392 Familial Mediterranean Fever and Other Hereditary Autoinflammatory Diseases

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Familial Mediterranean fever (FMF) is the prototype of a group of inherited diseases (Table 392-1) that are characterized by recurrent episodes of fever with serosal, synovial, or cutaneous inflammation and, in some individuals, the eventual development of systemic AA amyloidosis (Chap. 137). Because of the relative infrequency of high-titer autoantibodies or antigen-specific T cells, the term *autoinflammatory* has been proposed to describe these disorders, rather than autoimmune. The innate immune system, with its myeloid effector cells and germline receptors for pathogen-associated molecular patterns and endogenous danger signals, plays a predominant role in the pathogenesis of the autoinflammatory diseases. Although the hereditary recurrent fevers comprise a major category of the autoinflammatory diseases, other inherited disorders of inflammation in which recurrent fever plays a less prominent role are now also considered to be autoinflammatory.

BACKGROUND AND PATHOPHYSIOLOGY

FMF was first recognized among Armenians, Arabs, Turks, and non-Ashkenazi (primarily North African and Iraqi) Jews. With the advent of genetic testing, FMF has been documented with increasing frequency among Ashkenazi Jews, Italians, and other Mediterranean populations, and occasional cases have been confirmed even in the absence of known Mediterranean ancestry. FMF is generally regarded as recessively inherited, but there is an increasing awareness of clear-cut clinical cases with only a single demonstrable genetic mutation, and, for certain relatively rare FMF mutations, there is strong evidence for dominant inheritance. Particularly in countries where families are small, a positive family history can only be elicited in ~50% of cases. DNA testing demonstrates carrier frequencies as high as 1:3 among affected populations, suggesting a heterozygote advantage.

The FMF gene encodes a 781-amino acid, ~95 kDa protein denoted *pyrin* (or *marenostrin*) that is expressed in granulocytes, eosinophils, monocytes, dendritic cells, and synovial and peritoneal fibroblasts. The N-terminal 92 amino acids of pyrin define a motif, the PYRIN domain, that is similar in structure to death domains, death effector