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RESEARCH

Relationship between genetic and clinical findings in pediatric patients with Familial Mediterranean Fever

Ailevi Akdeniz Ateşi tanısı ile takipli hastalarımızda genetik ve klinik bulguların ilişkisi

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Abstract

Purpose: Familial Mediterranean Fever (FMF) (OMIM #249100) exhibits varying clinical severity, influenced by genetic mutations. This study aimed to assess the relationship between FMF genotypes and disease severity in pediatric patients.

Materials and Methods: This retrospective cross-sectional study included FMF patients aged 0-18 years who were followed up between January 1, 2016, and June 1, 2017. Demographic data, clinical findings, Pras disease severity scores (Pras score), and MEFV gene mutations were analyzed. Patients were classified into four genetic groups: homozygous, heterozygous, compound heterozygous, and those without detected mutations. Clinical characteristics and disease severity were compared.

Results: Among 126 FMF patients (49.2% female), the median age at symptom onset was 60 (12–168) months, and the median age at diagnosis was 76 (23–180) months, resulting in a median diagnostic delay of 12 (0–120) months. Common symptoms included abdominal pain (98%), fever (87.3%), arthralgia (60.3%), and myalgia (60.3%). The median Pras score was 6 (range: 4–11), with 40.5% classified as mild, 43.7% as moderate, and 15.8% as severe. Genetic analysis revealed that 50% of the individuals had compound heterozygous mutations, 30.2% had homozygous mutations, 13.5% had heterozygous mutations, and 6.3% had no mutations. No significant differences were found among mutation groups regarding clinical characteristics or disease severity.

Conclusion: Pediatric FMF exhibits clinical heterogeneity, and genotype alone may not be an effective predictor of severity. A comprehensive clinical approach remains essential for diagnosis and management.

Keywords: Familial Mediterranean Fever, MEFV mutation, genotype-fenotype, pediatrics

Öz

Amaç: Ailevi Akdeniz Ateşi (AAA) (OMIM #249100), genetik mutasyonlardan etkilenebilen ve farklı klinik şiddetle seyreden bir hastalıktır. Bu çalışmada pediatrik AAA hastalarında genotip ile klinik ve hastalık şiddeti arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Bu çalışma, 1 Ocak 2016-1 Haziran 2017 tarihleri arasında AAA tanısı ile izlenen 0-18 yaş arası hastaları kapsamaktadır. Retrospektif kesitsel olarak planlanmıştır. Demografik veriler, klinik bulgular, Pras hastalık şiddet puanları ve MEFV gen mutasyonları incelenmiştir. Hastalar genetik analiz sonuçlarına göre dört gruba ayrılmıştır: homozigot, heterozigot, bileşik heterozigot mutasyon saptananlar ve mutasyon tespit edilemeyenler. Klinik özellikler ve hastalık şiddeti gruplar arasında karşılaştırılmıştır.

Bulgular: Toplam 126 AAA hastası çalışmaya dahil edilmiş olup, % 49,2'si kızdı. Medyan semptom başlangıç yaşı 60 (12-168) ay, medyan tanı yaşı 76 (23-180) ay ve tanıda gecikme süresi 12 (0-120) ay olarak bulunmuştur. En sık saptanan semptomlar arasında karın ağrısı (% 98), ateş (% 87,3), artralji (% 60,3) ve miyalji (% 60,3) yer almaktadır. Hastaların medyan Pras şiddet skoru 6 (4-11) olup, % 40,5'i hafif, % 43,7'si orta, % 15,8'i ise şiddetli olarak sınıflandırılmıştır. Genetik analizde hastaların %50'sinde bileşik heterozigot, % 30,2'sinde homozigot, %13,5'inde heterozigot mutasyon saptanmıştır ve % 6,3'ünde ise mutasyon tespit edilmemiştir. Mutasyon grupları arasında klinik özellikler veya hastalık şiddeti açısından anlamlı bir fark bulunmamıştır.

Sonuç: Pediatrik AAA, klinik olarak heterojen bir seyir göstermektedir ve genotip hastalık şiddetini tek başına öngöremez. Tanı ve tedavi için kapsamlı bir klinik yaklaşımın önemi vurgulanmaktadır.

Anahtar kelimeler: Ailevi Akdeniz Ateşi, MEFV mutasyonu, genotip-fenotip, pediatri

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INTRODUCTION

Familial Mediterranean Fever (FMF) is the most prevalent monogenic autoinflammatory disorder, passed down in an autosomal recessive way and marked by recurring, self-limiting spells of fever, abdominal discomfort, chest pain, and joint pain caused by serosal inflammation. Although it was initially identified in populations of Mediterranean descent, including Turks, Armenians, Jews, and Arabs, FMF has been reported globally, with migration contributing to its wider distribution. In Turkey, the prevalence is notably higher, with a reported incidence of 1 in 1,000 individuals in central Anatolia[1-5].

Historically, the clinical features of FMF were first described in ancient Mediterranean populations, characterized by periodic fever and abdominal pain similar to those observed in FMF. However, it was not until 1945 that Siegal provided a comprehensive clinical description of the condition as "benign paroxysmal peritonitis." In 1955, the term "Familial Mediterranean Fever" was formally introduced. FMF diagnosis relies on clinical criteria, particularly the Tel-Hashomer and Livneh criteria, which are commonly utilized for children and adults. However, specific criteria for the pediatric population were introduced by Yalçınkaya et al. in 2009, addressing the unique clinical presentation in children. Mutations in the MEFV gene, found on chromosome 16p13.3, play a crucial role in FMF pathogenesis. This gene encodes pyrin, a protein that regulates the inflammatory response. Since its identification in 1997, over 400 MEFV variants have been documented and categorized based on pathogenic potential. Despite extensive research, the genotype-phenotype correlation remains inconsistent, with environmental factors and other genetic modifiers potentially influencing disease severity[5-12].

The clinical burden of FMF extends beyond acute episodes of fever and serositis, as recurrent inflammation can lead to severe complications, including nephrotic amyloidosis, growth retardation, and psychosocial distress. The introduction of colchicine as a prophylactic therapy has markedly reduced the risk of amyloidosis, but treatment challenges persist, particularly in colchicine-resistant cases, where biologics are now being explored[13].

Hatay Province, situated in southern Turkey by the Mediterranean Sea and adjacent to Syria, has a long-standing history of high FMF prevalence. Its strategic position as a gateway for migration and cultural exchange may have contributed to genetic diversity and phenotypic variability in FMF. Despite the extensive body of research on FMF, studies focusing specifically on pediatric populations and regional genetic variations remain limited.

This study aims to investigate the demographic and clinical characteristics, as well as the impact of MEFV mutations on disease severity scores, in pediatric FMF patients in Hatay. By focusing on a pediatric cohort from a genetically diverse region with a high prevalence of FMF, the study seeks to provide new insights into the clinical heterogeneity of FMF. The hypothesis suggests that genetic diversity in the Hatay region may influence MEFV mutations and that these mutations may be associated with more severe clinical phenotypes and higher disease severity scores in pediatric patients.

MATERIALS AND METHODS

Study design

This cross-sectional retrospective study was conducted at the Department of Child Health and Diseases, Faculty of Medicine, Hatay Mustafa Kemal University, a tertiary care university hospital with a well-established pediatric unit experienced in managing FMF patients. Patient data were obtained from both electronic medical records and paper-based medical files, ensuring comprehensive data retrieval. Pediatric specialists verified the data to maintain its integrity. Genetic analyses, particularly Sanger sequencing, were performed to confirm FMF diagnoses and assess genetic mutations. Clinical assessments, including disease severity scoring and genetic testing, were conducted by pediatric specialists, with additional consultation from genetic counselors when necessary.

Sample

Participants were selected based on specific inclusion and exclusion criteria to ensure the consistency and reliability of the study sample. The inclusion criteria were as follows: ages 0-18 years, diagnosed with FMF based on clinical findings and genetic analysis, receiving regular colchicine treatment, and having sufficient follow-up data for at least 12 months. The exclusion criteria included: uncertain FMF diagnosis,

lack of genetic analysis, incomplete medical records, and missing disease severity scores.

A priori power analysis was conducted using G*Power version 3.1 to assess whether the sample size was adequate for detecting differences in variables across four genetic mutation groups: homozygous, heterozygous, compound heterozygous, and mutation-negative. Assuming a medium effect size (f = 0.30), an alpha level of 0.05, and a power (1–β) of 0.80, the required sample size for a Kruskal-Wallis test was calculated to be approximately 120 participants. The final sample size of 126 was considered sufficient to detect effects of this magnitude.

Procedure

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its subsequent revisions. Ethical approval was obtained from the Clinical Research Ethics Committee of Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine (Hatay, Turkey) on July 13, 2017, with protocol number 2017/124.

The diagnosis of FMF in the patients was established based on the clinical criteria defined by Yalçınkaya et al. According to the Yalçınkaya criteria for FMF diagnosis, at least two of the following criteria must be present: fever (axillary temperature ≥38°C, at least three attacks lasting 6–72 hours), abdominal pain (at least three attacks lasting 6–72 hours), chest pain (at least three attacks lasting 6–72 hours), arthritis (oligoarthritis, each attack lasting at least 6–72 hours), and a family history of FMF [6,12]. In addition, MEFV gene analysis was performed on all patients.

Clinical findings for the patients were evaluated during each outpatient clinic visit, and a disease severity score was calculated for each patient. Genetic analysis was conducted as part of the clinical assessment. All patients received regular colchicine treatment. Patient data were systematically recorded in patient files and electronic medical records during each visit.

Data collection

Clinical and demographic data were retrieved from patient medical records. Collected data included demographic characteristics, clinical history (fever, abdominal pain, arthritis, arthralgia, myalgia), past medical history (age at symptom onset, age at diagnosis, history of appendectomy), and family history (presence of consanguinity, family members with FMF). Clinical data, including the presence of proteinuria, vasculitis, and suspicion of amyloidosis, were also recorded. Genetic analysis results were obtained to classify patients based on their MEFV mutation status.

The severity of FMF was assessed using the Pras disease severity scores (Pras score), which considers the following parameters: age at disease onset, number of attacks per month, presence of arthritis, erysipelas-like erythema (ELE), amyloidosis, and colchicine dose (mg/m^2). The severity score was categorized as mild (3-5 points), moderate (6-8 points), or severe (>9 points)[14].

Patients were classified based on their genetic mutation status as homozygous, heterozygous, compound heterozygous, or having no detected mutation. The analysis explored the relationship between disease severity scores, genetic mutation status, and demographic and clinical characteristics.

Genetic analysis

Genetic testing for MEFV mutations was conducted using the Sanger DNA sequencing method. Genomic DNA was extracted from EDTA-treated whole blood samples via a commercial isolation kit (Macherey-Nagel GmbH & Co. KG, Germany). Polymerase chain reaction (PCR) amplification utilized forward and reverse primers targeting Exons 2, 3, 5, and 10 of the MEFV gene. The amplified products were sequenced with the ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA, USA) and analyzed using an automated fluorescent sequencer (ABI PRISM 3500, Applied Biosystems). Confirmatory analyses of mutations were carried out by sequencing complementary DNA strands.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 22.0 (IBM, Armonk, NY, USA). Categorical variables were presented as frequencies and percentages, while continuous variables were reported as mean ± standard deviation and median (range). The Pearson chi-square test and Fisher's exact test were applied for the analysis of categorical data. For continuous data, the Mann–Whitney U test was employed to compare two independent groups when the data did not meet the assumption of normality, whereas the independent samples t-test

was used for normally distributed data. In cases involving three or more groups, one-way analysis of variance (ANOVA) was implemented for parametric data, and the Kruskal–Wallis H test was used for non-parametric data. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 152 pediatric patients diagnosed with FMF were initially identified. Of these, 26 patients were excluded due to incomplete follow-up data, lack of genetic analysis, and missing Pras scores. Therefore, 126 patients were included in the study, consisting of 62 (49.2%) females and 64 (50.8%) males. The male-to-female ratio was 1.03:1. The median age at symptom onset was 60 months (range: 12-168), while the median age at diagnosis of FMF was 76 months (range: 23-180). The median duration of diagnostic delay was 12 months (range: 0-120). When evaluating the age of disease onset, it was most common in the 3 to 5-year age range. Among the parents of 34 (27%) patients, consanguineous marriages with first- and second-degree cousins were reported. FMF was identified in 47 (37.3%) of the patients' first- and second-degree relatives. The most common presenting symptoms in the patients, in order of frequency, were abdominal pain in 121 (98%), fever in 110 (87.3%), arthralgia in 76 (60.3%), and myalgia in 76 (60.3%). Seven patients had a history of appendectomy, and in all cases, the surgery occurred before the diagnosis of FMF. The median disease severity score was 6 (range: 4-11). When classified by disease severity score, 51 (40.5%) had a mild score, 55 (43.7%) had a moderate score, and 20 (15.8%) had a severe score.

Among the patients, 63 (50%) had a compound heterozygous mutation, 38 (30.2%) had a homozygous mutation, and 17 (13.5%) had a heterozygous mutation, while no mutations were detected in 8 (6.3%) patients. The study flow diagram is presented in Figure 1. Demographic characteristics, clinical data, disease severity scores, and classifications are summarized in Table 1.

The patients were divided into four groups based on the presence of mutations: homozygous, heterozygous, compound heterozygous, and those with no detected mutations. These groups were compared, and no statistically significant differences were found in terms of gender, age at symptom onset, age at FMF diagnosis, duration of diagnostic delay, clinical findings, disease severity score, or disease severity classification. A comparison of demographic characteristics, clinical findings, and disease severity among the groups is presented in Table 2.

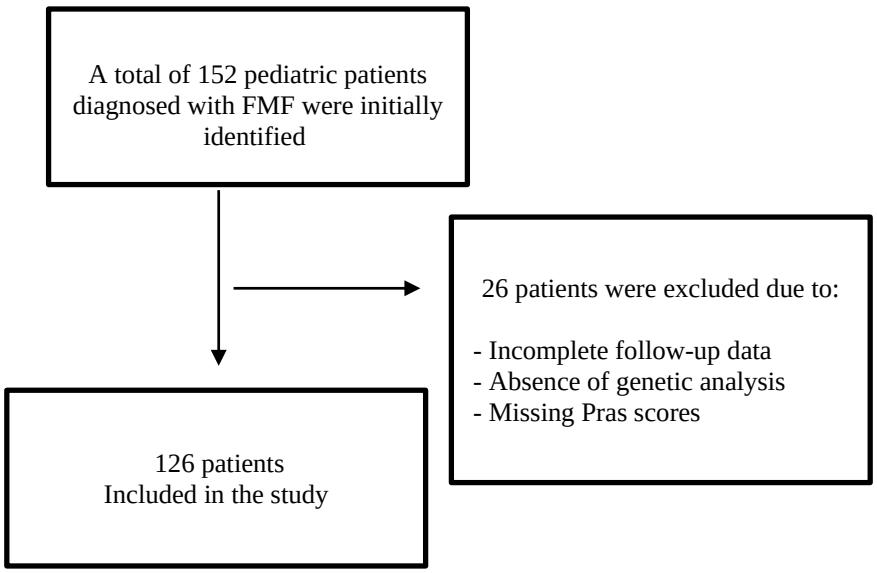

Figure 1. Flow diagram of the study

Table 1. Demographic characteristics, clinical data and disease severity

Parameter	n (%), median (min-max)
Number of patients included in the study	126 (100)
Female n(%)	62 (49.2)
Male n(%)	64 (50.8)
Age of onset of symptoms (months)	60 (12-168)
Diagnose age (months)	76 (23-180)
Delay in diagnosis FMF (months)	12 (0-120)
Distribution of age at onset of disease	
≤ 2 years	17 (13.5)
3-5 years	53 (42.1)
6-10 years	48 (38.1)
>10 years	8 (6.3)
Parental consanguinity	34 (27)
Presence of FMF in 1st and 2nd degree relatives	47 (37.3)
Clinical finding	
Abdominal pain	121 (96)
Fever	110 (87.3)
Arthralgia	76 (60.3)
Myalgia	76 (60.3)
Headache	40 (31.7)
Arthritis	30 (23.8)
ELE	20 (15.9)
Chest pain	19 (15.1)
Proteinuria	9 (7.1)
Appendectomy	7 (5.6)
Vasculitis	7 (5.6)
Scrotal pain	2 (1.6)
Disease severity score	6 (4-11)
Disease severity score classification	
Mild	51 (40.5)
Moderate	55 (43.7)
Severe	20 (15.8)
Mutation Groups of Patients	
Compound Heterozygote	63 (50)
Homozygous	38 (30.2)
Heterozygous	17 (13.5)
No mutation detected	8 (6.3)

FMF: Familial Mediterranean Fever, ELE: erysipelas-like erythema.

When evaluating the MEFV gene allele analysis, the most frequently detected mutations, in order, were A165A 121 (30.2%), G138G 118 (29.5%), R202Q 83 (20.7%), E148Q 19 (4.7%), and M694V 18 (4.5%). The MEFV gene allele frequency analysis is shown in Table 3.

Table 2. Comparison of the demographic characteristics, clinical findings and disease severity of the groups

	Homozygous	Heterozygous	Compound Heterozygote	No mutation detected	p
Female n (%)	15 (24.2)	8 (12.9)	32 (51.6)	7 (11.3)	0.10
Male n (%)	23 (35.9)	9 (14.1)	31 (48.4)	1 (1.6)	
Age of onset of symptoms (months) median (min-max)	66 (12-144)	48 (20-96)	60 (18-168)	56 (29-96)	0.51
Diagnose age (months) median (min-max)	79 (24-168)	65 (23-115)	84 (24-180)	67 (39-168)	0.54
Delay in diagnosis (months) median (min-max)	12 (1-120)	12 (2-60)	12 (0-96)	17 (3-108)	0.55
Clinical finding					
Abdominal pain	36 (94.7)	16 (88.9)	61 (98.4)	8 (100)	0.28
Fever	31 (81.6)	17 (94.4)	55 (88.7)	7 (87.5)	0.56
Myalgia	27 (71.1)	8 (44.4)	37 (59.7)	4 (50 9)	0.25
Arthralgia	22 (57.9)	10 (55.6)	39 (62.9)	5 (62.5)	0.92
Headache	14 (36.8)	5 (27.8)	19 (30.6)	2 (25.0)	0.85
Arthritis	11 (28.9)	4 (22.2)	15 (24.2)	0 (0.0)	0.18
ELE	9 (23.7)	2 (11.1)	9 (14.5)	0 (0.0)	0.19
Chest pain	5 (13.2)	2 (11.1)	11 (17.7)	1 (12.5)	0.87
Proteinuria	4 (10.5)	1 (5.6)	4 (6.5)	0 (0.0)	0.59
Appendectomy	3 (7.9)	0 (0.0)	3 (4.8)	1 (12.5)	0.52
Vasculitis	3 (7.9)	2 (11.1)	2 (3.2)	0 (0.0)	0.41
Disease severity score median (min-max)	6 (4-11)	6 (5-11)	6 (4-11)	5 (4-7)	0.44
Disease severity score classification					
Mild	12 (31.6)	8 (47.1)	27 (42.9)	4 (50.0)	
Moderate	19 (50.0)	7 (41.2)	25 (39.7)	4 (50.0)	0.73
Severe	7 (18.4)	2 (11.8)	11 (17.5)	0 (0.0)	

ELE: erysipelas-like erythema

Table 3. MEFV gene allele analysis

Mutation	n (%)	Exon	Classification
A165A	121 (30.2)	2	Benign
G138G	118 (29.5)	2	Benign
R202Q	83 (20.7)	2	Benign
E148Q	19 (4.7)	2	VUS
M694V	18 (4.5)	10	Pathogenic
M680I	8 (2)	10	Pathogenic
R314R	8 (2)	3	Benign
V726A	7 (1.7)	10	Pathogenic
A744S	7 (1.75)	10	VUS
R761H	3 (0.7)	10	Likely Pathogenic
G196W	2 (0.5)	2	VUS
D661N	2 (0.5)	10	Unsolved
M680L	1 (0.2)	10	Likely Pathogenic
G632A	1 (0.2)	10	Likely benign
P706P	1 (0.2)	10	Likely benign
V659F	1 (0.2)	10	Likely Pathogenic

VUS: Variant Unsignificant

DISCUSSION

In this study, we investigated the relationship between clinical features and genetic mutation profiles in children with FMF. We found no significant differences in clinical presentation or disease severity across the different mutation groups. Our findings highlight that abdominal pain and fever were the most common symptoms, and that diagnostic delay remains a significant issue. Additionally, we observed that half of the patients carried compound heterozygous MEFV mutations, while no mutations were detected in 6.3% of the cohort. These results underscore the clinical heterogeneity of FMF and emphasize the importance of comprehensive clinical evaluation rather than relying solely on genetic testing for diagnosis.

FMF symptoms typically appear in childhood, with 90% of patients diagnosed before age 20 and 65% before age 10. In our study, 93.7% of patients exhibited symptoms before the age of 10, with a median onset age of 5 years and a median diagnosis age of 6.3 years, resulting in a median diagnostic delay of 1 year. Previous studies have reported a later age of diagnosis. Yalçınkaya et al. found a median diagnosis age of 11.9 years, and Düşünsel et al. reported a median age of 9.7 years, with delays of 5.67 and 2.9 years, respectively [15,16]. In a 2021 study conducted by Ozdemir et al., the age of onset was found to be 4.9 ± 3.7 years, and the diagnosis age was 7.5 ± 4 years, which is similar to our findings [17]. Our findings suggest that earlier diagnoses and shorter delays are likely due to the high prevalence of FMF in our region, as well as the widespread use of genetic analysis methods today. The early recognition of FMF in patients with early-onset and recurrent symptoms is crucial for prompt management and effective treatment.

Consanguineous marriage is a significant risk factor for monogenic diseases, such as FMF. A study conducted in our region demonstrated high rates of first- and second-degree cousin marriages, with 38.4% in rural areas and 30.8% in urban areas[18]. In the cohort of patients in our study, 27% of parents were involved in consanguineous marriages, which appears to contribute to the higher prevalence of FMF, as evidenced by the 37.3% familial history of the disease among our patients. This finding is consistent with the 34% familial incidence reported in the literature [2]. In a study conducted in Egypt, parental consanguinity was found to be 58%, and the family history of FMF was 35.6%[19]. The presence of FMF in family members highlights the importance of utilizing family history as a diagnostic tool, as thorough inquiries can facilitate early diagnosis. In the context of consanguinity and genetic transmission, offering genetic counseling could help reduce FMF prevalence, particularly considering the serious complications, such as amyloidosis, associated with the disease.

Clinical manifestations, incidence, and disease patterns of FMF vary by age, geographical region, and ethnicity. In previous studies, abdominal pain has been reported in the range of 86.2%-96.8%, and fever in the range of 80.7%-100%[20-22]. In our study, abdominal pain was the most prevalent symptom, occurring in 96% of patients, followed by fever in 87.3%. Although fever is commonly observed during FMF attacks, it is important to note that some patients may experience attacks without fever, or may have both febrile and afebrile episodes. These findings highlight the significance of abdominal pain in FMF, as it can mimic acute abdomen presentations, potentially leading to misdiagnosis and unnecessary appendectomies[23]. In our cohort, 7 (5.6%) of patients underwent appendectomy: 3 with homozygous mutations, 3 with compound heterozygous mutations, and 1 with no mutations detected. Previous studies have reported higher appendectomy rates, ranging from 11.3% to 30% in FMF patients[2,24-26]. Our lower rate may be attributed to heightened awareness of FMF in our region. In communities where FMF is common, it is vital to assess patients presenting with abdominal pain for potential FMF attacks to avoid unnecessary surgical interventions. However, it should also be noted that true acute appendicitis can occasionally occur in patients with FMF, and clinical differentiation may be difficult.

FMF can clinically coexist with vasculitic diseases such as Henoch-Schönlein purpura (HSP) and polyarteritis nodosa, as well as inflammatory bowel diseases; this phenomenon occurs more frequently than in the general population. In our cohort, we identified HSP in 7 patients (5.6%). A study of 192 cases reported a vasculitis rate of 6.25%, and our findings closely align with this figure 20. Notably, in patients with recurrent symptoms, the presence of skin manifestations like HSP may serve as an indicator of FMF, and in some cases, HSP might be the first clinical manifestation of FMF. This underscores the importance of considering FMF in

the differential diagnosis when these conditions coexist.

Secondary amyloidosis, although rare, is the most severe complication of FMF. In patients with FMF, nephrotic-range proteinuria may indicate the presence of amyloidosis. In our study, proteinuria was detected in eight patients: four with homozygous mutations and four with compound heterozygous mutations. Proteinuria was transient in seven of these patients, necessitating close monitoring for potential amyloidosis. Only one patient exhibited nephrotic-range proteinuria and was referred to a tertiary center for further evaluation, treatment, and biopsy due to suspected amyloidosis. Studies conducted in our country have reported varying rates. Özlü et al. found proteinuria in 15.1% and amyloidosis in 2.6% of patients, while Coşkun et al. reported proteinuria in 15% and amyloidosis in 0.3%. The absence of amyloidosis in our cohort is likely attributable to the earlier diagnosis and treatment of FMF [20,21].

A study by Marek-Yagel et al. examining the clinical and genetic characteristics of heterozygous FMF patients found that individuals with heterozygous mutations in the MEFV gene exhibited milder disease. However, despite these milder manifestations, the clinical symptoms of heterozygous patients were similar to those of homozygous patients, making it difficult to differentiate between the two clinically. Furthermore, higher Pras scores were closely associated with homozygous FMF patients. This highlights the complexity of diagnosing FMF in patients with heterozygous mutations or those with undetectable mutations, as it suggests that modifier genes, such as the serum amyloid A (SAA) gene, which plays a role in inflammation and indirectly activates IL-1β through the NLRP3 pathway, may influence disease expression [27-30].

An Italian study investigating genotype-phenotype correlations found no significant clinical differences between patients with homozygous, heterozygous, and compound heterozygous mutations, aligning with our findings[29]. In our study, no significant differences were observed among the groups (homozygous, heterozygous, compound heterozygous, and those without detected mutations) across various clinical parameters, including fever, abdominal pain, arthralgia, myalgia, arthritis, headache, chest pain, erysipelas-like erythema, proteinuria, vasculitis, history of appendectomy, age of disease onset, age at diagnosis, diagnostic delay, and disease severity scores.

Recent studies suggest that, in addition to the clinical-genetic relationship, other factors may contribute to the disease course. For patients without detectable mutations, the presence of FMF may be linked to unidentified mutations or environmental factors that influence its etiology. Epigenetic factors, including DNA methylation, histone modifications, microRNAs, and noncoding RNAs, are also believed to play a role, with ongoing research investigating their impact [1]. Given these complexities, if FMF is strongly suspected clinically, treatment should be initiated, even if genetic analysis is negative [31]. In cases where the clinical diagnosis remains uncertain, genetic mutation analysis may be helpful. Treatment should proceed if pathogenic mutations are detected in homozygous cases.

Limitations of this study include the exclusion of patients for whom sufficient medical information could not be obtained, those who did not attend regular outpatient clinic follow-ups, and those who did not receive regular colchicine treatment. This may have resulted in sampling bias. Additionally, in some patients who underwent appendectomy before FMF diagnosis, pathology reports were not accessible, making it impossible to determine whether the surgery was performed due to true appendicitis or FMF attacks mimicking an acute abdomen. SAA values were not available across the study population; therefore, this parameter could not be included in the analysis.

In conclusion, this study highlights that higher Pras scores are more commonly observed in patients with compound heterozygous mutations; however, the observed difference is not statistically significant, contrary to existing literature. These findings suggest that additional genetic or epigenetic modifiers may play an essential role in disease expression. Notably, the identification of mutations underscores genetic diversity and the potential presence of unidentified variants that influence the clinical course of FMF. To the best of our knowledge, including mutation profiles and allele frequencies in our cohort provides valuable insights into the genetic landscape of FMF in a region with high rates of consanguinity. Future research should focus on identifying these modifiers through comprehensive genetic screening and molecular studies. Furthermore, extended follow-up of patients with atypical or severe phenotypes may help clarify the impact of specific alleles or novel

variants, refining genetic counseling strategies and personalized treatment approaches in FMF management.

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Ethical Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Tayfur Ata Sökmen Faculty of Medicine of Mustafa Kemal University with the decision dated 13.07.2017 and numbered 2017/124.
Written informed consent for both participation in the study and publication of the findings was obtained from all individual participants. For participants under the age of 18, consent was obtained from their parents or legal guardians.
Peer-review: Externally peer-reviewed.
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