American Journal of
Health, Medicine and Nursing Practice
(AJHMN)

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American Journal of Health, Medicine and Nursing Practice
ISSN 2520-4017 (Online)
Vol.10, Issue 5, pp 1 – 10, 2024
www.ajpojournals.org

The Phenotype-Genotype Correlations of FMF Patients: A Single Center Study

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Article history
Submitted 16.06.2024 Revised Version Received 25.07.2024 Accepted 26.08.2024

Abstract

Purpose: Familial Mediterranean Fever (FMF) is an autosomal recessive, auto-inflammatory disease that is characterized by recurrent fever and polyserositis episodes like peritonitis, arthritis, and pleuritis. The disease occurs most commonly in populations of Jewish, Turkish, Armenian, and Arabian origin. We aimed to show the genotype-phenotype relationship in FMF patients in our centre.

Materials and Methods: We conducted a retrospective analysis of the medical registries of 200 FMF pediatric patients from Sisli Hamidiye Etfal Education and Research Hospital, Department of Pediatrics, Pediatric Nephrology Policlinic between 2011 and 2017. The diagnosis was based on the Tel-Hashomer clinical diagnostic criteria. We used the severity score recommended by Pras in 1998. Clinical data and baseline investigations were collected. Mutation analysis was performed by the amplification-refractory mutation system (ARMS)-PCR method.

Findings: Females represented 54% and ages ranged from 40-210 months. The most frequent symptoms were abdominal pain, fever, and arthralgia.Among the 200 patients, 41 (20,5%) were homozygous, 63 (31,5%) were compound heterozygous, and 96 (48%) were heterozygous for MEFV mutations. The first 3 most common mutations were heterozygotus R202Q, M694V/R202Q and heterozygotus E148Q respectively., which was statistically significant. M694V mutation was positive in at least one allele in 72 patients studied. The symptom of fever and arthralgia were found to be significantly higher in patients with M694V mutation. Also, the number of episodes in one year before treatment, PRAS score and the values of fibrinogen during episodes were higher in M694V patients as a result, the age at diagnosis was found to be earlier in patients with homozygotus M694V mutation. The ratio of female gender and myalgia was significantly higher in patinets with the mutation of R202Q homozygotus. The number of episodes in one year before treatment was lower in R202Q patients when compared to the M694V carriers, therefore the initiation age to colchicine was later in the R202Q group which was statistically significant.

İmplications to Theory, Practice and Policy: Our results support the notion that the genotype influences the phenotype as regards clinical manifestations, disease severity, and colchicine response.

Keywords: *Diagnosis, Familial Mediterranean Fever, Genetic, MEFV, Treatment*

1.0 INTRODUCTİON

Familial Mediterranean Fever (FMF) is an autosomal resessive, autoinflammatory disease that is characterazed by recurrent fever and polyserousitis episodes like peritonitis, arthritis and pleuritis (1,2). The disease occurs most commonly in populations of Jewish Turkish Armenian Arab (1,3) . The incidence of the disease is 1/1073 among Turkish population (4,5). Considering the regional distribution, it is known that contrary to its name, it is frequently seen not only in the Mediterranean region but also in all other regions. The diagnosis of FMF is made on the basis of clinical criterias. It is inherited autosomal recessively. The gene ,FMF (MEFV; MEditerranean FeVer) ,is shown on the short arm of 16th chromosome in 1992. A protein that is formed by 781 aminoacids, containing 10 exons and 7781 codones,is encoded by the MEFV gene.

To date, more than 40 disease-related mutations have been identified and these mutations are found in 80-85% of carrier chromosomes. However, genotype-phenotype relationship has not been fully defined yet. Studies show that clinical findings are highly variable from person to person. In this study, in istanbul, where is an ethnically and locally heterogeneous region,we aimed to reveal the genotype- phenotype relationship of 200 patients who were clinically diagnosed with FMF.

Problem Statement

The genotype-phenotype relationship in FMF is still not fully understood, with clinical manifestations varying widely among individuals. A recent study conducted in Istanbul aimed to investigate the genotype-phenotype correlation in 200 pediatric FMF patients. Results of the study showed that patients with the M694V mutation had a more severe clinical course compared to other mutations, with higher disease severity scores and more frequent fever and joint symptoms. Patients with the E148Q mutation exhibited milder symptoms and lower rates of comorbidities. Patients with the R202Q mutation were more likely to experience myalgia and had a lower number of attacks compared to patients with the M694V mutation.

The study also highlighted the importance of family history in diagnosing FMF, as a significant number of patients had family members with the disease. The findings suggest that genotype can influence the clinical presentation of FMF, but other factors such as ethnicity and environmental factors may also play a role. Larger studies are needed to confirm these observations and further explore the genotype-phenotype relationship in FMF.

2.0 MATERİALS AND METHODS

This study was conducted in the clinic of Şişli Hamidiye Etfal Education and Research Hospital, Department of Pediatrics, Pediatric Nephrology Policlinic between 2011- 2017. We analyzed demographic, clinical, and genetic data for 200 FMF patients enrolled in the study. Clinical diagnosis of FMF was made according to the Tel-Hashomer criteria (6). The major criteria are: 1) recurrent febrile episodes accompanied by peritonitis, synovitis, or pleuritis; 2) amyloidosis of the AA-type without predisposing disease; and 3) favorable response to colchicine treatment. Minor criteria are: 1) recurrent febrile episodes; 2) erysipelas-like erythema; and 3) FMF in a first-degree relative. Patients who have two major or one major and two minor criteria were diagnosed FMF.

Patients who aged 2-18 years under medical treatment were included in the study. All patients included in the study had a genetic diagnosis. Genomic DNA was isolated by the spin-column method from peripheral blood samples (collected in vacutainers containing EDTA). The

demographic, clinical and laboratory data of the patients were recorded from the medical charts of the patients in a retrospective manner.

We used the severity score recommended by Pras in 1998. The disease is grouped as mild, moderate and severe by scoring the parameters including age of onset, number of attacks in a month, chronic or acute joint involvement, presence of amyloidosis, erysipelas, and colchicine dose in remission of the disease with Pras score (7). Identity information of the patients, family histories, clinical and laboratory findings of the disease, genetic results, treatment information, disease severity scoring (Pras score) data were recorded.

We compared 3 different groups. The first comparison was patient groups with the most frequently detected Heterozygous R202Q, Heterozygous E148Q, and M694V/R202Q mutations, the second comparison of the patients with positive M694V mutation in at least one allele gene, the third comparison of patients with M694V/M694V mutations and patients with R202Q/R202Q mutations.

3.0 FINDINGS

Of the patients, 54% (107) were females and 46% (93) were males. The mean age of the patients included in the study was 140.8±43.5 months (40-210 months). The patients age of complaint onset and the mean age at the time of diagnosis were respectively 66.5±46.9 months (0-181 months), and 101.7±42.8 months (16-197 months) The mean diagnostic delay was calculated to be 34.9±38.1 months (0-182 months).

When the patients' family histories were examined, it was found that FMF was present in at least one individual in 90 patients (45%) families. When the degree of relationship between our patients' parents was examined, it was discovered that 39 patients' (19.5%) parents were second-degree relatives, and 10 patients' (5.5%) parents were more distant than second-degree relatives, totaling 49 patients (25%). When the patients were distributed by hometown, Sivas (46 patients, 23%), Giresun (17 patients, 8.5%), and Kastamonu (16 patients, 8%) were the top three. When the patients were evaluated based on their admission complaints, abdominal pain (92.5%) was found to be the most common symptom. Fever (68.5%), arthralgia (39.5%), myalgia (34.5%), chest pain (26%), headache and fatigue (21.5%), nausea and vomiting (19.5%), erysipelas-like erythema (18%), oral aphtha (12%), and arthritis (12%) were the following most common symptoms (Table 1).

Table 1: FMF Characteristics of All Patients (n,%)

	n	%
Abdominal pain	185	92,5
Fever	137	68,5
Arthralgia	79	39,5
Myalgia	69	34,5
Chest pain	52	26,0
Headache	43	21,5
Fatigue	43	21,5
Nausea and vomitting	39	19,5
Erysipelas-like erythema	36	18,0
Oral aphta	24	12
Arthritis	24	12

Among the 200 patients, 41 (20,5%) were homozygous, 63 (31,5%) were compound heterozygous, and 96 (48%) were heterozygous for MEFV mutations. Table 2 and 3 shows the distribution of MEFV mutations in this cohort.

Table 2: Distribution of MEFV Mutations

Homozygote mutation	R202Q/R202Q	19	9,5
	M694V/M694V	19	9,5
	M694I/M694I	1	0,5
	M680I/M680I	1	0,5
	R761H/R761H	1	0,5
Heterozygote mutation	R202Q/-	35	17,5
	E148Q/-	31	15,5
	M694V/-	14	7,0
	M680I/-	7	3,5
	V726A/-	6	3,0
	R761H/-	2	1,0
	K695R/-	1	0,5
Compound heterozygotes Mutation	M694V/R202Q	22	11,0
	R202Q/E148Q	6	3,0
	M694V/R202Q/V726A	4	2,0
	R202Q/V726A	4	2,0
	M694V/M680I	3	1,5
	E148Q/V276A	3	1,5
	M694V/R202Q/R761H	2	1,0
	M680I/V726A	2	1,0
	R761H/V726A	1	0,5
	R761H/R202Q/M694V	1	0,5
	V726A/M694I	1	0,5
	M694V/P396S	1	0,5
	M694V/V726A	1	0,5
	M694V/K695R	1	0,5
	M694V/R202Q/R408Q/P396S	1	0,5
	M694V/R202Q/M680I	1	0,5
	M694V/E148Q/V726A	1	0,5
	R408Q/P396S	1	0,5
	R202Q/K695R	1	0,5
	M694V/R202Q/V726A	1	0,5
	R202Q/R408Q/P396S.	1	0,5
	R202Q/M680I	1	0,5
	M680I/E148Q	1	0,5
	E148Q/K695R	1	0,5
	E148Q/R408Q/P396S	1	0,5

Table 3: Allele Frequencies of the MEFV Gene Mutations

	n	%
R202Q	118	29,5
M694V	91	22,75
E148Q	44	11
V726A	24	6
M680I	17	4,25
R761H	8	2
P396S	5	1,25
K695R	4	1
R408Q	4	1
M694I	3	0,75

The Comparison of the Patients with Heterozygous R202Q, Heterozygous E148Q and M694V/R202Q Mutations

The three most common mutations were Heterozygous R202Q (35 patients, 17%), M694V/R202Q (32 patients, 16%) and Heterozygous E148Q (31 patients, 15%) (Table 2). When the mean ages, the ages of symptom onset, age at diagnosis, the time between symptoms and diagnosis, family histories, attacks, PRAS scores, laboratory parameters, and treatment approaches of the groups were compared, no statistically significant difference was found.

In terms of FMF symptoms and fever rates, a statistically significant difference was found between the groups. Fever was less common in patients with E148Q ($p<0,05$). There was a statistically significant difference in the rates of comorbidities (urinary system diseases, asthma, inflammatory bowel diseases, HSP, Thalassemia, cardiac anomalies, ARA, epilepsy, TBC, Behçet's disease, psoriasis, Hashimoto, glaucoma, JRA, diabetes mellitus) ($p=0.026$). It was found that patients with the Heterozygous E148Q mutation had a significantly lower rate of comorbidity disease.

The Comparison of the Patients with Positive M694V Mutation in at Least One Allele Gene and Patients with Heterozygous R202Q and Heterozygous E148Q Mutations

The M694V mutation was found to be positive in at least one allele of the 72 patients included in the study. Heterozygous R202Q and Heterozygous E148Q, which are the other most common mutations, were compared. When the mean ages, the ages of symptom onset, age at diagnosis, the time between symptoms and diagnosis, family histories, attacks, and treatment approaches of the groups were compared, no statistically significant difference was found. When the patients were evaluated based on their FMF symptoms, it was found that fever and arthralgia were significantly more common in the patients with the M694V mutation ($p<0,005$). The mean PRAS score of the patients with M694V mutation in at least one allele was found to be 7.3 ± 1.9 ($p<0,005$). There was a significant difference between the laboratory parameters of the patients during and after an attack. All groups' laboratory values were high during an attack ($p<0,005$). The mean fibrinogen values during the attack in the patients with the M694V mutation were found to be 383.5 ± 103.1 g/l and they were significantly high ($p<0,005$).

The Comparison of Patients with M694V/M694V Mutations and Patients with R202Q/R202Q Mutations

The most common homozygous mutation groups, M694V and R202Q were compared. When the mean ages, the ages of symptom onset, the time between symptom and diagnosis, family histories, attacks, PRAS scores, and laboratory parameters of the groups were compared, no

statistically significant difference was found. It was found that the patients with the M694V homozygous mutation were diagnosed at a younger age (p<0,005). Patients carrying the R202Q mutation were more likely to be female (p<0.005). Myalgia was found to be significantly more common in patients with the R202Q homozygous mutation (p<0.005). The mean attack number of the patients with R202Q homozygous mutation was statistically significantly lower compared to the patients with M694V homozygous mutation, and the mean colchicine initiation age was statistically significantly higher (p<0.005).

Discussion

In our study, 200 pediatric patients with genetic mutations who were followed up with FMF diagnosis and whose treatments were started were evaluated. Of the patients, 54% were females and 46% were males. According to the data of the Turkish FMF Study Group, there was no dominant sex in FMF patients, and the female/male ratio was 1:1.2 (5). In our study, the female/male ratio was 1.1:1. Although the number of females was higher, no statistically significant difference was found.

The age of onset of the symptom was determined to be 66,5±46,9 months, which was consistent with the literature. The mean diagnosis age of our patients was 101,7±42,8 months, while the mean diagnostic delay was 34,9±38,1. These data support the notion that FMF is diagnosed late, which is consistent with the study of Yılmaz et al. (2015). This period was found to be 3.5 years in the series of Ergüven et al., which included 120 pediatric patients, which is similar to our study (8).

The distribution of the patients' hometowns in our study was centered on Sivas, Giresun, and Kastamonu, which was consistent with the findings of the Turkish FMF Study Group's study of 2838 patients (5). The rate of consanguineous marriage between the patients' parents was discovered to be 25%. This was consistent with Türkiye's consanguineous marriage rate of 22% (9). In the previous studies, it was found that the presence of other people with the same disease in the family history of FMF patients was quite common (10). In our study, we found that in 45% of our patients' families, there was at least one individual with FMF. Therefore, in patients with suspected FMF, the family history should be thoroughly investigated.

The most common symptom reported by patients in our study was abdominal pain. The abdominal pain frequency, which was 93.7% according to the Turkish FMF Study Group, was found to be 92.5% in our study (5). In contrast to our study, the most common symptom in the study of Kılıç et al. (2015) was fever, with a rate of 97.3% (11).

In our study's genotype distribution analysis, R202Q was found to be the most common, with a rate of 17.5%, similar to the study of Çankaya et al. (12). Similarly, in a study conducted on 230 patients in Hatay in 2012 by Başarslan et al., the most common mutations were respectively R202Q (30.4%), E148Q (16.1%), and M694V (10.4%), which is consistent with our study (13). When the literature is examined in this regard, it can be seen that different genotypes are prominent in studies conducted in various regions. For example, M680I was the most common mutation with a rate of 32.7% in a study conducted on 44 patients in Italy between 2010 and 2015 by Procopio et al., whereas E148Q was the most common mutation with a rate of 40.2% in a 2014 study conducted in Japan. In the 2015 study by Kılıç et al. conducted on 562 patients in Türkiye, the M694V mutation was found to be the most common mutation (11). M694V was the most common mutation in Battal et al.'s study of 60 patients in Çanakkale, with a rate of 20%. Furthermore, in the study of Akar et al. on 230 patients, and the multicenter international study of Özen et al., the most common mutation in Turkish people were found to be M694V. (14,15).

In contrast, the R202Q mutation was frequently observed in our study. Despite evidence in the literature that Heterozygous R202Q mutation does not cause disease on its own, in our study 35 patients with Heterozygous R202Q mutation were diagnosed using the Tel Hashomer criteria, and their treatments were initiated. In the 2012 study by Çankaya et al., it was found that the R202Q mutation in the MEFV gene may cause FMF-like symptoms. On the other hand, compound heterozygosity of R202Q/M694V is more associated with the mild phenotype than compound mutations of M694V (12).

Several studies have made different remarks about the E148Q mutation, which was the second most common mutation in our study. Mansfield et al. stated that while those with the E148Q mutation were not ill, the disease could occur if additional mutations were present (16). Topaloğlu et al. reported that 22 of 26 E148Q homozygous patients had typical FMF attacks (17). Fever, a symptom of FMF, was found to be less common in patients with the E148Q mutation than in patients with other mutations in our study. The comorbidity rates in E148Q mutation patients were also found to be low. Based on these findings, patients with the E148Q mutation having a milder phenotype were consistent with the literature. Although the patients with E148Q mutation have a milder phenotype, it is critical to diagnose them and initiate treatment.

The disease severity score (PRAS) of the patients with M694V mutation in at least one allele was found to be higher than that of other patients (75). According to the 2015 study by Rami A. Jarjour conducted on 103 refugee patients, patients with M694V had a significantly higher disease severity score (18).

The number of pre-treatment attacks in patients with the M694V mutation was found to be significantly higher. In the study of Topaloğlu et al., it was found that when the E148Q mutation was combined with the M694V mutation, the disease severity score increased. The PRAS score of patients with the M694V mutation in at least one allele was found to be higher in our study when compared to patients with other mutations, and it was compatible with our study. Patients with the M694V mutation in at least one allele had more fever and arthralgia symptoms than patients with other mutations. Berdeli et al. discovered the M694V mutation to be associated with amyloidosis development, fever attacks, and joint symptoms, which was consistent with our study (19). We know that acute-phase reactants increase in FMF patients during an attack; and the fibrinogen value during an attack was found to be significantly higher in patients with the M694V mutation in our study.

Although the number of patients with homozygous mutations was low in our study, we compared them within themselves and found results that were consistent with those found in the literature. The age of diagnosis of patients with homozygous M694V mutation was found to be significantly lower, as was the mean age of colchicine initiation. Many studies found that patients with the M694V mutation had a more severe course of disease than patients with other mutations. Of the patients, 10 patients with the M694V mutation had chest pain, and echocardiography revealed pericardial effusion in 2 of them. In the study of Kılıç et al., patients with chest pain and pericardial effusion had the M694V mutation, similar to our study (11). Medlej-Hashim et al. discovered that patients with a homozygous M694V mutation had a more severe course of the disease, and amyloidosis development was more common in these patients in their study conducted on 70 pediatric patients (20). Only one patient with the homozygous M694V mutation developed amyloidosis in our study. In a study conducted in Germany in 2013, it was found that the M694V mutation caused a more severe clinical course, and the amyloidosis risk was higher (21). In their study conducted on North African Jews and Arab-origin patients, Brik et al. discovered that there was a relationship between homozygous M694V

mutation and the severity of the disease, the disease had an earlier onset in these people, had a more severe course, progressed with more joint involvement and more complications were developed, similar to our study (22).

Homozygous R202Q mutation was detected in 19 patients (9.5%) Giaglis et al. discovered 9.2% homozygous R202Q mutation in their study conducted in Greece with 152 patients, which was consistent with our study (23). The complaint of myalgia was more common in patients with homozygous R202Q mutation. There are studies in the literature that associate fibromyalgia syndrome with the R202Q genotype. For example, in the 2009 study by Feng et al., a homozygous R202Q mutation was found in 6% of 100 patients with fibromyalgia syndrome. In a 2012 study conducted on 377 cases in Samsun by Karakuş et al., it was discovered that patients with the R202Q genotype had a higher risk of developing Fibromyalgia Syndrome (24)

FMF is still a clinically diagnosed disease. Family history, the presence of MEFV gene mutation, and other laboratory findings are among the supporting criteria for the diagnosis. we examined many demographics, clinical, and laboratory parameters in our study, we discovered that the age of onset of symptoms, symptoms at admission, disease severity score, and laboratory parameters' values at the time of an attack were particularly related to genotype. As a result, it can be said that there is a relationship between genotype and phenotype; patients with the E148Q mutation showed milder symptoms, while the clinical condition of M694V carriers was more severe. Also we can say that the mutation of R202Q could be related to the disease, especially in the presence of myalgia. However, we still believe that genotype is not effective on phenotype on its own and that variables such as ethnicity, family history, and environmental factors are also effective. Due to the small content, this observations need to be confirmed in larger studies.

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