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ORIGINAL ARTICLE

THE *MEFV* GENE PATHOGENIC VARIANTS AND PHENOTYPE-GENOTYPE CORRELATION IN CHILDREN WITH FAMILIAL MEDITERRANEAN FEVER IN THE ÇANAKKALE POPULATION

Battal F[1], Silan F[2], Topaloğlu N[1], Aylanç H[1], Yıldırım Ş[1,*], Köksal Binnetoğlu F[1], Tekin M[1], Kaymaz N[1], Ozdemir O[2,3]

***Corresponding Author:** Assistant Professor Dr. Şule Yıldırım, Department of Pediatrics, Faculty of Medicine, Çanakkale Onsekiz Mart University, Terzioğlu Yerleşkesi Ek Bina, 17100, Çanakkale, Turkey. Tel: +90-286-2180018/2107. Fax: +90-286-263-59-56. E-mail: sule.yildirim@comu.edu.tr

ABSTRACT

The aim of the current study was to determine the frequency of the Mediterranean fever (*MEFV*) gene pathogenic variants in 60 children diagnosed with familial Mediterranean fever (FMF) and to compare the phenotype-genotype correlation. Genomic DNA was isolated by the spin-column method from peripheral blood samples (collected in vacutainers containing EDTA) and buccal smears. The *MEFV* gene profiles for the current FMF cohort were genotyped by pyrosequencing and direct Sanger sequencing techniques for the target pathogenic variants. The most prominent clinical symptoms were abdominal pain (53.4%), fever (23.4%) and arthritis (23.3%). Eighteen different pathogenic variants were identified and the most frequent were p.Met694Val (20.0%), p.Glu148Gln (13.3%), p.Met680 Ile (11.7%) and p.Arg202Gln (11.7%). Abdominal pain, fever and arthritis were the most common presenting clinical characteristics. Results showed that not only clinical characteristics, but also genotyping of the *MEFV* gene is needed to establish the correct diagnosis of FMF in children and other family members.

Keywords: Amyloidosis; Children; Familial Mediterranean fever (FMF); Genotype-phenotype correlations; Pathogenic variant.

INTRODUCTION

Familial Mediterranean fever (FMF) is an inherited inflammatory disease that primarily affects patients in the Mediterranean and Middle Eastern populations such as Arabs, Jews, Armenians, Cypriots, Italians, Spaniards and Turks [1-7]. The disease is caused by pathogenic variants in the Mediterranean fever (*MEFV*) gene and is characterized by short, recurrent episodes of fever accompanied by peritonitis, arthritis or pleuritis and insidious development of systemic amyloidosis. Familial Mediterranean fever is an autosomal recessive disorder but there is also an autosomal dominant form, which is caused by heterozygous pathogenic variants in the *MEFV* gene [8-12]. Mostly, these symptoms (90.0%) occur in early childhood [2]. The *MEFV* gene responsible for FMF is on the short arm of chromosome 16, and more than 120 pathogenic variants that are specifically located on exons 2, 5 and 10, have been identified in affected individuals [13-17]. The *MEFV* gene encodes pyrin, a 781 amino acid protein that plays an important role in innate immunity. It functions *via* the regulation of interleukin-1β (IL-1β)processing, through binding apoptosis associated with a speck-like protein containing a caspase recruitment domain [5,8]. Some researchers have claimed that homozygous pathogenic variants on both alleles of the *MEFV* gene play a crucial role in FMF pathogenesis [16,18,19]. Shinar *et al.* [20] claimed that the pathogenic variant in codon p.Met694Val has more severe clinical implications than p.Val726Ala. From these results, our aim was to compare the minor and/or major clinical characteristics and common *MEFV* gene pathogenic variants in children suspected of having FMF in the Çanakkale population.

[1] Department of Pediatrics, Faculty of Medicine, Çanakkale Onsekiz Mart University 17100, Çanakkale, Turkey

[2] Department of Medical Genetics, Faculty of Medicine, Çanakkale Onsekiz Mart University 17100, Çanakkale, Turkey

[3] Department of Medical Genetics, Faculty of Medicine, Cumhuriyet University 58140, Sivas, Turkey

MATERIALS AND METHODS

Patient Group. In this case-control study, the aim was to investigate the type and prevalence of *MEFV* gene pathogenic variants in children/patients presenting with minor and/or major manifestations of FMF. The *MEFV* gene spans were genotyped in a total of 60 patients, using pyrosequencing and direct sequencing methods for the current cohort. Sixty peripheral blood samples were obtained from a group suspected of having FMF: 28 males (46.7%), 32 females (53.3%), with a mean age (minimum-maximum): 10.48 ± 4.83 (3-18 years). This retrospective case-control study was carried out in collaboration with the Department of Medical Genetics and Pediatrics, Çanakkale Onsekiz Mart University, Çanakkale, Turkey, between March 2012 and October 2013.

Genotyping. Peripheral blood samples (collected in vacutainers containing EDTA as anticoagulant) and buccal smears were used for genomic DNA isolation, and this was carried out by the spin-column method (Roche, Mannheim, Germany). The *MEFV* gene profiles for the current FMF cohort were genotyped by pyrosequencing and direct Sanger sequencing techniques. The 22 common pathogenic variants profiles (p.Glu148Gln, p.Pro369Ser, p.His478Tyr, p.Phe479Leu, p.Ser675Asn, p.Gly678Glu, p.Met680Leu, p.Met680Ile (G>A), p.Met680Ile (G>C), p.Thr681Ile, p.(Ile692del), p.Met694Val, p.Met694Leu, p.Met694Ile, p.Lys695Arg, p.Lys695Met, p.Arg718Ser, p.Ile720Met, p.Val722Met, p.Val726Ala, p.Ala744Ser and p.Arg761 His) were genotyped by pyrosequencing (Qiagen, Hilden, Germany). Some patients who had clinical features without mutated pyrosequencing profiles were genotyped for *MEFV* exon 2 and 10 by direct sequencing analysis in the current cohort. The GML (GML AG, Wollerau, Switzerland) kit for specific FMF sequencing was used for target exon genotyping. The polymerase chain reaction (PCR) products were purified and sequenced on both strands by an ABI PRISM® 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Statistical Analysis. Alternative mutated frequencies for the *MEFV* gene in children presenting with FMF and some clinical findings were compared using Pearson χ^2 and multiple logistic regression analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 19 (SPSS Inc., Chicago, IL, USA) and a p value <0.05 was considered statistically significant.

RESULTS

The cohort was composed of 60 FMF children with mean ages of 10.48 ± 4.83 (3-18 years), and a 28 male (46.7%) to 32 female (53.3%) ratio of 1:1.14. Various combinations and point pathogenic variants were detected in all patients. Forty-six (70.0%) were heterozygous, six (10.0%) were homozygous and 12 (20.0%) were compound pathogenic variant profiles (Table 1). The genetic analysis of the current 60 mutated FMF children revealed that p.Met694Val was the most frequent pathogenic variant, followed by p.Glu148Gln, p.Met680Ile, p.Arg202Gln, p.Val726Ala, p.Pro369Ser and p.Lys695Arg (Table 2).

The main clinical features of the patients were as follows: parental consanguinity was detected in eight (13.3%), appendectomy was detected in four (6.7%), abdominal pain was observed in 32 (53.3%), colchicine

Table 1. Analysis of presenting gender and clinical manifestations of familial Mediterranean fever cases in the current study.

Clinical Characteristics	FMF Patients (*n* and %)
Mean age (3-18 years)	10.48 ± 4.83
Gender:	
males	28 (46.7)
females	32 (53.3)
Pathogenic variant type:	
heterozygous	42 (70.0)
homozygous	6 (10.0)
compound	12 (20.0)
Appendectomy history:	
yes	4 (6.7)
no	56 (93.3)
Parental consanguinity:	
yes	8 (13.3)
no	52 (86.7)
Erysipelas-like erythema:	
yes	3 (5.0)
no	57 (95.0)
Fever:	
yes	14 (23.3)
no	46 (76.6)
Arthritis:	
yes	14 (23.3)
no	46 (76.6)
Abdominal pain:	
yes	32 (53.3)
no	28 (46.7)
Colchicine therapy (1-2 mg/day):	
treated	48 (80.0)
untreated	12 (20.0)

FMF: familial Mediterranean fever; *MEFV* gene: Mediterranean fever gene.

Table 2. Frequency of common clinical manifestations related to the 12 pathogenic variant types in the presented cases and genotype-phenotype correlation in patients with familial Mediterranean fever according to the method of Mor *et al.* [11].

	FMF Patients		Clinical Characteristics											
			Erythema			Fever			Abdominal Pain			Arthritis		
Mutation Type	*n*	%	*n*	With (%)	Total (%)	*n*	With (%)	Total (%)	*n*	With (%)	Total (%)	*n*	With (%)	Total (%)
p.Met694Val	12	20.0	2	66.7	3.3	3	21.4	5.0	6	18.8	10.0	3	21.4	5.0
p.Glu148Gln	8	13.3	0	–	–	0	–	–	4	12.5	6.7	1	7.1	1.7
p.Met680Ile	7	11.7	0	–	–	1	7.1	1.7	4	12.5	6.7	2	14.3	3.3
p.Arg202Gln	7	11.7	0	–	–	3	21.4	5.0	5	15.6	8.3	2	14.3	3.3
p.Val726Ala	4	6.7	0	–	–	0	–	–	2	6.3	3.3	0	–	–
p.Pro369Ser	3	5.0	1	33.3	1.7	2	14.3	3.3	2	6.3	3.3	3	21.4	5.0
p.Lys695Arg	3	5.0	0	–	–	0	–	–	1	3.1	1.7	2	14.3	3.3
p.Arg761His	2	3.3	0	–	–	1	7.1	1.7	2	6.3	3.3	0	–	–
IL28B	1	1.7	0	–	–	1	7.1	1.7	1	3.1	1.7	0	–	–
p.Glu244Asp	1	1.7	0	–	–	0	–	–	0	–	–	0	–	–
p.Met680Ile/p.Met694Val	4	6.7	0	–	–	0	–	–	2	6.3	3.3	1	7.1	1.7
p.Met694Val/p.Met694Ile	2	3.3	0	–	–	0	–	–	0	–	–	0	–	–
p.Glu148Gln/p.Met694Val	1	1.7	0	–	–	0	–	–	0	–	–	0	–	–
p.Met680Leu/p.Glu148Gln	1	1.7	0	–	–	2	14.3	3.3	1	3.1	1.7	0	–	–
p.Arg200Gln/p.Met694Val	1	1.7	0	–	–	0	–	–	0	–	–	0	–	–
p.Val726Ala/p.Arg202Gln	1	1.7	0	–	–	1	7.1	1.7	1	3.1	1.7	0	–	–
p.Pro369Ser/p.Glu148Gln	1	1.7	0	–	–	0	–	–	1	3.1	1.7	0	–	–
p.Lys695Arg/p.Arg202Gln/p.Glu244Asp	1	1.7	0	–	–	0	–	–	0	–	–	0	–	–
Total	60		3	100.0	5.0	14	100.0	23.4	32	100.0	53.4	14	100.0	23.3

FMF: familial Mediterranean fever.

therapy in 48 (80%), fever in 14 (23.3%), arthritis in 14 (23.3%) and erysipelas-like erythema in three (5.0%). The detected pathogenic variants were mainly located at codons p.Met694Val, p.Glu148Gln, p.Met6801le, p.Arg202Gln, p.Val726Ala, p.Pro369Ser and p.Lys695Arg. The most common pathogenic variant was the p.Met694Val heterozygote (20.0%), followed by the p.Glu148Gln heterozygote (13.3%). The p.Met680Ile, p.Arg202Gln, p.Val726 Ala, p.Pro369Ser and p.Lys695Arg pathogenic variants were 11.7, 11.7, 6.7, 5.0 and 5.0%, respectively.

Table 2 shows the pathogenic variant prevalence as a function of the clinical characteristics in the current FMF cohort. The compound pathogenic variants of p.Met680 Leu and p.Glu148Gln were frequently found in 14.3% of the fever cases. Notably, both the p.Met694Val and p.Met694Ile pathogenic variants were found in 6.3% of the abdominal pain group, and in 7.1% of the arthritis group (Table 2). Phenotype severity was evaluated according to the subsequent genotype (11) in 60 patients (Table 2).

No difference was found when FMF patients carrying two mutated alleles (homozygous or compound heterozygous) were compared with those carrying only one mutated allele (heterozygous) ($p > 0.05$). Two heterozygous pathogenic variants at codon p.Arg202Gln, one at codon p.Lys695 Arg and one compound heterozygous pathogenic variant at codons p.Met680Ile/p.Met694Ile were detected in children with evidence of an appendectomy. Two heterozygous pathogenic variants at codon p.Met694Val and one at codon p.Pro369Ser were detected in three children with erythema.

Genotype results for 32 children (53.4%) with abdominal pain showed: two homozygotes for p.Met694Val, two homozygotes for p.Met680Ile and 20 heterozygotes for the p.Met694Val, p.Glu148Gln, p.Met680Ile, p.Val726Ala and p.Arg761His codons, and five compound heterozygotes for the codons p.Met680Ile/p.Met694Val, p.Met680 Leu/p.Glu148Gln, p.Val726Ala/p.Arg202Gln and p.Pro 369Ser/p.Glu148Gln (Table 2).

Ten children with fever showed heterozygous pathogenic variants for p.Met694Val (three patients), p.Metl80 Ile (one patient), p.Arg202Gln (three patients), p.Pro369 Ser (two patients) and IL-28β (one patient). Four children

with fever showed compound heterozygous pathogenic variants for codons p.Met680Leu/Pro, p.Glu148Gln and p.Val726Ala/p.Arg202Gln (Table 2).

One compound heterozygous pathogenic variant at codons p.Met694Val/p.Met680Ile, one homozygous pathogenic variant at codon p.Met694Val and 12 heterozygous pathogenic variants at codons p.Met694Val, p.Met680Ile, p.Lys695Arg, p.Glu148Gln, p.Arg202Gln, p.Pro396Ser were detected in children with arthritis. Forty-eight FMF children (80.0%) were treated with colchicine (1-2 mg/ per day). One patient was unresponsive to the colchicine therapy (Table 1).

DISCUSSION

We studied the spectrum of *MEFV* gene distribution and the clinical characteristics of patients who have *MEFV* gene pathogenic variants. The most common pathogenic variant seen in our country was also prevalent for our region. Of the three patients with a homozygous pathogenic variant, one had arthritis and two had abdominal pain. All the other clinical signs belonged to heterozygous or compound heterozygous pathogenic variant groups.

Abdominal pain is the most common symptom and is seen in 75.0-90.0% of patients. It usually starts suddenly, localized to a quadrant or all quadrants. It has a very broad spectrum ranging from mild abdominal to severe peritonitis. It was also the most common symptom in our study, with an incidence of 53.3% (32 patients). In the study by Kaşifoğlu *et al.* [21], it was reported to be 94.6% and it was more prominent in p.Met694Val gene pathogenic variants. In this study, abdominal pain was found to be more common in the homozygous and compound heterozygous p.Met694Val (eight), p.Met680Ile (six), p.Arg202 Gln (six) and p.Glu148Gln (five) pathogenic variants.

Four patients (6.7%) had a history of appendectomy. In the study of the Turkish FMF group it was reported to be 19.0% [16]. Yolbaş *et al.* [22] showed that in patients initially diagnosed with appendicitis, most had the p.Met694 Val pathogenic variant (19.0%). In our patients there were different pathogenic variants, but the number of patients was few and the geographical region of our study was different.

In the case of FMF, the fever generally had a broad spectrum in terms of degree and duration. Afebrile attacks were rarely seen [21]. In our study, 14 (23.3%) patients had febrile attacks. In these patients, the most common pathogenic variants were p.Met694Val (three), p.Arg202 Gln (three) and p.Pro369Ser (two).

Arthritis is another common condition found in FMF [14]. It is generally acute or subacute but in 5.0% of cases it can be chronic. In a multicenter study by Kaşifoğlu *et al.* [21], the incidence of arthritis was reported as 39.8%. In this study, it was reported in 14 patients (23.3%) and the most common pathogenic variants in these patients were p.Met694Val (four), p.Met680Ile (three), p.Pro369Ser (three) and p.Arg202 Gln (two).

An erysipelas-like rash was seen in 3.0-46.0% of FMF patients [14,16,23]. It was more common in patients with arthritis. In our study, three patients (5.0%) had an erysipelas-like rash. In the case of p.Met694Val and p.Pro369 Ser pathogenic variants, arthritis-rash association was more common.

Tunca *et al.* [16] in their multicenter study, reported that the most common pathogenic variant in the Turkish population was p.Met694Val (51.4%), followed by p.Met 680Ile (14.4%) and p.Val726Ala (8.6%). In another multicenter study from Turkey, the p.Met694Val pathogenic variant was again the most common with an incidence of 24.0% [21]. In our study, the incidence of the p.Met694Val pathogenic variant was 20.0% and it was the most common of the pathogenic variants. This demonstrated that our region is similar to the general population of Turkey in terms of FMF pathogenic variants.

The second most common pathogenic variant in this study was found to be p.Glu148Gln (13.3%), which is similar to the finding of the study by Ülgenalp [24] for the Aegean region. This may be due to the proximity of the two regions. Although the incidence of p.Glu148Gln was not specified in the report of the Turkish FMF Study Group, Yılmaz *et al.* [25] reported it to be 3.5% in Turkish FMF patients. They also discovered that 12.0% of the healthy population had the p.Glu148Gln pathogenic variant and claimed that this variant causes mild clinical form [25]. In contrast Topaloğlu *et al.* [26] reported that patients with homozygous p.Glu148Gln pathogenic variants are symptomatic and require treatment. In our study, patients with heterozygous and compound heterozygous p.Glu148 Gln pathogenic variants had arthritis and abdominal pain and they also required treatment.

In conclusion, all patients were clinically examined according to the Tell-Hashomer FMF criteria and were screened genetically for the 16 common *MEFV* pathogenic variants. Various pathogenic variants were detected in all children examined (100.0%). The most frequent pathogenic variant was p.Met694Val followed by p.Glu148Gln, p.Met6801le, p.Arg202Gln, p.Val726Ala, p.Pro369Ser and p.Lys695Arg. These results indicate that the Çanakkale

population has a wide range of heterozygous mutation carriers of the *MEFV* gene and the mutated p.Glu148Gln allele showed a higher incidence when compared to other Mediterranean children. The results indicated that not only clinical characteristics, but also genotyping of the *MEFV* gene is needed to establish the correct diagnosis of carriers and/or FMF children and other family members. The heterozygous carriers (especially codons p.Met694Val, p.Glu148 Gln and/or compound heterozygotes and compound mutated patients showed the same clinical characteristics as homozygous children in the current report. The results also demonstrated that carriers showed a good response to col-chicine therapy and that this treatment can play a crucial role in heterozygous and compound heterozygous groups as well as in the homozygous group.

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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