Familial Mediterranean fever
A bird's eye review of the recent literature

edited by Eldad Ben-Chetrit

Diagnosis

Title: A new set of criteria for the diagnosis of familial Mediterranean fever in childhood.
Authors: Yalçinkaya F, Ozen S, Ozçakar ZB, Aktay N, Cakar N, Düzova A, Kasapçopur O, Elhan AH, Doganay B, Ekim M, Kara N, Uncu N, Bakkaloglu A.
Rheumatology (Oxford) 2009; 48: 395-8. Epub 2009 Feb 4.
Summary: The aim of the present study was to validate the most widely used diagnostic Tel Hashomer criteria in children and to establish a new set of criteria for use in childhood. The study group consisted of 170 recently diagnosed FMF patients who had mutations at both alleles. Controls were consecutive patients without FMF (n=141) who had episodes of fever and clinical features mimicking that of FMF. The sensitivity and specificity of the Tel Hashomer criteria in this study group were 98.8 and 54.6%, respectively. Multiple logistic regression analysis showed that 5 (fever, abdominal pain, chest pain, arthritis and family history of FMF) of 35 candidate criteria discriminate FMF from controls with a sensitivity and specificity of 88.8 and 92.2%, respectively. The authors conclude that the specificity of the Tel Hashomer criteria was low in diagnosing the FMF patients in childhood. They offer a new set of criteria for the diagnosis of FMF.
Editor's note: We believe that any new set of criteria should include presence of MEFV mutations

Pathogenesis

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: 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) - an autoinflammatory disease. PSTPIP1 binds to pyrin and mutations in pyrin result in familial Mediterranean fever (FMF). Since disease-associated mutations in PSTPIP1 enhance pyrin binding, PAPA syndrome and FMF are thought to share a common pathoetiology. The studies outlined in this paper describe several new aspects of PSTPIP1 and pyrin interactions. These interactions involve tubulin and ASC (another pyrin binding protein) and shed more light on the autoinflammatory process.

Title: Pyrin and ASC co-localize to cellular sites that are rich in polymerizing actin.
Authors: Waite AL, Schaner P, Hu C, Richards N, Balci-Peynircioglu B, Hong A, Fox M, Gumucio DL.
Exp Biol Med (Maywood) 2009; 234: 40-52.
Summary: While it is known that pyrin is expressed in myeloid cells and several fibroblastic cell types, the exact function of pyrin in these cells and the mechanism underlying the pathological effect of pyrin mutations have yet to be revealed. In the present study the authors document that in migrating human monocytes, pyrin protein is dramatically polarized at the leading edge, where it co-localizes with polymerizing actin. Furthermore, ASC (Apoptosis-associated Speck protein with CARD domain, a critical component of the inflammasome), is also located at the leading edge in migrating monocytes. The co-localization of pyrin and ASC together at such sites may provide an important link between cytoskeletal signaling and inflammasome function.

Title: The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF-kappaB through its N-terminal fragment.
Authors: Chae JJ, Wood G, Richard K, Jaffe H, Colburn NT, Masters SL, Gumucio DL, Shoham NG, Kastner DL.
Blood 2008;112:1794-803. Epub 2008 Jun 24
Summary: It is already known that pyrin regulates caspase-1 activation and IL-1beta production through interaction of its N-terminal PYD motif with the ASC adaptor protein, and also modulates IL-1beta production by interaction of its C-terminal B30.2 domain with the catalytic domains of caspase-1. In the present study the authors show that pyrin is cleaved by caspase-1 at Asp330, a site remote from the B30.2 domain. The N-terminal cleaved fragment interacts with the p65 subunit of NF-kappaB. This interaction enhances entrance of p65 into the nucleus while the interaction of N-terminal pyrin with IkappaB-alpha induced potentiates NF-kappaB activation. These observations support a new pyrin/caspase-1 pathway (by-passing ASC) for NF-kappaB activation.

Title: Serum adenosine deaminase activities during acute attacks and attack-free periods of familial Mediterranean fever.
Authors: Kisacik B, Akdogan A, Yilmaz G, Karadag O, Yilmaz FM, Koklu S, Yuksel O, Ertenli AI, Kiraz S.
Eur J Intern Med 2009;20:44-7. Epub 2008 Jun 20.
Summary: Adenosine deaminase (ADA) is an enzyme widely distribute in tissues and body fluids. Circulating levels of ADA have been shown to increase in several inflammatory conditions. This study was designed to evaluate the serum ADA in patients with FMF during acute attacks and

attack-free periods. Patients with acute attack had significantly higher ADA levels than both patients with attack-free periods and healthy controls. The authors suggest that ADA may have a role in the cytokine network of the inflammatory cascade of FMF.

Title: Increased asymmetric dimethylarginine levels in young men with familial Mediterranean fever (FMF): is it early evidence of interaction between inflammation and endothelial dysfunction in FMF?
Authors: Terekeci HM, Oktenli C, Ozgurtas T, Nalbant S, Top C, Celik S, Tapan S, Kucukardali Y, Sanisoglu YS, Solmazgul E, Sahan B, Sayan O.
J Rheumatol 2008; 35: 2024-9. Epub 2008 Sep 1.
Summary: Asymmetric dimethylarginine (ADMA) is considered an indicator for endothelial dysfunction and a sensitive marker for cardiovascular risk. In the present study the authors determine serum ADMA concentrations in patients with FMF and age- and body mass index-matched healthy volunteers. They found that in patients with FMF, ADMA and CRP levels were higher than in healthy controls. Patients taking colchicine had lower serum ADMA levels than non-colchicine users. There was a positive strong correlation between ADMA and CRP in patients with FMF. These data imply that higher serum ADMA levels in FMF may indicate inflammation-related "endothelial dysfunction".

Atherosclerosis and FMF

Title: Intima-media thickening in patients with familial Mediterranean fever.
Authors: Ugurlu S, Seyahi E, Cetinkaya F, Ozbakir F, Balci H, Ozdogan H.
Rheumatology (Oxford). 2009; 48: 911-5. Epub 2009 May 28.
Summary: The aim of this study was to assess the frequency of atherosclerotic plaques and intima-media thickness (IMT) in patients with FMF and suitable controls (including SLE patients). Subclinical atherosclerosis was assessed by using B-mode ultrasonography (USG). Based upon their findings the authors claim that increased atherosclerosis defined as the presence of plaques was not observed in patients with FMF. However, there was an increased in Carotid - and Femoral-IMT among patients with FMF. The significance of this finding should be further assessed.

Title: Evaluation of intima media thickness of the common and internal carotid arteries with inflammatory markers in familial Mediterranean fever as possible predictors for atherosclerosis.
Authors: Bilginer Y, Ozaltin F, Basaran C, Duzova A, Besbas N, Topaloglu R, Ozen S, Bakkaloglu A.
Rheumatol Int 2008; 28: 1211-6. Epub 2008 May 24.
Summary: The aim of the present study was to determine whether intima-media thickness (IMT) of the common carotid arteries (CCA) and internal carotid arteries (ICA) is increased compared with healthy controls. All the patients were homozygous or compound heterozygous for MEFV mutations. IMT of both CCA and ICA was evaluated with a high resolution B-mode ultrasonography. Intima media thickness of the common carotid artery was found to be significantly higher in FMF patients when compared to those in healthy. The authors conclude that intima media thickness-may be an early predictor of atherosclerosis. They hypothesize that it may result from subclinical inflammation FMF since childhood.

Title: Platelet activation in patients with Familial Mediterranean Fever.
Authors: Coban E, Adanir H.
Platelets 2008; 19: 405-8.
Summary: Increased platelet activation and aggregation are central processes in the pathophysiology of atherosclerosis. Increased platelet activity is associated with increased platelet volume. Mean platelet volume (MPV), a determinant of platelet function, is a newly emerging risk factor for atherothrombosis. The present study was designed to evaluate levels of MPV in FMF patients compared with healthy subjects. The levels of MPV were significantly higher in the FMF group. The MPV levels were negatively correlated with duration of colchicine treatment. The authors suggest that patients with FMF tend to have increased platelet activation. Increased platelet activity could contribute to increasing atherosclerosis.

MEFV mutations in other diseases

Title: Detection of MEFV gene mutations in patients with inflammatory bowel disease.
Authors: Yurtcu E, Gokcan H, Yilmaz U, Sahin FI.
Genet Test Mol Biomarkers 2009; 13: 87-90.
Summary: In the current study MEFV mutations were studied in 47 patients with IBD and 25 healthy individuals and their effects on the clinical status of IBD were investigated. Twelve mutations were analyzed by reverse hybridization after multiplex PCR amplification of DNA samples. The authors did not find an association between FMF gene mutations and IBD phenotypic characteristics. However, in patients without Mediterranean fever (MEFV) mutations, extraintestinal disease frequencies were higher.
Editor's note: Does it mean that MEFV mutations prevent extraintestinal manifestations of IBD?

Title: MEFV mutations in Japanese rheumatoid arthritis patients.
Authors: Migita K, Nakamura T, Maeda Y, Miyashita T, Koga T, Tanaka M, Nakamura M, Komori A, Ishibashi H, Origuchi T, Ida H, Kawasaki E, Yasunami M, Eguchi K.
Clin Exp Rheumatol 2008; 26: 1091-4.
Summary: The aim of this study was to assess the involvement of MEFV gene mutations among Japanese rheumatoid arthritis patients with or without amyloid A (AA) amyloidosis. The frequency of the MEFV mutations, which were

identified in Japanese FMF patients, was determined in 126 Japanese RA patients and 76 Japanese healthy subjects. The M694I mutation was not observed among RA patients and healthy subjects. Allele frequency of R408Q, P369S, E148Q, L110P mutations account respectively for 3.3%, 3.9%, 23.7%, 9.2% in healthy subjects and 5.6%, 6.7%, 24.2%, 9.5% in RA patients. The overall mutation rate was comparable between the RA patients and healthy subjects, as well as between the RA patients with and without amyloidosis. This study shows that the MEFV gene mutations may not be a genetic factor affecting the susceptibility of RA or the development of amyloidosis in the Japanese population.

Title: MEFV mutations in systemic onset juvenile idiopathic arthritis.
Authors: Ayaz NA, Ozen S, Bilginer Y, Ergüven M, Taşkiran E, Yilmaz E, Beşbaş N, Topaloğlu R, Bakkaloğlu A.
Rheumatology (Oxford) 2009; 48: 23-5. Epub 2008 Nov 4.
Summary: The aim of the study was to search for MEFV mutations in patients with SoJIA and see whether these mutations had an effect on disease course or complications. The authors found that disease-causing mutations were found to be significantly more frequent in the SoJIA patients than the general population ($P < 0.01$). Among these, M694V was the leading mutation with a frequency of 10% in SoJIA. Patients carrying MEFV mutations were among the most resistant cases requiring biological therapy.

Title: MEFV mutations modify the clinical presentation of Henoch-Schönlein purpura.
Authors: Ozçakar ZB, Yalçinkaya F, Cakar N, Acar B, Kasapçopur O, Ugüten D, Soy D, Kara N, Uncu N, Arisoy N, Ekim M.
J Rheumatol. 2008; 35: 2427-9. Epub 2008 Oct 1.
Summary: The aim of the study was to investigate the prevalence of MEFV gene mutations in Turkish patients with Henoch-Schönlein purpura (HSP) but with no symptoms of familial Mediterranean fever (FMF). In addition, the authors assessed the clinical and laboratory characteristics of HSP patients with and without MEFV mutations. Twenty-seven of eighty (34%) patients were found to be heterozygous for one of the screened MEFV mutations; p.M694V in 16, p.M680I in 5, p.V726A in 3, and p.E148Q in 3 patients. Patients with MEFV mutations were younger than those without mutations and they had edema and arthritis more frequently. Also, the frequencies of elevated erythrocyte sedimentation rate and C-reactive protein values were found to be significantly higher in patients who had MEFV mutations. The authors concluded that MEFV mutations are important susceptibility factors for the development of HSP and also affect its clinical presentation.

Title: The rate and significance of Mediterranean fever gene mutations in patients with ankylosing spondylitis: a three-month, longitudinal clinical study.
Authors: Cinar M, Dinc A, Simsek I, Erdem H, Koc B, Pay S, Tunca Y, Kilic S, Gul D.
Rheumatol Int 2008; 29: 37-42. Epub 2008 Jul 3.
Summary: The aim of this study, was to investigate the prevalence of MEFVgene mutations in patients with ankylosing spondylitis (AS) and assessing their clinical significance. Ninety-five consecutive patients (12 women, 83 men) with active AS were included in the study. The frequency of the eight most common MEFV mutations: M694V, V726A, E148Q, M680I, M694I, P369S, F479L, and the R761H were determined. 30.5% of AS patients were found to have at least one mutation. No clinical or laboratory difference between MEFV mutation carriers and non-carriers was found.

Genetics and environment

Title: Familial Mediterranean fever with a single MEFV mutation: where is the second hit?
Authors: Booty MG, Chae JJ, Masters SL, Remmers EF, Barham B, Le JM, Barron KS, HollandSM, Kastner DL, Aksentijevich I.
Arthritis Rheum 2009; 60: 1851-61.
Summary: Familial Mediterranean fever (FMF) has traditionally been considered an autosomal-recessive disease; however, it has been observed that a substantial number of patients with clinical FMF possess only 1 demonstrable MEFV mutation. The purpose of this study was to perform an extensive search for a second MEFV mutation in 46 patients diagnosed clinically as having FMF and carrying only 1 high-penetrance FMF mutation. A second MEFV mutation was not identified in any of the patients who were screened. Haplotype analysis did not identify a common haplotype that might be associated with the transmission of a second FMF allele. Western blots did not demonstrate a significant difference in pyrin levels between patients with a single mutation and those with a double mutation; however, FMF patients of both types showed higher protein expression as compared with controls and with non-FMF patients with active inflammation. Screening of genes encoding pyrin-interacting proteins identified rare mutations in a small number of patients, suggesting the possibility of digenic inheritance. It seems that complete MEFV sequencing in heterozygote patients is not likely to yield a second mutation. Screening for the set of the most common mutations and detection of a single mutation appears to be sufficient in the presence of clinical symptoms for the diagnosis of FMF and the initiation of a trial of colchicine.

Title: Clinical disease among patients heterozygous for familial Mediterranean fever.
Authors: Marek-Yagel D, Berkun Y, Padeh S, Abu A, Reznik-Wolf H, Livneh A, Pras M, Pras E.
Arthritis Rheum 2009; 60: 1862-6.
Summary: In this study the authors aimed to define the molecular basis of familial Mediterranean fever (FMF) in patients with only 1 mutation in the MEFV gene. Their analysis included full sequencing of complementary DNA (cDNA) samples and multiplex ligation-dependent probe

amplification analysis. In patients with first-degree relatives with FMF, haplotype analysis was also performed. A second mutation was not found in 18 out of the 20 patients studied. Analysis of single-nucleotide polymorphisms along the cDNA ruled out a lack of expression of 1 of the alleles. In 2 of the 3 families in which more than 1 sibling had FMF, the authors showed that the affected siblings inherited a different MEFV allele from the parent who did not have the MEFV mutation. These findings are highly consistent with the existence of a clinical phenotype among some patients who are heterozygous for FMF and could explain the vertical transmission in some families.

Title: Characterization of new mutations in the 5'-flanking region of the familial Mediterranean fever gene.
Authors: Notarnicola C, Boizet-Bonhoure B, de Santa Barbara P, Osta MA, Cattan D, Touitou I.
Genes Immun 2009; 10: 273-9. Epub 2009 Mar 5.
Summary: Genetic diagnosis of FMF has developed since the discovery of the causative gene MEFV in 1997. As many patients could not be confirmed genetically by routine exon screening these authors searched for mutations in the 5'-flanking region of this gene. They found six novel sequence variants in a region extending -825 bp upstream of the first translated codon. Investigation of the sequence variants found in two patients demonstrated that c.-614C>G resulted in a 70% decrease in promoter activity, whereas c.-382C>T induced a 100% increase in activity, when compared to the wild type. They also observed specific DNA-protein binding to both wild-type sites, suggesting that transcription factors may bind to these sequences to modulate MEFV expression.

Title: MEFV gene 3'-UTR Alu repeat polymorphisms in patients with familial Mediterranean fever.
Authors: Ustek D, Ekmekçi C, Oku B, Coşan F, Cakiris A, Abaci N, Celik S, Kamali S, Hatemi G, Kasapçopur O, Ozdoğan H, Gül A.
Clin Exp Rheumatol 2008; 26 (4 Suppl. 50): S72-6.
Summary: This study aimed to investigate the promoter region and 3'-UTR polymorphisms of the MEFV gene in a group of FMF patients with no coding region mutations. The study group consisted of 289 patients with FMF and 103 healthy controls. After screening all 10 exons in the patients with none of the 5 common mutations, the authors identified 36 patients (12.5%) who had no coding region mutations. Analysis of the 3'-UTR region in these patients showed two Alu repeats (AluSx and AluSq), which were located in the 3'-UTR of the reference mRNA sequence. Sequencing of the 3'-UTR of the MEFV gene showed several SNPs that were clustered in 2 haplotypes. When they genotyped all study groups for two of the 3'-UTR SNPs (rs2741918 and rs450021), they observed a significant increase in the frequency of heterozygotes for the 3'-UTR haplotypes in the FMF patients with no coding region polymorphisms compared to the healthy controls. This study showed a group of 3'-UTR polymorphisms in the MEFV gene that are clustered in two haplotypes. These findings may suggest a role for 3'-UTR sequences in the regulation of MEFV expression.

Title: Disease severity in children and adolescents with familial Mediterranean fever: a comparative study to explore environmental effects on a monogenic disease.
Authors: Ozen S, Aktay N, Lainka E, Duzova A, Bakkaloglu A, Kallinich T.
Ann Rheum Dis 2009; 68: 246-8. Epub 2008 Sep 18.
Summary: It has been suggested that environmental factors affect the phenotype of FMF patients. In the present study the authors compared disease severity in Turkish children with FMF, living in Turkey and Germany. They found that according to the modified Sheba Center score, 78.2% of patients from the group living in Turkey had a severe course compared with 34.1% from the group living in Germany. These results suggest that the environment affects the phenotype of FMF.

FMF in the world

Authors: Tsuchiya-Suzuki A, Yazaki M, Nakamura A, Yamazaki K, Agematsu K, Matsuda M, Ikeda SI.
Title: Clinical and Genetic Features of Familial Mediterranean Fever in Japan.
J Rheumatol 2009 June 16. [Epub ahead of print].
Summary: In this survey the authors try to elucidate the clinical characteristics of FMF in Japanese patients. They found that a larger than expected number of patients with FMF exists in Japan and that the clinical presentation of Japanese FMF patients seems to be relatively milder than those of Mediterranean FMF patients. AA amyloidosis rarely occurs in Japanese patients, probably due to difference in patterns of the MEFV genotype between Japanese and Mediterranean patients.