

## Familial Mediterranean Fever

[*Recurrent Polyserositis. Includes: Familial Mediterranean Fever Type 1, Familial Mediterranean Fever Type 2*]

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## Summary

**Disease characteristics.** Familial Mediterranean fever (FMF) type 1 is characterized by recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis and meningitis. 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. FMF type 2 is characterized by amyloidosis as the first clinical manifestation of FMF in an otherwise asymptomatic individual.

**Diagnosis/testing.** The diagnosis of FMF is clinical and is suspected in individuals with recurrent episodes of fever associated with abdominal pain (peritonitis) and/or pleuritic pain and/or arthritis (ankle/knee) usually lasting two to three days. A high erythrocyte sedimentation rate, leukocytosis, and a high serum concentration of fibrinogen are characteristic. *MEFV* is the only gene currently known to be associated with FMF. *MEFV* molecular genetic testing is used to confirm the diagnosis.

**Management.** *Treatment of manifestations:* treatment of febrile and inflammatory episodes with nonsteroidal anti-inflammatory drugs (NSAIDs); routine treatment of end-stage renal disease (ESRD), including live related-donor renal transplantation. *Prevention of primary manifestations:* lifelong treatment of homozygotes for the p.Met694Val mutation or compound heterozygotes for p.Met694Val and another disease-causing allele with colchicine (1-2 mg/day orally in adults and 0.5-1 mg/day in children according to age and weight). Colchicine prevents the inflammatory attacks and the deposition of amyloid. Treatment with colchicine for those with other mutations varies. *Surveillance:* annual physical examination and urine spot test for protein for those treated with colchicine. *Agents/circumstances to avoid:* possible worsening of symptoms with cisplatin; possible adverse effect on renal transplant graft survival with cyclosporin A. *Testing of relatives at risk:* Offer molecular genetic testing to all first-degree relatives and other family members (regardless of symptoms) especially when the p.Met694Val allele is present because renal amyloidosis can be prevented with colchicine treatment.

**Genetic counseling.** FMF is inherited in an autosomal recessive manner. In general, both parents of a proband are considered to be obligate carriers. However, in populations with a high carrier rate and/or a high rate of consanguineous marriages, it is possible that affected children may be born to an affected individual and a carrier, or even to two affected individuals. Thus, it is appropriate to consider molecular genetic testing of the parents of the proband to establish their genetic status. If both parents are heterozygotes, the risk to sibs of being affected is 25%. Prenatal testing is possible if the *MEFV* mutations in an affected family member are known.

## Diagnosis

### Clinical Diagnosis

Features suggesting the diagnosis of familial Mediterranean fever (FMF) include the following:

- 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
- At-risk ethnic group

The minimal criteria for diagnosis of FMF [Pras 1998] are fever plus one more of the following major signs and one of the following minor signs, or fever plus two minor signs.

#### Major signs

- Fever
- Abdominal pain
- Chest pain
- Joint pain \*
- Skin eruption

\* 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 [Lidar et al 2005].

#### Minor signs

- Increased erythrocyte sedimentation rate (ESR)

Normal values:

- Men age <50 years: <15 mm/h
- Men age 50-85 years: <20 mm/h
- Women age <50 years: <20 mm/h

— Women age 50-85 years: <30 mm/h

- Leukocytosis  
Normal values: 4.5 to 11.0 times  $10^3 \mu\text{L}$  ( $4.5-11.0 \times 10^9 \text{ L}$ )
- Elevated serum concentration of fibrinogen

Normal values: 200-400 mg/dL (2.00-4.00 g/L)

### Molecular Genetic Testing

*GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.*

**Gene.** *MEFV* is the only gene currently known to be associated with FMF.

#### Clinical uses

- Confirmatory diagnostic testing
- Predictive testing
- Carrier testing
- Prenatal diagnosis

#### Clinical testing

- **Targeted mutation analysis.** Laboratories may offer testing for the common mutation p.Glu148Gln in exon 2, mutation p.Pro369Ser in exon 3, and the eight common mutations in exon 10 observed in Mediterranean populations. Mutation detection frequency varies by ethnicity (see Table 1).
- **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.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Familial Mediterranean Fever

Test Method	Mutations Detected	Mutation Detection Frequency for Both Mutations <sup>1</sup>	Test Availability	
Targeted mutation analysis <sup>2</sup>	Exon 2: p.Glu148Gln Exon 3: p.Arg408Gln, p.Pro369Ser Exon 10: p.Met694Val, p.Val726Ala, p.Met680Ile, p.Met694Ile, p.Lys695Arg, p.Ala744Ser, p.Arg761His, 692del, p.Arg653His	Armenian: 90%	Clinical Testing	
		Turkish: 90%		
		Arab: 70%		
		North African Jewish: 95%		
		Iraqi Jewish: 80%		
		Ashkenazi Jewish: 90%		
Sequence analysis	<i>MEFV</i> sequence variants in exon 10	All groups: 90%		
	<i>MEFV</i> sequence variants outside exon 10			

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method
2. Panel may vary by laboratory

**Interpretation of test results.** For issues to consider in interpretation of sequence analysis results, click [here](#).

**Linkage analysis.** Linkage analysis is available on a clinical basis and may be an option for carrier testing for families in which neither or only one *MEFV* mutation has been identified. Samples from multiple family members, including at least one affected individual, are necessary to perform linkage analysis. The accuracy of linkage analysis is dependent on (1) the informativeness of genetic markers in the individual's family and (2) the accuracy of the clinical diagnosis of FMF in the affected family member.

### Genetically Related (Allelic) Disorders

It is possible that mutations in the *MEFV* gene could be an additional susceptibility genetic factor in the following:

- **Behçet's disease** [Cattan 2005, Imirzalioglu et al 2005]
- **Ulcerative colitis.** An increased frequency of *MEFV* mutations has been found in persons with ulcerative colitis, especially those with episodic arthritis, and this may suggest a possible modifying effect of *MEFV* in the disease process [Cattan 2005, Giaglis et al 2006].
- **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 [Rabinovich et al 2005].

## Clinical Description

### Natural History

Familial Mediterranean fever (FMF) is divided into types 1 and 2:

- **FMF type 1** is characterized by recurrent short episodes of inflammation 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 [Pras 1998, Langevitz et al 1999, Shohat et al 1999, Koné Paut et al 2000].

Common manifestations of FMF include the following:

- **Recurrent fever.** Recurrent fever during early childhood may be the only manifestation of FMF.
- **Abdominal attacks.** Experienced by 90% of affected individuals, abdominal attacks 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.** Experienced by about 75% of individuals with FMF, articular attacks 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 [Lidar et al 2005].  
Attacks subside spontaneously only after several weeks or months; severe damage to the joint can result, and permanent deformity may require joint replacement. Around 5% of affected individuals have protracted arthritic attacks. Recent evidence indicates that arthritis, arthralgia, myalgia, and erysipelas-like erythema occur significantly more often among individuals with disease onset before age 18 years than in those with onset after age 18 years [Sayarlioglu et al 2005, Tunca et al 2005].
- **Prodrome.** A prodrome (pre-attack symptoms) is experienced by about 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) [Lidar et al 2006].
- **Pleural attacks.** Experienced by about 45% of those with FMF, pleural attacks are the sudden onset of an acute, one-sided febrile pleuritis, which resolves rapidly. 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 resolve within 48 hours.
- **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.
- **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 (ESRD). Affected individuals who are otherwise asymptomatic can develop renal amyloidosis as the first and only manifestation of FMF. 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 [Livneh et al 1999, Shohat et al 1999].

The age of onset of FMF attacks appears 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 [Cefle et al 2005].

Clinically detectable pulmonary amyloidosis secondary to FMF is rare; only three cases have been reported so far [Erdem et al 2006].

### Rarer manifestations of FMF attacks:

- **Protracted febrile myalgia** 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 six to eight weeks and responds to treatment with prednisone. Streptococci could be one of the agents triggering this syndrome [Soylu et al 2006].
- **Erysipelas-like erythema** is characterized by fever and hot, tender, swollen, sharply bordered red lesions that are typically 10-35 cm<sup>2</sup> 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 one to two days. Isolated temperature elevation lasting a few hours can occur without any pain or inflammation.
- **Vasculitides** are rare and include Henoch-Schönlein purpura (in ~5% of individuals with FMF) and polyarteritis nodosa [Cattan 2005].

**Reduced fertility.** Untreated individuals with FMF, especially those with multiple attacks and/or amyloidosis, have a higher chance of infertility. Colchicine treatment increases fertility, but in some instances may induce oligospermia/azoospermia [Ben-Chetrit & Levy 2003].

**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 to 20% in the general population) [Sackesen et al 2004].

**Peritoneal malignant mesothelioma.** A possible association was suggested by the finding of peritoneal malignant mesothelioma 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 [Hershcovici et al 2006].

### 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. Some studies have found that this mutation is also associated with a generally more severe form of the disease, but other studies have not confirmed this. Amyloidosis occurs less frequently in the presence of mutations other than p.Met694Val [Pras et al 1997, Shohat et al 1999, Shinar et al 2000].

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. Further studies are needed to determine the exact influence of these and other modifiers [Akar et al 2003, Gershoni-Baruch et al 2003, Yilmaz et al 2003].

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 [Tunca et al 2005].

A more recent study found that the genotype SAA1 -13T has at least an effect on the development of amyloidosis [Akar et al 2006].

## Nomenclature

Previously used names no longer in common use for the disease that is now generally known as familial Mediterranean fever are "familial paroxysmal polyserositis" and "periodic disease."

## Prevalence

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

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 is for a mild form of FMF and thus, the prevalence of the disease in this ethnic group is not high [Stoffman et al 2000].

The clinical picture of FMF in Arabs appears to be distinct, and the range and distribution of *MEFV* mutations is different from that noted in other affected ethnic groups [El-Shanti et al 2006]. 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 [Majeed et al 2005].
- In another study in Jordan and Lebanon, the mutations p.Met694Val and p.Met694Ile were the most common. In addition, three novel mutations not observed in other groups (p.Thr177Ile, p.Ser108Arg, and p.Glu474Lys) were found in the Lebanese [Medlej-Hashim et al 2005].
- In North African Arabs with FMF, p.Met694Val was relatively common among Moroccans (49%) and Tunisians (50%), while 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 [Belmahi et al 2006]. In a significant number of Arabs with FMF only one disease-causing mutation was identified using a panel of common alleles, suggesting the presence of other less common mutations in this population [El-Shanti et al 2006].
- 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, indicating the presence of as-yet unidentified mutations in this population [Ayesh et al 2005].

Among Armenians with FMF, the spectrum of mutations was similar to that in the non-Ashkenazi Jewish population [Sarkisian et al 2005].

## Differential Diagnosis

*For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.*

**Recurrent fever.** Recurrent fever syndromes are reviewed by [Padeh 2005].

**PFAPA (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. Treatment with steroids in the early stages of an attack is effective.

HIDS (**hyperimmunoglobulinemia D** and **periodic fever syndrome**) 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 [Simon et al 2001].

TRAPS (**TNF receptor-associated periodic syndrome**) (**TNF** = tumor necrosis factor) is an autosomal dominant disorder caused by a mutation in the *TNFRSF1A* gene. This mutation results in decreased serum levels of soluble TNF receptor leading to inflammation as a result of unopposed TNF-alpha action. The disease, also called familial Hibernian fever, is characterized by attacks of fever, sterile peritonitis, arthralgia, myalgia, skin rash, and conjunctivitis. Some individuals develop amyloidosis. Treatment with recombinant TNF-receptor analogues is promising. The clinical picture in TRAPS may be similar to that in FMF; the mode of inheritance and the results of molecular testing differentiate between the two conditions [Aksentijevich et al 2001].

ELA-related neutropenia 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 (MDS) and acute myelogenous leukemia (AML). 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.

In western European Caucasians with a clinical diagnosis of FMF, the frequency of common *MEFV* mutations was 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 [Tchernitchko et al 2005].

**Amyloidosis.** Muckle-Wells syndrome and familial cold urticaria, which are probably allelic disorders caused by a mutation in the *CIA1* gene, are transmitted by autosomal dominant inheritance. They are characterized by urticaria, deafness, and renal amyloidosis.

Transthyretin-related amyloidosis needs to be considered. This autosomal dominant disorder is characterized by a slowly progressive peripheral sensorimotor neuropathy and autonomic neuropathy as well as non-neuropathic changes of nephropathy, cardiomyopathy, vitreous opacities, and CNS amyloidosis. 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. CNS effects can include dementia, psychosis, visual impairment, headache, seizures, motor paresis, ataxia, myelopathy, hydrocephalus, or intracranial hemorrhage. Molecular genetic testing of the *TTR* gene is clinically available.

**Abdominal pain.** Acute abdomen 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**

- Acute rheumatoid arthritis
- Rheumatic fever
- Septic arthritis
- Collagen vascular diseases

### **Pleuritic pain**

- Pleurisy
- Pulmonary embolism

## **Management**

### **Evaluations Following Initial Diagnosis**

To establish the extent of disease in an individual diagnosed with familial Mediterranean fever (FMF):

- Complete past 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 anti-inflammatory drugs (NSAIDs).

End-stage renal disease (ESRD) 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 [Sherif et al 2003].

### **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 [Zemer et al 1986].

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

Continuous treatment with colchicine appears 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.

Colchicine should be continued in pregnancy.

Some individuals appear 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 [Lidar et al 2004] or from poor compliance. In one study of 13 individuals [Lidar et al 2003], the supplementation of oral colchicine with weekly intravenous colchicine (1 mg) resulted in a 50% reduction (excepting 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 [Zemer et al 1986].

### **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 [Toubi et al 2003].

Cyclosporin A appears to adversely affect renal transplant graft survival in FMF [Shabtai et al 2002].

### **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) and thus need to be treated with colchicine (1 mg/day) to prevent the development of renal amyloidosis.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

### **Therapies Under Investigation**

Further studies are needed to confirm single reports of successful treatment of FMF with ImmunoGuard® (*Andrographis paniculata* Nees) [Amaryan et al 2003] and thalidomide [Seyahi et al 2002].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

### **Other**

**Genetics clinics** are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

**Support groups** have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.*

### Mode of Inheritance

Familial Mediterranean fever (FMF) is inherited in an autosomal recessive manner.

### Risk to Family Members

#### Parents of a proband

- The parents are obligate heterozygotes and therefore carry a single copy of a disease-causing mutation.
- Heterozygotes are asymptomatic.
- In populations with a high carrier rate and/or with a high rate of consanguinity, it is possible that affected children may be born to an affected individual and a carrier, or even to two affected individuals. Thus, it is appropriate to consider molecular genetic testing of the parents of the proband.

**Sibs of a proband.** If both parents are carriers:

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes are asymptomatic.

If one parent is affected and one parent is a carrier:

- At conception, each sib of an affected individual has a 50% chance of being affected and a 50% chance of being an asymptomatic carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 100%.
- Heterozygotes are asymptomatic.

#### Offspring of a proband

- All of the offspring inherit one *MEFV* gene mutation from the proband.
- In populations with a high carrier rate and/or a high rate of consanguinity, it is possible that the reproductive partner of the proband may be affected or be a carrier. Thus, the risk to offspring is most accurately determined after molecular genetic testing of the proband's reproductive partner.

**Other family members of a proband.** Each sib of an obligate heterozygote is at a 50% risk of being a carrier.

### Carrier Detection

Carrier testing is available on a clinical basis once the mutations have been identified in the proband.

### Related Genetic Counseling Issues

**Testing of at-risk asymptomatic family members.** Since treatment for FMF is readily available, easy to administer, and effective, the testing and possible treatment of asymptomatic at-risk family members is warranted.

**Family planning.** The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

**DNA banking.** DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See

**Testing** for a list of laboratories offering DNA banking.

### Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

**Other issues to consider.** Prenatal diagnosis of FMF, a treatable condition associated with a good prognosis with early treatment, may be controversial if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider this to be the choice of the parents, careful discussion and examination of these issues is appropriate.

**Preimplantation genetic diagnosis (PGD)** may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see **Testing**.

### Molecular Genetics

*Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.*

Table A. Molecular Genetics of Familial Mediterranean Fever

Gene Symbol	Chromosomal Locus	Protein Name
<i>MEFV</i>	16p13	Pyrin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

**Table B. OMIM Entries for Familial Mediterranean Fever**

249100	FAMILIAL MEDITERRANEAN FEVER; FMF
608107	FAMILIAL MEDITERRANEAN FEVER GENE; MEFV

**Table C. Genomic Databases for Familial Mediterranean Fever**

Gene Symbol	Locus Specific	Entrez Gene	HGMD
<i>MEFV</i>	MEFV	4210 (MIM No. 608107)	MEFV

For a description of the genomic databases listed, click [here](#).

**Note:** HGMD requires registration.

### Molecular Genetic Pathogenesis

To date, the causative genes for nine autoinflammatory diseases have been identified. These are FMF, NOMID, FCAS, MWS, Blau syndrome, Crohn disease, TRAPS, HIDS, and a syndrome marked by PAPA. The related genes — *MEFV*, *CIAS1*, *CARD15/NOD2*, *TNFRSF1A*, *MVK*, and *CD2BP1/PSTPIP* — comprise the pyrin gene family based on their nucleotide sequences and predicted protein structures. Pyrins are important in the regulation of molecular signaling pathways involved in inflammation, as well as in cytokine and chemokine processing and apoptosis. This is consistent with the systemic inflammation that occurs in autoinflammatory diseases. Biochemical analysis suggests that pyrin family members, such as pyrin and cryopyrin, are components of signaling complexes that often involve other pyrin domain-containing proteins. In accordance with their ability to interact with a wide spectrum of immunologic signaling pathways, mutations in the genes in the pyrin family result in dysregulated immunity and autoinflammatory diseases [Shinkai et al 2005].

The normal pyrin protein interacts directly at the C-terminal B30.2 domain (where most of the FMF mutations are situated) to regulate caspase-1 activation and consequently IL-1 $\beta$  production. The assumption is that mutations in persons with FMF result in less IL-1 $\beta$  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 [Chae et al 2006].

**Normal allelic variants:** The gene has ten exons.

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 [Aksentijevich et al 1999, Tchernitchko et al 2003]. Studies that describe p.Glu148Gln as a disease-causing mutation include those by Stoffman et al 2000, Gershoni-Baruch et al 2002, Konstantopoulos et al 2005, and Topaloglu et al 2005. 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 [Ben-Chetrit et al 2000, Tchernitchko et al 2003, Tchernitchko et al 2006].

**Pathologic allelic variants/variants of unknown clinical significance:** To date, 129 variants have been identified, not all of which are pathologic [Infevers Web site]. (For more information, see Genomic Databases table above.)

**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, and marenostin by the French FMF Consortium. The protein contains 781 amino acids and its normal function is probably to assist in controlling inflammation by deactivating the immune response. Without this 'brake,' an inappropriate full-blown inflammatory reaction of the serosal membranes — i.e., an attack of FMF — occurs [French FMF Consortium 1997, International FMF Consortium 1997, Samuels et al 1998].

The pyrin protein exists in several isoforms of unknown function. The recombinant full-length isoform (pyrin.fl) is cytoplasmic, whereas an alternatively spliced isoform lacking exon 2 (pyrin.DeltaEx2) concentrates in the nucleus. Native pyrin, mainly consisting of pyrin.fl, is also cytoplasmic in monocytes but is predominantly nuclear in other cell types [Jeru et al 2005].

**Abnormal gene product:** Mutations in *MEFV* result in less active pyrin.

## Resources

*GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests for this disorder and select [Resources](#) for the most up-to-date Resources information.*—ED.

### Medline Plus

Familial Mediterranean fever

### National Library of Medicine Genetics Home Reference

Familial mediterranean fever

### NCBI Genes and Disease

Familial Mediterranean fever

## References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. [PubMed](#)

## Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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## Suggested Readings

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## Chapter Notes

### Author Notes

Professor Mordechai Shohat, MD has been involved with research into familial Mediterranean fever, including the molecular analysis of the *MEFV* gene and phenotype-genotype correlation studies, for over ten years.

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## Revision History

- 25 February 2008 (ms) Revision: clarification of PFAPA in Differential Diagnosis
- 2 January 2008 (ms) Revision: Molecular Genetics, Pathologic allelic variants
- 28 February 2007 (me) Comprehensive update posted to live Web site
- 5 November 2004 (me) Comprehensive update posted to live Web site
- 13 November 2002 (me) Comprehensive update posted to live Web site

- 8 August 2000 (me) Review posted to live Web site
- 4 April 2000 (ms) Original submission

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