TABLE 392-1 THE HEREDITARY RECURRENT FEVER SYNDROMES

	FMF	TRAPS	HIDS	MWS	FCAS	NOMID
Ethnicity	Jewish, Arab, Turkish, Armenian, Italian	Any ethnic group	Predominantly Dutch, northern European	Any ethnic group	Any ethnic group	Any ethnic group
Inheritance	Recessive[a]	Dominant	Recessive	Dominant	Dominant	Most commonly de novo mutations; somatic mosaicism in a significant minority
Gene/chromosome	*MEFV*/16p13.3	*TNFRSF1A*/12p13	*MVK*/12q24	*NLRP3*/1q44	*NLRP3*/1q44	*NLRP3*/1q44
Protein	Pyrin	p55 TNF receptor	Mevalonate kinase	Cryopyrin (NLRP3)	Cryopyrin (NLRP3)	Cryopyrin (NLRP3)
Attack length	1–3 days	Often >7 days	3–7 days	1–2 days	Minutes–3 days	Continuous, with flares
Serosa	Pleurisy, peritonitis; asymptomatic pericardial effusions	Pleurisy, peritonitis, pericarditis	Abdominal pain, but seldom peritonitis; pleurisy, pericarditis uncommon	Abdominal pain; pleurisy, pericarditis rare	Rare	Rare
Skin	Erysipeloid erythema	Centrifugally migrating erythema	Diffuse maculopapular rash; oral ulcers	Diffuse urticaria-like rash	Cold-induced urticaria-like rash	Diffuse urticaria-like rash
Joints	Acute monoarthritis; chronic hip arthritis (rare)	Acute monoarthritis, arthralgia	Arthralgia, oligoarthritis	Arthralgia, large joint oligoarthritis	Polyarthralgia	Epiphyseal, patellar overgrowth, clubbing
Muscle	Exercise-induced myalgia common; protracted febrile myalgia rare	Migratory myalgia	Uncommon	Myalgia common	Sometimes myalgia	Sometimes myalgia
Eyes, ears	Uncommon	Periorbital edema, conjunctivitis, rarely uveitis	Uncommon	Conjunctivitis, episcleritis, optic disc edema; sensorineural hearing loss	Conjunctivitis	Conjunctivitis, uveitis, optic disc edema, blindness, sensorineural hearing loss
CNS	Aseptic meningitis rare	Headache	Headache	Headache	Headache	Aseptic meningitis, seizures
Amyloidosis	Most common in M694V homozygotes	~15% of cases, most often cysteine mutations, T50M	Uncommon	~25% of cases	Uncommon	Late complication
Treatment	Oral colchicine prophylaxis, IL-1 inhibitors for refractory cases	Glucocorticoids, etanercept, IL-1 inhibitors	NSAIDs for fever; IL-1 and TNF inhibitors	Anakinra, rilonacept, canakinumab	Anakinra, rilonacept, canakinumab	Anakinra

[a]A substantial percentage of patients with clinical FMF have only a single demonstrable MEFV mutation on DNA sequencing.

Abbreviations: FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; NSAIDs, nonsteroidal anti-inflammatories; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome.

domains, and caspase recruitment domains. PYRIN domains mediate homotypic protein-protein interactions and have been found in several other proteins, including cryopyrin (NLRP3), which is mutated in three other recurrent fever syndromes. Through a number of mechanisms, including the interaction of the PYRIN domain with an intermediary adaptor protein, pyrin regulates caspase-1 (interleukin [IL] 1β-converting enzyme), and thereby IL-1β secretion. Mice bearing FMF-associated pyrin mutations exhibit inflammation and excessive IL-1 production.

ACUTE ATTACKS

Febrile episodes in FMF may begin even in early infancy; 90% of patients have had their first attack by age 20. Typical FMF episodes generally last 24–72 h, with arthritic attacks tending to last somewhat longer. In some patients, the episodes occur with great regularity, but more often, the frequency of attacks varies over time, ranging from as often as once every few days to remissions lasting several years. Attacks are often unpredictable, although some patients relate them to physical exertion, emotional stress, or menses; pregnancy may be associated with remission.

If measured, fever is nearly always present throughout FMF attacks. Severe hyperpyrexia and even febrile seizures may be seen in infants, and fever is sometimes the only manifestation of FMF in young children.

Over 90% of FMF patients experience abdominal attacks at some time. Episodes range in severity from dull, aching pain and distention with mild tenderness on direct palpation to severe generalized pain with absent bowel sounds, rigidity, rebound tenderness, and air-fluid levels on upright radiographs. Computed tomography (CT) scanning may demonstrate a small amount of fluid in the abdominal cavity. If such patients undergo exploratory laparotomy, a sterile, neutrophil-rich peritoneal exudate is present, sometimes with adhesions from previous episodes. Ascites is rare.

Pleural attacks are usually manifested by unilateral, sharp, stabbing chest pain. Radiographs may show atelectasis and sometimes an effusion. If performed, thoracentesis demonstrates an exudative fluid rich in neutrophils. After repeated attacks, pleural thickening may develop.

FMF arthritis is most frequent among individuals homozygous for the M694V mutation, which is especially common in the non-Ashkenazi Jewish population. Acute arthritis in FMF is usually monoarticular, affecting the knee, ankle, or hip, although other patterns can be seen, particularly in children. Large sterile effusions rich in neutrophils are frequent, without commensurate erythema or warmth. Even after repeated arthritic attacks, radiographic changes are rare. Before the advent of colchicine prophylaxis, chronic arthritis of the knee or hip was seen in ~5% of FMF patients with arthritis. Chronic sacroiliitis can occur in FMF irrespective of the HLA-B27 antigen, even in the face of