Familial Mediterranean fever (FMF) and other hereditary periodic fever syndromes – A bird's eye view of the recent literature

Edited by M. Tunca and H. Ozdogan

FMF diagnosis

Authors: Moutereau S, Narwa R, Matheron C, Vongmany N, Simon E, Goossens M.
Title: An improved electronic microarray-based diagnostic assay for identification of MEFV mutations.
Hum Mutat 2004; 23: 621-8.

Authors: Delague V, Kriegshauser G, Oberkanins C, Megarbane A.
Title: Reverse hybridization vs. DNAsequencing in the molecular diagnosis of Familial Mediterranean fever.
Genet Test 2004; 8: 65-8.
Summary: These two papers propose less expensive and less time consuming methods for detection of mutations on MEFV gene. Discovery of this gene and the recent rise in the interest toward hereditary periodic syndromes has increased the demand for cheap and quick screening tests in clinical practice.

Authors: Islek I, Simsek T, Baskin E *et al*.
Title: Low serum apolipoprotein AI levels in amyloidosis related to familial Mediterranean fever.
Pediatr Nephrol 2003; 18: 1005-8.
Summary: Since FMF patients with amyloidosis have only intermittent proteinuria initially, laboratory tests which can detect cases in an early phase would be very useful. These patients would benefit from escalated doses of colchicine which would delay subsequent development of renal failure. The authors of this study have found that serum levels of apolipoprotein AI were significantly lower in FMF patients with amyloidosis than those with childhood nephrotic syndrome and healthy controls. This test would be much more expensive than urinanalysis but may prove valuable for those patients (with positive family history of amyloidosis etc) whose risk is substantially higher.

Genetics

Authors: Zaks N, Shinar Y, Padeh S *et al.*
Title: Analysis of the three most common MEFV mutations in 412 patients with familial Mediterranean fever.
Isr Med Assoc J 2003; 5: 585-8.
Summary: This is an extensive genetic study (412 patients) from a leading institute of FMF. The authors have genotyped these patients for the 3 leading mutations (M694V, V726A and E148Q) and full genotype was assessed in 57% of them. Their results are generally in accordance with the existing knowledge and they emphasize the limitations of genetic analysis as a diagnostic tool in FMF.

Authors: Aldea A, Calafell F, Arostegui JI *et al.*
Title: The west side story: MEFVhaplotype in Spanish FMF patients and controls, and evidence of high LD and a recombination "hot-spot" at the MEFV locus.
Hum Mutat 2004; 23: 399.
Summary: These authors have analyzed the genotypes of 50 unrelated Spanish FMF patients along with 14 Chueta (crypto-Jews) unrelated cases and 200 Spanish healthy controls, who had a carrier rate of 2.5% or less. The MEFV mutation spectrum of the Spanish patients was closest to French and Italian spectra, while the Chueta had a spectrum most resembling the North African Jews. The authors comment that the diffusion of FMF mutations may have been determined by various factors along with Jewish diaspora.

Authors: Aganna E, Hawkins PN, Ozen S *et al*.
Title: Allelic variants in genes associated with hereditary periodic fever syndromes as susceptibility factors for reactive systemic AAamyloidosis.
Genes Immun 2004; 5: 289-293.
Summary: This study tested the role of low penetrance mutations associated with hereditary periodic fever syndromes in the development of AA amyloidosis secondary to chronic inflammatory diseases like rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease and also recurrent fevers themselves. Among 67 patients with RA and amyloidosis, 4 had various MEFV mutations compared to none of the 34 RApatients without amyloidosis ($P = 0.03$). Two of the 3 TRAPS patients with amyloidosis from 2 separate multiplex families had E148Q mutation of MEFV gene. The single patient with Muckle-Wells syndrome complicated with amyloidosis was homozygous for E148Q mutation. Among the 61 patients with JIAand amyloidosis, 2 had the R92Q variant of TNFRSF1Agene compared with none of 31 JIApatients without amyloidosis. Hereditary periodic fever syndromes gene mutations were not present in 130 healthy controls. The authors concluded that these mutations were not major susceptibility factors in the development of AA amyloidosis in chronic inflammatory disorders yet low-penetrance variants of MEFV and TNFRSF1A might have significant proinflammatory effects.

Authors: Touitou I, Notarnicola C, Grandemange S.
Title: Identifying mutations in autoinflammatory diseases: toward novel genetic tests and therapies?
Am J Pharmacogenomics 2004; 4: 109-118.
Summary: This paper describes autoinflammatory diseases as illnesses caused by primary dysfunction of the innate immune system and gives an overview of the disorders included under this title. It mainly concentrates on periodic fevers [familial Mediterranean fever (FMF), mevalonate kinase deficiency (MVK),

tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS)], Crohn's disease and Blau syndrome. The authors underline the important role of molecular screening of the responsible genes in improving diagnosis, treatment and consequently patient quality of life. The molecular confirmation of the clinical link between the above mentioned disorders is also addressed in this paper. The majority of the altered proteins are related to the death domain fold superfamily which is involved in inflammation and apoptosis.

Colchicine toxicity

Authors: Sayarlioglu M, Sayarlioglu H, Ozen S, Erkoc R, Gul A.
Title: Colchicine-induced myopathy in a teenager with familial Mediterranean fever.
Ann Pharmacother. 2003; 37: 1821-4.

Authors: Kissin EY, Corbo JC, Farraye FA, Merkel PA.
Title: Colchicine myopathy in a patient with familial Mediterranean fever and normal renal function.
*Arthritis Rheum 2*003; 49: 614-6.

Authors: Ben-Chetrit E, Navon P.
Title: Colchicine-induced leukopenia in a patient with familial Mediterranean fever: the cause and a possible approach.
Clin Exp Rheumatol 2003; 21 (Suppl. 30): S38-40.
Summary: These 3 papers focus on one consequence of colchicine treatment which is rarely encountered in clinical practice: Serious colchicine toxicity in a patient on therapeutic dosage and having neither renal nor hepatic dysfunction. Sayarlioglu et al had to decrease the colchicine dose to 0.5 mg/day and added azathioprine 2 mg/kg/day with beneficial outcome. Since azathioprine has not yet been shown to have efficacy in FMF, the paper is interesting from this aspect also. The second case had concurrently Crohn's disease and was on rather higher dose of colchicine (1.8-2.4 mg/day). The 3rd patient reported by Ben-Chetrit and Navon had concomitant cytomegalovirus infection which could by itself cause the observed leukopenia. These authors further propose supplementing patients who develop leukopenia secondary to colchicine with granulocyte colony stimulating factor for the cases whose bone marrow is suppressed, or cortisone for those with hypercellular marrow. Although these 3 case reports represent an extremely small proportion of patients on colchicine, it would be appropriate to educate the patients and their parents on symptoms and signs of myopathy and neutropenia.

Therapeutic trials

Authors: Lidar M, Scherrmann JM, Shinar Y *et al*.
Title: Colchicine nonresponsiveness in familial Mediterranean fever: Clinical, genetic, pharmocokinetic and socioeconomic characterization.
Semin Arthritis Rheum 2004; 33: 273-82.
Summary: Colchicine is the mainstay of FMF treatment. Approximately in 5-10% of FMF patients, attacks can not be controlled despite adequate doses of colchicine (2 mg/d or more). This study aims to characterize this unresponsive group in order to provide insight for future research and treatment. The study group included 59 patients who were unresponsive and 51 who were responsive to colchicine treatment. Nonresponsiveness was defined as an attack frequency of more than once in 3 months, at any typical site, while on a colchicine regimen of 2 mg/d or over. MEFV and SAA1 genetic analysis and determination of colchicine levels in serum and white blood cells were performed. Both groups were comparable with regard to demographic parameters and genetic wise. Colchicine concentrations in plasma and polymorphonuclear cells were not different among the 2 groups, however there was a 2-fold elevation of colchicine concentration in the mononuclear cells of the responders. Nonresponders were from lower socioeconomic background, had less education and more severe disease. The authors conclude that colchicine nonresponsiveness is associated with reduced concentration of the drug in mononuclear cells, probably due to a defect unrelated to FMF.

Authors: Lidar M, Kedem R, Langevitz P, Pras M, Livneh A.
Title: Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine.
J Rheumatol 2003; 30: 2620-3.
Summary: The authors have supplemented their patients who did not respond to colchicine, with once-weekly (1mg) IV form of the same agent. The main rational of this approach is to increase the serum level of colchicine which might be low due to insufficient intestinal absorption or defective intracellular transport of the drug. By the end of 3 months their patients were almost 50% better, while articular complaints remained unchanged. Lidar *et al.* did not observe any side effect and this treatment was well-tolerated. Although IV therapy for prolonged periods may not seem practical initially, the colchicine nonresponding patients will probably welcome this option with enthusiasm. It is worth reminding that parenteral administration of colchicine is potentially more toxic.

Authors: Ozkaya N, Yalcinkaya F.
Title: Colchicine treatment in children with familial Mediterranean fever
Clin Rheumatol 2003; 22: 314-7.
Summary: The aim of this paper was to determine the effective colchicine dosage for children in terms of body weight and body surface area. Sixty-two children with FMF were followed for a mean of 45.6± 35.5 months with regular 2-monthly visits. The treatment was initiated with 0.5-1 mg/d and increased up to a maximum of 2 mg/d according to the response of the patient. The dose that reduced the frequency of the attacks and controlled the acute phase response during attack-free intervals was described as the 'optimal effective dosage'. When this dose was achieved, it was calculated according to body weight and surface area of each patient. The mean colchicine dosage for the whole group was calculated as 0.03 ± 0.02 mg/kg/d and 1.16 ± 0.45 mg/m^2/d. The patients whose 'optimal effective dosage' were highest constituted the youngest age group. The results indicate that if given according to body weight or body surface area, colchicine prophylaxis will be more effective in children.

Authors: Takada K, Aksentijevich I, Mahadevan V, Dean JA, Kelley RI, Kastner DL.
Title: Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome.
Arthritis Rheum 2003; 48: 2645-51.
Summary: Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) has no established treatment. The authors have tried etanercept, a soluble p75 TNF alpha receptor-Fc fusion protein, in 2 patients with HIDS with a favorable response. In fact, one of these 2 patients had a remarkable response and the number of days sick per 6 months were reduced from about 30 to less than 10. The serum levels of CRP gradually normalized in this patient who was monitored for several acute phase reactants, while other parameters remained the same or increased (TNF alpha). Both patients are being kept on etanercept 0.4 mg/kg sc once a week. The authors suggest that neutralization of TNF alpha with etanercept may be an effective treatment for HIDS.

Pathogenesis and molecular aspects

Authors: Shoham NG, Centola M, Mansfield E, Hull KM, Wood G, Wise CA, Kastner DL.
Title: Pyrin binds the PSTPIP1/CD2BP1 protein, defining fa milial Mediterranean fever and PAPAsyndrome as disorders in the same pathway.
Proc Natl Acad Sci USA 2003; 100: 13501-6.
Summary: This is yet another study revealing the close relations between the hereditary autoinflammatory diseases. The authors have demonstrated that pyrin binds to PSTPIP1/CD2BP1 (the protein, when mutated, causes the syndrome of pyogenic arthritis, pyoderma gangrenosum, and acne-PAPA). The mutations in PSTPIP1 increase its strength of interaction with pyrin, this strong binding augments the proinflammatory pathways with the resultant overproduction of IL-1 beta. They also offer anakinra, a recombinant IL-1 receptor antagonist, as a promising therapeutic agent.

Authors: Papin S, Cazeneuve C, Duquesnoy P, Jeru I, Sahali D, Amselem S.
Title: The tumor necrosis factor alpha-dependent activation of the human Mediterranean fever (MEFV) promoter is mediated by a synergistic interaction between C/EBPbeta and NF kappaB p65.
J Biol Chem 2003; 278: 48839-47.
Summary: TNF alpha is known to induce the gene expression of MEFV. The authors of this study put forward the 1013-bp fragment of the 5'-flanking sequence of MEFV as a region possessing promoter activity for this gene, since deletions of this region decreased TNF alpha responsiveness by 50-75%. They further conclude that this TNF alpha-dependent transcription is a result of a synergy between C/EBPbeta, a member of the C/EBP family of transcription factors, and NF kappaB p65. C/EBPbeta and NF kappaB p65 synergy resulted a 8.5-fold activation of MEFVpromoter, while NF kappaB, by itself, had no effect. The paper has an interesting figure depicting their model for upregulation of MEFV transcription.

Clinical aspects

Authors: Sackesen C, Bakkaloglu A, Sekerel BE *et al.*
Title: Decreased prevalence of atopy in pediatric patients with familial Mediterranean fever.
Ann Rheum Dis 2004; 63: 187-90.
Summary: The authors tested the hypothesis that FMF or mutations of the MEFV gene, confer protection against atopic diseases, mainly asthma, which are associated with an increased Th2 activity. Sixty children with FMF and their first degree relatives were screened for allergic diseases and atopic sensitization. The results were compared with an age and ethnic matched population of 3041, from the International Study of Asthma and Allergies in Childhood (ISAAC study). Skin prick tests were performed on all study subjects. Comparison of the prevalences of asthma, allergic rhinitis and eczema showed that only the difference in the frequency of allergic rhinitis between the two groups was significant ($p < 0.001$). The prevalence of atopy was also significantly lower in the FMF group ($p < 0.001$). These results suggest that FMF may be protective against allergic rhinitis and atopic sensitization but not asthma which is not a purely Th2 driven disease.

Authors: Mor A, Gal R, Livneh A.
Title: Abdominal and digestive system associations of familial Mediterranean fever.
Am J Gastroenterol 2003; 98: 2594-611.
Summary: The major attack type in FMF is peritoneal which affects about 95% of FMF patients. This article reviews both common and uncommon symptoms and signs like abdominal pain, ileus, diarrhea, constipation, ascites, malabsorption, bowel infarction, amyloidosis as well as those signs secondary to other entities associated with FMF such as vasculitis and inflammatory bowel disease. Colchicine side effects are also discussed in detail.

Authors: Ben-Chetrit E, Levy M.
Title: Reproductive system in familial Mediterranean fever: An overview
Ann Rheum Dis 2003; 62: 916-9.
Summary: This is an extensive overview of the effects of disease itself, as well as amyloidosis and colchicine treatment on male and female fertility, pregnancy, lactation and menstruation. This review also points out the need for update figures on these issues.

FMF and amyloidosis

Authors: Atagunduz MP, Tuglular S, Kantarci G, Akoglu E, Direskeneli H.
Title: Association of FMF-related (MEFV) point mutations with secondary and FMF amyloidosis
Nephron Clin Pract 2004; 96: 131-5.
Summary: The authors study the role of 3 most common MEFV gene mutations in AA-amyloidosis related to FMF and non-FMF inflammatory disorders. Both groups had significantly higher MEFVmutations compared to controls (81 and 62.7 vs 4.2%). M694V was the most common mutation in patients with

both FMF and non-FMF related amyloidosis, however homozygosity for this mutation was not different among groups. The authors suggest that MEFV mutations may serve as severity markers for other inflammatory conditions.

Authors: Bakkaloglu A, Duzova A, Ozen S, Balci B, Besbas N, Topaloglu R, Ozaltin F, Yilmaz E.
Title: Influence of serum amyloid A(SAA1) and SAA2 gene polymorphisms on renal amyloidosis, and on SAA/C-reactive protein values in patients with familial Mediterranean fever in the Turkish population.
J Rheumatol 2004; 31: 1139-42.
Summary: The authors examined the effect of serum amyloid A (SAA)1 and SAA2 polymorphisms on SAAand CRPlevels and amyloidosis in 74 patients with FMF. Of the 8 patients with amyloidosis 7 had SAA1 a/a genotype. SAA2 was found to be unrelated with amyloiosis. Neither SAA1 nor SAA2 genotypes had any effect on SAAor CRPlevels.

FMF and other inflammatory diseases

Authors: Atagunduz P, Ergun T, Direskeneli H.
Title: MEFVmutations are increased in Behcet's disease (BD) and are associated with vascular involvement.
Clin Exp Rheumatol 2003; 21 (Suppl. 30): S35-7.
Authors: Gershoni-Baruch R, Broza Y, Brik R.

Title: Prevalence and significance of mutations in the familial Mediterranean fever gene in Henoch-Schonlein purpura.
J Pediatr 2003; 143: 658-61.
Authors: Ozen S, Bakkaloglu A, Yilmaz E, Duzova A, Balci B, Topaloglu R, Besbas N.

Title: Mutations in the gene for familial Mediterranean fever: do they predispose to inflammation?
J Rheumatol 2003; 30: 2014-8.

Summary: These 3 papers address a major peculiarity of FMF and MEFV mutations from three different aspects: Do FMF patients have a predisposition to certain inflammatory diseases such as Henoch-Schönlein purpura (HSP) or Behcet's disease (BD), are the carriers of MEFVmutations over-represented among such patients and do MEFV carriers have an ongoing subclinical inflammation whose existence is already well-established in FMF patients? Atagunduz *et al*. have found that 26% of their 57 BD patients were FMF carriers, significantly more than the controls (9%). However, the general carrier rate is around 20% among healthy Turks. What may be more important clinically is that carrier rate was 55% among BD cases with vascular involvement (11% in those without such involvement). This observation does imply that MEFV mutations may aggravate another concomitant inflammatory disease. Gershoni-Baruch *et al*. have found 9 heterozygotes, 3 homozygotes and 2 compound heterozygotes among 52 children treated for HSP. The rate of carrying two mutated MEFV alleles (10%) was significantly higher than the general Israeli population (1-2%). Some of them may become overt FMF patients in the future or remain so-called "phenotype III" cases. Ozen *et al*. have analyzed 70 MEFVcarriers and genotyped 72 patients with childhood rheumatic diseases, 59 of them juvenile idiopathic arthritis. About a quarter of the patients with juvenile idiopathic arthritis were MEFV carriers or homozygotes. When the MEFV carriers were re-assessed clinically, about 4% had recurrent abdominal pains but none had definite FMF, however 21.4% had a well-defined rheumatic disease, and the ESR and CRP levels of the group in general was elevated. Thus they also have observed an ongoing subclinical inflammation among majority of the carriers, and being a MEFV carrier may increase the risk of acquiring more severe forms of rheumatic diseases.