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Spectrum of *MEFV* gene mutations in 4,256 familial Mediterranean fever patients from Iran: a comprehensive systematic review

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Abstract

Background: Familial Mediterranean fever (FMF), known as a disease with a high prevalence rate among Armenian, Turkish, Jewish, and Arab descent populations, occurs as a result of pathogenic variants in mediterranean fever (*MEFV*) gene. The aim of this study was to review the spectrum and frequency of *MEFV* gene mutations reported among Iranian FMF patients.

Methods: After performing a systematic review of the literature and implementation of inclusion and exclusion criteria, 16 articles published between 2004 and 2020, involving 4,256 Iranian FMF patients, were included.

Results: A total of 38 different *MEFV* gene mutations were identified. The most common mutations among Iranian FMF patients were: p.M694V (c.2080A > G) (20.27%), p.E148Q (c.442G > C) (10.27%), p.V726A (c.2177T > C) (8.24%), p.M680I (both c.2040G > C and c.2040G > A) (7.20%), p.R761H (c.2282G > A) (2.1%), and p.M694I (c.2082G > A) (2. 1%). The frequencies of these mutations were significantly different in different parts of the country.

Conclusions: The ranks and frequencies of p.M694V, p.E148Q, p.V726A, p.M680I, and p.M694I in our population were closer to those observed in the Mediterranean countries, especially in the Middle Eastern Arab populations. Although some comprehensive studies have been performed on Azeri Turkish patients living in northwestern Iran, studies in other areas, especially in eastern Iran, have been very limited. One reason for this observation could be due to the low frequency of FMF patients in those areas. Regardless of the reason for this, the exact spectrum and frequency of *MEFV* gene mutations in Iranian FMF patients remain unclear. Therefore, comprehensive future studies in different parts of the country are recommended.

Keywords: Familial Mediterranean fever, *MEFV* gene, Mutation, Iran

Background

As the most common form of monogenic autoinflammatory diseases [1], familial Mediterranean fever (FMF) has been known as a disease with a high prevalence rate among Armenian, Turkish, Jewish, and Arab descent populations [2]. This disease is characterized by recurrent fever and serositis (e.g., peritonitis, pleuritis, synovitis) symptoms [1, 3]. Most of FMF patients experience the first attacks before the age of 20, with a mean age of onset between 3 and 9 years. However, the disease is not unlikely to occur after the age of 40 [1].

Although FMF has typically been described as an autosomal recessive inherited disease, there are rare studies that support the autosomal dominant pattern of the disease [4–6]. FMF disease occurs as a result of pathogenic variants in Mediterranean fever (*MEFV*) gene. This gene is located on the short arm of chromosome 16 (16p13.3),

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consists of ten exons and encodes a 781-amino acid protein called pyrin [1, 7]. The Infevers database (https://infevers.umai-montpellier.fr/web/) is an online databank for mutations that play a role in autoinflammatory diseases. The current total number of *MEFV* gene sequence variants in this database is 384, most of which are found in exons 2, 10, 3, 5, and 1, respectively. In addition, more than 96% of the mutations are classified as substitutions.

Only a limited number of *MEFV* gene mutations are common; the others are rare mutations with no clinical phenotypes and are mainly observed in populations where FMF is not prevalent [7]. Although the mutations of p.M694V (c.2080A > G), p.M680I (c.2040G > C), p.V726A (c.2177T > C), p.M694I (c.2082G > A), and p.E148Q (c.442G > C) have been observed in more than two thirds of FMF cases in at risk populations, their frequencies may differ between ethnic groups [1].

Iran is a country with a mixture of different ethnicities including Persians, Azeri Turks, Kurds, Arabs, Lurs, Gilaks, and so on. There is no comprehensive data on the prevalence of FMF disease in the Iranian population. However, based on published studies, the focus of the disease seems to be among Azeri Turks living in the northwest. In this study, the spectrum and frequency of *MEFV* gene mutations previously reported among Iranian FMF patients have been reviewed.

Methods

Search strategy

Using the keywords of Familial Mediterranean Fever, FMF, MEFV, and Iran, as well as their Persian equivalents, in all possible combinations, a comprehensive search was performed on the online databases of Scopus, Web of Science, PubMed, ProQuest, Cochrane, Science Direct, Magiran, and SID. An example of a combined search in the PubMed database is as follows: (((Familial Mediterranean Fever[Title/Abstract]) OR (FMF[Title/Abstract])) AND (MEFV[Title/Abstract])) AND (Iran[Title/Abstract]). No time or language limitations were considered. To maximize the comprehensiveness of the search, references used in all associated articles were manually reviewed.

Inclusion and exclusion criteria

The inclusion criteria were as follows: all studies investigated the spectrum of *MEFV* gene mutations in Iranian FMF patients, with sufficient data and full text availability. The exclusion criteria were non-Iranian, review, duplicate, irrelevant, and conference studies.

Study selection

The extracted articles were reviewed independently by two investigators. If they did not agree on a particular article, it was discussed by all authors. Three steps including the exclusion of duplicated articles, the exclusion of irrelevant articles based on the title and abstract, and the exclusion of irrelevant articles based on the full text of the articles were our process in selecting articles.

Quality evaluation

The quality of the studies was evaluated using the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) checklist. The checklist consists of 32 sections that cover different parts of a report. Considering the threshold score of 16, articles with this score or higher were selected and the remainder were excluded from the study.

Data extraction

A checklist was used to extract the required information including article title, first author's name, year of publication, region/province, sample size (total, males, and females), mean age of disease onset, mutation detection rate, the rate of consanguineous marriages, and patients' clinical symptoms from each article.

The gene reference sequence was NG_007871.1. NM_000243.2 was used to determine the variant position. Position of the variants in protein was determined based on UniProtKB/SwissProt O15553-2.

Results

Using the PRISMA guidelines, a systematic review on the mutation spectrum of the *MEFV* gene in Iranian FMF patients was carried out and a total of 444 articles were found. Following the exclusion of 428 articles due to duplication and irrelevant to our subject, 16 articles published between 2004 and 2020, involving 4,256 Iranian FMF patients, were included in this systematic review. Nine studies were performed on patients from different regions [8–16], six studies were performed on Azeri Turkish patients living in the northwest [17–22], and one study was performed in the southwest of Iran [23] (Table 1). The ratio of male to female varied from 0.57 to 1.68. The mean age of disease onset, the rate of consanguineous marriages among the patients' parents, and clinical symptoms were not reported in many of the articles. Therefore, they were presented in Table 1.

Out of a total of 4,256 patients, at least one mutation had been reported for 2933 patients (68.9%) (Table 1). As shown in Table 2, 38 different *MEFV* gene mutations, including 37 substitutions and one small deletion, were identified. The highest number of mutations were found in exons 10, 2, 3, 5, and 1, respectively. No mutations were reported in other five exons. According to the Infevers database, 11 mutations were classified as pathogenic or likely pathogenic. The most common mutations among

Table 1 Characteristics of included studies in the systematic review

Row	Geographic region (ethnicity)	Cases (n)		Mutation detection rate (%)	References
		Total	Male:female ratio		
1	Different (multiple)	30	17:13 (1.31)	14:30 (46.7)	Mirhassani et al. [11]
2	Different (multiple)	30	14:16 (0.88)	27:30 (90.0)	Farivar et al. [9]
3	Different (multiple)	36	16:20 (0.80)	35:36 (97.2)	Bidari et al. [8]
4	Different (multiple)	51	32:19 (1.68)	24:51 (47.1)	Mohebbi et al. [12]
5	Northwest (Azari)	130	78:52 (1.50)	78:130 (60.0)	Mohammadnejad and Farajnia [20]
6	Different (multiple)	85	31:54 (0.57)	67:85 (78.8)	Sabokbar et al. [13]
7	Different (multiple)	59	32:27 (1.19)	49:59 (83.1)	Hosseini et al. [10]
8	Northwest (Azari)	82	–	75:82 (91.5)	Gharesouran et al. [19]
9	Northwest (Azari)	1330	711:619 (1.15)	1330:1330 (100.0)	Bonyadi et al. [18]
10	Northwest (Azari)	239	–	188:239 (78.7)	Salehzadeh [22]
11	Different (multiple)	743	421:322 (1.31)	391:743 (52.6)	Beheshtian et al. [14]
12	Different (multiple)	390	236:154 (1.53)	234:390 (60.0)	Ebadi et al. [15]
13	Northwest (Azari)	630	268:362 (0.74)	164:630 (26.0)	Bagheri and AbdiRad [17]
14	Different (multiple)	20	9:11 (0.82)	8:20 (40.0)	Haghighat et al. [16]
15	Southwest	1	–	1 (100.0)	Farjadian et al. [23]
16	Northwest (Azari)	400	194:206 (0.94)	248:400 (62.0)	Rostamizadeh et al. [21]
	Total	4,256	–	2,933:4,256 (68.9)	–

Iranian FMF patients were: p.M694V (20.27%), p.E148Q (10.27%), p.V726A (8.24%), p.M680I (both c.2040G > C and c.2040G > A) (7.2%), p.R761H (c.2282G > A) (2.1%), p.M694I (2.1%), p.P369S (c.1105C > T) (0.49%), p.A744S (c.2230G > T) (0.45%), and p.F479L (c.1437C > G) (0.18%). Each of these mutations was identified on 15 or more FMF mutated alleles. Other mutations had been reported on only one or a few alleles. Therefore, they were considered as rare in this study. In addition, the heterozygous forms of p.M694V (15.36%) and p.E148Q (14.93%), the homozygous form of p.M694V (11.45%), and the compound heterozygous form of p.M694V/p.V726A (7.44%) were the most frequent genotypes in our population (data not shown).

Not all 16 articles reported the geographic location or ethnic origin of the patients, however, we categorized FMF patients into six groups originated from northwest, north, central, south, west, and southwest. Our results showed that the frequencies of six common mutations in Iran, including p.M694V, p.E148Q, p.V726A, p.M680I, p.R761H, and p.M694I are significantly different in different parts of the country (Fig. 1). The variants of p.K618N (c.1854G > C), p.K716M (c.2147A > T), p.S614F (c.1841C > T), p.H300Q (c.900T > G), p.A66P (c.196G > C), p.R202W (c.604C > T), p.P313S (c.937C > T) , and p.A310D (c.929C > A) were not reported in the Infevers database. In addition, based on this database, 19 variants were categorized as likely benign, VUS, and not classified (Table 2).

Discussion

To our knowledge, this is the first systematic review study on the spectrum of *MEFV* gene mutations among Iranian FMF patients. Our findings are in consistent with the results of global review studies. In fact, the mutations of p.M694V, p.E148Q, p.V726A, p.M680I (c.2040G > C), and p.M694I are responsible for three quarters or more of FMF patients originating from Middle Eastern populations [1, 2, 7, 24]. Based on haplotype analysis, it has been shown that many of the modern-day FMF chromosomes are of common ancestry and probably date back to pre-biblical times. This could be a possible reason for the high prevalence of the above five mutations [24, 25].

p.E148Q was found to be the second most common mutation among Iranian FMF patients (Table 2). This mutation has been reported to be the most common variant in the general population. Moreover, it is common even in parts of the world where FMF is rare [1]. The pathogenicity of this variant is still controversial; some studies have described it as benign and others have described it as VUS [26]. In addition, it may not cause an FMF phenotype even in the homozygous state [7]. Therefore, some researchers refer to it as a polymorphism rather than a mutation [7].

The third and fourth most common mutations in our population were p.V726A and p.M680I, respectively. Both of these mutations were classified as pathogenic in the Infevers database. It should be noted that p.M680I were reported in both forms of c.2040G > C

Table 2 Distribution of *MEFV* gene mutations among Iranian FMF patients

Row	Genomic position/rs ID	Transcript consequence	Protein consequence	Exon/ Intron	Pathogenicity (based on Infevers db)	Allele frequency (%)
Common mutations						
1	16:3293407 T/C (rs61752717)	c.2080A > G	p.Met694Val (p.M694V)	Exon10	Pathogenic	1725 (20.27)
2	16:3304626 C/G (rs3743930)	c.442G > C	p.Glu148Gln (p.E148Q)	Exon2	VUS	874 (10.27)
3	16:3293310 A/G (rs28940579)	c.2177T > C	p.Val726Ala (p.V726A)	Exon10	Pathogenic	701 (8.24)
4	16:3293447 C/G or T (rs28940580)	c.2040G > C or c.2040G > A	p.Met680Ile (p.M680I)	Exon10	Pathogenic	613 (7.20)
5	16:3293205 C/T (rs104895097)	c.2282G > A	p.Arg761His (p.R761H)	Exon10	Likely pathogenic	179 (2.10)
6	16:3293405 C/T (rs28940578)	c.2082G > A	p.Met694Ile (p.M694I)	Exon10	Pathogenic	179 (2.10)
7	16:3299586 G/A (rs11466023)	c.1105C > T	p.Pro369Ser (p.P369S)	Exon3	VUS	42 (0.49)
8	16:3293257 C/A (rs61732874)	c.2230G > T	p.Ala744Ser (p.A744S)	Exon10	VUS	38 (0.45)
9	16:3297166 G/C (rs104895083)	c.1437C > G	p.Phe479Leu (p.F479L)	Exon5	Likely pathogenic	15 (0.18)
Detected mutated alleles						4366 (51.29)
Total alleles						8512 (100.00)
Rare mutations						
10	16:3299468 C/T (rs11466024)	c.1223G > A	p.Arg408Gln (p.R408Q)	Exon3	VUS	Rare
11	16:3304567 C/G (rs104895079)	c.501G > C	p.Glu167Asp (p.E167D)	Exon2	Likely pathogenic	Rare
12	16:3293403T/C (rs104895094)	c.2084A > G	p.Lys695Arg (p.K695R)	Exon10	Likely pathogenic	Rare
13	16:3293633 C/G (rs766576175)	c.1854G > C	p.Lys618Asn (p.K618N)	Exon10	NA	Rare
14	16:3293409_3293411delATT (rs104895093)	c.2076_2078del	p.Ile692del (p.I692Del)	Exon10	Likely pathogenic	Rare
15	16:3293592 C/G (rs967990798)	c.1895G > C	p.Gly632Ala (p.G632A)	Exon10	Likely benign	Rare
16	16:3293340T/A (rs1596349932)	c.2147A > T	p.Lys716Met (p.K716M)	Exon10	NA	Rare
17	16:3293646 G/A (rs1332372034)	c.1841C > T	p.Ser614Phe (p.S614F)	Exon10	NA	Rare
18	16:3304661 C/T (rs876660989)	c.407G > A	p.Gly136Glu (p.G136E)	Exon2	VUS	Rare
19	16:3304168 A/C	c.900T > G	p.His300Gln (p.H300Q)	Exon2	NA	Rare
20	16:3306392 C/G (rs765151968)	c.196G > C	p.Ala66Pro (p.A66P)	Exon1	NA	Rare
21	16:3304464 G/A	c.604C > T	p.Arg202Trp (p.R202W)	Exon2	NA	Rare
22	16:3293529 C/T (rs104895085)	c.1958G > A	p.Arg653His (p.R653H)	Exon10	VUS	Rare
23	16:3293463 C/T (rs104895087)	c.2024G > A	p.Ser675Asn (p.S675N)	Exon10	Likely benign	Rare
24	16:3293454 C/T (rs104895088)	c.2033G > A	p.Gly678Glu (p.G678E)	Exon10	VUS	Rare
25	16:3293449T/G (rs104895089)	c.2038A > C	p.Met680Leu (p.M680L)	Exon10	Likely pathogenic	Rare
26	16:3293327 G/C (rs104895102)	c.2160C > G	p.Ile720Met (p.I720M)	Exon10	VUS	Rare
27	16:3293407T/A (rs61752717)	c.2080A > T	p.Met694Leu (p.M694L)	Exon10	Likely pathogenic	Rare
28	16:3293445 G/A (rs104895090)	c.2042C > T	p.Thr681Ile (p.T681I)	Exon10	VUS	Rare
29	16:3304529 G/C (rs104895134)	c.539C > G	p.Pro180Arg (p.P180R)	Exon2	VUS	Rare
30	16:3304202 G/A (rs104895132)	c.866C > T	p.Ala289Val (p.A289V)	Exon2	VUS	Rare
31	16:3304457 C/T (rs775663363)	c.611G > A	p.Arg204His (p.R204H)	Exon2	Not classified	Rare
32	16:3304725 G/T (rs147557169)	c.343C > A	p.Pro115Thr (p.P115T)	Exon2	Likely benign	Rare
33	16:3304158 C/T (rs75977701)	c.910G > A	p.Gly304Arg (p.G304R)	Exon2	Likely benign	Rare

Table 2 (continued)

Row	Genomic position/rs ID	Transcript consequence	Protein consequence	Exon/ Intron	Pathogenicity (based on Infevers db)	Allele frequency (%)
34	16:3304380 C/T (rs104895080)	c.688G > A	p.Glu230Lys (p.E230K)	Exon2	VUS	Rare
35	16:3297080 A/T	c.1523T > A	p.Leu508Gln (p.L508Q)	Exon5	VUS	Rare
36	16:3299754 G/A (rs771254090)	c.937C > T	p.Pro313Ser (p.P313S)	Exon3	NA	Rare
37	16:3299762 G/T	c.929C > A	p.Ala310Asp (p.A310D)	Exon3	NA	Rare
38	16:3293542 G/A	c.1945C > T	p.Leu649Phe (p.L649F)	Exon10	Not classified	Rare

and c.2040G > A in our population. Given that both

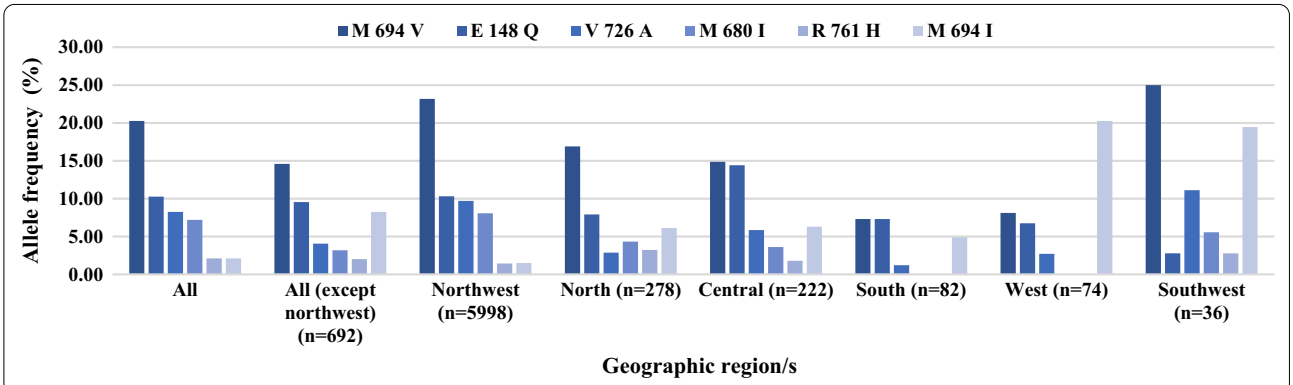

Fig. 1 Distribution of common *MEFV* gene mutations in different regions of Iran. It should be noted that only in nine articles it was possible to extract mutations based on the geographical location of patients (Mohammadnejad and Farajnia [20] & Sabokbar et al. [14] & Hosseini et al. [10] & Gharesouran et al. [19] & Bonyadi et al. [18] & Salehzadeh [22] & Ebadi et al. [15] & Bagheri and AbdiRad [17] & Rostamizadeh et al. [21]). Therefore, data presented here is taken from those nine articles

forms were pathogenic in the Infevers database, the total frequency of them was calculated in this study. The frequency of p.R761H and p.M694I mutations in the current study was about 2%. In the Infevers database, these mutations had been categorized as likely pathogenic and pathogenic, respectively.

Examination of the literature revealed that certain *MEFV* gene mutations are more common in certain populations. For example, p.M694V is the most frequent mutation in patients from Denmark [27], Germany [28], Turkey [29, 30], Armenia [31–33], Western European populations including Italy [34, 35], Greek [36] and Spain [37], and Middle eastern populations including Lebanon [38, 39], Jordan [40, 41], Palestine [42] and Syria [43]. In addition, while p.M694I and p.V726A are known to be common among Arab populations in the Middle East [44], p.M680I is common in Turkish FMF patients [29, 30]. The frequency of these mutations is not the same among North African countries [44–49]. In total, it seems that the order of five most common *MEFV* gene mutations among Iranian FMF patients is most similar to that observed in Middle Eastern Arab populations [44].

To our knowledge, no studies have been carried out specifically to investigate *MEFV* gene mutations in FMF patients living in the eastern provinces of Iran. Therefore, the patients enrolled in the studies reviewed by us were categorized into six groups originated from northwest, north, central, south, west, and southwest (Fig. 1). The order and frequency of common mutations in the northwest were very similar to those observed at the country level. This could be due to the high number of Azeri Turkish patients in this study, who accounted for more than 65% of the total number of patients. Each of the other regions had distinct mutational orders and frequencies. The high frequency of p.M694I in the north, central, south, west, and southwest was the most important distinguishing feature of the mutations observed in these regions compared to those observed at the country level as well as at the northwest area.

Limitations

Using of different mutation detection methods in different studies may have resulted in a bias in the estimation frequency of *MEFV* gene mutations in this systematic review. As another limitation, patients were not sorted

based on their geographical location in a number of studies. These subjects as well as the lack of information or limited information about the spectrum and frequency of *MEFV* gene mutations in some provinces of Iran were our challenges in achieving the exact spectrum and frequency of mutations in different geographical regions.

Conclusion

In conclusion, the five FMF founder mutations including p.M694V, p.E148Q, p.V726A, p.M680I, and p.M694I were the most common among Iranian FMF patients. The ranks and frequencies of these mutations were closer to those observed in the Mediterranean countries, especially in the Middle Eastern Arab populations. Although some comprehensive studies have been performed on Azeri Turkish patients living in northwestern Iran, studies in other areas, especially in eastern Iran, have been very limited. One reason for this observation could be due to the low frequency of FMF patients in those areas. Regardless of the reason for this, the exact spectrum and frequency of *MEFV* gene mutations among Iranian FMF patients remain unclear. Therefore, comprehensive future studies in different parts of the country are recommended.

Abbreviations

FMF: Familial Mediterranean Fever; *MEFV* gene: Mediterranean fever gene; STROBE checklist: Strengthening of the Reporting of Observational Studies in Epidemiology checklist.

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Authors' contributions

KM, Dr. RA and KG had the idea of the topic. KM, AM, SK and MK performed the literature search. KM analyzed data and drafted the manuscript. RA and KG supervised the study process and critically reviewed the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (Ethics code: IR.KUMS.REC.1399.976, project number: 990822).

Consent for publication

Not applicable.

Competing interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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