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MEFV mutation frequency and effect on disease severity in ankylosing spondylitis

Yüksel MARAŞ[1,*], Ali AKDOĞAN[2], Bünyamin KISACIK[2], Levent KILIÇ[2], Engin YILMAZ[3], Abdurrahman TUFAN[2], Umut KALYONCU[2], Şaziye Şule APRAŞ BİLGEN[2], Sedat KİRAZ[2], Ali İhsan ERTENLİ[2], Meral ÇALGÜNERİ[2]

[1]Department of Rheumatology, Ankara Atatürk Education and Research Hospital, Ankara, Turkey
[2]Department of Internal Medicine, Division of Rheumatology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[3]Department of Medical Biology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

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Background/aim: To define the frequency of familial Mediterranean fever gene (MEFV) mutations in ankylosing spondylitis (AS) and describe different clinical aspects of MEFV mutation carrier and noncarrier AS patients.

Materials and methods: In 112 AS patients, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were calculated. The frequencies of 12 different MEFV mutations were studied by multiplex polymerase chain reaction/reverse hybridization method and were compared to those of previously studied healthy controls for 5 common MEFV mutations.

Results: MEFV mutations were identified in 46 of 224 (20%) alleles and in 39 (35%) of AS patients. The distribution of mutations was: M694V, 30% (14); E148Q, 30% (14); P369S, 17% (8); V726A, 13% (6); A744S, 8% (4); and K695R, 2% (1). There were no significant differences between MEFV mutation carriers and noncarriers with respect to sex, age of symptom onset, disease duration, peripheral joint involvement, acute phase reactant levels, and BASDAI and BASFI scores ($P > 0.05$ all). MEFV mutation allelic frequency was not different between AS patients and healthy controls after adjusting for mutations studied (34/224 versus 22/200; $P > 0.05$).

Conclusion: Although we did not find significant clinical and laboratory differences between MEFV mutation carrier and noncarrier AS patients, further investigations are needed to define the impact of MEFV mutations on AS disease course.

Key words: Familial Mediterranean fever, ankylosing spondylitis, familial Mediterranean fever gene, seronegative spondyloarthropathy

1. Introduction

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease of uncertain etiology that primarily affects the axial skeleton (1). Familial Mediterranean fever (FMF), which primarily affects populations surrounding the Mediterranean Basin, is an autosomal recessive disorder characterized by recurrent acute attacks of fever accompanied by abdominal pain, arthritis, and pleurisy (2). The FMF gene (MEFV), which is responsible for FMF, was identified in 1997 (3). MEFV mutation carriers include about 20%–30% of the population in certain ethnic groups (4). The impact of MEFV mutations on the clinical course of chronic inflammatory diseases other than FMF, such as Crohn's disease, childhood arthritis, and rheumatoid arthritis, has been shown (5–8). The presence of MEFV mutations in AS patients was investigated in previous studies but their association with clinical features of AS is controversial (9–11). The aim of this study is to define the frequency of MEFV mutations and describe different clinical aspects of MEFV mutation carrier and noncarrier AS patients.

2. Materials and methods

AS patients were consecutively selected at the Rheumatology Outpatient Clinic of the Hacettepe University Hospital. All patients met the modified New York criteria for the classification of AS (12). Patients with inflammatory diseases other than AS or amyloidosis, current pregnancy, or infectious disease were excluded. Patients who had symptoms suggesting FMF or had first-degree relatives with the diagnosis of FMF were also excluded. Among 127 AS patients, 112 were eligible for the study. Eight patients did not consent, 1 was pregnant, 2 had amyloidosis, 1 had tuberculosis, 2 had recurrent fever attacks within the last 1–2 days (1 of whom also had a second-degree relative with FMF), and 1 had recurrent abdominal pain. The study protocol was approved by the Hacettepe University Local Research Ethics Committee. All subjects gave written informed consent.

* Correspondence: ymaras@hotmail.com

MEFV mutation frequency of the patient population in this study was compared to that of previously studied healthy controls for 5 common MEFV mutations (M694V, E148Q, M680I, M694I, and V726A) by our group (13).

All AS patients had a complete patient history and physical examination. Both Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were calculated (14,15). Hemoglobin, serum C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) of all AS patients were recorded. Blood samples were stored at – 80 °C until analyzed for MEFV mutations. All samples were analyzed for 12 different MEFV mutations (M694V, E148Q, V726A, P369S, A744S, R761H, K695R, M694I, F479L, M680I/c, M680I/a, and 1693del) by multiplex polymerase chain reaction (PCR)/reverse hybridization method.

2.1. Statistics

SPSS 11.0 was used for analysis. Distribution of data was assessed by using the one-sample Kolmogorov–Smirnov test. Values are expressed as mean ± standard deviation unless indicated otherwise. For comparison of categorical variables or percentages we used Fisher's exact and chi-square tests whenever appropriate. Differences between numerical variables were tested with Student's t-test or the Mann–Whitney U test. The significance level was set at $P < 0.05$.

3. Results

We studied 112 AS patients (male/female: 48/64). The mean age of the AS patients and the disease duration were 39 ± 11 years and 13 ± 9 years, respectively. MEFV mutations were identified in 46 of 224 (20%) alleles and in 39 (35%) of AS patients. The distribution of mutations was: M694V, 30% (14 cases); E148Q, 30% (14 cases); P369S, 17% (8 cases); V726A, 13% (6 cases); A744S, 8% (4 cases); and K695R, 2% (1 case). Among 39 patients, 32 (82%) had heterozygote mutations, 7 (18%) had mutations in both alleles, 5 patients had compound heterozygote mutations, 1 patient had homozygote M694V mutation, and 1 patient had complex mutation with M694V/E148Q-P369S (Table 1).

General characteristics and laboratory results of the AS patients with and without MEFV mutations are shown in Table 2. There were no significant differences between MEFV mutation carriers and noncarriers with respect to sex, age of symptom onset, disease duration, peripheral joint involvement, acute phase reactants, and BASDAI and BASFI scores ($P > 0.05$ for all; Table 2). Acute phase reactant levels, peripheral joint involvement, and BASDAI and BASFI scores were not significantly different in AS patents with M694V mutation as compared to AS patients without any MEFV mutations ($P > 0.05$ for all; Table 3). Acute phase reactant levels, peripheral joint involvement, and BASDAI and BASFI scores were not significantly different in AS patients with more than one MEFV mutation or patients with M694V mutation as compared to other AS patients ($P > 0.05$ for all).

The frequencies of MEFV mutations in the control group in our previous study were E148Q, 12%; M680I, 5%; M694V, 2%; V726A, 2%; and M694I, 0%. No difference was detected between the number of MEFV mutation carriers and MEFV mutation allelic frequency (34/224 versus 22/200; $P > 0.05$) when the current data set was compared to the previous 5 mutations studied. M694V was the most common mutation together with E148Q in AS patients. M694V mutations were more frequent among AS patients as compared to healthy controls (14/224 versus 3/200; $P = 0.013$). There were also more patients who had more than one mutation as compared to the healthy control group, but the difference was not statistically significant (5/112 versus 1/100; $P > 0.05$).

4. Discussion

In this study, although allelic frequency of MEFV mutations did not differ between AS patients and healthy controls, M694V was one of the most common mutations in AS patients and was more frequent in AS patients

Table 1. Distribution of MEFV mutations in AS patients.

Number of patients with heterozygote MEFV mutations		Number of patients with more than 1 MEFV mutations	
E148Q/–	9	E148Q/M694V	2
M694V/–	8	E148Q/P369S	2
V726A/–	5	M694V–E148Q/P369S	1
P369S/–	5	M694V/M694V	1
A744S/–	4	M694V/V726A	1
K695R/–	1		

MEFV: Familial Mediterranean fever gene, AS: ankylosing spondylitis.

Table 2. Clinical and laboratory results of ankylosing spondylitis patients with and without MEFV mutations.

	Patients with MEFV mutation (n = 39)	Patients without MEFV mutation (n = 73)	P-value
Age (years)	39 ± 10	38 ± 11	NS
Female/male	15/24	33/40	NS
Disease duration (years)	12 (1–35)*	10 (1–45)*	NS
Age at symptom onset (years)	25 ± 7	26 ± 9	NS
BASDAI	3.0 (0.4–8.7)*	3.8 (0.2–9.0)*	NS
BASFI	1.0 (0.0–9.8)*	2.3 (0.0–8.0)*	NS
Total peripheral joint involvement, n (%)	16 (41%)	31 (42%)	NS
Hip involvement	12 (31%)	18 (25%)	NS
Uveitis	7 (18%)	7 (10%)	NS
ESR (mm/h)	16 (2–66)*	9 (2–77)*	NS
CRP (mg/dL)	0.75 (0.30–8.81)*	0.40 (0.20–9.20)*	NS

MEFV: Familial Mediterranean Fever gene, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, *: median (minimum–maximum).

Table 3. Clinical and laboratory results of ankylosing spondylitis patients with M694V mutations and without MEFV mutations.

	Patients with M694V mutation (n = 13)	Patients without MEFV mutation (n = 73)	P-value
Age (years)	39 ± 7	38 ± 11	NS
Female/male	5/8	33/40	NS
Disease duration (years)	12 (4–31)*	10 (1–45)*	NS
Age at symptom onset (years)	24 ± 6	26 ± 9	NS
BASDAI	3.8 (0.9–7.2)*	3.8 (0.2–9.0)*	NS
BASFI	1.5 (0.0–9.8)*	2.3 (0.0–8.0)*	NS
Total peripheral joint involvement, n (%)	4 (31%)	31 (42%)	NS
Hip involvement	3 (23%)	18 (25%)	NS
Uveitis	1 (8%)	7 (10%)	NS
ESR (mm/h)	8 (2–66)*	9 (2–77)*	NS
CRP (mg/dL)	0.4 (0.30–7.56)*	0.40 (0.20–9.20)*	NS

MEFV: Familial Mediterranean Fever gene, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, *: median (minimum–maximum).

than in healthy controls. We did not find any clinical and laboratory difference between MEFV mutation carriers and noncarriers in AS patients.

The frequency of MEFV mutation carriers was reported between 22% and 30% in AS patients (9–11,16). MEFV mutation frequency was found to be increased as compared to controls in 2 of 3 previous studies (9–11). However, in all studies, M684V mutation was the most common mutation detected in AS patients and the frequency of M694V mutation was increased in AS patients as compared to controls (9–11,17). In this regard, our results are consistent with the previous results. The IL-1 pathway is considered to be involved in AS pathogenesis and is also related with MEFV mutations (18,19). Our

results also support the suggested association between M694V mutation and development of AS (17).

Musculoskeletal manifestations are common and include peripheral arthritis and sacroiliitis in FMF (8,20). Some authors suggested that FMF may be included in the spectrum of diseases with seronegative spondyloarthropathy (8). On the other hand, the absence of HLA B27 and lumbar spinal involvement are considered to be characteristics of FMF musculoskeletal manifestations (8,21,22). The frequency of sacroiliitis in FMF patients has been reported to be higher than expected in Turkish patients (20,21). In our experience, AS is common in FMF patients and has a more severe disease course. FMF-AS patients had more peripheral joint involvement, total hip replacement, higher acute phase reactant levels, and proteinuria (23). The presence of MEFV mutations is shown to be associated with disease severity in inflammatory diseases such as Crohn's disease, childhood arthritis, and rheumatoid arthritis (5–8). However, unexpectedly, we could not demonstrate any clinical or laboratory difference between MEFV mutation carriers and noncarriers in AS patients. Data about the impact of MEFV mutations on the clinical course of AS are controversial. In one study, authors reported higher BASDAI/BASFI scores and more hip involvement in MEFV mutation carrier AS patients (11). In other studies, authors either did not assess the clinical significance of MEFV mutations or found no clinical difference between MEFV mutation carrier and noncarrier AS patients (9,10). Response to nonsteroidal antiinflammatory drugs was found to be similar among MEFV mutation carrier and noncarrier AS patients (16). On the other hand, in a recent study, higher enthesopathy scores were reported in FMF patients with the M694V mutation as compared to patients with other variants (24). At this point, it is clear that we need more data for defining the impact of MEFV mutations on AS.

There were 7 AS patients who had more than one MEFV mutation but did not have typical FMF attacks and had no family history of FMF in our study. FMF attacks may be mild and incomplete; therefore, patients may not feel uncomfortable during attacks. On the other hand, M694V mutation has the highest penetrance rate and is associated with arthritis in FMF (25,26). Arthritis can be the initiating and sole manifestation of FMF (27). FMF patients with musculoskeletal manifestations may also satisfy the criteria of AS and chronic arthritis in FMF (21,22). Both in spondylarthropathies and in FMF, the symptoms of the patients fluctuate. Therefore, it is also possible that some of the FMF patients could be misdiagnosed with AS. In other words, AS-like presentation can be the sole manifestation of FMF.

In this study we excluded AS patients who had FMF-like symptoms or had first-degree relatives with the diagnosis of FMF in order to separate patients who could have concomitant AS and FMF. However, our study has some limitations, as HLA B27 is associated with the development and severity of AS (1). MEFV mutations were observed more frequently in HLA B27-negative patients with AS (9). On the other hand, FMF patients with HLA B27-negative sacroiliitis were reported to have milder spinal involvement as compared to HLA-positive patients (21). We did not assess HLA B7 status or the severity of vertebral damage of the AS patients in this study.

In conclusion, although allelic frequency of MEFV mutations did not differ between AS patients and healthy controls, M694V mutation was more frequent in AS patients than in healthy controls, and it was also one of the most common mutations in AS patients in our study. Our results and current data indicate an association between MEFV mutations, the M694V mutation in particular, and AS. Colchicine is an effective treatment option for FMF. Further investigations conducted to test the effect of colchicine on the clinical course of MEFV mutation carriers and HLA B27-negative AS patients, and long term follow-up of FMF patients with HLA B27-negative sacroiliitis, will provide useful data to define the impact of MEFV mutations in AS.

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