Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis

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INTRODUCTION

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent attacks of fever and serosal inflammation. This topic will review the epidemiology, genetics, and pathogenesis of FMF. The clinical manifestations, diagnosis, and management of FMF are discussed in detail separately. (See "Clinical manifestations and diagnosis of familial Mediterranean fever" and "Management of familial Mediterranean fever".)

EPIDEMIOLOGY

Familial Mediterranean fever (FMF) is most prevalent in individuals of Turkish, Armenian, Middle Eastern and North African Jewish, and Arab descent. Among Armenian individuals, the carrier rate for FMF is approximately one in seven, with an observed disease rate of roughly 1 in 500 [1]. Among the Jewish population in Israel, the carrier rate varies from one in eight in those of Ashkenazi origin, to one in six in those of North African origin, to one in four in those of Iraqi origin [2].

However, FMF is not restricted to these ethnic groups. It has also been reported at a lower prevalence in many other populations such as in Greece, Italy, Japan, and China [2-5]. In the United States, FMF is frequently encountered in Ashkenazi Jews and immigrants from the Middle East and Armenia. In Germany, most FMF patients are of Turkish origin. In France, there

is a relatively large FMF population that originated in North Africa. In the Balkans, the number of FMF patients and the rate of *MEFV* mutations carriage is decreasing as the country is farther from Turkey [6]. This may reflect the expansion of the Ottoman Empire in this area. In Italy, the prevalence of FMF is highest in the southern part and decreases gradually toward the northern area, suggesting that the disease spread from the southeastern to the northwestern part of the country. It is hypothesized that the origin of FMF was more than 3000 years ago in Mesopotamia [7]. From there, the disease was spread to Armenia and Turkey in the Ancient World. In the modern world, the spread of the disease to countries far from the Mediterranean basin can be explained by easy transportation overseas and later by the air.

FMF shows considerable variability in severity and type of clinical manifestations by region. This variability is probably due to differences in *MEFV* mutations, additional genetic modifiers, and associated environmental factors. (See "Clinical manifestations and diagnosis of familial Mediterranean fever" and 'Genotype-phenotype correlation' below.)

GENETICS

MEFV gene mutations — Familial Mediterranean fever (FMF) is usually considered an autosomal recessive disease, and affected individuals have biallelic pathogenic mutations in the Mediterranean fever (*MEFV*) gene located on the short arm of chromosome 16 (16p 13.3) [8,9]. The *MEFV* gene has 10 exons, and there are more than 370 variants identified to date [10]. The number of variants is increasing with the use of genome sequencing. Five founder mutations, V726A, M694V, M694I, M680I, and E148Q, account for approximately 75 percent of FMF chromosomes from typical cases in Armenian, Arab, Jewish, and Turkish populations [11]. Among them, M694V is the most frequent mutation in all four populations, with a prevalence ranging from 20 to 65 percent. However, approximately 10 to 20 percent of individuals who meet diagnostic criteria for FMF have no *MEFV* mutations. It is contentious whether this condition is FMF-like disease or true FMF with as-yet unidentified genetic variations [12].

Approximately 30 percent of FMF patients in endemic countries harbor a single pathogenic variant (monoallelic disease) [13,14]. This observation raises the question of whether the disease is also transmitted as an autosomal dominant trait. Indeed, some reports describe a dominant trait among patients with specific mutations such as M694VDel, a deletion mutation, and H478Y, T577N, and P373L, which are missense mutations [15-18]. The deletion mutation may cause a serious defect in the encoded pyrin protein, leading to full expression of FMF. However, there is no clear explanation for the presence of FMF in those individuals carrying the other single missense mutations. Since more than 95 percent of the carriers of a single *MEFV* mutation (heterozygotes) are **asymptomatic**, it is hypothesized that there are additional

genetic and environmental modifiers that influence the phenotypic expression of the disease. In a study using a statistical approach to estimate the contribution of heterozygosity to disease prevalence, a genotype comparison in siblings from 63 familial forms and a genotype study in 557 patients from 4 Mediterranean populations were performed [19]. This study demonstrated that heterozygosity is not responsible for classical Mendelian FMF per se but constitutes a risk factor to develop FMF, with the risk six- to eightfold higher compared with noncarriers of *MEFV* mutation.

Genotype-phenotype correlation — Although mutations are found throughout the entire *MEFV* gene in patients with FMF, the mutations with the most severe forms of disease (M694V and M680I) are clustered in exon 10, which encodes a motif known as the B30.2/SPRY domain at the C terminus of the protein. M694V homozygotes have a severe phenotype and are more likely to have early disease onset, arthritis, erysipelas-like skin lesions, high fever, splenomegaly, more frequent attacks as compared with individuals with other *MEFV* mutations, and renal amyloidosis [20]. In addition, patients with these mutations require higher doses of colchicine to prevent attacks as compared with patients with other genotypes. The M694V mutation affects the majority of North African Jews with FMF; these patients are known to have more severe attacks and in the pre-colchicine era, they had a high frequency of amyloidosis [21]. Ashkenazi Jews and Druze, who have a relatively low frequency of the M694V mutation, tend to have milder versions of FMF, with a low prevalence of amyloidosis.

Genetic variants found in exons 2 (eg, E148Q, R202Q) and 3 (P369S) are usually associated with less severe clinical presentations of FMF or even just mild nonspecific inflammatory manifestations. However, this is not always the case, and reports exist of more severe or atypical disease with these variants. For example, several studies showed that E148Q, P369S, and R408Q may exist on a single allele (in cis) and present with FMF-like disease or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome [22-24]. Additional studies from Greece and Turkey reported that the R202Q mutation is also associated with an inflammatory phenotype of FMF [25,26]. Hence, the typical clinical findings of FMF, especially arthritis, were observed in patients with compound mutations including R202Q [24].

In Japan, where most mutations are in exons 2, 3, and 4, FMF tends to be mild and easily controlled with low-dose colchicine [27]. Individuals with one or no pathogenic *MEFV* mutation usually tend to have milder disease compared with those with biallelic pathogenic variants [28]. These observations suggest an additional role for environmental factors in the FMF phenotype.

A pathogenicity score of the *MEFV* genetic variants is available [29].

It is still unclear if the E148Q mutation alone is a polymorphism or a disease-causing sequence alteration [30-32]. The E148Q mutation has reduced penetrance and E148Q homozygotes are asymptomatic or may have a mild disease; amyloidosis is rare in individuals with these mutations. However, patients carrying the E148Q mutation with an additional different mutation are almost always symptomatic. In one study, it was found that the penetrance of M694V/E148Q was more than 17 times higher that of M694V/-, suggesting an active role for E148Q mutation when combined with M694V mutation [33]. (See "Clinical manifestations and diagnosis of familial Mediterranean fever", section on 'Clinical manifestations'.)

Other genetic factors — The incomplete penetrance and the varying expression of FMF suggest the presence of other, possibly genetic factors that could influence the expression of illness. Evidence that another gene may modulate the clinical expression of the *MEFV* gene is the segregation of different alleles of the major histocompatibility class I chain-related gene A (*MICA*) among FMF patients with different clinical features. In one study that evaluated 151 affected patients and their family members for the presence of five common *MICA* alleles, the A-9 allele was strongly associated with early disease onset in M694V homozygotes, while the A-4 allele appeared to have a beneficial effect on the frequency of FMF attacks [34]. The possibility that another gene tightly linked to *MICA*, and in linkage disequilibrium with the different *MICA* alleles, has not been excluded. The mechanism through which *MICA*, or another closely linked gene, influences the FMF phenotype is unclear.

Heterogeneity among additional disease-modifying proteins may also contribute to the variable phenotypes among patients with identical *MEFV* genotypes [35]. This was illustrated in a study that evaluated the genotype of 137 Armenian patients from 127 families [36]. In this study, the presence of the serum amyloid A1 (*SAA1*) alpha homozygous genotype was associated with a sevenfold increased risk for renal amyloidosis as compared with other *SAA1* genotypes. The Arg753Gln polymorphism may affect the severity of FMF by altering the innate immune response to pathogens and may change the phenotype of FMF in geographic areas where bacterial insult is more common [37]. *SAA1* gene polymorphisms, consisting of -13T/C SNP in the 59-flanking region and SNPs within exon 3 (2995C/T and 3010C/T polymorphisms) of the *SAA1* gene, are associated with susceptibility to FMF in the Japanese population [38].

PATHOGENESIS

The *MEFV* gene encodes pyrin, a 781 amino acid protein that is expressed predominantly in the cytoplasm in cells of the myeloid lineage (among circulating cells) along with synovial fibroblasts and dendritic cells [39]. Pyrin plays an important role in the innate immune system, which constitutes a primary defense against external pathogens and other noxious agents [40].

Its exact role and mechanism of action appear to be in sensing changes in the Rho-GTPases interaction [41]. Ras homolog gene family, member A (Rho A) peptide is important in controlling GTPases and other protein kinase activity. GTPases and protein kinases are important in phosphorylation of intracellular proteins, which include pyrin. Peptides called 14.3.3 are proteins that can identify phosphorylated proteins, trap them, and block their activity [42].

It has been demonstrated that pyrin may serve as a pattern recognition receptor (PRR), which detects pathogen virulence activity. However, in contrast to most mammalian PRRs, it does not directly recognize microbial products but responds to their downstream effect on the Rho-GTPase system [41]. Cytotoxin TcdB6-8, a major virulence factor of *Clostridioides difficile*, which causes most cases of nosocomial diarrhea, triggers the assembling of pyrin inflammasome by recruiting apoptosis-associated speck-like protein containing a CARD (ASC) peptide and procaspase, which is responsible for the inflammatory process fighting this infection [41,43]. This effect of *Clostridium* toxin on pyrin is mediated primarily by its direct effect on Rho and GTPases. During exposure to *Clostridium* toxin, the Rho is inactivated; thereby, the GTPases reduce their rate of pyrin phosphorylation [43]. This, in turn, decreases the rate of pyrin trapping by 14.3.3 peptides, leaving a higher amount of nonphosphorylated pyrin for assembling the pyrin inflammasome. The production of the inflammasome aims to activate the procaspase to caspase, which in turn converts pro-interleukin (IL) 1 and pro-IL-18 into their active state. In parallel, caspase cleaves Gasdermin D (a pore-forming protein), causing cell membrane rupture (pyroptosis) and releasing the cytokines out of the cell in order to continue the inflammatory process [44]. These studies and observations explain the role of pyrin in inflammation induced by *Clostridium* toxin or by other infective agents.

Following an insignificant trigger (eg, emotional stress) in patients with FMF and *MEFV* mutation(s), the mutated pyrin protein is, a priori, far less phosphorylated. Therefore, more active (nonphosphorylated) pyrin remains, which in turn is capable of constructing the pyrin inflammasome for propagating inflammation. This suggests that mutations in the *MEFV* gene cause gain of function of pyrin protein so that it acts without needing an external provocation such as a toxin or an infective agent. The outcome of this process is secretion of IL-1, IL-18, and other mediators of inflammation that enhance chemotaxis and neutrophilia, inducing an attack of FMF [43]. (See "Clinical manifestations and diagnosis of familial Mediterranean fever", section on 'Clinical manifestations'.)

Dysregulation of the inflammasome due to mutated components also underlies other autoinflammatory diseases (eg, Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and neonatal-onset multisystem inflammatory disease). (See "Cryopyrin-associated periodic syndromes and related disorders".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Familial Mediterranean fever".)

SUMMARY

- Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent bouts of fever and serosal inflammation. (See 'Introduction' above.)
- FMF is most prevalent in individuals of North African, Jewish, Armenian, Turkish, and Arab descent. However, FMF is not restricted to these groups and has been reported at a lower prevalence in other populations. (See 'Epidemiology' above.)
- FMF is usually an autosomal recessive disease, and affected individuals have biallelic pathogenic mutations in the *MEFV* gene. Phenotypic expression of FMF has been reported in a subset of patients who carry only one *MEFV* mutation; however, more than 90 percent of those carrying a single *MEFV* gene are asymptomatic. Approximately 10 to 20 percent of individuals who meet diagnostic criteria for FMF have no *MEFV* mutations. (See 'MEFV gene mutations' above.)
- Five founder mutations, V726A, M694V, M694I, M680I, and E148Q, account for approximately 75 percent of FMF chromosomes from typical cases in Armenians, Arabs, Jews, and Turks. M694V homozygotes have a severe form of the disease and are more likely to have early disease onset, arthritis, erysipelas-like skin lesions, high fever, splenomegaly, more frequent attacks as compared with individuals with other *MEFV* mutations, and renal amyloidosis. In addition, patients who are M694V homozygotes require higher doses of colchicine to prevent attacks as compared with patients with other genotypes. (See 'Genotype-phenotype correlation' above.)
- FMF has a variable expression, possibly due to other genetic and environmental factors that influence the clinical features of this illness. (See 'Other genetic factors' above.)
- The *MEFV* gene encodes pyrin, a protein that is expressed predominantly in cells of myeloid lineage along with synovial fibroblasts and dendritic cells. Pyrin appears to act as a specific immune sensor (pattern recognition receptor [PRR]) for bacterial toxin

modifications of Rho GTPases interaction. Pathogenic mutations in the *MEFV* gene cause gain of function of pyrin protein so that it can start the cascade of inflammation even in the absence of provocation by a toxin or infection, resulting in an attack of FMF. (See 'Pathogenesis' above.)

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Contributor Disclosures

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