

M694V and E148Q Mutations as Potential Molecular Markers for the Diagnosis of Familial Mediterranean Fever among Patients in the East Mediterranean Region of Turkey

Ilhami Gök^{1*}, Ozkan Oztas², Murat Celik³ and Cem Ozic¹

¹*Department of Bioengineering, Faculty of Engineering and Architecture, Kafkas University Kars, 36100, Kars, Turkey*

²*Departments of Biology, Faculty of Science and Literature, Kafkas University, 36100, Kars, Turkey*

³*Departments of Internal Medicine, School of Medicine, Mustafa Kemal University, Hatay, 31100, Turkey*

KEYWORDS Familial Mediterranean Fever. MEFV Gene. Mutation Analysis. Turkish Population

ABSTRACT The purpose of the present study was to estimate frequency of M694V and E148Q mutations in the Mediterranean Fever (MEFV) gene among different families living in the East Mediterranean region of Turkey. A total of 78 members from 19 families, who had the Familial Mediterranean Fever (FMF) disease as diagnosed in clinics, and a control group consisting of 100 members were examined in this work. The member who was clinically diagnosed with FMF gene had attracted the researchers' focus to take blood examples from the entire family members. The M694V and E148Q are point mutations located in different exons of the affected gene. It is employed PCR method with specific oligonucleotides primers pair to detect mutations in the populations. The gel electrophoresis procedure was used to visualize the presence of point mutations in FMF and control group. The M694V mutation turned to be present in 75 out of 78 members (96%) of 19 FMF-diagnosed families. Among 100 members of the control group, in 26 members 26% carried the M694V. The E148Q mutation was observed in 28 members (35.89%) of the FMF group and 8 members (8%) of the control group. To the extent of the researchers' knowledge, this is to study target E148Q mutation for FMF gene in Turkey, so this research assumed to have crucial importance in clinics to diagnose FMF gene.

INTRODUCTION

The FMF is an autosomal recessive disorder auto-inflammatory disease which is frequently encountered in the communities living in the Mediterranean region. It is characterized with the fever together with the stomach ache, pleuritis, arthritis, erysipelas-like skin lesions and development of the amyloidosis in time (Önen 2006). In approximately 90% of the FMF patients, the clinical symptoms arise before the age of 20. On average, the starting age of the disease is 4, which makes it truly a childhood disease (Kasapçopur et al. 2006). FMF is encountered in many ethnical groups but it is more commonly observed in Turks, Armenians, Arabs and Jews. The epidemiological studies revealed that the carrier frequency was 1/7 in Armenians and it

was 1/8-1/46 in Sephardic Jews. In the same groups, the FMF prevalence varies around 1/250-1/1000 (Al-Alami et al. 2003). According to the results of the Turkish FMF study group, the incidence of the disease in Turkey is quite high (1/1000), with the carrier rate (1/5) even higher than in other regions (Tunca et al. 2005). The MEFV gene is 10-kilobase long with 10 is located on the small branch of the 16th chromosome and codes for a 781 amino acid protein (Consortium 2004). The gene responsible for the disease defined in 1992 was cloned by two different working groups (International FMF consortium and French FMF consortium) and was published in 1997 (French et al. 1997; El-Shanti et al. 2006). Classically, it is inherited in an autosomal recessive manner, however, although rarely, the autosomal dominant inheritance was reported. In 1997, first mutations related to the disease were detected. Analysis of the cloned complementary DNA (cDNA) revealed four missense mutations: Met680Ile, Met694Val, Val726Ala and Met694Ile (Touitou et al. 2004). In 1998, three additional rare mutations (Lys695Arg, Ala744Ser, and Arg761His) were by one mutation in the 5th exon and three mutations in the 2nd exon (Glu148Gln,

*Address for correspondence:

Ilhami Gök

Department of Bioengineering,
Faculty of Engineering and Architecture,
Kafkas University 36100, Kars, Turkey

Phone: + 90 474 225 12 79

Fax: +90 474 225 12 82

E-mail: dnzgoki@gmail.com

FMF patients (n=78)					Control group (n=100)					
Age	Female (N)	%	Male (N)	%	Age	Female (N)	%	Male (N)	%	P
18-20	11	14.10	16	20.1	18-20	14	14.00	25	25.00	0.02
20-40	13	16.66	12	15.38	20-40	10	10.00	21	21.00	0.14
40-60	10	12.82	6	7.69	40-60	6	06.00	14	14.00	0.004
>60	4	5.12	6	7.69	>60	2	02.00	8	08.00	0.14
36±06	38	48.71	40	51.29	33±06	32	32.00	68	68.00	0.33

reverse primer, 5'-AGGCCCTCCGAGGCCT-TCTCTCTG-3'. Primers for the MEFV gene mutation E148Q; forward primer, 5'-GCCTGAA-GACTCCAGACCACCCCG-3'; reverse primer, 5'-AGGCCCTCCGAGGCCTTCTCTCTG-3' (Zakset al. 2003; El Sayed et al. 2012). Each 50 µl PCR reaction contained 5µl of Taq polymerase buffer (10X), 5µl of magnesium chloride (2 mmol/L), 5µl of dNTP mix (0.5 mM), 5 µl of forward primer (12.5 pmol), 5 µl of reverse primer (12.5 pmol), 2 µl of genomic DNA (100ng/µl), 1 µl of Taq DNA polymerase (5u/µl) and sterile distilled water to bring the volume up to 50 µl (Zaks et al. 2003; El Sayed et al. 2012). PCR cycling conditions were as follows: initial denaturation for 3 min at 94 °C, than, 40 cycles of 94 °C for 1 min, 58 °C for 1 min, 72 °C for 1 min, followed by the final extension at 72 °C for 10 min. The PCR products were detected by agarose gel electrophoresis (90V, 300A for 1 h) in 2 % agarose gel containing ethidium bromide and the fluorescent intensity of each band was evaluated with a UV transilluminator (Gel Logic Pro 2200, Montreal, Canada). For M694V mutation the PCR amplification double bands were observed as 300 bp and the researchers accepted as a positive. Other patients were negative and E148Q amplification as bands as 300 bp and we accepted positive for only that mutation.

Statistical Analysis

In this study, statistical analyses were made with the Graph Pad Prism 6 software package. In

the evaluation of the data, the students' t - test was used for the comparison of the means associated with the FMF and control groups. The students' t - test was used in the comparisons of the qualitative data. The significance level of P: 0.05 value of 0.05 was taken as a basis in the evaluation of the results.

RESULTS

The clinical pre-diagnosis results of the FMF patients were determined as the abdominal pains in 39 persons (50%), high fever in 35 persons (44.87%), arthritis/arthralgia in 19 persons (24.35%) and erysipelas-like erythema in 5 persons (6.41%). In the study, as a result of the genomic analyses, the MEFV gene M694V mutation was observed in 75 out of 78 test persons (96%) and in 26 of 100 control individuals (26%). The MEFV gene E148Q mutation was observed in 28 out of the 78 test cases (35.89%) and in 8 out of 100 control persons (8%). In the FMF patients, the incidence rate of M694V and E148Q mutations together was 35.89%. It was also evident that the incidence rate of both mutations in males was higher than in females. Statistical significances of these differences are given in Tables 2 and 3.

DISCUSSION

This study was designed with the aim of examining the prevalence of M694V and E148Q mutations of MEFV gene in 78 individuals of 19

Table 2: Distribution of the MEFV gene mutations M694V and E148Q among patients with FMF and control individuals

Gene	FMF patients (n=78)				Group (n=100)				P
	(+) Mutation	%	(-) Mutation	%	(+) Mutation	%	(-) Mutation	%	
M694V	75	96.00	3	04.4	26	26.00	74	74.00	0.0001
E148Q	28	35.89	50	64.11	8	08.00	92	92.00	0.0001

Table 3: Statistical distributions of M694 and E148Q mutations according to the gender among patients with FMF and control group (+) : explains that there is nucleotide change, (-) : explains that there is no nucleotide change

Gene	FMF patients (n=78)				Group (n=100)				P
	(+) Mutation	%	(-) Mutation	%	(+) Mutation	%	(-) Mutation	%	
M694V	75	96.00	3	04.4	26	26.00	74	74.00	0.0001
Mutation	35	46.60	40	53.40	11	39.28	17	60.72	0.39
Gene	FMF patients (+) Mutation (n=26)				Control group (+) Mutation (n:8)				
E148Q	12	15.38	16	20.51	3	37.50	5	62.50	0.78

different families living in the Hatay province, the East Mediterranean region of Turkey. An important factor in this study was that at least one individual from each studied family was an FMF patient with preliminary diagnosis. The present study was knowingly focused on two mutations of MEFV gene, M694V and E148Q, because in FMF patients, simultaneous presence of the two mutations is associated with a more severe course of the disease (Zaks et al. 2003; Öztüzcu et al. 2014). Besides, the selection of the controls from Kars region gave us information on the frequency of these mutations in the North Eastern Anatolia region, which to our knowledge has not been covered by systematic analyses of their occurrence. In some studies, it is reported that mutations M694V and E148Q comprise 85% of the mutations associated with the AAA disease in the Middle East region (Karadağ et al. 2003; Sayin Kocakap et al. 2001). However, most of them were relatively rarely observed in populations in which they have been found were not phenotyped in the clinics and were not frequently associated with the AAA disease (Kümpfel et al. 2012; Öztürk et al. 2012). In a study that Brik and associates made with 67 Israeli children in 2003, it was determined that 92% of the Jewish origin children (Northern Africa or Iraqi Jews) carried the M694V mutation at least in one allele (Brik et al. 2003). In the same study, it was shown that the M694V mutation was observed at the rate of 30% in the Arabic children (Tchernitchko et al. 2003; Touitou et al. 2004). In this study, it is observed, the M694V mutation at the rate of 96%. While the E148Q mutation was reported to be common in Europe, its frequency was found to be 13% in a study realized in the Central Anatolia region, where it was not rare (Coker et al. 2011; Yolbaş et al. 2012). Different interpretations related to the phenotypic effect of this mutation are given by different observations (Öztüzcu et al. 2014). In a study in the USA in 2001, it was highlighted that individuals homozygous for the E148Q mutation were not patients, and that other mutations were also required for the emergence of the disease (Konstantopoulos et al. 2005). Other researchers, however, suggested that this mutation played a role in the pathophysiology of FMF (Kümpfel et al. 2012 b). In a study that Tchernitchko and associates conducted in France in 2006, it was mentioned that E148Q was a polymorphic variant that was not harmful (Tcherni-

tchko et al. 2006). Findings in the present study are novel with regard to the E148Q mutation, because none of the previous studies employed familial structure of the test group, being rather focused on classical population analyses. As the researchers mentioned earlier, two studies realized in Turkey highlighted higher severity of the FMF disease in patients carrying the M694V and the E148Q mutations together (Topaloglu et al. 2005; Ece et al. 2014). In 2004, Touitou and associates examined the MEFV gene mutation frequencies in different populations in France. In this study, the most frequently observed mutation in the MEFV gene among 1301 Jewish patients was M694V (65%) followed by the E148Q mutation (5%) (Touitou et al. 2004). Likewise, a study on 378 Armenian patients found the M694V mutation prevailing (37%), with the E148Q mutation observed in 2% of the patients (El-Shanti et al. 2006). While the M694V was the most frequently observed mutation (20%) in the group of 706 patients from the Arabic countries, the E148Q mutation was observed at the frequency of 6% (Belhami et al. 2006). Similarly, the M694V was detected with the frequency of 45% in the group of 1390 unrelated patients in Turkey, while the E148Q mutation was found in 2% of the patients (Tunca et al. 2005; Soylu et al. 2008). In the FMF mutation screening conducted by Stoffman and associates among the Jewish community in Israel, the frequencies of these mutations turned to be remarkably high in healthy individuals (29% and 53% for the M694V and E148Q, respectively). In contrast, the M694V was at the level of 84.4% and the E148Q at the level of 6.6% in the patients (Stoffman et al. 2000). According to this study, the M694V incidence is higher in Jewish community than in Turkish community. In the study that Yilmaz and associates realized in Turkey in 2013, frequency of the E148Q mutation in the healthy individuals and osteoarthritis patients was 8.1%, with no difference between the patients and controls (Yilmaz et al. 2013). In the present study, the frequency of that mutation among healthy individuals was 8%. Even though the researchers do not have accurate information on the overall carrier frequency of the MEFV gene mutations in Turkey, the carrier rate is known for different regions (Akin et al. 2010). In 2005, the Turkish FMF Study Group in Antalya collected information on a wide population with various ethnic background and health status. According to this

Table 4: Frequency of M69V and E148Q mutations of the MEFV gene in our familial study in comparison to other studied populations

<i>MEFV gene M694V mutation</i>			<i>MEFV gene 148Q mutation</i>		
<i>First author and year</i>	<i>Countries</i>	<i>% rate</i>	<i>First author and year</i>	<i>Countries</i>	<i>% rat</i>
Nurit et al. (2003)	Israel	47.00	Touitou et al. (2003)	Austria	I*
Al-Alami et al. (2003)	Egypt, Syria, Iraq and Saudi Arabia	53.48	Suzuki et al.(2005)	Japan	I*
Zekri et al. (2004)	Egypt	100.00	Tchernitchko et al. (2006)	France	26.00
Majeed et al. (2005)	Jordan	38.00	El Shanti et al. (2006)	Saudi Arabia	I*
Mattit et al. (2006).	Syria	89.00	Konstatopoulos et al. (2006)	Greece	I*
Lidar and Livneh (2007)	India	57.00	Lidar et al. (2007)	India	I*
Ozçakar et al. (2008)	Turkey	34.00	Ozçakar et al. (2008)	Turkey	11.11
Gunel-Ozcan et al. (2009)	Turkey	8.00	Gunel-Ozcan et al. (2009)	Turkey	12.10
Banyadi et al. (2010)	Turkey	11.50	Banyadi et al. (2010)	Turkey	11.50
Akin et al. (2010)	Turkey	60.00	Akyn et al. (2010)	Turkey	25.75
El Gezeri et al. (2012)	Misir	34.00	El Gezeri et al. (2012)	Mýsýr	22.70
Coker et al. (2011)	Turkey	48.40	Coker et al. (2011)	Turkey	16.50
Ait-Idir et al. (2011)	Turkey	17.6	Ait-Idir et al. (2011)	Turkey	04.20
Kilim et al. (2011)	Israel	55.00	Kilim et al. (2011)	Israel	21.00
Akpolat et al. (2012)	Turkey	47.00	Akpolat et al. (2012)	Turkey	2.00
Yolbas et al. (2012)	Turkey	39.00	Yolba° et al. (2012)	Turkey	31.00
El sayed et al. (2012)	Saudi Arabia	8.33	El sayed et al. (2012)	Saudi Arabia	Null
Mohammadnejad et al. (2013)	Iran	40.19	Mohammadnejad et al. (2013)	Iran	17.64
In the present study	Turkey	96.00	In the present study	Turkey	35.80

I*: Determination country.

evaluation report, the genetic analysis was conducted for 1090 patients, and the M694V found at the rate of 51.4% was the most frequently observed type of the MEFV gene mutation (4). By setting off from the study that the FMF study group realized, it is thought that the genetic diagnosis can be established in the majority of the patients with the assignment of two mutation types that the researchers researched. In the Tepecik Training Hospital Tissue Typing and Molecular Diagnosis Laboratory, the MEFV gene mutation analysis was paralleled by the FMF diagnosis and the most frequently detected mutation was again the M694V (48.4%). The E148Q mutation rate was at the frequency of 16.5% (Tunca et al. 2005; Ozçakar et al. 2006). The results observed in the comprehensive study performed in 2013 on the Azerbaijani Turkish population in the Northern Iran are very similar to those observed in the analysis of these mutations in Turkey (Eroglu et al. 2013; Mohammadnejad et al. 2013). The studies realized in the last ten years on the M694V and E148Q mutations are summarized in Table 4. Their results suggested that our findings are in line with the data obtained by other research groups.

CONCLUSION

In the present study, the researchers obtained quantitative data on occurrence of two muta-

tions in the MEFV gene, M694V and E148Q, and tried to correlate those frequencies with the incidence of the FMF disease. Familial structure of our test group, as well as the focus on previously uninvestigated region of Turkey (Hatay province), are major novelty points in the present study. It is also obtained information on frequencies of the studied mutations among healthy population of the North East of Anatolia (Kars province), which can be used for reference by subsequent studies. In conclusion, it is suggested that molecular detection of the two mutations in the MEFV gene in clinical blood samples can be useful for early diagnosis of the FMF disease, which is important for the adequate treatment.

ACKNOWLEDGEMENTS

This work was supported by a grant from Kafkas University Scientific Research Fund (Grant Number MMF-61).

NOTE

Ethical approval was received from the medical ethics committee of Ataturk University, the protocol number B.30.2.ATA.0.01.00/55 from 31.07.2012.

REFERENCES

- Ait-Idir D, Khilani A, Djerdjouri B, El-Shanti H 2010. Spectrum of mutations and carrier frequency of Familial Mediterranean Fever gene in the Algerian population. *Rheumatology*, 50: 2306-2310.
- Akin H, Onay H, Turker E, Cogulu O, Ozkinay F 2010. MEFV mutations in patients with Familial Mediterranean Fever from the Aegean region of Turkey. *Mol Biol Rep*, 37: 93-98.
- Al-Alami JR, Tayeh MK, Najib DA, Abu-Rubaiha ZA, Majeed HA, Al-Khateeb MS, El-Shanti HI 2003. Familial Mediterranean Fever mutation frequencies and carrier rates among a mixed Arabic population. *Saudi Med J*, 24: 1055-1059.
- Belmahi L, Sefiani A, Fouveau C, Feingold J, Delpech M, Grateau G, Dodé 2006. Prevalence and distribution of MEFV mutations among Arabs from the Maghreb patients suffering from Familial Mediterranean Fever. *C R Biol*, 23: 71-74.
- Bonyadi M, Esmaili M, Karimi A, Dastgiri S 2010. Common Mediterranean Fever gene mutations in the Azeri Turkish population of Iran. *Genet Test Mol Biomarkers*, 14: 149-151.
- Brik R, Gershoni-Baruch R, Shinawi M, Barak L, Bentur L 2003. Pulmonary manifestations and function tests in children genetically diagnosed with FMF. *Pediatr Pulmonol*, 35: 452-455.
- Coker I, Colak A, Yolcu I, Türkön H, Nalbantoglu SM 2011. MEFV gene mutation spectrum in Familial Mediterranean Fever (FMF): A single center study in the Aegean region of Turkey. *Z Rheumatol*, 70: 511-516.
- Ece A, Çakmak E, Ulucu Ü, Kelekçi S, Yolbaş I et al. 2014. The MEFV mutations and their clinical correlations in children with Familial Mediterranean Fever in southeast Turkey. *Rheumatol Int*, 34: 207-212.
- El Gezery DA, Abou-Zeid AA, Hashad DI, El-Sayegh HK 2010. MEFV gene mutations in Egyptian patients with Familial Mediterranean Fever. *Genet Test Mol Biomarkers*, 14: 263-268.
- El Sayed M, Al Jarallah B 2012. Molecular diagnosis of Familial Mediterranean Fever among subjects from Al-Qassim Region. *Natur and Sci*, 10: 7-12.
- El-Shanti H, Abdel Majeed H, El-Khateeb M 2006. Familial Mediterranean Fever in Arabs. *Lancet*, 367: 1016-1024.
- Eroglu E, Kocyigit I, Ates O, Unal A, Sipahioglu MH, Akgun H, Tokgoz B, Oymak O 2013. Mesangial proliferative glomerulonephritis in familial Mediterranean Fever patient with E148Q mutation: The first case report. *Int Urol Nephrol*, 45: 91-94.
- French FMF Consortium 1997. A candidate gene for Familial Mediterranean Fever. *Nature Genetics*, 17: 25-31.
- Goulielmos GN, Fragouli E, Aksentijevich I, Sidiropoulos P, Boumpas DT, Eliopoulos E 2004. Mutational analysis of the PRYSPRY domain of pyrin and implications for Familial Mediterranean Fever (FMF). *Biochem Biophys Res Commun*, 345: 1326-1332.
- International Human Genome Sequencing Consortium 2004. Finishing the euchromatic sequence of the human genome. *Nature*, 431: 931-945.
- Karadag O, Tufan A, Yazisiz V, Ureten K, Yilmaz S, Cinar M, Akdogan A, Erdem H, Ozturk MA, Pay S, Dinc A 2013. The factors considered as trigger for the attacks in patients with Familial Mediterranean Fever. *Rheumatol Int*, 33: 893-897.
- Kasapçopur Ö, Arisoy N 2006. Familial Mediterranean Fever and other hereditary auto-inflammatory diseases. *Turkish Pediatr Arc*, 41: 9-17.
- Konstantopoulos K, Kanta A, Lilakos K, Papanikolaou G, Meletism I 2005. Familial Mediterranean Fever and E148Q pyrin gene mutation in Greece. *Int J Hematol*, 81: 26-28.
- Kümpfel T, Gerdes LA, Wacker T, Blaschek A, Havla J, Krumbholz M, Pöhlmann W, Feneberg W, Hohlfeld R, Lohse P 2012. Familial Mediterranean Fever-associated mutation pyrin E148Q as a potential risk factor for multiple sclerosis. *Mult Scler*, 18: 1229-1238.
- Medlej-Hashim M, Chouery E, Salem N, Delague V, Lefranc G, Loiselet, Mégarbané A 2011. Familial Mediterranean Fever in a large Lebanese family: Multiple MEFV mutations and evidence for a Founder effect of the p[M694I] mutation. *Eur J Med Genet*, 54: 50-54.
- Medlej-Hashim M, Loiselet J, Lefranc G, Megarbane A 2004. Familial Mediterranean Fever (FMF): From diagnosis to treatment. *Sante*, 14: 261-266.
- Mikula M, Buller A, Sun W, Strom CM 2008. Prevalence of known mutations in the familial Mediterranean fever gene (MEFV) in various carrier screening populations. *Genet Med*, 10: 349-352.
- Mohammadnejad L, Farajnia S 2013. Mediterranean Fever gene analysis in the Azeri Turk population with Familial Mediterranean Fever: Evidence for new mutations associated with disease. *Cell J*, 15: 152-159.
- Moutereau S, Narwa R, Matheron C, Vongmany N, Simon, Goossens M 2006. An improved electronic microarray-based diagnostic assay for identification of MEFV mutations. *Hum Mutat*, 23: 621-628.
- Ozçakar ZB, Yalçinkaya F, Cakar N, Acar B, Kasapçopur Ö, Uğüten D, Soy D, Kara N, Uncu N, Arisoy N, Ekim M 2006. MEFV mutations modify the clinical presentation of Henoch-Schönlein purpura. *J Rheumatol*, 35: 2427-2429.
- Ozturk C, Halicioğlu O, Coker I, Gulez N, Sutcuoglu S, Karaca N, Aksu G, Kutukculer N 2012. Association of clinical and genetical features in FMF with focus on MEFV strip assay sensitivity in 452 children from western Anatolia, Turkey. *Clin Rheumatol*, 31: 493-501.
- Oztuzcu S, Ulasli M, Ergun S, İdci YZ, Igci M, Bayraktar R, Nacarkahya G, Tamer A, Cevik MO, Çakmak EA, Arslan A 2014. Screening of common and novel Familial Mediterranean Fever mutations in south-east part of Turkey. *Mol Biol Rep*, 41: 2601-2607.
- Önen F 2006. Familial Mediterranean Fever. *Rheumatol Int*, 26: 489-96.
- Özen, S, Besbas, N, Bakkaloglu A, Yilmaz E 2002. Pyrin Q148 mutation and Familial Mediterranean Fever. *QJM*, 95: 332-333.
- Rapley R, Walker JM 2008. *The Nucleic Acid Protocol Handbook*. Ottawa, New Jersey: Humana Press.
- Sayin Kocakap DB, Günel-Özcan A, Çabuk F, Ensari C 2014. The frequency of Familial Mediterranean fe-

- ver gene mutations and genotypes at Kirikkale and comparison with the mean of regional MEFV mutation frequency of Turkey. *Mol Biol Rep*, 41: 1419-1426.
- Soylu A, Kasap B, Türkmen M, Ulgenalp A, Uzuner N, Kavukçu S 2008. Protracted febrile myalgia syndrome in a patient with Familial Mediterranean Fever homozygous for the E148Q mutation. *Semin Arthritis Rheum*, 38: 161-162.
- Tchernitchko D, Legendre M, Cazeneuve C, Delahaye A, Niel F, Amselem S 2003. The E148Q MEFV allele is not implicated in the development of Familial Mediterranean Fever. *Hum Mutat*, 22: 339-340.
- Tchernitchko DO, Gérard-Blanluet M, Legendre M, Grateau G, Amselem S 2006. Intrafamilial segregation analysis of the p.E148Q MEFV allele in familial Mediterranean fever. *Ann Rheum Dis*, 65: 1154-1157.
- Tekin M, Yalçinkaya F, Cakar N, Akar N, Misirlioğlu M, Taştan H, Tümer N 2000. MEFV mutations in multiplex families with Familial Mediterranean Fever: Is a particular genotype necessary for amyloidosis? *Clin Genet*, 57: 430-437.
- Topaloglu R, Ozaltin F, Yilmaz E, Ozen S, Balci B, Besbas N, Bakkaloglu A 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, Lesage S, Mcdemott M, Cuisset L, Hoffman H, Dade C, Shoam N, Aganna E, Hugot JP, Wise C, Waterham H, Pugnere D, Demaille J, Menthier CS 2004. Infevers: An evolving mutation database for auto-inflammatory syndromes: *Hum Mutat*, 24: 194-198.
- Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, Tutar E, Ozen S, Topaloglu R, Yilmaz E, Arici M, Bakkaloglu A, Besbas N, Akpolat T, Dinc A, Erken E 2005. Turkish FMF study group- Familial Mediterranean Fever (FMF) in Turkey: Results of a nationwide multicenter study. *Medicine Baltimore*, 84: 1-11.
- Vergara C, Borzutzky A, Gutierrez MA, Iacobelli S, Talesnik E, Martinez ME, Stange L, Basualdo J, Maluje V, Jimenez R, Wiener R, Tinoco J, Jarpa E, Aróstegui JI, Yagüe J, Alvarez-Lobos M 2012. Clinical and genetic features of hereditary periodic fever syndromes in Hispanic patients: The Chilean experience. *Clin Rheumatol*, 31: 829-834.
- Yilmaz S, Erdem H, Tunay S, Torun D, Genc H, Tunca Y, Karadag O, Simsek I, Bahce M, Pay S, Dinç A 2013. The presence of MEFV gene mutations in patients with primary osteoarthritis who require surgery. *Korean J Intern Med*, 28: 594-598.
- Yolbas I, Ozen F, Kocak N, Kelekci S, Gunes A, Yel S 2012. The frequency of MEFV gene mutation in patients admitted to hospital with preliminary diagnosis of Familial Mediterranean Fever who had undergone a prior appendectomy. *Eur Rev Med Pharmacol Sci*, 16: 949-951.
- Zaks N, Shinar Y, Pade S, Lidar M, Mor A, Tokov I, Pras M, Langevitz P, Pras E, Livneh A 2003. Analysis of the three most common MEFV mutations in 412 patients with Familial Mediterranean Fever. *Isr Med Assoc J*, 8: 585-588.