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

edited by E. Ben-Chetrit

Phenotype-Genotype correlation

Authors: Majeed HA, El-Shanti H, Al-Khateeb MS, Rabaiha ZA.

Title: Genotype/phenotype correlations in Arab patients with familial Mediterranean fever.

Semin Arthritis Rheum 2002 Jun; 31: 371-376 .

Summary: The authors studied the phenotype/genotype correlations in Arab patients with familial Mediterranean fever (FMF).

They found that out of the 278 patients, only 50 (18%) had 2 mutations identified, and 76 (27%) other patients had only 1 mutation identified. The M694V/M694V and the M694V/V726A and M694I/M694I genotypes were the most common (30%, 16%, and 14%, respectively) in these 50 patients.

Three homozygous genotypes (M694V/M694V, V726A/V726A, and M694I/M694I) and 2 compound heterozygous genotypes (M694V/V726A and V726A/M680I) accounted for 78% of mutations. The difference in the mean severity score of the M694V/M694V group and the V726A/V726A and M694I/M694I groups was statistically significant. They concluded that the genotypes M694V/M694V and M694V/V726A have a severe clinical course in Arab patients with FMF, whereas the M694I/M694I is associated with mild disease.

Authors: Gershoni-Baruch R, Brik R, Shinawi M, Livneh A.

Title: The differential contribution of MEFV mutant alleles to the clinical profile of familial Mediterranean fever.

Eur J Hum Genet 2002 Feb; 10: 145-9.

Summary: The aims of this study were to characterise the phenotypic profile associated with the major MEFV mutations. The authors investigated 220 FMF patients, in whom both FMF alleles have been identified and found that different genotypes were characterised by a specific allelic related clinical profile and penetrance. Homozygotes for the M694V mutation and the complex V726A-E148Q allele were the most severely affected and often endure renal amyloidosis. Homozygotes for the M680I and V726A alleles and compound heterozygotes for either the M694V or the V726A-E148Q alleles in combination with either the E148Q, the V726A or the M680I alleles were significantly less severely affected. The morbidity associated with the complex V726A-E148Q allele by far outweighed that associated with the V726A allele, bearing evidence to the fact that the E148Q mutation is not a benign polymorphism.

Authors: Booth DR, Lachmann HJ, Gillmore JD, Booth SE, Hawkins PN.

Title: Prevalence and significance of the familial Mediterranean fever gene mutation encoding pyrin Q148.

QJM 2001; 94: 527-31.

Summary: In this study the authors looked for the prevalence of pyrin Q148 in healthy British, Indian and Chinese subjects. The gene frequency was also sought in 50 British Caucasian patients with inflammatory arthritis, 25 of whom had AA amyloidosis, five Punjabi Indians with AA amyloidosis complicating inflammatory arthritis, and seven British Caucasian patients with uncharacterized longstanding fever syndromes. The allele frequency for pyrin Q148 was 21%, 15% and 0%, respectively, among Punjab Indian, Chinese and Caucasian British controls, and was significantly increased among the patients with AA amyloidosis and the patients with obscure fever syndromes ($p < 0.01$). Pyrin Q148 is a polymorphism and occurs widely in global terms, and, although it may cause FMF

when associated with certain other MEFV mutations, homozygosity for Q148 alone must usually be insufficient to produce FMF in the populations studied. The association of pyrin Q148 with AA amyloidosis and with obscure chronic inflammatory diseases suggests the variant may augment inflammation non-specifically.

Authors: Gershoni-Baruch R, Shinawi M, Leah K, Badarnah K, Brik R.

Title: Familial Mediterranean fever: prevalence, penetrance and genetic drift.

Eur J Hum Genet 2001; 9: 634-7.

Summary: The authors investigated the frequencies and distribution of five founder mutations in 146 FMF patients of Arab and Jewish descent and in 1173 healthy individuals of pertinent ethnic groups. The five mutations (M680I, M694V, V726A, E148Q, M694I), accounted for 91% of FMF chromosomes in their patients. Mutation M694V, predominant in North African Jews, was observed in all patients other than Ashkenazi Jews; mutation V726A was prevalent among all patients other than North African Jews; mutations M694I and M680I were mainly confined to Arab patients. Overall carrier rates, for four mutations (M680I, M694V, V726A, E148Q), were extremely high in their healthy cohort, composed of Ashkenazi ($n = 407$); Moroccan ($n = 243$); Iraqi Jews ($n = 205$); and Muslim Arabs ($n = 318$); calculated at 1 : 4.5; 1 : 4.7; 1 : 3.5 and 1 : 4.3 respectively.

Authors: Kogan A, Shinar Y, Lidar M, Revivo A, Langevitz P, Padeh S, Pras M, Livneh A.

Title: Common MEFV mutations among Jewish ethnic groups in Israel: high frequency of carrier and phenotype III states and absence of a perceptible biological advantage for the carrier state.

Am J Med Genet 2001; 102: 272-6.

Summary: The authors investigated the carrier rate of the most common MEFV mutations among different Jewish ethnic groups in Israel. They also tried to elucidate the possible biological advantage that the heterozygote state may confer. Three hundred Ashkenazi, 101 Iraqi, and 120 Moroccan Jews were screened for the E148Q, V726A, and M694V mutations (at least two most common mutations per group), with a resulting overall carrier frequency in the respective ethnic group of 14%, 29%, and 21%. No difference in morbidity between Ashkenazi carriers and non-carriers of MEFV mutations was discerned. The frequency of subjects with two MEFV mutations but not expressing FMF (phenotype III) was 1:300 in Ashkenazi Jews and 1:25 in Iraqi Jews, exceeding the reported rate of overt FMF in these ethnic groups by 40-240 fold. These results affirm the high carrier rate among the studied Jewish ethnic groups in Israel and suggest that most subjects with FMF mutations are unaffected.

Inflammation

Authors: Shiohara M, Taniguchi S, Masumoto J, Yasui K, Koike K, Komiyama A, Sagara J.

Title: ASC, which is composed of a PYD and a CARD, is up-regulated by inflammation and apoptosis in human neutrophils.

Biochem Biophys Res Commun 2002; 293: 1314-8.

Summary: ASC is an adaptor protein that is composed of two protein-protein interaction domains, a PYRIN domain (PYD), and a caspase-recruitment domain (CARD). Recently, ASC was identified as a binding partner of pyrin, which is the product of MEFV, a gene

causing familial Mediterranean fever (FMF). Mutations in MEFV result in defects in control of neutrophil-mediated inflammation. In the present study the authors focused on the expression of ASC in neutrophils. They showed that ASC is increased in neutrophils in severe inflammatory sites such as gangrenous appendicitis. Then, they tested whether proinflammatory mediators induce ASC using peripheral blood neutrophils in vitro. They found that ASC expression was transiently up-regulated by IL-1 α , IL-1 β , IFN- α , IFN- γ , TNF α , and LPS. ASC was also increased by incubation with either anti-Fas antibody or recombinant soluble Fas ligand. These findings suggest that up-regulation of ASC is closely associated with inflammation and apoptosis in neutrophils.

Authors: Notarnicola C, Didelot MN, Seguret F, Demaille J, Touitou I.

Title: Enhanced cytokine mRNA levels in attack-free patients with familial Mediterranean fever.

Genes Immun 2002; 3: 43-5.

Summary: In this study the authors investigated cytokine expression at the transcriptional level, in patients that could be genetically ascertained. They have measured the transcript abundance of tumor necrosis factor α , interleukin-1 β , interleukin-6 and interleukin-8, in circulating leukocytes and showed that these were more elevated in attack-free FMF patients than in controls. There was no significant difference according to MEFV genotype or colchicine treatment. These results suggest that cytokine transcriptional pathways are misregulated in attack-free FMF patients, and further supports the hypothesis that these patients have subclinical inflammation between attacks.

Authors: Medlej-Hashim M, Petit I, Adib S, Chouery E, Salem N, Delague V, Rawashdeh M, Mansour I, Lefranc G, Naman R, Loiselet J, Lecron JC, Serre JL, Megarbane A.

Title: Familial Mediterranean Fever: association of elevated IgD plasma levels with specific MEFV mutations.

Eur J Hum Genet 2001; 9: 849-54.

Summary: The authors tried to evaluate the association between known FMF-related mutations and IgD levels in confirmed patients, as well as the correlation between those levels and the presence of specific clinical signs in 148 Lebanese and Jordanian FMF patients. They found that homozygotic status for M694V, and to a lesser extent V726A, was associated with increased risk for higher IgD plasma levels, regardless of colchicine use. Elevated IgD plasma levels were also correlated with the severity of FMF manifestations, and especially with arthritis.

Authors: Korkmaz C, Ozdogan H, Kasapcopur O, Yazici H.

Title: Acute phase response in familial Mediterranean fever.

Ann Rheum Dis 2002; 61: 79-81.

Summary: The authors tested the hypothesis that not all acute phase reactants respond in the same way during attacks of familial Mediterranean fever (FMF) and that there is a subclinical acute phase response (APR) in a proportion of patients during the interval between attacks. A marked APR was seen during the FMF attacks which was comparable with that obtained in the diseased control groups (patients with juvenile idiopathic arthritis or with various infectious diseases). CRP was the only acute phase protein that was raised during all attacks. Neither thrombocytosis nor an increase in ferritin levels was noted in any attack. Serum albumin levels remained unchanged. In two thirds of the patients with FMF a continuing APR was seen in between the attacks. The authors concluded that platelet, ferritin, and albumin responses are not part of the significant APR seen during short lived attacks of FMF, and inflammation continues in about two thirds of the patients during an attack-free period.

Authors: Abedat S, Urieli-Shoval S, Shapira E, Calko S, Ben-Chetrit E, Matzner Y.

Title: Effect of colchicine and cytokines on MEFV expression and C5a inhibitor activity in human primary fibroblast cultures. *Isr Med Assoc J* 2002; 4: 7-12.

Summary: The aim of the study was to investigate the effect of colchicine and certain inflammatory cytokines (IL-1 β , TNF- α , IFN- α , IFN- γ) on MEFV expression and C5a inhibitor activity in neutrophils and primary peritoneal fibroblast culture. The authors found that MEFV expression in neutrophils was high and could not be induced further. Its expression in the peritoneal fibroblasts was lower than in neutrophils and could be induced using colchicine and cytokines parallel with induction of C5a inhibitor activity. Semi-quantitative RT-PCR assays enabled estimation of MEFV induction by the cytokines at 10-100-fold and could not be further increased by concomitant addition of colchicine. They conclude that serosal tissues, which are afflicted in FMF, express colchicine and cytokine-inducible MEFV and contain inducible C5a inhibitor activity.

Authors: Ertenli I, Kiraz S, Ozturk MA, Haznedaroglu IC, Celik I, Kirazli S, Calguneri M.

Title: Plasma fibronectin- and thrombospondin-adhesive molecules during acute attacks and attack-free periods of familial Mediterranean fever.

Rheumatol Int 2001; 20: 217-20.

Summary: The authors assessed plasma concentrations of fibronectin (FN) and thrombospondin (TSP) during acute attacks and attack-free periods of patients with familial Mediterranean fever (FMF). Erythrocyte sedimentation rate, C-reactive protein, and white blood cell count were evaluated concurrently. They found that the plasma levels of FN and TSP increase during acute attacks. Significant correlations were found between FN and TSP levels and the concentrations of acute-phase response indicators ($P < 0.05$). They suggest that the two matrix glycoproteins may play precipitating and/or regulatory roles in the inflammatory processes of these attacks.

Authors: Poland DC, Drenth JP, Rabinovitz E, Livneh A, Bijzet J, van het Hof B, van Dijk W.

Title: Specific glycosylation of α (1)-acid glycoprotein characterises patients with familial Mediterranean fever and obligatory carriers of MEFV.

Ann Rheum Dis 2001; 60: 777-80.

Summary: The authors tried to determine the state of inflammation in homozygotic and heterozygotic MEFV genotypes by measuring CRP, SAA and the rate of glycosylation of the acute phase protein, α (1)-acid glycoprotein (AGP). They found that FMF attacks were associated with an increase ($p < 0.05$) in the serum inflammation parameters CRP, SAA, and AGP. The glycosylation of AGP showed an increase ($p < 0.05$) in fucosylated AGP glycoforms, whereas the branching of the glycans remained unaffected. The glycosylation of AGP in the MEFV carrier group, compared with that in a healthy control group, was characterised by a significant increase ($p < 0.05$) in branching of the glycans, whereas the fucosylation remained unaffected. Based upon these findings they suggest that an FMF-specific release of cytokines, resulting in a different glycosylation of AGP between a homozygotic and heterozygotic MEFV genotype.

Authors: Langevitz P, Livneh A, Neumann L, Buskila D, Shemer J, Amolsky D, Pras M.

Title: Prevalence of ischemic heart disease in patients with familial Mediterranean fever.

Isr Med Assoc J 2001; 3: 9-12.

Summary: The authors studied the effect of inflammation and its prevention on the occurrence of IHD, using FMF as a model. They looked for the presence of IHD and its risk factors in 290 FMF patients aged 40 years or more, and in two control groups-233 spouses of the FMF patients, and 126 patients with inflammatory diseases obtained from other outpatient clinics. FMF patients were also compared with age and gender-matched individuals from the population reference data of the Israel Ministry of Health. They found that the prevalence of IHD in FMF patients was significantly lower than in the group of controls from other outpatient clinics (15.5% vs. 30.2%, $P < 0.05$) and comparable with their spouses (11.2%) and with the matched general population in Israel (16%). Their findings suggest that despite the evidence of recurrent inflammation, colchicine-treated FMF patients are not more predisposed to IHD than the normal population.

Pediatrics

Authors: Ince E, Cakar N, Tekin M, Kendirli T, Ozkaya N, Akar N, Yalcinkaya F.

Title: Arthritis in children with familial Mediterranean fever.

Rheumatol Int 2002; 21: 213-7.

Summary: The clinical spectrum of arthritis in 124 children with well-documented familial Mediterranean fever (FMF) was investigated in a retrospective study. Mean age at the onset of FMF arthritis was 5.93 ± 3.50 years. 75% of the patients were under 10 years of age. Arthritis in the lower extremities, upper extremities, and small joints of the hands and feet was noted in 122 (98%), 17 (14%), and 15 (12%) patients, respectively. Although most of the arthritic attacks resolved within a few weeks, 12 (10%) patients developed protracted arthritis persisting for months. Amyloidosis was demonstrated in 17 (14%) patients who had not received colchicine treatment. Mutation analysis confirmed the diagnosis of FMF in 77 (62%) children. The authors claim that the clinical presentations of arthritis in FMF may be an important source of diagnostic confusion and that mutation analysis may be of value in these situations.

Authors: Brik R, Shinawi M, Kasinetz L, Gershoni-Baruch R.

Title: The musculoskeletal manifestations of familial Mediterranean fever in children genetically diagnosed with the disease.

Arthritis Rheum 2001; 44: 1416-9.

Summary: The authors describe the articular and musculoskeletal manifestations in a group of 136 pediatric patients who were found by genetic screening to be homozygous for FMF. They found that acute episodes of monoarthritis were the most common musculoskeletal manifestation of FMF in children bearing the M964V mutation. Nevertheless children with the M694V mutation may also present with diverse nonspecific musculoskeletal manifestations. They suggest that genetic screening for FMF would help in the evaluation of unexplained musculoskeletal symptoms in children of Mediterranean extraction.

Vasculitis

Authors: Ben-Chetrit E, Cohen R, Chajek-Shaul T.

Title: Familial mediterranean fever and Behcet's disease - Are they associated?

J Rheumatol 2002; 29: 530-4.

Summary: This study tested whether the coexistence of familial Mediterranean fever (FMF) and Behcet's disease (BD) is more frequent than expected and whether each disease affects the severity of the other. They found that none of 353 patients with FMF had concomitant BD. Sixteen patients with BD bore MEFV mutations, 2 of whom were symptomatic homozygotes and had concomitant FMF. No patient with BD with a single MEFV mutation had FMF. Both BD groups (with or without MEFV mutations) were similar in their clinical manifestations and disease course. They concluded that BD and FMF are 2 separate entities that have a mild trend toward a higher than expected association. However, there was no mutual effect of FMF on BD or vice versa.

Amyloidosis

Authors: Shtrasburg S, Pras M, Gal R, Salai M, Livneh A.

Title: Inhibition of the second phase of amyloidogenesis in a mouse model by a single-dose colchicine regimen.

J Lab Clin Med 2001; 138: 107-11.

Summary: In this study the authors tried to determine whether colchicine inhibits the second phase of amyloidogenesis (deposition of amyloid fibrils) and to study the time correlate of such an effect. Amyloid was induced in Swiss male mice with AEF and AgNO(3) (an inflammatory stimulus). Two amyloid induction protocols were used: a standard protocol, in which AEF and AgNO(3) were administered concurrently, and a prolonged protocol, in which the administration of AgNO(3) was delayed by 24 hours or 7 days. They found that Colchicine inhibited the second phase of amyloidogenesis. Its best effect was achieved when administered 48 hours after initiation of AgNO(3) injections. The pattern of colchicine-inhibition-in-time in the standard and the prolonged amyloid induction protocols was similar, indicating that colchicine exerts inhibition through its effect on the inflammatory stimulus (AgNO(3)). These findings suggest that (1) colchicine suppresses amyloidogenesis in the late (second) stage and that (2) this suppression is possibly related to the anti-inflammatory effect of colchicine.

Miscellaneous

Authors: Ben-Chetrit E, Ben-Chetrit A.

Title: Familial Mediterranean fever and menstruation.

Brit J Obstet Gynaecol 2001; 108: 403-7

Summary: The authors looked for the prevalence, the nature and the genotype correlation of menstruation associated familial Mediterranean fever attacks. One hundred and forty-one female patients with familial Mediterranean fever were studied. They found ten out of 141 familial Mediterranean fever female patients (7%) had menstruation-associated familial Mediterranean fever attacks. These patients varied in their disease age of onset and disease duration. Increase of colchicine dose, daily or during the perimenstrual period or oral contraceptives were beneficial in preventing these familial Mediterranean fever attacks. No correlation was found with specific mutations causing familial Mediterranean fever. They speculate that a decrease in oestrogen level during menstruation may have a role in this unique manifestation of familial Mediterranean fever.