Familial Mediterranean Fever
A Bird's Eye View of the Recent Literature

edited by E. Ben-Chetrit

FMF pathophysiology

Authors: Gidron Y, Berkovitch M, Press J.
Title: Psychosocial correlates of incidence of attacks in children with Familial Mediterranean Fever.
J Behav Med 2003; 26: 95-104.
Summary: This study tested the relationship between psychosocial factors and the incidence of familial Mediterranean fever (FMF) attacks. Forty-five children with FMF were studied retrospectively. Parents assessed their child's hostility, perceived control, illness-behavior encouragement (IBE), family dysfunction, and reported number of attacks during the last 12 months. Hostility was positively correlated with the number of attacks, especially in children below age 10 and in girls. Family dysfunction was positively correlated with attacks in girls and in children at or above age 10. IBE was inversely correlated with attacks in older children. In children below age 10, the number of siblings was positively correlated with the attacks, and negatively correlated with attacks in the older group.
Psychosocial factors explained 27% of the variability in attacks, after controlling for age and number of siblings, with hostility remaining the only significant predictor of attacks.

Authors: Chae JJ, Komarow HD, Cheng J, Wood G, Raben N, Liu PP, Kastner DL.
Title: Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis.
Mol Cell 2003; 11: 591-604.
Summary: In order to study the physiologic role of pyrin, the authors generated mice expressing a truncated pyrin molecule that, similar to the one in FMF patients, retains the full PYRIN domain. Bacterial lipopolysaccharide (LPS) induced accentuated body temperatures and increased lethality in homozygous mutant mice. When stimulated, macrophages from these mice produced increased amounts of activated caspase-1 and, consequently, elevated levels of mature IL-1beta. Full-length pyrin competed *in vitro* with caspase-1 for binding to ASC, a known caspase-1 activator. Apoptosis was impaired in macrophages from pyrin-truncation mice through an IL-1-independent pathway. These data support a critical role for pyrin in the innate immune response, possibly by acting on ASC.

Authors: Dowds TA, Masumoto J, Chen FF, Ogura Y, Inohara N, Nunez G.
Title: Regulation of cryopyrin/Pypaf1 signaling by pyrin, the familial Mediterranean fever gene product.
Biochem Biophys Res Commun 2003; 302(3): 575-80.
Summary: In the present paper the authors report that co-expression of cryopyrin with its binding partner, ASC, induced both apoptosis and NF-kappaB activation. This signaling was mimicked by the oligomerization of ASC, suggesting that cryopyrin (a gene associated with familial cold urticaria and Muckle-Wells syndromes) activates downstream targets as reported for other Nod family members. Notably, pyrin, the product of the familial Mediterranean fever gene, inhibited cryopyrin-mediated apoptosis and NF-kappaB activation by disrupting the cryopyrin-ASC interaction. These results provide evidence for a cryopyrin signaling pathway activated through the induced proximity of ASC, which is negatively regulated by pyrin.

Authors: Kiraz S, Ertenli I, Ozturk MA, Haznedaroglu IC, Calguneri M, Atalar E, Ozbalkan Z, Kirazli S, Celik I.
Title: Increased soluble FAS suggests delayed apoptosis in familial Mediterranean fever complicated with amyloidosis.
J Rheumatol 2003; 30: 313-5.
Summary: In this cross sectional study, the authors investigated the role of soluble FAS (sFAS) protein in attack-free patients with familial Mediterranean fever (FMF) with and without amyloidosis. Twelve FMF patients without amyloidosis, 10 FMF patients with amyloidosis and 14 controls were enrolled in the study. Serum sFAS concentrations were studied by ELISA. The findings showed that serum sFAS concentrations were 4630 (2580-12,270), 1338 (453-3240), and 3430 (2110-5960) pg/ml in FMF patients without amyloidosis, FMF patients with amyloidosis, and controls, respectively. Intergroup differences were all statistically significant ($p < 0.05$). They conclude that elevated serum sFAS concentrations in attack-free FMF patients might be due to dysregulated apoptosis of polymorphonuclear leukocytes together with the ongoing subclinical inflammatory activity. On the other hand, decreased sFAS concentrations could contribute to the augmented apoptosis together with the alterations in immune response leading to the amyloidosis.

Authors: Notarnicola C, Didelot MN, Kone-Paut I, Seguret F, Demaille J, Touitou I.
Title: Reduced MEFV messenger RNA expression in patients with familial Mediterranean fever.
Arthritis Rheum 2002; 46: 2785-93.
Summary: Since most known mutations are conservative, the authors sought to determine how minor DNA defects can give rise to the dramatic phenotypic features seen in FMF. To address whether the molecular basis of the phenotype-genotype correlation could be related to altered MEFV messenger RNA (mRNA) expression, they quantified the relative abundance of MEFV transcripts in peripheral blood leukocytes from patients with FMF, healthy carriers of a single MEFV mutation, and healthy control subjects. They found significantly lower expression of MEFV mRNA in genetically ascertained FMF patients than in healthy controls. In healthy carriers, the mRNA levels were intermediate, suggesting a true dose-response relationship between the number of muta-

tions and the abundance of MEFV transcripts. The difference between healthy controls and healthy carriers was significant, demonstrating that the decrease in mRNA expression is related to a molecular defect independent of FMF symptoms. MEFV mRNA expression was also found to be a function of the type of mutations. The lowest MEFV levels were found in healthy carriers and patients with M694V.
These results demonstrate that MEFV message levels are related to both the genotype and the phenotype, and suggest that the pathophysiology of FMF relies on a quantitative defect of MEFV mRNA expression.

FMF and amyloidosis

Authors: Akar N, Hasipek M, Akar E, Ekim M, Yalcinkaya F, Cakar N.
Title: Serum amyloid A1 and tumor necrosis factor-alpha alleles in Turkish familial Mediterranean fever patients with and without amyloidosis.
Amyloid 2003; 10: 12-6.
Summary: Serum amyloid A is a serum precursor of AA amyloid that is induced by inflammatory cytokines including TNF-alpha. Analysis of SAA1.1 frequency in Turkish FMF-amyloidosis patients revealed a higher frequency compared to non FMF-amyloidosis patients, but the difference was not significant. On the other hand, the distribution of SAA1.1 homozygosity among FMF-amyloidosis patients was 55.5% compared to FMF-non-amyloidosis patients (30.8%), a difference which was statistically significant and revealed a 2.5 fold higher risk for the occurrence of amyloidosis. There was no significant difference between the controls and FMF patients with and without amyloidosis for the TNF-alpha-308 G-A allele. A finding worth noting was that all TNF-alpha-308 G-A carriers (n = 6) in thee FMF-amyloidosis group had SAA1.1 homozygosity compared to 2/11 in the FMF-non-amyloidosis group.

Authors: Baskin E, Saatci U, Ciliv G, Bakkaloglu A, Besbas N, Topaloglu R, Ozen S.
Title: Urinary glycosaminoglycans in the course of familial Mediterranean fever
Eur J Pediatr 2003; 162: 305-8.
Summary: In this study the authors examined the role of urinary glycosaminoglycans (GAG) in FMF and amyloidosis. The study group included 123 FMF patients without an attack and 11 patients with FMF-associated amyloidosis. Ten healthy children and 10 patients with primary nephrotic syndrome served as controls. In patients with amyloidosis, urinary GAG were lower than in patients with FMF, patients with nephrotic syndrome and controls. There was a significant negative correlation between the duration of the disease and urinary GAG (r = -043, P = 0.002). In 49 FMF patients with a low GAG, urinary GAG increased significantly after an increase in the colchicine. These results suggest that urinary glycosaminoglycan levels may be a predictor of amyloidosis in patients with familial Mediterranean fever. It was also suggested that effective colchicine doses may be monitored by following urinary glycosaminoglycan excretion.

Authors: Gershoni-Baruch R, Brik R, Zacks N, Shinawi M, Lidar M, Livneh A.
Title: The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever.
Arthritis Rheum 2003; 48: 1149-55.
Summary: In this study, the contribution of genotypes at the MEFV and SAA1 loci to disease severity and to the development of amyloidosis were analyzed. The results showed that the male:female ratio (154:123, or 1.3) was higher among patients with amyloidosis (40:22, or 1.8) compared with patients without amyloidosis (114:101, or 1.1). Logistic regression analysis showed that homozygosity for the M694V allele, the presence of the SAAalpha/alpha genotype and male sex were significantly and independently associated with renal amyloidosis. Disease severity was mainly influenced by MEFV mutations and was not associated with genotypes at the SAA1 locus. The SAA1 13T allele was rare, being associated mainly with the SAA gamma isoform, and not related to renal amyloidosis. These results support previous reports [Cazeneuve *et al*. (2000) Ben-Chetrit *et al*. (2000)].

Authors: Gershoni-Baruch R, Brik R, Lidar M, Shinawi M, Livneh A.
Title: Male sex coupled with articular manifestations cause a 4-fold increase in susceptibility to amyloidosis in patients with familial Mediterranean fever homozygous for the M694V-MEFV mutation.
J Rheumatol 2003; 30: 308-12.
Summary: The authors investigated the role of sex as an independent contributor to the phenotypic profile in FMF and further defined the factors affecting disease expression and severity. A total of 124 patients with FMF who were all homozygous for the M694V mutation, including 47 patients with nephropathic amyloidosis, were identified. A preponderance of male patients was documented (73:51; 1.4). The overall male:female ratio was significantly higher among patients with amyloidosis (32:15; 2.1) compared to patients without amyloidosis (41:36; 1.1).
FMF severity scores, independently calculated for the male and female patients, were equally high (9.5 ± 3.0 and 9.7 ± 2.8, respectively). The frequency of arthritic attacks, significantly higher in women than in men ($p = 0.015$), remained notably higher in male FMF patients with amyloidosis compared to male FMF patients without amyloidosis ($p = 0.002$). Significant correlation between arthritis attacks and amyloidosis was found ($R > 0.285$, $p < 0.001$). They conclude that susceptibility to renal amyloidosis is influenced both by sex and the occurrence of joint attacks, acting as two MEFV-independent factors.

Authors: Balci B, Tinaztepe K, Yilmaz E, Gucer S, Ozen S, Topaloglu R, Besbas N, Ozguc M, Bakkaloglu A.
Title: MEFV gene mutations in familial Mediterranean fever phenotype II patients with renal amyloidosis in childhood: a retrospective clinicopathological and molecular study.

Nephrol Dial Transplant 2002; 17(11): 1921-3.
Summary: In a group of patients clinically designated as phenotype II amyloidosis patients, renal amyloidosis develops without being preceded by typical attacks of the disease. In this study, the mutations of the MEFV gene were analysed in a group of patients clinically recognized as phenotype II. PCR-RFLP methods were used to analyse the M694V, M680I,V726A and E148Q mutations. The distribution of the four most common mutations among phenotype II patients was 38% for M694V, 8% for M680I, 4% for V726A and 4% for E148Q. The authors concluded that in phenotype II amyloidosis patients in Turkey, the distribution of the four common MEFV mutations was not significantly different from that found in all FMF patients with typical symptoms who do or do not develop amyloidosis.

FMF and colchicine

Authors: Oner A, Erdogan O, Demircin G, Bulbul M, Memis L.
Title: Efficacy of colchicine therapy in amyloid nephropathy of familial Mediterranean fever.
Pediatr Nephrol 2003; 18: 521-6.
Summary: This study investigated the effect of colchicine therapy on the outcome of amyloid nephropathy of familial Mediterranean fever (FMF) in childhood. The diagnosis of amyloidosis type AA was confirmed by renal biopsy in 38 patients. During a mean follow-up period of 30.5 months (range 6-88 months), the patients received colchicine therapy. While 24 of these patients were compliant with the treatment, 14 remained non-compliant. Of the 24 compliant patients, 19 had normal renal function at the onset; in 13 the proteinuria improved, in 5 patients it remained stable, and in 1 it deteriorated from a proteinuric to a nephrotic stage. Partial resolution of amyloidosis was demonstrated by repeat renal biopsy in 1 patient who showed a complete resolution of proteinuria. In contrast, none of the 14 non-compliant patients improved, and while only 1 patient was in renal failure initially, 10 patients deteriorated to renal failure during the follow-up period. The presence of tubulointerstitial injury at presentation adversely affected the prognosis.

FMF and ethnicity

Authors: Konstantopoulos K, Kanta A, Deltas C, Atamian V, Mavrogianni D, Tzioufas AG, Kollainis I, Ritis K, Moutsopoulos HM.
Title: Familial Mediterranean fever associated pyrin mutations in Greece.
Ann Rheum Dis 2003; 62: 479-81.
Summary: In this study the authors searched for pyrin mutations associated with familial Mediterranean fever (FMF) in Greece. Sixty-two patients fulfilling the Tel Hashomer diagnostic criteria for definite (33) or probable (29) FMF were studied. Eight point mutations of the pyrin gene were tested by standard methods. Of the 62 patients tested, 48 were Greek, 4 were Jewish, 7 were Armenian, and 3 were Arab. Forty-four patients were found to be homozygote for pyrin mutations; 11 patients were found to carry only one of the tested mutations; in 9 patients no mutations were detected. The authors concluded that the molecular detection of pyrin gene mutations seems to be useful in confirming suspected cases and in detecting asymptomatic cases of Mediterranean fever in Greece. Nevertheless, still in 15% no mutation was found.

Authors: La Regina M, Nucera G, Diaco M, Procopio A, Gasbarrini G, Notarnicola C, Kone-Paut I, Touitou I, Manna R.
Title: Familial Mediterranean fever is no longer a rare disease in Italy.
Eur J Hum Genet 2003; 11: 50-6.
Summary: Traditionally, Italians have been considered to be little affected by FMF, despite the geographical position of Italy (northern Mediterranean basin) and the migratory changes in its population. In this study the authors characterised the demographic, clinical and genetic features of FMF in Italy. Patients of Italian origin were recruited from those referred to Italian-French medical centres for FUO (Fever of Unknown Origin) or 'surgical' emergencies. Mutational analysis of the gene responsible for FMF (MEFV on 16p13.3) was performed, after which geno-phenotypical correlations were established. Italian FMF patients, 40 women and 31 men, aged from 3 to 75 years, have shown all the clinical manifestations indicative of FMF described in the literature, but with a lower incidence of amyloidosis. The genetic tests have been contributive in 42% of cases. The frequency of each different mutation has been similar to that found in a series of 'endemic' countries. Among Italians FMF seems to be more frequent than was believed in the past. The data presented are consistent with their geographical location and their history.

FMF: Genetic testing

Authors: Padeh S, Shinar Y, Pras E, Zemer D, Langevitz P, Pras M, Livneh A.
Title: Clinical and diagnostic value of genetic testing in 216 Israeli children with Familial Mediterranean fever.
J Rheumatol 2003; 30: 185-90.
Summary. In this paper the authors appraised the value of mutation analysis as a diagnostic test for FMF in symptomatic pediatric patients, and explored the possible correlations between MEFV genotypes and the diverse phenotypic expression of the disease. 216 children who met the clinical criteria for FMF underwent molecular genetic studies to detect the 3 most common mutations in the Israeli FMF patient population (M694V, V726A, E148Q). Of the 216 children, 82 (38.0%) had 2 of the tested mutations, 73 (33.8%) had only one mutation, and 61 (28.2%) had none of the mutations studied. M694V was the most frequent mutation, detected in 174 of 432 MEFV alleles (40.0%). The V726A mutation was found in 39 alleles (9.0%) and the E148Q mutation in 25 (5.8%). The severity score correlated with the number of mutations. Children with no mutations

presented at an older age compared to children with one or 2 mutations. Children homozygous for the M694V mutation presented at a younger age, had a higher severity score, and more commonly had arthritis.

Authors: Tunca M, Akar S, Hawkins PN, Booth SE, Sengul B, Yavuzsen TU, Oktem S, Soyturk M, Akkoc N, Booth DR.
Title: The significance of paired MEFV mutations in individuals without symptoms of familial Mediterranean fever.
Eur J Hum Genet 2002; 10: 786-9.
Summary: The majority of patients with familial Mediterranean fever (FMF) have identifiable mutations in both alleles of the MEFV gene, while some individuals with paired MEFV mutations do not have clinical symptoms of the disease. During family studies the authors identified 9 such individuals from six kindreds, most of whom either subsequently developed FMF or had other clinically significant inflammatory disease; one case benefited substantially from colchicine therapy.
Four individuals remained asymptomatic. Two further asymptomatic subjects with paired MEFV mutations were identified among 49 healthy controls from western Turkey, of whom a further 18.4% were simple heterozygotes. This carrier rate was higher than would be expected from the prevalence of FMF in this region, suggesting that penetrance of paired recognised pathogenic MEFV mutations may frequently be incomplete. It is suggested that MEFV genotyping results be interpreted with due caution, and follow-up of apparently asymptomatic subjects with paired mutationsis advisable.

Miscellaneous

Authors: Zissin R, Rathaus V, Gayer G, Shapiro-Feinberg M, Hertz M.
Title: CT findings in patients with familial Mediterranean fever during an acute abdominal attack
Br J Radiol 2003; 76: 22-5.
Summary: In this study the authors present the abdominal CT findings of patients with familial Mediterranean fever (FMF) examined during an acute abdominal attack. CT scans of 17 patients (10 women and 7 men; age range 11-45 years) were retrospectively reviewed. Attention was directed to mesenteric or peritoneal abnormalities and to the presence of appendiceal pathology. Characteristic CT findings of acute abdomen in FMF included mesenteric pathology (n = 12), mainly of engorged vessels with thickened mesenteric folds, mesenteric lymphadenopathy (n=6) and ascites (n=6). Signs of focal peritonitis were found in 4 patients. Radiologists should be familiar with such CT findings of peritoneal irritation in patients with FMF during an acute attack, and may suggest this clinical diagnosis in the proper clinical setting in a patient who has not been previously diagnosed.

Authors: Shabtai M, Ben-Haim M, Zemer D, Malinger-Saavedra P, Rosin D, Kuriansky J, Lustig S, Shabtai EL, Shapira Z, Ayalon A.
Title: Detrimental effects of cyclosporin A on long-term graft survival in familial Mediterranean fever renal allograft recipients: Experience of two transplantation centers.
Isr Med Assoc J 2002; 4 (Suppl. 11): 935-9.
Summary: In this study the authors compared long-term graft function and survival between cyclosporine A (CsA) - based and CsA-free immunosuppressive protocols in FMF recipients of renal allograft. Data on the FMF recipients were analyzed retrospectively. Graft survival and function and the incidence of acute rejection were correlated to graft source (living donor vs. cadaveric donor), colchicine dose, presence of proteinuria, and immunosuppression protocol (CsA-based triple drug therapy vs. azathioprine-prednisone alone). There were 35 FMF patients with primary renal grafts (13 from living donors and 22 from cadaveric donors. One-year survival was 94% and 96.6% for CsA-treated vs. non-CsA patients (not significant), but 5- and 10-year survival rates were 76% and 46%, compared to 94.5% and 86% respectively (P = 0.05 at 5 years and 0.001 at 10 years). Mean serum creatinine at the time of data collection was 2.3 ± 1.5 mg/dl in the CsA group vs. 1.6 ± 0.7 mg/dl in the AZA-Pred group (P = 0.02). There were 14 and 13 reversible rejection episodes in the AZA-Pred and CsA groups respectively (not significant). The authors conclude that CsA may exert detrimental effects on long-term renal graft function and survival in FMF patients.

Authors: Fidder HH, Chowers Y, Lidar M, Sternberg M, Langevitz P, Livneh A.
Title: Crohn disease in patients with familial Mediterranean fever.
Medicine (Baltimore) 2002; 81: 411-6.
Summary: In the present study the authors determined the prevalence of Crohn disease in FMF and characterized FMF-CD patients clinically and genetically. Control groups of ethnically and sex-matched patients suffering from either Crohn disease or FMF alone were used for comparison. They identified 7 patients with concomitant Crohn disease and FMF, which was more than the expected prevalence in the general population ($p = 0.03$). Crohn disease presented at a significantly later age in the FMF-CD group. Disease severity and other characteristics of Crohn disease were comparable to the CD control group. Contrary to the FMF control group patients, FMF in FMF-CD patients was characterized by a higher frequency of attacks ($p < 0.05$) and increased prevalence of amyloidosis ($p < 0.02$). The overall severity score was similar in both groups. The authors conclude that Crohn disease appears to be more prevalent in FMF and presents later than in patients without FMF. FMF in this group of patients shows a higher attack frequency and is more often complicated by amyloidosis.