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

*edited by E. Ben-Chetrit*

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**FMF - Clinical studies**


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.


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.


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.


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%).


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.


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.


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.


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%).

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**FMF - Gene and genetics**

Authors: Schaner P, Richards N, Wadhwa A, Aksentijevich I, Kastner D, Tucker P, Gumucio D.


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.


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: Notarmioca 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 nonsense 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, Coppéy-Moisan M, Dargemont C, Ansemle S.
Title: Alternative splicing at the MEFV locus involved in familial Mediterranean fever regulates translocation of the marenostrin/pyrin protein to the nucleus.
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.

Title: Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever.
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.

Title: Expression of the familial Mediterranean fever gene and activity of the inhibitor in human primary fibroblast cultures.
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 expression analysis of the mouse, and the rat homologs of MEFV, the gene for familial Mediterranean fever.
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.

Title: The gene for familial Mediterranean fever, MEFV, is expressed in early development and is regulated in response to inflammatory mediators.
Summary: In this study the investigators showed that the MEFV was up-regulated by INF-gamma, INF-alpha and the combination of INF-alpha 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-Ghodsi N.
Title: The familial Mediterranean fever protein interacats and colocalizes with Golgi transporter.
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, Soyurtm K, Akar S, Peps MB, Tunca M, Hawkins PN.
Title: The genetic basis of autosomal dominant familial Mediterranean fever.
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 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

Title: Polyreratiritis nodosa in patients with Familial Mediterranean Fever (FMF): a concomitant disease or a feature of FMF?
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.

Title: MEFV mutations in Behçet’s disease.
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.
Behavior's disease - A Bird's Eye Review of the Recent Literature

**Authors:** Schirmer M, Calamia KT, Direskeneli H
**Title:** Ninth International Conference on Behcet’s Disease, Seoul, Korea, May 27-29, 2000.
**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)
**Summary:** A commentary on the recent literature on BD

**Behcet’s Disease - Clinical**

**Authors:** Zouboulis CC, Katsantonis J, Ketteler R, Treudler R, Kaklamanis 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, Inan M, Ocal L, Aral O, Konice M
**Title:** Familial aggregation of Behcet’s disease in Turkey.
**Summary:** For the first time, a sibling recurrence rate (4.2%) and a lambda-s value (11.2 - 32.5%) 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 Behcet’s disease.
**Summary:** Myeloperoxidase levels are increased in the sera and PMN leukocyte cultures of patients with BD, especially during active disease.

**Authors:** Dine A, Karaayvaz M, Caliskaner AZ, Pay S, Erdem H, Turan M
**Title:** Dermographism and atopy in patients with Behcet’s disease.
**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 Behcet’s disease.
**Summary:** In a prospective study among a sizeable group of BD patients, the authors report that cessation of smoking exacerbates mucocutaneous lesions.

**Authors:** Kawai M, Hirohata S
**Title:** Cerebrospinal fluid beta(2)-microglobulin in neuro-Behçet’s syndrome.
**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, Kantarcı 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.