UDC 575
DOI: 10.2298/GENSR1402611G
Original scientific paper

MUTATION SCREENING OF FAMILIAL MEDITERRANEAN FEVER IN THE AZERI TURKISH POPULATION: GENOTYPE–PHENOTYPE CORRELATION AND THE CLINICAL PROFILE VARIABILITY

Jalal GHARESOURAN[1], Maryam REZAZADEH[1,2], Morteza GHOJAZADEH[3], Mojtaba MOHADDES ARDABILI[1]

[1]Department of Medical Genetics, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
[3] Liver and Gastrointestinal Disease Research Center, Tabriz University of Medical Sciences ,Tabriz, Iran

Gharesouran J., M. Rezazadeh, M. Ghojazadeh, M. Mohaddes Ardabili (2014): *Mutation screening of familial mediterranean fever in the azeri turkish population: genotype–phenotype correlation and the clinical profile variability.* Genetika, Vol 46, No. 2, 611-620.

Familial Mediterranean fever is known as a most frequent hereditary autoin-Xammatory among the autoinflammatory syndromes characterised by fever, arthritis and serosal inflammation. Clinically, the foremost severe symptom of the disease is amyloidosis, which may cause to renal failure. MEFV renal failure consists of ten exons and conservative mutations clustered in exon ten (M694V, V726A, M680I, M694I) and exon two (E148Q) are considered more common mutations within this coding region and that they are detected with a distinct frequency changes in line with ethnicity. The aim of this study was to research the spectrum of mutations in Azeri Turkish population.

We evaluated the molecular test results of 82 patients and their parents from eighty families identified as having FMF clinical symptoms referred to Molecular Genetics Laboratory of the Department of Medical Genetics. Patients were referred by their physicians for MEFV mutation detection. The most frequent mutations were M694V respectively followed by M680I (G/C), V726A, M694I and E148Q mutations. A phenotypic variability was also ascertained between patients with different mutations and it must be considered within the daily management of FMF patients.

Key words: Familial Mediterranean fever, 16p13.3, Azeri Turkish

Corresponding author: Jalal Gharesouran,Member of Academic Board,Faculty of medicine,Tabriz University of Medical Sciences,Tabriz-Iran,Tel/Fax: ++98-411-3371587,e-mail: Jalal.Gharesouran@gmail.com

INTRODUCTION

Familial Mediterranean fever (FMF, MIM249100) is one among the autosomal recessive disorders that characterised by continual attacks of fever and inflammation within the peritoneum, synovium and pleura, accompanied by pain. The clinical symptoms can be developed variously in different patients, sometimes even within the same family by recurring serositis leading to pain in the abdomen, chest, joints and muscles. Amyloidosis just like that seen in other chronic inflammatory diseases like rheumatoid arthritis, is that the most severe complication of FMF and leads to renal failure. Also, concerning these destructive arthritis and potentially life threatening secondary amyloidosis are assumed because the major long-term complications associated with the disease (PRAS *et al*. 1998; CAZENEUVE *et al*. 1999; LIVNEH *et al.* 1999; SHOHAT *et al.* 1999; TAMIR *et al.* 1999; BRIK *et al*. 2001; NOTARNICOLA *et al.* 2002; GERSHONI-BARUCH *et al.* 2003).

FMF is reported more frequently in the people with the origin from the Mediterranean region (non-Ashkenazi Jews, Armenians, Sephardic Jews, Turks, Greeks, Druze and Arabs), which are considered as classically at risk ethnic groups. This phenotype is less common in other populations of Mediterranean ancestry, with the carrier individuals and the severity of the clinical symptoms of the disease varying considerably both among and within different races.

The discovery of FMF causing gene (GenBank af018080) has prepared possibilities to study the distribution of various mutations in geographically and ethnically different groups (HOLMES *et al*. 1998; PRAS *et al*. 1998; AKSENTIJEVICH *et al.* 1999; CAZENEUVE *et al*. 1999; TAMIR *et al.* 1999; BOOTH *et al*. 2001; BRIK *et al*. 2001; MANSOUR *et al*. 2001; YILMAZ *et al.* 2001; NOTARNICOLA *et al*. 2002; AL-ALAMI *et al*. 2003; GERSHONI-BARUCH *et al.* 2003; ALDEA 2004; ATAGUNDUZ *et al.* 2004; AYESH *et al*. 2005; SARKISIAN *et al.* 2005; BELMAHI *et al*. 2006; MATTIT *et al.* 2006). The candidate gene is located on chromosome 16p13.3 and it has been recognized by positional cloning in the summer of 1997. The locus composes of 10 exons and encodes 781 amino acid protein that named pyrin/marenostrin that is predominantly expressed in polymorph nuclear cells as well as in cytokine activated monocytes. It seems that assist normally in keeping inflammation under control by inhibiting interleukin-1 (IL-1) processing and permitting macrophageapoptosis, without this control, an in appropriate full-blown inflammatory reaction occurs. To date, 218 MEFV gene alterations (polymorphisms/mutations) have been reported as responsible for the phenotypic variance seen in the disease that most of them are substitutions; 78 of them are missense, one nonsense, 39 silent mutations, 17 are located in introns, two in UTS, one is duplication, two are insertions and two are deletions (Holmes *et al.* 1998; Hull *et al*. 2003).

Between the investigated mutation frequencies in classically affected populations, five responsible for more than 70% of affected patient (V726A, M694V, M694I, M680I and E148Q7) (SHINAWI *et al*. 2000; GERSHONI-BARUCH *et al*. 2001). The tenth exon has the first four mutations reported in FMF and has the forty-eight of the MEFV mutations. Numerous reports have revealed that FMF may be provoked in carriers of a single mutation by factors unrelated to the other MEFV allele (LIVNEH *et al.* 2001). These secondary factors such as modifier genes, sex and ethnicity can alter the pattern and appearances of the disorder beside the detected mutations that can cause the different rate of clinical manifestation (DEWALLE *et al.* 1998; PRAS *et al.* 1998; AKSENTIJEVICH *et al.* 1999; TAMIR *et al.* 1999; YALÇINKAYA *et al.* 2000; LIVNEH *et al*. 2001; TOUITOU 2001; TOUITOU *et al*. 2001; NOTARNICOLA *et al.* 2002; CAZENEUVE *et al.* 2003; PADEH *et al*. 2003).

MATERIALS AND METHODS

Subjects

This study was conducted in the Department of Medical Genetics, Faculty of Medicine, University of Medical Sciences, and Tabriz, Iran. Our patients were screened by their physicians for MEFV mutation detection.

Criteria for Diagnosis of FMF Patients

Our patients were selected from north-west of Iran with Azeri Turkish origin and clinical diagnosis of FMF has until recently been based upon the published clinical criteria (Livneh et al. 1997) and all FMF subjects were diagnosed by expert clinicians regarding to: 1- probands and/or sibs with two FMF causing mutations in the MEFV gene (homozygotes or compound heterozygotes); and 2- probands found to carry only one known mutation but who demonstrated characteristic FMF symptoms that met the diagnostic criteria and who had no family history of FMF that could suggest a carrier state by descent. The diagnosis of phenotype in siblings when the proband was found to have two FMF mutations has been evaluated for presence of these same mutations in the sibling and when the proband had only one known mutation, it was based on the detection of the sharing of two alleles with the proband. Asymptomatic individuals with carrying mutations in both alleles were considered affected. Written consent was obtained from the parents of the children.

Genomic DNA extraction

Genomic DNA was isolated from EDTA anticoagulated blood using the total DNA extraction kit (Qiagen, Hilden, Germany), according to manufacturer's instructions.

Mutation Analysis

To screen for these mutations, we have selected direct PCR cleavage methods based on the in compliance of constitutive restriction sites or the implementation of a restriction site in either the wild type or the mutant allele. Identification of mutations M694V and V726A were executed by PCR with primers (FMF-A: 5'-GAATGGCTACTGGGTGGAGAT-3') and (FMF-B: 5'-GGCTGTCACATTGTAAAAGGAG-3'). Amplification conditions were 94$^{\circ C}$ for 4 min followed by 30 cycles of: 40s at94$^{\circ C}$, 30s at 56.2$^{\circ C}$, and 1 min at 72°Cand 10 min incubation at 72$^{\circ C}$. Normal allele does not have any *Hph*-I restriction site for M694V proximal to the mutation, on the contrary, creates a site in the PCR product of the mutant allele. Digestion with *Hph*-I the mutant allele yields one 118-bp and one 36-bp fragments and the normal allele gives a 154-bp uncut fragment. Mutant allele have an *Alu*-I restriction site in the PCR product for theV726A. Subsequent digestion by *Alu*-I, the normal allele yields a 154-bp uncut fragment whilst the mutant allele gives one 122-bp and one 32-bp fragment. Mutation detection for M694I was done by substituting a base in the sequence of primer FMF-C turn this way locates adjacent to the mutation locus and a *BspH*-I restriction site was produced in the normal allele. Designated conditions above were used to fragment amplification with FMF-C (5'-GCTACTGGGTGGTGATAATCAT-3') and FMF-B primers. After cleavage with *BspH*-I, the mutant allele gives a 149-bp uninterrupted fragment whilst yields a 130-bp and a 19-bp fragments for the normal allele. Mutation M680I was investigated by primers FMF-D (5'-TATCATTGTTCTGGGCTC-3') and FMF-E (5'-CTGGTACTCATTTTCCTTC-3'). The normal allele, following digestion with *Hinf*-I, shows one 124-bp and one 60-bp fragments whilst

the mutant allele yields a 184-bp uncut fragment. The amplification conditions for these primers were 94°C for 4 min that followed by 30 cycles of: 40s at 94°C, 45s at 55°C, and 1 min at 72°C and 10 min final incubation at 72°C. The PCR products were separated on 8% non-denaturating polyacrylamide gel. The comprising region of E148Q mutation was analyzed using primers F: 5'-GCCTGAAGACTCCAGACCACCCCG-3'and R: 5'-GGCCCTCCGAGGCCTTCTCTCTG-3' with an annealing temperature of 69°CC. 157bp PCR product was restricted with BstN1, which recognizes the mutation.

We analyzed exon 2, 3, 4 and exon 10 of the MEFVgene for all patients by bidirectional sequencing method that did not appeared above mentioned mutations. We tested 5´ end of exon 2 by PCR amplification using the forward primer F: 5´-ATCATTTTGCATCTGGTTGTCCTTCC-3 and the reverse primer R:5-TCCCCTGTAGAAATGGTGACCTCAAG-3. The PCR reaction was performed under the following conditions: 95°C for 2 minutes followed by 30 cycles of 95°C for 30s, 59.6°C for 30s and 72°C for 30s, and final extension at 72°C for 10 minutes. Also 3´ end of exon 2 was amplified by forward primer F: 5´-GGCCGGGAGGGGGCTGTCGAGGAAGC-3 and the reverse primer R: 5-TCGTGCCCGGCCAGCCATTCTTTCTC-3. Exon 10 primers were forward primer F: 5´-CCAGAAGAACTACCCTGTCCC-3 and the reverse primer R: 5-CAGAGCAGCTGGCGAATGTAT-3. PCR products were purified with the High Pure PCR Product Purification kit (Roche, Germany) and sequenced directly; using specific primers. Twenty one individuals without any symptoms of FMF were also investigated in the study as controls. Also, exons 3 and 4 were amplified by forward primer F: 5´-CACAGCAGAATCTCGGGG-3 and the reverse primer R: 5- GCACATCTCAGGCAAGGG-3.

RESULTS

The MEFV gene has recently been identified and major missense mutations causing FMF were described (FRENCH FMF CONSORTIUM, 1997; INTERNATIONAL FMF CONSORTIUM, 1997). Using this panel of direct PCR based tests we characterized mutation bearing chromosomes from our patient group comprised 82 unrelated Azeri Turkish FMF patients, of whom 27 were homozygous M694V and 24 were heterozygous for one MEFV mutation (M694V=22; M694I =4; V726A=6; M680I=4; E148Q=2). Sixteen different mutations were identified in these cases; five of them were frequently observed (Table1), while others were only detected at the heterozygous state (Table1) in affected individuals.

Table 1: Frequencies of the studied founder mutations in analyzed alleles in the target population.

Mutation type	Number of alleles	Genotype Status		Total Allele frequency (%)
		Homozygous	Heterozygous	
M694V	76	27	22	46.34
M694I	14	5	4	8.54
V726A	18	6	6	10.97
M680I	22	9	4	13.41
E148Q	8	3	2	4.89
Other*	12	1	-	7.31
Unknown	14	-	-	8.54
Total	164			100

* R202Q, R653H, R408Q, S675N, G678E, M680L, I720M, I692del, M694L, T681I and A744SM mutations.

On the other hand, E148Q and R202Q mutations in exon 2 were detected in each homozygous and heterozygous states and R408Q in exon 3 were detected only in heterozygous state. The observed MEFV genotypes are summarized in Table 1. Since the majority of FMF patients can be carrier of one or two of five mutations, obtained clinical information from them showed phenotypic variability in compare with the genotypic data (Table2).

Table 2. Analysis of presenting clinical manifestations of FMF cases

Clinical manifestations	Score		
	1	2	3
Family history	Negative (67.8%)	Positive (32.2%)	-
Consanguinity	Negative (42.7%)	Positive (57.3%)	>5 days
Duration of each attack	3> days (27.6%)	3-5 days (69.1%)	>30 year (3.3%)
Frequency of attacks	10> year (12.2%)	10-30 year (71.4%)	(16.4%)
Fever	Negative (10.6%)	Up to 39o ^{C} (12.3%)	<39^{o} ^{C} (77.1%)
Abdominal pain*	Negative (9.3%)	Moderate (19.1%)	Severe (71.6%)
Joint affection	Negative (52.7%)	Arthralgia (44.8%)	Arthritis (2.5%)
Chest pain*	Negative (41.2%)	Moderate (56.9%)	Severe (1.9%)
Myalgia*	Negative (54.1%)	Moderate (45.3%)	Severe (1.6%)
Operations	Negative (82.5%)	Positive (17.5%)	-

DISCUSSION

Polymorphism in the exon 2 region of the *DRB1* gene in Iranian Makuie sheep breed (fat-tailed sheep breed) was studied by PCR-RFLP. Compared to cattle and other animals, *Ovar-DRB1* locus is poorly studied in Iranian sheep breeds. Different methods have been used to study genetic variation in the *Ovar-DRB1* gene in various sheep breeds. Among different methods, PCR-RFLP analysis has been found a valuable technique in identifying genetic variation of the *DRB1* gene in farm animals (KONNAI *et al.,* 2003a, b; GRUSZYNSKA *et al.,* 2005).

Ten alleles and eighteen genotypes were identified in the exon 2 region of the *MHC-DRB1* gene in Makuie sheep breed population. The most frequent allele and genotype were A allele and AA genotype in the frequencies of 0.4756 and 0.317, respectively. Our results partly were in agreement with the results of KONNAI *et al*. (2003b) and GRUSZCZYNSKA *et al*. (2005). KONNAI *et al*. (2003a) reported alleles Q and P in Polish Heath and Polish Lowland sheep breeds with 6 and 13 different patterns respectively. GRUSZCZYNSKA *et al*. (2005) reported alleles B, E, D and F in Suffolk sheep breed. Other alleles (A, I, M, O and V) were not reported in sheep breeds until now. CHARON *et al.* (2000) have shown positive association between *MHC-DRB1* alleles with reduced faecal egg counts in parasitic infestations. Ovine *MHC* class II *DRB1* alleles reported to be associated with susceptibility to development of bovine leukemia virus-induced ovine lymphoma (NAGAOKA *et al.,* 1999). In recent researches we couldn't find any creature without *MHC* molecules. This truth can indicate that creatures without *MHC* couldn't survive longtime after their birth because any slight defect or mutation in *MHC* molecules would cause intense immunological disorder (DUKKIPATI *et al.,* 2006b).

Shannon's information index revealed high genetic diversity within studied population. The chi-square test showed significant ($P \geq 0.05$) deviation from Hardy-Weinberg equilibrium at the *MHC-DRB1* gene in the studied population. This was the first report on studying the polymorphism in the *MHC-DRB1* locus in Makuie sheep breed. The previous breeding programs in the most research centers of Iran were based on only phenotypic characters. This study may be considered as an introductory to understanding the genetic variability on native sheep breeds in the Azerbaijan regions by using molecular techniques that do not affect by environmental effects.

Table 3: A comparison of results obtained from various studies in population with different origins

Origin	Main gene mutation respectively by percent
Algeria	M694I, M694V, E148Q, A744S, M680I
Azeri Turks	M694V, M680I, V726A, M694I, E148Q
Armenia	M694V, V726A, M680I, E148Q, M694I, R761H
Egypt	V726A, M694V, M680I, E148Q, M694I
France	E148Q, M694V, M694I,
Greece	M694V, V726A, E148Q, M694I
Jews	M694V, V726A, M680I, M694I, E148Q
Jordan	M694V, V726A, M680I, E148Q, M694I
Italy	M694V, E148Q, M680I,M694I, V726A
Iraq	M694V, V726A, E148Q
Kuwait	V726A, M694I, M694V, A744S
Lebanon	M694V, V726A, M694I, M680I, E148Q
Morocco	M694V, M694I, A744S, M680L, E148Q
Palestine	M694V, V726A, M694I, M680I, E148Q
Syria	M694V, M694I, M680I, V726A, E148Q
Spain	M694V, E148Q
Tunisia	M694V, M694I, A744S, E148Q
Turks	M694V, E148Q, M680I, V726A, P369S

ACKNOWLEDGEMENT

The authors thank the FMF families for participating in our study.

. Received May 02h, 2014
Accepted July 22th, 2014

REFERENCES

AKSENTIJEVICH, I, Y TOROSYAN, J SAMUELS, , M CENTOLA, E,PRAS JJ CHAE, C ODDOUX, G WOOD, MP AZZARO, G PALUMBO, R GIUSTOLISI, M PRAS, H OSTRER, DL KASTNER (1999): Mutation and haplotype studies of familial Mediterranean fever reveal newancestral relationships and evidence for a high carrier frequencywith reduced penetrance in the Ashkenazi Jewish population. Am J Hum Genet. *64*:949–962.

ALDEA, A, F CALAFELL, JI ARÓSTEGUI, O LAO, J RIUS, S PLAZA (2004) :The West Side Story: MEFV haplotype in Spanish FMF patients and controls, and evidence of high LD and a recombination ''hot-spot'' at the MEFV locus. Hum Mutat. 23:e399.

AL-ALAMI, JR, MK TAYEH, DA NAJIB, ZA ABU-RUBAIHA, HA MAJEED, MS,AL-KHATEEB HI EL-SHANTI (2003): Familial Mediterranean fever mutation frequencies and carrier rates among a mixed Arabic population. Saudi Med J. *24*:1055–1059.

ATAGUNDUZ, MP, S TUGLULAR, G KANTARCI, E AKOGLU, H DIRESKENELI (2004): Association of FMF-related (MEFV) point mutations with secondary and FMF amyloidosis. Nephron Clin Pract. *96*:131–135.

AYESH, SK, SM NASSAR, WA AL-SHAREF, BY ABU-LIBDEH, HM DARWISH (2005): Genetic screening of familial Mediterranean fever mutations in the Palestinian population. Saudi Med J. *26:*732–737.

BELMAHI, L, A SEFIANI, C FOUVEAU, J FEINGOLD, M DELPECH, G GRATEAU, C DODÉ (2006): Prevalence and distribution of MEFV mutations among Arabs from the Maghreb patients suffering from familial Mediterranean fever. C R Biol. *329*:71–74.

BEN-CHETRIT, E, I LERER, E MALAMUD, C DOMINGO, D ABELIOVICH (2000): The E148Q mutation in the MEFV gene: is it a disease causing mutation or a sequence variant? Hum Mutat. *15*:e385–e386.

BOOTH, DR, HJ LACHMANN, JD GILLMORE, SE BOOTH, PN HAWKINS (2001): Prevalence and significance of the familial Mediterranean fever gene mutation encoding pyrin Q148. Q JMed. *94*: 527–531.

BRIK, R, M SHINAWI, L KASINETZ, R GERSHONI-BARUCH (2001): The musculoskeletalmanifestations of familial Mediterranean fever inchildren genetically diagnosed with the disease. Arthritis Rheum. *44*:1416–1419.

CAZENEUVE, C, T SARKISIAN, C PÊCHEUX, M DERVICHIAN, B,NÉDELEC P REINERT, A AYVAZYAN, JC KOUYOUMDJIAN, H AJRAPETYAN, M,DELPECH GOOSSENS M, C DODÉ, G GRATEAU, S AMSELEM (1999): MEFV-gene analysis in Armenians patients with FMF: diagnostic value, unfavorable renalprognosis of the M694V homozygous genotype, genetic and therapeutic implications. Am J Hum Genet. *65*:88– 97.

CAZENEUVE ,C, H AJRAPETYAN, S PAPIN, F ROUDOT-THORAVAL, D GENEVIÈVE, E MNDJOYAN, M PAPAZIAN, A SARKISIAN, A BABLOYAN, B BOISSIER, P DUQUESNOY, JC KOUYOUMDJIAN, E GIRODON-BOULANDET, G GRATEAU, T SARKISIAN, S AMSELEM (2000): Identification of MEFV independent modifying genetic factors for familial Mediterranean fever. Am J Hum Genet. *67*:1136–1143.

CAZENEUVE, C, Z HOVANNESYAN, D GENEVIÈVE, H HAYRAPETYAN, S PAPIN, E GIRODON-BOULANDET, B BOISSIER, J FEINGOLD, K ATAYAN, T SARKISIAN, S AMSELEM (2003): Familial Mediterranean fever among patients from Karabakh and the diagnostic value of MEFV gene analysis in all classically affected populations. Arthritis Rheum. **48**:2324–2331.

DEWALLE, M, C DOMINGO, M ROZENBAUM, E BEN-CHÉTRIT, D CATTAN, A BERNOT, C DROSS, M DUPONT, C NOTARNICOLA, M LEVY, I ROSNER, J DEMAILLE, I TOUITOU (1998): Phenotype genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). Eur J Hum Genet. 6:95–97.

GERSHONI-BARUCH, R, M SHINAWI, K LEAH, K BADARNAH, R BRIK (2001): Familial Mediterranean fever: prevalence, penetrance and genetic drift. Eur J Hum Genet. **9**:634–637.

GERSHONI-BARUCH, R, R BRIK, N ZACKS, M SHINAWI, M LIDAR, A LIVNEH (2003): The contribution of genotypes at the MEFV and SAA1 loci toamyloidosis and disease severity in patients with familial Mediterranean fever. Arthritis Rheum. *48:*1149–1155.

HOLMES ,AH, DR BOOTH, PN HAWKINS (1998): Familial Mediterranean fever gene. N Engl J Med. *338*:992–993.

HULL ,KM, N SHOHAM, JJ CHAE, I AKSENTIJEVICH, DL KASTNER (2003): The expanding spectrum of systemic autoin Xammatory disorders and their rheumatic manifestations. Curr Opin Rheumatol. *15:*61–69.

LIVNEH, A, P LANGEVITZ, D ZEMER, N ZAKS, S KEES, T LIDAR, A MIGDAL, S PADEH, M PRAS (1997): Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum. *40*:1879-85.

LIVNEH, A, P LANGEVITZ, Y SHINAR, N ZAKS, DL KASTNER, M PRAS, E PRAS (1999): MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterraneanfever. Amyloid. *6*:1–6.

LIVNEH, A, I AKSENTIJEVICH, P LANGEVITZ, Y TOROSYAN, N G-SHOHAM, Y SHINAR, E PRAS, N ZAKS, S PADEH, DL KASTNER, M PRAS (2001) A single mutated MEFV allele in Israeli patients suffering from familial Mediterranean fever and Behchet's disease (FMF-BD). Eur J Hum Genet. *9:*191–196.

MANSOUR, I, V DELAGUE, C CAZENEUVE, C DODÉ, E CHOUERY, C PÊCHEUX, M MEDLEJ-HASHIM, N SALEM, L EL ZEIN, I LEVAN-PETIT, G LEFRANC, M GOOSSENS, M DELPECH, S AMSELEM, J LOISELET, G GRATEAU, A MÉGARBANE, R NAMAN (2001): Familial Mediterranean fever in Lebanon: mutation spectrum, evidence for cases inMaronites, Greek orthodoxes, Greek catholics, Syriacs and Chiitesand for an association between amyloidosis and M694V and M694I mutations. Eur J Hum Genet. *9*:51–55.

MATTIT ,H, M JOMA, S AL-CHEIKH, M EL-KHATEEB, M MEDLEJ-HASHIM, N SALEM, V DELAGUE, , A MÉGARBANÉ (2006): Familial Mediterranean fever in the Syrian population: gene mutation frequencies, carrier rates and phenotype–genotype correlation. Eur J Med Genet. *49*:481–486.

NOTARNICOLA, C, MN DIDELOT, I KONÉ-PAUT, F SEGURET, J DEMAILLE, I TOUITOU (2002):Reduced MEFV Messenger RNA expression in patients with familial Mediterranean fever. Arthritis Rheum. *46*:2785–2793.

PADEH, S, Y SHINAR, E PRAS, D ZEMER, P LANGEVITZ, M PRAS, A LIVNEH (2003): Clinical and diagnostic value of genetic testing in 216 Israeli children with Familial Mediterranean fever. J Rheumatol. *30*:185–190.

PRAS, E, A LIVNEH, JE BALOW, E JR PRAS, DL KASTNER, M PRAS, P LANGEVITZ (1998): Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet. *75:*216–19.

SARKISIAN, T, H AJRAPETYAN, G SHAHSUVARYAN (2005): Molecular study of FMF patients in Armenia. Currt Drug Targets Inflamm Allergy. *4*:113–116.

SAYIN KOCAKAP, DB, A GÜNEL-ÖZCAN, F CABUK, C ENSARI (2014): The frequency of Familial Mediterranean fever gene mutations and genotypes at Kirikkale and comparison with the mean of regional MEFV mutation frequency of Turkey. Mol Biol Rep. *41*(3):1419-26.

SHINAWI ,M, R BRIK, M BERANT, L KASINETZ, R GERSHONI-BARUCH (2000): Familial Mediterranean fever: high gene frequency and heterogeneous disease among an Israeli-Arab population. J Rheumatol. *27*:1492–1495.

SHOHAT, M, N MAGAL, T SHOHAT, X CHEN, T DAGAN, A MIMOUNI, Y DANON, R LOTAN, G OGUR, A SIRIN, M SCHLEZINGER, GJ HALPERN, A SCHWABE, D KASTNER, JI ROTTER, N FISCHEL- GHODSIAN (1999): Phenotype –genotype correlation in familial Mediterranean fever: evidence for anassociation between Met694Val and amyloidosis. Eur J Hum Genet. *7*:287–292.

TAMIR, N, P LANGEVITZ, D ZEMER, E PRAS, Y SHINAR, S PADEH, N, ZAKS M PRAS, A LIVNEH (1999): Late-onset familial Mediterranean fever (FMF): a subset with distinct clinical, demographic, and molecular genetic characteristics. Am J Hum Genet. *87*:30–35.

TASLIYURT, T, S YIGIT, RUSTEMOGLU, U GUL, O ATES (2013): Common MEFV gene mutations in Turkish patients A with Behcet's disease. Gene. *530*(1):100-3.

THE INTERNATIONAL FMF CONSORTIUM: Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever (1977): Cell. *90*:797– 807.

TIMERMAN ,D, NY FRANK (2013): Novel double heterozygous mutations in MEFV and NLRP3 genes in a patient with familial Mediterranean fever. J Clin Rheumatol. *19*(8):452-3.

TOPALOGLU,R, F OZALTIN, E YILMAZ, S OZEN, B BALCI, N BESBAS, A BAKKALOGLU (2005): E148Q is a disease-causing MEFV mutation: a phenotypic evaluation in patients with familial Mediterranean fever. Ann Rheum Dis. *64*:750–752.

TOUITOU, I. (2001): The spectrum of familial Mediterranean fever (FMF) mutations. Eur J Hum Genet. 9:473–483.

TOUITOU, I., MC PICOT, C DOMINGO, C NOTARNICOLA, D CATTAN, J DEMAILLE, I KONÉ-PAUT (2001): The MICA region determines the first modifier locus in familial Mediterranean fever. Arthritis Rheum. *44*:163–169.

TOUITOU, I., T SARKISIAN, M MEDLEJ-HASHIM, M TUNCA, A LIVNEH, D CATTAN, F YALÇINKAYA, S OZEN, H MAJEED, H OZDOGAN, D KASTNER, D BOOTH, E BEN-CHETRIT, D PUGNÈRE, C MICHELON, F SÉGURET, R GERSHONI-BARUCH; International Study Group for Phenotype-Genotype Correlation in Familial Mediterranean Fever (2007): Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum. *56*:1706–12.

TUNCA, M., S AKAR, F ONEN, H OZDOGAN, O KASAPCOPUR, F YALCINKAYA, E TUTAR, S OZEN, R TOPALOGLU, E YILMAZ, M ARICI, A BAKKALOGLU, N BESBAS, T AKPOLAT, A DINC (2005) :Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine. *84*:1–11.

YALÇINKAYA F, N CAKAR, M MISIRLIOĞLU, N TÜMER, N AKAR, M TEKIN, H TAŞTAN, H KOÇAK, N OZKAYA, AH ELHAN (2000): Genotype–phenotype correlation in a large group of Turkish patients with familial Mediterranean fever: evidence for mutation-independent amyloidosis. Rheumatology. *39*:67–72.

YESILADA. E, H TASKAPAN, G GULBAY (2012): Prevalence of known mutations and a novel missense mutation (M694K) in the MEFV gene in a population from the Eastern Anatolia Region of Turkey. Gene. *511*(2):371-4.

YILMAZ E, S OZEN, B BALCI, A DUZOVA, R TOPALOGLU, N BESBAS, U SAATCI, A BAKKALOGLU, M OZGUC (2001): Mutation frequency of familial Mediterranean fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet. *9*:553–555.

SKRINING MUTACIJA PORODIČNE MEDITERANSKE GROZNICE U AZERI TURSKOJ POPULACIJI: KORELACIJA GENOTIPA I FENOTIPA I VARIJABILNOST KLINIČKOG PROFILA

Jalal GHARESOURAN[1], Maryam REZAZADEH[1,2], Morteza GHOJAZADEH[3], Mojtaba MOHADDES ARDABILI[1]

[1] Odelenje medicinske genetike, Medicinski fakultet, Tabriz Univerzitet medicinskih nauka, Tabriz, Iran.
[2] Centar za neurološka istraživanja,Tabriz Univerzitet medicinskih nauka, Tabriz, Iran
[3] Centar za istraživanja bolesti jetre i gastrointestinalnih bolesti, Tabriz Univerzitet medicinskih nauka, Tabriz, Iran

Izvod

Porodična Mediteranska groznica (FMF) je poznata kao najučestalija nasledna recesivna bolest unutar autoinflamatornog sindroma čije karakteristike su groznica, arthritis i ozbiljne upale. Klinički, simptom najistaknutiji symptom ove bolesti je amiloidoza, koja može da izazove otkazivanje funkcije bubrega. Gen kandidat koji kontroliše ovu bolest je lociran na hromozomu 16p13.3 koji je identifikovan pozicionim kloniranjem 1997. godine i kodira protein pyrin/marenostrin. Lokus čine 10 egzona i konzervativne mutacije grupisane u egzonu 10 ((M694V, V726A, M680I, M694I) i egzonu 2 ((E148Q). Cilj ovog rada je bio ispitivanje spektra mutacija u Azeri Turskoj populaciji. Vršena je ocena rezultata molekularnog testa kod 82 pacijenta i njihovih roditelja iz 8 porodica koje su imale ovu bolest (FMF) sa kliničkim simptomima uutvrđenim u laboratoriji za molekularnu genetika odelenja medicinske genetike. Najučestalije utvrđene mutacije su M694V a zatim M680I (G/C), V726A, M694I and E148Q. Utvrđena je i fenotipska varijabilnost među pacijentima sa različitim mutacijama.

Primljeno 02. V 2014.
Odobreno 22. VII. 2014.