Familial Mediterranean fever—A review

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Abstract: Familial Mediterranean fever is inherited in an autosomal recessive manner. There are two phenotypes: types 1 and 2. Familial Mediterranean fever type 1 is characterized by recurrent short episodes of inflammation and serositis, including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis. The symptoms and severity vary among affected individuals, sometimes even among members of the same family. Amyloidosis, which can lead to renal failure, is the most severe complication. Familial Mediterranean fever type 2 is characterized by amyloidosis as the first clinical manifestation of familial Mediterranean fever in an otherwise asymptomatic individual. Routine treatment of end-stage renal disease, including renal transplantation, is advised. Lifelong treatment with colchicine is required for homozygotes for the p.Met694Val mutation or compound heterozygotes for p.Met694Val and another disease-causing allele; this prevents the inflammatory attacks and the deposition of amyloid. Individuals who do not have the p.Met694Val mutation and who are only mildly affected should be either treated with colchicine or monitored every 6 months for the presence of proteinuria. Molecular genetic testing of the *MEFV* gene, the only gene currently known to be associated with familial Mediterranean fever, can be offered to family members, especially when the p.Met694Val allele is present, because renal amyloidosis can be prevented by colchicine. ***Genet Med* 2011:13(6):487–498.**

Key Words: *familial Mediterranean fever, mutation, pyrin, proteinuria, amyloidosis, colchicine*

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NATURAL HISTORY

Familial Mediterranean fever (FMF) has traditionally always been regarded as being inherited in an autosomal recessive manner, although some recent articles have reported a significant number of patients with only one mutation who were diagnosed clinically as having FMF and responded well to colchicine (see later).[1–3]

FMF is divided into two phenotypes, types 1 and 2. FMF type 1 is characterized by recurrent short episodes of inflam-

mation and serositis including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis and meningitis. The symptoms vary among affected individuals, sometimes even among members of the same family. Amyloidosis, which can lead to renal failure, is the most severe complication of FMF type 1. FMF type 2 is characterized by amyloidosis as the first clinical manifestation of disease in an otherwise asymptomatic individual.[4–7]

Common manifestations

Common manifestations of FMF type 1 include the following.

Recurrent fever

Recurrent fever during early childhood may be the only manifestation of FMF.

Abdominal attacks

These are experienced by 90% of affected individuals and start with the sudden onset of fever and pain affecting the entire abdomen. Physical examination reveals board-like rigidity of the abdominal muscles, rebound tenderness, abdominal distension, and loss of peristaltic sounds. Radiographs reveal multiple small air-fluid levels in the small bowel. The diagnosis of "acute abdomen" usually results in laparotomy, but if not, the signs and symptoms resolve without sequelae over 24–48 hours.

Articular attacks

These are experienced by approximately 75% of individuals with FMF, occur suddenly, and may be precipitated by minor trauma or effort, such as prolonged walking. The three characteristic features are (1) a very high fever in the first 24 hours, (2) involvement of one of the large joints of the leg (knee, ankle, or hip), and (3) gradual resolution of the signs and symptoms after peaking in 24–48 hours, leaving no sequelae. Often a sterile synovial effusion is present. The attacks are commonly in the hip or knee but may occur in other joints such as the ankle, shoulder, temporomandibular joint, or sternoclavicular joint. The joint remains swollen and painful, as in chronic monoarthritis. Recurrent monoarthritis can be the sole manifestation of FMF; in such cases, the true diagnosis may not be established for some time and only after extensive investigations.[8] Attacks subside spontaneously only after several weeks or months; severe damage to the joint can result, and permanent deformity may require joint replacement. Approximately 5% of affected individuals have protracted arthritic attacks. Arthritis, arthralgia, and myalgia occur significantly more often among individuals with disease onset before age 18 years than in those with onset after age 18 years.[9,10]

Prodrome

A prodrome (preattack symptoms) is experienced by approximately 50% of persons with FMF. The prodrome recurs in most attacks, lasts a mean of 20 hours, and manifests with either a mildly unpleasant sensation at the site of the forthcoming spell (discomfort prodrome), or with a spectrum of physical, emotional, and neuropsychological complaints (variant prodrome).[11]

Pleural attacks

These are experienced by approximately 45% of patients with FMF and are the sudden onset of an acute, one-sided febrile pleuritis, which resolves within 48 hours. The individual complains of painful breathing, and breath sounds are diminished on the affected side. Radiographs may reveal a small exudate in the costophrenic angle. Attacks can rarely occur as the sole manifestation of FMF.[12,13]

Pericarditis

Pericarditis is a rare occurrence. It is characterized by retrosternal pain. Electrocardiogram shows an elevated ST segment, radiographs may reveal transient enlargement of the cardiac silhouette, and echocardiography may show evidence of pericardial effusion. It can rarely occur as the sole manifestation of FMF.[14,15]

Amyloidosis

Type AA amyloidosis is common in untreated individuals, especially in Jews of North African origin. It presents with persistent, heavy proteinuria leading to nephrotic syndrome and progressive nephropathy leading to end-stage renal disease. Affected individuals who are otherwise asymptomatic can develop renal amyloidosis as the first and only manifestation of FMF; this is termed FMF type 2. With increased longevity of individuals with renal failure through dialysis and/or renal transplantation, amyloid deposits are being found in other organs as well. The prevalence of amyloidosis varies by ethnicity, genotype, and gender. In untreated individuals, amyloidosis can occur in 60% of individuals of Turkish heritage and in up to 75% of North African Jews.[6,16] The age of onset of FMF attacks seems to be lower in persons with amyloidosis than in those without amyloidosis. FMF-related manifestations of chest pain, arthritis, and erysipelas-like erythema are more common in those with amyloidosis. Long periods between disease onset and diagnosis are associated with a high risk of developing amyloidosis.[17] Clinically detectable pulmonary amyloidosis secondary to FMF is rare; only a few cases have been reported so far.[18,19]

Rarer manifestations

Rarer manifestations of FMF attacks include the following.

Protracted febrile myalgia

This is a severe debilitating myalgia with prolonged low-grade fever, increased erythrocyte sedimentation rate (~100), leukocytosis, and hyperglobulinemia. The symptoms may also include high fever, abdominal pain, diarrhea, arthritis/arthralgia, and transient vasculitic rashes mimicking Henoch-Schönlein purpura. Protracted febrile myalgia usually lasts 6–8 weeks and responds to treatment with prednisone. *Streptococci* could be one of the agents triggering this syndrome.[20]

Erysipelas-like erythema

This is characterized by fever and hot, tender, swollen, sharply bordered red lesions that are typically 10–35 cm^2 in area and occur mainly on the legs, between the ankle and the knee, or on the dorsum of the foot. The lesions usually last 1–2 days. Isolated temperature elevation lasting a few hours can occur without any pain or inflammation. Erysipelas-like erythema occurs significantly more often among individuals with disease onset before age 18 years than in those with onset after age 18 years.[9,10]

Vasculitides

These occur rarely and include Henoch-Schönlein purpura (in ~5% of individuals with FMF) and polyarteritis nodosa.[21]

Reduced fertility

Untreated individuals with FMF, especially those with multiple attacks and/or amyloidosis, have a higher chance of infer-

tility. Colchicine treatment increases fertility but in some instances may induce oligospermia/azoospermia.[22,23]

Decreased atopy

Several studies have shown that FMF may have a protective effect against development of asthma, atopic sensitization, and allergic rhinitis (7% in individuals with FMF compared with 20% in the general population).[24]

Chronic ascites and peritoneal malignant mesothelioma

A female patient with FMF who developed chronic ascites has been reported recently by Ureten et al.[25] She was a compound heterozygote for the mutations p.Met694Val and p.Met680Ile, and after dose adjustment of colchicine, the amount of ascites decreased.

A possible association between FMF and peritoneal malignant mesothelioma was suggested by the finding of this condition in two persons with FMF who had recurrent peritoneal involvement during childhood, suggesting that local inflammation can lead to cancer at the same site. Both were homozygous for the mutation p.Met694Val.[26] Another case has been reported in a 56-year-old woman, on hemodialysis for 4 years, who had a history of FMF since childhood. She was a compound heterozygote for p.Met694Val and p.Arg761His, suffered from recurrent ascites, and did not take colchicine.[27]

CLINICAL DIAGNOSIS

Features suggesting the diagnosis of FMF include recurrent febrile episodes accompanied by peritonitis, synovitis, or pleuritis; recurrent erysipelas-like erythema; repeated laparotomies for "acute abdomen" with no pathology found; amyloidosis of the AA type that characteristically develops after age 15 years in untreated individuals, even those who do not have a history of recurrent inflammatory attacks; favorable response to continuous colchicine treatment; FMF in a first-degree relative; and being a member of an at-risk ethnic group.

The minimal and most current criteria for diagnosis of FMF are the Tel Hashomer clinical criteria.[28] These are fever plus one more of the following major signs and one of the following minor signs, or fever plus two minor signs.[28]

The major signs include fever, abdominal pain, chest pain, skin eruption, and joint pain. It is important to make the correct diagnosis in individuals with recurrent monoarthritis. The criteria that suggest a diagnosis of FMF in persons with monoarthritis include a high fever, favorable response to colchicine, history of FMF in sibs and other family members, and an appropriate genotype.[8]

The minor signs include an increased erythrocyte sedimentation rate (where normal values are as follows: men age <50 years: <15 mm/hour; men age 50–85 years: <20 mm/hour; women age <50 years: <20 mm/hour, and women age 50–85 years: <30 mm/hour); leukocytosis (normal values: $4.5–11.0 \times 10^3$ μL [$4.5–11.0 \times 10^{-9}$ L]); and elevated serum concentration of fibrinogen (normal values: 200–400 mg/dL [2.00–4.00 g/L]).

MOLECULAR GENETICS

The gene symbol for FMF is *MEFV* (Mediterranean fever), and the gene is situated at the chromosomal locus 16p13. It has 10 exons. The data are compiled from the following standard references: gene symbol from HGNC (HUGO [Human Genome Organizations, http://www.hugo-international.org/] Gene Nomenclature Committee, http://www.genenames.org/) and chromosomal locus, locus name, critical region, complementation group from OMIM (http://www.ncbi.nlm.nih.gov/omim), and protein name from UniProt. Databases include the Catalogue of Somatic Mutations in Cancer (http://www.sanger.ac.uk/genetics/CGP/cosmic/), the registry of *MEFV* sequence variants (Infevers, http://fmf.igh.cnrs.fr/ISSAID/infevers/), and Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php).

Normal gene product

The normal gene is a member of a family of nuclear factors homologous to the Ro52 autoantigen. It encodes a 3.7-kb transcript that is expressed exclusively in granulocytes, white blood cells important in the immune response. The protein encoded by *MEFV* has been called pyrin by the International FMF Consortium[29] and marenostrin by the French FMF Consortium.[30] The protein contains 781 amino acids and its normal function is probably to assist in controlling inflammation by deactivating the immune response. Pyrin contains B-box, bZIP basic, and coiled-coil domains and is also known as tripartite motif-20 (TRIM20), as it is a part of a larger family termed the tripartite motif proteins. Initially, pyrin was thought to be a transcription factor. Although pyrin has no DNA-binding activity, the protein does contain two nuclear localization motifs, and the endogenous protein localizes to the nucleus in granulocytes and dendritic cells. In addition, a specific *N*-terminal fragment of pyrin is translocated to the nucleus after cleavage by caspase-1. *N*-terminal pyrin seems to activate NF-κB through increased calpain-mediated degradation of IκB-α and is also observed in patient leukocytes. Pyrin can also be demonstrated in the cytoplasm of monocytes, and pyrin interacts with tubulin and colocalizes with microtubules, suggesting a rationale for the current highly efficacious treatment of the disease with colchicine, a microtubule-destabilizing agent.[31] More recently, pyrin has been found to interact with ASC, an apoptosis-associated speck-like protein with a caspase-recruitment domain (CARD), through cognate pyrin domain association. Wild-type pyrin, when overexpressed in HeLa cells, seems to increase ASC speck formation and, paradoxically, increase the survival of these cells. In addition to its role in apoptosis, ASC also nucleates inflammasome complexes through the homotypic interactions of its pyrin domain and CARD with NLRP proteins and inflammatory caspases, respectively, thus activating IL-1β. The direct interaction of pyrin with ASC suggests potential molecular mechanisms for the inflammatory hallmarks of FMF, either if pyrin inhibits IL-1β activation by competing with caspase-1 for ASC or if pyrin itself forms an inflammasome complex.[31–36] The normal pyrin protein interacts directly at the C-terminal B30.2 domain, where most of the FMF-causing mutations are situated, to regulate caspase-1 activation and consequently IL-1β production. The assumption is that mutations in persons with FMF result in less IL-1β activation and as a consequence heightened IL-1 responsiveness, resulting in increased inflammatory attacks. Heightened IL-1 responsiveness may also be one of the factors selecting for pyrin mutations, giving a genetic advantage.[37]

The recombinant full-length isoform (pyrin.fl) is cytoplasmic, whereas an alternatively spliced isoform lacking exon 2 (pyrin.DeltaEx2) concentrates in the nucleus.[38] Native pyrin, mainly consisting of pyrin.fl, is also cytoplasmic in monocytes but is predominantly nuclear in other cell types.[39]

Abnormal gene product

Mutations in *MEFV* may result in less active pyrin.[31]

Sequence variants

To date, 198 sequence variants have been identified, of which 84 are regarded as having an associated phenotype and result in disease-related symptoms, 82 have an unknown associated phenotype and may or may not result in disease-related symptoms, and 32 are nonpathologic (Infevers).

MOLECULAR GENETIC TESTING

MEFV is the only gene currently known to be associated with FMF. Clinical testing can be carried out by two methods.

Targeted mutation analysis

Laboratories may offer testing for the common mutation p.Glu148Gln in exon 2 and four common mutations in exon 10. Other laboratories test for mutations p.Glu148Gln in exon 2, p.Pro369Ser in exon 3, and the eight common mutations in exon 10 observed in Mediterranean populations. Mutation detection frequency varies by ethnicity.

Sequence analysis of select exons

Because most of the known *MEFV* mutations are in exon 10, laboratories offering sequence analysis of select exons include exon 10 and variably include other exons.

CONFIRMING THE DIAGNOSIS AND IDENTIFICATION OF THE MUTATIONS

In a proband

Molecular diagnosis of patients with FMF is carried out either by the testing of the five mutations that are the most frequently detected in patients with FMF (p.Met694Val, p.Met694Ile, p.Val726Ala, p.Met680IleGC, and p.Glu148Gln) or by *MEFV* exon 10 sequencing together with restriction analysis, which together enable the detection of additional mutations. In most individuals with classic FMF, analysis of the five common mutations (targeted mutation analysis) confirms the diagnosis. However, it has been shown that by expanding the panel of mutations tested to include an additional five (p.Arg761His, p.Ala744Ser, p.Lys695Arg, p.Met680IleGA, and p.Pro369Ser), at no extra cost, many mutations that would have been missed can be detected (Y. Kilim, unpublished data).

In individuals with nonclassic FMF or a mild clinical presentation, additional sequence analysis may be considered. In all instances in which the clinical picture is suggestive of FMF and molecular testing is not diagnostic, the diagnosis of FMF can be confirmed if a 6-month trial of colchicine therapy results in relief of the attacks, which then recur after cessation of this treatment.

Carrier testing for at-risk relatives

This requires prior identification of the disease-causing mutations in the family.

GENOTYPE-PHENOTYPE CORRELATIONS

A significant association has been identified between the mutation p.Met694Val, found in more than 90% of affected Jewish persons of North African origin, and the development of amyloidosis, especially in those who are homozygous for this mutation. Amyloidosis occurs less frequently in the presence of mutations other than p.Met694Val.[6,40–42] Some studies have also found that p.Met694Val is also associated with a generally more severe form of the disease,[43–45] but other studies have not confirmed this.[46] One study found that p.Met694Val was not associated with increased severity of the disease but was significantly associated with amyloidosis.[47]

Overall, disease severity, including the major clinical manifestations, amyloidosis, and other associated manifestations are influenced by the *MEFV* mutations themselves. However, based on the intra- and interfamilial clinical differences, these parameters are also influenced by other genes (outside the *MEFV* locus) and/or environmental factors. Studies have suggested that gender, serum amyloid A concentration, and genes involved in predisposition to arthritis may play a role as modifiers.[48–50] A more recent study found that the genotype SAA1–13T has at least an effect on the development of amyloidosis.[51]

The effects of the major histocompatibility complex class I chain-related gene A (MICA) on the course of FMF have been studied, and no MICA allele was found to have any independent risk factor effect,[52] although one study suggested that the A5 allele had a protective effect against the development of amyloidosis in a subgroup of p.Met694Val homozygotes.[53] Another study found that the impact of p.Met694Val homozygosity on the age at disease onset was aggravated if patients also inherited MICA-A9, whereas the frequency of attacks was found to be dramatically reduced in patients with MICA-A4. The authors commented that these results clarify, at least partly, the inconsistent phenotype-*MEFV* correlation in FMF.[54]

Persons who are homozygous for the mutation p.Met694Val have an earlier age of onset and higher frequencies of arthritis and arthralgia compared with the other groups.[10]

Disagreement exists as to whether p.Glu148Gln is a mutation or simply a polymorphism; p.Glu148Gln is predominant in Ashkenazi and Iraqi Jews, Armenians, and Turks and has been found to be associated with a generally mild form of FMF. Indeed, many individuals who are either homozygous for p.Glu148Gln or compound heterozygous for this variant and a mutation other than p.Met694Val are asymptomatic. Such individuals are also at a low risk, if any, of developing amyloidosis. The possible exception is those individuals who are compound heterozygous for the mutations p.Glu148Gln/p.Met694Val; such individuals may be clinically affected and also at risk of developing amyloidosis.[55,56]

Several studies describe p.Glu148Gln as a disease-causing mutation.[57–62] The Infevers Web site also lists it as causing disease-related symptoms. Other studies have not found p.Glu148Gln to be associated with clinical disease and have, therefore, considered it a benign polymorphism.[56,63,64]

With regard to the mutation p.Pro369Ser, one study found that this was unlikely to represent a classical FMF disease-associated mutation.[65]

Mattit et al.[43] tested for five mutations (p.Met694Val, p.Met694Ile, p.Met680Ile, p.Val726Ala, and p.Glu148Gln) in 83 unrelated patients who fulfilled the international FMF criteria and 242 unrelated apparently healthy controls. Among the 83 patients, 30.1% were homozygotes, 39.8% compound heterozygotes, 19.3% heterozygotes, and 10.8% had no identifiable mutation. Sequence analysis of the entire coding region of exon 10 in patients in whom only one or no mutation was detected identified the mutations p.Ala744Ser and p.Arg761His in a few cases. It is, therefore, possible that a significant number of affected individuals in the "one or no mutation" category did, in fact, have mutations that could not be detected by the methods used in this study. Among the 242 controls, the mutation p.Glu148Gln was the most common, a finding that they attributed to the reduced penetrance of this mutation, and they suggested that the presence of this mutation explained the consid-

erable proportion of genetically affected individuals in this population who remained asymptomatic.

Patients with only one identified mutation

New studies have cast considerable doubt on whether FMF is, in fact, a traditional autosomal recessive disease. Booty et al.[1] performed an extensive search for a second *MEFV* mutation in 46 patients diagnosed clinically as having FMF and carrying only one high-penetrance FMF mutation. In 10 patients, they resequenced the entire 15-kb *MEFV* genomic region using hybridization-based chip technology. They also determined *MEFV* gene expression levels and measured pyrin protein levels. They did not identify a second *MEFV* mutation in any of the patients screened, and haplotype analysis did not identify a common haplotype that might be associated with the transmission of a second FMF allele. They found no significant difference in pyrin levels between patients with a single mutation and those with a double mutation. Screening of genes encoding pyrin-interacting proteins identified rare mutations in a small number of patients, suggesting the possibility of digenic inheritance. The authors concluded that there exists a significant subset of patients with FMF who have only one *MEFV* mutation and that in such patients detection of a single mutation seems to be sufficient in the presence of clinical symptoms for the diagnosis of FMF and the initiation of a trial of colchicine.

Marek-Yagel et al.[2] carried out a similar study in which they performed full sequencing of complementary DNA samples and multiplex ligation-dependent probe amplification analysis on 20 patients with FMF with only one *MEFV* mutation. They found a second mutation in two patients but none in the remaining 18. They concluded that a single mutation in the *MEFV* gene may be much more common than was previously thought and may include up to 25% of patients who are diagnosed as having FMF.

Özen[3] discussed possible explanations as to how a person carrying only one *MEFV* mutation can present with the clinical manifestations of full-blown FMF. She admits that the easiest explanation would be the presence of less common mutations missed by routine testing; however, against this is the fact that studies in a substantial number of patients failed to reveal a second mutation, even when the gene and promoter region were fully sequenced, and haplotype analysis did not show a common haplotype in families of patients with one mutation.[1,2]

Another suggestion by Özen[3] is the coexistence of another autoinflammatory disease, which would have to be carefully excluded. Such diseases include hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), and the cryopyrin-associated periodic syndromes (CAPS). Digenic inheritance (the interaction of two genes resulting in the expression of a phenotype) is known to occur with autoinflammatory diseases, and it may be that patients with FMF with only one mutation may produce a disease phenotype if there is a mutation in a gene for other autoinflammatory diseases or a gene that acts in concert.[66] Against this theory, however, is the study by Booty et al.,[1] in which in a subset of patients, they analyzed the genes for HIDS and TRAPS and failed to show a digenic model of inheritance.

Another suggestion[3] is epigenetics—changes in gene expression that do not involve changes in the underlying DNA sequence. These mechanisms may silence the normal, functional allele. However, Booty et al.[1] found that allelic expression analysis in their patients showed that both *MEFV* transcripts were expressed. Polymorphisms in relevant genes can affect the course of FMF; for example, it is well known that a specific polymorphism in the *SAA* gene can result in a significant risk of developing amyloidosis in some patients with FMF, and the question is raised as to whether polymorphisms in relevant genes could produce an FMF phenotype with one mutation only.

The final possibility suggested by Özen[3] is the effect of environment. She postulates that a plausible explanation might be that if a person with one *MEFV* mutation who also carries a combination of polymorphisms that would favor more inflammation is exposed to the wrong environmental factors, he or she may cross the threshold of manifesting an FMF phenotype.

Further support for the finding that patients with only one mutation can suffer from classical FMF comes from a study carried out by Moradian et al.[67] They analyzed the symptoms and genotypes of 1299 patients, including 236 affected heterozygous patients with a definite diagnosis of FMF. They selected a subset of 63 heterozygous, homozygous, and asymptomatic normal individuals and completely sequenced their *MEFV* genes (exons) to discover any other mutations potentially missed by the currently used screening method. Apart from four synonymous polymorphisms in exons 2 and 5, they found a p.Thr267Ile mutation in one heterozygous patient with a severe case of FMF who should have been designated as compound heterozygous, but the other genotypes were all accurate. The authors recommend that heterozygous patients presenting with severe phenotypes should be further analyzed for a less common second *MEFV* mutation using gene sequencing.

Other genomic alterations

van Gijn et al.[68] addressed the question as to whether larger genomic alterations are also involved in the pathophysiology of FMF. They used multiplex ligation-dependent probe amplification on a total of 216 patients with FMF symptoms and found that that not a single deletion/duplication could be detected in this large cohort of patients. This result suggested that single or multiexon *MEFV* gene copy number changes do not contribute substantially, if at all, to the *MEFV* mutation spectrum.

PREVALENCE

FMF predominantly affects populations living in the Mediterranean region, especially North African Jews, Armenians, Turks, and Arabs.

The clinical picture of FMF in Arabs seems to be distinct, and the range and distribution of *MEFV* mutations are different from those noted in other ethnic groups.[69] Among the Arab populations, the distribution of mutations varies by country. In Jordan, p.Met694Val is the most common mutation, but the frequency of p.Val726Ala is also high, and the frequency of p.Met694Ile especially so.[70] In another study in Jordan and Lebanon, the mutations p.Met694Val and p.Met694Ile were found to be the most common, and in addition, three novel mutations not observed in other groups (p.Thr177Ile, p.Ser108Arg, and p.Glu474Lys) were found in the Lebanese.[71]

In Syria, p.Met694Val was the commonest mutation found in a study by Jarjour[72]; this accounted for 36.5% of the mutations detected in 97 patients with FMF. Other mutations were less common—p.Val726Ala accounted for 15.2% of the mutations, p.Glu148Gln for 14.5%, p.Met680Ile g/c for 13.3%, p.Met694Ile for 10.2%, and other mutations were rarer.

Among Egyptian patients with FMF, according to a study by El-Garf et al.,[73] the most frequent gene mutation was p.Val726Ala, which accounted for 41.2%, followed by p.Met694Val (32.4%), p.Met680Ile (29.4%), p.Glu148Gln (25%), and p.Met694Ile (20.6%). However, in another study, El

Gezery et al.[74] found a somewhat different distribution of mutations among Egyptian patients with FMF. They found that the most common were p.Met694Ile (34%), p.Glu148Gln (22.7%), p.Val726Ala (15.6%), p.Met680Ile (12.1%), and p.Met694Val (7.8%).

In North African Arabs with FMF, p.Met694Val was relatively common among Moroccans (49%) and Tunisians (50%), whereas p.Met694Ile accounted for 80% of the *MEFV* mutations in Algerian Arabs with FMF. The estimated *MEFV* mutation carrier frequency in North African Arabs is 1:100, considerably lower than among North African Jews.[75] In a significant number of Arabs with FMF, only one disease-causing mutation was identified using a panel of common alleles, suggesting the possible presence of other less common mutations in this population.[69,76,77]

Among Moslem Israeli Arabs, the most prevalent mutation was p.Val726Ala, followed by p.Met680Ile, p.Met694Val, and p.Met694Ile. The total carrier frequency for the four mutations was 10.4%, and no significant difference in phenotypic characteristics was found between the patients with the diverse mutations.[78] The mutation p.Met680Ile has been found to exist in two forms, one by the transition of c/g (g/c) (p.Met680Ile GC) and the second by the transition of c/t (g/a) (p.Met680Ile GA).[54] In the Arab population in the north of Israel, both the c/g (GC) and the c/t (GA) forms of the mutation are present. The c/t form cannot be detected by the diagnostic test that is commonly used but is detected by expanding the panel of mutations tested to include additional mutations, thereby expanding the percentage of patients that can be diagnosed molecularly (Y. Kilim, unpublished data).

In Palestinians, a study found that while two common mutations were identified in many persons with FMF, only one common mutation was found in almost one third, possibly indicating the presence of untested or as-yet unidentified mutations in this population.[79]

Bidari et al.[80] examined the 12 commonest FMF mutations among Iranian patients and found that the most frequent was p.Met680Ile, followed by p.Met694Val and p.Val726Ala.

A study among Turkish patients with FMF found that p.Met694Val was the most frequent mutation (51.4%), followed by p.Met680Ile (14.4%) and p.Val726Ala (8.6%).[10]

The carrier rate for FMF has been calculated to be as high as 1:3–1:7 in North African Jews, Iraqi Jews, Armenians, and Turks. Although molecular genetic testing has confirmed the carrier frequency to be as high as 1:5 in Ashkenazi Jews, the predominant mutation, p.Glu148Gln, is for a mild form of FMF, and thus, the prevalence of the disease in this ethnic group is not high.[57] A study by Feld et al.[81] showed that a high *MEFV* mutation frequency was also found among Jews of Bucharian, Georgian, and Bulgarian origin (20%), whereas intermediate and low rates were detected in Jews of Turkish and Yemenite extraction (14 and 8%, respectively). Shinar et al.[82] studied a group of Iranian Jews with FMF and found that in addition to the common mutations, one rare mutation, p.Arg653His, and one new mutation, p.Gly632Ser, were present in this group. The mutation p.Gly632Ser was associated with a distinct phenotype regarding sites involved in the attack, mild severity, sole expression of febrile episodes, and a male bias. Among Armenians with FMF, the spectrum of mutations is similar to that in the non-Ashkenazi Jewish population.[83]

DIFFERENTIAL DIAGNOSIS

Recurrent fever

Recurrent fever syndromes are reviewed by Padeh.[84]

To date, the causative genes for nine autoinflammatory diseases have been identified. These are FMF, chronic infantile neurologic cutaneous and articular syndrome (also called neonatal-onset multisystem inflammatory disease), familial cold autoinflammatory syndrome (FCAS, also known as familial cold urticaria), Muckle-Wells syndrome (MWS), Blau syndrome, Crohn disease (CD), TRAPS, HIDS, and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA). Chronic infantile neurologic cutaneous and articular/neonatal-onset multisystem inflammatory disease, MWS ,and FCAS belong to the spectrum of CAPS. CAPS are associated with autosomal dominant mutations in the *NLRP3* gene (formerly *CIAS1*), which encodes the protein cryopyrin. The genes *MEFV* and *CIAS1/NLRP3* belong to the pyrin gene family based on their nucleotide sequences and predicted protein structures. The *CARD15/NOD2*, *TNFRSF1A*, *MVK*, and *CD2BP1/PSTPIP* genes are associated with some of the other aforementioned inflammatory diseases. No gene for periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome (PFAPA) has been discovered to date.

Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome

The episodes of periodic fever in PFAPA are frequently indistinguishable from those in FMF; molecular testing of *MEFV* and/or close follow-up (with and without treatment) may be needed to make the correct diagnosis. Although no genetic basis for PFAPA syndrome has been discovered to date, it may well be that the syndrome does not represent a homogenous entity and may include some yet-uncharacterized genetic disease.[85] Treatment with steroids in the early stages of an attack is effective.

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne

PAPA syndrome is a rare inherited disorder of early onset, primarily affecting skin and joint tissues. Recurring inflammatory episodes lead to accumulation of sterile, pyogenic, neutrophil-rich material within the affected joints, ultimately resulting in significant destruction. It is caused by mutations in the *PSTPIP/CD2BP1* gene.[86] It has also been shown that pyrin binds the *PSTPIP1/CD2BP1* protein, defining FMF and PAPA syndrome as disorders in the same pathway.[87]

Hyperimmunoglobulinemia D and periodic fever syndrome

This is an autosomal recessive disorder characterized by recurrent attacks of fever, abdominal pain, and arthralgia. HIDS is caused by a mutation in the *MVK* gene, which encodes mevalonate kinase. A subgroup of HIDS is caused by another as-yet unknown gene. The recurrent episodes of fever and abdominal pains in HIDS are frequently indistinguishable from those in FMF, and correct diagnosis may depend on ascertainment of the effectiveness of colchicine as a treatment and on molecular testing.[88]

TNF receptor-associated periodic syndrome

This is an autosomal dominant disorder caused by a mutation in the *TNFRSF1A* gene. To date, 103 mutations have been identified, 68 of which have an associated phenotype (Infevers). It is likely that TRAPS is caused, at least in part, by excessive signaling through TNFRSF1A at the cell membrane and reduced pools of soluble p55 in the serum. The disease, also called familial Hibernian fever, is characterized by attacks of

fever, sterile peritonitis, arthralgia, myalgia, skin rash, and conjunctivitis. Approximately 10% of TRAPS patients develop amyloidosis. Treatment with TNF blocking agents is promising. The clinical picture in TRAPS may be similar to that in FMF; the mode of inheritance and the results of molecular testing distinguish the two conditions.[89]

ELA2-related neutropenia

This includes congenital neutropenia and cyclic neutropenia, which are autosomal dominant disorders characterized by recurrent fever, skin and oropharyngeal inflammation, and cervical adenopathy. In congenital neutropenia, diarrhea, pneumonia, and deep abscesses in the liver, lung, and subcutaneous tissues are common in the first year of life. Individuals with congenital neutropenia have a significant risk of developing myelodysplasia and acute myelogenous leukemia. In cyclic neutropenia, cellulitis, especially perianal cellulitis, is common during the neutropenic periods. Between neutropenic periods, individuals are generally healthy, and symptoms improve in adulthood. Molecular genetic testing of the *ELA2* gene, which encodes leukocyte elastase, is available on a clinical basis.[90,91]

In Western European whites with a clinical diagnosis of FMF, the frequency of common *MEFV* mutations was found to be extremely low and no affected individual had two identified *MEFV* mutations. It was concluded that persons with FMF-like syndromes from these populations in fact do not have FMF but another condition with a similar clinical picture that cannot be explained by *MEFV* mutations, and therefore, a search should be made for other causes in these individuals.[92]

Blau syndrome

This rare autosomal dominant disease is characterized by arthritis, uveitis, skin rash, and granulomatous inflammation. It is caused by mutations in the *CARD15/NOD2* gene that affect the central nucleotide-binding NACHT domain and has variable expressivity, usually affecting children younger than 4 years.[93]

Amyloidosis

MWS and FCAS, which are allelic disorders caused by a mutation in the *CIAS1* gene, are transmitted by autosomal dominant inheritance.[94,95] MWS is characterized by urticaria, deafness, and renal amyloidosis, and FCAS patients have cold-induced attacks of fever, rash, and arthralgia but no deafness or amyloidosis. Transthyretin-related amyloidosis also needs to be considered; this autosomal dominant disorder is characterized by a slowly progressive peripheral sensorimotor neuropathy and autonomic neuropathy and nonneuropathic changes of nephropathy, cardiomyopathy, vitreous opacities, and central nervous system amyloidosis.[96,97] The disease usually begins in the third or fourth decade with paresthesia and hypesthesia of the feet and is followed by motor neuropathy within a few years. Autonomic neuropathy includes orthostatic hypotension, constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis, and urinary retention or incontinence. Cardiac amyloidosis causes progressive cardiomyopathy. Central nervous system effects can include dementia, psychosis, visual impairment, headache, seizures, motor paresis, ataxia, myelopathy, hydrocephalus, or intracranial hemorrhage. A mutation in *TTR* is causative.

Abdominal pain

Acute abdominal pain from any cause needs to be considered. This includes acute appendicitis, perforated ulcer, intestinal obstruction, acute pyelitis, acute pancreatitis, cholecystitis, diverticulitis, and in females, gynecologic conditions such as ectopic pregnancy, acute or chronic salpingitis, torsion of ovarian cyst, bilateral pyosalpinx, and endometriosis.

Arthralgia

The conditions that require to be considered include acute rheumatoid arthritis, rheumatic fever, septic arthritis, systemic juvenile idiopathic arthritis, oligoarticular juvenile idiopathic arthritis, and collagen vascular diseases.

Pleuritic pain

Pleuritic pain can also occur in pleurisy and pulmonary embolism.

ATYPICAL PRESENTATIONS AND RARE MANIFESTATIONS

Until recently, the *MEFV* gene was considered to be responsible only for FMF. However, it is now known that it can also be associated with other clinical conditions. Additionally, various atypical presentations have been reported in which the clinical features were not typical of FMF, and which, in many cases, resulted initially in misdiagnoses.

Recurrent monoarthritis

Recurrent monoarthritis can be the sole manifestation of FMF; in such cases, the true diagnosis may not be established for some time and only after extensive investigations. Lidar et al.[8] conducted a study to clinically and genetically characterize patients with FMF in whom arthritis constituted the only manifestation. Their study population comprised 14 patients with episodes of arthritis as the only manifestation of FMF who nevertheless fulfilled the diagnostic criteria for FMF (ethnicity [North African Jewish origin], earlier age of disease onset, family history of FMF, favorable response to colchicine, fever during the attack, exertional leg pain, and a predominance of *MEFV* mutated alleles), whereas their control group consisted of 28 patients with episodic mono/oligoarthritis of different disease entities. The two groups differed significantly in features of arthritis (which were febrile and of short duration in FMF), family history of FMF, mutation analysis, and response to colchicine. The authors concluded that the clinical, ethnic, and genetic features of recurrent monoarthritis of FMF are specific and may separate FMF from other entities with mono/oligoarthritis.

Ayaz et al.[98] screened 35 children with the diagnosis of systemic onset juvenile idiopathic arthritis (SoJIA) for 12 *MEFV* mutations and found that two patients were homozygous and three patients were heterozygous for the p.Met694Val mutation. One patient was a compound heterozygote for the p.Met680Ile/p.Val726Ala mutations. Heterozygous p.Val726Ala mutation was found in one patient. The overall mutation frequency of patients was 14.28%, whereas the rate of disease-causing mutations in Turkey was 5%. Disease-causing mutations were found to be significantly more frequent in the SoJIA patients than the population ($P < 0.01$). Among these, p.Met694Val was the leading mutation with a frequency of 10% in SoJIA. Six patients carrying *MEFV* mutations were among the most resistant cases requiring biological therapy.

Ben-Chetrit et al.[99] also found that the gene *MEFV* can be associated with other clinical conditions. They conducted an extensive study of patients, reports in the medical literature, and the "Infevers" Website. They encountered three patients carrying *MEFV* mutations, each of whom presented with a distinct clinical picture that was not typical of FMF and each of whom

responded very favorably to colchicine; in each case, the disease manifestations disappeared completely with colchicine treatment, reappeared when this was stopped after approximately 1 year, and disappeared again with resumption of colchicine. They also identified additional reports about *MEFV*-related non-FMF disease entities such as palindromic rheumatism, and their survey of the "Infevers" Website revealed 13 cases with *MEFV* mutations defined as associated with "atypical FMF" and four cases categorized as "recurrent arthritis." The authors comment that higher awareness among physicians of the possibility of atypical phenotypes caused by *MEFV* will justify a therapeutic trial with colchicine and thereby relieve the suffering of many patients who up till now have been misdiagnosed.

Pleuritis

Pleuritis can rarely present as the sole manifestation of FMF. ten Oever and de Munck[12] reported on an 18-year-old woman of Turkish descent with a 12-year history of recurrent self-limiting febrile attacks accompanied by chest pain. At first, the symptoms were attributed to recurrent lower airway infections. However, the persistent nature of the attacks combined with her ethnic background and the spontaneous recovery from the short paroxysmal episodes led to the consideration of FMF. After undergoing treatment with colchicine, the patient was free of symptoms. Her 28-year-old brother had the same clinical manifestations of FMF, and he was also successfully treated with colchicine. The authors suggest that in patients with paroxysmal febrile attacks and chest pain, especially if they originate from the eastern Mediterranean area, FMF should be considered and colchicine be prescribed to relieve symptoms and prevent amyloidosis.

Lega et al.[13] reported on a 26-year-old man of Tunisian descent who had febrile episodes of right-sided pleuritis without any extrathoracic complaints. Disappearance of attacks with one dose of colchicine (1 mg/day) strengthened the presumptive diagnosis of atypical FMF, which was further confirmed by genetic testing identifying the homozygous mutation p.Met694Ile in the *MEFV* gene.

Recurrent pericarditis

Recurrent pericarditis, though rare, can present as the sole manifestation of FMF. Okutur et al.[15] described a 25-year-old Turkish woman who presented with recurrent pericarditis of no obvious cause. After several episodes, she was treated with colchicine, with complete resolution of the attacks. Genetic testing showed her to be a compound heterozygote for the *MEFV* mutations p.Met694Val/p.Met680Ile. Another case was an 8-year-old Turkish girl who had three attacks of pericarditis within a 3-month period.[14] After the third attack, she was commenced on colchicine, resulting in complete resolution of all the symptoms and signs, and she had no further episodes of pericarditis or other types of FMF attacks during the subsequent 20 months while she was receiving colchicine. *MEFV* mutation analysis showed her to be a compound heterozygote.

Recurrent urticaria

Recurrent urticaria has been reported as a rare manifestation of FMF. Alonso et al.[100] described a patient referred for recurrent urticaria. After allergy had been ruled out, the urticaria was attributed to previously undiagnosed symptoms of FMF, confirmed by genetic analysis.

Meningitis

Meningitis can occur rarely in FMF.[101–104] In each of the reported cases, the patients' attacks of recurrent aseptic meningitis resolved after treatment with colchicine.

It is also possible that mutations in the *MEFV* gene could be an additional susceptibility genetic factor in certain other disorders. These include the following.

Behçet disease

An increased frequency of *MEFV* mutations has been found in individuals with Behçet disease.[21,105–107] FMF carriers with Behçet disease have been found to have an increased risk for venous thrombosis.[106]

Inflammatory bowel disease

The protein encoded by *MEFV*, pyrin, has been shown to interact with the gene product of *NLRP3*, NALP3/cryopyrin, an important active member of the inflammasome. The *NLRP3* region has recently been reported to be associated with CD susceptibility, and in a recent study, Villani et al.[108] evaluated *MEFV* as an inflammatory bowel disease (IBD) susceptibility gene. Their results suggested that common variants in the *MEFV* region did not contribute to CD and ulcerative colitis (UC) susceptibility. Mutations in the gene *NOD2/CARD15* are also associated with CD.[109]

However, some studies have found an increased frequency of *MEFV* mutations in persons with UC, especially those with episodic arthritis, and this may suggest a possible modifying effect of *MEFV* in the disease process.[21,110,111] Other studies have found that CD seems to be more prevalent in FMF and presents later than in patients without FMF.[112,113] FMF in this group of patients shows a higher attack frequency and is more often complicated by amyloidosis.[112] However, in a later study by Fidder et al.,[114] the authors concluded that *MEFV* mutations were not associated with CD susceptibility.

In a study from Turkey, Sari et al.[115] reported on the concurrent manifestation of IBD and FMF in three infants (<6 months of age) in whom infantile UC was associated with the *MEFV* mutation. One patient required colectomy before the diagnosis of FMF, and in the other two, the UC could not be controlled until colchicine was added to the drug regimen. The authors suggested that the onset of UC in infants should prompt a search for *MEFV* mutations as this association may influence the management of the disease.

In a new study of Turkish children with IBD, Uslu et al.[116] found that disease-causing *MEFV* mutations and FMF disease rate were increased in these patients. The increase was prominent among patients with CD, whereas in UC, the rate was similar to the Turkish healthy control population.

Rheumatoid arthritis

Mutations in *MEFV*, in particular the p.Glu148Gln mutation, have been found to be an independent modifier of the clinical manifestations of rheumatoid arthritis.[117,118]

Multiple sclerosis

Topçuoğlu and Karabudak[119] reported on three patients with FMF whose neurologic findings and magnetic resonance imaging abnormalities resembled multiple sclerosis (MS). The authors commented that these two conditions in the same patient could arise from either coincidence or an unknown pathophysiological relationship and suggested further investigation of this possible association. A more recent study found that MS patients with *MEFV* mutations seem to have the susceptibility to

develop a more progressive disease and also that *MEFV* mutations may increase the risk of MS development.[120]

MANAGEMENT

Evaluations after initial diagnosis

To establish the extent of disease in an individual diagnosed with FMF, the following evaluations are recommended:

- Complete medical history, including family history.
- Physical examination to assess joint problems.
- Urinalysis for the presence of protein. If proteinuria is found, further evaluation is required, including 24-hour urinary protein assay and renal function tests, and also, if indicated, rectal biopsy for the presence of amyloid.

Treatment of manifestations

Febrile and inflammatory episodes are usually treated with nonsteroidal antiinflammatory drugs.

End-stage renal disease caused by renal amyloidosis should be treated as for other causes of renal failure. The long-term outcome of live-related donor renal transplantation in individuals with FMF amyloidosis is similar to that in the general transplant population.[121]

Prevention of primary manifestations

Individuals who are homozygous for the mutation p.Met694Val or compound heterozygous for p.Met694Val and another disease-causing allele should be treated with colchicine as soon as the diagnosis is confirmed, as this drug prevents both the inflammatory attacks and the deposition of amyloid. Colchicine is given orally, 1–2 mg/day in adults. Children may need 0.5–1 mg/day according to age and weight. Affected individuals should receive colchicine for life.

Individuals who do not have the p.Met694Val mutation and who are only mildly affected (those with infrequent inflammatory attacks) should be either treated with colchicine or monitored every 6 months for the presence of proteinuria.

Continuous treatment with colchicine seems to be less indicated for individuals who are homozygous or compound heterozygous for the mutation p.Glu148Gln. Colchicine should only be given to these individuals if they develop severe inflammatory episodes and/or proteinuria as a result of amyloidosis.

Complications of colchicine use occasionally include myopathy and toxic epidermal necrolysis-like reaction. Although colchicine is a mitotic inhibitor and transplacental crossing of colchicine has been demonstrated, no increased risk of fetal abnormalities in colchicine-treated pregnant patients with FMF has been found. Therefore, colchicine should be continued in pregnancy, and amniocentesis should not be done for reassurance alone.[23]

Some individuals seem to be unresponsive to colchicine treatment. This was associated with inadequate colchicine concentration in mononuclear cells in one study, possibly resulting from a genetic defect underlying FMF[122] or from poor compliance. In one study of 13 individuals,[123] the supplementation of oral colchicine with weekly intravenous colchicine (1 mg) resulted in a 50% reduction (except for joint attacks) in attack frequency.

Prevention of secondary complications

Treatment with colchicine 1 mg/day prevents renal amyloidosis even if the FMF attacks do not respond to the drug.

Surveillance

Individuals treated with colchicine should undergo an annual physical examination, including a urine spot test for protein.

Agents/circumstances to avoid

One report suggests that cisplatin worsens symptoms of FMF.[124] Cyclosporin A seems to adversely affect renal transplant graft survival in individuals with FMF.[125]

Newer therapies

Further studies are needed to confirm a single report of successful treatment of FMF with ImmunoGuard® (*Andrographis paniculata* Nees).[126] There are a few reports of the successful use of thalidomide[127,128] and etanercept,[128–130] especially in persons resistant to colchicine.

More recently, anakinra, an IL-1-receptor inhibitor, has been shown to have a dramatic therapeutic advantage in persons with FMF who are resistant to colchicine. Several reports indicate that this offers a relatively safe and effective treatment (100 mg daily or every other day) for persons who do not respond to colchicine.[131–138] This drug is expensive and has mild side effects, such as painful local reactions at the site of injections and possibly bronchopulmonary infection complications, especially in persons with other risk factors for pulmonary infections. Further studies are needed to investigate the long-term effects and side effects of this drug if it is to be taken continuously as required in severely affected individuals with FMF.

The use of sulfasalazine has been reported in an 8-year-old girl with a 5-year history of typical FMF attacks. She was homozygous for the mutation p.Met694Val and had had arthritis of one knee for several months that had not responded to nonsteroidal antiinflammatory drugs or colchicine. Resolution was achieved after the addition of sulfasalazine at a dose of 50 mg/kg/day.[139]

Testing of relatives at risk

Molecular genetic testing should be offered to all first-degree relatives and other family members whether or not they have symptoms. This is especially important when the p.Met694Val allele is present because other affected family members may not have inflammatory attacks but nevertheless remain at risk for amyloidosis (FMF type 2).

The country of residence of the patient, rather than *MEFV* genotype, seems to be the key risk factor for renal amyloidosis in FMF.[140] This risk indicates a possible environmental origin of amyloidosis susceptibility, and therefore, the patient's country should be considered in addition to *MEFV* genotype as an indication for prophylactic colchicine. Even though it is indisputable that some *MEFV* allele combinations contribute to severe manifestations of FMF, notably, renal amyloidosis, the *MEFV* effect likely ranks lower than that of other, as-yet-unknown at-risk components of the country of recruitment variable. These data also have important ramifications from a practical point of view as they challenge the rationale of initiating prophylactic treatment with colchicine to asymptomatic individuals who are incidentally discovered to be p.Met694Val homozygous, as has been previously suggested,[16] without taking into account the patient's country of residence. In areas with a low risk of renal amyloidosis, particularly in Western countries, taking a different preventive approach, such as urinalysis every 6 months, may be more justified. However, in countries where the risk is higher, such as Arab countries, Turkey, and Armenia, asymptomatic individuals homozygous for mutation

p.Met694Val, especially if there is a family history of amyloidosis, should be treated with colchicine.[140]

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