics, clinical features, laboratory findings, Mediterranean FeVer (*MEFV*) genotypes, severity scores, and treatment data were compared.

**Results.** The cohort comprised 549 patients: 477 (86.9%) Turkish and 72 (13.1%) Azerbaijani. Azerbaijani patients had earlier symptom onset (30 [IQR 16-67] vs. 48 [IQR: 24–72] months, p=0.044) but a longer diagnostic delay (14 [IQR: 11.4–48.7] vs. 12 [IQR: 6–23] months, p<0.001). Turkish patients showed higher rates of chest pain (22.6% vs. 8.3%, p=0.005), arthralgia (52.6% vs. 32 %, p= 0.001), annual attack frequency (12 [IQR: 6–12] vs. 6 [IQR: 4–8], p<0.001), International Severity Score for Familial Mediterranean Fever (ISSF) scores (2 [IQR: 1–3] vs. 2 [IQR: 1–2], p=0.002), and C-reactive protein (CRP) levels (56 [IQR: 34–96] vs. 17.9 [IQR: 3.2–35.6] mg/L, p<0.001). Confirmatory exon 10 genotypes predominated in Turkish patients (66.7%) whereas unconfirmatory genotypes in Azerbaijani patients (59.7%). M694V was the most common variant in both groups. Within exon 10 homozygotes, Turkish patients had higher ISSF scores (median 3 [IQR: 2–4] vs. 2 [IQR: 1–3], p=0.037) and more arthritis (39% vs 6.3%, p=0.032). Colchicine response was comparable (90.6% vs. 93.1%), but anti–IL-1 use was higher in Turkish patients (11.5% vs. 2.9%, p=0.028).

**Conclusion.** This first systematic Türkiye–Azerbaijan comparison reveals distinct genotype–phenotype correlations in pediatric FMF, with Turkish patients showing a higher burden of confirmatory exon 10 genotypes and more severe disease, highlighting the need for center- and population-aware management strategies.

**Key words:** familial Mediterranean fever, genotype-phenotype correlation, phenotype.

✉ Nuray Aktay Ayaz ▪ nurayaktay@gmail.com

Received 6th Apr 2026, revised 25th Jun 2026, 26th Jul 2026, accepted 1st Aug 2026.

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease (AID) worldwide, characterized by recurrent episodes of febrile serositis.[1] The disease is caused by gain-of-function mutations in the *MEFV* (Mediterranean FeVer) gene encoding the pyrin protein.[2] An overactive pyrin inflammasome leads to uncontrolled interleukin (IL)-1β secretion, resulting in FMF symptoms that range from mild, infrequent attacks to severe, debilitating disease with potential complications such as AA amyloidosis.[3] In pediatric populations, FMF poses unique diagnostic and therapeutic challenges, as early-onset disease is often associated with more severe clinical manifestations and a higher disease burden.[4]

FMF predominantly affects populations from the Mediterranean basin, particularly Turks, Armenians, Arabs, and non-Ashkenazi Jews.[1,5] Türkiye harbors one of the world's largest FMF populations, with an estimated carrier frequency of 1:5 to 1:3 in certain regions and a disease prevalence of approximately 1:1000.[6,7] The most comprehensive Turkish pediatric FMF cohort, comprising 3,454 patients demonstrated that exon 10 mutations correlate with earlier disease onset, more frequent attacks, and higher rates of severe clinical manifestations.[4]

Azerbaijan, sharing geographic proximity and ethnic ties with Türkiye, represents another high-prevalence region for FMF. However, systematic data on pediatric FMF characteristics in Azerbaijan remain limited.[8] While common ancestral origins suggest potential similarities in disease patterns, geographic separation, environmental influences, and differences in healthcare systems may have shaped distinct mutation distributions, clinical phenotypes, and treatment responses. A comprehensive evaluation of pediatric FMF in Azerbaijan is therefore needed to clarify whether the disease profile parallels that observed in Türkiye or exhibits region-specific characteristics. Given the limited comparative data between these closely related populations, we conducted a bicentric retrospective cohort study using data from specialized pediatric rheumatology centers in Azerbaijan and Türkiye. The study aimed to compare clinical characteristics, *MEFV* mutation distributions, disease severity, treatment responses, and genotype–phenotype associations between pediatric FMF patients in the two countries.

## Materials and Methods

### *Study design, setting and population*

This retrospective cohort study was conducted at two specialized pediatric rheumatology centers in Türkiye and Azerbaijan between November 2023 and June 2025. We included pediatric patients aged 0–18 years diagnosed with FMF according to the Eurofever/Pediatric Rheumatology International Trials Organisation (PRINTO) classification criteria for hereditary recurrent fevers.[9] All enrolled patients had been under regular surveillance for a minimum of 12 months, with routine clinical evaluations conducted at 3-month intervals. Patients with inadequate clinical documentation or insufficient follow-up records were excluded from the analysis.

To ensure diagnostic precision, true juvenile idiopathic arthritis (JIA) and IgA vasculitis were strictly differentiated from FMF-related arthritis using the ILAR and EULAR/PRINTO/PRES criteria (respectively), and patients with these concomitant conditions were excluded.[10,11]

### *Data collection and clinical definitions*

Data were extracted from medical records using a standardized data collection form. Recorded parameters included demographic characteristics, family history of FMF, clinical characteristics of the attacks, laboratory findings, *MEFV* gene analysis, severity scores, and treatment modalities.

Genetic analyses were performed at both centers using either Sanger sequencing or next-generation sequencing, covering all coding exons of the *MEFV* gene. Identified variants

were interpreted according to the Infevers database (https://infevers.umai-montpellier.fr/web/), a curated international repository for autoinflammatory disease-associated variants.[12]

*MEFV* genotype distributions were compared between Turkish and Azerbaijani patients. Patients were classified into three groups according to the genetic mutation categories defined by the Eurofever/PRINTO classification criteria: (i) homozygous pathogenic variants, (ii) compound heterozygous pathogenic variants, and (iii) genotype-unconfirmed patients (carrying one pathogenic variant with one variant of uncertain significance [VUS], a single pathogenic variant, or two VUS variants).[9]

Colchicine was dosed according to age: 0.5 mg/day for children under 5 years, 0.5–1 mg/day for those aged 5–10 years, and 1.5 mg/day for children older than 10 years.[13] In colchicine-resistant cases, the maximum tolerated dose was administered under careful monitoring (maximum 1.5 mg/day for ages 5–10 years; maximum 2 mg/day for those older than 10 years). Colchicine resistance was defined as the occurrence of one or more attacks per month over a minimum period of six months and/or the presence of subclinical inflammation, despite treatment with the maximum tolerated dose of colchicine.[13] The same oral colchicine tablet formulation was used in both centers. In patients meeting the criteria for colchicine resistance, anti–IL-1 biological therapy (anakinra at 2 mg/kg/day or canakinumab at 2 mg/kg every 4 weeks) was initiated.[14,15]

Colchicine-related adverse effects monitored during follow-up included gastrointestinal symptoms (nausea, vomiting, diarrhea) and elevated liver function tests.

Amyloidosis was diagnosed by renal biopsy in patients presenting with elevated serum amyloid A levels, persistent proteinuria, and impaired renal clearance.[16]

Disease severity was assessed using the International Severity Score for Familial Mediterranean Fever (ISSF), a validated scoring tool evaluating attack frequency, duration, types of manifestations, inter-attack inflammation, and disease-related complications, with higher scores indicating greater disease severity.[17,18]

C-reactive protein (CRP) and serum amyloid A (SAA) levels were measured using immunoturbidimetric assays, with values greater than 5 mg/L for CRP and greater than 10 mg/L for SAA considered elevated at both centers.

### *Statistical analysis*

Statistical analyses were performed using IBM SPSS Statistics (version 22.0; IBM Corp., Armonk, NY, USA).

Normality of continuous variables was assessed using visual methods and the Kolmogorov–Smirnov and Shapiro–Wilk tests. As most variables were not normally distributed, data were expressed as medians (IQRs) and compared between groups using the Mann–Whitney U test.

Categorical variables were presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. Genotype distributions were analyzed according to Eurofever-recommended categories. All tests were two-tailed, and a p value $<0.05$ was considered statistically significant.

### *Ethical approval*

The study protocol was approved by the Local Ethics Committees of both participating centers (Ethics Committee 1, date/no: 25.06.2025: 3429655 and Ethics Committee 2, date/no: 15.05.2025: 013/25). Since this study is retrospective, routinely archived patient data (November 2023–June 2025) were accessed and analyzed only after formal ethical approvals were granted. The research was conducted in accordance with the principles of the Declaration of Helsinki and complied with all applicable local laws and regulations.

## Results

### *Demographic and clinical comparison*

The study cohort comprised 549 pediatric FMF patients: 477 (86.9%) from Türkiye and 72 (13.1%) from Azerbaijan (Fig. 1.). The proportion of female patients was comparable between the groups, with females comprising 48% (n = 229) of Turkish patients and 38.9% (n = 28) of Azerbaijani patients (p = 0.131). The median age at diagnosis for the entire cohort was 63.5 months (IQR: 40-96), with a median age at symptom onset of 48 months (IQR: 24-72). The overall median diagnostic delay was recorded as 12 months (IQR: 7-24). Comparative analysis between the Azerbaijani and Turkish cohorts revealed that symptom onset occurred significantly earlier in the Azerbaijani group (30 months [IQR: 16–67] vs. 48 months [IQR: 24–72]; p=0.044). Although the median age at diagnosis was similar between the two groups (67.3 months [IQR: 37–117] vs. 63 months [IQR: 40–96]), the median diagnostic delay was significantly longer in the Azerbaijani cohort than in the Turkish cohort (14 months [IQR: 11.4–48.7] vs. 12.0 months [IQR: 6–23]; p<0.001) (Table I).

Comorbid diseases were observed significantly more frequently in Azerbaijani patients than in Turkish patients (12.5% vs 4.0%, p < 0.001). The most common inflammatory comorbidities in both cohorts were JIA (8.3% in Azerbaijani patients vs 3.4% in Turkish patients, p = 0.055) and IgA vasculitis (4.2% vs 0.6%, respectively; p=0.032).

A family history of FMF was significantly more frequent among Turkish patients than among Azerbaijani patients (67.3% vs 27.8%, p < 0.001). The frequencies of parental consanguinity was similar between Turkish and Azerbaijani patients (25.2% vs 20.8%, p = 0.427) (Table I).

During acute attacks, Turkish patients exhibited significantly higher rates of both chest pain

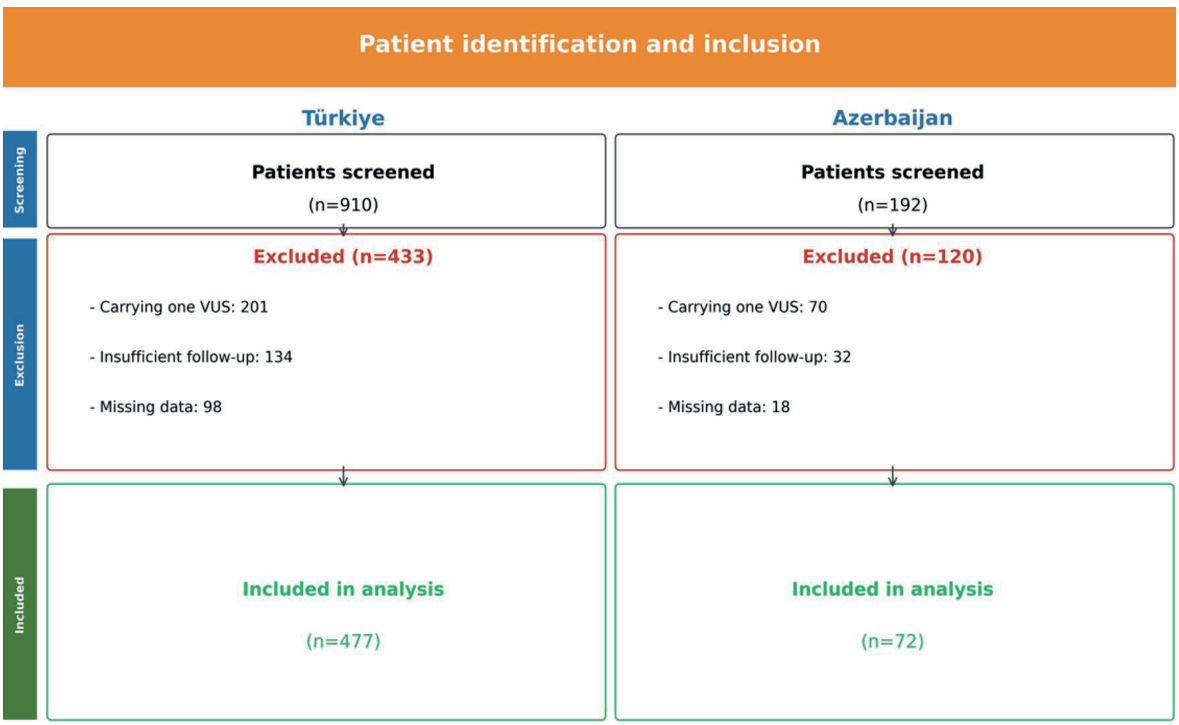


**Fig. 1.** Flowchart for the selection of the study population.
VUS, variant of uncertain significance.

(22.6% vs. 8.3%, p = 0.005) and arthralgia (52.6% vs. 32%, p =0.001) than Azerbaijani patients. Fever, abdominal pain, arthritis, erysipelas-like erythema, vomiting, diarrhea, and orchitis frequencies were similar between the two groups (Table I).

The median attack duration was longer in the Azerbaijani cohort than in the Turkish cohort [2 (1–5) days vs. 2 (1–4) days, respectively; p=0.027]. Additionally, very short attacks (<24 hours) were more frequently observed in the Azerbaijani cohort than in the Turkish cohort

**Table I.** Comparison of demographic and clinical features between Turkish and Azerbaijani FMF cohorts.

| | Turkish patients (n = 477) | Azerbaijani patients (n = 72) | p value |
|---|---|---|---|
| Demographic features | | | |
| Sex | | | 0.131 |
| Female, n (%) | 229 (48.0) | 28 (38.9) | |
| Male, n (%) | 248 (52.0) | 44 (61.1) | |
| Age at onset (months), median (IQR) | 48 (24–72) | 30 (16–67) | 0.044 |
| Age at diagnosis (months), median (IQR) | 63 (40–96) | 67.3 (37–117) | 0.448 |
| Diagnostic delay (months), median (IQR) | 12.0 (6–23) | 14 (11.4–48.7) | <0.001 |
| Family history of FMF, n (%) | 321 (67.3) | 20 (27.8) | <0.001 |
| Parental consanguinity, n (%) | 120 (25.2) | 15 (20.8) | 0.427 |
| Clinical findings | | | |
| Fever during attacks, n (%) | 423 (88.7) | 59 (81.9) | 0.104 |
| Abdominal pain, n (%) | 393 (82.4) | 57 (79.2) | 0.507 |
| Chest pain, n (%) | 108 (22.6) | 6 (8.3) | 0.005 |
| Arthritis, n (%) | 117 (24.5) | 11 (15.2) | 0.204 |
| Arthralgia, n (%) | 251 (52.6) | 23 (32) | 0.001 |
| Erysipelas-like erythema, n (%) | 61 (12.7) | 6 (8.3) | 0.208 |
| Vomiting, n (%) | 38 (8.0%) | 8 (11.1%) | 0. 292 |
| Diarrhea, n (%) | 66 (13.8%) | 4 (5.6%) | 0. 050 |
| Orchitis, n (%) | 6 (1.3%) | 1 (1.4%) | 1.000 |
| Amyloidosis, n (%) | 4 (0.8) | 0 | 0.031 |
| ISSF score, median (IQR) | 2 (1–3) | 2 (1–2) | 0.002 |
| Annual attack frequency, median (IQR) | 12 (6–12) | 6 (4-8) | <0.001 |
| WBC ($\times 10^3$ /$mm^3$ ), median (IQR) | 9.58 (4.97–20.19) | 8.52 (4.7–18.9) | 0.523 |
| Hemoglobin (g/dL), median (IQR) | 12 (6.9–15.7) | 12.5 (6.95–15.1) | 0.228 |
| Thrombocyte ($\times 10^3/\mu L$), median (IQR) | 323 (159–738) | 229 (149.5–683) | 0.151 |
| CRP during attacks (mg/L), median (IQR) | 56 (34–96) | 17.9 (3.2–35.6) | <0.001 |
| Serum amyloid A (mg/L), median (IQR) | 27.5 (1.7–105.8) | 75.3 (30–208) | 0.068 |
| Anti–IL-1 therapy, n (%) | 55 (11.5) | 2 (2.9) | 0.028 |
| Colchicine resistance, n (%) | 45 (9.4) | 5 (6.9) | 0.494 |
| Colchicine adverse effects, n (%) | 22 (4.6) | 2 (2.8) | 0.498 |

Data are expressed as n (%) or median (IQR). Group comparisons were performed using chi-square/Fisher's exact test or Mann–Whitney U test, as appropriate.
p value <0.05 was considered statistically significant.
IQR, Interquartile range; FMF, Familial Mediterranean fever; ISSF, International Severity Score for Familial Mediterranean Fever; WBC, White blood cell count; CRP, C-reactive protein; IL-1, interleukin-1

(26.2% vs. 18.5%). The annual attack frequency was significantly lower in Azerbaijani patients (6 vs 12 attacks/year, p < 0.001).

ISSF scores were significantly higher in Turkish patients than in Azerbaijani patients (median [IQR]: 2 [1–3] vs 2 [1–2], respectively; p = 0.002).

During acute attacks, median CRP levels were significantly higher in Turkish patients than in Azerbaijani patients (56 vs. 17.9 mg/L, p < 0.001), whereas median SAA levels were comparable between the groups (27.5 vs. 75.3 mg/L, p = 0.068).

### *MEFV genotype distribution*

There was a significant difference in the distribution of *MEFV* genotypes between the two cohorts (p< 0.001). Confirmatory genotypes (exon 10 homozygous and compound heterozygote genotypes) were more prevalent in Turkish patients (35.6% and 31%, respectively), while unconfirmatory genotypes (exon 10 heterozygous and other/VUS combinations) were significantly more prevalent in the Azerbaijani cohort (59.7%) (Table II). In terms of allele frequency (calculated from the total of 2n alleles), M694V was the most frequently

**Table II.** Distribution of *MEFV* genotypes in pediatric Turkish and Azerbaijani FMF patients.

| Variant group | Turkish cohort (n=477) | Azerbaijani cohort (n=72) | p |
|---|---|---|---|
| Confirmatory genotypes, n (%) | 318 (66.7) | 29 (40.3) | <0.001 |
| Homozygous variants | 170 (35.6) | 16 (22.2) | 0.032 |
| M694V/M694V | 146 (30.6) | 13 (18.1) | |
| M680I/M680I | 15 (3.1) | 1 (1.4) | |
| V726A/V726A | 5 (1.0) | 1 (1.4) | |
| R761H/R761H | 2 (0.4) | – | |
| M694I/M694I | 1 (0.2) | 1 (1.4) | |
| A744S/A744S | 1 (0.2) | – | |
| Compound heterozygous | 148 (31.0) | 13 (18.1) | 0.026 |
| M680I/M694V | 59 (12.4) | – | |
| M694V/V726A | 38 (8.0) | 9 (12.5) | |
| M694V/R761H | 15 (3.1) | 2 (2.8) | |
| M680I/V726A | 21 (4.4) | 1 (1.4) | |
| M680I/R761H | 5 (1.0) | – | |
| V726A/R761H | 4 (0.8) | – | |
| Other compound heterozygous | 6 (1.3) | 1 (1.4) | |
| Non-confirmatory genotypes, n (%) | 159 (33.3) | 43 (59.7) | <0.001 |
| Single heterozygous / genotype not confirmed | 159 (33.3) | 43 (59.7) | |
| M694V | 48 (10.1) | 6 (8.3) | |
| M680I | 6 (1.3) | 3 (4.2) | |
| V726A | 23 (4.8) | 5 (6.9) | |
| A744S | 2 (0.4) | 1 (1.4) | |
| Other / VUS combinations | 80 (16.8) | 28 (38.9) | |

Values are presented as n (% within cohort). Confirmatory genotypes comprise exon 10 homozygous and compound heterozygous pathogenic variants; non-confirmatory genotypes comprise single heterozygous and genotype-not-confirmed cases (single pathogenic variant, one pathogenic variant plus a VUS, or two VUS variants). The distribution of confirmatory versus non-confirmatory genotypes differed significantly between cohorts ($\chi 2 = 17.6$, $p < 0.001$). Homozygous and compound heterozygous subgroups were each compared with the remaining genotypes (Fisher's exact test; p = 0.032 and p = 0.026, respectively).
VUS, variant of uncertain significance. FMF, Familial Mediterranean fever

detected allele in both cohorts (Türkiye: n = 452, 47.4%; Azerbaijan: n = 43, 29.9%; p < 0.001), followed by M680I (Türkiye: n = 121, 12.7%; Azerbaijan: n = 6, 4.2%; p = 0.005) and *V726A* (Türkiye: n = 96, 10.1%; Azerbaijan: n = 17, 11.8%; p = 0.621).

### *Subgroup analysis of confirmatory genotypes*

When the analysis was restricted to patients carrying exon 10 homozygous genotypes (Turkish cohort: n=170; Azerbaijani cohort: n=16), Turkish patients demonstrated significantly higher ISSF scores than their Azerbaijani counterparts (median 3 [IQR: 2–4] vs. 2 [IQR: 1–3], p=0.037). Regarding clinical manifestations within this subgroup, the frequencies of fever (88% in Turkish patients vs. 75%, p=0.396) and abdominal pain (83.5% in Turkish patients vs. 81.3%, p=1.000) were similar between the two cohorts; however, arthritis was significantly more frequent among Turkish patients with exon 10 homozygous genotypes (39% vs. 6.3 %, p=0.032).

### *Treatment outcomes*

The response to colchicine treatment was similar between Turkish and Azerbaijani patients (90.6% vs 93.1%, p = 0.422). The frequency of colchicine-related adverse effects did not differ significantly between the two groups (4.6% vs 2.8%, p = 0.498). Colchicine-related adverse effects were observed in 2 Azerbaijani patients, both of whom experienced gastrointestinal symptoms. In the Turkish cohort, 22 patients experienced colchicine-related adverse effects, including elevated liver function tests in 8 patients and gastrointestinal intolerance in 14 patients. The use of anti–IL-1 therapy was significantly higher among Turkish patients than among Azerbaijani patients (11.5% vs 2.9%, p = 0.028). Amyloidosis was present in 4 Turkish patients (0.8%).

## Discussion

In this comparative analysis of Turkish and Azerbaijani pediatric FMF patients, the principal finding was a clear difference in overall disease severity between the two cohorts. Azerbaijani patients had an earlier age at symptom onset but experienced significantly lower annual attack frequency and a predominance of unconfirmatory genotypes. In contrast, Turkish patients demonstrated a more severe disease profile, characterized by higher attack frequency and a greater prevalence of confirmatory exon 10 genotypes. In light of these findings, the clinical course of FMF appears to differ meaningfully between the two populations, potentially reflecting differences in underlying genetic architecture and contextual factors.

Notably, although Azerbaijani patients exhibited an earlier age at symptom onset, they experienced a longer diagnostic delay. This discrepancy may partly reflect structural differences in healthcare systems. Pediatric rheumatology has been an established subspecialty in Türkiye since 2011, with wider access to trained specialists, whereas in Azerbaijan the field is not yet formally structured as a subspecialty and the number of pediatric rheumatologists remains limited. In addition, the lower annual attack frequency observed in Azerbaijani patients may further contribute to delayed recognition, as less frequent episodes can obscure the typical recurrent pattern required to establish a clinical diagnosis of FMF.

Another noteworthy finding was the higher frequency of inflammatory comorbidities in the Azerbaijani cohort than in the Turkish cohort. This difference may reflect referral bias (complex cases preferentially reaching tertiary centers), shared genetic susceptibility between FMF and other autoinflammatory conditions, population-specific immune modifiers. Given the smaller size of the Azerbaijani cohort, this finding should be interpreted with caution. A positive family history of FMF was significantly more common among Turkish patients than among those in the Azerbaijani cohort. This disparity may partly reflect greater disease awareness and more structured subspecialty care in Türkiye. Moreover, the

higher prevalence of confirmatory exon 10 genotypes in the Turkish cohort may promote stronger familial clustering due to increased penetrance.[19] Supporting this interpretation, a multicenter analysis from the Eurofever Project identified a positive family history as an independent predictor of FMF severity.[20] In contrast, the lower frequency of reported family history in Azerbaijani patients may relate to a predominance of milder genotypes, reduced intergenerational recognition of disease, or historical limitations in access to rheumatology care and genetic testing.

During acute attacks, Turkish patients more frequently exhibited chest pain and arthralgia, whereas fever and abdominal pain were comparable between the cohorts. This distribution is consistent with previous comparative studies of genetically related FMF populations demonstrating variation in the predominance of serositis and musculoskeletal features.[4,20-22] In a comparative analysis of Turkish and Crimean Tatar patients, chest pain was reported more frequently in Turkish patients, while joint involvement was relatively more prominent in Crimean Tatars.[21] Similarly, a large-scale study comparing FMF patients residing in the Eastern Mediterranean with genetically similar individuals who had migrated to Western Europe showed that those remaining in the Mediterranean region experienced more frequent attacks and higher rates of arthritis and pleurisy.[20] These findings indicate that even among populations with overlapping genetic architectures, the clinical expression of FMF, particularly serosal and musculoskeletal involvement, may be shaped by environmental exposures, healthcare context, and other population-specific modifiers. In this framework, the higher frequency of chest pain and arthralgia observed in our Turkish cohort may reflect an interaction between genetic background and contextual influences rather than genotype alone.[21,23]

In our study, attack characteristics further highlighted this variability: although the median attack duration was only slightly longer in Azerbaijani patients, they experienced significantly fewer attacks per year. Taken together with previous reports, these findings suggest that FMF expression may differ in both symptom profile and attack dynamics among closely related populations, likely reflecting an interaction between genetic background and region-specific modifiers rather than a uniform clinical course.[20-22]

Disease severity indices and acute-phase reactants further supported the overall difference in inflammatory burden between the cohorts. Turkish patients had significantly higher ISSF scores, consistent with a more severe clinical phenotype. This observation aligns with the higher prevalence of *M694V* and other confirmatory exon 10 genotypes in the Turkish cohort. Prior studies have repeatedly demonstrated that M694V, particularly in homozygous or compound heterozygous states, is associated with increased disease severity, higher attack frequency, and greater cumulative inflammatory burden.[4,20,24] In parallel, CRP levels during acute attacks were significantly higher in Turkish patients, reinforcing the impression of a more intense inflammatory response in this group. Taken together, the concordance between genotype distribution, higher ISSF scores, and elevated CRP levels supports the presence of a more inflammatory and genetically driven disease spectrum in the Turkish cohort. Although CRP levels were lower in Azerbaijani patients during acute attacks, SAA levels were comparable between cohorts ($p=0.07$), likely reflecting SAA's higher sensitivity as an earlier and more pronounced acute-phase marker. Both markers were measured during acute attacks in all patients, ruling out timing bias. Notably, prior studies on autoinflammatory amyloidosis have reported elevated SAA despite normal CRP, suggesting that SAA can capture chronic subclinical inflammation missed by CRP. The relatively higher SAA levels in the Azerbaijani cohort, despite milder clinical features, may reflect persistent subclinical inflammation. However, given the shorter follow-up in this

group, the long-term amyloidosis risk and its link to SAA levels remain unclear.[16]

The significant difference in *MEFV* genotype distribution represents a central finding. Turkish patients more frequently carried confirmatory exon 10 genotypes, whereas unconfirmatory genotypes predominated in the Azerbaijani cohort, consistent with the previously discussed association between genotype burden, higher ISSF scores, and greater inflammatory activity. The frequency of M694V in our Azerbaijani cohort closely mirrors previous reports, including a study of adult FMF patients in Azerbaijan and a large analysis of 1,330 individuals of Azerbaijani ethnicity from northwestern Iran, in which M694V was likewise the predominant mutation (42%), followed by V726A (19%), M680I (14%), and M694I (2%).[8,25] Notably, *V726A*—often reported as highly prevalent in Arab populations—was detected at a relatively higher frequency in our Azerbaijani cohort compared with Turkish patients, suggesting subtle regional differences in allele distribution.[26] The predominance of non-confirmatory or heterozygous genotypes in the Azerbaijani cohort may partially explain the milder and more heterogeneous clinical phenotype observed, given the well-established relationship between exon 10 genotype burden and disease severity.[4,27] This has practical implications, as diagnostic algorithms and clinical thresholds developed in populations with a high prevalence of classical confirmatory genotypes, may perform differently in settings where non-confirmatory genotypes predominate. In addition, some of these genetically unconfirmed patients might initially mimic FMF but could develop clinical features of other periodic fever syndromes during follow-up.

An important observation was that even within the subgroup of patients carrying homozygous exon 10 mutations, Turkish patients exhibited higher ISSF scores and a greater frequency of arthritis than Azerbaijani patients harboring the same high-risk genotype. This is particularly notable because exon 10 variants, especially M694V in the homozygous state, have consistently been associated with more severe disease, earlier onset, and increased musculoskeletal involvement in multiple cohorts, including the seminal work of Livneh and Touitou and subsequent Eurofever analyses.[20,28-30] Nevertheless, previous studies have also demonstrated that genotype–phenotype correlations in FMF are not absolute, and substantial clinical variability can occur even among individuals with identical mutations.[20-22,26,31] The intra-genotype differences observed between the two populations in our study therefore suggest that disease severity is not determined solely by *MEFV* mutation status but is likely modulated by additional factors such as environmental influences, epigenetic mechanisms, healthcare context, and broader genetic background.

Colchicine remains the cornerstone of FMF management, with approximately 90–95% of adherent patients achieving adequate disease control and a small subset requiring biologic escalation.[32] In our study, colchicine response rates were high and comparable between Turkish and Azerbaijani patients (approximately 90–93%), despite differences in genotype distribution and overall disease severity. This preserved efficacy across geographically and genetically distinct cohorts reinforces the central and universal role of colchicine as first-line therapy in pediatric FMF.[33,34] However, anti–IL-1 therapy was used significantly more frequently in Turkish patients than in Azerbaijani patients. This difference likely reflects the greater clinical severity and higher burden of confirmatory exon 10 genotypes in the Turkish cohort, as well as broader access to biologic therapies within the Turkish healthcare system. Given that anti–IL-1 agents are the standard of care for colchicine-resistant or -intolerant FMF, disparities in biologic utilization may also be influenced by differences in referral structures and treatment availability. In Azerbaijan specifically, biologic therapies are not covered by national insurance and remain largely inaccessible due to financial constraints,

which may have further contributed to the lower rate of biologic therapy use in this cohort. The occurrence of amyloidosis exclusively in Turkish patients, albeit infrequent, further parallels the more severe genotype–phenotype profile observed in this group. Together, these findings suggest that while colchicine effectiveness is consistent across populations, escalation to advanced therapies appears to track underlying disease burden and healthcare infrastructure rather than intrinsic differences in colchicine responsiveness.

### *Study limitations*

This study has several limitations. Its retrospective bicentric design, conducted at a single tertiary referral center in each country, may have introduced selection bias and limited the generalizability of the findings, as center-specific factors such as referral patterns, diagnostic thresholds, and local clinical practices may have contributed to the observed differences independently of true population-level variation. The smaller size of the Azerbaijani cohort may further limit generalizability and reduce statistical power for certain analyses, including subgroup comparisons. In addition, because multiple subgroup comparisons were performed without formal adjustment for multiplicity, some statistically significant associations may represent chance findings. Therefore, these results should be considered exploratory and require validation in larger, independent cohorts. Differences in access to biologic therapies and subspecialty care between healthcare systems may also have influenced treatment patterns and complication rates. In addition, environmental and socioeconomic factors, such as infection burden, living conditions, nutrition, and healthcare accessibility, were not systematically evaluated, although they may contribute to inter-population differences in disease expression.

In conclusion, this bicentric study provides the first systematic comparison of pediatric FMF patients from Türkiye and Azerbaijan and demonstrates that, despite shared ethnic and genetic backgrounds, the disease may manifest with distinct clinical and genetic patterns. The observed divergence in severity, genotype distribution, and inflammatory burden indicates that FMF expression is not uniform across closely related populations. While *MEFV* mutation burden remains a key determinant of phenotype, our findings suggest that genetic architecture interacts with healthcare context and population-specific modifiers to shape disease presentation. These results underscore the need to interpret FMF within regional frameworks, acknowledging potential center-specific influences and to incorporate such diversity into future diagnostic strategies and precision medicine approaches in autoinflammatory diseases.

## Ethical approval

The study was approved by Istanbul University Ethics Committee (date: June 25, 2025, number: 3429655) and by the Medical Research Ethics Committee of the ''New Clinic'' Public Legal Entity (date: May 15, 2025, number: 013/25).

## Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: NAA, VG; data collection: VG, GV, LS, PPA, BM; analysis and interpretation of results: VG, ÖA, BM, SDA, FGD; draft manuscript preparation: NAA, VG. All authors reviewed the results and approved the final version of the manuscript.

## Source of funding

The authors declare the study received no funding.

## Conflict of interest

The authors declare that there is no conflict of interest.

## REFERENCES


1. Ben-Chetrit E, 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. The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 1997; 90: 797-807. https://doi.org/10.1016/s0092-8674(00)80539-5
4. Öztürk K, Coşkuner T, Baglan E, et al. Real-life data from the largest pediatric familial Mediterranean fever cohort. Front Pediatr 2022; 9: 805919. https://doi.org/10.3389/fped.2021.805919
5. Sag E, Bilginer Y, Ozen S. Autoinflammatory diseases with periodic fevers. Curr Rheumatol Rep 2017; 19: 41. https://doi.org/10.1007/s11926-017-0670-8
6. Ozen S, Karaaslan Y, Ozdemir O, et al. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study. J Rheumatol 1998; 25: 2445-2449.
7. Turkish FMF Study Group. 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
8. Huseynova LS, Mammadova SN, Aliyeva K. Frequencies of the MEFV gene mutations in Azerbaijan. Balkan J Med Genet 2022; 24: 33-38. https://doi.org/10.2478/bjmg-2021-0017
9. Gattorno M, Hofer M, Federici S, et al. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis 2019; 78: 1025-1032. https://doi.org/10.1136/annrheumdis-2019-215048
10. 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.
11. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 2010; 69: 798-806. https://doi.org/10.1136/ard.2009.116657
12. Touitou I. The registry of Hereditary Auto-Inflammatory Disorders Mutations. Available at: https://infevers.umai-montpellier.fr/web/search.php?n=1
13. Ozen S, Demirkaya E, Erer B, et al. EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis 2016; 75: 644-651. https://doi.org/10.1136/annrheumdis-2015-208690
14. Cam V, Unal D, Sag E, et al. How physicians manage colchicine-resistant familial Mediterranean fever: insights from a multinational survey in high-prevalence countries. J Rheumatol 2026; 53: 556-561. https://doi.org/10.3899/jrheum.2025-0804
15. Kavrul Kayaalp G, Çağlayan Ş, Ulu K, et al. Three-year follow-up of canakinumab dose extension in children with colchicine-resistant familial Mediterranean fever: PeRA-RG Experience. Rheumatology (Oxford) 2025; 64: 6366-6370. https://doi.org/10.1093/rheumatology/keaf403
16. Aytekin ES, Tagiyev A, Silleli O, et al. Amyloidosis in human inborn errors of immunity predicts poor prognosis. J Clin Immunol 2025; 45: 88. https://doi.org/10.1007/s10875-025-01875-1
17. 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
18. Ozcan G, Cayci S, Celikel Acar B, et al. Is the performance of the international severity scoring system for familial mediterranean fever in children better than other scoring systems? Int J Clin Pract 2021; 75: e14678. https://doi.org/10.1111/ijcp.14678
19. 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
20. Ozen S, Demirkaya E, Amaryan G, et al. Results from a multicentre international registry of familial Mediterranean fever: impact of environment on the expression of a monogenic disease in children. Ann Rheum Dis 2014; 73: 662-667. https://doi.org/10.1136/annrheumdis-2012-202708
21. Kostik M, Akca Kaya U, Zhogova OV, et al. The comparison of pediatric patients with familial Mediterranean fever originated from Turkey and Crimea. Turk Arch Pediatr 2022; 57: 551-557. https://doi.org/10.5152/TurkArchPediatr.2022.22106
22. 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

23. Touitou I, Sarkisian T, Medlej-Hashim M, et al. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum 2007; 56: 1706-1712. https://doi.org/10.1002/art.22507

24. Özdel S, Özçakar ZB, Kunt SŞ, Elhan AH, Yalçınkaya F. Late-onset disease is associated with a mild phenotype in children with familial Mediterranean fever. Clin Rheumatol 2016; 35: 1837-1840. https://doi.org/10.1007/s10067-016-3196-y

25. Bonyadi MJ, Gerami SMN, Somi MH, Dastgiri S. MEFV mutations in Northwest of Iran: a cross sectional study. Iran J Basic Med Sci 2015; 18: 53-57.

26. Lancieri M, Bustaffa M, Palmeri S, et al. An update on familial Mediterranean fever. Int J Mol Sci 2023; 24: 9584. https://doi.org/10.3390/ijms24119584

27. Tunce E, Atamyıldız Uçar S, Polat MC, et al. Predicting homozygous M694V genotype in paediatric FMF: multicentre analysis and scoring system proposal. Rheumatology (Oxford) 2025; 64: 4816-4824. https://doi.org/10.1093/rheumatology/keaf221

28. Grossman C, Kassel Y, Livneh A, Ben-Zvi I. Familial Mediterranean fever (FMF) phenotype in patients homozygous to the MEFV M694V mutation. Eur J Med Genet 2019; 62: 103532. https://doi.org/10.1016/j.ejmg.2018.08.013

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

30. Gershoni-Baruch R, Brik R, Shinawi M, Livneh A. The differential contribution of MEFV mutant alleles to the clinical profile of familial Mediterranean fever. Eur J Hum Genet 2002; 10: 145-149. https://doi.org/10.1038/sj.ejhg.5200776

31. Di Ciaula A, Iacoviello M, Bonfrate L, et al. Genetic and clinical features of familial Mediterranean fever (FMF) in a homogeneous cohort of patients from South-Eastern Italy. Eur J Intern Med 2023; 115: 79-87. https://doi.org/10.1016/j.ejim.2023.05.015

32. Ben-Chetrit E, Ozdogan H. Non-response to colchicine in FMF-definition, causes and suggested solutions. Clin Exp Rheumatol 2008; 26: S49-S51.

33. Kaye AD, Islam RK, Nguyen ID, et al. Familial Mediterranean fever (FMF): emerging concepts in diagnosis, pain management, and novel treatment options: a narrative review. Curr Pain Headache Rep 2025; 29: 22. https://doi.org/10.1007/s11916-024-01345-0

34. Ozen S, Sağ E, Oton T, et al. EULAR/PReS endorsed recommendations for the management of familial Mediterranean fever (FMF): 2024 update. Ann Rheum Dis 2025; 84: 899-909. https://doi.org/10.1016/j.ard.2025.01.028