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A Turkish Family with A89T (p. Ala89Thr, c.265G>A) Mutation on The MEFV Gene, Their Clinical Findings and Review of The Literature *

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Objective: Familial Mediterranean fever (FMF) is the most commonly seen fever syndrome and characterized by recurrent attacks of fever and serosal and/or synovial inflammation and primarily prevalent in Mediterranean populations. The MEFV gene on the short arm of chromosome 16 is responsible for the disease and its' protein product pyrin or marenostrin is substantially related with the regulation of the inflammatory reactions.

Materials and Methods: A Turkish non-consanguineous family with a total of three members clinically diagnosed as FMF are presented accompanied with literature. After the amplification of all exons of MEFV gene from family members'DNA using PCR technic, whole exom sequencing analysis of MEFV gene was done for all members of family.

Results: A rare missense mutation named A89T (p.Ala89Thr, c.265G>A) resulting in a mutated Pyrin/Marenostrin protein on exon 1 of MEFV was shown (both proband and her mother). This detected mutation is a rare in exon 1 of the MEFV gene.

Conclusions: To our knowledge, this is the first report from Turkish family and second report from world with A89T mutation. We thought that the current manucsript may provide significant knowledge for more accurate understanding of the disease and further studies on FMF pathogenesis.

***Key Words*:** *FMF, MEFV gene mutation, complete exom sequencing analysis*

MEFV Geninde A89T(p. Ala89Thr, c.265G>A) Mutasyonlu Bir Türk Ailesi, Onların Klinik Bulguları ve Literatür Taraması

Amaç: Ailesel Akdeniz Ateşi, tekrarlayan ateş atakları, serozal ve ya sinoviyal inflamasyon ile karakterize olan ve birincil olarak Akdeniz populasyonunda yaygın olarak görülen en sık ateşli sendromdur. 16. Kromozomun kısa kolu üzerindeki MEFV geni hastalıktan sorumludur ve genin protein ürünü olan pyrin ya da marenostrin esasen inflamatuar reaksiyonun düzenlenmesi ile ilişkilidir.

Gereç ve Yöntem: Klinik olarak FMF tanısı almış, akraba olmayan üç fertli bir aile literatür eşliğinde sunulmuştur. Aile bireylerinin DNA'sından PCR tekniği kullanımı ile MEFV geninin tüm ekzonlarının çoğaltılmasından sonra, aile bireyleri için MEFV geninin tüm ekzom dizi analizi yapıldı.

Bulgular: Mutasyona uğramış bir Pyrin/Marenostrin protein oluşturan, MEFV geninin 1. Ekzonu kodlama bölgesinde yer alan A89T (p.Ala89Thr, c.265G>A) heterozigot mutasyonu görüldü (hem probandda, hemde onun annesinde). Bu tespit edilen mutasyon ekzon 1 de nadir görülen bir mutasyondur.

Sonuç: Bildiğimiz kadarıyla bu bildirilen ilk Türk ailesi ve dünyada bildirilen ikinci vakadır. Biz şu anki makalenin hastalığın daha açık anlaşılması için ve FMF patogenezisi üzerinde ilerleyen dönemlerde yapılacak olan çalışmalar için önemli bilgi sağlayacağını düşünüyoruz.

Anahtar Kelimeler: *FMF, MEFV geni mutasyon, tüm ekzom dizi analizi*

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Introduction

Familial Mediterranean fever (FMF) (MIM #249100) is the most common heritable inflammatory illness, which is defined with self-limited recurrent attacks of fever and serositis and affects primarily mankind of Mediterranean ancestry, most generally Turks, Sephardic Jews, Arabs and Armenians (1, 2). Patients have also been more rarely defined in country away from the Mediterranean region such as Japan, Australia, Brazil and this situation is explained by migration patterns (3).

Before the colchisin treatment, renal amyloidosis (the most severe complication of FMF) was the reason of mortality in these cases (4). The FMF gene (MEFV) was

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identified in 1997 and it consists of 10 exons that placed on chromosome 16p13.3. MEFV is liable for the disease and its product, pyrin or marenostrin consisting of 781 amino acids that plays a crucial role in the arrangement of the inflammatory response (2, 5). Marenostrin/pyrin (M/P) the protein product of the MEFV gene, interface with the ASC (apoptosis associated speck-like protein with a caspase-recruitment domain (CARD) (6). Pyrin consist in differential isoforms, involving M/P-fl and the M/P-d2. ASC is coded by the PYCARD gene and it has functions to arrange inflammatory and apoptotic signalling in multiprotein complexes named 'inflammasomes (6, 7). ASC and pyrin interact entirely their PyD domains. It was reported that both pyrin and ASC proteins regulates the response of cellular inflammation either inducers or suppressors in different studies (8, 9).

Autosomal recessive pattern of inheritance is usually evident but the studies have reported that cases with just one heterozygous mutation described by routine screening can be prescribed colchicine in the existence of clinical symptoms (10, 11). In 2009, Marek-Yagel et al., researched the molecular and clinical characteristics of heterozygous FMF cases. Their research showed that even though the heterozygotes tend to have a mild disease, the disease could not be discriminated from that of homozygous cases (12). As noted previously made in similar studies, this syndrome shows a heterogeneous genetic basis (10-13).

Materials and Methods

In this study, a Turkish non-consanguineous family with a total of three members clinically diagnosed as FMF are presented. After the amplification of all exons of MEFV gene via PCR technique, whole exom sequencing analysis of MEFV gene was done for all members of family and a rare missense mutation in the coding region on exon 1 of MEFV gene was shown.

Selected mutation analysis approves the diagnosis in most cases with classic FMF. The sequence analysis may be required for patients with atypical FMF or mild clinical presentation. Molecular diagnostic testing for FMF is a non-invasive and specific technique, which can be used for the right diagnosis before the occurrence of the all clinical symptoms. More than 314 gene mutations and polymorphisms have been discovered in the MEFV gene to date (14). Still new mutations are identified and their relationship with FMF clinic is investigated (15).

Results

In our study a missense mutation, named A89T (p.Ala89Thr, c.265G>A) that cause a mutated Pyrin/Marenostrin protein was identified in exon 1 of MEFV gene (Figure 1). A89T was first described in 2004 by Cazeneuve and his friends (7). But they were shared limited information about clinical datas of the patient. They were said that the patient was from Armenian origin and had FMF-related symptoms. To our knowledge, this was the second report of this mutation in the literature and first report from Turkish origin. Mutations and polymorphisms are very rare on exon 1 in the MEFV gene. The only 3% of the described changes of FMF gene have been detected in exon 1 region of MEFV. Ten sequence variants have been identified in exon 1 of the MEFV gene so far. Of these patients, six had missense, 4 of them had silent mutations. Except one, all patients were symptomatic and it should be noted that no insertion or deletion mutation was reported in exon 1 up to date (14).

Our patient didn't have a brother or a sister and clinically diagnosed with FMF two years ago. Our investigation indicated that in addition to the proband, her mother had clinical findings with FMF and we detected the same mutation, too. Proband's father had no complaints with FMF. According to family history, there are no clinical symptomes of the disease in sisters and brothers of the probands' parents (Figure 1). But it was reported us by probands' mother, there was an abdominal pain in the probands grandfather. Because he has passed away, the genetic analaysis of patient was not performed for MEFV gene. Despite there was no clinical symptomes of the disease in probans' grandmother, we invited the grandmother to apply the clinics. Because the probands' grandmother did not apply the clinics because of the geographical reason, the mutation analysis of the grandmother was not done for MEFV gene.

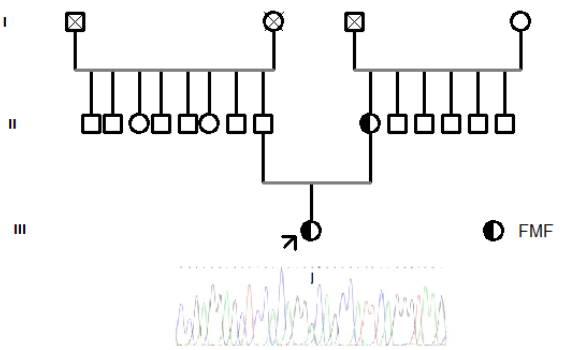

Figure 1. Family Pedigree of proband and nucleotide sequence of exon 1 of the MEFV gene showing a single base substitution in our patient, A89T (p.Ala89Thr, c.265G>A).

The proband had fever, abdominal pain, chest pain, arthritis but no family history of FMF. Also there was an appendectomy story with our patient. The recurrency of the attack was once a month. She didn't use colchicine regularly. Clinical data of the patients are given in Table 1.

Table 1. Clinical data of the proband and her family

Cases	Age	Age at started symptoms	Fever	Recurrency of the attack	Abdominal pain	Chest pain	Arthrit	Erythema	Amyloidosis
Proband	18	14	+	Once a months	+	+	+	-	-
Proband's father	48	-	-	-	-	-	-	-	-
Proband's mother	47	30	-	Once in 4 months	-	+	+	-	-

This family has been under clinical follow-up especially for their complaints and will be periodically checked for the parameters such as erythrocyte-sedimentation rate, C-reactive protein, CBC (complete blood count), SAA (systemic amyloid AA protein) that can be associated with inflammation.

Discussion

According to the Mutation Taster and SIFT bioinformatics programs, this detected alteration seems to be nonpathogenic. Variant was neither found in the Exome Aggregation Consortium (ExAC) nor in 1000G databases. Because it was a very rare mutation, it was necessary that ~~the~~ additional works are needed to acquire more certain information about the A89T mutation.

ASC is an essential adaptor protein in the inflammatory pathway and interacts with marenostrin which is the key component and defective in FMF. There are several studies on this subject in the literature. In a recent study, Nalbantoglu et all., demonstrated that ASC mRNA expression was up-regulated in patients with MEFV mutations free of mutation type in Caucasian FMF patients (16). Cazeneuve and his friends (7) investigated the subcellular localisation of marenostrin isoforms with the patients who had MEFV mutations. A89T mutation was described in one patient of Armenian origin who had FMF and it is localised at the PYD domain. This domain is a protein–protein interaction domain in pyrin encoded by the first MEFV exon. A89T mutation was studied because of it directly interacts with the protein–protein interaction. To identify the effects of the MEFV mutations on the subcellular localisation of pyrin isoforms, the researchers expressed normal or mutated pyrin-fl or -d2 in HeLa cells in the absence or existence of ASC. At the end of the study, the results revealed that the functional result of the FMF related mutations are probably unrelated to a mislocalisation of the mutant pyrin even if the existence of its connective partner ASC (17).

Due to A89T was very rare, we thought that when the number of individuals having this mutation increased, the effects of the mutation will be understood more easily. Also this mutation may ensure significant knowledges for further researches on FMF pathogenesis and particularly genotype-phenotype association studies.

The majority of FMF cases are larger in Eastern Mediterranean populations. The Turkish population with more than 79 million inhabitants have important number of FMF patients in the world. The prevalence of FMF is 1:500–1:1000 in Anatolia and the carrier frequency is as high as 1/5 among Turks (2). Thus, it is an obligatory to have more exact data about the FMF for more efficient public health services. In our study, we reported a rare mutation of the MEFV gene from Turkish family. Additionally in our previously performed studies, we identified two new mutations that also appear very rare (18-20). As shown, because of the MEFV heterogenity in Turkish FMF cases, larger serial analyses are necessary to define the distribution of MEFV mutations and to explore genotype-phenotype associations. Several studies related to newborn screening with FMF were done as yet (21) and this issue will be discussed further in the coming period. In this study, we purposed to contribute to a rare A89T mutation and its clinical features accompanied with literature.

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