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ORIGINAL ARTICLE – OPEN ACCESS

Exon-2 Genotypes May Explain Typical Clinical Features of Familial Mediterranean Fever with Milder Disease Activity

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is the most prevalent monogenic autoinflammatory disease worldwide. The diagnosis is primarily clinical, based on severity of the disease, and confirmed by mutations of the MEFV gene. The aim of this study was to evaluate the effect of exon-2 genotypic variants on clinical signs and symptoms and the severity of FMF in children in comparison with those with an exon-10 genotypic variant.

Materials and Methods: The demographic, clinical, and laboratory data of 164 pediatric FMF patients were evaluated. The patients were classified into 3 groups according to MEFV mutations: patients with a variation in only the exon-2 genotype, both the exon-2 and exon-10 genotypes, and only the exon-10 genotype.

Results: There was no statistically significant difference between the 3 groups in terms of the sex or age at diagnosis, medical history of recurrent tonsillitis, history of appendectomy, or anthropometric features (p>0.05, for both parameters). However, the median age at the first attack was significantly lower in patients with only an exon-10 genotypic variant (median: 4.16 years [interquartile range: 2.5-5.5 years]) (p=0.038). Evaluation of the clinical features of all of the groups revealed that the frequency of attack and attack-free period symptoms were similar (p>0.05). However, the median disease severity score was lower in patients with only exon-2 genotypic variants than patients with exon-10 and compound heterozygous genotype variants (p=0.017).

Conclusion: FMF should be carefully evaluated according to the genotypic and phenotypic characteristics; all potential MEFV gene mutations should be considered. Variants of exon-2 appear to result in milder clinical symptoms in comparison with exon-10 variants.

Keywords: Arthritis, exon-2, familial Mediterranean fever, MEFV mutations, severity score

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INTRODUCTION

Familial Mediterranean fever (FMF) is the most common monogenic hereditary autoinflammatory disease in the world, and is most often seen in families originating from the Eastern Mediterranean region, including Turkey (1). Self-limiting recurrent attacks, which can include fever, peritonitis, pleuritis, pericarditis, and synovitis, are characteristic features of the disease (2). The underlying pathophysiology of the attacks is the exaggerated secretion of interleukin (IL) 1 beta (3).

A mutation responsible for the disease was identified in 1997 in the MEFV gene, located on the short arm of chromosome 16 (16p13.3). The MEFV gene encodes the protein pyrin (marenostrin), which regulates the transformation of pro-IL 1 to its active form (4). This gene has 10 exons and to date, 379 different variants have been reported in exons 2, 3, 5, and 10 (5). The distribution and diversity of these genetic variants differs. Exon-10 variants, such as M694V, M680I, and V726A, in addition to exon-2 genotypic variants, such as R202Q and E148Q, are the most common genotypic alterations seen in Turkey (6–8). Although a relationship between exon-10 mutations and disease severity has been well established and is widely accepted, the effects of common genotypic mutations in exon-2, such as E148Q and R202Q, on the disease have not yet been clarified (9, 10). The R202Q genotype (c.605G>A) was first described as a polymorphism in 1998 by Bernot et al. (11). Later studies revealed that this polymorphism was observed more frequently in FMF patients than in the healthy population, and authors suggested that this might be a disease-causing genotype (12–14). Similarly, E148Q (c.442G>C) is also situated in exon 2, and the clinical implications are not yet clear (15). Early reports suggested that it may be a disease-causing mutation with low penetrance (15, 16). However, the exact role in an FMF diagnosis is not known, and it is most often regarded as a variation rather than a mutation (17, 18). The Infevers genetic database describes E148Q as a functional polymorphism (19).

The aim of this study was to evaluate the effect of exon-2 genotypic changes on the clinical signs and symptoms and the severity of FMF in children in comparison with those with exon-10 genotypic variants.

MATERIALS and METHODS

Ethics approval was obtained from the Dokuz Eylül University Ethics Committee on February 22, 2021 (no: 2021/06-33).

Patients

The charts of 164 pediatric FMF patients who were followed up between 1990 and 2020 at the Dokuz Eylül University Department of Pediatric Rheumatology were retrospectively analyzed. Patients were diagnosed as FMF based on the Ankara criteria (20). Patients with R202Q, E148Q, and exon-10 genotypic variants were selected from 1100 pediatric FMF patients. In all, 63 patients with only an exon-2 genotypic variant, 71 patients with compound heterozygous exon-2 and exon-10 genotypic variants, and 30 patients with only an exon-10 variant were included in this study.

Demographic, Clinical and Laboratory Features

Demographic and clinical data of age, sex, body weight and height at the last visit, age at the first attack and diagnosis, length of time until diagnosis, and complaints during attacks were reviewed. Details of any family history related to FMF or consanguineous marriage were also noted. Body weight and height percentiles were calculated according to the references provided by Neyzi et al. (21). All of the patients were treated with colchicine at a dosage adjusted for age and body weight; none received biological agents. The efficacy of treatment was assessed using the FMF50 score (22). Musculoskeletal complaints in attack-free periods (exercise-induced leg pain, enthesitis, myalgia, etc.), any medical history of recurrent tonsillitis, surgical history of appendectomy, and daily colchicine doses were recorded. The severity of disease was assessed using the FMF severity score defined by Pras et al. (23). Hematological parameter values (hemoglobin, white blood cell, and platelet counts, as well as the neutrophil/lymphocyte ratio) were also recorded from an attack-free period (preferably at the last visit). In addition, acute phase responses (erythrocyte sedimentation rate and C-reactive protein level), liver and kidney function test findings (creatine and alanine aminotransferase), and urine protein excretion results were also noted.

Genetic Analysis

The results of MEFV gene analysis of all 164 patients were reviewed. The genetic analyses were performed by evaluating DNA samples obtained from peripheral blood, using the real-time polymerized chain reaction (RT-PCR) method, a Cobas z480 RT-PCR LightCycler device and a SimpleProbe (Roche Diagnostics, Basel, Switzerland) with a LightSNiP assay kit (TIB Molbiol, Berlin, Germany). The 9 most common variants (E148Q, R202Q, M680I, M694V, M694I, K695R, V726A, R761H, and A744S) were noted.

Statistical Analysis

The statistical analysis was performed using SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was performed to evaluate the homogeneity of the values. Normally distributed values were reported as the mean±SD, while heterogeneously distributed values were reported as the median and interquartile range (IQR; 25^{th}–75^{th} percentile). A chi-squared test was used to define categorical differences (gender) between groups. The Kruskal-Wallis test was used to compare non-parametric and numeric values, while one-way analysis of variance (ANOVA) was used for numeric and parametric values. Dunn's test was used to test multiple comparisons following Kruskall-Wallis analysis. Power analysis of this study conducted using the G*Power 3.1.9.4 program (Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A.) determined a power of 0.81. ANOVA F tests were used to further assess variability. $P<0.05$ was considered statistically significant.

RESULTS

Demographic, Clinical, and Laboratory Results

A total of 164 patients, 79 girls (48.2%) and 85 boys (51.8%), with a median age of 9.4 years (IQR: 7.4–11.6 years) were included in the study. The median age at the time of the first attack was 5 years (IQR: 3–9.9 years) and 7 years (IQR: 4.5–11 years) at diagnosis. The median length of time until diagnosis was 12 months (IQR: 6–24 months). The median body weight and height percentile was 52 (26–85) and 70 (35–86), respectively.

The most common symptom was a fever, observed in 136 patients (82.9%), followed by abdominal pain in 129 patients (78.7%), arthralgia in 75 (45.7%), arthritis in 33 (20.1%), chest pain in 11 (6.7%), and orchitis in 1 patient (0.6%). Forty-nine patients (29.9%) had musculoskeletal symptoms in an attack-free period. A history of recurrent tonsillitis was observed in 19 (11.6%) and a surgical history of appendectomy was seen in 5 (3%) patients. The laboratory features are presented in Table 1.

Genetic Assessment Results

The most common mutations seen in the MEFV gene were a compound heterozygous M694V/R202Q variant in 26 patients (15.9%) and a R202Q/E148Q variant in 19 patients (11.5%). The MEFV gene analysis of all of the patients is provided in Table 2.

Comparison of Exon-2 and Exon-10 Genotypes

The patients were classified into 3 groups according to MEFV gene mutation: Group 1 had only exon-2 genotypic variants, Group 2 had both exon-2 and exon-10 genotypic variants, and Group 3 had only exon-10 genotypic variants.

There was no statistically significant difference between the 3 groups in terms of sex or age at the time of diagnosis, the medical history of recurrent tonsillitis, surgical history of appendectomy, or anthropometric features ($p>0.05$, for both parameters). A positive family history of FMF was lowest in Group 1 (n=15, 24.2%) ($p=0.021$). The median age at the first attack was significantly lower in Group 3 (median: 4.16 years [IQR: 2.5–5.5 years]) ($p=0.038$) and the length of time until diagnosis was lowest in Group 2 (median: 11 months [IQR: 4–18 months]) ($p=0.016$).

The clinical features of the frequency of attack and the attack-free-period symptoms of all of the groups were similar ($p>0.05$). However, the median disease severity score was lower in Group 1 than in Groups 2 and 3 ($p=0.023$). The laboratory parameters in the attack-free period did not differ significantly between the 3 groups ($p>0.05$) (Table 3).

The patients carrying only exon-2 genotypic variants were further classified and compared in order to see if there was any clinical dif-

Table 1. Demographic, anthropometric, clinical, and laboratory features of 164 FMF patients

Gender (female/male)	79/85
Age (years)	9.4 (7.4–11.6)
Age at the first attack (years)	5 (3–9.9)
Age at diagnosis (years)	7.0 (4.5–11.0)
Time until diagnosis (months)	12 (6–24)
Family history of FMF (first- and second-degree relatives)	62 (37.8%)
History of consanguineous marriage (first- and second-degree relatives)	11 (6.7%)
Medical history of recurrent tonsillitis	19 (11.6%)
Surgical history of appendectomy	5 (3%)
Percentage of body weight (%)	52 (26–85)
Percentage of body height (%)	70 (35–86)
Daily colchicine dosage (mg/day)	1.0 (0.5–1.0)
Symptoms of FMF attacks	
Fever	136 (82.9%)
Abdominal pain	129 (78.7)
Arthralgia	75 (45.7%)
Arthritis	33 (20.6%)
Chest pain	11 (6.7%)
Orchitis	1 (0.6%)
Musculoskeletal symptoms in attack-free period	49 (29.9%)
Laboratory features in attack-free period	
WBC	7540±1919*
Hb	12.8±1.2*
Plt	316.6±88.1*
NLR	1.2 (0.8–1.6)
CRP	0.75 (0.3–2.3)
ESR	7 (3–13)
ALT	17 (13–24)
Cr	0.43 (0.34–0.56)

P<0.05; Median (25–75th percentiles); *: Mean±SD. ALT: Alanine aminotransferase; Cr: Creatinine; CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate; FMF: Familial Mediterranean fever; Hb: Hemoglobin; Plt: Platelet; NLR: Neutrophil/lymphocyte ratio; WBC: White blood cell

Table 2. Distribution of mutations observed in the MEFV gene

M694V/R202Q	26 (15.9%)
R202Q/E148Q	19 (11.5%)
R202Q/R202Q	16 (9.8%)
E148Q	15 (9.1%)
R202Q	13 (7.9%)
M694V/E148Q	10 (6.1%)
M694V	8 (4.9%)
M694V/M694V/R202Q/R202Q	6 (3.7%)
M694V/M680I/R202Q	5 (3%)
M694V/M694V/R202Q	5 (3%)
V726A	5 (3%)
M694V/M694V	4 (2.4%)
M680I/E148Q	4 (2.4%)
M694V/R202Q/R202Q	3 (1.8%)
K695R/E148Q	3 (1.8%)
V726A/E148Q	3 (1.8%)
M694V/E148Q/R202Q	2 (1.2%)
K695R	2 (1.2%)
R761H	2 (1.2%)
A744S	2 (1.2%)
M680I	1 (0.6%)
M680I/R202Q	1 (0.6%)
M694V/R761H	1 (0.6%)
M694V/M680I	1 (0.6%)
M680I/V726A	1 (0.6%)
M680I/V726A/R202Q	1 (0.6%)
M694V/A744S/R202Q	1 (0.6%)
M680I/R761H	1 (0.6%)
M680I/A744S/R202Q	1 (0.6%)
A744S/R202Q	1 (0.6%)
V726A/R202Q	1 (0.6%)

ference between the groups. Four subgroups were created: Group 1: R202Q homozygous (n=16), Group 2: R202Q heterozygous (n=13), Group 3: E148Q heterozygous (n=15), and Group 4: E148Q/R202Q compound heterozygous. No statistically significant clinical difference was observed (p>0.05).

DISCUSSION

Several genotypic changes in the MEFV gene can play role in the pathogenesis of FMF, which can affect the clinical severity. The findings of this study indicated that an exon-2 genotypic variant, such as E148Q and R202Q, could be defined as a disease-causing genotypic alteration in pediatric FMF patients, with milder disease severity and a later age of disease onset compared with exon-10 mutations.

There are contradicting data in the literature regarding exon-2 genotypes, which were most often defined as genetic polymorphisms when first described. R202Q is the most common genotypic variant (24, 25). It was defined as a common polymorphism in the first reported description (13). Özturk et al. (13) reported that a group of patients with a homozygous R202Q genotype and a clinical phenotype of FMF responded to colchicine. Yiğit et al. (14) observed that the rate of an R202Q heterozygous genotype was similar in both FMF and healthy groups, while patients with an R202Q homozygote genotype had typical FMF symptoms (14.7% vs 2.7%). Another study by Nursal et al. (26) found that R202Q might be related to FMF-associated AA amyloidosis, and they suggested that it should be evaluated as a disease-causing mutation for Turkish FMF patients (26).

Table 3. Comparison of patients in terms of anthropometric, demographic, clinical, and laboratory features according to MEFV genotype

	Group 1 Only exon-2 n=63	Group 2 Exon-10/exon-2 n=71	Group 3 Only exon-10 n=30	p
Gender (female/male)	26/36	38/34	15/15	0.438
Age at first attack (years)	4.8 (3.8–10)	5.7 (3–10)	4.1 (2.5–5.5)¥	0.039
Age at diagnosis (years)	7.1 (4.4–11)	7 (4.5–11)	5.5 (4.8–9)	0.058
Time until diagnosis (months)	12 (6–24.5)	11 (4–18)¥	12 (7–33)	0.019
Family history of FMF (1st and 2nd degree relatives)	15 (24.2%)	33 (45.8%)¥	14 (46.7%)	0.015
History of consanguineous marriage (1st and 2nd degree relatives)	3 (4.8%)	5 (6.9%)	3 (1.8)	0.635
Medical history of recurrent tonsillitis	7 (11.3%)	8 (11.1%)	4 (13.3%)	0.949
Surgical history of appendectomy	2 (3.2%)	3 (4.2%)	0	
Percentage of body weight (%)	41 (15–76)	51 (31–95)	85 (30–95)	0.056
Percentage of body height (%)	67 (30–85)	66 (35–87)	76 (35–86)	0.787
FMF severity score (points)	5 (4–6)¥	5 (6–7)	6 (5–6.25)	0.017
Daily colchicine (mg/day)	0.87 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (0.9–1.1)	0.976
Symptoms of attacks				
Fever	48 (77.4%)	60 (83.3%)	28 (93.3%)	0.158
Abdominal pain	51 (82.3%)	54 (75%)	24 (80%)	0.577
Arthralgia	29 (46.8%)	32 (44.4%)	14 (46.7%)	0.945
Arthritis	13 (21%)	14 (19.4%)	6 (20%)	0.966
Chest pain	2 (3.2%)	5 (6.9%)	4 (13.3%)	0.203
Orchitis	0	1 (1.4%)	0	
Musculoskeletal symptoms in attack-free period	19 (30.6%)	19 (26.4%)	11 (36.7%)	0.578
Laboratory features in attack-free period				
WBC	7407.9±1660	7646.6±2132	7470.6±1760	0.616
Hb	12.87±1.12	12.75±1.2	12.67±1.0	0.111
Plt	313.7±79.05	320.1±98.1	310.76±72.9	0.640
NLR	1.1 (0.8–1.6)	1.3 (0.9–1.6)	1.2 (0.7–1.4)	0.554
CRP	0.45 (0.3–1.1)	0.95 (0.4–3.7)	0.35 (0.7–3.1)	0.058
ESR	6.5 (3–13.2)	14 (8–33)	5 (3–10)	0.276
ALT	18 (12.8–22)	15 (13–24)	20 (13.5–24.5)	0.829
Cr	0.41 (0.31–0.56)	0.44 (0.38–0.54)	0.44 (0.36–0.54)	0.464

P<0.05; median (25–75th percentile); *: Mean±SD; ¥: Kruskall-Wallis, Dunn's test. ALT: Alanine aminotransferase; Cr: Creatinine; CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate; FMF: Familial Mediterranean fever; Hb: Hemoglobin; Plt: Platelet; NLR: Neutrophil/lymphocyte ratio; WBC: White blood cell

E148Q is another genotypic alteration in exon 2. Aksentijevich et al. (15) described it as a mild disease-causing mutation with low penetrance in a Jewish population. Topaloğlu et al. (16) reported that among 26 Turkish FMF patients with a homozygous E148Q genotype, 22 had typical FMF attacks, and they defined this genotype as a disease-causing genotypic mutation. In contrast, Ben-Chetrit et al. (18), from Israel, reported many cases and family members with E148Q genotype with no attacks and commented that E148Q was not significantly pathogenic. Tchernitchko et al. (17), in a report from France, found their population-based study that the frequency of E148Q was similar between FMF and healthy control groups, and they described it as a benign polymorphism, not a disease-causing mutation.

In the current study, 63 patients with only an exon-2 genotypic variant (R202Q or E148Q), were clinically diagnosed as FMF, and all of them responded to colchicine treatment. They also had similar clinical features in attack and attack-free periods to those with exon-10 variations. These findings indicate that exon-2 genotypic variants might be defined as a pathogenic mutation in symptomatic patients in Turkey.

Alterations in the genotypic characteristics of the disease based on geographical and epigenetic factors lead to variation in phenotypic characteristics. In the literature, it has been demonstrated that exon 10 alterations were associated with early and severe attacks, severe joint complaints, and increased amyloidosis risk (6–10). There are also studies that have noted that exon 2 changes also affected clinical findings, and reflected a milder disease course. It has

been reported in recent studies that pediatric patients with exon 2 genotypic variants had clinical symptoms of FMF, but the first attack occurred at an older age, and the severity of the disease was milder than that of those with exon-10 variants (23, 27). Our findings revealed a lower disease severity score in patients with exon-2 genotypic variants compared with exon-10 variants. In addition, the results showed that those with exon-10 genotypic variants had an earlier age of disease onset than those with exon-2 variants. These results are consistent with the literature.

Patients with exon 10 genotypic variants, particularly homozygous M694V, have well-known risk factors related to ongoing chronic inflammation, i.e., consistent acute phase response (28). Balkarlı et al. (29) found an increased risk of metabolic syndrome in patients with an R202Q variant (attributed risk: 4.42), and associated these results with chronic inflammation. Similarly, Yabuuchi et al. (30) reported a case with FMF-related AA-amyloidosis who only had exon-2 and 3 genotypic variants, emphasizing the severity of these genotypical alterations.

This research has some limitations related to our MEFV gene analysis. The study was retrospective in design and used only the available genetic data in patient charts. The RT-PCR method is not able to detect as wide a range of mutations as next-generation sequencing methods, however, it is cost-effective and is generally sufficient for clinical conditions (6–10).

CONCLUSION

Cases of FMF should be carefully evaluated with consideration for genotypic and phenotypic characteristics. Typical FMF clinical findings may be observed in patients with exon-2 genotypic variants, as well as exon 10 variants. Geographic and epigenetic factors may have considerable effects. Additional international studies with varied patient groups (geographic area and ethnicity) will be helpful.

Ethics Committee Approval: The Dokuz Eylül University Clinical Research Ethics Committee granted approval for this study (date: 22.02.2021, number: 2021/06-33).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ST; Design – ST, EÜ; Supervision – EÜ; Resource – ST, HAD, CY, EÜ; Materials – ST, CY, EÜ; Data Collection and/or Processing – ST, CY; Analysis and/or Interpretation – ST, EÜ; Literature Search – ST, EÜ; Writing – ST, EÜ; Critical Reviews – EÜ.

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