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Original Research

The Clinical Characteristics and Prognosis of Exon 2 Mutations in Familial Mediterranean Fever

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ABSTRACT

Objective: It is unclear whether exon 2 mutations are variations or mutations that causes the disease. This study aimed to evaluate the clinical features and prognosis exon 2 mutations in Familial Mediterranean Fever.

Methods: The clinical features, disease severity and prognosis of all patients with at least one exon 2 mutations were evaluated retrospectively. These data were compared separately for homozygous (Group 1), heterozygous (Group 2), compound heterozygous (Group 3), and complex alleles (Group 4), and the data were compared by grouping patients into those with and without exon 10 mutations.

Results: There were a total of 119 patients with exon 2 mutations, including 11.7% in Group 1, 36.1% in Group 2, 21.8% in Group 3, and 30.2% in Group 4 were similar in terms of demographic data, clinical characteristics, and disease course. When compared patients with exon 10 mutations (+) to those with exon 10 mutations (-), the exon 10 mutations (+) group had a higher presence of chest pain (100%, p=0.02) and a significantly higher mean Pras severity score (6.66±1.87, 6.01±1.40; p=0.02). Additionally, a higher number of patients with exon 10 mutation (-) achieved remission with treatment (76 (67.9%), 36 (32.1%); p=0.03).

Conclusion: Exon 2 mutations have a milder course and higher remission rates but they should be considered as Familial Mediterranean Fever disease because of their similar clinical presentation and response to colchicine treatment with exon 10 mutations. Early treatment and close follow-up should be performed.

Keywords: Genetic variation; mutation; genetic disease, inborn; child

INTRODUCTION

Familial Mediterranean Fever (FMF) is a self-limited, recurrent fever syndrome characterized by attacks accompanied by fever, abdominal pain, chest pain, arthritis or arthralgia, and erysipelas-like rash. It is most commonly observed in Turkish, Jewish, Arab, Armenian, and Italian populations. Mutations in the *MEditerranean FeVer* (*MEFV*) gene are responsible for autosomal recessive FMF [1]. The mutations M694V, M680I, M694I, and V726A in exon 10 of the *MEFV* gene are commonly observed [1, 2]. The R202Q and E148Q mutations in exon 2 are also frequently observed in our country [2, 3]. The disease is clinically diagnosed with the support of *MEFV* gene mutation analysis, especially in atypical cases [4].

In FMF, the repeated episodes of polyserositis are a result of the unregulated secretion of interleukin 1-β due to the mutations

in the *MEFV* gene. The disease's clinical manifestation and progression can differ based on the specific genetic mutations involved. Although the impact of exon 10 mutations on disease symptoms and progression has been extensively studied and established, the influence of exon 2 mutations on the disease remains uncertain. The most commonly observed R202Q and E148Q exon 2 mutations were initially described as genetic polymorphisms. However, increasing studies have shown that patients with these mutations also have similar attack characteristics and disease course to patients with exon 10 mutations [5-7]. There is a continuous inflammation in the subclinical periods, except for the attack periods, and subclinical periods has a significant impact on the course and prognosis of the FMF patients. A good understanding and knowledge of the clinical signs and course of the disease provides early diagnosis and treatment, thus providing a better prognosis and disease course.

The objective of this study is to assess the clinical characteristics and progression of exon 2 mutations and to compare the characteristics of this group with the group carrying exon 10 mutations with exon 2 mutations.

MATERIALS AND METHODS

A retrospective analysis was conducted on the medical records of pediatric patients diagnosed with FMF who received follow-up care at the Department of Pediatric Nephrology in the Baskent University Adana Dr. Turgut Noyan Application and Research Center from 2010 to 2022.

Patients who met at least two of Yalçınkaya et al.'s FMF diagnostic criteria, which include fever lasting between 6-72 hours, abdominal pain, chest pain, and arthritis attacks, accompanied by a family history of FMF, were diagnosed with FMF [8]. In the evaluation of *MEFV* gene analysis in the patients, those carrying exon 2 mutations, whose medical records were accessible and who were monitored for a minimum one year, were included in the study.

Main Points;

- It is unclear whether exon 2 mutations, which most commonly observed in our country, are variations or mutations that cause the disease, FMF.
- Exon 2 mutations have a milder course and remission rates are higher than those with exon 10 variants, however with the similarity of clinical findings and response to colchicine treatment, it should be considered as FMF.
- Clinical suspicion should prompt *MEFV* gene analysis to be conducted to confirm the diagnosis.
- In cases where clinical suspicious findings are supported by the presence of genetic analysis, colchicine treatment should also be initiated for exon 2 mutations.

The genetic analysis of the patients was conducted at the Department of Medical Genetics, Baskent University.After isolating DNA from blood samples in tubes containing EDTA, Reverse Hybridization (RH) assay was performed. Twelve FMF mutations were analyzed by RH assay (FMF StripAssay, Viennalab, Vienna, Austria) kit. A multiplex PCR was performed for each patient to amplify exons 2, 3, 5, and 10 of the MEFV gene. PCR products were then hybridized with test strips using the profiblot T48 (Tecan, Grodig, Austria) system with an appropriate program. Interpretation of results followed the manufacturer's instructions.

Patients carrying mutations of the exon 2 gene were grouped as homozygous (Group 1), heterozygous (Group 2), compound heterozygous (Group 3), and those with complex alleles (Group 4). Age, consanguinity and family history, age when symptoms began, age of diagnosis (start of colchicine), time interval from onset of symptoms (fever, abdominal pain, chest pain, arthralgia, arthritis, myalgia, erysipelas-like rash), acute phase reactants (APRs) during attack-free periods (complete blood count, C-reactive protein (CRP), sedimentation rate, fibrinogen, and serum amyloid A (SAA)), colchicine dose for FMF (mg/day), and clinical findings at the end of the follow-up period were retrospectively evaluated in all patients with exon 2 mutations. Additionally, groups divided according to exon 2 mutation types were assessed based on these datas.

Disease severity was calculated according to the Pras disease severity score, and its adaptation for children by Ozen and colleagues were used [9,10]. Pras criteria, including disease onset age, number of attacks within one month, presence of arthritis, erysipelas-like erythema, and amyloidosis, as well as the colchicine dose, were individually scored and recorded. Patients were then grouped as having mild disease (3-5 points), moderate disease (6-8 points), or severe disease (9 points or above), based on their score values. Patients who have no attacks and no subclinical inflammation under the appropriate colchicine dose were considered in remission. Patients whose colchicine was discontinued, some of them had their medication

stopped by their families due to the absence of complaints. In some of them, colchicine was temporarily suspended by us clinicians in patients who were in remission, as their clinical and laboratory parameters were normal and their families wanted not to continue the medication.

The included exon 2 patients were categorized into two groups based on carrying of exon 10 mutations: those who carried the mutation (exon 10 mutation (+)) and those who did not (exon 10 mutation (-)). Demographic and clinical findings were compared between the two groups, and statistically significant differences were identified.

The study was conducted in accordance with the Declaration of Helsinki and local regulations, and it was approved by Baskent University Institutional Review Board. (Project no: KA22/297) and supported by Baskent University Research Fund.

Statistical Analysis

We conducted statistical analysis using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). For normally distributed continuous variables with p-values greater than 0.05 in a Kolmogorov-Smirnov test or Shapiro-Wilk test (n<30), we reported mean values and standard deviations. For non-normally distributed continuous variables, we reported median values. To compare continuous variables between groups, we used either Student's t-test for parametric values or Mann-Whitney U test for non-parametric values. Categorical variables between groups were analyzed using the chi-square test or Fisher's exact test. Statistical significance was determined at a pre-defined level of $p < 0.05$.

RESULTS

Demographic, clinical characteristics, disease severity, prognosis of the patients with exon 2 mutations

The study comprised 119 patients who had been diagnosed with FMF, of whom 69 were male (58%) and 50 were female (42%). Consanguinity history was present in 16 patients (13%), and a family history of FMF was present in 40 patients (34%). The mean age when symptoms began was 57.45±36.03 months, the mean age of diagnosis was 79.66±37.83 months, and the mean delay in diagnosis was 22.87±26.78 months. Prior to starting colchicine treatment, the number of attacks per month was 1 or fewer in 85 patients (71%), 1-2 attacks per month in 32 patients (27%), and more than 2 attacks per month in 2 patients (2%).

The most common symptom observed during FMF attacks was abdominal pain, which was detected in 102 patients (86%). This was followed by fever in 78 patients (66%) and arthralgia in 31 patients (26%). However, arthritis was observed in 9 patients (8%), chest pain in 5 patients (4%), erysipelas-like erythema in 3 patients (3%), and myalgia in only 1 patient (1%). One patient (1%) had vasculitis (IgA vasculitis) accompanying FMF. During attack-free periods, APRs such as SAA and others were found to be elevated in only 5 patients (4%). The disease severity levels of the patients, as determined by the Pras disease severity score, were mild in 43 patients (36%), moderate in 70 patients (59%), and severe in 6 patients (5%). The mean Pras score for all patients was 6.24±1.60. The doses of colchicine used were 1 mg/day in 108 patients (91%) and 1.5 mg/day in 11 patients (9%). None of our patients used colchicine at a dose of 2 mg/day or higher, colchicine treatment was discontinued in 38 patients (32%) during follow-up. Out of the 38 patients whose colchicine was discontinued, 3/4 of them had their medication stopped by their families, in 1/3 of them, colchicine was temporarily suspended by us clinicians. The mean duration of colchicine use in patients who discontinued colchicine treatment was 29.13±21.42 months. Additional treatments with anakinra and canakinumab were administered to 2 patients (2%) who were categorized as severe according to the Pras disease severity score and continued to receive colchicine treatment. The patients included in the study were followed up for a mean of 52.44±31.16 months, and at the end of the follow-up period, remission was observed in 112 patients (94%). Table 1 presents the demographic and clinical profiles of the patients.

Demographic, clinical features and disease severity, prognosis by exon 2 mutation type: homozygous, heterozygous, compound heterozygous, and complex alleles

When the patients carrying exon 2 mutation were grouped according to the type of mutation, 14 patients (11.7%) were in Group 1, 43 patients (36.1%) were in Group 2, 26 patients (21.8%) were in Group 3, and 36 patients (30.2%) were in Group 4. Table 2 presents the demographic and clinical data of patients categorized based on the type of exon 2 mutation. The groups exhibited no significant differences with regard to demographic data and clinical findings. Among exon 2 mutations, 49 patients (41.2%) had at least one variant of E148Q, 60 patients (50.4%) had at least one variant of R202Q, and 10 patients (8.4%) had both variants.

Table 1. Demographic, clinical characteristics, disease severity and prognosis of the patients with exon 2 mutations

	Patients (n= 119)
Male, n (%)	69 (58%)
Consanguinity, n (%)	16 (13%)
Family history of FMF, n (%)	40 (34%)
Age when symptoms began, month (mean±SD)	57.45±36.03
Age of diagnosis, month (mean±SD)	79.66±37.83
Delay in diagnosis, month (mean±SD)	22.87±26.78
Attack frequency, (before colchicine) <1 times/month, n (%) 1-2 times/month, n (%) >2 times/month, n (%)	 85 (71%) 32 (27%) 2 (2%)
Symptoms during attack Abdominal pain, n (%) Fever, n (%) Arthralgia, n (%) Arthritis, n (%) Chest pain, n (%) Erysipelas like erythema, n (%)	 102 (86%) 78 (66%) 31 (26%) 9 (8%) 5 (4%) 3 (3%)
Pras severity score (Pras) (mean±SD)	6.24±1.60
Pras severity category Mild, n (%) Moderate, n (%) Severe, n (%)	 43 (36%) 70 (59%) 6 (5%)
Colchicine treatment discontinued, n (%)	38 (3%2)
Colchicine usage time (those in whom colchicine was discontinued) (mean±SD)	29.13±21.42
Other treatment, n (%) Anakinra, n (%) Canakinumab, n (%)	 2 (2%) 2 (2%)
Remission, n (%)	112 (94%)
Follow-up period, month (mean±SD)	52.44±31.16

Table 2. Demographic, clinical features and disease severity, prognosis by exon 2 mutation type

	Group 1 (n=14, 11.7%)	**Group 2 (n=43, 36.1%)**	**Group 3 (n=26, 21.8%)**	**Group 4 (n=36, 30.2%)**	**p value**
Male, n (%) Female, n (%)	7 (10.1%) 7 (14%)	28 (40.6%) 15 (30%)	13(18.8%) 13 (26%)	21 (30,4%) 15 (30%)	*0.58*
Consanguinity, n (%)	3 (18.8%)	5 (31.3%)	4 (25%)	4 (25%)	*0.77*
Family history of FMF, n (%)	6 (15%)	13 (32.5%)	7 (17.5%)	14 (35%)	*0.63*
Age when symptoms began, month (mean±SD)	59.21±40.54	59.65±33.78	62.04±41.71	50.81±32.94	*0.61*
Age of diagnosis, month (mean±SD)	77.29±47.32	79.23±35.69	82.77±42.74	78.86±33.92	*0.97*
Delay in diagnosis, month (mean±SD)	17.64±24.61	19.16±25.56	20.38±23.43	27.78±33.76	*0.49*
Attack frequency (before colchicine, n (%)) times/month <1 1-2 >2	 8 (9.4%) 5 (15.6%) 1 (50.0%)	 33 (38.8%) 10 (31.3%) -	 21 (24.7%) 4 (12.5%) 1 (50.0%)	 23 (27.1%) 13 (40.6%) -	*0.18*

Symptoms during attack, n (%) Abdominal pain Fever Arthralgia Arthritis Chest pain Erysipelas like erythema, n (%)	12 (11.8%) 10 (12.8%) 3 (9.7%) 2 (22.2%) 1 (20%) 0	33 (32.4%) 27 (34.6%) 12 (38.7%) 2 (22.2%) 0 1 (33.3%)	23 (22.5%) 17(21.8%) 6 (19.4%) 1 (11.1%) 1 (20%) 0	34 (33.3%) 24 (30.8%) 10 (32.3%) 4 (44.4%) 3 (60%) 2 (66.7%)	0.15 0.24 0.93 0.46 0.29 0.49
Pras severity score (Pras) (mean±SD)	6.93±2.02	5.88±1.12	5.92±1.41	6.61±1.90	*0.05*
Pras severity category Mild, n (%) Moderate, n (%) Severe, n (%)	 3 (7%) 9 (12.9%) 2 (33.3%)	 17 (39.5%) 26 (37.1%) -	 12 (27.9%) 13 (18.6%) 1 (16.7%)	 11 (25.6%) 22 (31.4%) 3 (50%)	 *0.25*
High levels of APRs in the attack free period, n (%)	1 (20%)	1 (20%)	2 (40%)	1 (20%)	*0.65*
Remission n (%)	13 (11.6%)	43 (38.4%)	22 (19.6%)	34 (30.4%)	*0.07*
Follow-up period, month(mean±SD)	62.78±41.44	44.25±26.46	54.54±34.17	56.66±28.54	*0.15*

*APRs: Acute phase reactants

Table 3. Differences between those with exon 10 mutations and those without exon 10 mutations in terms of demographic, clinical characteristics, disease severity and prognosis of patients with exon 2 mutations.

	Exon 10 mutation (+) (n=41)	**Exon 10 mutation (-) (n=78)**	**p value**
Male, n Female, n	23 (56.1%) 18 (43.9%)	46 (59.0%) 32 (41.0%)	*0.76*
Consanguinity, n (%)	6 (14.6%)	10 (12.8%)	*0.78*
Family history of FMF, n (%)	16 (39.0%)	24 (30.8%)	*0.37*
Age when symptoms began, month (mean±SD)	48.1539.89	62.3333.05	*0.30*
Age of diagnosis, month (mean±SD)	76.0941.32	81.5336.01	*0.14*
Delay in diagnosis, month (mean±SD)	27.6135.40	20.3820.75	*0.16*
Attack frequency <1 times/month, n (%) 1-2 times/month, n (%) >2 times/month, n (%)	 25 (61.0%) 14 (34.1%) 2 (4.9%)	 60 (76.9%) 18 (23.1%) 0	 *0.05*
Symptoms during attack Abdominal pain, n (%) Fever, n (%) Arthralgia, n (%) Chest pain, n (%) Arthritis, n (%) Erysipelas like erythema, n (%)	 37 (90.2%) 29 (70.7%) 11 (26.8%) 5 (12.2%) 1 (2.4%) 2 (4.9%)	 65 (83.3%) 49 (62.8%) 70 (89.7%) 0 70 (89.7%) 1 (1.3%)	 *0.31* *0.39* *0.23* ***0.02*** *0.13* *0.23*
Pras severity score (mean±SD)	6.661.87	6.011.40	***0.02***
Pras severity category Mild, n (%) Moderate, n (%) Severe, n (%)	 12 (29.3%) 25 (61.0%) 4 (9.7%)	 31 (39.7%) 45 (57.7%) 2 (2.6%)	 *0.16*
High levels of APRs in the attack free period, n (%)	3 (7.3%)	2 (2.6%)	*0.22*
Remission, n (%)	36 (87.8%)	76 (97.4%)	***0.03***
Follow-up period, month(mean±SD)	57.9534.66	49.5428.97	*0.11*

*APRs: acute phase reactants

Differences between patients with exon 2 mutation carrying exon 10 mutation (exon 10 mutation (+)) and patients without exon 10 mutation (exon 10 mutation (-))

Table 3 presents the demographic and clinical features of both patients with and without exon 10 mutation. In the group of patients studied, those who had a mutation in exon 2 were identified, 41 (34.5%) had exon 10 mutation. All 5 patients who experienced chest pain as an attack symptom were exon 10 mutation (+) (12.2%). This result indicate a significant difference between patients with and without exon 10 mutation (p=0.02). Patients with exon 10 mutation had a significantly higher mean disease severity score compared to those without the exon 10 mutation (6.66±1.87 vs. 6.01±1.40; p=0.02). The number of exon 10 mutation (-) patients who achieved remission with treatment was higher (76 (97.4%) vs. 36 (87.8%); p=0.03). Both groups were similar in terms of gender, consanguinity and family history of FMF, age when symptoms began, age of diagnosis, delay in diagnosis, and duration of follow-up. There was no significant difference between the two groups in terms of frequency of attacks, symptoms other than chest pain during attacks, Pras classification and elevation of acute phase reactants during attack-free periods.

DISCUSSION

Our study showed that patients with exon 2 mutations, which are common in our country, exhibit similar clinical characteristics and disease progression as those with exon 10 mutations, and have high remission rates with colchicine treatment. When exon 2 mutation variants were grouped as homozygous, heterozygous, compound heterozygous, and complex alleles, the groups had similar characteristics. However, in patients with exon 10 mutations, chest pain was more frequently reported, the disease course was more severe, and the remission rate was lower to those without exon 10 mutations.

It is known that more commonly seen exon 10 mutations lead to typical clinical findings and a more severe disease in FMF [11]. Benign variants, which are usually found in exon 2, are thought to not cause typical FMF phenotype [12]. The E148Q mutation in exon 2 has been described as an insignificant polymorphism [13], showing no typical phenotype characteristics and being an asymptomatic variant [14, 15]. However, various studies have shown that especially homozygous forms of this mutation are symptomatic and require colchicine treatment [4, 7, 16-18].

The R202Q mutation, initially identified as a genetic polymorphism in exon 2 and classified as a benign variant in the Infevers database (Infevers (2020). *MEFV* sequence variants [online] website https://infevers.umai-montpellier.fr) [13] has been shown to be regionally common in our country and consistent with the known FMF clinic [6, 19, 20]. In our study group consisting of patients with mutations in exon 2, the R202Q variant was found to be more common; 50.4% of the patients had at least one variant of R202Q, and 41.2% had at least one variant of E148Q.

In our study, which included patients diagnosed with FMF and carrying mutations in exon 2, the mean age when symptoms began was found to be 57.45±36.03 months (4.8±3.0 years), and the mean age of diagnosis (start of colchicine treatment) was 79.66±37.83 months (6.64±3.15 years). Based on data collected from a large population of pediatric FMF cases, similar mean age when symptoms began (5.1±3.8 years) and mean age of diagnosis (7.3±4.0 years) were observed [17]. In our study, the most common clinical findings during FMF attacks were abdominal pain (86%), followed by fever (66%), arthralgia (26%), arthritis (8%), chest pain (4%), and erysipelas-like erythema (3%). Similarly, Öztürk et al. reported the frequency of clinical findings as follows: abdominal pain in 88.2% of patients, fever in 86.7%, arthritis in 27.7%, chest pain in 20.2%, myalgia in 23%, and erysipelas-like erythema in 13.1%. However, in this study, the R202Q variant was not included due to its acceptance as a polymorphism [17]. In our study investigating exon 2 mutations, R202Q was identified as the most common exon 2 mutation variant, and similar clinical features were observed. In Kandur et al.'s study comparing M694V/R202Q and M694V/- heterozygous mutations, like our study, they showed that the R202Q mutation was associated with the inflammatory phenotype of FMF and that typical clinical findings of FMF could be observed in patients [21]. To summarize, our findings suggest that the R202Q variant can lead to a clinical phenotype resembling that of FMF patients carrying exon 10 mutations. Furthermore, our study revealed that colchicine treatment resulted in regression of clinical symptoms, decrease in attack frequency and a high remission rate.

In our study, patients with mutations in exon 2 were categorized according to the specific type of mutation, and the frequencies were found to be 11.7% homozygous, 36.1% heterozygous, 21.8% compound heterozygous, and 30.2% complex alleles. In Arpaci et al.'s study, the frequencies of R202Q mutation homozygous, heterozygous, compound heterozygous, and complex alleles

were found to be 4.05%, 30.13%, 8.94%, and 6.86%, respectively [20]. In contrast to our study, complex alleles were found to be less frequent. Our study evaluated not only R202Q mutations but also all exon 2 mutations.

Although not statistically significant, the average PRAS score in patients with homozygous exon 2 mutation (Group 1), the fact that colchine treatment was discontinued in only one patient (resumed in adulthood follow-up), and the lower remission rate compared to other groups indicate that homozygous variants have a more severe course. In a previous study by Aktaş et al., it was shown that patients with homozygous variants had more severe disease severity and a higher rate of amyloidosis compared to heterozygous and compound heterozygous patient groups [22]. However, in a study that determined the phenotypic characteristics of patients carrying the E148Q mutation, although not statistically significant, compound heterozygotes and those with complex alleles had a higher frequency of abdominal pain, fever, arthralgia, arthritis, myalgia, and chest pain than patients homozygous for E148Q [16].

The comparison of individuals homozygous for the E148Q mutation in exon 10 of the *MEFV* gene indicates that the disease course is milder, and onset is later in E148Q homozygotes [16, 18]. Tanatar et al. revealed that patients with mutations in exon 10 exhibited more frequent chest pain, arthritis, erysipelas-like erythema, relapsing fever, and higher PRAS scores than patients homozygous or heterozygous for the E148Q variant. They also found high levels of APRs in individuals with exon 10 mutations during the asymptomatic period and suggested that the E148Q variant leads to a milder disease course [23]. However, as indicated by the various data patients carrying the prevalent exon 10 mutation, M694V, exhibit earlier onset of symptoms, more frequent attacks, and a higher incidence of chest pain when they also carry variants in exon 2. Previous studies have hinted that the co-occurrence of exon 2 variants in patients with exon 10 mutations could impact the progression of FMF in distinct ways [5]. Our study also showed that patients carrying mutations in exon 2 along with exon 10 mutation variants had a higher incidence of chest pain, higher PRAS scores, and lower rates of remission. The co-occurrence of exon 10 mutations, which are associated with a more severe clinical phenotype, and exon 2 mutations may lead to a worsening of the severity of the latter. Nevertheless, it is important to mention that neither our study nor the study conducted by Endo Y. et al. [5] included patients homozygous for the M694V mutation.

Compared to individuals carrying exon 10 mutations, those with R202Q variants did not show any significant differences in demographic, clinical, or laboratory data based on our statistical analysis [6]. Sönmezgöz et al. reported that R202Q is the most common *MEFV* gene variation observed with M694V mutation and that chest pain is prevalent in individuals carrying this variant [24]. Similarly, Aydın et al. found a lower prevalence of chest pain in patients with E148Q compared to those with exon 10 mutations [7]. In our study, a higher rate of chest pain was observed in patients with exon 2 mutations, including exon 10 mutations.

It has been shown that *MEFV* mutations are associated with other rheumatic diseases; the E148Q variant has been frequently associated with IgA vasculitis (IgAV), and polyarteritis nodosa [18, 25]. In our study group, one patient had coexisting IgAV, and *MEFV* gene analysis was a compound heterozygous with M694V/R202Q/E148Q.

Exon 2 mutations compared with those containing exon 10 mutations, did not show significant differences in other clinical findings, as previously demonstrated in other studies [7, 18].

Limitations

Although our study has limitations such as being retrospective, small sample size and relatively short follow-up period, it is thought that it will contribute to the literature by evaluating the common exon 2 mutations in our country. It is expected that future prospective studies with adequate sample size and follow-up times will further support our findings, in which exon 2 mutations compared also with homozygous M694V variants, which are the most common among exon 10 mutations and are associated with severe clinical course.

CONCLUSIONS

In conclusion, although exon 2 mutations have a milder course and remission rates are higher than those with exon 10 variants, with the similarity of clinical findings and response to colchicine treatment, it should be considered as FMF, and early treatment and close follow-up should be performed. Given the high prevalence of FMF in our country, clinical suspicion should prompt *MEFV* gene analysis to be conducted to confirm the diagnosis. Even if there is no homozygous variant, colchicine treatment should be started in case of carrying exon 10 mutation or exon 2 mutation, and close follow-up with FMF disease.

Conflict of interest: The authors have no competing interests to declare that are relevant to the content of this article.

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REFERENCES

[1] Barron K, Kastner DL (2021) Periodic Fever Syndromes and Other Inherited Autoinflammatory Diseases. Textbook of Pediatric Rheumatology. 8 th ed. In; Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, Mellins ED, Fuhlbrigge RC, (eds). Elsevier; Philadelphia: p.525-543.

[2] Yaşar Bilge Ş, Sarı İ, Solmaz D, Şenel S, Emmungil H, Kılıç L, et al (2019) The distribution of MEFV mutations in Turkish FMF patients: multicenter study representing results of Anatolia. Turk J Med Sci. 49(2):472-477. https://doi.org/10.3906/sag-1809-100

[3] Celep G, Durmaz ZH, Erdogan Y, Akpinar S, Kaya SA, Guckan R (2019) The Spectrum of MEFV Gene Mutations and Genotypes in the Middle Northern Region of Turkey. Eurasian J Med. 51(3):252-256. https://doi.org/10.5152/eurasianjmed.2019.18396

[4] Ozen S, Bilginer Y (2014) A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. Nat Rev Rheumatol. 10(3):135-47. https://doi.org/10.1038/nrrheum.2013.174

[5] Endo Y, Koga T, Hara K, Furukawa K, Agematsu K, Yachie A, Masumoto J, Migita K, Kawakami A (2020) The possession of exon 2 or exon 3 variants in the MEFV gene promotes inflammasome activation in Japanese patients with familial Mediterranean fever with a heterozygous exon 10 mutation. Clin Exp Rheumatol. 38 Suppl 127(5):49-52.

[6] Türkuçar S, Adıgüzel H, Yılmaz C., Ünsal E (2021) Effect of R202Q gene alteration on familial Mediterranean fever clinic: a single center experience [R202Q gen değişikliğinin ailesel akdeniz ateşi kliniği üzerine etkisi: tek merkez deneyimi]. Pamukkale Tıp Dergisi. 14 (4), 870-877. ([In Turkish]) https://doi.org/10.31362/patd.885049.

[7] Aydın F, Çakar N, **Özçakar** ZB, Uncu N, Başaran Ö, **Özdel** S, Celikel E, Elhan AH, Yalçınkaya F(2019) Clinical features and disease severity of Turkish FMF children carrying E148Q mutation. J Clin Lab Anal. 33(4):e22852. https://doi.org/10.1002/jcla.22852.

[8] Yalçinkaya F, Ozen S, Ozçakar ZB, Aktay N, Cakar N, Düzova A, Kasapçopur O, Elhan AH, Doganay B, Ekim M, Kara N, Uncu N, Bakkaloglu A (2009) A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) ;48:395-398. https://doi.org/10.1093/rheumatology/ken509

[9] Pras E, Livneh A, Balow JE Jr, Pras E, Kastner DL, Pras M, Langevitz P (1998)Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet. 75(2):216-9. https://doi.org/10.1002/(sici)1096-8628(19980113)75:2<216::aid-ajmg20>3.0.co;2-r

[10] Ozen S, Demirkaya E, Amaryan G, Koné-Paut I, Polat A, Woo P, et al (2014) Paediatric Rheumatology International Trials Organisation; Eurofever Project. Results from a multicentre international registry of familial Mediterranean fever: impact of environment on the expression of a monogenic disease in children. Ann Rheum Dis. 73(4):662-7. https://doi.org/10.1136/annrheumdis-2012-202708

[11] Ben-Chetrit E, Yazici H (2019) Familial Mediterranean fever: different faces around the world. Clinical and Experimental Rheumatology. 37 Suppl 121(6): 18-22.

[12] Accetturo M, D'Uggento AM, Portincasa P, Stella A (2010) Improvement of MEFV gene variants classification to aid treatment decision making in familial Mediterranean fever. Rheumatology. 59 (4): 754-761. https://doi.org/10.1093/rheumatology/kez332

[13] Tufan A, Lachmann HJ (2020) Familial Mediterranean fever, from pathogenesis to treatment: a contemporary

review. Turk J Med Sci. 50(SI-2):1591-1610. https://doi.org/10.3906/sag-2008-11

[14] Aksentijevich I, Torosyan Y, Samuels J, Centola M, Pras E, Chae JJ, Oddoux C, Wood G, Azzaro MP, Palumbo G, Giustolisi R, Pras M, Ostrer H, Kastner DL (1999) Mutation and haplotype studies of familial Mediterranean fever reveal new ancestral relationships and evidence for a high carrier frequency with reduced penetrance in the Ashkenazi Jewish population. Am J Hum Genet. 64(4):949-62. https://doi.org/10.1086/302327

[15] Ben-Chetrit E, Lerer I, Malamud E, Domingo C, Abeliovich D (2000) The E148Q mutation in the MEFV gene: is it a disease-causing mutation or a sequence variant? Hum Mutat. 15(4):385-6. https://doi.org/10.1002/(SICI)1098-1004(200004)15:4<385::AID-HUMU22>3.0.CO;2-A

[16] Topaloglu R, Ozaltin F, Yilmaz E, Ozen S, Balci B, Besbas N, Bakkaloglu A (2005) E148Q is a disease-causing MEFV mutation: a phenotypic evaluation in patients with familial Mediterranean fever. Ann Rheum Dis. 64(5):750-2. https://doi.org/10.1136/ard.2004.026963

[17] Öztürk K, Coşkuner T, Baglan E, Sönmez HE, Yener GO, Çakmak F, Demirkan FG, Tanatar A, Karadag SG, Ozdel S, Demir F, Çakan M, Aktay Ayaz N, Sözeri B (2022) Real-Life Data From the Largest Pediatric Familial Mediterranean Fever Cohort. Front Pediatr. 9:805919. https://doi.org/10.3389/fped.2021.805919

[18] Topaloglu R, Batu ED, Yıldız Ç, Korkmaz E, Özen S, Beşbaş N, Özaltın F (2018) Familial Mediterranean fever patients homozygous for E148Q variant may have milder disease. Int J Rheum Dis. 21(10):1857-1862. https://doi.org/10.1111/1756-185X.12929

[19] Çapraz M, Düz ME (2022) R202Q prevalence in clinically diagnosed Familial Mediterranean Fever patients: 9 years of data analysis from 1570 patients living Central Black Sea region, Turkey. Ir J Med Sci. Nov 28. https://doi.org/10.1007/s11845-022-03233-1

[20] Arpacı A, Doğan S, Erdoğan HF, El Ç, Cura SE (2021) Presentation of a new mutation in FMF and evaluating the frequency of distribution of the MEFV gene mutation in our region with clinical findings. Mol Biol Rep. 48(3):2025-2033. https://doi.org/10.1007/s11033-020-06040-y

[21] Kandur Y, Kocakap DBS, Alpcan A, Tursun S (2022) Clinical significance of MEFV gene variation R202Q. Clin Rheumatol. 41(1):271-274. https://doi.org/10.1007/s10067-021-05906-1

[22] Aktaş A, Karadavut M, Cansu DÜ, Korkmaz C (2019) The influence of genotype on disease severity and concomitant diseases in familial Mediterranean fever patients. Clin Exp Rheumatol. 37 Suppl 121(6):93-97.

[23] Tanatar A, Karadağ ŞG, Sönmez HE, Çakan M, Ayaz NA (2021) Comparison of Pediatric Familial Mediterranean Fever Patients Carrying Only E148Q Variant With the Ones Carrying Homozygous Pathogenic Mutations. J Clin Rheumatol. 27(5):182-186. https://doi.org/10.1097/RHU.0000000000001261

[24] Sönmezgöz E, Özer S, Gül A, Yılmaz R, Kasap T, Takcı Ş, Gümüşer R, Demir O (2019) Clinical and Demographic Evaluation According to MEFV Genes in Patients with Familial Mediterranean Fever. Biochem Genet. 57(2):289-300. https://doi.org/10.1007/s10528-018-9889-y

[25] Ozen S, Ben-Chetrit E, Bakkaloglu A, Gur H, Tinaztepe K, Calguneri M, Turgan C, Turkmen A, Akpolat I, Danaci M, Besbas N, Akpolat T (2001) Polyarteritis nodosa in patients with Familial Mediterranean Fever (FMF): a concomitant disease or a feature of FMF? Semin Arthritis Rheum. 30(4):281-7. https://doi.org/10.1053/sarh.2001.19958

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