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

edited by E. Ben-Chetrit

Pathogenesis

Authors: Chae JJ, Wood G, Masters SL, Richard K, Park G, Smith BJ, Kastner DL.
Title: The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1beta production.
Proc Natl Acad Sci U S A 2006; 103: 9982-7.
Summary: Pyrin, the protein mutated in FMF, regulates caspase-1 activation and consequently IL-1beta production through cognate interaction of its N-terminal PYRIN motif with the ASC adaptor protein. However, the preponderance of mutations reside in pyrin's C-terminal B30.2 domain. In this excellent study the authors demonstrate direct interaction of this domain with the p20 and p10 catalytic subunits of caspase-1. The C-terminal B30.2 domain of pyrin is necessary and sufficient for this interaction, and binding was reduced by FMF-associated B30.2 mutations. Full-length pyrin attenuated IL-1beta production in cells transfected with a caspase-1/IL-1beta construct, an effect diminished by FMF-associated B30.2 mutations and in B30.2 deletion mutants. These data support a direct, ASC-independent effect of pyrin on IL-1beta activation and suggest heightened IL-1 responsiveness as one factor selecting for pyrin mutations.

Clinical Features

Authors: Lidar M, Yaqubov M, Zaks N, Ben-Horin S, Langevitz P, Livneh A.
Title: The prodrome: a prominent yet overlooked pre-attack manifestation of familial Mediterranean fever.
J Rheumatol 2006 33: 1089-92.
Summary: The aim of the study was to identify and characterize pre-attack symptoms (prodrome) in patients with familial Mediterranean fever (FMF). Forty-eight patients with FMF whose attacks are preceded by a prodromal period composed the study population. Clinical, demographic, and genetic characteristics of the study group were compared to those of a control group of 48 patients with FMF whose attacks begin without a premonitory phase. A prodrome was experienced by about 50% of the patients. In affected patients prodrome recurs in most attacks, lasts a mean of 20 hours, and manifests with either a mildly unpleasant sensation at the site of the forthcoming spell (discomfort prodrome), or with a spectrum of physical, emotional, and neuropsychological complaints (variant prodrome). The 2 types of prodromata are frequently accompanied by a host of constitutional symptoms.

Authors: Akman-Demir G, Gul A, Gurol E, Ozdogan H, Bahar S, Oge AE, Gurvit H, Saruhan-Direskeneli G, Yazici H, Eraksoy M.
Title: Inflammatory/demyelinating central nervous system involvement in familial Mediterranean fever (FMF): coincidence or association?
J Neurol 2006 Mar 6; [Epub ahead of print]

Summary: Central nervous system (CNS) involvement in FMF is uncommon, but recently cases with multiple sclerosis (MS) and FMF have been reported. In the present study the authors assess patients with both FMF and MS, in order to clarify any relationship between FMF and MS, and to evaluate disease characteristics. There were 12 patients with FMF, who developed a CNS disorder with multi-focal white matter lesions. Nine patients (including two siblings) had definite MS according to clinical and MRI findings. The rate of FMF among the FMF patients with definite MS was almost 4 times the expected prevalence in Turkey. These series including a sibling pair concordant for FMF and MS may suggest that similar genetic susceptibility and environmental factors might be responsible, although coincidence still remains a possibility. A prospective study on a larger sample seems to be justified.

Authors: Lachmann HJ, Sengul B, Yavuzsen TU, Booth DR, Booth SE, Bybee A, Gallimore JR, Soyturk M, Akar S, Tunca M, Hawkins PN.
Title: Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations.
Rheumatology (Oxford) 2006; 45: 746-50.
Summary: The aim of this study was to prospectively monitor inflammatory activity over a prolonged period in a cohort of Turkish patients with FMF, their healthy relatives and healthy controls and to relate this to their MEFV genotypes. Substantial acute phase reactivity was seen among the patients with FMF during attacks (median SAA 693 mg/l, CRP 115mg/l). Between attacks there was also some inflammatory activity (median SAA 6 mg/l, CRP 4 mg/l). Asymptomatic MEFV heterozygotes had elevated acute phase proteins compared to wild type subjects. Substantial sub-clinical inflammation occurs widely and over prolonged periods in patients with FMF, indicating that the relatively infrequent clinically overt attacks represent the 'tip of the iceberg' in this disorder. Up-regulation of the acute phase response among carriers of FMF may augment their innate host response and contribute to better resistance to infection.

Diagnosis of FMF

Authors: Tchernitchko D, Moutereau S, Legendre M, Delahaye A, Cazeneuve C, Lacombe C, Grateau G, Amselem S.
Title: MEFV analysis is of particularly weak diagnostic value for recurrent fevers in Western European Caucasian patients.
Arthritis Rheum 2005; 52: 3603-5.
Summary: FMF is particularly common in Mediterranean populations, while other populations are rarely affected. MEFV gene analysis provides the only objective diagnostic criterion for FMF. However, the spectrum of MEFV mutations, which was first established in classically affected populations, remains insufficiently studied in other populations. The purpose of this study was to assess involvement of MEFV in the phenotype of western European Caucasian patients with a clinical diagnosis of FMF. Mutation analysis was performed in 208 Caucasian patients from western Europe, by screening for the most common MEFV mutations in exons 2, 3, 5, and 10, and by sequencing the promoter region and the whole MEFV coding sequence in 21 of these patients. None of the patients carried 2 mutated alleles. Only 2 patients carried 1 mutated allele. FMF-like syndromes in western European Caucasian populations cannot be explained by MEFV mutations. These results should be helpful in avoiding laborious and costly MEFV molecular analyses that, at the population level, seem to be of poor diagnostic value in the case of western European Caucasian patients, and rather should prompt a search for other causes in those patients.

Genetics

Authors: Tchernitchko DO, Gerard-Blanluet M, Legendre M, Cazeneuve C, Grateau G, Amselem S.
Title: Intrafamilial segregation analysis of the p.E148Q MEFV allele in familial Mediterranean fever.
Ann Rheum Dis 2006 Feb 13; [Epub ahead of print]
Summary: In the absence of any functional test, epidemiologic studies and/or pedigree analyses are the only means to prove the deleterious character of the sequence variations causing FMF. Here the author studied the segregation of the E148Q allele within FMF families. They found that the segregation analysis of this allele was compatible with a Mendelian autosomal recessive transmission of the disease phenotype in only three families. In 15 out of 18 families, segregation was partly or completely defective. The p.E148Q allele was not transmitted to 14 of 19 (74%) affected children. This shows that there is no evidence of preferential transmission of p.E148Q from heterozygous parents to their affected offspring. MEFV is not involved in the clinical manifestations of several patients carrying this variant. Considering p.E148Q as a benign polymorphism should reduce the possibility of false positive diagnoses, while highlighting genetic heterogeneity in FMF.

Phenotype/Genotype

Authors: Grimaldi MP, Candore G, Vasto S, Caruso M, Caimi G, Hoffmann E, Colonna-Romano G, Lio D, Shinar Y, Franceschi C, Caruso C.
Title: Role of the pyrin M694V (A2080G) allele in acute myocardial infarction and longevity: a study in the Sicilian population.
J Leukoc Biol 2006; 79: 611-5.
Summary: A proinflammatory genotype seems to contribute significantly to the risk of developing coronary heart disease (CHD). Conversely, the susceptibility alleles to inflammatory disease should be infrequent in the genetic background favoring longevity. To evaluate whether inflammatory alleles of pyrin, the gene responsible for familial Mediterranean fever (FMF) may play an opposite role in CHD and in longevity, the authors examined three FMF-associated mutations, M694V, M694I, and V726A, encoded by the FMF gene (MEFV) in 121 patients affected by acute myocardial infarction (AMI), in 68 centenarians, and in 196 age-matched controls from Sicily. The pro-inflammatory M694V mutation was the only one found to be over-represented significantly in CHD patients and under-represented in the elderly, and intermediate values were in healthy, young controls. So, according to these results, they suggest that carrying the pro-inflammatory M694V pyrin allele may increase the risk to develop AMI. Conversely, the wild-type pyrin genotype may predispose to a greater chance to live longer in a modern environment. All these data indicate a strong relationship among inflammation, genetics, CHD, and longevity.

FMF and the endocrine system

Authors: Tansu S, Omer O, Fahrettin K, Sebnem G, Mevlut B, Mustafa K, Munis D.
Title: Adrenal axis functions in patients with familial Mediterranean fever.
Clin Rheumatol 2006; 25: 458-61.
Summary: It is unclear what are the effects of FMF in itself on the endocrine system. There is a large body of evidence to show that cytokines (IL-1, IL-6 and TNF-alpha) activate the hypothalamic-pituitary-adrenal (HPA) axis. In the present study the authors investigated the HPA axis in FMF patients without amyloidosis. ACTH stimulation test was performed on healthy subjects and during attack period in 21 FMF patients. In the patient group, same test was repeated during remission period. Peak cortisol levels were significantly higher in the attack period than those in the remission period of patients ($p<0.05$).It seems that the cytokines play a role on the activation of the HPA axis. HPA axis is more activated in an FMF attack. Since adrenal hormones are increased in acute inflammatory events it seems that the HPA axis is regulated normally in FMF patients.

Amyloidosis

Authors: Kelkitli E, Bilgici B, Tokgoz B, Dilek M, Bedir A, Akpolat I, Utas C, Akpolat T.
Title: SAA1 alpha/alpha alleles in amyloidosis.
J Nephrol 2006; 19: 189-91.
Summary: AA type amyloidosis is a complication of familial Mediterranean fever (FMF). A controversy exists in the literature regarding the relationship between SAA1 genotypes and AA type amyloidosis. This study aimed to investigate SAA1 gene polymorphism in different patient groups: 1) amyloidosis, 2) FMF and 3) healthy controls. The homozygous alpha/alpha genotype is the most common SAA1 genotype among patient groups with amyloidosis, and the alpha/alpha genotype frequency is significantly higher than in healthy controls (68 vs. 38%, $p<0.05$).

Colchicine

Authors: Berkenstadt M, Weisz B, Cuckle H, Di-Castro M, Guetta E, Barkai G.
Title: Chromosomal abnormalities and birth defects among couples with colchicine treated familial Mediterranean fever.
Am J Obstet Gynecol 2005; 19: 1513-6.
Summary: The aim of the study was to determine whether colchicine prescribed for familial Mediterranean fever is teratogenic. Reproductive histories were analyzed from 326 couples referred for prenatal diagnosis because 1 partner was affected. Numbers of chromosomal abnormalities and birth defects were compared with numbers expected from published rates. There were 901 pregnancies, and amniocentesis had been performed in 566, all but 3 conceived while taking colchicine. Seven numerical chromosomal abnormalities were found, not statistically significantly greater than the 4.99 expected from maternal age and gestation of diagnosis (P = .24): unbalanced structural abnormalities were 6, compared with 3.22 expected (P = .11). There were 7 birth defects, a considerably lower rate than reported in local malformation registers. The current policy of routine amniocentesis in pregnancies of couples taking colchicine should not be changed until sufficient data accumulates to establish whether the higher number of chromosomal anomalies in this group is significant.

Authors: Ben-Chetrit E, Bergmann S, Sood R.
Title: Mechanism of the anti-inflammatory effect of colchicine in rheumatic diseases: a possible new outlook through microarray analysis.
Rheumatology (Oxford) 2006; 45: 274-82.
Summary: It is believed that colchicine exerts its anti-inflammatory effect through direct interaction with microtubules. The aim of the study was to investigate the molecular basis of colchicine action by analyzing the effect of this drug on global gene expression of HUVEC (human umbilical vein endothelial cell line) cells. HUVEC cells were exposed to various concentrations of colchicine and were harvested at different time points. Ribonucleic acid was extracted, amplified, reverse transcribed and hybridized to complementary deoxyribonucleic acid microarrrays containing more than 40,000 probes to human expressed sequence tags. Colchicine changed the expression of many genes involved in neutrophil migration or other inflammatory processes mainly after 12 to 24 h. It seems that the anti-inflammatory effect of colchicine may be mediated not only through direct interaction with microtubules but also via changes at the transcriptional level.

Other periodic fever syndromes

Authors: Lachmann HJ, Goodman HJ, Andrews PA, Gallagher H, Marsh J, Breuer S, Rowczenio DM, Bybee A, Hawkins PN.
Title: AA amyloidosis complicating hyperimmunoglobulinemia D with periodic fever syndrome: a report of two cases.
Arthritis Rheum 2006; 54: 2010-4.
Summary: AA amyloidosis is the most serious potential complication of the inherited autoinflammatory syndromes and frequently results in end-stage renal failure. The authors describe 2 patients with hyperimmunoglobulinemia D periodic fever syndrome (HIDS who developed AA amyloidosis. Both of them developed dialysis-dependent renal failure, and one of them had renal transplant.

Authors: Rynne M, Maclean C, Bybee A, McDermott MF, Emery P.
Title: Hearing improvement in a patient with variant Muckle-Wells syndrome in response to interleukin 1 receptor antagonism.
Ann Rheum Dis 2006; 65: 533-4
Summary: Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCU), and neonatal onset multisystem inflammatory disease (NOMID), also called chronic, infantile, neurological, cutaneous, and articular syndrome (CINCA), are three hereditary autoinflammatory syndromes caused by mutations affecting the CIAS1/NALP3 gene on chromosome 1q44. The proinflammatory cytokine, interleukin 1beta, is believed to have a fundamental role in their pathogenesis. A dramatic response to interleukin 1beta inhibitor - anakinra – is described in a patient with MWS. The intracranial pressure was reduced and sensorineural deafness improved as well.

Authors: Simon A, van der Meer JW, Vesely R, Myrdal U, Yoshimura K, Duys P, Drenth JP;
Title: Approach to genetic analysis in the diagnosis of hereditary autoinflammatory syndromes.
Rheumatology (Oxford) 2006; 45: 269-73.
Summary: Hereditary autoinflammatory syndromes are characterized by recurrent episodes of fever and inflammation. Seven subtypes have been described, caused by mutations in four different genes. Apart from a common phenotype of lifelong recurrent inflammatory attacks, all subtypes

have distinct features and specific therapeutic options, which emphasizes the need for a specific diagnosis in each case. The aim of the study was to examine whether genetic screening would allow classification of previously unclassified patients. Sixty patients with an unclassified autoinflammatory syndrome, 87 patients diagnosed with either hyper-IgD syndrome, familial Mediterranean fever (FMF) or tumour necrosis factor (TNF)-receptor-associated periodic syndrome and 50 healthy controls were included. They were screened for the most prevalent mutations in the MEFV, TNFRSF1A, MVK and CIAS1 genes. Only one possible diagnosis of FMF in the 60 previously unclassified patients was found. Two low-penetrance mutations were found in equal numbers in the groups of patients and controls. The conclusion was that screening of highly prevalent mutations in known genes involved in these disorders does not yield additional relevant information. Diagnosis of hereditary autoinflammatory syndromes can be made by thorough clinical examination followed by targeted genetic analysis of the one or two most likely syndromes.

Authors: van der Hilst JC, Drenth JP, Bodar EJ, Bijzet J, van der Meer JW, Simon A.

Title: Serum amyloid A serum concentrations and genotype do not explain low incidence of amyloidosis in Hyper-IgD syndrome.

Amyloid 2005; 12: 115-9.

Summary: Unlike other chronic inflammatory conditions, amyloidosis is very rare in HIDS. The SAA1.1 genotype predisposes for amyloidosis, while SAA1.5 genotype exerts a protective effect. The aim of the study was to determine if SAA concentrations and SAA1 gene polymorphisms could explain the virtual absence of amyloidosis in HIDS patients. SAA and CRP concentrations in serum were measured in 20 HIDS patients during an attack and during the asymptomatic phase. SAA serum concentrations during attacks were very high. During attack-free periods 45% of patients still had elevated SAA concentrations. The distribution of the genotype of SAA1 gene in HIDS was similar to healthy controls. The low incidence of amyloidosis cannot be explained by a predominance of non amyloidogenic SAA related genotypes.