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Research Article

Comprehensive *MEFV* Variant Spectrum in Pediatric Patients with Suspected Familial Mediterranean Fever: A Whole-Gene Sequencing Study

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ABSTRACT

Objective: To determine the *Mediterranean Fever (MEFV)* variant spectrum using whole-gene next-generation sequencing (NGS) in pediatric cases with suspected Familial Mediterranean Fever (FMF).

Methods: This retrospective cross-sectional study included 471 pediatric cases referred for *MEFV* analysis. All exons were analyzed using NGS, and variants were classified according to American College of Medical Genetics and Genomics criteria.

Results: At least one *MEFV* variant was detected in 59.4% of cases. A total of 23 variants were identified, predominantly in exon 10 (43.5%) and exon 2 (34.8%). The most frequent variants were R202Q (43.3%), E148Q (16.3%), and M694V (13.7%). A low-frequency variants of uncertain significance, G150R, was detected in one case. Heterozygous genotypes were the most common (59.6%).

Conclusion: Whole-gene sequencing enables the detection of both common and rare *MEFV* variants that may be missed by limited mutation panels. However, frequently detected variants, such as R202Q, require careful interpretation because of their high population frequency and controversial pathogenicity.

Keywords: Familial Mediterranean Fever, *MEFV*, pediatric, next-generation sequencing, variant spectrum, whole-gene sequencing

INTRODUCTION

Familial Mediterranean Fever (FMF) (OMIM #249100) is one of the most common monogenic autoinflammatory diseases and is characterized by recurrent fever attacks and inflammatory findings such as peritonitis, pleuritis, arthritis, and erysipelas-like erythema.[1,2,3] The disease is particularly common in populations living in the Mediterranean basin; Türkiye is among the countries with a high prevalence of FMF.[4,5] In cases that begin in childhood, early diagnosis is important for initiating appropriate treatment and preventing long-term complications.[6,7]

FMF is mainly associated with variants in the *Mediterranean Fever (MEFV)* gene, which is located on the short arm of chromosome 16 and encodes the pyrin protein.[2,4] Although numerous variants have been identified in the *MEFV gene*, commonly observed variants such as M694V, V726A, M680I, M694I, and E148Q are detected in a significant proportion of cases.[1,5] However, when examinations are performed with standard panels, no diagnostic result can be reached in some cases, suggesting that rare or out-of-panel variants, in particular, may be overlooked.[1,3] In an FMF-specific study, broader next-generation sequencing (NGS)-based analysis of patients with negative or single-heterozygous results after traditional 16-variant screening identified clinically relevant variants in 34% of cases and detected previously missed *MEFV* variants in 54 patients.[8] This indicates that traditional

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genetic screening approaches focusing only on certain exons may remain limited in the diagnostic evaluation of cases with atypical clinical features or rare variants.

In the pediatric population, the diagnosis of FMF is of particular importance because symptoms often begin in the first decade of life and serious complications, such as amyloidosis, can be prevented.[6,7] In the literature, a substantial proportion of studies focusing on the pediatric age group, both in Türkiye and in other populations, have been conducted using limited variant panels, whereas NGS-based studies covering all exons of the *MEFV* gene remain limited.[1,2] Whole-gene analysis may expand the scope of genetic evaluation by enabling the detection of rare or previously undescribed variants that may be missed in standard tests.[2,3]

Given the limited number of studies that analyze all exons of the *MEFV* gene in pediatric cases evaluated with a preliminary diagnosis of FMF in Türkiye, this study is expected to fill an important gap. This study aimed to determine, using NGS, the distribution of variants across all exons of the *MEFV* gene in pediatric cases referred for genetic evaluation with a preliminary diagnosis of FMF in our region. Thus, it aimed to comprehensively reveal the regional variant spectrum, to more accurately evaluate the frequency of variants that may be overlooked in limited panels, and to provide a data infrastructure that will form the basis for future genotype-phenotype correlation studies.

MATERIALS AND METHODS

Design and Case Group

This was a retrospective, cross-sectional, descriptive study. The study included 471 pediatric cases who were evaluated with a preliminary diagnosis of FMF according to the Tel-Hashomer criteria and who were requested to undergo *MEFV* gene analysis at Erzincan Binali Yıldırım University-Mengücek Gazi Training and Research Hospital between 01.01.2024 and 31.12.2024. The cases had been referred from pediatric outpatient clinics for genetic evaluation because of clinical findings compatible with FMF, such as recurrent fever, abdominal pain, chest pain, arthralgia, and/or erysipelas-like erythema. Cases younger than 18 years and those who underwent NGS of all exons of the *MEFV* gene were included in the study. Cases with completed genetic data were included in the study. This study was conducted in accordance with the World Medical Association's Declaration of Helsinki, and ethics committee approval was obtained from the Erzincan Binali Yıldırım University Non-Interventional Clinical Research Ethics Committee (decision number: 2026-04/12, date: 19.02.2026).

MAIN POINTS

- Whole-gene next-generation sequencing identified *MEFV* variants in 59.4% of pediatric cases referred for suspected Familial Mediterranean Fever.
- A total of 23 distinct *MEFV* variants were detected, most located in exons 2 and 10.
- R202Q was the most frequently detected variant; however, its clinical significance remains controversial and requires cautious interpretation.
- Whole-gene analysis contributed to the detection of low-frequency and potentially panel-excluded variants, including G150R, I259V, and C355S.
- The findings support the use of whole-gene sequencing for broader variant detection and more comprehensive characterization of the regional *MEFV* variant spectrum.

Data Collection

Demographic data and genetic analysis results of the cases were retrospectively obtained from the hospital information system and laboratory records. In this study, age, sex, detected *MEFV* variants, zygosity status, and the distribution of variants across exons were evaluated.

Whole-gene Sequencing of the *MEFV* Gene

For *MEFV* gene analysis, 2 mL of peripheral venous blood was obtained from each case and placed into tubes containing ethylenediaminetetraacetic acid. Genomic DNA was isolated using an automated DNA isolation system. The concentration and purity of the obtained DNA samples were evaluated using a spectrophotometric method, and samples of suitable quality for analysis were included in the study.

NGS was used for genetic analysis. For this purpose, library preparation and target region enrichment were performed to capture all coding regions of the *MEFV* gene and exon-intron junctions. Sequencing was performed on the Illumina MiSeq platform. The obtained sequencing data were analyzed using the Genomize bioinformatics platform and compared with the reference genome. NM_000243.3 was used as the reference transcript for *MEFV* gene analysis. Quality control and variant calling were performed according to the workflow of the Genomize platform. Variant calls were reviewed considering read depth, variant allele fraction, and overall call quality. Only variants located within the targeted coding regions and exon-intron junctions and that were considered reportable by the software were included in the final analysis. Low-quality calls, insufficiently covered regions, and variants outside the targeted regions were excluded from interpretation.

Variant Classification

Detected *MEFV* variants were evaluated according to the criteria of the American College of Medical Genetics and Genomics (ACMG).[9] The variants were classified as pathogenic, likely pathogenic, of uncertain significance (VUS), or benign. In cases where different clinical interpretations were present among databases or literature sources, the variants were additionally indicated as ''variants with conflicting classifications'' In addition, ClinVar, INFEVERS, and the Human Gene Mutation Database were used to evaluate the variants.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 22.0. Continuous variables were expressed as mean ± standard deviation and median (minimum-maximum), whereas categorical variables

were expressed as number and percentage. Descriptive statistical methods were used to evaluate demographic data, the distribution of detected *MEFV* variants, zygosity status, and allele frequencies.

RESULTS

Demographic Characteristics and Overall Variant Distribution

A total of 471 pediatric patients who had a preliminary diagnosis of FMF and underwent *MEFV* gene analysis were included in the study. Of these, 259 (55.0%) were female and 212 (45.0%) were male, with a female-to-male ratio of 1.2:1. The mean age was 7.3 ± 4.1 years. At least one *MEFV* variant was detected in 280 cases (59.4%), whereas no variant was identified in 191 cases (40.6%) (Table 1).

Whole-gene *MEFV* Analysis Findings

Analysis of all exons of the *MEFV* gene detected 23 variants. Of these variants, 8 (34.8%) were localized in exon 2, 4 (17.4%) in exon 3, 1 (4.3%) in exon 9, and 10 (43.5%) in exon 10. Based on ACMG criteria, 6 variants were classified as pathogenic, 1 as likely pathogenic, 9 as variants of uncertain significance (VUS), 5 as benign, and 2 as having conflicting classifications (Table 2). Among the low-frequency variants, G150R was detected in one case in the heterozygous state and

Table 1. Demographic Characteristics of The Study Cohort and *MEFV* Variant Status

Total cases, n	**471**
Gender, n (%)	
Female	259 (55)
Male	212 (45)
Age (years), mean ± SD	7.3 ± 4.1
Variant status, n (%)	
Positive	280 (59.4)
Negative	191 (40.6)

Table 2. *MEFV* Variants Detected in the Study Cohort (n=23)

Exon	Coding change (HGVS, c.)	Protein change (HGVS, p.)	Protein change (short)	ACMG classification
2	c.329T > C	p.Leu110Pro	L110P	B
2	c.442G > C	p.Glu148Gln	E148Q	B
2	c.443A > T	p.Glu148Val	E148V	VUS
2	c.448G > A	p.Gly150Arg	G150R	VUS
2	c.605G > A	p.Arg202Gln	R202Q	B
2	c.688G > A	p.Glu230Lys	E230K	VUS
2	c.775A > G	p.Ile259Val	I259V	Conflicting (VUS/B)
2	c.866C > T	p.Ala289Val	A289V	VUS
3	c.1016C > T	p.Ser339Phe	S339F	VUS
3	c.1063T > A	p.Cys355Ser	C355S	B
3	c.1105C > T	p.Pro369Ser	P369S	VUS
3	c.1223G > A	p.Arg408Gln	R408Q	VUS
9	c.1772T > C	p.Ile591Thr	I591T	B
10	c.1958G > A	p.Arg653His	R653H	Conflicting (VUS/P)
10	c.2040G > C	p.Met680Ile	M680I	P
10	c.2060G > A	p.Gly687Asp	G687D	LP
10	c.2082G > A	p.Met694Ile	M694I	P
10	c.2080A > G	p.Met694Val	M694V	P
10	c.2084A > G	p.Lys695Arg	K695R	P
10	c.2110G > A	p.Val704Ile	V704I	VUS
10	c.2177T > C	p.Val726Ala	V726A	P
10	c.2230G > T	p.Ala744Ser	A744S	VUS
10	c.2282G > A	p.Arg761His	R761H	P

*P, pathogenic; LP, likely pathogenic; VUS, variant of uncertain significance; ACMG, American College of Medical Genetics and Genomics; B, benign; Conflicting, variants with discordant clinical classifications across databases/sources.

was classified as VUS.

When the genotype distribution was evaluated among 280 cases in which *MEFV* variants were detected, the most common genotype was heterozygous, observed in 167 cases (59.6%). This was followed by compound heterozygous genotypes in 64 cases (22.9%), complex genotypes in 33 cases (11.8%), and homozygous genotypes in 16 cases (5.7%) (Table 3a and 3b).

In the heterozygous group, the most frequently observed genotype was R202Q/- (n=75, 26.8%), followed by E148Q/- (n=42, 15.0%) and M680I/- (n=13, 4.6%). A total of 15 heterozygous genotypes were identified. In the homozygous group, the most frequently observed genotype was R202Q/R202Q (n=12, 4.3%); this was followed by V726A/V726A (n=3, 1.1%) and E148Q/E148Q (n=1, 0.4%) (Table 3a).

Among genotypes classified as compound heterozygous, the most frequent combination was R202Q/M694V (n=30, 10.7%). This was followed by R202Q/E148Q (n=6, 2.1%) and R202Q/V726A (n=4, 1.4%). A total of 19 different genotypes were identified in this group. In the complex genotype group, the most frequent combinations were those containing R202Q/M694V (n=11, 3.9%); these were followed by R202Q/E148Q/M694V (n=5, 1.8%) and R202Q/P369S/R408Q (n=4, 1.4%). A total of 12 complex genotypes were identified, including one case carrying four variants (Table 3b).

Table 3a. Distribution of Heterozygous and Homozygous Genotypes Among Variant-Positive Cases

Genotype Type	Genotype	n (%)
Heterozygous	R202Q/-	75 (26.8)
	E148Q/-	42 (15.0)
	M680I/-	13 (4.6)
	V726A/-	12 (4.3)
	R761H/-	6 (2.1)
	M694V/-	5 (1.8)
	E148V/-	4 (1.4)
	A744S/-	2 (0.7)
	K695R/-	2 (0.7)
	G150R/-	1 (0.4)
	G687D/-	1 (0.4)
	I259V/-	1 (0.4)
	I591T/-	1 (0.4)
	M694I/-	1 (0.4)
	S339F/-	1 (0.4)
Subtotal		**167 (59.6)**
Homozygous	R202Q/R202Q	12 (4.3)
	V726A/V726A	3 (1.1)
	E148Q/E148Q	1 (0.4)
Subtotal		**16 (5.7)**
Total		**183 (65.3)**

A total of 430 variant alleles were identified in 280 cases with detected variants. Among 23 variants, the five most frequently detected accounted for 85.1% of all variant alleles. R202Q was the most frequently detected variant (n=186, 43.3%), followed by E148Q (n=70, 16.3%), M694V (n=59, 13.7%), V726A (n=28, 6.5%), and M680I (n=23, 5.3%) (Table 4).

Table 3b. Distribution of Compound Heterozygous and Complex Genotypes Among Variant-Positive Cases

Genotype Type	Genotype	n (%)
Compound Heterozygous	R202Q/M694V	30 (10.7)
	R202Q/E148Q	6 (2.1)
	R202Q/V726A	4 (1.4)
	E148Q/M680I	3 (1.1)
	P369S/R408Q	3 (1.1)
	A744S/M680I	2 (0.7)
	R202Q/M680I	2 (0.7)
	E148Q/V726A	2 (0.7)
	E148V/V726A	2 (0.7)
	A289V/R202Q	1 (0.4)
	A744S/R202Q	1 (0.4)
	R202Q/R761H	1 (0.4)
	R202Q/C355S	1 (0.4)
	R202Q/E230K	1 (0.4)
	E148Q/E148V	1 (0.4)
	E148Q/L110P	1 (0.4)
	E148Q/M694V	1 (0.4)
	M680I/R761H	1 (0.4)
	S339F/V726A	1 (0.4)
Subtotal		**64 (22.9)**
Complex Genotype	R202Q/M694V*	11 (3.9)
	R202Q/E148Q/M694V	5 (1.8)
	R202Q/P369S/R408Q	4 (1.4)
	E148Q/P369S/R408Q	4 (1.4)
	R202Q/M680I/M694V	2 (0.7)
	R202Q/E148Q/P369S/R408Q	1 (0.4)
	R202Q/E148Q/R653H	1 (0.4)
	R202Q/E148Q/L110P	1 (0.4)
	R202Q/M694V/K695R	1 (0.4)
	R202Q/M694V/V726A	1 (0.4)
	R202Q/V704I*	1 (0.4)
	E230K/P369S/R408Q	1 (0.4)
Subtotal		**33 (11.8)**
Total		**97 (34.7)**

*Genotypes containing a variant also observed in the homozygous state in this cohort.

Table 4. Allele Distribution of Detected *MEFV* variants (n=430 variant alleles)

Variant	n	%	Variant	n	%
R202Q	186	43.3	S339F	2	0.5
E148Q	70	16.3	E230K	2	0.5
M694V	59	13.7	A289V	1	0.2
V726A	28	6.5	G150R	1	0.2
M680I	23	5.3	C355S	1	0.2
P369S	13	3.0	G687D	1	0.2
R408Q	13	3.0	I259V	1	0.2
R761H	8	1.9	I591T	1	0.2
E148V	7	1.6	M694I	1	0.2
A744S	5	1.2	R653H	1	0.2
K695R	3	0.7	V704I	1	0.2
L110P	2	0.5			
			Total	**430**	**100**

DISCUSSION

In this study, analysis of all exons of the *MEFV* gene by NGS in 471 pediatric cases referred for genetic evaluation with a preliminary diagnosis of FMF revealed a comprehensive profile of regional variant distribution. Detection of at least one *MEFV* variant in 59.4% of cases shows that genetic evaluation plays an important role in the pediatric referral population. This rate is generally consistent with data reported in large Turkish NGS-based series. Kırnaz et al.[2] reported a variant positivity rate of 56.9% in their series of 3230 cases, whereas Düzkale Teker and Öz[10] similarly showed that variants were detected at a rate of approximately 59%. In contrast, this rate may vary across studies with different panel coverage or referral populations. This suggests that variant positivity rates are influenced not only by population characteristics but also by the scope of the genetic method used.

In our study, the most frequently detected variants, R202Q, E148Q, M694V, V726A, and M680I, are largely consistent with the general distribution reported in the Turkish population. However, the relative ranking and frequencies of these variants may differ among studies. In particular, R202Q ranking first with an allele frequency of 43.3% is consistent with the high rates reported by Kırnaz et al.[2] and Aksoy et al.[5] In the previous study conducted in the same region using a limited panel, R202Q was not evaluated, and M694V was reported as the most frequently detected variant, clearly demonstrating the effect of test coverage on variant distribution.[11] From this perspective, whole-gene analysis appears to reveal the regional variant spectrum more broadly.

Although the R202Q variant was detected at high frequency in our cohort, its clinical significance remains controversial. Although this variant is classified as benign or of low clinical effect in some databases, studies such as Kandur et al.[11] and Dundar et al.[12] have reported it either alone or together with other *MEFV* variants in symptomatic cases. Nevertheless, in several international recommendations and variant interpretation frameworks, R202Q is regarded primarily as a polymorphism or a low-penetrance (modifier) allele rather as a primary disease-causing variant when present alone. Therefore, R202Q should not be interpreted as a standalone diagnostic marker in the absence of typical Tel-Hashomer clinical features; its clinical relevance should be assessed in conjunction with *MEFV* variants and possible complex haplotypes.

E148Q was identified as the second most frequent variant in our study, with an allele frequency of 16.3%. This rate is consistent with the rates of 17.49% reported by Kırnaz et al.[2] and 11.5% reported by Aksoy et al.[5] and is lower than the rate of 32.5% reported by Binici et al.[13] in Southeastern Anatolia. The clinical significance of E148Q has long been controversial in the literature; in some studies it has been associated with incomplete attack forms and a relatively mild clinical phenotype, whereas in others it has been regarded as a change close to the benign boundary.[15,16] Therefore, although the frequent detection of E148Q in our study is noteworthy, direct interpretation of its clinical effect is not appropriate. Taken together, our findings suggest that although NGS may increase the detection of R202Q and E148Q, these variants should be interpreted as low-penetrance or modifier alleles rather than primary diagnostic markers in the absence of typical Tel-Hashomer clinical features.

In our study, M694V was the third most frequent variant detected, with an allele frequency of 13.7%. This rate is markedly lower than that reported in many studies of the Turkish population. Coşkunpınar et al.[16] reported an M694V frequency of 48.3%, Demir and Admış[10] 48.3%, Düzkale Teker and Öz[10] 46.6%, Çilingir et al.[17] 40.13%, Bayrak et al.[18] 34.9%, and Barış et al.[4] 30.2%. The main reason for this marked difference in frequency is that all exons, including R202Q, were screened in our study, resulting in a decreased relative proportion of M694V as the total number of alleles increased. Indeed, in the studies by Aksoy et al.[5] and Kırnaz et al.[2], which included R202Q in their panels, the frequency of M694V was reported as 25.1% and 16.84%, respectively, which is consistent with our findings. Although genotype-phenotype correlation could not be performed in our study, M694V is the variant in the *MEFV*

gene most strongly associated in the literature with the most severe phenotype and, particularly in the homozygous form, it is characterized by severe attacks of peritonitis, pleuritis, and arthritis and is accepted as the most important genetic risk factor for the development of secondary amyloidosis.[20,21] Beshlawy et al.[7] reported in their Egyptian pediatric cohort that the homozygous M694V genotype was associated with a severe phenotype at a rate of 65.2%. Because clinical findings, attack severity, and treatment response were not evaluated in our study, this relationship could not be demonstrated directly in cases carrying the M694V mutation.

V726A (6.5%) and M680I (5.3%) were the fourth and fifth most frequent variants, respectively, in our study. These rates are consistent with those for V726A (5.30%) and M680I (5.12%) reported by Kırnaz et al.[2] However, Düzkale Teker and Öz[10] reported V726A and M680I frequencies of 14.5% and 14.0%, respectively, whereas Taşdemir[21] reported an M680I rate of 9.85% in the Konya region. These differences indicate that the distribution of *MEFV* gene variants is heterogeneous across the geographical regions of Türkiye. Bayrak et al.[18] also emphasized that the frequency of *MEFV* mutation types may vary from region to region and from population to population. According to literature data, the V726A mutation is generally associated with a moderate disease phenotype, and Beshlawy et al.[7] reported a moderate clinical picture in 50% of heterozygous V726A carriers. The M680I variant is associated, particularly in the homozygous form, with a severe clinical course and risk of amyloidosis.[23,24] Detection of these two variants at relatively low rates in our study reflects regional genetic heterogeneity, but does not reduce the importance of clinical follow-up of carriers.

The predominance of heterozygosity observed in the genotypic distribution is consistent with other Turkish studies. Kırnaz et al.[2] reported heterozygous, compound heterozygous, complex genotype, and homozygous rates of 57.8%, 22.3%, 12.9%, and 7.0%, respectively. Demir and Admış[10] reported rates of 70.1% heterozygous, 16.8% compound heterozygous, and 13.1% homozygous in the same region. In our study, the higher rates of compound-heterozygous and complex genotypes may be due to whole-gene analysis more effectively revealing carriage of multiple variants. Nevertheless, particularly for heterozygous or complex genotypes, it is inappropriate to infer the clinical effects of variants solely from the genotype. Since penetrance, the presence of accompanying second variants, and the relationship with the clinical phenotype may vary in pediatric cases, the clinical counterparts of genotypes should be evaluated in conjunction with more detailed phenotypic data.

In our study, 12 complex genotypes were identified, and the complex genotype rate was 11.8%; one patient carried four variants (R202Q/E148Q/P369S/R408Q). This rate is similar to the complex genotype finding of 12.9% reported by Kırnaz et al.[2] Aksoy et al.[5], in their larger series, reported a complex genotype (compound homozygous/heterozygous) rate of 19.6%. The high rate of detection of complex genotypes can be explained by the ability of NGS-based whole-gene analysis to identify more than one variant simultaneously. This suggests that the true frequency of complex genotypes may have been underestimated in studies using limited mutation panels. In terms of clinical reflection, the literature reports that cases with complex genotypes carrying more than one pathogenic variant may face earlier age at symptom onset, more frequent and severe attacks, and a higher risk of amyloidosis.[20,25]

Examination of the distribution of the 23 detected variants across exons showed that most changes were concentrated in exon 10 (43.5%) and exon 2 (34.8%). This finding is consistent with studies reporting that *MEFV* variants cluster particularly in these two hotspot regions. Çilingir et al.[17] reported that the most frequent mutations in the Turkish population are concentrated in exon 2 and exon 10 and that these hotspot regions account for 90% of molecular diagnosis. In addition, the detection in our study of 4 variants in exon 3 and 1 variant in exon 9 suggests that testing approaches focusing only on classical hotspot regions may overlook some variants. Sağ et al.[1] also emphasized that including rare mutations in routine genetic panels may significantly affect diagnosis and treatment planning. According to the literature, variants clustered in exon 10 (M694V, M680I, M694I, V726A, K695R, R761H) affect the B30.2 (SPRY) domain of the pyrin protein; mutations in this region are generally associated with a more severe clinical phenotype, higher penetrance, and increased risk of amyloidosis.[15] In contrast, variants in exon 2 (E148Q, R202Q) have been reported to present with relatively mild or variable clinical manifestations.[12,16] In this respect, the study demonstrates that not only common variants, but also changes in less frequently screened regions should be evaluated within the diagnostic framework.

Another relevant finding of our study was the detection of low-frequency and potentially panel-excluded variants, including G150R, I259V, and C355S. G150R and I259V are located in exon 2, whereas C355S is located in exon 3. G150R was classified as a variant of uncertain significance (VUS), I259V was given a conflicting classification (VUS/benign), and C355S was classified as benign. The detection of such variants suggests that whole-gene analysis may reveal not only common *MEFV* variants but also low-frequency and potentially panel-excluded changes. However, further evaluation through detailed phenotype correlations, segregation analyses, and functional studies is required to clarify the clinical significance of variants with uncertain or conflicting interpretations, such as G150R and I259V.

The sex distribution (55% female, 45% male) and mean age (7.3 ± 4.1 years)in our study are generally consistent with other studies in the Turkish population. Elmas et al.[6] reported a female/male ratio of 1.5 and a mean age at presentation of 10.74 ± 4.06 years in pediatric FMF cases in Afyonkarahisar, whereas Beshlawy et al.[7] reported male predominance (54%) in an Egyptian pediatric cohort. Barış et al.[4] reported a female patient rate of 55.18% and a symptom onset age of 4.8 ± 2.3 years in their study. The slight female predominance in our study was a noteworthy finding.

Overall, our study stands out as one of the regional studies in Türkiye that reveal the distribution of *MEFV* variants at the whole-gene level in pediatric cases referred for genetic evaluation with a preliminary diagnosis of FMF. The findings

from our study show that in addition to common variants, low-frequency and out-of-panel changes are present in this referral population at a level that should not be ignored. This suggests that restricting genetic evaluation to the most common variants may not fully capture variant diversity in some cases. Because clinical findings, attack characteristics, treatment response, and complication data were not evaluated in this study, definitive conclusions about the effects of the detected variants on disease severity or clinical course cannot be drawn. Therefore, the genetic findings obtained should be considered not as direct clinical determinants but as molecular data that can form the basis for future genotype-phenotype association studies.

These findings highlight the importance of comprehensive genetic analysis in regions with a high prevalence of FMF, particularly in referral populations. Whole-gene sequencing may provide a broader understanding of variant diversity compared to limited mutation panels.

Study Limitations

Our study has some limitations. First, its retrospective and single-center design may limit the generalizability of the findings to the broader Turkish pediatric population. Second, genotype-phenotype correlation could not be performed because detailed clinical and treatment-response data were unavailable. Third, Sanger confirmation was not performed for all detected variants, particularly low-frequency variants. Fourth, variant phasing was not available; therefore, compound heterozygous and complex genotypes should be interpreted in light of the lack of cis/trans information. Fifth, the clinical significance of variants with uncertain or conflicting interpretations, such as G150R and I259V, could not be clarified because segregation and functional validation analyses were not available. Deep intronic variants and copy-number changes were outside the scope of this study.

CONCLUSION

This study presents a large pediatric series from our region in which all exons of the *MEFV* gene were analyzed using NGS. R202Q was identified as the most frequently detected variant; however, its clinical significance remains controversial and should be interpreted with caution. The identification of 23 different variants, including low-frequency and potentially panel-excluded variants, demonstrates that whole-gene sequencing contributes to broader variant detection and more comprehensive characterization of the regional variant spectrum. Further multicenter studies incorporating detailed clinical data and functional analyses are needed to clarify the clinical significance of the detected variants.

Ethics

Ethics Committee Approval: Approval was obtained from Erzincan Binali Yıldırım University Non-Interventional Clinical Research Ethics Committee (decision number 2026-04/12, date: 19.02.2026).

Informed Consent: This was a retrospective, cross-sectional, descriptive study. Permissions were obtained from the hospital management to collect study data from the hospital information system and laboratory records.

Footnotes

Author Contributions: Concept Design – B.Y., A.Y.D., M.G.; Data Collection or Processing – A.Y.D.; Analysis or Interpretation – A.Y.D.; Literature Review – B.Y., A.Y.D., M.G.; Writing, Reviewing and Editing – B.Y., A.Y.D.

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