THE MEFV VARIANTS IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER AND THEIR CLINICAL CORRELATIONS

AİLEVİ AKDENİZ ATEŞİ HASTALARINDA MEFV VARYANTLARI VE KLİNİK KORELASYONLARI

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ABSTRACT

INTRODUCTION: Familial Mediterranean Fever (FMF) is the most common auto-inflammatory disease characterized by recurrent attacks.FMF was found to be correlated with the mutation in MEFV gene. Patients with M694V homozygous mutation have been reported to have a more severe disease. However, there is no clear study of clinical correlation in other variants. In this study, we aimed to investigate the frequency and clinical correlation of MEFV gene variants.

METHODS: Electronic medical records of FMF cohort were retrospectively analyzed. FMF cohort was established in year 2010 and since then all patients who fulfilled Tel-Hashomer criteria. Demographic information, attack characteristics, treatment information and MEFV gene outcomes of the patients were analysed using the records. In MEFV gene analysis, M694V, M694I, M680I, V726A, R761H, A744S, F479L, P369S, R202Q and E148Q variants are evaluated.

RESULTS: A total of 605 patients were included in the study. In patients who had M694V mutation, arthritis and erysipelas were observed more frequently (p=0.04, p=0.008).Increased family history of FMF was identified in patients with M694V mutation (p<0.001). In patients with M694V mutation, it was found that age of onset of FMF symptoms, age of diagnosis, and age of treatment initiation were younger (p=0.003, p=0.014, p=0.025). In patients with M694Vhomozygous, frequency of amyloidosis was higher (p<0.001). The risk of developing amyloidosis was higher in M694Vhomozygous (Odds ratio 7.46, 95% confidence interval: 2.92-19.05).

CONCLUSIONS: In conclusion, homozygous M694V mutation leads to severe disease. There was no clinical variability in other MEFV gene variants.

Keywords: *Familial Mediterranean Fever, MEFV gene, Amyloidosis*

ÖZET

AMAÇ: Ailesel Akdeniz Ateşi (FMF), tekrarlayan ataklarla karakterize en sık görülen oto-enflamatuar hastalıktır. MEFV genindeki mutasyonun FMF'e neden olduğu saptanmışır. M694V homozigot mutasyonu olan hastaların daha ciddi hastalığı olduğu bildirilmiştir. Ancak, diğer MEFV gen varyantların klinik korelasyonu ile ilgili net bir çalışma yoktur. Bu çalışmada, MEFV gen varyantlarının sıklığı ve klinik korelasyonunun araştırılması amaçlanmıştır.

METOD: FMF kohortunun elektronik tıbbi kayıtları retrospektif olarak incelendi. Tel-Hashomer kriterlerine göre tanı konulan FMF hastalarının demografik bilgileri, atak özellikleri, tedavi bilgileri ve MEFV gen sonuçları hastaların kayıtları kullanılarak analiz edildi. MEFV gen analizinde, M694V, M694I, M680I, V726A, R761H, A744S, F479L, P369S, R202Q ve E148Q varyantları değerlendirildi.

BULGULAR: Çalışmaya toplam 605 hasta dahil edildi. M694V mutasyonu olan hastalarda artrit ve erizipel daha sık gözlendi (p = 0.04, p = 0.008). M694V mutasyonu olan hastalarda artmış aile FMF öyküsü saptandı (p <0.001). M694V mutasyonu olan hastalarda FMF semptomlarının başlama yaşı, tanı yaşı ve tedavi başlama yaşının daha genç olduğu bulundu (p = 0.003, p = 0.014, p = 0.025). M694V homozigozlu hastalarda amiloidoz sıklığı daha yüksekti (p <0.001). M694V homozigozda amiloidoz gelişme riski daha yüksekti (Oran oranı 7.46, % 95 güven aralığı: 2.92-19.05).

SONUÇ: Sonuç olarak, homozigot M694V mutasyonu şiddetli hastalığa yol açmaktadır. Diğer MEFV gen varyantları ile klinik arasında anlamlı ilişki saptanamadı.

Anahtar kelimeler: *Ailevi Akdeniz ateşi, MEFV geni, Amiloidoz*

INTRODUCTION

Familial Mediterranean Fever (FMF) is the most common auto-inflammatory disease characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis and erysipelas like erythema. FMF was found to be correlated with the mutation in MEFV gene (1-3). Colchicine is the mainstay of FMF treatment due to its proven efficacy for reducing frequency, severity and duration of attacks in most patients and prevention from amyloidosis (4).

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Pyrin is believed to be a regulator of inflammation. Pyrin is mainly expressed in innate immune cells and plays a major role in the regulation of inflammation. Pyrin encoded by MEFV gene (5).The mutation in the MEFV gene located at the short arm of the 16th chromosome impairs the encoding of the pyrin protein. Pyrin regulates neutrophil and inflammasome activity (2,3). The N-terminal pyrin domain allows pyrin to interact with a CARD (ASC), an adaptor protein that mediates the proteolytic activation of caspase-1 in the inflammasomes (6).

Until now, numerous variants of the MEFV gene have been identified (7,8). While some of these are clinical, others are not significantly reflected in the phenotype (7). M694V, M680I, V726A on exon 10 and E148Q on exon 2 are the most frequently reported mutations (9,10). There are various publications in the literature on how MEFV gene variants are reflected in the phenotype. Patients with M694V homozygous mutation have been reported to have a more severe disease (11-13). However, there is no clear study of clinical correlation in other variants. In this study, we aimed to investigate the frequency and clinical correlation of MEFV gene variants.

MATERIAL AND METHODS

Study design and patients

Electronic medical records of FMF cohort were retrospectively analyzed. FMF cohort was established in year 2010 and since then all patients who fulfilled Tel-Hashomer criteria have been registered at baseline, including dataon demographic features, co-morbidities, clinical manifestations, detailed attack characteristics, treatment responses, disease complications, family history and MEFV mutations (14). Local ethics committee approved the study.

Patients over 18 years old with known MEFV gene results were included in the study. Demographic information, attack characteristics, treatment information and MEFV gene outcomes of the patients were analysed.

Age, gender and family history were recorded. Age of disease onset, age of diagnosis and age of treatment initiation were recorded. Peritonitis, pleuritis, arthritis, erythema,pericarditis and orchitis were recorded. Patients with amyloidosis were recorded. Colchicine-resistant patients defined as patients who received IL-1 antagonist treatment due to frequent attacks despite receiving maximum dose of colchicine.

Genomic DNA isolation from venous blood sample is performed using standard methodology. In MEFV gene analysis, M694V, M694I, M680I, V726A, R761H, A744S, F479L, P369S, R202Q and E148Q variants are evaluated.

Statistical Analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) 15.0 Package (SPSS Inc., Chicago, IL, USA). Chi-square test, where appropriate, was used to compare these proportiondifferent groups. Student T-test was used to compare onset of disease, age of diagnosis and age at treatment on different groups. A p-value equal or less than 0.05 is considered statistically significant.

RESULTS

A total of 605 patients were included in the study. Of these patients, 366 were female (60.5%) and 239 were male (39.5%). The mean age was 36.76 (±11.01). The mean age of FMF onset was 16.03 (±11.54), the mean age of FMF diagnosis was 24.86 (±12.54), and the mean age of FMF treatment initiation was 25.18 (±12.38). The clinical characteristic of attacks was presented in **table 1**. Amyloidosis was detected in twenty-five patients (4.1%). It was found that thirty-eight patients had frequent attacks despite using the maximum dosage of colchicine and thus received IL-1 antagonist treatment. FMF was detected in the 1st and 2nd degree relatives of 337 patients (65.5%). Family history could not be detected in 267 patients (44.1%).

Table 1 Clinical characteristic of patients

Fever N (%)	437 (71.8)
Peritonitis N (%)	526 (86.4)
Pleuritis N (%)	342 (56.2)
Arthritis N (%)	411 (67.5)
Myalgia N (%)	408 (67)
ELE N (%)	209 (34.3)
Orchitis N (%)	31 (5.1)
Pericarditis N (%)	33 (5.4)
Amyloidoysis N (%)	25 (4.1)
Family history N (%)	337 (65.5)
Colchicine unresponsive N (%)	39 (6.4)
Age at diagnosis onset (±SD)	16.03 (11.54)
Age at diagnosis (±SD)	24.86 (12.54)
Age at treatment onset (±SD)	25.18 (12.38)

MEFV gene mutation was homozygous in 208 patients (34.1%), heterozygous in 158 patients (25.9%), compound in 243 patients (39.3%). MEFV gene analysis was negative in 50 patients (8.21%). The distribution of MEFV genotypes was presented in **table 2.**

In patients who had M694V mutation, arthritis and erysipelas were observed more frequently (p=0.04, p=0.008). No significant difference was detected in other attack types. It was found that M694V mutation did not cause any differences in terms of pericarditis and orchitis attacks. Increased family history of FMF was identified in M694V mutation (p<0.001). In patients with M694V mutation, it was found that age of onset of FMF symptoms, age of diagnosis, and age of treatment initiation were younger (p=0.003, p=0.014, p=0.025) **(Table 3).**

Table 2 The distribution of MEFV genotypes

One allel	N (%)	Two allel	N (%)
M694v/-	104 (17.07%)	M694V/M694V	178 (29.2%)
V726A/-	17 (2.79%)	M694V/V726A	46 (7.5%)
M680I/-	15 (2.46%)	M694V/M680I	63 (10.3%)
E148Q/-	12 (1.97%)	M694V/R761H	9 (1.47%)
R202Q/-	4 (0.65%)	M694V/M694I	4 (0.65%)
P369S/-	3 (0.49%)	M694V/R202Q	4 (0.65%)
F479L/-	1 (0.16%)	M694V/E148Q	31 (5.09%)
A744S/-	1 (0.16%)	M694V/A744S	2 (0.32%)
R761H/-	1 (0.16%)	V726A/V726A	4 (0.65%)
		V726A/M680I	19 (3.11%)
negative	50 (8.2%)	V726A/F479L	3 (0.49%)
		V726A/E148Q	2 (0.32%)
		M680I/M680I	21 (3.4%)
		M680I/R761H	3 (0.49%)
		M680I/E148Q	3 (0.49%)
		M694I/E148Q	2 (0.32%)
		F479L/F479L	2 (0.32%)
		E148Q/E148Q	1 (0.16%)
		R202Q/R202Q	1 (0.16%)
		P369S/P369S	1 (0.16%)
		P369S/E148Q	2 (0.32%)

The results were analysed after being divided into subgroups according to MEFV gene type. Arthritis and erysipelas were more frequently observed in M694Vhomozygous (p<0.001, p<0.001). No significant difference was detected in other attack types. In patients with M694Vhomozygous, it was found that age of onset of symptoms, age of diagnosis and age of treatment initiation were younger (p<0.001, p<0.001, p<0.001). It was found that colchicine resistance was higher in patients with M694Vhomozygous (p<0.001). **(Table 4)**

In patients with M694Vhomozygous, frequency of amyloidosis was higher (p<0.001). The risk of developing amyloidosis was higher in M694Vhomozygous (Odds ratio 7.46, 95% confidence interval: 2.92-19.05). Of the patients with amyloidosis, four had M694V/M680I, two had M680/M680I mutations. However, in patients with these two mutations, no increase in the risk of amyloidosis was detected. **(Table 4)**

DISCUSSION

FMF was found to be correlated with the mutation in MEFV gene. MEFV is located at the short arm of chromosome 16 and encodes pyrin protein (3). Pyrin protein is involved in the regulation of inflammation. Pyrin-related proteins interact with ASC and create inflammasome response (15). Because of the mutation in MEFV gene, uncontrolled inflammation develops (16).

Until today, over 300 gene polymorphisms have been identified, but while some of them were found to be associated with clinical picture, some did not have any clinical significance (7). It was found that patients with M694V gene mutation had a more severe disease course.

Table 3 Clinical features associated with MEFV gene variants

	A	B	C	p
Fever (%)	73.2	71.4	77.8	0.8
Peritonitis(%)	85.9	89	92.6	0.48
Pleuritis (%)	59.2	54.9	40.7	0.14
Arthritis (%)	71.4	58.2	66.7	0.04
ELE (%)	38.8	25.3	18.5	0.008
Myalgia (%)	67.6	61.5	74.1	0.38
Orchitis (%)	5.4	2.2	7.4	0.36
Pericarditis (%)	5.4	3.3	7.4	0.61
Amyloidosis (%)	5.2	2.2	0	0.23
Family History (%)	62.4	44	22.2	<0.001
Colchicine Unresponsive (%)	7.7	5.5	0	0.25
Age at disease onset (±SD)	14.7 (11.1)	19.1 (12.3)	18.1 (12.6)	0.003
Age at diagnosis (±SD)	23.7 (12.7)	27.1 (12.2)	29.2 (12.2)	0.014
Age at treatment onset (±SD)	24.1 (12.5)	27.2 (12.2)	29.2 (12.3)	0.025

A: M694V / (M694V, M680I, V726A, R761H, A744S, M694I, E148Q, R202Q, P369S, F479L, negative)
B: (M680I, V726A, R761H, A744S, M694I) / (M680I, V726A, R761H, A744S, M694I, E148Q, R202Q, P369S, F479L, negative
C: Other exon variant

Table 4 Clinical features associated with MEFV gene variants

	A	B	C	D	E	F	G	p
Fever (%)	78.2	63.5	75.4	68.8	70.8	72.1	77.8	0.21
Peritonitis (%)	84.9	84.6	89.7	81.3	89.6	88.4	92.6	0.68
Pleuritis (%)	64.8	52.9	57.9	53.1	58.3	51.2	40.7	0.17
Arthritis (%)	82.7	62.5	66.7	56.3	62.5	53.5	69.1	**<0.001**
ELE (%)	54.2	25	33.3	18.8	31.3	18.6	18.5	**<0.001**
Myalgia (%)	67.0	73.1	65.1	62.5	62.5	60.5	74.1	0.66
Orchitis (%)	7.3	4.8	3.2	6.3	2.1	2.3	7.4	0.57
Pericarditis (%)	6.1	5.8	4	6.3	4.2	2.3	7.4	0.92
Amyloidosis (%)	10.6	0	3.2	0	4.2	0	0	**<0.001**
Family History (%)	66.5	66.3	52.4	65.6	43.7	44.2	32.2	**<0.001**
Colchicine Unresponsive (%)	14.5	1	4.8	3.1	4.2	7	0	**<0.001**
Age at disease onset (±SD)	10.3 (9.7)	18.5 (10.5)	15.5 (10.8)	23.6 (11.3)	20.1 (14.2)	18 (9.78)	18.4 (12.6)	**<0.001**
Age at diagnosis (±SD)	19.2 (12.9)	27 (11.4)	25.4 (11.6)	31.4 (11.7)	29.2 (13.7)	24.6 (9.9)	29.2 (12.2)	**<0.001**
Age at treatment onset (±SD)	19.7 (12.7)	26.9 (11.3)	26.1 (11.4)	32.2 (11.06)	29.4 (13.4)	24.5 (10.1)	29.2 (12.3)	**<0.001**

A: M694 homozygous mutation **B:** M694V heterezygous mutation **C:** M694V / (M680I, V726A, R761H, A744S, M694)
D: M694V / (E148Q, R202Q, P369S, F479L) **E:** (M680I, V726A, R761H, A744S, M694I) / (M680I, V726A, R761H, A744S, M694I)
F: (M680I, V726A, R761H, A744S, M694I) / (negative, E148Q, R202Q, P369S, F479L) **G:** other exon variant

This is thought to be related particularly to the location of the mutation at the C-terminal B30.2 domain of the pyrin protein. This domain was shown to be directly related to caspase and has a critically functional structure (13,17,18). Many studies were performed on the clinical significance of the other gene variants, and no clear information on their clinical significance could be revealed. In this study, the objective is to investigate the clinical correlation of the most frequently detected MEFV gene variants.

In our study, M694V mutation was the most frequently identified MEFV gene variant. In 72.4% of the patients, M694V mutation was found. In a study on 2246 FMF patients, M694V mutation was detected in 43.7% patients (16). Coşkun et al. reported that M694V mutation rate was 41.5% (19). In a study in Iran, M694V mutation rate was identified as 42.46% (20). In fifty patients (8.2%), MEFV gene mutation was found to be negative. This can be due to rare gene variants or unidentified polymorphisms.

In our study, it was found that patients with M694V mutations had more arthritis and erysipelas attacks. No significant difference was detected in other attack types. No difference was detected in terms of the duration and severity of attacks. It was found that patients with M694V mutation had more FMF family history. Similarly, Kasifoglu et al. stated that those who had M694V homozygous mutation have more family history (16). In our study, no difference was detected in terms of the attack types, severity, and duration. It was reported that V726A and E148Q mutations combined is the risk of severe disease, but no such thing was detected in our study (1). It was reported that those with K695R, P369 and M680I mutations are severe disease (21). In our study no result significant with these can be detected. M680I homozygous and M694V-M680I compound mutations were reported to cause a disease more severe than M694V homozygous mutation (22). In our study, it was found that for patients with M694V mutation, age of symptom onset, diagnosis and age of treatment onset were found to be smaller. It was shown that for patients with M694V, the age of onset is earlier (23). Similarly, Kasifoglu et al. reported that M694V mutation was more frequent who had symptoms before 18 years old (16).

In our study, it was found that patients with M694V mutations had more frequent arthritis and erysipelas attacks. It was found that the attacks were more frequent in patients with M694V homozygous (9). Kasifoglu et al. have found that arthritis attacks were frequent in those with M694V mutation (16). Erysipelas attacks were more frequently reported inM694Vhomozygous (24,9,16). In our study, no significant difference was detected in other attack types. In a study on Armenian FMF patients, no difference was detected in terms of the attack types between those with M694V homozygous, M694V-V726A compound and M694V-M680I compound mutations (25). In our study, colchicine resistance was detected more frequently in M694Vhomozygous. Similarly, Soylemezoğlu et al.was found that response to colchicine was weaker in M694Vhomozygous mutation (26). In our study, it was found that patients with M694V mutations

had increased risk of amyloidosis. In a study with 400 amyloidosis patients, the M694V homozygous mutation rate was found to be higher (27). In numerous studies, patients with M694V homozygous mutation have been reported to have an increased risk of amyloidosis (16,27-29).

Our study had some limitations. The number of MEFV variants used in the study were limited, it was not possible to compare the clinical characteristics of more variants. As our study was single-centre, most of the patients were from the central Anatolia region of Turkey. Thus, it might not reflect the whole population. Simultaneous presence of spondylitis and vasculitis was not investigated.

In conclusion, homozygous M694V mutation leads to severe disease. There was no clinical variability in other MEFV gene variants.

Conflict of Interest None of authors reported conflict of interest with pharma agencies.

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