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# Familial Mediterranean fever

## A bird's eye review of the recent literature

edited by Eldad Ben-Chetrit

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### Epidemiology

**Authors:** Tomiyama N, Higashiuesato Y, Oda T, Baba E, Harada M, Azuma M, Yamashita T, Uehara K, Miyazato A, Hatta K, Ohya Y, Iseki K, Jinno Y, Takishita S.

**Title:** MEFV mutation analysis of familial Mediterranean fever in Japan.

*Clin Exp Rheumatol* 2008; 26: 13-7.

**Summary:** In this report the authors studied FMF patients and their relatives to examine the clinical and genetic features of this disease in the Japanese population. Twelve Japanese FMF patients and a total of 17 relatives from 5 of 10 families underwent molecular genetic studies to detect MEFV mutations. In their 12 FMF patients, they detected the substitutions E84K, L110P, E148Q, R761H and M694I and newly diagnosed 2 relatives as having FMF. One patient was homozygous for E148Q, one patient with systemic amyloidosis was a homozygote for M694I and 4 patients were compound heterozygotes for E148Q and M694I. Three patients were compound heterozygotes for E148Q, L110P and M694I. Three more patients were heterozygous for E84K, L110P-E148Q or M694I. E148Q and M694I were the most frequently detected substitutions in this study. Though FMF is rare in Japan, MEFV mutations occur in Japanese population in whom E148Q and M694I are the most frequent alleles.

### Pathophysiology

**Authors:** Jae Jin Chae, Geryl Wood, Katharina Richard, Howard Jaffe, Nona T. Colburn, Seth L Masters, Deborah L. Gumucio, Nitza G. Shoham, Daniel L. Kastner

**Title:** The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF- $\kappa$ B through its N-terminal fragment.

*Blood* 2008 (in press).

**Summary:** Previously these investigators have shown that pyrin regulates caspase-1 activation and IL-1 $\beta$  production through interaction of its N-terminal PYD motif with the ASC adapter protein, and also modulates IL-1 $\beta$  production by interaction of its C-terminal B30.2 domain with the catalytic domains of caspase-1. In the present study, they asked whether pyrin might itself be a caspase-1 substrate, and found that pyrin is cleaved by caspase-1 at Asp330, a site remote from the B30.2 domain. Pyrin variants harboring FMF-associated B30.2 mutations were cleaved more efficiently than wild type pyrin. The N-terminal cleaved fragment interacted with the p65 subunit of NF- $\kappa$ B and with I $\kappa$ B- $\alpha$  through its 15 aa bZIP basic domain

and adjacent sequences, respectively. The interaction of the N-terminal fragment with p65 enhanced entrance of p65 into the nucleus. The interaction of N-terminal pyrin with I $\kappa$ B- $\alpha$  induced calpain-mediated degradation of I $\kappa$ B- $\alpha$ , thus potentiating NF- $\kappa$ B activation. Absolute and relative quantities of cleaved pyrin and I $\kappa$ B- $\alpha$  degradation products were substantially increased in leukocytes from FMF patients compared with healthy controls. These results support a new pyrin/caspase-1 pathway for NF- $\kappa$ B activation

**Authors:** Balci-Peynircioglu B, Waite AL, Hu C, Richards N, Staubach-Grosse A, Yilmaz E, Gumucio DL.

**Title:** Pyrin, product of the MEFV locus, interacts with the proapoptotic protein, Siva.

*J Cell Physiol* 2008; Mar 10 [Epub ahead of print].

**Summary:** The identification of pyrin-interacting proteins has the potential to increase our understanding of the cellular networks in which pyrin functions. Previous reports have established that pyrin interacts with the apoptotic protein ASC, the cytoskeletal adaptor protein PSTPIP1, the inflammatory caspase, Caspase-1 and certain forms of the cytosolic anchoring protein 14-3-3. Here, the authors report that pyrin also interacts with Siva, a pro-apoptotic protein first identified for its interaction with the cytosolic tail of CD27, a TNF family receptor. The interaction between pyrin and Siva involves the C-terminal B30.2/rfp/SRPY domain of pyrin and exon 1 of Siva. It was also shown that Siva and pyrin are indeed co-expressed in human neutrophils, monocytes, and synovial cells. Furthermore, pyrin can recruit Siva to ASC specks, establishing a potential platform for intersection of ASC and Siva function. Moreover, pyrin modulates the apoptotic response to oxidative stress mediated by Siva. Thus, the Siva-pyrin interaction may be a potential target for future therapeutic strategies.

### Treatment

**Authors:** Al-Daraji WI, Al-Mahmoud RM, Ilyas M.

**Title:** Gastric changes following colchicine therapy in patients with FMF.

*Dig Dis Sci* 2007 Dec 15 [Epub ahead of print].

**Summary:** Colchicine is used to treat a variety of conditions but it has gastrointestinal (GI) side effects. In this study, effects of colchicine on the gastrointestinal tract were evaluated in patients with FMF treated with colchicine. One hundred and twelve GI biopsies, obtained from 43 FMF patients over a 14-year period, were reviewed. This included biopsies from

stomach body (38), stomach antrum (50), and colon (24). In addition, gastric biopsies were reviewed from 17 control patients who did not have FMF and were not on colchicine. Results disclosed that only three patients known to have FMF and on colchicine therapy had typical histological features of colchicine (metaphase mitoses, epithelial pseudoproliferation, mucin depletion, and frequent apoptosis). These features were seen only in gastric antral biopsies and not in colonic biopsies. None of the control group showed the characteristic morphological features of colchicine toxicity.

**Authors:** Nakamura A, Matsuda M, Tazawa K, Shimojima Y, Ikeda S.

**Title:** Successful treatment with infliximab and low-dose methotrexate in a Japanese patient with familial Mediterranean fever.

*Intern Med* 2007; 46(15): 1247-9.

**Summary:** in this report a Japanese patient with familial Mediterranean fever (FMF) was successfully treated with the anti-tumor necrosis factor (TNF)-alpha monoclonal antibody, infliximab, and low-dose methotrexate. This patient had polyarthralgia typical of this disease and was heterozygote. Combination therapy with infliximab and low-dose methotrexate may be a potent therapeutic option for FMF patients when conventional treatment is ineffective or cannot be employed because of adverse events.

### Atherosclerosis and FMF

**Authors:** Bilginer Y, Ozaltin F, Basaran C, Duzova A, Besbas N, Topaloglu R, Ozen S, Bakkaloglu A.

**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.

*Rheumatol Int* 2008; May 24 [Epub ahead of print].

**Summary:** The aim of the present study was to determine whether intima-media thickness (IMT) of the common (CCA) and internal carotid arteries (ICA) was increased due to chronic inflammation occurring in children with familial Mediterranean fever (FMF). Inflammatory parameters were examined in 70 FMF patients in an attack free period and in 50 healthy. IMT of both CCA and ICA was evaluated with a high resolution B-mode ultrasonography. Intima media thickness of the common carotid artery and the median ICA-IMT were significantly increased in the patients when compared to controls. The authors concluded that intima media thickness, an early predictor of atherosclerosis, may be associated with subclinical inflammation in children with FMF.

**Authors:** Peru H, Altun B, Doğan M, Kara F, Elmaci AM, Oran B.

**Title:** The evaluation of carotid intima-media thickness in children with familial Mediterranean fever.

*Clin Rheumatol* 2008; 27: 689-94.

**Summary:** The aim of the study was to investigate whether pediatric familial Mediterranean fever (FMF) patients have an increased risk of premature atherosclerosis and to determine the possible strength of association between atherosclerosis and Mediterranean fever (MEFV) gene mutation gene type. Demographic characteristics and MEFV mutations were defined in 49 children diagnosed with FMF. Twenty-six age-, sex-, and body-mass-index-matched healthy children constituted the control group. Carotid artery intima-media thickness (CCA-IMT) were significantly higher in the study group than the mean values of control group ( $p < 0.05$ ). However, no correlation was found between CCA-IMT and CRP, SAA, Hcy, and Lp-a. There was no correlation between CCA-IMT and MEFV mutation subgroups. The authors conclude that FMF patients should be considered to have an increased risk of early vascular atherosclerosis.

### MEFV mutations in diseases other than FMF

**Authors:** Kukuy OL, Kopolovic J, Blau A, Ben-David A, Lotan D, Shaked M, Shinar Y, Dinour D, Langevitz P, Livneh A.

**Title:** Mutations in the familial Mediterranean fever gene of patients with IgA nephropathy and other forms of glomerulonephritis.

*Clin Genet* 2008; 73: 146-51.

**Summary:** The present study was aimed to determine, in populations not suffering from FMF, whether carriage of MEFV mutations may modify or precipitate IgA nephropathy (IgAN) and other forms of primary glomerulonephritis (PGN). Forty patients with biopsy proven IgAN and 40 with PGN were surveyed for the presence of the three most common MEFV mutations (M694V, V726A and E148Q). The rate of MEFV mutations in the patients was related to the expected carrier rate in the general population of the same ethnic extraction. Carriage of mutated MEFV was not associated with the course and severity of the disease or findings in kidney biopsy and urine analysis.

**Authors:** Tweezer-Zaks N, Doron-Libner A, Weiss P, Ben-Horin S, Barshack I, Lidar M, Livneh A.

**Title:** Familial Mediterranean fever and cryptogenic cirrhosis.

*Medicine* (Baltimore) 2007; 86(6): 355-62.

**Summary:** The authors conducted the current study to describe

cryptogenic cirrhosis in FMF and to examine the possible relationship between the 2 entities. Patients with chronic liver disease were retrospectively identified through a computer search of a registry of 6000 patients with FMF followed in Tel Hashomer. Cryptogenic cause of cirrhosis was determined by exclusion of known causes of liver disease. Nine patients with cryptogenic cirrhosis were identified, comprising 0.15% of the FMF patient population, a rate significantly higher than the rate of 0.015% of cirrhosis of all types expected in the total population of Israel ( $p < 0.000$ ).

Seven patients who underwent mutation analysis had 2 mutations. Five of them were homozygous for M694V. Child-Pugh classification was determined in 6 patients at the time of cirrhosis diagnosis, and was classified as A in 4 of them. These findings suggest that MEFV may serve as a modifier gene in cryptogenic cirrhosis.

**Authors:** Yalçinkaya F, Ozçakar ZB, Kasapçopur O, Oztürk A, Akar N, Bakkaloğlu A, Arisoy N, Ekim M, Ozen S.

**Title:** Prevalence of the MEFV gene mutations in childhood polyarteritis nodosa.

*J Pediatr* 2007; 151: 675-8.

**Summary:** The aim of the study was to investigate the prevalence of MEFV mutations in patients with polyarteritis nodosa (PAN) without any symptoms of familial Mediterranean fever (FMF). Pediatric patients with PAN (n=29) were enrolled in this study. Six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the MEFV gene were studied. Eleven of the 29 patients (38%) were found to carry MEFV mutations. Three (10.3%) of them had homozygous p.M694V mutation, and one of the patients (3.4%) had compound heterozygous mutation (p.V726A/p.E148Q). The study confirms that alterations in the MEFV gene are important susceptibility factors for the development of PAN.

**Authors:** Sari S, Egritas O, Dalgic B.

**Title:** The familial Mediterranean fever (MEFV) gene may be a modifier factor of inflammatory bowel disease in infancy.

*Eur J Pediatr* 2008; 167: 391-3.

**Summary:** The authors report the concurrent manifestation of IBD and familial Mediterranean fever (FMF) in three infants (less than 6 months of age) in whom infantile ulcerative colitis (UC) was associated with the MEFV mutation. One

patient required colectomy before the diagnosis of FMF, and in the other two patients, the UC could not be controlled until colchicine was added to the drug regimen. The Authors suggest that the onset of UC in infants should prompt a search for MEFV mutations as this association may influence the management of the disease.

## Periodic fever syndromes other than FMF

**Authors:** Jéru I, Duquesnoy P, Fernandes-Alnemri T, Cochet E, Yu JW, Lackmy-Port-Lis M, Grimpel E, Landman-Parker J, Hentgen V, Marlin S, McElreavey K, Sarkisian T, Grateau G, Alnemri ES, Amselem S.

**Title:** Mutations in NALP12 cause hereditary periodic fever syndromes

*Proc Natl Acad Sci USA* 2008; 105: 1614-9.

**Summary:** NALP proteins, also known as NLRPs, belong to the CATERPILLER protein family involved, like Toll-like receptors, in the recognition of microbial molecules and the subsequent activation of inflammatory and immune responses. Using a candidate gene approach, these investigators identified non-ambiguous mutations in NALP12 (i.e., nonsense and splice site) in two families with periodic fever syndromes. As shown by means of functional studies, these two NALP12 mutations have a deleterious effect on NF-kappaB signaling. Overall, these data identify a group of hereditary periodic fever syndromes defined by molecular defects in NALP12, opening up new ways to manage these disorders. The identification of these first NALP12 mutations in patients with autoinflammatory disorder also clearly demonstrates the crucial role of NALP12 in inflammatory signaling pathways.