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شی
Mediterranean Fever Gene Analysis in The Azeri Turk Population with Familial Mediterranean Fever: Evidence for New Mutations Associated with Disease

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Abstract

Objective: Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent febrile attacks accompanied by serosal and synovial membrane inflammation. FMF is caused by mutations in the MEFV gene and are found usually among Mediterranean populations, Armenians, Turks, Arabs and Jews. The aim of this study was to determine the frequency of MEFV gene mutations among FMF patients in the Azeri Turk population in North-West of Iran.

Materials and Methods: In this descriptive study, 130 FMF patients with Azeri Turk origin were screened for mutations in four exons (2, 3, 5 and 10) of MEFV gene. Genomic DNA was extracted from whole blood and entered in ARMS-PCR and PCR-RFLP reactions. When cases were negative in ARMS-PCR and PCR-RFLP, the exons were amplified and subjected to direct sequencing.

Results: Our results showed that the most common mutations in this study population was M694V (40.19%) followed by E148Q (17.64%), V726A (13.72%), M680I (12.74%) and M694I (2.94%) mutations. Four new mutations including K618N, K716M, S614F and G136E were identified in our study.

Conclusion: The prevalence of five common mutations in our study was highly similar to previous studies analysing the Mediterranean basin populations. Investigation by sequencing also revealed four new variants in the study population. The main genotype-phenotype correlation finding was the presence of M694V mutation in homozygote or compound heterozygote state in the patients with renal manifestations.

Keywords: Familial Mediterranean Fever, MEFV Gene, Mutation, PCR, Sequence Analysis

Introduction

Familial Mediterranean fever (FMF), the most common hereditary periodic fever, is an autosomal recessive acute inflammatory disorder characterized by relapsing self-resolving febrile attacks and inflammation. It is accompanied by peritonitis, pleuritis, arthritis, skin rash and pain. The most severe complication of FMF is secondary amyloidosis commonly influencing the kidneys (11% of cases), and sometimes the adrenals, intestine, spleen, lung and testis (1-3). Moreover, clinical characteristics of the disease are different among patients from different ethnic groups (4). FMF mainly affects people from the Mediterranean basin countries especially Turks, Arabs, Armenians, and Sephardic Jews with a genetic prevalence of 6-8%. However, sporadic cases are also reported from other ethnicities (1, 2, 5). The carrier frequen-
cy for MEFV mutations in the populations that are more affected is very high, ranging from 37-39% in Armenians and Iraqi Jews and up to 20% in Turks, North African and Ashkenazi Jews, and Arabs. Despite high carrier prevalence in these populations, the frequency of FMF is less than anticipated, implying that the disease is either under diagnosed or that disease-related mutations have low penetrance (6). Until recently, the diagnosis of FMF was based on clinical signs, ethnicity, family history and response to colchicine. The identification of FMF causing gene (MEFV) has led to many studies analyzing the frequency of various mutations in different populations (7). The gene responsible for FMF (MEFV) is located on chromosome 16p13.3 and includes 10 exons. MEFV encodes a 781-amino-acid protein termed pyrin/marenostrin which probably assists the negative regulation of granulocyte-mediated inflammation. Nowadays, more than 200 sequence variants have been reported in the MEFV gene but not all are pathologic (1, 2). Most of these mutations are substitutions in exon 10. Five most commonly observed mutations i.e M694V, M680I, M694I, V726A and E148Q are responsible for a large percentage (about 65-95%) of observed mutations in different ethnic groups (1).

Iran is a country with different ethnic groups, including Persian (51%), Azeri Turk (24%), Kurd (7%), Arab (3%), and other smaller groups, such as Armenian. Although there are several FMF susceptible ethnic groups in Iran, the prevalence of FMF related mutations in the Iranian population has not been well defined. Only few MEFV gene mutational studies have been carried out about common FMF mutations in the Iranian population (5, 8-10). In this study the frequency of mutations in 4 exons of MEFV gene were investigated in clinically diagnosed FMF patients of Azeri Turk origin.

Materials and Methods

Patients

This descriptive study was carried out in the molecular biology lab in Tabriz biotechnology research center over a three year period of 2008-2010. The subjects include 130 (78 males, 52 females) Azeri Turk individuals living in the North West region of Iran. The subjects included 117 patients who fulfilled published diagnostic criteria for FMF and 13 of their asymptomatic first-degree relatives. The clinical inclusion and exclusion criteria were based on the standard Tell Hoshomer criteria for FMF diagnosis (2). A complete medical report and family history was collected for each individual and all of them provided informed consent before entering the study. This research was approved by the Ethical Committee of Tabriz University of Medical Sciences.

DNA extraction and PCR analysis

DNA was extracted from peripheral blood leukocytes of the patients by standard methods (5, 11). According to previous studies, ARMS-PCR (amplification refractory mutation system-PCR) and PCR-RFLP (PCR-restriction fragment length polymorphism) techniques were reliable methods to detect the point mutations (12, 13). Accordingly, we decided to use these techniques for detection of common MEFV mutations. Four common mutations in exon 10 (Met694Val, Met680Ile, Val726Ala, Met694Ile) were investigated by ARMS PCR and E148Q mutation in exon 2 was detected by PCR-RFLP using Ava1 restriction enzyme (Fermentas, Lithuania). The primers were designed by Oligo software version 5.0 and the expected product sizes are shown in table 1. Polymerase chain reaction (PCR) was performed in 25 microliter reaction volumes containing 100 ng genomic DNA, 25 pmols primers (MWG, Germany), 0.2 mM dNTPs (Fermentas, Lithuania), 2.5 mL reaction buffer (Fermentas, Lithuania) and 1U Taq DNA polymerase (Fermentas, Lithuania). Cycling conditions were 94˚C, for 4 minutes, followed by 30 cycles of denaturation at 94˚C, one minute, annealing (at 58˚C for M694V and V726A, 66˚C for M680I, 64˚C for M694I and 63˚C for E148Q), 30 seconds, extension at 72˚C for 30 seconds and a final extension of 72˚C for 5 minutes. PCR reactions were carried out in a thermo cycler (Eppendorf, Germany). The proper positive and negative controls were used for each reaction. PCR products and restriction enzyme-digested fragments were separated by electrophoresis on a 2% agarose gel (Sigma Aldrich, Germany). Ethidium bromide staining of the agarose gel was used to detect the amplified fragments. The results of PCR-RFLP and ARMS-PCR were checked by sequencing of randomly selected samples.
Table 1: The sequence of oligonucleotides used in ARMS-PCR and PCR-RFLP methods and expected product sizes

| Primer name       | Sequence                                      | Expected product size |
|-------------------|-----------------------------------------------|-----------------------|
| M694V common      | 5’-TATCATGTGTCTGGGCTC-3’                     | 183 bp                |
| Mutant            | 5’-TGGTACTCATTTCTTCAC-3’                     |                       |
| Normal            | 5’-TGGTACTCATTTCTTCAT-3’                     |                       |
| M694I common      | 5’-TATCATGTGTCTGGGCTC-3’                     | 183 bp                |
| Mutant            | 5’-CTGGTACTCATTTCTTCAT-3’                    |                       |
| Normal            | 5’-CTGGTACTCATTTCTTCAT-3’                    |                       |
| M680I common      | 5’-GGAAACAAGTGGAGAGGCTGC-3’                  | 197 bp                |
| Mutant            | 5’-GTCACATTGAAAGGAGATGCTGTGCT-3’             |                       |
| Normal            | 5’-GTCACATTGAAAGGAGATGCTGTGCT-3’             |                       |
| V726A common      | 5’-TTGGAGACAAGACAGCAGATGCC-3’                | 230 bp                |
| Mutant            | 5’-GTGCCATTCTCTTAGCAGATGCCGCT-3’             |                       |
| Normal            | 5’-GTGCCATTCTCTTAGCAGATGCCGCT-3’             |                       |
| E148Q forward     | 5’-ATATTCCACACAAGAAAAAGGCG-3’                | 247 bp                |
| E148Q reverse     | 5’-GAGGCTTGCCCTGCAGC-3’                      |                       |

Direct Sequencing

Direct sequencing was used for samples with negative results in ARMS-PCR and PCR-RFLP. Entire exons (2, 3, 5, 10) were amplified and subjected to sequencing by dideoxy method using sequencing primers (Table 2). The sequencing results were compared with the MEFV reference coding sequence available at NCBI with GenBank accession number AF111163.

Table 2: The sequence of primers used in direct sequencing method

| Method   | Primer sequence  |
|----------|------------------|
| FMF-E2-F | 5’- TTGCATCTGTGTTCCCTCC - 3’ |
| FMF-E2-R | 5’- CGGATTTAGAGGAAAGCAACATGCA - 3’ |
| FMF-E3-F | 5’- TCACGTGCAAGCCGCCGG - 3’ |
| FMF-E3-R | 5’- CAAGTGCTGGCAGAGAACGC - 3’ |
| FMF-E5-F | 5’- CATGCCTAGGCACAGACGGCC - 3’ |
| FMF-E5-R | 5’- CGGATTTAGAGGAAAGCAACATGCA - 3’ |
| FMF-E10-F | 5’- CCCATGAGCCCACTACCTGCC - 3’ |
| FMF-E10-R | 5’- TTGGAGACAAGACAGCAGATGCC - 3’ |

Statistical analysis

Descriptive statistics including Mean, percentage and standard deviation were used for the analysis of data obtained in this study. The significance of differences between the means was assessed by t test analysis.

Results

Clinical criteria

According to the recorded demographic data, all of the patients were from Azeri Turk origin. The age range of subjects was between 4 months to 51 years (mean of 22 ± 14.4 years) and the mean age of onset was 5.2 ± 3.9 years. Analysis of clinical symptoms according to the Tel-Hashomer criteria (2) showed a classic pattern where fever (84.03%) and peritonitis (78.15%) were the most common clinical symptoms. Clinical criteria is summarized in table 3.

Table 3: Frequency of FMF symptoms in our cohort study

| Clinical symptom | Fever | Peritonitis | Pleuritis | Arthritis | Renal manifestations | Erysipelas-like erithema |
|------------------|-------|-------------|-----------|-----------|----------------------|-------------------------|
| No (%)           | 100 (84.03) | 93 (78.15) | 50 (42.01) | 58 (48.73) | 19 (15.96) | 7 (5.88) |
MEFV genotyping

Molecular diagnosis of mutations was carried out by ARMS-PCR, PCR-RFLP and sequencing methods. A total of twenty one different genotypes were identified between 78 FMF patients. No MEFV mutations were found in 52 cases. Among 117 cases with FMF diagnosis and 13 asymptomatic relatives, 28 (21.53%) patients had homozygote mutations, 26 (19.95%) cases were found to have one heterozygote mutation and the remaining 24 (18.46%) were compound heterozygotes (Table 4). Four healthy relatives of patients were found to carry one heterozygote MEFV mutation (M694V and M680I), two of them were parents of an affected child with M694V/M680I compound heterozygote genotype. Two remaining relatives were parents of two patients with single heterozygote M694V and M680I mutations. Figures 1-5 show mutation analysis for 5 common MEFV gene mutations by ARMS-PCR and PCR-RFLP.

Table 4: MEFV genotypes in 130 FMF patients from North-West of Iran

| Mutation       | Genotype      | Number (%) |
|----------------|---------------|------------|
| **Heterozygote** |               |            |
| M694V-         | 6 (4.61)      |            |
| E148Q-         | 8 (6.15)      |            |
| V726A-         | 3 (2.3)       |            |
| M694I-         | 1 (0.76)      |            |
| R761H-         | 2 (1.53)      |            |
| A744S-         | 2 (1.53)      |            |
| new variant /- | 4 (3.07)      |            |
| M694V/V726A    | 6 (4.61)      |            |
| M694V/M680I    | 6 (4.61)      |            |
| M694V/E148Q    | 4 (3.07)      |            |
| M680I/V726A    | 2 (1.53)      |            |
| V726A/E148Q    | 2 (1.53)      |            |
| M694V/M694I    | 2 (1.53)      |            |
| G632A / new variant | 2 (1.53) |          |
| **Compound heterozygote** |           |            |
| M694V         | 17 (13.07)    |            |
| M680I         | 5 (3.84)      |            |
| **Homozygote** |               |            |
| E148Q         | 4 (3.07)      |            |
| V726A         | 1 (0.76)      |            |
| New variant   | 1 (0.76)      |            |
| **Total patients with mutation** | 78 (60) |            |

M694V accounted for the majority of FMF mutations with a frequency of 40.19% followed by E148Q (17.64%), V726A (13.72%), M680I (12.74%) and M694I (2.94%). Other/novel mutations detected by complete exon sequencing were found in 11 (8.42%) cases as shown in table 4. The results also indicated that five common missense mutations namely M64V, M680I, M694I, V726A and E148Q accounted for 87.25% of detected MEFV mutations.

Fig 1: ARMS-PCR result for M694V mutation. Detection of four common MEFV gene mutations by ARMS-PCR. For each mutation, the ARMS assay consists of two PCR reactions specific for the normal and mutant alleles. Lane 1, 3, 5 and 7 are reactions for mutant alleles and lanes 2, 4, 6 and 8 are reactions for normal alleles. Lane 9 and 10 are for no DNA controls and lane 11 is the DNA ladder.

Fig 2: ARMS-PCR result for M680I mutation. Detection of four common MEFV gene mutations by ARMS-PCR. For each mutation, the ARMS assay consists of two PCR reactions specific for the normal and mutant alleles. Lane 1, 3, 5 and 7 are reactions for mutant alleles and lanes 2, 4, 6 and 8 are reactions for normal alleles. Lane 9 and 10 are for no DNA controls and lane 11 is the DNA ladder.
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Fig 3: ARMS-PCR result for V726A mutation. Detection of four common MEFV gene mutations by ARMS-PCR. For each mutation, the ARMS assay consists of two PCR reactions specific for the normal and mutant alleles. Lane 1, 3, 5 and 7 are reactions for mutant alleles and lanes 2, 4, 6 and 8 are reactions for normal alleles. Lane 9 and 10 are for no DNA controls and lane 11 is the DNA ladder.

Fig 4: ARMS-PCR result for M694I mutation. Detection of four common MEFV gene mutations by ARMS-PCR. For each mutation, the ARMS assay consists of two PCR reactions specific for the normal and mutant alleles. Lane 1, 3, 5 and 7 are reactions for mutant alleles and lanes 2, 4, 6 and 8 are reactions for normal alleles. Lane 9 and 10 are for no DNA controls and lane 11 is the DNA ladder.

Fig 5: PCR-RFLP analysis of E148-Q mutation in FMF patients. Lane 1. undigested PCR product; lane 2, mutant heterozygote; lanes 3 and 4, mutant homozygote, lane 5, normal and lane 6. size marker.

Sequencing analysis

In the course of screening via direct sequencing, seven different mutations were found in 11 patients with negative results in ARMS- and RFLP-PCR. Three of these mutations i.e. A744S, G632A and R761H have been reported in previous studies, whereas four mutations were novel to this study. Nucleotide change 1853G>C causing lysine-to-asparagine substitution in codon 618 (K618N) was detected in homozygote and heterozygote form in one and three symptomatic FMF cases respectively. Also this new variant was found in a compound heterozygote state with G632A, a previously reported mutation, in two patients. Patient affected by K618N homozygote mutation have a severe form of disease whereas other new mutations was found in the symptomatic patients with mild to moderate state. All other novel variants were found on only one MEFV allele in the symptomatic patients as summarized in table 5.

Table 5: The list of novel variants of MEFV gene found in this study

| Nucleotide change | Amino acid change | State       | Number of affected patients | Number of exon |
|-------------------|-------------------|-------------|-----------------------------|----------------|
| 2147A>T           | K716 M            | Heterozygote| 1                           | 10             |
| 1853G>C           | K618N             | Heterozygote| 3                           | 10             |
| 1853G>C           | K618N             | Homozygote  | 1                           | 10             |
| 1841C>T           | S614F             | Heterozygote| 1                           | 10             |
| 407G>A            | G136E             | Heterozygote| 1                           | 2              |
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Genotype-phenotype correlation

Among 13 cases with renal manifestation, six patients were homozygote for the M694V mutation and 2 cases were M680I homozygotes. The remaining 5 affected people were compound heterozygotes with the following genotypes: M694V/M680I in 2 cases, M694V/M694I, M694V/V726A and G632A/K618N in one patient. The results also indicated that homozygote M694V mutation is associated with the severe form of the disease (p<0.05). However, there was no significant association between other clinical criteria and the specific mutations (p>0.05).

Discussion

The allele frequency of MEFV mutations varies among ethnic groups. The Iranian Azeri Turk ethnicity is considered to be a susceptible population to FMF, but there are scant reports on the prevalence of MEFV mutations in this population (1, 2, 9, 14). In the present study we have analyzed the frequency of MEFV mutations in Azeri Turk population living in North West of Iran. This is the first study that was undertaken by sequencing method for mutation analysis of four MEFV exons in this ethnic group.

The results of our study indicated that M694V variant was the most common mutation (40.19%) in this cohort study, followed by E148Q (17.64%), V726A (13.72%), M680I (12.74%) and M694I (2.94%). These results are consistent with previous studies in Azeri Turk population by PCR and Strip assay methods (8-10). However in a study on 16 FMF patients in the central part of Iran (Tehran city), the most common mutations were M680I, M694V, V726A, E148Q and M694I with the frequency of 23.6, 22.6, 15.3, 6.9 and 2.8%, respectively (10). The different frequency distribution of mutations may be related to the small sample size or genetic heterogeneity. Also the mutation frequency in our study group was in agreement with those of other populations (2, 3). The genotype frequency in our study and their comparison to other studies are summarized in table 6.

It has been shown that some rare MEFV mutations tend to be over represented in particular ethnic groups, but have been sporadically seen in other populations. For instance, R761H is more prevalent in Armenians and Turks, K695R in Jews, A744S in Arabs and F479L in Armenians (1). Screening by sequencing found several rare mutations in our study population, where three of them (R761H, A744S, G632A) had previously been reported in FMF subjects in other studies and four mutations (K716M, K618N, S614F, G136E) were novel. K618M mutation was detected in homozygote once and compound heterozygote state in three symptomatic FMF patients. The other three mutations were found in heterozygote form in FMF affected patients in the absence of any other mutations. All of these new variants were found in patients with clinical symptoms characteristic of FMF. Two of these novel changes were discovered in compound heterozygote form with G632A, a mutation known to be associated with FMF. Also no other mutations were identified in the complete exon sequencing of MEFV in patients affected with one novel heterozygote mutation. Consequently, these changes may be considered as FMF causes mutation and recommended to study in future studies. Also, the relevance of these novel mutations to FMF should be confirmed by studying in a large patients group and control subjects in different ethnic groups.

Different studies reported a significant association between M694V mutation and the severity of disease (3, 27, 28). It has been shown that patients with homozygote M694V mutation have an earlier onset and higher frequency of arthritis compared to the other genotypes. Also the prevalence of renal amyloidosis is higher in M694V homozygous patients than in patients with other MEFV genotypes (29-31). In this study we found an association between M694V mutation and severity of the disease and renal manifestation. But, we did not find any association between specific mutation or genotypes and other clinical features, such as, age of onset, attack frequency etc.

The presence of only one MEFV mutation in clinically diagnosed FMF patients have always been a subject of concern. At first, some researchers supposed the presence of mutations in the second MEFV allele, but a number of studies have not detected any other mutation in the complete gene sequencing (18, 32). It has been suggested that modifying genes such as major histocompatibility complex (MHC) class-I-chain-related gene A (MICA) and serum amyloid A (SAA) could be a possible reason for such observations. In some cases, FMF has been reported as a dominant state with low penetrance (6, 33). Our results are consistent with the hypothesis about the clinical implications of some FMF mutations in heterozygous forms. The frequency of heterozygote subjects in our study was 19.95%. So it seems that, the presence of a given mutation is enough to cause FMF clinical symptoms in some patients.
Conclusion

This study analyzed the spectrum of MEFV mutations among FMF patients of Azeri Turk origin in the North West region of Iran. A genotype-phenotype correlation showed an association between the M694V mutation and the severe form of the disease and renal manifestation. Also the results of our study revealed presence of novel mutations in Iranian Azeri Turk population.

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References

1. Toutou I. The spectrum of familial Mediterranean fever (FMF) mutations. Eur J Hum Genet. 2001; 9(7): 473-483.
2. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum. 1997; 40(10): 1879-1885.
3. Tunca M, Akar S, Onen F, Ozdogan H, Kasacopur O, Yalcinkaya F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore). 2005; 84(1): 1-11.
4. Chen X, Fischel-Ghodsian N, Cercek A, Hamon M, Ogur G, Lotan R, et al. Assessment of pyrin gene mutations in Turks with familial Mediterranean fever (FMF). Hum Mutat. 1998; 11(6): 456-460.
5. Farajnia S, Nakhlaband A, Rafaeey M, Sakha K. Early age onset familial Mediterranean fever associated with compound heterozygote M680I/M694V mutation. AFR J Biotechnol. 2006; 5(19): 1713-1716.
6. Booty MG, Chae JJ, Masters SL, Remmers EF, Barham B, Le JM, et al. Familial Mediterranean fever with a single MEFV mutation: Where is the second hit? Arthritis Rheum. 2009; 60(6): 1851-1861.
7. Pras E, Aksentijevich I, Gruberg L, Balow JE Jr, Prosen L, Dean M, et al. Mapping of a gene causing familial Mediterranean fever to the short arm of chromosome 16. N Engl J Med. 1992; 326(23): 1509-1513.
8. Esmaeili M, Bonyadi M, Rafaeey M, Sakha K, Somi MH. Common MEFV mutation analysis in Iranian Azeri Turkish patients with familial Mediterranean fever. Semin Arthritis Rheum. 2008; 37(5): 334-338.
9. Bonyadi M, Esmaeili M, Jalali H, Somi MH, Ghaffari A, Rafaeey M, et al. MEFV mutations in Iranian Azeri Turkish patients with familial Mediterranean fever. Clin Genet. 2009; 76(5): 477-480.
10. Bidari A, Ghavidel-Parsa B, Najmabadi H, Talachian E, Haghhighat-Shoor M, Broumand B, et al. Common MEFV mutation analysis in 36 Iranian patients with familial Mediterranean fever: clinical and demographic significance. Mod Rheumatol. 2010; 20(6): 566-572.
11. Sayad A, Noruzinia M, Zamani M, Harihriish MH, Kazemnejad A. Lipoprotein lipase hindIII intronic polymorphism in a subset of Iranian patients with late-onset Alzheimer’s disease. Cell J. 2012; 14(1): 67-72.
12. Eisenberg S, Aksentijevich I, Deng Z, Kastner DL, Matzner Y. Diagnosis of familial Mediterranean fever by a molecular genetics method. Ann Int Med. 1998; 129(7): 539-542.
13. Shariati S A M, Behmanesh M, Gahlehtari H. A Study of the association between SNP NRG214390 in the 5' End of neurogin 1 gene with schizophrenia in a group of Iranian patients. Cell J. 2011; 13(2): 91-96.
14. Nobakht H, Zamani F, Ajdarkosh H, Mohamadzadeh Z, Fereshtehnejad SM, Nassaji M. Adult-Onset familial Mediterranean fever: clinical and demographic significance. Mod Rheumatol. 2010; 20(6): 566-572.
15. Akar N, Misiroglu M, Yalcinkaya F, Akar E, Cakar N, Turner N, et al. MEFV mutations in Turkish patients suffering from familial Mediterranean fever. Hum Mutat. 2000; 15(1): 118-119.
16. Yilmaz E, Ozen S, Balci B, Duzova A, Topaloglu R, Besbas N, et al. Mutation frequency of familial Mediterranean fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet. 1991; 9(7): 493-498.
17. Tunca M, Akar S, Hawkins PN, E Booth SE, Sengü B, Yavuzsen TU, et al. The significance of paired MEFV mutations in individuals without symptoms of familial Mediterranean fever. Eur J Hum Genet. 2002; 10(12): 786-789.
18. Ettem EO, Deveci SD, Erol, Yuce H, Elyas H. Familial Mediterranean fever: a retrospective clinical and molecular study in the East of Anatolia region of Turkey. Open Rheumatol J. 2010; 4: 1-8.
19. Sarkisian T, Ajrapetyan H, Shahsvaryan G. Molecular study of FMF patients in Armenia. Curr Drug Targets In-

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Table 6: The MEFV mutation frequency in our cohort study in comparison to other study populations

| Descent/ references | M694V | E148Q | V726A | M680I | M694I | Other/new mutations |
|---------------------|------|-------|-------|-------|-------|---------------------|
| Turkish (3, 15-18)  | 45 (41-73) | 3.5 (1-13) | 11 (2-14) | 13 (6-31) | 7 (0-14) | 1 (0-3) |
| Jewish (3, 21-23)   | 65 (56-100) | 5 (4-10) | 3 (0-12) | 1 (0-8) | 0 (0-1) | 6 (2-10) |
| Armenian (3, 19, 20)| 37 (21-52) | 3 (1-11) | 19 (11-26) | 20 (5-27) | 2 (0-10) | 2 (1-5) |
| Arabs (3, 24-26)    | 20 (9-23) | 6 (0-11) | 14 (0-29) | 7 (0-21) | 12 (0-42) | 3 (0-7) |
| Iranian (8-10)      | 39 (22-54) | 12 (6-16) | 16 (15-17) | 17 (12-23) | 2 (2-3) | 19 (10-28) |
| Our study           | 40.19 | 17.64 | 13.72 | 12.74 | 2.94 | 8.42 |
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20. Cazeneuve C, Sarkisian T, Pecheux C, Dervichian M, Nedelec B, Reinert P, et al. MEFV-gene analysis in Armenian patients with familial Mediterranean fever: diagnostic value and unfavorable renal prognosis of the M694V homozygous genotype-genetic and therapeutic implications. Am J Hum Gene. 1999; 65(1): 88-97.

21. French FMF consortium. A candidate gene for the familial Mediterranean fever. Nat Genet. 1997; 17(1): 25-31.

22. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF consortium. Cell. 1997; 90(4): 797-807.

23. Aksexntihevich I, Torosyan Y, Samuels J, Centola M, Pras E, Chae JJ, et al. Mutation and haplotype studies of familial Mediterranean fever reveal new ancestral relationships and evidence for a high carrier frequency with reduced penetrance in the Ashkenazi Jewish population. Am J Hum Genet. 1999; 64(4): 949-962.

24. Majeed HA, El-Khateeb M, El-Shanti H, Abu Rabaiha Z, Tayeh M, Najib D. The spectrum of familial Mediterranean fever gene mutations in Arabs: report of a large series. Semin Arthritis Rheum. 2005; 34(6): 813-818.

25. Al-Alami JR, Tayeh MK, Najib DA, Abu-Rubaiha ZA, Majeed HA, Al-Khateeb MS, et al. Familial Mediterranean fever mutation frequencies and carrier rates among a mixed Arabian population. Saudi Med J. 2003; 24(10): 1055-1059.

26. Papadopoulos VP, Giaglis S, Mitroulis I, Ritis K. The population genetics of familial Mediterranean fever: a meta-analysis study. Ann Hum Genet. 2008; 72(p86): 752-761.

27. Shohat M, Magal N, Shohat T, Chen X, Dagan T, Mimouni A, et al. Phenotype-genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis. Eur J Hum Genet. 1999; 7(3): 287-292.

28. Yalçinkaya F, Çakar N, Misirifoğlu M, Tümer N, Akar N, Tekin M, et al. Genotype-phenotype correlation in a large group of Turkish patients with familial Mediterranean fever: evidence for mutation-independent amyloidosis. Rheumatology (Oxford). 2000; 39(1): 67-72.

29. Akpolat T, Özkaya O, Özen S. Homozygous M694V as a risk factor for amyloidosis in Turkish FMF patients. Gene. 2012; 492(1): 285-289.

30. Dewalle M, Domingo C, Rozenbaum M, Ben-Chétrit E, Cattan D, Bernot A, et al. Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). Eur J Hum Genet. 1998; 6(1): 95-97.

31. Gershoni-Baruch R, Brik R, Shinawi M, Livneh A. The differential contribution of MEFV mutant alleles to the clinical profile of familial Mediterranean fever. Eur J Hum Genet. 2002; 10(2): 145-149.

32. Bernot A, da Silva C, Peito J, Cruaud C, Caloustian C, Castet V, et al. Non-founder mutations in the MEFV gene establish gene as the cause of familial Mediterranean fever. Hum Mol Genet. 1998; 7(8): 1317-1325.

33. Lachmann HJ, Sengul B, Yavuzsen TU, Booth DR, Booth SE, Bybee A, et al. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford). 2006; 45(6): 746-750.
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اصول تنظیم قراردادها

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