
Familial Mediterranean Fever

A bird's eye review of the recent literature

edited by Eldad Ben-Chetrit

FMF and other diseases

Title: Evaluation of common mutations in the Mediterranean fever gene in Multiple Sclerosis patients: is it a susceptibility gene?

Authors: Unal A, Dursun A, Emre U, Tascilar NF, Ankarali H.

J Neurol Sci 2010; 294: 38-42.

Summary: This study was designed to determine if known mutations in pyrin domain of MEFV gene are involved in MS and associated with MS morbidity. Fifty-three patients with MS and 66 healthy subjects, who were all Turkish, were included in this study. Five pyrin gene mutations (E148Q, M680I, M694V, M694I and V726A) were tested in the patients and controls. Pyrin gene mutations were found in 20 of the 53 MS patients (38%) and in seven of the 66 healthy subjects (11%). The frequencies of M694V, E148Q and V726A mutations were significantly higher in the patients than in the healthy subjects ($p=0.02$, $p=0.013$, $p=0.004$ respectively).

Title: Missense mutations in the MEFV gene are associated with fibromyalgia syndrome and correlate with elevated IL-1beta plasma levels.

Authors: Feng J, Zhang Z, Li W, Shen X, Song W, Yang C, Chang F, Longmate J, Marek C, St Amand RP, Krontriris TG, Shively JE, Sommer SS.

PLoS One 2009; 4: e8480.

Summary: Patients with fibromyalgia and their parents have high plasma levels of the chemokines MCP-1 and eotaxin, providing evidence for both a genetic and an immunological/inflammatory origin for the syndrome. In a search for a candidate gene affecting inflammatory pathways, among five screened in their patient samples (100 probands with FMS and their parents), the authors found 10 rare and one common mutation in the MEFV gene. These data provide evidence that rare missense variants of the MEFV gene are, collectively, associated with risk of FMS and are present in a subset of 15% of FMS patients. This subset had, on average, high levels of plasma IL-1beta ($p=0.019$) compared to FMS patients without rare variants. Since misregulation of IL-1beta expression has been predicted for patients with mutations in the MEFV gene, the authors conclude that patients heterozygous for rare missense variants of this gene may be predisposed to FMS, possibly triggered by environmental factors.

Title: The Association of inflammatory bowel disease and Mediterranean fever gene (MEFV) mutations in Turkish children.

Authors: Uslu N, Yüce A, Demir H, Saltik-Temizel IN, Usta Y, Yilmaz E, Beşbaş N, Gürakan F, Ozen H, Ozen S.

Dig Dis Sci 2010 Mar 21.(Epub ahead of print)

Summary: The authors investigated MEFV mutations and prevalence of FMF disease in Turkish children with IBD. Sixteen patients with ulcerative colitis (UC), 14 with Crohn's disease (CD) and three with indeterminate colitis (IC) were enrolled in the study. All patients were screened for 12 common MEFV mutations. MEFV mutations were detected in 17 of 66 (25.7%) alleles. Seven patients were also diagnosed as FMF (21.2%). M694V was the leading mutation, and as a disease-causing mutation, it was found to be significantly more frequent in CD patients than UC patients. Disease-causing MEFV mutations and FMF disease rate were increased among the patients with IBD. The increase was prominent among CD patients, whereas in UC the rate was similar to the Turkish healthy control population.

Title: Genetic variation in the familial Mediterranean fever gene (MEFV) and risk for Crohn's disease and ulcerative colitis.

Authors: Villani AC, Lemire M, Louis E, Silverberg MS, Collette C, Fortin G, Nimmo ER, Renaud Y, Brunet S, Libioulle C, Belaiche J, Bitton A, Gaudet D, Cohen A, Langelier D, Rioux JD, Arnott ID, Wild GE, Rutgeerts P, Satsangi J, Vermeire S, Hudson TJ, Franchimont D.

PLoS One 2009; 4:e7154

Summary: The NLRP3 region was recently reported to be associated with Crohn's disease (CD) susceptibility. The authors sought to evaluate MEFV as an inflammatory bowel disease (IBD) susceptibility gene. Comprehensive genetic screening of the MEFV region in the Belgian exploratory sample identified SNPs located in the MEFV 5' haplotype block that were significantly associated with UC but not in CD. Sequencing and subsequent genotyping of variants located in this associated haplotype block identified three synonymous variants (D102D/rs224225, G138G/rs224224, A165A/rs224223) and one non-synonymous variant (R202Q/rs224222) located in MEFV exon 2 that were significantly associated with UC. No consistent associations were observed in additional Canadian and Scottish sample sets. None of the NLRP3 common variants were associated with UC in the Belgian-Canadian UC samples and no significant interactions were observed between NLRP3 and MEFV that could explain the observed flip-flop of the rs224222 risk allele. The present results suggest that common variants in the MEFV region do not contribute to CD and UC susceptibility.

Potential genetic modifiers

Title: The role of the R92Q TNFRSF1A mutation in patients with familial mediterranean fever.

Authors: Marek-Yagel D, Berkun Y, Padeh S, Lidar M, Shinar Y, Bar-Joseph I, Reznik-Wolf H, Langevitz P, Livneh A, Pras E.

Arthritis Care Res (Hoboken) 2010 Apr 9. [Epub ahead of print]

Summary: The aim of the study was to define the frequency of the R92Q Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) mutation in patients with familial Mediterranean fever (FMF) and to study the role of this mutation in FMF. Ninety two FMF patients and 250 controls were genotyped for the R92Q mutation. R92Q was found in 6% of the controls, with an especially high carrier rate among Moroccan Jews (8%). R92Q was found in 3 of the 92 FMF patients (3.2%). All 3 patients showed partial response to colchicine. R92Q was not found in patients unresponsive to colchicine, nor was it found in patients with amyloidosis. The frequency of the R92Q mutation in FMF patients is comparable to that of controls. Despite the fact that TRAPS and FMF share common biochemical pathways no evidence was found for an interaction between these two genes.

Title: Involvement of the modifier gene of a human Mendelian disorder in a negative selection process.

Authors: Jéru I, Hayrapetyan H, Duquesnoy P, Cochet E, Serre JL, Feingold J, Grateau G, Sarkisian T, Jeanpierre M, Amselem S.

PLoS One 2009; 4(10): e7676.

Summary: SAA1 is one of the few modifiers identified in humans which influence the risk of renal amyloidosis (RA) in patients with familial Mediterranean fever (FMF). Indeed, the SAA1 alpha homozygous genotype and the p.Met694Val homozygous genotype at the MEFV locus are two main risk factors for RA. In the present study the authors investigated two neighboring countries: Armenia, where RA is frequent (24%), and Karabakh, where RA is rare (2.5%). Sequencing of MEFV revealed similar frequencies of p.Met694Val homozygotes in the two groups of patients. However, a major deficit of SAA1 alpha homozygotes was found among Karabakhian patients (4%) as compared to Armenian patients (24%). The excess of SAA1alpha homozygotes among Armenian patients could be explained by the recruitment of patients with severe phenotypes. In contrast, a population-based study revealed that the deficit of alpha/alpha among Karabakhian patients would result from a negative selection against carriers of this genotype.

Title: Expression of the familial Mediterranean fever gene is regulated by nonsense-mediated decay.

Authors: Grandemange S, Soler S, Touitou I
Hum Mol Genet 2009; 18(24): 4746-55.

Summary: The FMF protein named pyrin or marenostrin (P/M) is thought to be involved in regulating innate immunity but its function remains subject to controversy. Recent studies postulate that a defect in MEFV expression regula-

tion may play a role in FMF physiopathology. The group of the authors, along with others, has identified several alternatively spliced MEFV transcripts in leukocytes. Since alternative splicing and nonsense-mediated decay (NMD) pathways are usually coupled in the post-transcriptional regulation of gene expression, they hypothesised that NMD could contribute to the regulation of the MEFV gene. To address this issue, they examined the effect of indirect and direct inhibition of NMD on expression of the MEFV transcripts in THP1, monocyte and neutrophil cells. They showed that MEFV is the first auto-inflammatory gene regulated by NMD in both a cell- and transcript-specific manner. These results introduce a novel hypothesis that variation of NMD efficiency could play an important role in FMF physiopathology as a potent phenotypic modifier.

Phenotype-genotype in FMF

Title: The spectrum of MEFV clinical presentations – is it familial Mediterranean fever only?

Authors: Ben-Chetrit E, Peleg H, Amar S, Heyman SN.
Rheumatology (Oxford) 2009; 48(11): 1455-9.

Summary: In the present study, the authors tried to find out whether the MEFV gene is associated with or responsible for clinical conditions other than FMF. They looked for patients who presented with signs and symptoms not typical for FMF but carried MEFV mutations. They also searched for reports about similar conditions in the English medical literature. The authors encountered four patients carrying MEFV mutations who presented with distinct clinical presentations not typical of FMF. They also identified additional reports about MEFV-related non-FMF disease entities such as palindromic rheumatism. These findings suggest that the MEFV gene is associated with clinical conditions other than FMF. Furthermore, a correct diagnosis of these MEFV gene mutation-associated syndromes will justify a therapeutic trial with colchicine, thereby relieving suffering of many patients who up to now have been misdiagnosed.

Title: Clinical features and functional significance of the P369S/R408Q variant in pyrin, the familial Mediterranean fever protein.

Authors: Ryan JG, Masters SL, Booty MG, Habal N, Alexander JD, Barham BK, Remmers EF, Barron KS, Kastner DL, Aksentjevich I.
Ann Rheum Dis 2010; 69(7): 1383-8.

Summary: The aim of the study was to characterise the phenotype of patients with P369S and R408Q MEFV substitutions and to determine their functional significance. A database of genetic tests undertaken at the US National Institutes of Health was interrogated. Symptoms and signs were classified. Coimmunoprecipitation techniques were employed to determine the variants' effects on pyrin/PSTPIP1 interactions. A total of 40 symptomatic and 4 asymptomatic family members with these substitutions were identified. P369S and R408Q were found in cis, and cosegregated in all patients

sequenced. Clinical details were available on 22 patients. In all, 5 patients had symptoms and signs fulfilling a clinical diagnosis of FMF, and 15 received colchicine. Coimmunoprecipitation studies demonstrated that these pyrin variants did not affect binding to PSTPIP1. P369S/R408Q substitutions are associated with a highly variable phenotype, and are infrequently associated with typical FMF symptoms, however a trial of colchicine is warranted in all.

Title: Clinical and genetic features of familial Mediterranean fever in Japan.

Authors: Tsuchiya-Suzuki A, Yazaki M, Nakamura A, Yamazaki K, Agematsu K, Matsuda M, Ikeda S
J Rheumatol 2009; 36(8): 1671-6. Epub 2009 Jun 16.

Summary: The aim of the study was to elucidate the clinical characteristics of FMF in Japanese patients. The authors analysed clinical and genetic data of 80 patients based on the results of a nationwide questionnaire survey and review of the literature. From clinical findings of 80 Japanese patients, high-grade fever was observed in 98.8%, chest attacks (pleuritis symptoms) in 61.2%, abdominal attacks (peritonitis symptoms) in 55.0%, and arthritis in 27.5%. Twenty-four percent of patients experienced their first attacks before 10 years of age, 40% in their teens, and 36% after age 20 years. Colchicine was effective in many patients at a relatively low dose (<1.0 mg/day). AA amyloidosis was seen in only 1 patient. Common MEFV mutation patterns were E148Q/M694I (25.0%), M694I alone (17.5%), and L110P/E148Q/M694I (17.5%), and no patient carried the M694V mutation. A larger than expected number of patients with FMF exist in Japan, and the clinical presentation of Japanese FMF patients seems to be relatively milder than those of Mediterranean FMF patients.

Laboratory tests in FMF

Title: Neutrophil-derived S100A12 as novel biomarker of inflammation in familial Mediterranean fever.

Authors: Kallinich T, Wittkowski H, Keitzer R, Roth J, Foell D
Ann Rheum Dis 2010; 69(4): 677-82. Epub 2009 Sep 17

Summary: The damage-associated molecular pattern (DAMP) protein S100A12 has proven to be a sensitive marker for disease activity and inflammation in numerous inflammatory disorders. The aim of this study was to analyse the role of S100A12 in FMF. Fifty-two children and adolescents with a clinical and/or genetic diagnosis of FMF were prospectively followed-up over 18 months. During clinical visits, erythrocyte sedimentation rate, C-reactive protein, serum amyloid A and S100A12 serum concentrations were determined. Serum concentrations of S100A12 were excessively increased in patients with a mean increase of about 290-fold in active FMF above normal controls. S100A12 decreased significantly after introduction of colchicine therapy. In contrast to classical markers of inflammation, S100A12 was significantly elevated in clinically unaffected homozygous

MEFV gene mutation carriers, indicating subclinical inflammation. S100A12 is a valuable biomarker for monitoring disease activity and response to colchicine treatment.

Title: Antibodies directed to cyclic citrullinated peptides in familial Mediterranean fever.

Authors: Uyanik A, Albayrak F, Uyanik MH, Dursun H, Keles M, Cetinkaya R
Rheumatol Int 2010; 30(4): 467-71.

Summary: The aim of this study was to find the prevalence of anti-cyclic citrullinated peptide (anti-CCP) in patients with familial Mediterranean fever. Serum levels of the anti-CCP antibodies was measured in patients with FMF (n=55) and healthy controls (n=43). Serum levels of rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, ferritin, erythrocyte sedimentation rate (ESR), and white blood cell (WBC) were also measured in all the samples. Fibrinogen, ferritin, erythrocyte sedimentation rate (ESR), and RF levels were normal in the patient and the control groups ($p>0.05$). There was a significant difference in anti-CCP between the patient and the control groups ($p=0.008$). There was a positive correlation between arthritis and anti-CCP ($p=0.001$). In patients without arthritis, there was no significant relationship between abdominal pain or fever and anti-CCP ($p>0.05$). Anti-CCP levels increased in FMF patients with arthritis independent from acute phase reactants such as CRP, ESR, and fibrinogen.

Title: Anti-cyclic citrullinated peptide antibodies are not associated with familial Mediterranean fever.

Authors: Karatay S, Yildirim K, Erdal A, Uzkeser H, Erdem FH, Yanmaz V. J
Back. Musculoskelet Rehabil 2010 ; 23(1): 21-3.

Summary: This study investigated the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies in familial Mediterranean fever (FMF) patients and controls. Forty-nine patients with FMF were enrolled (23 had a history of arthritis during attacks and 26 had no such history) with two control groups; 20 patients with rheumatoid arthritis (RA) and 30 healthy individuals. Erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), rheumatoid factor (RF), and anti-CCP antibody levels were measured. In RA patients' ESR and CRP levels, frequency of RF, and anti-CCP antibody levels were significantly higher than in both FMF patients and healthy controls ($p 0.001$). Moreover, anti-CCP was negative in all healthy controls as well as in all FMF patients

Pathophysiology of FMF

Title: Pyrin modulates the intracellular distribution of PSTPIP1.

Authors: Waite AL, Schaner P, Richards N, Balci-Peynircioglu B, Masters SL, Brydges SD, Fox M, Hong A, Yilmaz E, Kastner DL, Reinherz EL, Gumucio DL
PLoS One 2009; 4(7): e6147.

Summary: PSTPIP1 is a cytoskeleton-associated adaptor protein that links PEST-type phosphatases to their substrates. Mutations in PSTPIP1 cause PAPA syndrome (Pyogenic sterile Arthritis, Pyoderma gangrenosum, and Acne). PSTPIP1 binds to pyrin and mutations in pyrin result in familial Mediterranean fever (FMF). In the present study the authors show: 1. PSTPIP1, which has homology to membrane-deforming BAR proteins, forms homodimers and generates membrane-associated filaments in native and transfected cells. 2. PSTPIP1 filament network is dependent upon an intact tubulin cytoskeleton and the distribution of this network can be modulated by pyrin, indicating that this is a dynamic structure. 3. Pyrin can recruit PSTPIP1 into aggregations (specks) of ASC, another pyrin binding protein. ASC specks are associated with inflammasome activity.

Title: The crystal structure of human pyrin b30.2 domain: implications for mutations associated with familial Mediterranean fever.

Authors: Weinert C, Grütter C, Roschitzki-Voser H, Mittl PR, Grütter MG

J Mol Biol 2009; 394(2): 226-36.

Summary: The aim of the study was to investigate the molecular consequences of FMF-associated mutations. The authors determined the crystal structure of the pyrin B30.2 domain at 1.35-Å resolution. The comparison with other B30.2/ligand complex structures revealed a shallow cavity, which seems to be involved in binding the pyrin ligand. The bottom of this cavity is covered mainly with hydrophobic amino acids, suggesting that pyrin recognises its ligand by hydrophobic contacts and surface complementarities. FMF-associated mutations cluster around two sites on the B30.2 surface. Approximately two thirds, including those mutations with the most severe disease outcomes, are observed in the vicinity of the predicted peptide binding site, suggesting that they will have a direct impact on ligand binding. Although most FMF-associated mutations are solvent exposed, several will modify the main-chain conformation of loops. The experimental crystal structure of the pyrin B30.2 domain serves as a basis for an accurate modelling of these mutations.

Treatment and outcome

Title: Unresponsiveness to colchicine therapy in patients with familial Mediterranean fever homozygous for the M694V mutation.

Authors: Soylemezoglu O, Arga M, Fidan K, Gonen S, Emeksiz HC, Hasanoglu E, Buyan N.

J Rheumatol 2010; 37(1): 182-9. Epub 2009 Dec 15.

Summary: The aim of the study was to define the frequency of mutation type, genotype-phenotype correlation, and response to colchicine treatment in patients with FMF. This study included 222 pediatric FMF patients. All patients were investigated for 6 MEFV mutations. M694V/M694V was

denoted Group A, M694V/Other Group B, and Other/Other, Group C. Complete colchicine response was significantly lower while the rate of unresponsiveness was significantly higher in Group A compared to Groups B and C. No differences were found between the phenotypic features of 3 groups. Group C had the lowest rate of proteinuria development ($p=0.024$). All the amyloidosis patients were in Group A. These results indicate that the M694V/M694V mutation is associated with lower response to colchicine treatment.

A note: This study supports the already known notion that 694 homozygosity have the worst disease course and risk for amyloidosis because of lower response to colchicine.

Title: Pregnancy outcomes in women with familial Mediterranean fever receiving colchicine: is amniocentesis justified?

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

Arthritis Care Res (Hoboken) 2010; 62(2): 143-8.

Summary: The aim of the study was to evaluate the outcome of pregnancies in women with familial Mediterranean fever (FMF) who are taking colchicine, and to reconsider the justification for amniocentesis in these women. The outcome of 179 pregnancies in a group of women with FMF taking colchicine was compared with the outcome of 197 pregnancies in women with FMF who did not take colchicine during pregnancy and with 312 pregnancies in another cohort of healthy pregnant women of similar age and ethnicity. There was no difference in the 3 groups regarding early abortions, late abortions, or congenital malformations. Treatment with colchicine during pregnancy in patients with FMF is beneficial in controlling the disease while not affecting the outcome of the pregnancy; there is no justification for amniocentesis in women taking colchicine.

Title: Decrease in the rate of secondary amyloidosis in Turkish children with FMF: are we doing better?

Authors: Akse-Onal V, Sağ E, Ozen S, Bakkaloglu A, Cakar N, Besbas N, Gucer S.

Eur J Pediatr 2010; 169(8): 971-4.

Summary: The main objective of this study was to analyse whether there has been a substantial decrease of secondary amyloidosis in Turkey and possible effective factors. Clinical features of the patients diagnosed with secondary amyloidosis between the years 1978 and 1990 were compared with those diagnosed between 2000 and 2009. There were no significant differences between the two patient groups according to gender, age, age of onset, disease duration, and disease severity. There was, however, a clear decrease in the percentage of biopsies with secondary amyloidosis from 12.1% (1978–1990) to 2% (after 2000; $p<0.001$). These results have shown that there has been a significant decrease in the rate of secondary amyloidosis in Turkey. The main reason for this decrease is better medical care with increased awareness and treatment of the disease.