

## Mini Review

# Familial Mediterranean Fever

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Submitted: 17 February 2017

Accepted: 27 March 2017

Published: 28 March 2017

ISSN: 2333-6714

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## Keywords

• Familial mediterranean fever

**Abstract**

Familial Mediterranean fever is an inherited autosomal recessive auto inflammatory genetic disorder. FMF especially seen in Mediterranean-originated societies like Sephardic Jews, Armenians, Arabs and Turkish descent. Recent information reveals that the disease is not only seen in the Mediterranean region, but also found in distant regions. The diagnosis of this disease is strictly based on the clinical indication. However, identification of mutations with genetic analysis methods is important in terms of supporting diagnosis, arrangement of treatment, follow-up complications and also in family screenings. It was observed that especially using sequence analysis methods on genetic studies have more opportunities for finding to novel mutations.

The most common complication is accumulates amyloid protein in various tissues. Using colchicine may be beneficial effects of preventing the complications in patients with pathogen mutations of FMF. It is thought that phenotype-genotype relationship is important in clinical evaluation and more studies needed on this issue.

**ABBREVIATIONS**

FMF: Familial Mediterranean Fever; AA: Amyloid A Protein; IL: Interleukin

**INTRODUCTION**

Familial Mediterranean fever (FMF) is an inherited autosomal recessive genetic disorder characterized by recurrent abdominal pain, fever, arthritis, arthralgia, and erysipelas-like erythema [1]. FMF belongs to the genetic auto inflammatory disease group which are especially seen in Mediterranean-originated societies Sephardic Jews, Armenians, Arabs and Turks [2]. As a result, depending on migration FMF is seen at certain rates in many parts of the world. FMF is a disease characterized by recurrent features. Although the age of onset of attacks is usually under 20 years but can be seen at any time in life. Attacks usually appears ranging from few hours to few days. This short review mentioned that brief history of FMF, *MEFV* gene, pathogenic mutations, diagnosis and clinical features of common mutations and our own experiences.

**Brief history**

As far as is known, the existence of initial clinical information about FMF was revealed by Galen in the second century. After that, about 200 years, there were no researchers provided significant information about this disease [3]. But at the beginning of the eleventh century, Saffari M et al., interpreting the book of IbnSina (Avicenna) described that Colchicum as "Canon of Medicine" and used this plant for joint pain and gout disease [4]. After eight centuries, of IbnSina's work, the French chemists Pierre-Joseph Pelletier and Joseph Bienaime Caventou isolated colchicine from *Colchicum autumnale* in 1820 [3]. FMF patients were first time

defined by Janeway and Mosenthal in 1908 [5]. This disease was explained in detail with Sohar and Heller after the definition of Siegal as "Benign Paroxysmal Peritonitis" in 1945 [6-8]. Reimann used the name of periodic disease in 1948 [7]. Cattan and Mamou reported for the first time it is stated that FMF is familial in 1951 and they also mentioned could be developed amyloid in 1956 [8].

Heller and Sohar used the definition of familial Mediterranean fever in 1961, they also showed that the disease was autosomal recessive [7,8]. However, colchicine could not use in the treatment of FMF until 1972 [7].

**MEFV gene**

In 1992, the *MEFV* gene locus was found on the short arm of the 16th chromosome (16p13.3) and this gene was cloned completely independently in 1997 by the International FMF Consortium and the French FMF Consortium [9,10]. *MEFV* gene has 15 kilo bases of a large gene consisting of 3507 nucleotides and 10 exons [11]. It encodes a protein called pyrin that comprise of 781 amino acids [6]. We know that this protein has an important role in both inflammation and apoptosis. In the case of mutant pyrin, its occurrence leads to inflammation characterised by the increase of IL-1 $\beta$  release [12]. One of the prominent hypothesis was suggested in the pathogenesis of FMF: caspase associated IL-1 $\beta$  inhibited by pyrin. Pyrin binding to apoptosis-associated speck-like protein (ASC) and this weakens inflammation formation. Thus preventing the inflammatory events [13].

**Mutations with pathogenic role**

There are currently 317 mutations associated with FMF that were reported in Infervers cite [14]. (<http://fmf.igh.cnrs.fr/ISSAID/infervers/search.php?n=1>). Among these mutations, the

most common and pathogenic variant number is 14, which are M964V, V726A, M680I, M964I, R761H, A744S, E167D, T267I, I692del, K695R, E148Q, P369S, F479L and I591T [15]. The remaining variants are not found related to the disease of FMF. Although pathogenic mutations are expressed in this way, we believe that it is necessary to re-evaluate variants according to phenotypic-genotype studies results.

### Diagnosis

The people has pathogen mutant of FMF who start at certain times of life characterized by recurrent abdominal pain, fever, arthritis, arthralgia, and erysipelas-like erythema and diagnosis is based on clinical indication [1]. Nevertheless, mutation analysis of the *MEFV* gene can often be useful in differential diagnosis of patients with mutation types. In addition, genetic testing is also helpful for diagnosis if the patients have unusual clinical symptoms, if there is no family history, and there is uncertainty regarding ethnicity [16]. Tel-Hashomer and Livneh's diagnostic criteria are generally used in adult FMF patients [15,17]. The most widely used diagnostic criteria for the FMF is the Tel-Hashomer criteria since 1997 [18]. According to the Tel-Hashomer criterion,

### Absolute diagnosis

2 major or 1 major and one minor criteria.

### Probable diagnosis

One major and one minor criterion is helpful in recognition [19].

**Major criteria:** Repeated fever attacks with serositis, AA type amyloidosis which is not related to any other disease, responding to the use of regular colchicine.

**Minor criteria:** Repetitive fever attacks, Erysipel like erythema, FMF in first degree relatives. In Livneh criteria [18], there must be at least one major criterion or at least two minor criterions for definitive diagnosis.

Major criteria; typical repetitive fever attacks, diffuse peritonitis, unilateral chest pain (Pleuritis or pericarditis), monoarthritis (hip, knee or ankle), fever alone. Minor criteria; incomplete attacks (abdominal, chest, joint), leg pain with exercise, responding to the use of regular colchicine. Clinically, FMF separated into three phenotypes [20]; type 1 phenotypes, often recurrent short episodes of inflammation with serositis, fever, peritonitis, pleuritis, synovitis at some time pericarditis, orchitis or meningitis are seen, type 2, amyloidosis with the first type of symptoms, and type 3 characterized as silent and commonly homozygous or compound heterozygous cases that do not include any FMF clinical signs or amyloidosis. Because some patients could not be diagnosed as FMF they have been appendectomy due to misdiagnosis. This shows that it is still difficult to diagnose FMF in many regions [22]. The most important complication of this disease is amyloidosis [22]. However, it is likely that more advanced amyloidosis cases are seen in undiagnosed patients. It is reported that, in respect of clinical symptoms, the most symptomatic mutation type of FMF diseases is M694V [21]. Especially, homozygous or compound heterozygous cases have clinically severe forms. Clinical

symptoms vary according to low or high penetrance conditions. Federici et al. [22], show that FMF like symptoms are getting increase from carrying toward two high penetrance mutations in patients with FMF. Especially severe form of amyloidosis is seen in this mutation type.

### DISCUSSION & CONCLUSION

There have been many studies on FMF in Turkey and other countries [23-27]. When pathogenic mutation types are examined: most prevalent mutations types are M694V, M680I, V726A, and E148Q in Turkey [24-26]. According to mutation types clinical findings are: fever, peritonitis and arthritis are the most prominent symptom in M694V mutation type and using colchicine rate appears to be quite high in homozygous cases. Although M680I and V726A the clinical manifestations are similar but the incidence is lower. It was reported that especially V726A type is a milder form of the disease [27]. Clinical manifestations are more dominant in homozygous and compound hetero or homozygous cases. The most prevalent complication is amyloidosis and it is often seen in patients with M694V homozygous cases [27]. Because of the high carrier rate in certain regions, many patients who have not been diagnosed yet. In particular, it is necessary to clinically correct evaluate these patients and should be done genetic analysis. It is appropriate to take treatment according to the clinical diagnosis. Knowing mutation types can help in planning treatment and this will ensure that these persons are protected from complications as much as possible. It can be considered that the pathogens variants may expand further, which are also determined by the use of sequence analysis methods. This is likely to be revealed by genetic-phenotype studies.

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#### Cite this article

Kilinc M (2017) Familial Mediterranean Fever. *J Immunol Clin Res* 4(1): 1036.