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Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.

Familial Mediterranean Fever

Synonym: Recurrent Polyserositis

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Initial Posting: August 8, 2000; Last Update: December 15, 2016.

Summary

Clinical characteristics.

Familial Mediterranean fever (FMF) is divided into two phenotypes: type 1 and type 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 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, if untreated.
- 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 established in a proband with Tel Hashomer clinical criteria of major and minor features. Major features include fever, abdominal pain, chest pain, joint pain, and skin eruption. Minor features include increased erythrocyte sedimentation rate (ESR), leukocytosis, and elevated serum fibrinogen. Identification of biallelic *MEFV* pathogenic variants on molecular genetic testing confirms the diagnosis. Up to 25% of individuals with FMF have only one *MEFV* pathogenic variant identified. A six-month trial of colchicine therapy can establish the diagnosis if molecular testing is inconclusive.

Management.

Treatment of manifestations: Treatment of an acute episode is mainly supportive, including administration of intravenous saline for hydration and use of nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, or dipyrone for pain relief; treatment of febrile and inflammatory episodes with NSAIDs; routine treatment of end-stage renal disease, including renal transplantation.

Prevention of primary manifestations: Homozygotes for the p.Met694Val pathogenic variant or compound heterozygotes for p.Met694Val and another disease-causing allele require lifelong treatment 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. Individuals who do not have the p.Met694Val pathogenic variant 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. Individuals who are homozygous or compound heterozygous for p.Glu148Gln should only be treated with colchicine if they develop severe inflammatory episodes and/or proteinuria as a result of amyloidosis. Symptomatic individuals with a heterozygous *MEFV*pathogenic variant may benefit from a trial of colchicine. Individuals who are unresponsive to colchicine may respond to intravenous colchicine or one of several other medications.

Surveillance: Annual physical examination, urine spot test for protein, and evaluation for hematuria for all affected individuals including those treated with colchicine; consider monitoring of acute-phase reactants (ESR and fibrinogen levels) at regular intervals during attack-free periods, particularly in those with the p.Met694Val pathogenic variant.

Agents/circumstances to avoid: Possible worsening of symptoms with cisplatin; possible adverse effect on renal transplant graft survival with cyclosporin A.

Evaluation 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 usually inherited in an autosomal recessive manner, although recent studies have suggested that some heterozygotes manifest a spectrum of findings from classic FMF to mild FMF. For autosomal recessive FMF: In general, both parents of an affected individual with biallelic *MEFV* pathogenic variants are unaffected heterozygotes. However, in populations with a high carrier rate and/or a high rate of consanguineous marriages, it is possible that one or both parents have biallelic pathogenic variants and are affected. Symptomatic heterozygotes have also been reported. 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 inheriting two pathogenic variants and being affected is 25%. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the *MEFV* pathogenic variants in the family are known.

GeneReview Scope

Familial Mediterranean Fever: Included Phenotypes
• Familial Mediterranean fever type 1 • Familial Mediterranean fever type 2

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

Familial Mediterranean fever (FMF) **should be suspected** in individuals with 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 in those who do not have a history of recurrent inflammatory attacks
- Favorable response to continuous colchicine treatment
- A first-degree relative with FMF
- Membership in an at-risk ethnic group

Establishing the Diagnosis

The minimal (and most current) clinical criteria used **to establish** the diagnosis of FMF are the Tel Hashomer clinical criteria [Livneh et al 1997, Pras 1998]. Identification of biallelic *MEFV* pathogenic variants on molecular testing confirms the diagnosis if clinical features are inconclusive. A colchicine six-month therapy trial can be used to confirm the diagnosis if *MEFV* molecular testing is inconclusive.

Tel Hashomer Clinical Criteria

Fever AND:

- One additional major feature and one minor feature

  OR

- Two minor features

Major features

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

***Note:** 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 features

- 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 value: 4.5-11.0 x 10^3µL [4.5-11.0 x 10^9L])
- Elevated serum fibrinogen concentration (normal value: 200-400 mg/dL [2.00-4.00 g/L])

Note: Early in life FMF often begins with an atypical presentation characterized by attacks of fever alone, significantly delaying diagnosis and initiation of treatment. Although other diagnostic criteria for children have been suggested by Yalçinkaya et al [2009] and Padeh et al [2010], Kondi et al [2010] and Ozçakar et al [2011] found that the new criteria did not make a better contribution to FMF diagnosis than the Tel Hashomer criteria.

Molecular Genetic Testing

Molecular genetic testing approaches can include **single-gene testing**, use of a **multi-gene panel,** and **more comprehensive genomic testing**.

Single-gene testing. Sequence analysis of *MEFV* is performed first.

Note: Up to 25% of individuals with FMF have only one *MEFV* pathogenic variant identified; this appears to be sufficient to initiate a trial of colchicine [Booty et al 2009, Marek-Yagel et al 2009, Moradian et al 2010].

Targeted analysis for pathogenic variants can be performed first in individuals of Armenian, Turkish, Arab, North African Jewish, Iraqi Jewish, or Ashkenazi Jewish ancestry. Targeted analysis may include:

- **Exon 2.** c.442G>C (p.Glu148Gln)
- **Exon 3**
  - c.1105C>T (p.Pro369Ser)
  - c.1223G>A (p.Arg408Gln)

  Note: These two variants in exon 3 have been shown to be in linkage disequilibrium [Ryan et al 2010].
- **Exon 10**
  - c.1958G>A (p.Arg653His)
  - c.2040G>C (p.Met680Ile)
  - c.2076_2078del (p.Ile692del)
  - c.2080A>G (p.Met694Val)
  - c.2082G>A (p.Met694Ile)
  - c.2084A>G (p.Lys695Arg)
  - c.2177T>C (p.Val726Ala)
  - c.2230G>T (p.Ala744Ser)
  - c.2282G>A (p.Arg761His)

  Note: (1) Other variants with exons 2, 3, and 10 are also among the most common. (2) The exons included and pathogenic variants detected may vary by laboratory and over time.

In individuals with suspected autosomal dominant inheritance, in addition to the above pathogenic variants, targeted testing for a few additional pathogenic variants may be considered:

- **Exon 10**
  - c.1730C>A (p.Thr577Asn)
  - c.2064C>G (p.Tyr688Ter)

- c.2076_2078delAAT (p.Ile692del)
- c.2081_2083delTGA (p.Met694del)

A multi-gene panel that includes *MEFV* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time. (2) Some multi-gene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multi-gene panel provides the best opportunity to identify the genetic cause of the condition at the most reasonable cost while limiting secondary findings. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing based tests.

For more information on multi-gene panels click here.

More comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered if single-gene testing (and/or use of a multi-gene panel that includes *MEFV*) fails to confirm a diagnosis in an individual with features of FMF. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation). For more information on comprehensive genome sequencing click here.

Table 1.

Molecular Genetic Testing Used in Familial Mediterranean Fever

Gene [1]	Test Method	Proportion of Probands with Pathogenic Variants [2] Detectable by This Method
MEFV	Sequence analysis [3]	75%-90% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Up to 25% of individuals with FMF have only one *MEFV* pathogenic variant identified [Booty et al 2009, Marek-Yagel et al 2009, Moradian et al 2010].
5.

Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6.

van Gijn et al [2008]

7.

Given the proposed gain-of-function mechanism for FMF and the lack of observed large intragenic deletions or duplications, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Test characteristics. See Clinical Utility Gene Card [Witsch-Baumgartner & Touitou 2015] for information on test characteristics including sensitivity and specificity.

Colchicine Trial

In all instances in which the clinical picture suggests FMF but *MEFV* molecular genetic testing is not diagnostic, the diagnosis of FMF can be confirmed if a six-month trial of colchicine therapy results in relief of the attacks, which then recur after cessation of this treatment.

Clinical Characteristics

Clinical Description

Familial Mediterranean fever (FMF) is divided into two phenotypes (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 untreated FMF type 1.
- **FMF type 2** is characterized by amyloidosis as the first clinical manifestation of disease in an otherwise asymptomatic individual.

Common manifestations of FMF include the following:

- **Recurrent fever** during early childhood may be the only manifestation of FMF.
- **Abdominal attacks.** Experienced by 90% of 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, and (3) gradual resolution of the signs and symptoms after peaking in 24-48 hours. Often a sterile synovial effusion is present.

The attacks are commonly in the hip or knee, but may occur in 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 individuals with monoarthritis the true diagnosis may not be established for some time and only after extensive investigations.

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. There is evidence 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.

- **Prodrome** (pre-attack symptoms) are 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, are the sudden onset of an acute, febrile, unilateral pleuritis. 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. Pleuritis can rarely be the sole manifestation of FMF [Lega et al 2010, Ruiz & Gadea 2011].

- **Pericarditis,** a rare occurrence, 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. Rare though it is, recurrent pericarditis can be the sole manifestation of FMF [Okutur et al 2008].

- **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 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 [Livneh et al 1999, Shohat et al 1999].

  The age of onset of FMF attacks appears to be earlier 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.

  Clinically detectable pulmonary amyloidosis secondary to FMF is rare; only a few cases have been reported to date [Koksal et al 2012].

Less common manifestations of FMF include the following:

- **Protracted febrile myalgia** is a severe debilitating myalgia with prolonged low-grade fever, increased erythrocyte sedimentation rate (~100 mm/h), 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 [Senel et al 2010, Tufan & Demir 2010].

- **Erysipelas-like erythema (ELE)** 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 one to two days. Isolated temperature

elevation lasting a few hours can occur without any pain or inflammation [Kavukcu et al 2009]. Rarely ELE can be the first disease manifestation of FMF [Lidar et al 2013].

- **Vasculitides** are rare and include Henoch-Schönlein purpura (in ~5% of individuals with FMF) and polyarteritis nodosa [Cattan 2005, Girisgen et al 2012].
- **Recurrent urticaria** has been reported as a rare manifestation of FMF [Alonso et al 2002].
- **Aseptic meningitis** was considered to occur rarely in FMF [Karachaliou et al 2005]. Capron et al [2013] performed a systematic review of the literature and concluded that the finding of recurrent aseptic meningitis resulting from FMF was poorly supported; only one case report – in which the affected individual did not meet the current clinical diagnostic criteria of FMF – suggested a possible causal relationship between the two.
- **Reduced fertility.** Untreated individuals with FMF, especially those with multiple attacks and/or amyloidosis, are at higher risk for infertility. Colchicine treatment increases fertility, but in some instances may induce oligospermia/azoospermia [Sarica et al 1995, Ozturk et al 2011, Dotters-Katz et al 2012]. However, two studies found that males undergoing long-term colchicine therapy had normal sperm counts and normal levels of testosterone, follicle stimulating hormone, luteinizing hormone, and prolactin [Bremner & Paulsen 1976, Levy & Yaffe 1978]. It is important to continue colchicine treatment even when planning a pregnancy.

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, Yazici et al 2013].

Chronic ascites. A few reports have suggested that individuals with molecularly confirmed FMF have developed chronic ascites that responded to a dose adjustment of colchicine [Bektaş et al 2008, Sengul et al 2008, Ureten et al 2009, Cakir et al 2010, Aslan et al 2012]. This may be a rare manifestation of FMF; However, investigation for other causes of ascites is always recommended.

Psychological features. Depression is more common in individuals with FMF [Makay et al 2010, Deger et al 2011]. Anxiety is more frequent in persons with FMF than in healthy individuals [Deger et al 2011].

Clinical findings in individuals with FMF in whom only one *MEFV* pathogenic variant is identified. The majority of *MEFV* heterozygotes are asymptomatic throughout life. Most of the reported families with autosomal dominant FMF have pseudodominant transmission (i.e., the children of an individual with two pathogenic variants in *MEFV* and a carrier partner are at 50% risk of having FMF). In geographic regions where FMF is common, pseudodominant transmission is frequently seen and some families have been described through five generations.

However, heterozygotes with a severe pathogenic variant can be symptomatic, and autosomal dominant transmission can occur. Three severe variants in exon 10 (2 in-frame deletions and 1 nonsense variant) have been identified: p.Met694del (common in northern European, Iranian, and Azari Turkish populations [Bonyadi et al 2009, Rowczenio et al 2017]), p.Ile692del, and p.Tyr688Ter. Autosomal dominant transmission has also been described in a few families with heterozygous missense variants including p.Met694Val (the most common Mediterranean variant) and p.Thr577Asn [Stoffels et al 2014].

Heterozygotes typically have a later age of onset (mean age 18 years) and milder disease (manifest mainly by fever and abdominal symptoms) than persons with biallelic pathogenic variants. Most of the heterozygotes described by Booty et al [2009] had an incomplete abdominal attack (abdominal pain without frank peritonitis) as the major criterion of the disease; in most individuals the response to colchicine therapy was either complete or partial. Hentgen et al [2013a] have shown that the clinical signs of FMF completely disappeared at puberty in five of 18 individuals with a heterozygous *MEFV* pathogenic variant, allowing them to discontinue colchicine without recurrence of symptoms.

Rowczenio et al [2017] characterized the phenotype in 21 individuals heterozygous for the p.Met694del variant. These individuals shared an identical disease haplotype that appeared to have arisen about 550 years ago. The SAA1.1 allele was found in four affected individuals, including two with AA amyloidosis. The median age at onset was 18 years. Three individuals presented with AA amyloidosis, two of whom had a history of unrecognized symptoms of FMF. Fifteen individuals received colchicine treatment, all with excellent responses. The 14% incidence of AA amyloidosis may reflect delay in diagnosis associated with extreme rarity of FMF in this population.

Rarely reported associations that are not considered part of the FMF phenotype

- Peritoneal malignant mesothelioma was reported in two persons with FMF who had recurrent peritoneal involvement during childhood. Both were homozygous for the pathogenic variant p.Met694Val [Hershcovici et al 2006].
- Possible association with stroke, multiple sclerosis, and other demyelinating disorders was reported by Feld et al [2012].
- Lower bone mineral density was reported by Yildirim et al [2010].
- Increased serum homocysteine and lipoprotein(a) concentrations have been reported during attack-free periods [Karatay et al 2010].
- Moderate to severe periodontitis was more common in individuals with amyloidosis. Serum levels of acute-phase reactants in people with FMF were reduced significantly following nonsurgical periodontal therapy [Cengiz et al 2009].

Genotype-Phenotype Correlations

c.2080A>G (p.Met694Val). Persons who are homozygous for the pathogenic variant p.Met694Val have an earlier age of onset and higher frequencies of arthritis and arthralgia than persons who are homozygous or compound heterozygous for other pathogenic variants [Tunca et al 2005]. Individuals with the p.Met694Val pathogenic variant, particularly homozygous individuals, are at increased risk for amyloidosis [Duşunsel et al 2008] and have a decreased response to colchicine [Soylemezoglu et al 2010].

Other pathogenic variants. Amyloidosis occurs less frequently in the presence of pathogenic variants other than p.Met694Val [Shohat et al 1999, Shinar et al 2000, Ben-Chetrit & Backenroth 2001, Ben-Chetrit 2003].

Other possible modifiers. Intra- and interfamilial clinical differences independent of *MEFV* genotype suggest genetic and/or environmental modifiers. Suggested modifiers:

- Gender, serum amyloid A concentration, and genes involved in predisposition to arthritis [Akar et al 2003, Gershoni-Baruch et al 2003, Yilmaz et al 2003]
- Major histocompatibility complex class I chain-related gene A (*MICA*) potential modifiers including the following:
    - The A5 allele had a protective effect against amyloidosis in some p.Met694Val homozygotes [Turkcapar et al 2007].
    - The A9 allele exacerbated the age of onset in p.Met694Val homozygotes [Medlej-Hashim et al 2004].
    - The A4 allele dramatically reduced the frequency of attacks [Touitou et al 2001].
- *SAA1*-13T genotype 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 pathogenic variant p.Met694Val is found in more than 90% of affected Jewish persons of North African origin.

FMF occurs less frequently in many other countries, where it shows considerable clinical variability [Ben-Chetrit & Touitou 2009]; the variability may be attributable to the type of variant or to environmental factors. The limited number of individuals diagnosed with FMF in certain areas of the world is probably attributable to lack of awareness of the disorder [Ben-Chetrit & Touitou 2009].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be caused by pathogenic variants in *MEFV*; however, an increased frequency of *MEFV* pathogenic variants have been reported in individuals with the following diseases:

- **Behçet disease** [Rabinovich et al 2007, Ayesh et al 2008]
- **Ulcerative colitis**, especially those with episodic arthritis [Giaglis et al 2006, Yurtcu et al 2009, Uslu et al 2010, Akyuz et al 2013]. Two infants with ulcerative colitis (UC) were found to be heterozygous for *MEFV* pathogenic variant p.Met694Val; UC was not controlled until colchicine was added to the drug regimen. One infant was homozygous for p.Met694Val and required total colectomy before the diagnosis of FMF was made. The authors suggest that infants with UC should be tested for *MEFV* pathogenic variants so that colchicine therapy can be initiated if appropriate [Sari et al 2008].
- **Systemic-onset juvenile idiopathic arthritis** [Ayaz et al 2009]
- **Juvenile idiopathic arthritis** [Comak et al 2013]
- **Rheumatoid arthritis (RA).** *MEFV* pathogenic variants (p.Glu148Gln in particular) have been found to be independent modifiers of the clinical manifestations of RA [Rabinovich et al 2005, Kalyoncu et al 2006]. Subsequent studies showed conflicting results [Migita et al 2008, Koca et al 2010, Inanir et al 2013].

The following diseases have been reported to occur more commonly in individuals with familial Mediterranean fever:

- **Inflammatory bowel disease** [Cattan et al 2000, Beşer et al 2013] including Crohn disease, which is more common, presents earlier in individuals with FMF [Fidder et al 2002, Kuloğlu et al 2012], and is more often complicated by amyloidosis [Fidder et al 2002]
- **Juvenile idiopathic arthritis**. An individual with FMF and juvenile idiopathic arthritis with osteoporosis was successfully treated with etanercept [Kaya et al 2010].
- **Systemic lupus erythematosus (SLE).** There are several reports of the co-occurrence of SLE with FMF [Lidar et al 2008, Yildiz et al 2010, Shinar et al 2012]. While this co-occurrence could be coincidental, SLE may be caused by *MEFV* pathogenic variants. Manifestations of SLE and FMF show considerable overlap; in individuals who have both disorders, recognition of the two as separate entities is critical to avoiding over- or undertreatment of either disorder [Lidar et al 2008].

Differential Diagnosis

Individuals of western European heritage with clinical features of FMF rarely have *MEFV* pathogenic variants identified. Individuals from these populations likely have another condition with similar clinical features that cannot be accounted for by pathogenic variants in *MEFV*, and thus, another diagnosis should be considered in these individuals [Tchernitchko et al 2005].

Autoinflammatory diseases

- **Cryopyrin-associated periodic syndromes (CAPS)** include: chronic infantile neurologic cutaneous and articular syndrome (OMIM 607115); familial cold autoinflammatory syndrome (OMIM 120100), characterized by cold-induced attacks of fever, rash, and arthralgia but no deafness or amyloidosis; and Muckle-Wells syndrome (OMIM 191900), characterized by urticaria, deafness, and renal amyloidosis. CAPS are associated with pathogenic variants in *NLRP3* (formerly *CIAS1*). Inheritance in autosomal dominant.
- **Blau syndrome** (OMIM 186580) is characterized by arthritis, uveitis, skin rash, and granulomatous inflammation, usually affecting children younger than age four years. It is caused by pathogenic variants in *NOD2.* Inheritance is autosomal dominant.
- **Crohn disease** (OMIM 260920) can present with low-grade fever and abdominal pain. It is not typically associated with FMF, but individuals with FMF can be mistakenly diagnosed with Crohn disease. The cause of Crohn disease is unknown.
- **TRAPS (*T*NF *r*eceptor-*a*ssociated *p*eriodic *s*yndrome** (OMIM 142680) is characterized by attacks of fever, sterile peritonitis, arthralgia, myalgia, skin rash, and conjunctivitis. Some individuals develop amyloidosis. TRAPS is an autosomal dominant disorder caused by a pathogenic variant in *TNFRSF1A*. 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.
- **HIDS (*h*yper*i*mmunoglobulinemia *D* and periodic fever** s**yndrome** (OMIM 260920) is characterized by recurrent attacks of fever, abdominal pain, and arthralgia. HIDS is caused by a pathogenic variant in *MVK*. Inheritance is autosomal recessive. The recurrent episodes of fever and abdominal pain in HIDS are frequently indistinguishable from those in FMF; correct diagnosis may depend on ascertainment of the effectiveness of colchicine as a treatment and on molecular testing.
- ***ELANE*-related neutropenia** includes congenital neutropenia and cyclic neutropenia. Both are 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 are at 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. Inheritance is autosomal dominant.
- **PAPA (*p*yogenic sterile *a*rthritis, *p*yoderma gangrenosum, and *a*cne syndrome** (OMIM 604416) is a rare autoinflammatory disorder associated with noninfectious skin ulceration, typically accompanied by neutrophilic infiltration. Two pathogenic variants (p.Ala230Thr and p.Glu250Gln) in *PSTPIP1* have been identified in individuals with PAPA [Nesterovitch et al 2011]. Inheritance is autosomal dominant.
- **PFAPA (*p*eriodic *f*ever, *a*phthous stomatitis, *p*haryngitis, and *a*denopathy 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. To date, no genetic basis for PFAPA syndrome has been discovered [Gattorno et al 2009]. Treatment with steroids in the early stages of an attack is effective.

Amyloidosis

- **Familial transthyretin amyloidosis** 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. Pathogenic variants in *TTR* are causative. Inheritance is autosomal dominant.

Abdominal pain. Any cause of acute abdominal pain needs to be considered, including: 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. Consider the following:

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

Pleuritic pain. Consider the following:

- Pleurisy
- Pulmonary embolism

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with familial Mediterranean fever (FMF), the following evaluations are recommended:

- Physical examination to assess joint problems
- Urinalysis for the presence of protein. If proteinuria is found, further evaluation is required including measurement of 24-hour urinary protein, renal function tests, and consider a rectal biopsy for the presence of amyloid.
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

For information on treatment with colchicine see Prevention of Primary Manifestations. Colchicine is not effective as treatment for an acute FMF attack.

During an acute episode, the therapeutic approach should be mainly supportive, including administration of intravenous saline for hydration and use of nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol or dipyrone for pain relief [Ozturk et al 2011].

Febrile and inflammatory episodes are usually treated with NSAIDs.

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 [Sherif et al 2003].

Prevention of Primary Manifestations

Colchicine

- **Homozygotes/compound heterozygotes.** Individuals who are homozygous for the pathogenic variant 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 to prevent 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 pathogenic variant and who are only mildly affected (those with infrequent inflammatory attacks) should either be treated with colchicine or be 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 pathogenic variant p.Glu148Gln. Colchicine should only be given to these individuals if they develop severe inflammatory episodes and/or proteinuria as a result of amyloidosis.

- **Heterozygotes**. The presence of a single *MEFV* pathogenic variant together with clinical symptoms is sufficient to warrant the initiation of a trial of colchicine; therefore, manifesting heterozygotes should be treated [Booty et al 2009]. However, for asymptomatic heterozygotes there is no indication for treatment.

Complications of colchicine use occasionally include myopathy and toxic epidermal necrolysis-like reaction.

Treatment of affected individuals who are unresponsive to colchicine. Some individuals appear to be unresponsive to colchicine treatment. In one study this was associated with inadequate colchicine concentration in mononuclear cells, possibly resulting from a genetic defect underlying FMF [Lidar et al 2004] or from poor compliance.

- **Canakinumab** is an anti-IL-1β monoclonal antibody that binds human IL-1β and neutralizes its pro-inflammatory effects. Canakinumab has been recently approved by the FDA for the treatment of CAPS. Canakinumab differs from anakinra and rilonacept in that it has high specificity for IL-1β, it has a longer half-life than anakinra (26 days), it can be administered every two months, and its effectiveness lasts longer. In one individual with FMF with longstanding destructive arthritis, canakinumab, given as a first-line agent, induced a complete clinical remission [Mitroulis et al 2010, Meinzer et al 2011, Mitroulis et al 2011, Ozgocmen & Akgul 2011]. Canakinumab was effective in an individual with FMF who was unresponsive to colchicine and anakinra [Hacihamdioglu & Ozen 2012]. Alpa & Roccatello [2015] reported continued efficacy after two years of treatment.

- **Rilonacept,** an IL-1 receptor fusion protein, reduced the fever episodes by 76%, and improved quality of life [Hashkes et al 2012], but failed to reduce the duration of the attacks. Results were confirmed in a subsequent study extended to 14 colchicine-resistant individuals [Hashkes et al 2014]. Hentgen et al [2013b] recommended that rilonacept, which is a long half-life molecule, should be considered only if anakinra, a short half-life molecule, has been proven to be effective.

- **Anakinra,** an IL-1-receptor inhibitor with a short half-life, has been shown to have a 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 [Belkhir et al 2007, Bhat et al 2007, Gattringer et al 2007, Kuijk et al 2007, Calligaris et al

2008, Roldan et al 2008, Moser et al 2009, Petropoulou et al 2010, Meinzer et al 2011, Ozen et al 2011, Ozturk et al 2011, Hentgen et al 2013b]. Anakinra has been found to stop the attacks in 75% of individuals who did not respond to colchicine. Anakinra is expensive and has mild side effects, such as painful local reactions at the site of injections and possible risk of bronchopulmonary infection, especially in persons with other risk factors for pulmonary infections. Further studies are needed to investigate the long-term effects of this drug if it is to be taken continuously as required in severely affected individuals with FMF. Anakinra treatment should be considered in the presence of secondary amyloidosis, in candidates for renal transplantation due to end-stage renal amyloidosis, individuals who are unresponsive to colchicine, and individuals developing major side effects from colchicine.

- **Infliximab,** a chimeric monoclonal antibody against tumor necrosis factor alpha (TNF-α), was studied in a few individuals and found to be effective in the treatment of one individual with FMF who was resistant to colchicine, resulting in the complete remission of febrile abdominal episodes [Ozgocmen et al 2006]. In another individual, infliximab ameliorated the proteinuria and nephrotic syndrome secondary to amyloidosis and the recurrent attacks of arthritis and abdominal pain [Metyas et al 2004].
- **Weekly intravenous colchicine** (1.0 mg) to supplement oral colchicine resulted in a 50% reduction (except joint attacks) in attack frequency in one study of 13 individuals [Lidar et al 2003]. This is not a long-term solution.
- **Thalidomide** has been used successfully in sporadic cases [Seyahi et al 2002, Seyahi et al 2006] but is not frequently used.
- **Etanercept,** a TNF dimeric fusion protein, has been shown to decrease the disease severity in colchicine-resistant individuals; three of the 14 individuals included in the study had adverse effects and switched to IL-1-receptor inhibitor [Sakallioglu et al 2006, Seyahi et al 2006, Mor et al 2007].
- **Interferon alpha** is another therapeutic agent that has shown signs of promise in a few reports for affected individuals who are unresponsive to colchicine [Tunca et al 2004, Tweezer-Zaks et al 2008, Vandecasteele et al 2011]. In a double-blind, placebo-controlled study that included 34 individuals given interferon alpha or placebo, the authors could not demonstrate a definitive effect. Interferon alpha was effective in suppressing the acute inflammation of FMF only if administered at the earliest phase [Tunca et al 2004]. The possibility of interferon alpha side effects (e.g., chills and fatigue) should also be considered.
- **Sulphasalazine.** The use of sulphasalazine has been reported in a girl age eight years with a five-year history of typical FMF attacks. She was homozygous for the pathogenic variant p.Met694Val and for several months had had arthritis of one knee that was unresponsive to NSAIDs or colchicine. Resolution was achieved after the addition of sulphasalazine at a dose of 50 mg/kg/day [Bakkaloglu et al 2009].

Prevention of Secondary Complications

Treatment with colchicine 1.0 mg/day prevents renal amyloidosis even if the FMF attacks do not respond to the medication.

Surveillance

All individuals with FMF including those not currently being treated, those being treated with colchicine, and those receiving medication other than colchicine should undergo an annual physical examination, a urine spot test for protein, and an evaluation for hematuria [Twig et al 2014]. Kosan et al [2013] additionally recommended monitoring acute-phase reactants (ESR and fibrinogen levels) at regular intervals during attack-free periods, particularly in those with the p.Met694Val pathogenic variant.

Agents/Circumstances to Avoid

Cisplatin. One report suggests that cisplatin worsens symptoms of FMF [Toubi et al 2003].

Cyclosporin A appears to adversely affect renal transplant graft survival in individuals with FMF [Shabtai et al 2002]. It has also been reported to trigger FMF attacks, which responded well to colchicine in a previously asymptomatic individual with myelodysplastic syndrome who was heterozygous for the *MEFV* pathogenic variant p.Met694Ile [Sasaki et al 2009].

Evaluation of Relatives at Risk

Molecular genetic testing should be offered to all first-degree relatives and other at-risk family members as early as possible 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 (1.0 mg/day) to prevent the development of renal amyloidosis. Note: About 15% of individuals with autosomal dominant FMF develop amyloidosis and end-stage renal failure if untreated.

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

Pregnancy Management

Ben-Chetrit et al [2010] conducted a survey to evaluate the outcome of 179 pregnancies of women taking colchicine to treat FMF. No differences were found between the treated group and the control group regarding early abortions, late abortions, or congenital malformations. Similar findings were reported by Diav-Citrin et al [2010]. Nevertheless, it is still important to discuss the option of amniocentesis for every pregnancy in mothers treated with colchicine.

Therapies Under Investigation

The decrease of blood nitric oxide (NO) levels in individuals with FMF may trigger fever by initiating the production of IL-6. Plasma NO levels in those with FMF were significantly increased during attack-free periods following treatment with ImmunoGuard®, which has a normalizing effect both on NO and IL-6 blood levels in persons with FMF during attacks [Panossian et al 2003]. However, further studies are needed to confirm a single report of successful treatment of FMF with ImmunoGuard® (*Andrographis paniculata*Nees) [Amaryan et al 2003].

The role of biologics such as other anti-tumor necrosis factor (TNF) agents (adalimumab and golimumab) in the treatment of FMF has recently been investigated [Ozgocmen & Akgul 2011]. Anti-TNF agents have shown efficacy in rheumatic diseases, and there are many reports of persons with FMF responding favorably to treatment with these agents [Ozgocmen & Akgul 2011].

One study showed that the selective serotonin reuptake inhibitor (SSRI) paroxetine significantly decreased the number of acute attacks in individuals with colchicine-resistant FMF, several of whom also suffered from depression. The authors suggested that the depression may have triggered the attacks, and that treatment of the depression had the effect of suppressing the attacks [Onat et al 2007].

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

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. —ED.

Mode of Inheritance

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

For some affected individuals, the family history of FMF is consistent with an autosomal dominant manner of inheritance. In these families, presumed heterozygotes manifest FMF within a phenotypic spectrum from mild to classic findings.

- True autosomal dominant inheritance of FMF has been reported in individuals with severe pathogenic variants, including the in-frame deletion p.Met694del and two missense variants (p.Met694Val and p.Thr577Asn). Although the clinical severity of autosomal dominant FMF is typically reduced compared to autosomal recessive FMF, it is important to identify individuals with autosomal dominant FMF as about 15% of them develop amyloidosis and end-stage renal failure if untreated.
- The appearance of autosomal dominant inheritance may alternatively be the result of failure to detect a second, existing pathogenic variant. Identification of the second variant may require non-routine testing such as sequencing of the entire gene or sequencing of non-coding regions of the gene.
- Other possible explanations for the appearance of autosomal dominant inheritance include: digenic inheritance with a pathogenic variant in another recurrent fever-related gene, the presence of modifying alleles in related genes, the presence of certain environmental factors, or coexistence of another autoinflammatory disease [Ozen 2009].

Risk to Family Members – Autosomal Recessive Inheritance

Parents of a proband

- The parents of an individual with biallelic *MEFV* pathogenic variants are typically heterozygous for a single copy of an *MEFV* pathogenic variant.
- Heterozygotes are usually asymptomatic; however, a parent who is heterozygous for a severe *MEFV* pathogenic variant may have mild clinical features (see Clinical Characteristics).
- In populations with a high carrier rate and/or 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 resulting in pseudodominant inheritance (i.e., an autosomal recessive condition present in individuals in two or more generations). Thus, it is appropriate to consider molecular genetic testing of the parents of the proband.

Sibs of a Proband

- If both parents are heterozygous for an *MEFV* pathogenic variant:
    - At conception, each sib of an affected individual has a 25% chance of inheriting two *MEFV* pathogenic variants and being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not a carrier.
    - Heterozygotes are usually asymptomatic (see Clinical Characteristics).
- If one parent has two *MEFV* pathogenic variants and one parent is heterozygous:
    - At conception, each sib of an individual with two pathogenic variants has a 50% chance of inheriting two pathogenic variants and being affected and a 50% chance of being heterozygous.
    - Heterozygotes are usually asymptomatic (see Clinical Characteristics).

Offspring of a proband

- Offspring inherit one *MEFV* pathogenic variant from a parent with two *MEFV* pathogenic variants.

- 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 have two *MEFV* pathogenic variants or be heterozygous. Thus, the risk to offspring is most accurately determined after molecular genetic testing of the proband's reproductive partner.

Other family members. The risk to other family members depends on the genetic status of the parents of the proband: if the parents of the proband are heterozygotes, each sib of the proband's parents is at a 50% risk for being a carrier of an *MEFV* pathogenic variant.

Carrier (heterozygote) detection. Carrier testing for at-risk relatives requires prior identification of the *MEFV* pathogenic variants in the family.

Risk to Family Members – Autosomal Dominant Inheritance

Autosomal dominant inheritance of FMF has been reported in individuals with severe pathogenic variants, including frameshift variant p.Met694del, and two missense variants, p.Met694Val and p.Thr577Asn. The penetrance of autosomal dominant FMF is incomplete and the clinical severity is less than in autosomal recessive FMF. It is important to identify individuals with autosomal dominant FMF as about 15% of them develop amyloidosis and end-stage renal failure if untreated.

Parents of a proband

- To date, all individuals diagnosed with autosomal dominant FMF inherited an *MEFV* pathogenic variant from an affected parent.
- Recommendations for the evaluation of parents of a proband with autosomal dominant FMF include molecular genetic testing.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents: if one parent of the proband is heterozygous for an *MEFV* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- The actual risk to sibs of being affected may be lower than 50% because the penetrance of autosomal dominant FMF is incomplete.

Offspring of a proband. Each child of an individual with autosomal dominant FMF has a 50% chance of inheriting the MEFV pathogenic variant from their affected parent.

Other family members. The risk to other family members depends on the genetic status of the parents of the proband: if a parent of the proband is heterozygous, each sib of this parent is at a 50% risk of also being heterozygous for the *MEFV* pathogenic variant.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic family members. Given the ready availability of effective treatment for FMF, it is appropriate to test asymptomatic at-risk family members (particularly sibs of an affected individual). See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *MEFV* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for FMF are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Medline Plus**

  Familial Mediterranean fever

- **National Library of Medicine Genetics Home Reference**

  Familial mediterranean fever

- **NCBI Genes and Disease**

  Familial Mediterranean fever

- **Eurofever Registry**

  Largo Gaslini, 5

  Genova 16147

  Italy

  Phone: +39 010 382854; +39 010 393425

  Fax: +39 010 393324; +39 010 4211018

  Email: marcogattorno@ospedale-gaslini.ge.it; printo@ospedale-gaslini.ge.it

  Eurofever Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Familial Mediterranean Fever: Genes and Databases

Gene	Chromosome Locus	Protein	Locus Specific	HGMD
MEFV	16p13.3	Pyrin	The registry of MEFV sequence variants MEFV database	MEFV

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region, complementation group from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

Table B.

OMIM Entries for Familial Mediterranean Fever (View All in OMIM)

134610	FAMILIAL MEDITERRANEAN FEVER, AUTOSOMAL DOMINANT
249100	FAMILIAL MEDITERRANEAN FEVER; FMF
608107	FAMILIAL MEDITERRANEAN FEVER GENE; MEFV

Gene structure. *MEFV* comprises ten exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Some consider p.Glu148Gln to be a benign variant (see following discussion).

Pathogenic variants/variants of uncertain clinical significance. To date, more than 200 sequence variants have been identified, only some of which are regarded as having an associated phenotype and resulting in disease-related symptoms (For more information, see Table A, **The registry of *MEFV* sequence variants**.) Large deletions or duplications have not been observed [van Gijn et al 2008].

- **c.442G>C (p.Glu148Gln).** Disagreement exists as to whether the p.Glu148Gln substitution is a pathogenic [Stoffman et al 2000, Gershoni-Baruch et al 2002, Konstantopoulos et al 2005, Topaloglu et al 2005, Solak et al 2008, Tomiyama et al 2008] (see also Table A, **The registry of *MEFV* sequence variants**) or a benign allelic variant [Ben-Chetrit et al 2000, Tchernitchko et al 2003, Tchernitchko et al 2006].

  The p.Glu148Gln variant is predominant in Ashkenazi and Iraqi Jews, Armenians, and Turks, and has been 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 pathogenic variant other than p.Met694Val are asymptomatic. Such individuals are also at low risk (if any) of developing amyloidosis. The possible exception is those who are compound heterozygous for the alleles 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].

  Reduced penetrance of this pathogenic variant has been suggested and could explain the considerable proportion of genetically affected individuals in this population who remained asymptomatic [Mattit et al 2006].

- The **p.Pro369Ser** and **p.Arg408Gln** variants in exon 3 have been shown to be in linkage disequilibrium [Ryan et al 2010].
- **Affected individuals in the 'one or no detectable pathogenic variant' category.** Mattit et al [2006] tested for four pathogenic variants (p.Met694Val, p.Met694Ile, p.Met680Ile, and p.Val726Ala]) and the variant p.Glu148Gln in 83 unrelated individuals who fulfilled the international FMF criteria and 242 unrelated apparently healthy controls and found:
    - 30.1% were homozygous;
    - 39.8% were compound heterozygous;
    - 19.3% were heterozygous;
    - 10.8% had none of the listed variants, although p.Ala744Ser and p.Arg761His were detected in a few individuals after sequencing exon 10 only.

  Possible explanations:
    - The second undetected variant may be in an intron, or situated some distance from the gene itself, or possibly even in a neighboring gene (as with pathogenic variants in *GJB2* and *GJB6* that cause hearing loss), and thus missed by routine testing. This may explain the failure to detect in a substantial number of affected individuals either a second pathogenic variant when the gene and promoter region were fully sequenced or a common haplotype in their families [Booty et al 2009, Marek-Yagel et al 2009].
    - Ozen [2009] postulates that if a person with one *MEFV* pathogenic variant 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. See also Mode of Inheritance.

Table 3.

Selected *MEFV* Variants

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Uncertain clinical significance	c.442G>C	p.Glu148Gln	NM_000243.2 NP_000234.1
Pathogenic	c.1105C>T	p.Pro369Ser	
	c.1223G>A	p.Arg408Gln	
	c.1730C>A	p.Thr577Asn	
	c.1223G>A	p.Arg408Gln	
	c.1772T>C	p.Ile591Thr	

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
	c.1958G>A	p.Arg653His	
	c.2040G>C	p.Met680Ile	
	c.2064C>G	p.Tyr688Ter	
	c.2076_2078del	p.Ile692del	
	c.2080A>G	p.Met694Val	
	c.2081_2083delTGA	p.Met694del	
	c.2082G>A	p.Met694Ile	
	c.2084A>G	p.Lys695Arg	
	c.2177T>C	p.Val726Ala	
	c.2230G>T	p.Ala744Ser	
	c.2282G>A	p.Arg761His	

Note on variant classification: Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *MEFV* 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 marenostrin by the International FMF Consortium [IFMFC 1997]. The protein contains 781 amino acids and its normal function is probably to assist in controlling inflammation by deactivating the immune response.

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 [Jéru et al 2005].

Abnormal gene product. Normal pyrin protein interacts directly at the C-terminal B30.2 domain (where most of the FMF-causing pathogenic variants are situated) to regulate caspase-1 activation and consequently IL-1β production. The assumption is that pathogenic variants in persons with FMF result in less IL-1β activation and as a consequence heighten interleukin-1 (IL-1) responsiveness, resulting in increased inflammatory

attacks. *MEFV* pathogenic variants that cause FMF may be gain-of-function pyrin variants. It was shown in mice that the insertion of three different mutated human B30.2 domains induced inflammatory phenotypes similar to or more severe than those seen in persons with FMF, whereas deleting mouse pyrin produced no overt inflammatory phenotype [Chae et al 2011].

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Chapter Notes

Author Notes

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Revision History

- 15 December 2016 (sw) Comprehensive update posted live

- 19 June 2014 (me) Comprehensive update posted live
- 26 April 2012 (me) Comprehensive update posted live
- 30 April 2009 (me) Comprehensive update posted live
- 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

Bookshelf ID: NBK1227PMID: 20301405