



### Distribution of Familial Mediterranean Fever Mutations in Surgical Emergencies Including Nonspecific Abdominal Pain: Surgical Point of View

Nonspesifik Karın Ağrısı olan Cerrahi Acillerde Ailesel Akdeniz Ateşi Gen Mutasyon Dağılımı: Cerrahi Bakış Açısı

Pınar Yazıcı<sup>1</sup>, Bülent Aydın<sup>2</sup>, İbrahim Pirim<sup>3</sup>, Nilnur Egerci<sup>3</sup>, Hasan Doğan<sup>3</sup>, Ünal Aydın<sup>4</sup>, M. Rasih Yılmaz<sup>1</sup>

<sup>1</sup>Sisi Etfal Training and Research Hospital, General Surgery Clinic, İSTANBUL

<sup>2</sup>Ataturk University School of Medicine, Department of General Surgery and <sup>3</sup>Department of Medical Biology, ERZURUM

<sup>4</sup>Izmir University School of Medicine, Department of General Surgery, İZMİR

*Cukurova Medical Journal 2014;39(4):814-821.*

#### ABSTRACT

**Purpose:** Familial Mediterranean fever (FMF) is characterized by recurrent episodes of fever and serositis, resulting in pain in the abdomen, chest, joints and muscles. While patients diagnosed with FMF are under follow-up of the internal medicine doctors, surgeons are rarely responsible the initial diagnosis of FMF. We aimed to investigate the frequency of the FMF in the surgical emergency in those with acute nonspecific abdominal pain.

**Material and Methods:** All patients admitted to emergency service due to acute abdominal pain were evaluated and those resulted with nonspecific pain were enrolled. During six months period, patients consistent with above criteria were examined with abdominal x-ray and ultrasound(US), hematological and biochemical test, and physical examinations. Nine type of FMF mutations were investigated in the patients. All results were comparatively evaluated considering MEFV (+) or MEFV(-).

**Results:** There were 68 patients (35, 51.4% male and 33, 48.5% female) with a mean age of 29.5±10.1 (range: 17-49 years). All patients displayed mild or severe abdominal pain. Genetic analysis revealed that 19 [MEFV(+)] out of 68 patients (27,9%) carry mutation either homozygote or heterozygote. The most frequent mutation seen in seven patients was M694V (36.8%). In MEFV(+) patients, fibrinogen, CRP and lactate dehydrogenase levels(LDH) were significantly higher (p<0.05). On computed tomography, in six patients in whom US showed decompressed appendix, appendicitis was confirmed and appendectomy was performed.

**Conclusions:** The patients with nonspecific abdominal pain should also be considered for FMF before decision of surgery. High levels of fibrinogen, CRP and LDH in addition to clinical history of similar attacks that arise strong clinical suspicion can help diagnose FMF with genetic analysis. Our results need confirmation in larger prospective studies to confirm these preliminary results.

**Key Words:** Nonspecific abdominal pain, familial mediterranean fever, genetic analysis.

#### ÖZET

**Giriş:** Ailesel Akdeniz Ateşi ( FMF ) karın, göğüs, eklem ve kaslarda ağrı ile sonuçlanan , ateş ve serositis tekrarlayan nöbetleri ile karakterizedir. FMF tanılı hastalar dahiliye doktorlarının takibinde ike cerrahlar FMF başlangıç tanısında nadiren rol alır. Bu çalışmada akut karın ağrısı ile başvuran hastalarda FMF sorunun cerrahi önemini araştırmaktır.

**Materyal ve Metod:** Altı aylık dönem sürecinde servise akut karın ağrısı ile başvuran ve nonspesifik karın ağrısı olarak sonuçlanan hastalar çalışmaya dahil edildi. Tüm hastalardan onam alındı. Çalışma kriterlerine uyan hastalarda karın x-ray ve ultrasound (US), hematolojik ve biyokimyasal test ve fizik muayene gibi geleneksel rutin işlemler incelendi. Yanı sıra FMF gen mutasyonunun dokuz türü araştırıldı. Tüm sonuçlar, karşılaştırmalı olarak MEFV ( + ) ve MEFV (-) hastalarda değerlendirildi.

**Bulgular:** Yaş ortalaması  $29.5 \pm 10.1$  yıl (alt-üst sınırı: 17-49 yıl) olan 68 hasta ( 35 , % 51.4 erkek ve 33 , % 48.5 kadın ) tespit edildi. Yapılan genetik analiz sonucunda 68 hasta hastanın 19 tanesinde (%27,9) dışında homozigot ya da heterozigot mutasyon [MEFV ( + )] tespit edildi. En sık mutasyon M694V ( n=7 % 36,8) idi . MEFV ( + ) hastalarda, fibrinojen, CRP ve laktat dehidrogenaz(LDH) düzeyleri anlamlı derecede yüksek bulundu ( $p<0.05$ ). Bilgisayarlı tomografi, US'de appendisit gözlenen üç hastanın bulgularını doğruladı ve bu hastalara appendektomi yapıldı.

**Sonuç:** Tekrarlayan nonspesifik karın ağrısı olan hastalar için cerrahi kararı verilmeden önce FMF göz önünde bulundurulmalıdır. Hastanın öyküsünde yüksek klinik şüphe yaratan benzer ataklar olmasının yanı sıra yüksek fibrinojen, CRP ve LDH değerleri FMF genetik tanısına yardımcı olabilir. Bu sonuçların daha geniş çaplı prospektif çalışmalarla desteklenmesinin gerekli olduğunu düşünüyoruz.

**Anahtar Kelimeler:** Nonspesifik karın ağrısı, ailesel akdeniz ateşi, genetic analiz

## INTRODUCTION

Familial Mediterranean fever (FMF) is an inherited disorder of an autosomal recessive trait and the disease primarily affects the population surrounding the Mediterranean basin including Turkey<sup>1,2</sup>. The main clinical finding of FMF is recurrent and self-limited attacks of fever in addition to severe abdominal, articular and chest pain due to inflammation of the peritoneum, synovia or pleura. The genetic method is the only specific way to diagnose FMF.

Despite many types of mutations can cause the disease, four mutations including M694V, M680I, V726A and E148Q are more frequently detected in FMF patients in Turkey<sup>3</sup>.

Abdominal FMF attacks are quite similar to the clinical presentation of acute abdomen even progressed nonspecifically. Particularly the rate of appendectomy and negative appendectomy results in FMF patients is far above than the reported rate in the general population<sup>4</sup>.

Although there are numerous studies in the literature involving clinical characteristics in FMF patients and their needs for surgical intervention, we have established a surgical point of view for the patients admitted to emergency service with nonspecific abdominal pain (NSAP) and tried to find out their needs for surgical treatment. We aimed to investigate the frequency of FMF in the cases with NSAP in surgical emergencies.

## MATERIAL and METHODS

During six months period, we enrolled 68 patients who were admitted to the Department of General Surgery in Ege University due to NSAP. NSAP is defined as acute abdominal pain of under 7-day duration, and for which there is no diagnosis after examination and baseline investigations. Patients with pre-diagnosed with FMF were excluded. This study obtained ethical approval by Institutional Review Board.

On laboratory investigation, a complete blood count with lactate dehydrogenase, erythrocytes sedimentation rate, C-reactive protein (CRP), fibrinogen and urine analysis were performed. Radiological evaluations were made by plain abdominal radiography, abdominal ultrasonography (US) and computed tomography (CT) scanning. Some of these patients have had previous, at least a few times, abdominal pain history. After all these assessments, those with unexplained abdominal pain were included in this research and patients were evaluated for FMF gene mutations. Data collected were classified in regard to MEFV mutations were positive or not. The nine FMF-related MEFV mutations were investigated. MEFV mutation analysis of the various DNA samples was performed in different institute (Erzurum Ataturk University Hospital, Department of Molecular Biology) as described. MEFV gene were analyzed with an FMF Strip

Assay test kit (ViennaLab Labordiagnostika GmbH, Vienna, Austria). DNA was extracted from peripheral blood lymphocytes according to standard procedures. Mutation identification was performed by microchip DNA analysis system (Nanogen Inc., San Diego, CA).

Continuous variables are given as mean  $\pm$  standard deviation, and categorical variables as numbers and percentages. In order to determine the difference in the means of continuous variables Student's *t* test for independent data was applied to normally distributed variables. Qualitative comparisons of the data were analyzed with Chi-Square test and Fisher's Exact test. If statistically significant differences were found, further testing was conducted using the consecutive Mann-Whitney *U* test. A *p*-value  $<0.05$  was considered statistically significant. SPSS 13.0 (SPSS inc., Chicago, IL, USA) statistical software package was used for all calculations.

## RESULTS

The MEFV genotypes of 68 patients have been determined. Table 1 shows the different genotypes of the patients and comparative results between two groups. MEFV gene mutation was detected in 19 patients (27.9%). Of these, 6 subjects had homozygotic mutations (31.5%), and 13 were heterozygote (68.4%). M694V was the most frequent mutation with a rate of 36.8 % ( $n=7$ ) and followed by M680I(G/C) ( $n=4$ , 21%) (Figure 1).

Of the 68 patients, 35 (51.4%) were male, 33 (48.5%) were female, and the age ranged from 17 to 49 (mean= $29.5\pm 10.1$ ) years. The main clinical characteristics of the patients were as follows: abdominal pain was observed in 68 (100%), fever in 46 (67.6%), arthralgia in 12(17,6%), splenomegaly in 9 (13.2%), hepatomegaly in 4 (5,8%) and pericarditis in one (1.4%) patient. In one patient, amiloid nephropathy was detected. Twenty-one patients (30.4%) had clinical history of similar attacks of abdominal pain. In MEFV (+) group, ten patients (52.6%) had past history and

only 11 patients in MEFV (-) group (22.4%) ( $p=<0.05$ ).

Laboratory findings and differences between two groups were demonstrated in Table 2. Of the 68 patients, 49 (72%) patients had both elevated fibrinogen and CRP. Percentage of leukocytosis, lactate dehydrogenase (LDH), thrombocytosis, and proteinuria were as follow; 55 (%80), 31 (%45,5), 10 (%14.7), 2 (%4.4).

Table 3 shows radiological evaluation of patients. All patients were performed plain abdominal radiography. Gas-fluid levels in the colon were observed in seven patient's radiograph (10,2%). Ultrasonography (US) was also performed in all subjects and 33 patients (48.5%) were detected with abnormal findings [free pelvic fluid, intestinal edema and peri-intestinal fluid, noncompressible appendix ( $n=6$ )]. The other findings included ovarian cyst, renal parenchymal disease, liver hemangioma, fatty liver, hepatomegaly and splenomegaly. Surgical history of the patients including 13 appendectomy (19,1%) and 5 cholecystectomy (7.3%) was confirmed with US. One patient with endocarditis in cardiology department was consulted by surgeon because of abdominal pain. Laboratory results showed leucocytosis, increased fibrinogen (705 mg/dl) and CRP (21,1 mg/dl) levels. In US, free pelvic fluid and left ovarian cyst 5 cm in diameter was demonstrated. Therefore, genetic mutation was searched and heterozygous mutation (p.680I/p.726A) was detected.

On computed tomography (CT) scanning performed in 29 patients (42.6%), the common finding was non-specific mesenteric pathology. Ascites with or without focal peritonitis, splenomegaly and dilated small bowel loops were other findings (Table 3). In three patients with homozygous mutation, minimal peri-intestinal free fluid and enlarged lymphadenopathy in the right quadrant were observed. In six patients in whom US showed decompressed appendix, appendectomy was performed. Only three of the patients were MEFV(+) but pathological

examination was compatible with inflamed appendix in all.

Thirteen patients had a medical history of appendectomy. Two of them were performed in the last month. Three patients underwent appendectomy in our department. Statistical analysis considering the rate of appendectomy between two groups was insignificant (6 patients in MEFV(+) vs. 7 patients in MEFV(-) group,

$p=0.166$ ). Only two patients had a normal pathological examination of appendix [both in MEFV(+) group]. Mesenteric lymphadenitis was the cause of the abdominal pain in two patients who had CT result demonstrating pericecal fluid collection. Colchicine treatment was started in those with positive MEFV mutation. Follow-up was conducted by the rheumatology clinic.

	Homozigot mutation (n=6)	Heterozigot Mutation* (n=13)	Mutation (-), (n=49)	p **
Start age (years)	27.5	24.6	31.7	0.475
M/F	3/3	5/8	27/22	0.420
Clinical history <sup>x</sup>	5	5	11	0.021
Fever	5	12	29	0.020
Abdominal pain	6	13	49	1.000
Arthralgia	2	4	6	0.080
Pericarditis	0	1	0	0.279

\*Patients with compound heterozygous mutation was also included in this section.

\*\***p value** was determined between the patients with homozigot/heterozygous mutation and normal genetic result.

<sup>x</sup>Clinical history of similar abdominal pain attacks

	MEFV(+) (n=19)	MEFV(-)(n=49)	p
Leukocyte*(10 <sup>3</sup> /μL)	12.143(7800-17.700)	12.374(6300-22000)	0.273
CRP(mg/dL)	7.18±4.3 (1,5-23)	4.58±3.6 (0.3-14)	0.014
Fibrinogen (mg/dL)	482±134(315-755)	323±143 (171-593)	0.024
Platelets /mm <sup>3</sup>	267.10 <sup>3</sup> (174-345.10 <sup>3</sup> )	289. 10 <sup>3</sup> (145-410.10 <sup>3</sup> )	0.308
ESR** (mm/h)	19.3±13 (4-56)	16.3 ± 9(2-40)	0.287
Proteinuria	2	0	0.196
LDH(U/L)	659±205(345-1362)	503± 189(151-853)	0.005

LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

-mean laboratory findings were compared.

\*Leukocyte count at the first admission was used.

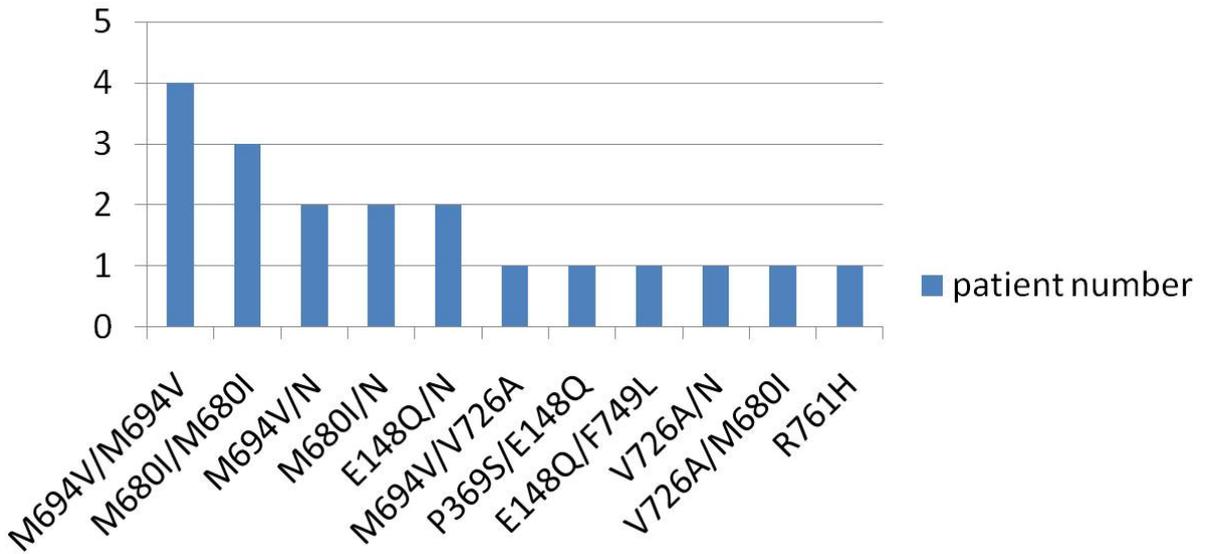
\*\*sedimentation in the second period was evaluated.

**Table 3. Radiological evaluations presenting with abnormalities in the patients with abdominal pain**

	MEFV(+) (n=19)	MEFV(-)(n=49)
Plain abdominal graphy*	5	2
Ultrasonography (+/-)*	12	21
Abdominal CT scan	11, (57.8%)	18, (36.7%)
i. mesenteric pathology	4	8
ii. ascites with/without peritonitis	2	2
iii. appendicitis	3	3
iv. small intestinal pathology	0	2
v. others**	1	1
vi. negative	1	2

CT: computed tomography, \* it was performed in all patients and those with abnormal findings were only defined. \*\* gynecological disorders were observed

### Distribution of mutation types



**Figure 1.** Distribution of the gene abnormalities considering the number of patients.

## DISCUSSION

In this study, we evaluated clinical features, laboratory results, radiological findings and FMF gene genotypes of the patients admitted to surgical emergency due to NSAP. In some series, fever was found the most common symptom<sup>3,5,6</sup> while others revealed peritonitis as the most frequent symptom<sup>7</sup>. In our series, all patients had different degree of peritonitis as the most common presentation. In MEFV(+) patients, history of recurrent abdominal pain was statistically significant. Likewise, they had also significantly higher CRP, fibrinogen and LDH levels while other laboratory parameters were observed similar compared to MEFV(-) cases.

Only 15-30% of patients admitted to emergency service due to abdominal pain need surgical intervention<sup>8</sup>. Recurrent episodes of peritonitis can mimic the acute abdomen and patients may undergo unnecessary surgical procedures before the main cause of the pathology is documented. Although the characteristic of pain is not generally characterized, it may be localized to a particular area. In such cases, the diagnosis of false acute abdomen is not unusual, nevertheless, the rate of negative explorations reach to 20–30%<sup>9,10</sup>. In our series, we observed significantly higher rate of similar abdominal pain attacks in MEFV(+) group when compared to MEFV(-) patients ( 52.6 % vs. 22.4%,  $p < 0.05$ ). Therefore, clinical history plays a pivotal role in the suspicion of FMF-related abdominal discomfort.

Clinical heterogeneity in FMF patients is associated with genetic heterogeneity. This entity is the plausible cause of false or delayed diagnosis. Several studies have demonstrated that MEFV mutations are related to nonspecifically increased inflammatory response. High levels of acute-phase reactants have been measured in asymptomatic individuals with heterozygous MEFV mutations, and inflammation was observed even during the asymptomatic phase in such

individuals<sup>11,12</sup>. In our study, etiology of nonspecific pain which was the target point can be explained by majority of the patients with heterozygous mutation (68.4%). The frequency of M694V mutation (36.8%) which was the most common was compatible with other series from Turkey ranging between 33,7% and 51,5 %<sup>7,13-16</sup>.

Many patients with undiagnosed FMF have undergone appendectomy because the severity of the peritoneal episodes seemed to indicate appendicitis. Kasifoglu et al investigated the surgical operations in FMF patients and appendectomy was the most frequent procedure with a rate of 26,6%<sup>17</sup>. In a multicenter study, this rate was 19%<sup>3</sup>. Also in our cases, appendectomy was the most performed surgical procedure. Lidar et al reported very high incidence of non-inflamed appendectomy in FMF patients reaching 80% which was significantly higher compared to general population (20%)<sup>4</sup>. In another study investigating the incidence of FMF in patients with negative appendectomy, 7.7% of the patients were diagnosed with FMF<sup>18</sup>.

As a result, almost half of the patients with nonspecific abdominal pain were diagnosed with FMF, either homozygous or heterozygous mutation. M694V was the most common presented MEFV gene mutation. Particularly in endemic areas for FMF, such as Turkey, in patients with NSAP usually accompanied by fever and high levels of inflammation markers, provisional diagnosis of FMF should be considered before the decision to perform surgery.

Conflict of interest: None to declare

**Acknowledgements:** I would like to thank all residents in Department of General Surgery at Ataturk University, School of Medicine for helping me in the collection of genetic test results.

## REFERENCES

1. Medlej-Hashim M, Serre JL, Corbani S, Saab O, Jalkh N, Delague V, Chouery E, Salem N, Loiselet J, Lefranc G, Mégarbané A. Familial Mediterranean fever (FMF) in Lebanon and Jordan: a population genetics study and report of three novel mutations. *Eur J Med Genet.* 2005;48:412-20.
2. Samuels J, Ozen S. Familial Mediterranean fever and the other autoinflammatory syndromes: evaluation of the patient with recurrent fever. *Curr Opin Rheumatol.* 2006;18:108-17.
3. 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. Turkish FMF Study Group. Familial Mediterranean Fever (FMF) in Turkey. *Medicine.* 2005;84:1-11.
4. Lidar M, Doron A, Kedem R, Yosepovich A, Langevitz P, Livneh A. Appendectomy in familial Mediterranean fever: clinical, genetic and pathological findings. *Clin Exp Rheumatol.* 2008;26:568-73.
5. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med.* 1967;43:227-53.
6. Rawashdeh MO, Majeed HA. Familial Mediterranean fever in Arab children: the high prevalence and gene frequency. *Eur J Pediatr.* 1996;155:540-4.
7. Yiğit S, Bağcı H, Ozkaya O, Ozdamar K, Cengiz K, Akpolat T. MEFV mutations in patients with familial Mediterranean fever in Black Sea region of Turkey: Samsun experience. *J Rheumatol.* 2008;35:106-13.
8. Irvin TT. Abdominal pain: a surgical audit of 1190 emergency admissions. *Br J Surg.* 1989;76:1121-5.
9. Andersson RE, Hugander A, Thulin AJ. Diagnostic accuracy and perforation rate in appendicitis: association with age and sex of the patient and with appendectomy rate. *Eur J Surg.* 1992;158:37-41.
10. Pieper R, Kager L, Nasman P. Acute appendicitis: a clinical study of 1018 cases of emergency appendectomy. *Acta. Chir. Scand.* 1982;148:51-62.
11. Kosan C, Cayir A, Turan M. Relationship between genetic mutation variations and acute-phase reactants in the attack-free period of children diagnosed with familial Mediterranean fever. *Braz J Med Biol Res* 2013;46(10). <http://dx.doi.org/10.1590/1414-431X20133178>.
12. Pras E, Langewitz P, Livneh A, Zemer D, Migdal A, Padeh S, Lubetzky A, Aksentijevich I, Centola M, Zaks N, Deng Z, Sood R, Kastner DL, Pras M. Genotype/phenotype correlation in familial Mediterranean fever (a preliminary report). Tel Aviv: Freund Publishing House 1997;260-4.
13. Yilmaz E, Ozen S, Balci B, Duzova A, Topaloglu R, Besbas N, Saatci U, Bakkaloglu A, Ozguc M. et al. Mutation frequency of Familial Mediterranean Fever and evidence for a high carrier rate in the Turkish population. *Eur J Hum Genet.* 2001;9:553-5.
14. Akar N, Mısırlıoğlu M, Yalçınkaya F, Akar E, Çakar N, Tümer N, Akcakus M, Tastan H, Matzner Y. MEFV mutations in Turkish patients suffering from familial Mediterranean fever. *Hum Mutat,* 2000;15:118-9.
15. Yalcinkaya F, Cakar N, Misirlioglu M, Tümer N, Akar N, Tekin M, Taştan H, Koçak H, Ozkaya N, Elhan AH. Genotype-phenotype correlation in a large group of Turkish patients with familial Mediterranean fever: evidence for mutation independent amyloidosis. *Rheumatol.* 2000;39:67-72.
16. Albayrak F, Selcuk NY, Odabas AR, Cetinkaya R, Pirim I. Genotype-phenotype correlation in patients with familial Mediterranean fever in East Anatolia (Turkey). *Genet Test Mol Biomarkers.* 2010;14:325-8.
17. Kaşifoğlu T, Cansu DU, Korkmaz C. Frequency of abdominal surgery in patients with familial Mediterranean fever. *Intern Med.* 2009;48:523-6.
18. Kisacik B, Karabicak I, Erol MF, Ozer S, Pehlivan Y, Onat AM, Tirpanci B, Ertenli I. Is familial Mediterranean fever (FMF) common in patients with negative appendectomy? *Mod Rheumatol.* 2013;23:330-3.

**Yazışma Adresi / Address for Correspondence:**

Dr. Pınar Yazıcı  
Sisli Etfal Training and Research Hospital,  
Halaskargazi Cad. Etfal Sokak , 34371  
İSTANBUL  
E-mail: drpinaryazici@gmail.com

Geliş tarihi/Received on : 07.06.2014

Kabul tarihi/Accepted on: 01.07.2014