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

edited by E. Ben-Chetrit

FMF - Clinical studies

Authors: Mansour I, Delague V, Cazeneuve C, Dode C, Chouery E, Pecheux C, Medlej-Hashim M, Salem N, El Zein L, Levan-Petit I, Lefranc G, Goosens M, Delpech M, Amselem S, Loiselet J, Grateau G, Megarbane A, Naman R.
Title: Familial Mediterranean fever in Lebanon: mutation spectrum, evidence in Maronites, Greek orthodoxes, Greek Catholics, Syriacs and Chiities and association between amyloidosis and M694V and M6941 mutations.
Eur J Hum Genet 2001; 1: 51-5.
Summary: A survey of 79 unrelated Lebanese patients with FMF. The most frequent mutations found were M694V (27%) and V726A (20%). The authors found an association between 694 alteration and amyloidosis.

Authors: Kone-Paut I, Dubuc M, Sportouch J, Minodier P, Garneir JM, Touitou I.
Title: Phenotype-genotype correlation in 91 patients with familial Mediterranean fever reveals a high frequency of cutaneoumucous features.
Rheumatology (Oxford) 2000; 11: 1275-9.
Summary: A retrospective chart review of 91 FMF patients. The authors found that homozygosity for the M694V mutation was associated with intensity of fever, splenomegaly, and with erysipelas-like erythema.

Authors: Melikoglu M, Ozdogan H, Korkmaz C, Kasapcopur O, Arisoy N, Akkus S, Fresko, Yazici H.
Title: A survey of phenotype II in familial Mediterranean fever.
Ann Rheum Dis 2000; 59: 910-3.
Summary: In this study, asymptomatic relatives of FMF patients with amyloidosis were screened for proteinuria. As a control asymptomatic relatives of patients with Juvenile chronic arthritis were also screened for proteinuria. They conclude that phenotype II is uncommon among relatives of patients with FMF and amyloidosis raising a doubt about its existence.

Authors: Majeed HA, Al-Qudah AK, Qubain H, Shahin HM.
Title: The clinical patterns of myalgia in children with familial Mediterranean fever.
Semin Arthritis Rheum 2000; 30: 138-43.
Summary: A prospective 4-year study of 264 children with FMF of whom 25% developed myalgia. Three clinical patterns of myalgia were identified: the spontaneous pattern (8%), the exercised induced pattern (81%) and the protracted febrile myalgia syndrome (11%).

Authors: Shinar Y, Livneh A, Langevitz P, Zaks N, Aksentijevich I, Koziol DE, Kastner DL, Pras M, Pras E.
Title: Genotype-phenotype assessment of common genotypes among patients with familial Mediterranean fever.
J Rheumatol 2000; 27: 1703-7.
Summary: A phenotype-genotype correlation study showing that the M694V/ M694V genotype is associated with more severe disease compared with other common genotypes in FMF patients.

Authors: Dode C, Pecheux C, Cazeneuve C, Cattan D, Dervichian M, Goosens M, Delpech R, M, Amselem S, Grateau G.
Title: Mutations in the MEFV gene in a large series of patients with a clinical diagnosis of familial Mediterranean fever.
Am J Med Genet 2000; 92: 241-6.
Summary: A study of the genotype of 303 unrelated and unselected patients with clinical suspicion of FMF. Sixty-two percent of the Sephardic, North-African Arabs Armenian and Turks were either homozygous or compound heterozygous for MEFV mutations. Two new mutations were also found.

Authors: Grateau G, Pecheux C, Cazeneuve C, Cattan D, Dervichian M, Goosens M, Delpech M, Amselem S, Dode C.
Title: Clinical versus genetic diagnosis of familial Mediterranean fever.
QJM 2000; 93: 223-9.
Summary: In this study the authors evaluated the utility of the molecular approach for the diagnosis of FMF. Their results suggest that the spectrum of FMF-associated signs is broader than previously believed and that wider indications for genotyping should lead to more frequent diagnosis of FMF.

Authors: Stoffman N, Magal N, Shohat T, Lotan R, Koman S, Oron A, Danon Y, Halpern GJ, Lifshitz Y, Shohat M.
Title: Higher than expected carrier rates for familial Mediterranean fever in various Jewish ethnic groups.
Eur J Hum Genet 2000; 8: 307-10.
Summary: In this study the carrier rates of the common MEFV mutations were investigated in 400 healthy individuals of four different ethnic groups in Israel. The authors found a high frequency of carriers among Jews from North Africa (22%), Iraq (39%), Ashkenazi Jews (21%) and from Iran (6%).

FMF - Gene and genetics

Authors: Schaner P, Richards N, Wadhwa A, Aksentijevich I, Kastner D, Tucker P, Gumucio D.
Title: Episodic evolution of pyrin in primates: human mutations recapitulate ancestral amino acid states.
Nat Genet 2001; 27: 318-21.
Summary: Human population studies have revealed extremely high allele frequencies for several different pyrin mutations,leading to the conclusion that the mutant alleles confer a selective advantage. In this study the researchers examined the rat finger protein (rfp) domain (which contains most of the disease-causing mutations) of pyrin during primate evolution. It was found that amino acids that cause human disease are often present as wild type in other species. This is true at positions 653 (a novel mutation), 680, 681, 726, 744 and 761. For several of these human mutations, the mutant represents the reappearance of an ancestral amino acid state. Examination of lineage-specific dN/ds ratios revealed a pattern consistent with the signature of episodic positive selection. These data, together with previous human population studies, indicate that selective pressures may have caused functional evolution of pyrin in humans and other primates.

Authors: Touitou I, Picot MC, Domingo C, Notarnicola C, Cattan D, Demaille J, Kone-Paut I.
Title: The MICA region determines the first modifier locus in familial Mediterranean fever.
Arthritis Rheum 2001; 44: 163-9.
Summary: In this study the researchers searched for other genes which could possible be implicated in the disease phenotype. They tested MICA (major histocompatibility complex class I chain-related gene A) because it has been associated with a number of other inflammatory disorders. They found that MEFV was individually

the most important prognostic factor for the disease. However, the impact of M694V homozygosity on the attacks at disease onset (OR2.3) was aggravated if patients also inherited MICA A9 (OR 6.3). In contrast, the frequency of attacks was found to be dramatically reduced (OR 0.16) in patients with MICA-A4.

Authors: Notarnicola C, Manna R, Rey JM, Touitou I.
Title: Y688X, the first nonsense mutation in familial Mediterranean fever (FMF).
Hum Mutat 2001; 17 :79.
Summary: Most of the mutations found so far in FMF were missense or small in frame deletions. Here, a nonsense mutation which results in a stop codon is described for the first time.

Authors: Akar E, Yalcinkaya F, Akar N.
Title: Is the Ala 38Gly alteration of MEFV gene important for amyloidosis?
Hum Mutat 2001; 17:71.
Summary: In this study the authors claim that carriers of the A138G alteration of MEFV gene are more prone to amyloidosis than a control group of FMF patients without this alteration.

Authors: Papin S, Duquesnoy P, Cazeneuve C, Pantel J, Coppey-Moisan M, Dargemont C, Amselem S.
Title: Alternative splicing at the MEFV locus involved in familial Mediterranean fever regulates translocation of the marenostrin/pyrin protein to the nucleus.
Hum Mol Gent 2000; 9: 2001.
Summary: In this study the researchers describe the isolation and expression of a novel human MEFV isoform, MEFV-d2, generated by in-frame alternative splicing of exon 2. This transcript, expressed in leukocytes, predicts a 570 residue protein designated marenostrin-d2. They also found that the localization pattern of marenostrin-d2 differs dramatically from that of marenostrin-fl. Marenostrin-fl is homogenously distributed over the entire cytoplasm, whereas marenostrin-d2 concentrates into the nucleus.

Authors: Cazenuve C, Ajrapetyan H, Papin S, Roudot-Thoraval F, genevieve D, Mindjoyan E, Papazian M, Sarkisian A, Babloyan A, Boissier B, Duquesnoy P, Kouyoumdjian JC, Girodon-Boulandet E, Grateau G, Sarkisian T, Amselem S.
Title: Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever.
Am J Hum Genet 2000; 67: 1136-43.
Summary: In this study the researchers provide new insights into the pathophysiology of FMF, demonstrating that susceptibility to renal amyloidosis in this Mendelian disorder is influenced by at least two MEFV-independent factors of genetic origin-SAA1 and sex - that act independently of each other.

Authors: Matzner Y, Abedat S, Shapiro E, Eisenberg S, Bar-Gil-Shetrit A, Stepensky P, Calco S, Azar Y, Urieli-Shoval S.
Title: Expression of the familial Mediterranean fever gene and activity of the inhibitor in human primary fibroblast cultures.
Blood 2000; 96: 727-31.
Summary: In this study the authors show concomitant expression of MEFV and C5a/IL-8 inhibitor activity in primary culture of human fibroblasts and in other cell lines that do not produce C5a/IL-8 inhibitor.

Authors: Chae JJ, Centola M, Aksentijevich I, Dutra A, Tran M.
Title: Isolation, genomic organization and eaxpression analysis of the mouse, and the rat homologs of MEFV, the gene for familial Mediterranean fever.
Mamm Genome 2000; 11: 428-35.
Summary: In this manuscript the authors report the mouse and rat homologs of MEFV. Neither the rat nor the mouse protein has an intact C-terminus B30.2 domain in which most FMF-associated mutations have been found.

Authors: Centola M, Wood G, Frucht DM, Galon J, Aringer M, Farrell C, Kingma DW, Horwitz ME, Mansfield E, Holland SM, O'Shea JJ, Rosenberg HF, Malech HL, Kastner DL.
Title: The gene for familial Mediterranean fever, MEFV, is expressed in early development and is regulated in response to inflammatory mediators.
Blood 2000; 95: 3223-31.
Summary: In this study the investigators showed that the MEFV was up-regulated by INF-gamma, INF- alfa and the combination of INF-alfa and colchicine while IL-4 and IL-10 inhibited such expression.

Authors: Chen X, Bykhovskay Y, Tidow N, Hamon M, Bercovitz Z, Spirina O, Fischel-Ghodsian N.
Title: The familial Mediterranean fever protein interacats and colocalizes with Golgi transporter.
Prog Soc Exp Biol Med 2000; 224: 32-40.
Summary: This study suggests that at some stage of its functional pathway, Pyrin resides in the cytoplasm and may be involved in or impacted by, cellular protein sorting by the Golgi apparatus.

Authors: Booth DR, Gillmore JD, Lachmann HJ, Booth SE, Bybee A, Soyturk M, Akar S, Pepys MB, Tunca M, Hawkins PN.
Title: The genetic basis of autosomal dominant familial Mediterranean fever.
QJM 2000; 93: 217-21.
Summary: In this study the researchers performed comprehensive MEFV genotyping in five families in whom FMF appeared to be inherited dominantly. They found that transmission proved to be pseudo-dominant in two cases, but true dominant inheritance of FMF with variable penetrance was supported by the genotyping results in the other three families.
The disease in these cases was associated with heterozygosity for either pyrin DeltaM694 alone or the compound pyrin variant E148Q/M694, the latter occurring in two unrelated families.

FMF and vasculitides

Authors: Ozen S, Ben-Chetrit E, Bakkaloglu A, Gur H, Tinaztepe K, Calguneri M, Turgan C, Turkmen A, Akpolat I, Danaci M, Besbas N, Akpolat T.
Title: Polyarteritis nodosa in patients with Familial Mediterranean Fever (FMF): a concomitant disease or a feature of FMF ?
Semin Arthritis Rheum 2001 Feb;30(4):281-7.
Summary: In this study 17 patients with concomitant FMF and polyarteritis nodosa were analyzed. It was found that comparing other PAN patients, those with FMF tended to have a younger age at PAN onset, more frequent perirenal hematomas and overall better prognosis. The cases with overlapping features of microscopic and classic PAN pose a problem for the current classification of vasculitis. They suggest that the clinical representation of PAN in FMF patients has certain characteristics and may be a feature of FMF *per se*.

Authors: Touitou I, Magne X, Molinari N, Navaro A, Quellec AL, Picco P, Seri M, Ozen S, Bakkaloglu A, Karaduman A, Garnier JM, Demaille J, Kone-Paut I.
Title: MEFV mutations in Behçet's disease.
Hum Mutat 2000; 16: 271-2.
Summary: Some of the FMF associated mutations in MEFV are found in patients with BD, albeit in a low prevalence. The authors suggest that the mutations might confer additional disease susceptibility in BD.

Authors: Schwartz T, Langevitz P, Zemer D, Gazit E, Pras M, Livneh A.
Title: Behçet's disease in Familial Mediterranean fever. Characterization of the association between the two diseases.
Semin Arthritis Rheum 2000; 29: 286-95.

In this study the researchers found that the prevalence of Behçet's disease was higher in FMF than in population known to be rich in BD. Patients with both diseases concomitantly do not differ clinically from those suffering from each of these diseases.

FMF amyloidosis

Authors: Ben-Chetrit E, Backenroth R.
Title: Amyloidosis induced, end-stage renal disease in patients with familial Mediterranean fever is highly associated with point mutations in the MEFV gene.
Ann Rheum Dis 2001; 60920;146-9.
Summary: Another study showing the association between the 694 alteration and amyloidosis in FMF patients in Israel.

Authors: Yalcinkaya F, TekIn M, Cakar N, Akar E, Akar N, Tumer N.
Title: Familial Mediterranean fever and systemic amyloidosis in untreated Turkish patients.
QJM 2000; 93: 68-4.
Summary: In this study a group of untreated Turkish FMF patients who did not develop amyloidosis was compared with a group of FMF Turkish patients with amyloidosis. The authors did not find any difference regarding their mutations frequencies including the M694V mutation.

Behçet's Disease - A Bird's Eye Review of the Recent Literature

edited by H. Yazici

Authors: Schirmer M, Calamia KT, Direskeneli H
Title: Ninth International Conference on Behcet's Disease, Seoul, Korea, May 27-29, 2000.
J Rheumatol 2001; 28: 636-9.
Summary: A comprehensive report on the latest get together of most of the current experts on BD.

Authors: Yazici H, Yurdakul S, Hamuryudan V
Title: Behcet's disease. (review)
Curr Opin Rheumatol 2001: 13: 18-22.
Summary: A commentary on the recent literature on BD

Behçet's Disease - Clinical

Authors: Zouboulis CC, Katsantonis J, Ketteler R, Treudler R, Kaklamani E S, Kaklamanis P, Orfanos CE.
Title: Adamantiades-Behcet's disease: Interleukin-8 is increased in serum of patients with active oral and neurological manifestations, and is secreted by small vessel endothelial cells.
Arch Dermatol Res 2000; 292: 279-84.
Summary: In a large group of patients with BD the pro-inflammatory lymphokine IL-8 was found to be increased in BD. Microvascular endothelial cells might be the source of this increased IL-8.

Authors: Gul A, Inanc M, Ocal L, Aral O, Konice M
Title: Familial aggregation of Behcet's disease in Turkey.
Ann Rheum Dis 2000; 59: 622-5.
Summary: For the first time, a sibling recurrence rate (4.2%) and a lambda-s value (11.2 - 52.5%) have been described in a study of 170 patients with BD and their relatives in Turkey.

Authors: Accardo-Palumbo A, Triolo G, Carbone MC, Ferrante A, Ciccia F, Giardina E, Triolo G.
Title: Polymorphonuclear leukocyte myeloperoxidase levels in patients with Behçet's disease.
Clin Exp Rheumatol 2000; 18: 495-8.
Summary: Myeloperoxidase levels are increased in the sera and PMN leukocyte cultures of patients with BD, especially during active disease.

Authors: Dinc A, Karaayvaz M, Caliskaner AZ, Pay S, Erdem H, Turan M
Title: Dermographism and atopy in patients with Behcet's disease.
J Invest Allergol Clin Immunol 2000; 368-71.
Summary: The authors report that dermagraphism is significantly increased among patients with BD while, despite the pathergy phenomenon, the results of skin testing for atopy are not different in patients with BD compared to healthy controls.

Authors: Soy M, Erken E, Konca K, Ozbek S
Title: Smoking and Behçet's disease.
Clin Rheumatol 2000;19: 508-9.
Summary: In a prospective study among a sizeable group of BD patients, the authors report that cessation of smoking exacerbates mucocutanous lesions.

Authors: Kawai M, Hirohata S
Title: Cerebrospinal fluid beta(2)-microglobulin in neuro-Behçet's syndrome.
J Neurol Sci 2000; 179 (Issues 1-2): 132-9.
Summary: Authors suggest that cerebrospinal fluid beta(2)-microglobulin levels are good indicators of disease activity in patients with Behçet's disease who have neurological disease.

Authors: Siva A, Kantarci OH, Saip S, Altintas A, Hamuryudan V, Islak C, Kocer N, Yazici H
Title: Behçet's disease: Diagnostic and prognostic aspects of neurological involvement.
J Neurol 2001; 248: 95-103.
Summary: A report on the clinical findings and the long-term prognosis of 164 patients with BD and CNS disease all followed at one center.