Seminar

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 erysipelas-like skin disease.

Despite its striking symptom pattern FMF was first described as a distinct entity only in 1945.[1] 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.[2] A new era opened in 1997 with the cloning of the mutated gene responsible for this disease.[3,4]

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.[5,6] 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.[7] 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).[8]

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.[9] A later strategy was linkage analysis and the putative gene was located mistakenly to chromosome 17.[10] In 1992 at the US National Institutes of Health, the FMF gene was mapped to the short arm of chromosome 16.[11] 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.[3,4] Their findings were reported in September, 1997, and were the highlight of the International Conference on FMF held in Jerusalem on the same month.

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Panel 1: **First three mutations detected in *MEFV* (FMF gene)**

Mutation	Description
M680I	G→C transversion at nucleotide 2040 that results in substitution of isoleucine for methionine
M694V	A→G transition at nucleotide 2080 causing substitution of valine for methionine
V726A	T→C transition at nucleotide 2177 which results in substitution of alanine for valine

The international consortium detected a full-length transcript of 3·7 kb encoding a protein consisting of 781 aminoacids. This protein product was termed "pyrin", indicating its relation to fever, the hallmark of FMF.[3] The French consortium isolated a 1·9 kb complementary DNA sequence coding partly a protein they named "marenostrin" ("our sea"), in reference to the Mediterranean focus of FMF.[4] Several conservative missense mutations were discovered in exon 10 of the gene at its carboxyterminal site. Three identical mutations were reported by both research groups (panel 1); the French consortium detected a fourth. The gene was novel, with no sequence identities in the protein database. One of these three mutations was found in 85% of carrier chromosomes so about 15% of FMF carrier chromosomes do not yet have demonstrable mutations. Additional mutations in exon 2 of the gene have recently been detected in several families from various ethnic groups.

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[1] 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.[6,12] Most data about

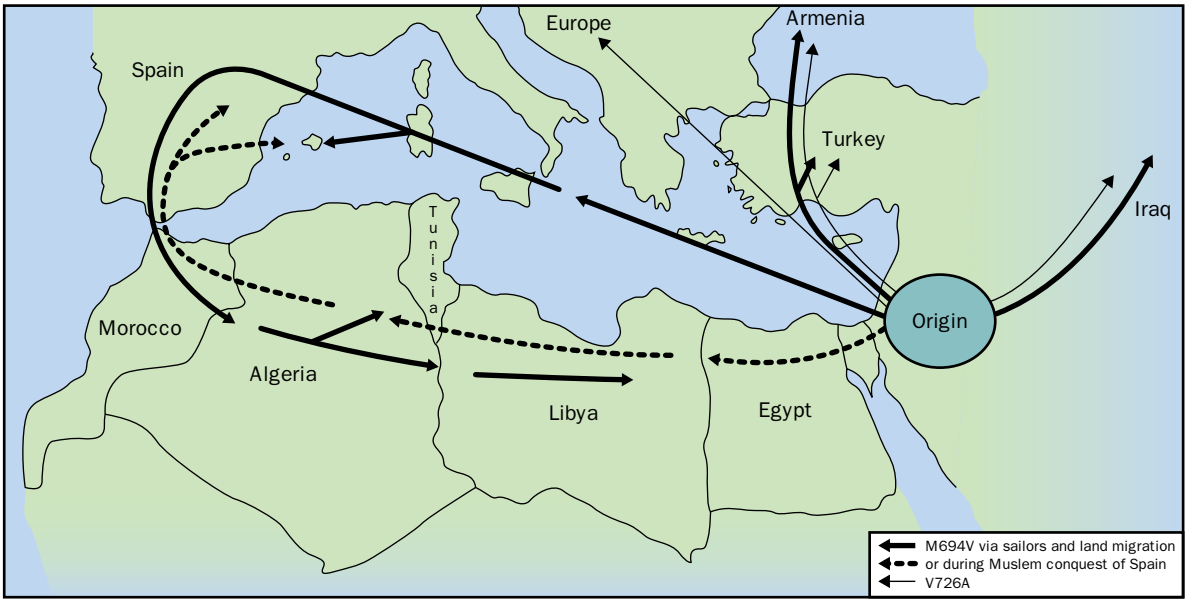

Figure 1: **Map suggesting likely distribution of two main mutations responsible for FMF**
These ancient mutations appear to have originated in the Middle East in biblical times. Mutation M694V migrated to Spain and north-Africa, either via early sailors from the Middle East or eastward via land migration later during the Moslem conquest of Spain. V726A also migrated from the Middle East to Armenia, Turkey, and Europe (Ashkenazi Jews). FMF in Mallorcan Chuetas could have originated as in Sephardic Jews, although additional mutations may also have occurred. (Adapted from ref 19).

Armenians have been derived from communities outside Armenia (Los Angeles and Lebanon). Most Turkish FMF patients originate from central Anatolia.[13] The exact frequency of FMF among Turks and Arabs is not available because formal epidemiological studies have not been done.[14–16]

Most studies have reported that FMF affects both sexes in a similar ratio, although some suggest a male predominance.[17]

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.[18] 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).[19] 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.[20] 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,[21] 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.[22] 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.[23,24]

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 NH_2 groups) and comprises several domains with various potential functions.[3,4] 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.[25] This sequence of aminoacids is shared by several peptides including the autoantigen Ro/SSA (52 kD), *Xenopus* nuclear factor 7, and butyrophilin.[26,27] The diversity of this group of proteins (transmembrane, intracellular, and secretory) stemming from different species suggests that marenostrin/pyrin is of

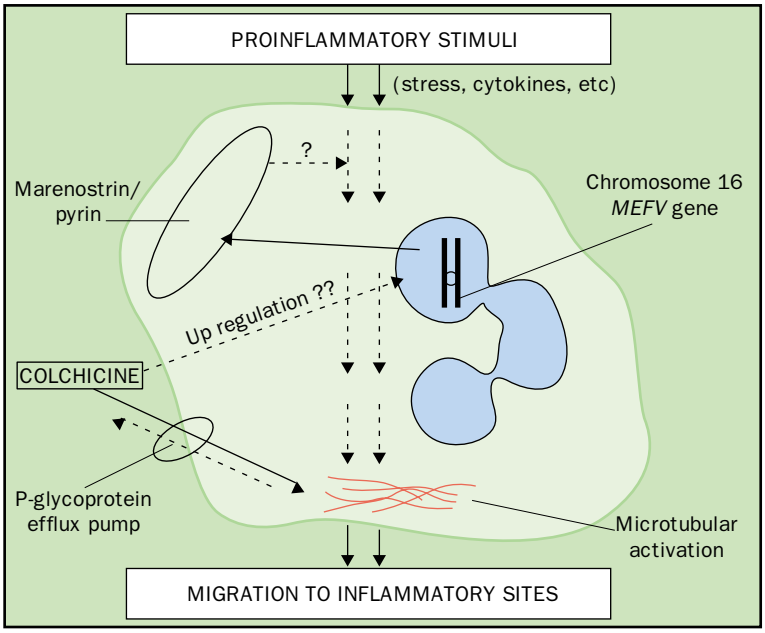

Figure 2: **Suggested pathogenesis of FMF**
Polymorphonuclear leucocytes (PMN) are site of action. Ongoing proinflammatory stimuli are normally balanced by marenostrin, a protein encoded by *MEFV* gene and expressed exclusively in mature PMN. Mutation of gene removes host control and allows microtubular activation and migration of PMN to inflammatory sites. Colchicine achieves high concentration in PMN due to deficient P-glycoprotein efflux pump functioin in these cells. It acts on microtubuli and possibly by upregulating *MEVF* gene expression.

ancient origin. Furthermore, the presence of B30·2 may suggest a potential protein-protein interaction of marenostrin/pyrin. Considerable homology (of about 23%) was also found between the marenostrin/pyrin and the rpt-1 (regulatory protein T-lymphocyte 1) which is a down-regulator of interleukin-2 receptor α directed gene expression.[28]

Marenostrin/pyrin is therefore probably involved in down-regulation of mediators of inflammation (figure 2). 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 prepromyelocytic cell line,[3] 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.

Panel 2: **Frequency (%) of clinical features of familial Mediterranean fever among various ethnic groups**

Clinical feature	Jews[17,32] (n=515)	Turks[13,14] (n=601)	Arabs[15,16*] (n=227)	Armenians[1,12] (n=215)
Fever	100	100	100	100
Peritonitis	96	93	94	89
Pleuritis	40	33	40	53
Arthritis	76	54	37	21
Rash	41	30	12	20

*Includes 10 Armenians.

Clinical manifestations

Symptoms of FMF (panel 2) start in the first decade of life in about 50% of cases, and only 5% develop the disease after the age of 30.[1,17] The incidence in the first year of life is difficult to ascertain, although there is no doubt that symptoms can start as early as 2 weeks after birth.

A typical attack consists of fever and serositis lasting from 1 to 4 days. Between attacks, FMF patients are free of symptoms and appear healthy. The frequency of the attacks varies from weekly to one every 3–4 months or less often. The severity of attacks and their frequency usually decreases as the patient gets older.

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.

Peritonitis

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.[29,30] 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.

Pleuritis

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.

Pericarditis

Recurrent pericarditis was reported in 0·5% of FMF patients.[31] The course of pericarditis in FMF resembles that of attacks at other sites; however, it tends to appear at a late stage of the disease. Underdiagnosis of pericarditis

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).[17,32] There are three forms of arthritis in FMF:

Asymmetrical, non-destructive arthritis (75%)—The attacks, usually of short duration, start abruptly with no prodome. 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.[33]

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.[12,34]

Erysipelas-like skin lesion

This manifestation, reported in 7–40% of FMF patients,[17,32] 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.[1] Fundoscopy may reveal retinal colloid bodies in some patients. Splenomegaly 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.[13] Acute orchitis with scrotal oedema and pain may be another rare manifestation.[35]

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.[36]

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".[17] 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.[17] 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.[36,37] The more severe disease seen in north African Jews than in Iraqi Jews can now be matched with the genotype analysis. Preliminary studies[38–40] 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.[39] Our three patients with amyloidosis were also homozygous for M694V.[38] 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.[41,42] Serosal fluids, especially from the peritoneal cavity or from the synovia, were reported to have reduced activity of C5a inhibitor.[21] 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.[1] In cases where these components were unhelpful FMF was difficult to diagnose. Diagnostic tests such as the metaraminol provocation test[22] and the measurement of dopamine β-hydroxylase[43] were either dangerous or non-contributory.[44,45]

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.[17,32] About 65% of patients respond with complete remission, and 20–30% experience significant improvement with 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.[46] 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.[47]

The discovery that marenostrin/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.[49,50] The high concentration of colchicine in neutrophils, which exclusively express marenostrin/pyrin, may exert a direct intracellular agonistic effect on this protein (figure 2).

Future possibilities

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

Research should now focus on the structure and function of marenostrin/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 marenostrin/pyrin in other inflammatory diseases.

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References

1 Eliakim M, Levy M, Ehrenfeld M. Recurrent polyserositis (familial Mediterranean fever). Amsterdam: Elsevier/North Holland Biomedical, 1981.

2 Goldfinger SE. Colchicine for familial Mediterranean fever. *N Engl J Med* 1972; **287:** 1302.

3 The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997; **90:** 797–807.

4 The French FMF Consortium: a candidate gene for familial Mediterranean fever. *Nat Genet* 1997; **17:** 25–31.

5 Daniels M, Shohat T, Brenner-Ullman A, Shohat M. Familial Mediterranean fever: high gene frequency among the non-Ashkenazic and Ashkenazic Jewish populations in Israel. *Am J Med Genet* 1995; **55:** 311–14.

6 Rogers DB, Shohat M, Petersen GM, et al. Familial Mediterranean fever in Armenians: autosomal recessive inheritance with high gene frequency. *Am J Med Genet* 1989; **34:** 168–72.

7 Brenner-Ullman A, Melzer-Ofir H, Daniels M, et al. Possible protection against asthma in heterozygotes for familial Mediterranean fever. *Am J Med Genet* 1994; **53:** 172–75.

8 Balow JE Jr, Shelton DA, Orsborn A, et al. A high resolution genetic map of the familial Mediterranean fever candidate region allows identification of haplotype-sharing among ethnic groups. *Genomics* 1997; **44:** 280–91.

9 Shohat M, Shohat T, Rotter JI, et al. Serum amyloid A and P protein genes in familial Mediterranean fever. *Genomics* 1990; **8:** 83–89.

10 Kastner DL, Aksentijevich I, Gruber L, et al. Familial Mediterranean fever: a 90 markers exclusion map and evidence for linkage to chromosome 17. *Cytogenet Cell Genet* 1991; **58:** 2115 (abstr).

11 Pras E, Aksentijevich I, Gruberg L, et al. Mapping of a gene causing familial Mediterranean fever to the short arm of chromosome 16. *N Engl J Med* 1992; **326:** 1507–13.

12 Schwabe AD, Peters RS. Familial Mediterranean fever in Armenians: analysis of 100 cases. *Medicine* 1974; **53:** 453–62.

13 Yazici H, Ozdogan H. Familial Mediterranean fever in Turkey. In: Sohar E, Gafni J, Pras M, eds. Proceedings of the 1st International Conference on FMF (Jerusalem, 1997). Tel Aviv: Freund, 1997: 66–71.

14 Ozdemir AI, Sokmen C. Familial Mediterranean fever among the Turkish people. *Am J Gastroenterol* 1969; **51:** 311–16.

15 Bitar E, Naffah J, Nsar W, Khoury K. La maladie periodique (polyserosite paroxystique familiare). *Rev Rhum Mal Osteoratic* 1976; **43:** 267–72.

16 Barakat MH, Karnik AM, Majeed HA, El-Sobki NI, Fenech FF. Familial Mediterranean fever (recurrent hereditary polyserositis) in Arabs: a study of 175 patients and review of the literature. *Q J Med* 1986; **233:** 837–47.

17 Sohar E, Gafni J, Pras M, et al. Familial Mediterranean fever: a survey of 470 cases and review of the literature. *Am J Med* 1967; **43:** 227–53.

18 Buades RJ, Ben-Chetrit E, Levy M. Familial Mediterranean fever in the "Chuetas" of Mallorca: origin in inquisition? *Isr J Med Sci* 1995; **31:** 497–99.

19 Aksentievitz I, Kastner DL and the International FMF Consortium. Microsatellite haplotypes and MEFV mutations: exploring the genealogy of FMF. In: Sohar E, Gafni J, Pras M, eds. Proceedings of the 1st International Conference on FMF (Jerusalem, 1997). Tel Aviv: Freund, 1997: 246–51.

20 Bar-Eli M, Ehrenfeld M, Levy M, et al. Leukocyte chemotaxis in recurrent polyserositis (familial Mediterranean fever). *Am J Med Sci* 1981; **281:** 15–18.

21 Matzner Y, Ayesh S, Hochner-Celniker D, et al. Proposed mechanism of the inflammatory attacks in familial Mediterranean fever. *Arch Intern Med* 1990; **150:** 1289–91.

22 Barakat MH, El-Khawad AO, Gumaa KA. Metaraminol provocative test: a specific diagnostic test for familial Mediterranean fever. *Lancet* 1984; i: 656–57.

23 Ben-Chetrit E, Levy M. Autoantibodies in familial Mediterranean fever (recurrent polyserositis). *Br J Rheumatol* 1990; **29:** 459–61.

24 Swissa M, Schul V, Korish S, et al. Determination of autoantibodies in patients with familial Mediterranean fever and their first degree relatives. *J Rheumatol* 1991; **18:** 606–08.

25 Henry J, Ribouchon MT, Offer C, Pontarotti P. B30·2-domain proteins: a growing family. *Biochem Biophys Res Comm* 1997; **235:** 162–65.

26 Ben-Chetrit E, Chan EKL, Sullivan KF, Tan EM. A 52 KD protein is a novel component of the SSA/Ro antigenic particle. *J Exp Med* 1988; **167:** 1560–71.

27 Jack LJW, Mather IH. Cloning and molecular analysis of cDNA encoding bovine butyrophilin, an apical glycoprotein expressed in mammary tissue and secreted in association with the milk-fat globule membrane during lactation. *J Biol Chem* 1990; **265:** 14481–86.

28 Patarca R, Freeman GJ, Schwartz J, et al. Rpt-1, an intracellular protein from helper/inducer T cells that regulates genes expression of interleukin 2 receptor and human immunodeficiency virus type 1. *Proc Natl Acad Sci USA* 1988; **85:** 2737–38.

29 Schwabe AD, Terasaki PI, Barnett EV, et al. Familial Mediterranean fever: recent advances in pathogenesis and management. *West J Med* 1997; **127:** 15–23.

30 Reissman P, Durst AL, Rivkind A, et al. Elective laparoscopic appendectomy in patients with familial Mediterranean fever. *World J Surg* 1994; **18:** 139–42.

31 Kees S, Langevitz P, Zemer D, et al. Attacks of pericarditis as a manifestation of familial Mediterranean fever. *QJM* 1997; **90:** 643–47.

32 Ben-Chetrit E, Levy M. Cholchicine prophylaxis in familial Mediterranean fever: reappraisal after 15 years. *Semin Arthritis Rheum* 1994; **20:** 241–46.

33 Langevitz P, Livneh A, Zemer D, et al. Seronegative spondyloarthropathy (SNSA) in familial Mediterranean fever (FMF). *Arthritis Rheum* 1994; **37:** S203 (suppl).

34 Langevitz P, Zemer D, Livneh A, et al. Protracted febrile myalgia in patients with familial Mediterranean fever. *J Rheumatol* 1994; **21:** 1708–09.

35 Eshel G, Vinograd I, Barr J, et al. Acute scrotal pain complicating familial Mediterranean fever in children. *Br J Surg* 1994; **81:** 894–96.

36 Pras M, Bronshpigel N, Zemer D, et al. Variable incidence of amyloidosis in familial Mediterranean fever among different ethnic groups. *Johns Hopkins Med J* 1982; **150:** 22–26.

37 Pras E, Livneh A, Balow SE Jr, et al. Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. *Am J Med Genet* 1998; **75:** 216–19.

38 Dewall M, Domingo C, Rosenbaum M, Ben-Chetrit E, et al. Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). *Eur J Hum Genet* (in press).

39 Pras E, Langevitz P, Livneh A, et al. Genotype-phenotype correlation in familial Mediterranean fever: a preliminary report. In: Sohar E, Gafni J, Pras M, eds. Proceedings of the 1st International Conference on FMF (Jerusalem, 1997). Tel Aviv: Freund, 1997: 260–64.

40 Dagan T, Danon Y, Lotan R, et al. Phenotype-genotype correlation in familial Mediterranean fever. In: Sohar E, Gafni J, Pras M, eds. Proceedings of the 1st International Conference on FMF (Jerusalem, 1997). Tel Aviv: Freund, 1997: 109–14.

41 Ozyilkan E, Simsek H, Telatar H. Tumor necrosis factor in familial Mediterranean fever. *Am J Med* 1992; **92:** 579–80.

42 Rozenbaum M, Katz R, Rozner I, et al. Decreased interleukin I activity released from circulating monocytes of patients with familial Mediterranean fever during in vitro stimulation by lipopolysaccharide. *J Rheumatol* 1992; **19:** 416–18.

43 Barakat MH, Gumaa KA, Malhas LN, et al. Plasma dopamine beta-hydroxylase: rapid diagnostic test for recurrent hereditary polyserositis. *Lancet* 1988; ii: 1280–83.

44 Ben-Chetrit E, Gutman A, Levy M. Dopamine beta hydroxylase activity in familial Mediterranean fever. *Lancet* 1990; **315:** 176.

45 Courillon-Mallet A, Cauet N, Dervichian M, et al. Plasma dopamine beta hydroxylase activity in familial Mediterranean fever. *Isr J Med Sci* 1992; **28:** 422–29.

46 Peters RS. Non-response to daily colchicine attack suppression in familial Mediterranean fever (FMF). The 1st International Conference on FMF (Jerusalem, 1997): 8 (abstr).

47 Zemer D, Livneh A, Langevitz P. Reversal of nephrotic syndrome by colchicine in amyloidosis of familial Mediterranean fever. *Ann Intern Med* 1992; **116:** 42–46.

48 Chapey OH, Niel E, Wautier JL, Hung PP, et al. Colchicine disposition in human leukocytes after single and multiple oral administration. *Clin Pharmacol Ther* 1993; **54:** 360–67.

49 Klimecki WT, Futscher BW, Grogan TM, Dalton WS. P-glycoprotein expression and function in circulating blood cells from normal volunteers. *Blood* 1994; **83:** 2451–58.

50 Ben-Chetrit E, Levy M. Does lack of the P-glycoprotein efflux pump in neutrophils explain the efficacy of colchicine in FMF and other inflammatory diseases. *Med Hypoth* (in press).

Further reading

General

Cook CG. Familial Mediterranean fever: underlying defect, clearer, but diagnostic problems persist. *Lancet* 1996; **348:** 1779–80.

Livneh A, Langevitz P, Zemer D, et al. The changing face of familial Mediterranean fever. *Semin Arthritis Rheum* 1996; **26:** 612–27.

Sohar E, Gafni J, Pras M, eds. Familial Mediterranean fever (FMF): proceedings of the 1st International Conference on FMF (Jerusalem, 1997). Tel Aviv: Freund, 1997.

Historical descriptions

Cattan R. Maladie périodique: dix observations et deux hypothèses. *Bull Mém Soc Méd Hôp Paris* 1954; **70:** 43–49.

Mamou H. Nouveaux cas de maladie périodique: remarque biologique et pathologique. *Bull Mém Soc Méd Hôp Paris* 1954; **70:** 520–24.

Reimann HA. Periodic disease: probable syndrome including periodic fever, benign paroxysmal peritonitis, cyclic neutropenia and intermittent arthralgia. *JAMA* 1948; **136:** 238–44.

Siegal S. Benign paroxysmal peritonitis. *Ann Intern Med* 1945; **23:** 1–21.

Clinical manifestations

Garcia-Gonzalez A, Weisman MH. The arthritis of familial Mediterranean fever. *Semin Arthritis Rheum* 1992; **22:** 139–50.

Gdalia A, Zamir S. Neurologic manifestations in familial Mediterranean fever. *Pediatr Neurol* 1993; **9:** 301–02.

Majeed HA, Quabazard Z, Farwana S, Harshani F. The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis): a six year study. *Q J Med* 1990; **75:** 607–16.

Zemer D, Livneh A, Pras M, Sohar E. The kidney in familial Mediterranean fever. *Contrib Nephrol* 1993; **102:** 187–97.

FMF in children

Gedalia A, Adar A, Gorodischer R. Familial Mediterranean fever in children. *J Rheumatol* 1992; **35:** 1–9.

Rawashdeh MO, Majeed HA. Familial Mediterranean fever in Arab children: the high prevalence and gene frequency. *Eur J Pediatr* 1996; **155:** 540–44.

Saatci U, Ozen S, Ozedmir S, et al. Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis. *Eur J Pediatr* 1997; **156:** 619–23.

Mediators of inflammation

Ayesh SK, Azar Y, Barghouti II, Ruedi JM, Babior BM, Matzner Y. Purification and characterization of a C5a inactivating enzyme from human peritoneal fluid. *Blood* 1995; **85:** 3503–09.

Erken E, Gunesacar R, Ozbek S, Konca K. Serum soluble interleukin 2 receptor levels in familial Mediterranean fever. *Ann Rheum Dis* 1996; **55:** 852–55.

Mege JI, Dilsen N, Sanguedolce V, et al. Overproduction of monocyte derived tumor necrosis factor alfa, interleukin (IL) 6, IL-8 and increased neutrophil superoxyde generation in Behçet's disease: a comparative study with familial Mediterranean fever. *J Rheumatol* 1993; **20:** 1544–49.

Schattner A, Gurevitz A, Zemer D, Hahn T. Induced TNF production in vitro as a test for familial Mediterranean fever. *QJM* 1996; **89:** 205–10.

Vasculitis

Ozdogen H, Arisoy N, Kasapcapur O, et al. Vasculitis in familial Mediterranean fever. *J Rheumatol* 1997; **24:** 323–27.

Ozen S, Saatci U, Balkanci F, Besbas N, Bakkaloglu A, Tacal T. Familial Mediterranean fever and polyarteritis nodosa. *Scand J Rheumatol* 1992; **21:** 3120–313.

Differential diagnosis

Drenth JP, Haagsma CJ, van-der Meer JW. Hyperimmunoglobulinemia D and periodic fever syndrome: the clinical spectrum in a series of 50 patients. (International Hyper-IgD Study Group). *Medicine* 1994; **74:** 133–44.

Knockaert DC, Vanneste LJ, Bobbaers JJ. Recurrent or episodic fever of unknown origin: review of 45 cases and survey of the literature. *Medicine* 1993; **72:** 184–96.

McDermott EM, Drenth JP, Powell RJ. Familial Mediterranean fever. *Lancet* 1996; **348:** 554–55.

Amyloidosis

Merry JP, Kenouch S. Familial Mediterranean fever-associated amylodosis. *Ren Fail* 1993; **15:** 379–84.

Sungur C, Sungur A, Ruacan S, et al. Diagnostic value of bone marrow biopsy in patients with renal disease secondary to familial Mediterranean fever. *Kidney Int* 1993; **44:** 834–36.

Treatment

Ben-Chetrit E, Scherrmann JM, Zylber-Katz E, Levy M. Colchicine disposition in patients with familial Mediterranean fever with renal impairment. *J Rheumatol* 1994; **21:** 710–13.

Ben-Chetrit E, Levy M. Colchicine update. *Sem Arthritis Rheum* (in press).

Livneh A, Zemer D, Langevitz P, Laor A, Sohar E, Pras M. Colchicine treatment of AA amyloidosis of familial Mediterranean fever: an analysis of factors affecting outcome. *Arthritis Rheum* 1994; **37:** 1804–11.

Majeed HA, Carroll JE, Khuffash FA, Hijazi Z. Long-term colchicine prophylaxis in children with familial Mediterranean fever (recurrent polyserositis). *J Pediatr* 1990; **116:** 997–99.