

# Periodic fever syndromes

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The term periodic fever syndrome has been used in a restricted sense to denote two diseases in which episodic fevers occur with a regular periodicity: cyclic neutropenia and the periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) syndrome. Other authors have used the term in a more general sense to encompass a larger group of disorders characterized by recurrent episodes of fever that do not necessarily follow a strictly periodic pattern. These include familial Mediterranean fever, the autosomal dominant familial fevers (also known as Hibernian fever), and the hyper-immunoglobulin D syndrome. This article follows the latter usage, and reviews recent advances in our understanding of the genetics and molecular pathology of this group of diseases, as well as their clinical characterization and treatment. *Curr Opin Pediatr* 2000, 12:563–566 © 2000 Lippincott Williams & Wilkins, Inc.

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## Abbreviations

<b>FHF</b>	familial Hibernian fever
<b>FMF</b>	familial Mediterranean fever
<b>FPF</b>	familial periodic fever
<b>HIDS</b>	hyper-IgD syndrome
<b>TNF</b>	tumor necrosis factor
<b>PFAPA</b>	periodic fever, aphthous stomatitis, pharyngitis, and adenopathy
<b>SICAM-1</b>	soluble intercellular adhesion molecule 1

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## Familial Mediterranean fever

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent, self-limiting episodes of fever, often accompanied by serositis, oligoarticular arthritis and an erysipelas-like rash [1]. Most FMF patients derive from four ethnic groups (non-Ashkenazi Jews, Turks, Arabs, and Armenians), and the frequency of carriers can be as high as 1:5 among susceptible populations. The onset of symptoms of FMF is usually in childhood. The presenting features and clinical course of 476 Arab children meeting clinical criteria for the diagnosis of FMF were recently reviewed [2]. This study is notable for highlighting several less frequently described manifestations of FMF in children, including scrotal swelling, severe myalgia, and a variety of cutaneous lesions.

The FMF gene, termed *MEFV*, which encodes a putative transcription factor known as pyrin or marenostin, was identified 3 years ago [3,4]. This landmark discovery has been followed by the characterization of *MEFV* mutations in large numbers of FMF patients. At least 20 different mutations have been characterized to date, and recent studies suggest that these account for 80 to 95% of patients who meet clinical criteria for the diagnosis of FMF, with the remaining patients expected to carry novel *MEFV* mutations [5•,6•]. Emerging data have begun to delineate correlations between *MEFV* genotype and clinical phenotype. A number of studies published in the past year have extended previous preliminary observations of a close association between homozygosity for a specific methionine-to-valine substitution mutation (M693V) in *MEFV* and a severe disease course, with onset of symptoms at an earlier age, more frequent attacks, more frequent arthritis, and a greater likelihood of amyloidosis [7•–10•]. Conversely, this mutation appears to be under-represented in patients with mild, late-onset FMF who do not have amyloidosis [11•]. Other factors besides *MEFV* genotype may affect the clinical phenotype. Aksentijevich *et al.* observed homozygous *MEFV* mutations (E148Q or P369S) both in patients with FMF and in apparently healthy Ashkenazi subjects, suggesting that other genetic or environmental factors influence the expression of the disease, and reinforcing the need to interpret the results of genetic testing in the context of clinical data [5•].

Other recent studies have addressed issues relevant to the pathophysiology of FMF and the physiologic role of

pyrin. During acute attacks of FMF, an intense acute-phase reaction occurs and increased serum levels of a variety of mediators have been demonstrated, including soluble intercellular adhesion molecule 1 (sICAM-1), soluble tumor necrosis factor receptors p55 and p75, interleukin-8, and interleukin-6 [12,13]. A leading hypothesis is that pyrin functions as a negative regulator of inflammation; this view is supported by recent data demonstrating that pyrin is preferentially expressed in inflammatory cells including neutrophils, eosinophils, and monocytes, and that the expression of pyrin is itself regulated by the cytokines interferon- $\gamma$  and tumor necrosis factor, which play important roles in inflammatory pathways [14,15].

### **Syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy**

This clinical entity was described by Marshall *et al.* [16] in 1987. The same group [17•] has recently published a long-term follow-up study of 94 patients. The clinical features of PFAPA syndrome include periodic episodes of fever ( $> 39^{\circ}\text{C}$ ) lasting 3 to 6 days and recurring every 3 to 8 weeks, accompanied by aphthous stomatitis, pharyngitis, and cervical adenopathy. In the 94 patients surveyed, fevers began in early childhood (mean age of onset 2.8 years), lasted a mean of 4.8 days, and recurred at a mean of 28.2 days. The most consistent clinical feature of this syndrome was the regular and predictable periodicity of fever. Abdominal pain was a common feature of attacks, but was usually mild. In many patients, attacks began to wane in frequency after several years and eventually ceased. No adverse long-term complications were observed in these children. Laboratory studies showed normal or elevated neutrophil counts and moderately elevated ESR. Another series of 28 patients with PFAPA syndrome was reported by Padeh *et al.* [18•].

In many of the children reported by Thomas *et al.* [17•], fever associated with PFAPA syndrome was poorly responsive to acetaminophen or ibuprofen. Both Thomas *et al.* [17•] and Padeh *et al.* [18•] found that a very short course of steroid treatment (either one or two doses of prednisone at 1–2 mg/kg/d) was highly effective in curtailing episodes of fever associated with PFAPA syndrome. An intriguing observation noted by both groups, and a potential disadvantage of steroid therapy in this setting, is the tendency for subsequent cycles of fever to become more closely spaced after a course of prednisone. Prophylactic treatment with cimetidine (150 mg daily for 6 months) was followed by a remission from further febrile episodes in 8 out of 28 patients so treated by Thomas *et al.* [17•]. Seven out of 11 patients who underwent tonsillectomy also experienced a complete remission, another intriguing observation and one that has

prompted speculation about the possible role of infection in the etiology of this syndrome [19•].

### **Cyclic neutropenia**

Both inherited and acquired forms of cyclic neutropenia have been described, in which episodes of severe neutropenia, often associated with fever and occurring with a period of 21 days, result from a periodic severe decline in the production of neutrophils from bone marrow. Horwitz *et al.* [20•] have recently identified mutations in the neutrophil elastase gene in patients with autosomal dominant cyclic neutropenia. A total of seven different mutations were observed in 13 families with the disorder. These mutations appear to interfere with the function of neutrophil elastase, but do not completely prevent its expression. The authors speculate that neutrophil elastase may participate in feedback control of neutrophil recruitment into the inflammatory response. Mathematical analysis of the patterns of hematopoietic cycling in patients with cyclic neutropenia supports the concept that a defect in such a feedback system may give rise to periodic cycling of neutrophil production [21•].

### **Hyper-IgD syndrome**

Hyper-IgD syndrome (HIDS) is a recessively inherited condition first described in 1984 [22] and characterized by recurrent fevers, often accompanied by chills, headache, cervical adenopathy, arthritis, and rash, and associated with a persistent polyclonal elevation of serum immunoglobulin D levels. Like FMF, HIDS attacks are self-limiting, and affected individuals are generally well between episodes. The onset of HIDS attacks is usually in infancy or very early childhood [23]. The attacks typically last 3 to 7 days, and recur with variable frequency; colchicine is usually ineffective in preventing recurrent attacks. Attacks tend to become less severe and less frequent with increasing age. The risk of amyloidosis and renal disease is very low. A single patient with HIDS who developed progressive crescentic glomerulonephritis and end-stage renal failure was recently reported [24]. Acute attacks of HIDS are accompanied by elevated blood levels of the inflammatory cytokines tumor necrosis factor and interleukin-6 [25].

In the past year, the identification of the gene causing HIDS syndrome was reported by two groups. Drenth *et al.* [26•] used gene mapping to establish linkage of HIDS to 12q24 on the long arm of chromosome 12. Analysis of candidate genes within this region led to the finding of mutations of the *MVK* (mevalonate kinase) gene, encoding the enzyme mevalonate kinase, in patients with HIDS. Most patients appear to be compound heterozygotes, and the most common mutation results in substitution of isoleucine for valine and residue 377 (V377I). Similar mutations were reported by Houten *et al.* [27•].

The peroxisomal enzyme *MVK* that plays a key role in cholesterol metabolism. Mutations in *MVK* have previously been described in patients with mevalonic aciduria, a multisystem disorder associated with progressive neurologic dysfunction and other systemic manifestations [28,29]. Houten *et al.* [27•] point out that there is some clinical overlap between HIDS and mevalonic aciduria, since recurrent fevers, rash, lymphadenopathy, gastrointestinal involvement, and arthralgia are all characteristic of both disorders. The two disorders are nevertheless distinguishable at the genetic and biochemical levels in several respects: 1) the recently identified *MVK* mutations associated with HIDS are different from the *MVK* mutations previously reported to cause mevalonic aciduria [28,29]; 2) urinary levels of mevalonic acid were at least 25-fold lower in patients with HIDS than in patients with mevalonic aciduria; and 3) there was higher residual *MVK* enzymatic activity in cells from patients with HIDS as compared with mevalonic aciduria. The relation between disordered mevalonate metabolism and the clinical features of HIDS, and the cause and pathophysiologic significance of elevated serum IgD in this condition remain to be determined.

### Autosomal dominant periodic fever syndromes

The dominantly inherited conditions, familial Hibernian fever (FHF), first described in an Irish/Scottish family in 1982, and familial periodic fever (FPF), described in an Australian family of Scottish descent in 1998, were mapped to the same locus on chromosome 12 in 1998 [30,31]. This locus contains the gene for one of the two tumor necrosis factor (TNF) receptors, p55, and McDermott *et al.* [32•] have now identified mutations in this gene in patients with both FHF and FPF. The mutations alter the extracellular portion of the p55 protein, and are associated with increased cell surface expression of this receptor on monocytes and polymorphs and with decreased shedding of soluble receptor. McDermott *et al.* [32•] suggest that these changes may lead to exaggerated inflammatory responses to TNF, and that agents that block the biologic effects of TNF, such as etanercept, may therefore be useful in treating FHF/FPF.

### Conclusions

The past year has seen exciting developments in the understanding of periodic fever syndromes. The identification of the genetic basis of several of these disorders has opened up new avenues for research into their pathophysiology, and has brought new refinement to their clinical definition and classification. Continuing advances in this area are certain to enhance our understanding of these and other inflammatory diseases and of the basic mechanisms of inflammatory responses.

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