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The spectrum of Familial Mediterranean Fever gene (*MEFV*) mutations and genotypes in Iran, and report of a novel missense variant (R204H)

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ABSTRACT

Background: Familial Mediterranean Fever (FMF) is an autosomal recessive disorder, characterized by recurrent and self-limited episodes of fever, abdominal pain, synovitis and pleuritis. FMF as the most common inherited monogenic autoinflammatory disease mainly affects ethnic groups of the Mediterranean basin, Arab, Jewish, Turkish, Armenian North Africans and Arabic descent.
Materials and methods: In the present study, we selected 390 unrelated FMF patients according to the Tel-Hashomer criteria, and analyzed all patients for 12 most common mutations of *MEFV* gene by reverse hybridization assay (FMF strip assay). We also investigated exon 2 and 10 of *MEFV* gene in 78 patients by Sanger sequencing.
Results: According to strip assay results, at least one mutation was found in 234 patients (60%), and no mutation was found in other 156 patients (40%). The five most common mutations and allelic frequencies were M694V (13.6%), E148Q (10.4%), M694I (6.5%), V726A (4.1%), and M680I (3.8%). Moreover, we detected a novel missense variant (R204H, c.611 G > A) (SCV000297822) and following rare mutations among sequenced samples; R202Q, P115T, G304R, and E230K.
Conclusion: This study describes the *MEFV* mutations spectrum and distribution in Iranian population, and shows different mutation patterns among Iranian ethnicities. Moreover, M694V is the most common *MEFV* mutation in Iran.

1. Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive disorder, characterized by recurrent and self-limited episodes of fever, abdominal pain, synovitis and pleuritis, lasting 1–3 days (Shohat and Halpern, 2011). Most of the patients are men and the mean age of onset is 10; about 65% of the cases experience their first symptoms before the age of 10 years and 90% of the patients experience primary signs before reaching the age of 20 (Onen, 2006). Amyloid A (AA) amyloidosis remains as the main long-term complication with a severe manifestation and poor prognosis. Amyloidosis of the AA type commonly occurs among untreated patients which are older than 15 years, even among those who do not have a history of recurrent inflammatory attacks (Shohat and Halpern, 2011). Colchicine therapy, as a standard treatment of FMF has been clinically proven to reduce the frequency and severity of acute attacks and prevent the development of amyloidosis in FMF patients (Akar et al., 2012).

FMF as the most common inherited monogenic autoinflammatory disease mainly affects ethnic groups of the Mediterranean basin, Arab, Jewish, Turkish, Armenian North Africans and Arabic descent (Ozen and Bilginer, 2014; Toplak et al., 2012). The mutated gene in patients with FMF is the Familial Mediterranean Fever gene (*MEFV*). This gene has been mapped on chromosome 16p13.3, it has 10 exons and encodes a 781 amino acids protein called pyrin or marenostrin or TRIM20. Pyrin is a regulatory protein of inflammasome. Mutations in *MEFV* are associated with

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Table 1
The Age of onset of first symptoms.

Age (Year)	Number	Percent
≤1 y	53	13.6%
1 to 10	229	58.8%
10 to 20	75	19.2%
≥20	33	8.5%

excess inflammation through increased IL-1β production (Yang et al., 2014).

Since the cloning of the *MEFV* gene, about 304 sequence variants have been reported, 167 of these variations associated with FMF (online at http://fmf.igh.cnrs.fr/ISSAID/infevers). According to studies, four mutations, M694V, V726A, M680I, M694I on exon 10 and the E148Q on exon 2 are the most common mutations and comprise 85% of all mutations in the countries where FMF is prevalent (Simon and van der Meer, 2007).

Frequency and spectrum of *MEFV* gene mutations on FMF have not been analyzed in the Iranian population, a large population with different ethnic groups including: Persian, Azeri Turk, Arab, Kurd and other minorities for instance Armenians. Almost all the large studies of FMF in Iran accomplished among the Azeri Turkish population ((Bonyadi et al., 2009; Esmaeili et al., 2008; Salehzadeh et al., 2015). In the present study 390 unrelated FMF patients from different ethnicities were selected to analyze the mutations of the *MEFV* gene over a period of 4 years. We aimed to determine the frequency and spectrum of *MEFV* gene mutations in an Iranian population with different ethnicities.

2. Materials and methods

In the current study, we selected 390 unrelated patients, suspected to suffer from FMF according to the Tel-Hashomer criteria (Livneh et al., 1997), who were referred to the Department of Pediatrics Valie Asr Hospital and Genetics Laboratory of Cancer Institute of Imam Khomeini Hospital between September 2011 and November 2015. Every family was informed about the study and written consents were signed by either patients or one of the parents for blood sampling. We analyzed 12 most frequent *MEFV* mutations: E148Q, P369S, F479L, M680I, M680I, I692del, M694V, M694I, K695R, V726A, A744S and R761H by reverse hybridization assay (FMF strip assay, Vienna lab, Vienna, Austria) according to instruction of manufacturer, which is based on polymerase chain reaction (PCR) and reverse hybridization methods.

In the first step, exons 2, 3, 5 and 10 were amplified for each patient by multiplex PCR reaction. The thermocycling program includes 35 cycles (94 °C for 15 s, 58 °C for 30 s and 72 °C for 30 s) and a final extension at 72 °C for 3 min was performed. PCR products were four DNA fragments 206, 236, 295 and 318 bp. PCR products resolved on a 3% agarose gel with Gel Green DNA Staining. Then these products were selectively hybridized on a test strip, presenting a parallel array of allele-specific oligonucleotide probes and detected by an enzymatic color reaction.

We also selected 78 patients from those 390 patients for Sanger sequencing of exons 2 and 10 of *MEFV* gene (ABI PRISM 3730XL). 24 of these patients had a heterozygous mutation and 44 patients had no mutation, according to strip assay method results.

Table 2
Percent of different symptoms among patients.

Clinical manifestations	Number	Percent
Periodic fever	353	90.28%
Abdominal pain	224	57.28%
Arthritis	59	15.08%
Bone pain	26	6.64%
Myalgia	20	5.11%
Vomiting	16	4.1%
Chest pain	15	3.83%
Aphthous stomatitis	14	3.58%
Seizures	10	2.55%
Headache	9	2.30%
Erysipeloid	2	0.5%
Amyloidosis	1	0.2%

3. Results

Among the 390 patients, 236 (60.5%) were male, and 154 (39.5%) were female. The mean age of the patients was 10 years. In the current study, 72.4% patients manifested the first symptoms of the disease under the age of 10 years and 91.6% have shown under 20 (Table 1). The main clinical finding are summarized in Table 2.

3.1. Results of strip assay

In the present study, strip assay results showed at least one mutation in 234 patients (60%), and no mutation in other 156 patients (40%). Out of the 234 patients, 137 (58.5%) had heterozygous mutations, 77 (33%) had compound heterozygous mutations and 20 (8.5%) had homozygous mutations (Table 3).

In our study, the most frequent mutation was M694V with a frequency of 13.7%. Also, the allele frequencies of the most common mutations were summarized in Table 4.

Due to the diversity of ethnicities among Iranian population, we summarized the 10 common mutations in Table 5 according to patient's geographical differences ethnicities. We have also summarized the frequency of the 10 common mutation within each ethnic group in Table 6.

3.2. Sequencing results of exon 2 and 10

Among 78 (24 with heterozygous mutation, 54 without mutation) patients which had been selected for sequencing of exon 2 and 10 in *MEFV* gene, 32 missense mutations have been shown in

Table 3
The mutation frequencies of the most common mutations and genotype distribution of patients.

Mutation	Genotype	Number	Percent
Heterozygous	M694V	45	19.2
(N = 137)	E148Q	40	17
(58.5%)	M694I	26	11
	M680I	7	3
	V726 A	6	2.5
	A744S	5	2.1
	P369S	4	1.7
	Other	4	1.7
Compound Heterozygous	M694V/E148Q	14	6
N = 77	M694V/V726A	12	5.1
(33%)	E148Q/M694I	10	4.2
	M694V/M694I	9	3.8
	M694V/M680I	6	2.5
	E148Q/V726A	5	2.1
	M694V/R761H	4	1.7
	M694I/R761H	4	1.7
	Other	13	5.5
Homozygous	M694V/M694V	8	3.4
(N = 20)	M680I/M680I	6	2.5
(8.5%)	E148Q/E148Q	4	1.7
	V726A/V726A	1	0.04
	R761H/R761H	1	0.04
Total		234	100

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Table 4
Allele frequencies of the most common mutations.

Mutation	Number	Frequency
M694V	107	13.7%
E148Q	80	10.25%
M694I	51	6.53%
V726A	32	4.1%
M680I	30	3.84%
R761H	13	1.66%
P369S	6	0.8%
A744S	6	0.8%
Other	2	0.25%
wild type	453	58.07%
Total	780	100%

addition to those reported in 24 patients with the heterozygous mutation.

R202Q mutation was detected in 11 patients with the heterozygous genotype, 6 patients with compound heterozygous, 2 patients with homozygous genotype (2.6%) and one with homozygous for R202Q and heterozygous M694V.

In this study, we detected a novel missense variant (R204H, c.611 G > A) (SCV000297822) in exon 2 of *MEFV* gene in heterozygous form (Fig. 1) in a 6-year-old boy. This mutation results in a substitution of Histidine (His) to Arginine (Arg) at codon 204. The clinical manifestations of this patient were periodic fever and abdominal pain which had started from the age of 3. Furthermore, we identified three rare mutations among sequenced samples including: P115T, G304R, and E230K.

4. Discussion

The situation of Ancient Great Iran on the path of Silk Road, and the immigration from the bordering countries, and further the incidence of multitude wars with foreign states, particularly Mediterranean ethnic groups, construct the genetic pool of this population extremely heterogeneous (Derenko et al., 2013; Regueiro et al., 2006). Moreover, the purity of several distinct races in this country has been mostly preserved by geographical borders and by an old culture that has consistently encouraged consanguineous marriages, a significant factor in the accumulation of recessive mutations (Saadat et al., 2004). Iran as a neighbor country to Turkey and Arab countries where FMF disease is common has a high prevalence of FMF disease, and due to the variety of ethnicities, it seems to have different patterns of mutations too. In our study, we analyzed 390 patients for 12 common mutations, 234 patients (60%) had at least one mutation (heterozygous genotype). This result is similar to different studies in Iran, Turkey and Arabic countries (Coskun et al., 2015; Dundar et al., 2011; Esmaeili et al., 2008; Salehzadeh et al., 2015), and among mutation positive patients the heterozygous genotype 137 patients (58.5%) was the highest genotype.

In present study, M694V with the allele frequency of 13.7% was the most frequent observed mutation among population study (Table 4). More specifically, M694V was the most common mutation among Turkish patients (16.7%) and patients from north of Iran (16.1%) (Table 6), similar to previous reports in other ethnicities such as Turks, Arabs, and Armenians (Dundar et al., 2011; Majeed et al., 2005; Sabokbar et al., 2014; Sarkisian et al., 2008; Sayin Kocakap et al., 2014). We identified M694V mutation 19.2% in

Table 5
Percent of mutations according to ethnicities.

mutations	All Ethnicities	Turkish (Azeri)	North	Near to Arabs		
				Kurdish	Central	South
Total allele	780 (100%)	264 (34%)	236 (30.2%)	60 (7.7%)	154 (19.7%)	66 (8.4%)
M694V	107	44 (41.1%)	38 (35.5%)	4 (3.8%)	16 (15%)	5 (4.6%)
E148Q	80	29 (36.2%)	19 (23.7%)	4 (5%)	23 (28.8%)	5 (6.3%)
M694I	51	17 (33.3%)	13 (25.5%)	10 (19.6%)	8 (15.7%)	3 (5.9%)
V726 A	32	17 (53%)	6 (18.7%)	1 (3%)	7 (21%)	1 (3%)
M680I	30	17 (56.6%)	8 (26.7%)	0	5 (16.7%)	0
R761H	13	6 (46.1%)	5 (38.5)	0	2 (15.4%)	0
A744S	6	2 (33.3%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	0
P369S	6	3 (50%)	1 (16.7%)	1 (16.7%)	0	1 (16.6%)
G605A	1	0	0	0	0	1 (100%)
R791H	1	1 (100%)	0	0	0	0
Number of patients	390	132	118	30	77	33

Table 6
The frequency of mutations within each ethnic group.

Mutation	All Ethnicities	Turkish (Azeri)	North	Near to Arabs		
				Kurdish	Central	South
M694V	107	44 (16.7%)	38 (16.1%)	4 (6.7%)	16 (10.4%)	5 (7.6%)
E148Q	80	29 (11%)	19 (8.1%)	4 (6.7%)	23 (14.9%)	5 (7.6%)
M694I	51	17 (6.4%)	13 (5.6%)	10 (16.6%)	8 (5.2%)	3 (4.5%)
V726 A	32	17 (6.4%)	6 (2.6%)	1 (1.7%)	7 (4.6%)	1 (1.5%)
M680I	30	17 (6.4%)	8 (3.3%)	0	5 (3.2%)	0
R761H	13	6 (2.3%)	5 (2.1%)	0	2 (1.3%)	0
A744S	6	2 (0.8%)	1 (0.4%)	2 (3.3%)	1 (0.7%)	0
P369S	6	3 (1.1%)	1 (0.4%)	1 (1.7%)	0	1 (1.5%)
G605A	1	0	0	0	0	1 (1.5%)
R791H	1	1 (0.4%)	0	0	0	0
wild type	453 (58%)	128 (48.5%)	145 (61.4%)	38 (63.3%)	92 (59.7%)	50 (75.8%)
total	780 (100%)	264 (100%)	236 (100%)	60 (100%)	154 (100%)	66 (100%)
Number of patients	390	132	118	30	77	33

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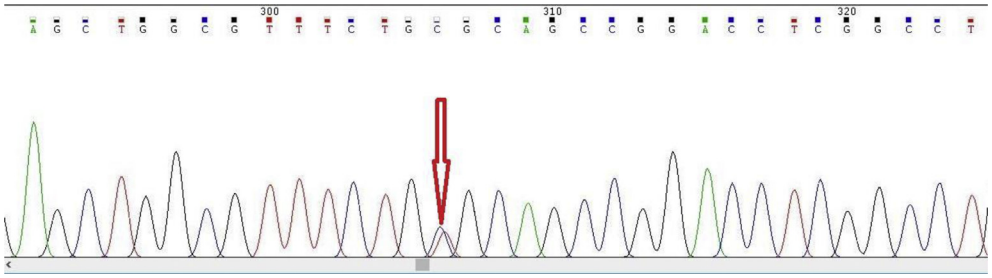

Fig. 1. Missense mutation (R204H, c.611 G > A) in exon 2 of *MEFV* gene in heterozygous form.

heterozygous form, 19.1% in compound heterozygous and 3.4% in homozygous form (Table 3). The other four most common mutations were E148Q, M694I, V726A, and M680I respectively. (Table 4).

We detected E148Q as the second common mutation with the population frequency of 10.25% (Table 4). We identified E148Q mutation 17% in heterozygous form, 10.2% compound heterozygous form, and 1.7% homozygous form (Table 3), which indicates major part of E148Q mutation were in heterozygous or compound heterozygous form rather than homozygous form. Moreover, E148Q was the most common mutation among patients from the central parts of Iran which are geographically near to Arab population (14.9%) (Table 6).Supporting our data, most of the studies have reported E148Q as one of four common mutations and most of them have reported E148Q as the second common mutation (Bonyadi et al., 2015; Coskun et al., 2015; Sabokbar et al., 2014).

In our study, M694I with the allele frequency of 6.5% was reported as the third common mutation, unlike reports in Turkey and among Iranian Azeri Turks, which is M694I is the less common mutation (Bonyadi et al., 2015; Dundar et al., 2011). Besides, M694I is one of three common mutations among Arabs (Ben-Chetrit and Touitou, 2009; Majeed et al., 2005; Mattit et al., 2006). Djouher et al. reported M694I as the most common mutation among Algerian Arabs (Ben-Chetrit and Touitou, 2009). This high frequency of M694I in our study can be due to Arabic ethnicity among Iranians, mostly among Kurdish and population in the south and central part. Table 5 shows the high mutation frequency of M694I (41.2%) among population geographically and ethnically near to Arabs (accumulation frequency of Kurdish, central, south). Moreover, M694I with the 16.6% frequency is the most common mutation among Kurdish patients (a subgroup of near to Arabs) (Table 6).

Mutations V726A and M680I with the population frequency of 4.1%, 3.8% respectively were the fourth and fifth common mutations. V726A frequently has been reported as one of three common mutations in Turkish, Iranian Azeri Turks and Arabs (Bonyadi et al., 2009; Esmaeili et al., 2008; Majeed et al., 2005; Salehzadeh et al., 2015). In our study, V726A mutation with the 6.4% mutation frequency among Azeri Turks was in the third common mutation along with M694I and M680I (Table 6).

As mentioned above, the variety of mutation frequencies among studies may relate to ethnical and geographical differences of the patients. In order to reveal the differences among ethnic groups, we categorized the mutation based on geographic and ethnic differences in Table 5.

Almost all of previous studies about FMF disease in Iran were carried among Azeri Turks which they have a high frequency of FMF disease (Bonyadi et al., 2009; Esmaeili et al., 2008; Salehzadeh et al., 2015). Our results also show the high frequency of FMF disease among Azeri Turks. Moreover, our findings indicate that FMF is also prevalent in other parts and ethnicities of Iran. We also had sequenced exon 2 and 10 of *MEFV* gene in 78 patients and identified mutation R202Q as the most frequent alteration among these 78 patients.

R202Q was detected in 11 patients (14.1%) with heterozygous genotype, 6 patients (7.6%) with compound heterozygous, 2 patients (2.6%) with homozygous genotype and one (1%) with homozygous for R202Q and heterozygous M694V. R202Q was initially reported by Bernot et al. as a benign alteration (Bernot et al., 1998). However, different studies have shown an association between R202Q and FMF symptoms (Comak et al., 2014; Yigit et al., 2012). The findings indicate that R202Q can be a disease-causing mutation rather than a polymorphism. Moreover, like other patients, R202Q homozygous and compound heterozygous patients had FMF symptoms, however, the symptoms among heterozygous patients were milder. Nonetheless in the present study due to the lack of healthy control group we cannot strongly suggest this alteration as a disease-causing mutation.

As a Conclusion, this study describes the *MEFV* mutational spectrum and distribution in the Iranian population, and shows different mutation patterns among Iranian ethnicities. Moreover, M694V was identified as the most common *MEFV* mutation among the Iranian population. We also found a novel missense variant (R204H, c.611 G > A) (SCV000297822) in exon 2 of *MEFV* gene in a 6-year-old boy.

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