Familial Mediterranean fever

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Familial Mediterranean fever (FMF; recurrent polyserositis, periodic disease) is an autosomal recessive hereditary disease which primarily affects populations surrounding the Mediterranean basin. It is characterised by recurrent attacks of fever and peritonitis, pleuritis, arthritis, or crysipelas-like skin disease.

Despite its striking symptom pattern FMF was first described as a distinct entity only in 1945. The first generation of investigators of FMF dealt with the definition and characterisation of the clinical manifestations. The second generation, from 1972, studied the effect of colchicine in the treatment of FMF. A new era opened in 1997 with the cloning of the mutated gene responsible for this disease.

**Genetics**

In the vast majority of affected families, the disease occurs in members of one generation, supporting recessive transmission. However, high consanguinity rates may account for the occurrence of FMF in two or more successive generations (pseudodominant inheritance). The carrier frequency has been estimated to be as high as 1 in 6 in north African Jews and 1 in 7 in Armenians. A high gene frequency in a given population can be explained by several mechanisms, which include genetic drift, founder effect, and heterozygote advantage. A lower rate of infections and a reduced incidence of asthma among heterozygotes for FMF remain to be confirmed. A founder effect would be a more plausible explanation since a common haplotype designated MED has been found in all FMF populations (Jews, Armenians, Turks, and Arabs).

At the beginning of the search for the mutated gene responsible for FMF, the "candidate gene" approach was used, with a focus on defects in proteins or mediators of inflammation. A later strategy was linkage analysis and the putative gene was located mistakenly to chromosome 17.

In 1992 at the US National Institutes of Health, the FMF gene was mapped to the short arm of chromosome 16. Since then, several groups from the USA, Israel (Sheba Hospital), and Australia have joined forces to form the International FMF Consortium. A second consortium comprises several French laboratories and clinicians from Israel (Bnei-Zion and Hadassah Hospitals).

Using the "positional cloning" approach both consortia isolated, in parallel and independently, the MEFV (Mediterranean fever) gene. Their findings were reported in September, 1997, and were the highlight of the International Conference on FMF held in Jerusalem on the same month.

**Epidemiology**

FMF is almost completely restricted to non-Ashkenazi Jews, Armenians, Arabs, and Turks. Patients with FMF have been reported from Germany, Poland, Australia, and Brazil but in most of these cases the exact ancestry was not disclosed or they could be cases of another form of periodic disease. More than 90% of Jewish FMF patients are of Sephardic or Middle Eastern origin. Sephardic Jews are descendants of those expelled from Spain in the 15th century, who were dispersed through various north African and Mediterranean countries. Middle Eastern Jews (mainly Iraqi) are descendants of Jews exiled to Mesopotamia by the Babylonians more than 2500 years ago. The Ashkenazi Jews stem mainly from eastern and western Europe and their origin is combined from Jews exiled from Judea by the Romans 2000 years ago and through later persecutions and conversions. FMF has been described very rarely in Yemenite Jews and not at all in Jews from Ethiopia.

In Israel there are about 5000 patients with FMF with a prevalence of about 1 in 500 (average carrier frequency of 1 in 11). However, the disease is not equally distributed among the various subgroups of the non-Ashkenazi Jews. For example, in north African Jews the carrier rate is 1 in 6 to 1 in 8 so in this population the prevalence of FMF can be more than 1 in 256. An evaluation of 150 FMF cases among Armenians living in Lebanon suggests a prevalence of 1 in 500, but the absolute number of Armenian FMF patients is not available.

Most data about
Armenians have been derived from communities outside Armenia (Los Angeles and Lebanon). Most Turkish FMF patients originate from central Anatolia. The exact frequency of FMF among Turks and Arabs is not available because formal epidemiological studies have not been done.

Most studies have reported that FMF affects both sexes in a similar ratio, although some suggest a male predominance.

The isolation of MEFV and analysis of the prevalence of mutations in the different ethnic groups has allowed some hypotheses on the genealogy of FMF. The M694V mutation is present in Iraqi Jews as well as in north African Jews and Armenians, whereas V726A occurs in Iraqi Jews, non-Ashkenazi Jews, Druze, and Armenians. These data support the notion that both mutations are very ancient and probably appeared in the Middle East from where they spread to Europe, north Africa, and to Armenia more than 2500 years ago (figure 1).

An interesting cluster of FMF patients has been identified among the “Chuetas” (believed to be descendants of converted Jews) in Palma, on the Spanish Mediterranean island of Mallorca. 30% of them have a genetic haplotype similar to those of north African FMF patients. This finding supports the notion that some of them are also descendants of Jews exiled from Spain (figure 1). However, some of those who are haplotype-negative share a common new mutation with Iraqi Jews, suggesting also a direct spread by the sea from the Middle-East to the island.

Pathogenesis

The hallmark of FMF is an inflammatory reaction affecting serosal tissues such as the pleura, peritoneum, and synovium. During attacks the chemotactic activity of the polymorphonuclear leucocytes is greatly increased and there is a massive influx of granulocytes to the affected tissues. Physical and emotional stress, menstruation, and a high-fat diet may trigger the attacks.

Until recently the exact biochemical and molecular basis for FMF was unknown, and several hypotheses were suggested. One was that FMF was a congenital disorder, caused by a deficiency of one of the lipocortin proteins involved in the biosynthesis of mediators of inflammation. Another was that FMF was due to an inherited deficiency of an inhibitory regulator of the inflammatory response, just as hereditary angio-oedema results from C1q esterase inhibitor deficiency. Matzner and colleagues found hardly any C5a inhibitor activity in joints and peritoneal fluid in FMF, and, since C5a is a highly potent chemoattractant of granulocytes, it was suggested that lack of its inhibitor might account for the acute attacks of inflammation. Others have claimed that the disorder in FMF is related to catecholamine metabolism since, metaraminol infusion may provoke an acute attack. None of these hypotheses has been confirmed. The fact that FMF has clinical manifestations resembling those of systemic lupus erythematosus (fever, arthritis, and serositis), raises the possibility of an underlying autoimmune pathogenicity. However, FMF does not respond to steroids and other immunosuppressive medications, and autoantibodies have not been found.

Identification of the function of the MEFV gene product would lead not only to an understanding of the pathogenesis of FMF but also to further elucidation of the inflammatory process generally. This protein (marenostrin/pyrin) is very basic (rich in NH2 groups) and comprises several domains with various potential functions. The presence of the domain bZIP usually suggests a DNA-binding site, whereas the finding of a nuclear localisation signal could mean that the protein is either a nuclear or a ribosomal polypeptide. The C-terminus of marenostrin/pyrin includes a rfp (ret finger protein) or B30·2-like domain. This sequence of aminoacids is shared by several peptides including the autoantigen Ro/SSA (52 kD), Xenopus nuclear factor 7, and butyrophilin. The diversity of this group of proteins (transmembrane, intracellular, and secretory) stemming from different species suggests that marenostrin/pyrin is of
Marrow or in a prepromyelocytic cell line, so it is may be crucial. Inflammation, the role of marenostrin/pyrin in these cells are the major cell population involved in acute neutrophils are the major cell population involved in acute microtubular activation and migration of PMN to inflammatory sites. Colchicine achieves high concentration in PMN due to deficient P-glycoprotein efflux pump function in these cells. It acts on microtubuli and possibly by upregulating MEVF gene expression. Mutation of gene removes host control and allows microtubular activation and migration of PMN to inflammatory sites. Colchicine achieves high concentration in PMN due to deficient P-glycoprotein efflux pump function in these cells. It acts on microtubuli and possibly by upregulating MEVF gene expression.28

Further support for this concept comes from the fact that this protein is expressed exclusively in granulocytes.3,4 Since neutrophils are the major cell population involved in acute inflammation, the role of marenostrin/pyrin in these cells may be crucial. MEFV mRNA was not detected in bone marrow or in a prepremyelocytic cell line, so it is hypothesised that the protein is expressed during the acute activation of mature neutrophils. Another important point is the lack of expression of marenostrin/pyrin in synovial and peritoneal cells, suggesting that it does not exert its effect in a tissue-specific manner. The disruption of marenostrin/pyrin in neutrophils, owing to the presence of one of the mutations, may lead to uncontrolled neutrophil activation and migration to the serosal tissues. However, it is still unclear why the serosal tissues are the main targets of inflammation in FMF.

Abdominal pain is present in 95% of patients, the clinical picture being typical of acute peritonitis. Some patients have constipation, whereas in children diarrhoea is more common. Abdominal pain usually precedes the fever by a few hours and persists for 1–2 days after the temperature returns to normal. It may remain localised and simulate appendicitis or cholecystitis. Less frequently, the posterior peritoneum is affected, mimicking renal colic or acute pelvic inflammatory disease. 30–40% of patients will eventually undergo exploratory surgery with appendicectomy or cholecystectomy. Since true appendicitis may occur in FMF patients, some clinicians recommend laparoscopic appendicectomy in the early stages of the disease for both diagnostic and preventive purposes.26,35 Peritoneal irritation during surgery or diagnostic procedures involving the serosal membranes may occasionally provoke violent FMF attacks. Fortunately, the recurrent peritonitis of FMF (sometimes on more than a hundred occasions) is rarely accompanied by the formation of adhesions, and the patient’s condition improves within 24 h.

The typical chest pain due to pleurisy is another frequent manifestation of FMF, occurring in about 25–80% of the cases reported in a summary of 11 series.1 Occasionally, transient effusions are detected at the costophrenic angle. The pleuritis may last as long as 7 days and be the presenting manifestation of FMF in 5% of patients. Its simultaneous occurrence with pericarditis has also been described.

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Fever
Fever is a feature of every acute attack. The temperature may rise to 38–40°C, though mild attacks may be accompanied by low-grade fever. In 20–30% of the patients the rise in temperature is preceded by chills. The fever usually lasts between 12 h and 3 days. It is rarely the only manifestation of FMF. In patients receiving colchicine, abortive attacks may lack the fever component.

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may result from failure to distinguish this disorder from pleuritis, which is relatively common. A few cases have been reported of constrictive pericarditis following acute pericardial FMF attacks.

**Arthritis**

This is a common and important feature of FMF. Joint involvement in Jews originating from north Africa is more common than it is in other ethnic groups (panel 2). There are three forms of arthritis in FMF:

- **Asymmetrical, non-destructive arthritis (75%)**—The attacks, usually of short duration, start abruptly with no prodrome. One or two joints swell rapidly with large effusions. The most frequent joints affected are knees, ankles, and wrists. These usually resolve completely.

- **Chronic destructive arthritis, including sacroiliitis (2-5%)**—Here the joints most commonly affected are the hips and knees. Permanent damage may result from one protracted attack or from repeated short attacks. Sacroiliitis is rare (0-4%). It is characterised by low-back pain with no involvement of the lumbar spine; HLA-typing is usually negative for B27.

- **Migratory polyarthritis, resembling acute rheumatic fever**—Since rheumatic fever and FMF are present in the same age and population groups it is plausible that cases of rheumatic fever are misdiagnosed for FMF and vice versa.

**Myalgia**

Severe myalgia during attacks usually appears in the arms and legs, and may be associated with arthritis. Only very rarely is it the presenting or sole manifestation of FMF. Attacks of myalgia may last more than 3 weeks.

**Erysipelas-like skin lesion**

This manifestation, reported in 7-40% of FMF patients, appears almost invariably on the extensor surfaces of the leg, over the ankle joint or dorsum of the foot, and it is most commonly unilateral. The lesion resembles erysipelas or cellulitis and is often accompanied by fever and sometimes with arthralgia. The symptoms intensify rapidly and the erythema fades away spontaneously within 2-3 days.

**Other organ involvement**

Basically, the central nervous system and the meninges are spared, although Mollaret's meningitis was reported to be part of FMF. Fundoscopy may reveal retinal colloid bodies in some patients. Spleenomegaly has been described in 30-50% of patients. In most of them rectal biopsy was negative for amyloidosis, suggesting that the spleen enlargement was not the result of amyloid deposition. Acute orchitis with scrotal oedema and pain may be another rare manifestation.

**Amyloidosis**

One of the most significant complications of FMF is amyloidosis, usually affecting the kidneys, resulting in renal insufficiency progressing to end-stage renal disease. Amyloidosis may also affect the gastrointestinal tract, liver, spleen, and at a later stage the heart and testes. The amyloid is of the AA type, which is typical of secondary amyloidosis. The frequency of amyloidosis differs among various ethnic groups and depends on whether patients are taking colchicine, which has significantly arrested the incidence. Some patients present with renal amyloidosis with no history of typical FMF attacks; however, questioning often reveals that other family members have characteristic FMF manifestations. This presentation of amyloidosis without the attacks of serositis has been called “phenotype II”. Patients with amyloidosis have a higher rate of family history for the disease and more frequent joint involvement, rash, and splenomegaly than FMF patients without this complication. Amyloidosis is more frequent among north African Jews and Turks, is less common in Armenians (in USA) and rare in Ashkenazi and Iraqi Jews. When present, amyloidosis develops in the vast majority of the cases before the age of 40.

**Genotype-phenotype correlation**

The presentation and severity of the disease vary. The more severe disease seen in north African Jews than in Iraqi Jews can now be matched with the genotype analysis. Preliminary studies reveal that the severe course of FMF correlates with homozygosity for M694V, the mutation found in about 94% of north African patients. In M694V homozygotes, FMF is characterised by an earlier onset, more frequent attacks, and by more joints being affected and by the requirement for a higher dose of colchicine. Also, amyloidosis was found in 12 of 70 FMF patients who were homozygous for M694V but in none of 13 patients heterozygous for this mutation or carrying the V726A mutation. Our three patients with amyloidosis were also homozygous for M694V. However, further studies are required to confirm these observations and to explain “phenotype II” patients, who present with amyloidosis but with no history of the typical attacks of fever or peritonitis. The relation between FMF and amyloidosis—namely, whether it is due to specific mutation or a secondary complication of the inflammatory attacks—is still obscure.

**Diagnosis**

There are no specific laboratory tests for FMF. During attacks, acute-phase reactants such as C-reactive protein, fibrinogen, and serum amyloid A are increased, and the erythrocyte-sedimentation rate and the white-blood-cell-count are raised too. All these tests are usually normal between attacks. The secretion of mediators of inflammation such as interleukin-1 and tumour necrosis factor (TNF) has been reported to be increased during the acute attack, whereas interferon activity was found to be decreased. Serosal fluids, especially from the peritoneal cavity or from the synovia, were reported to have reduced activity of C5a inhibitor. Urinalysis is usually normal. Proteinuria should raise the possibility of renal amyloidosis.

Until recently, the diagnosis of FMF was based on clinical manifestations (not always typical), ethnicity, family history, and response to colchicine. In cases where these components were unhelpful FMF was difficult to diagnose. Diagnostic tests such as the metaraminol provocation test and the measurement of dopamine β-hydroxylase were either dangerous or noncontributory.

Cloning of MEFV now allows a new and reliable diagnostic test for FMF. A set of PCR primers can be used to demonstrate the mutations responsible for disease. The three major mutations are present in 85% of FMF carrier chromosomes. If the carrier gene frequency is 1 in 8, 98% of FMF patients will carry one or two of these mutations and only 2% will carry yet unidentified mutations. Among north African Jews with FMF, of whom 94% bear M694V, this genetic test will be even more sensitive.
Treatment

Colchicine

Since the report of Goldfinger in 1972, colchicine remains the treatment of choice for FMF.2 The adult dose is 1-0 mg daily and in non-responsive patients it can be increased to 2-0 mg.12 About 65% of patients respond with complete remission, and 20-30% experience significant improvement.42 A reduction in the number and severity of attacks, 5-10% are non-responders but a recent study showed that the vast majority of the non-responders are non-compliant with the treatment.60 Colchicine can be taken once daily; when doses above 1-5 mg are required or in patients with gastrointestinal intolerance, the dose may be divided into twice daily. Discontinuation of colchicine may result in an acute attack of FMF within 24 h to a few days.

Colchicine is of paramount importance in preventing FMF amyloidosis; it may also arrest the progression of amyloidosis in those who already have it, and may even reverse proteinuria.28 The discovery that marenostin/pyrin is expressed exclusively in neutrophils may imply a direct effect of colchicine on this protein. Colchicine inhibits the increased chemotactic activity occurring during FMF attacks and is concentrated mainly in neutrophils.20,48 We have suggested that this “affinity” of colchicine for neutrophils is due to the absence of the P-glycoprotein efflux pump on their membranes.43,50 The high concentration of colchicine in neutrophils, which exclusively express marenostin/pyrin, may exert a direct intracellular agonistic effect on this protein (figure 2).

Future possibilities

Elucidation of the exact role of marenostin/pyrin should facilitate the search for measures that will correct the lack of regulation caused by the defective gene—eg, by imitating marenostin/pyrin function, or by enhancing production of the protein or inhibiting its degradation.

Research should now focus on the structure and function of marenostin/pyrin in vitro and in vivo. By the techniques of knock-out, knock-in, or insertion of a mutated human gene, an animal model for FMF could be developed, facilitating the search for alternatives to colchicine in FMF and for the therapeutic potential of marenostin/pyrin in other inflammatory diseases.

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Further reading

**General**


