Familial Mediterranean Fever – an Overview

Disease Summary

Familial Mediterranean fever (FMF) is an autosomal recessive disorder affecting primarily Mediterranean populations (Arabs, Armenians, Jews, and Turks).[1-2] This disorder has two distinct phenotypes: Type 1 FMF is characterized by periodic, short episodes of fever and inflammation including serositis, peritonitis, synovitis, pleuritis, and, less frequently, pericarditis, and meningitis.[1] Some patients also develop amyloidosis, which can lead to renal failure.[1-2] Type 2 FMF is characterized by amyloidosis as the first clinical manifestation.[1] The prevalence of FMF varies by population, but is estimated to range from 1 in 400 persons to 1 in 1,000 persons in the Mediterranean region.[3] In other populations, the disorder is less common. FMF symptoms almost always first occur before 20 years of age, and often before 10 years of age.[4] Early diagnosis of FMF is important, since timely treatment with colchicine decreases inflammatory attacks and prevents renal amyloidosis.[1,4] In fact, lifelong prophylactic treatment with colchicine is recommended for individuals with a known genetic predisposition for FMF.[1]

FMF has been linked to mutations in the gene *MEFV*, which codes for the protein pyrin, a component of the proinflammatory pathway.[1,5] Presentation of the disease is highly variable even among families with the same causative mutations in *MEFV*.[1] Five mutations account for about 85% of FMF cases in the Middle Eastern area: p.Met680Ile, p.Met694Val, p.Met694Ile, and p.Val726Ala on exon 10, and p.Glu148Gln on exon 2.[3] Among these, the p.Met694Val mutation, especially if present homozygously, has been associated with early onset, high penetrance and severity of disease, and a greater incidence of amyloidosis.[3,5] In general, however, severity or presentation of FMF is difficult to predict from the mutation due to the influence of environmental and other genetic factors.

FMF is diagnosed based on clinical symptoms and is suspected in individuals with periodic episodes of fever in association with abdominal, joint, or chest pain or serositis.[1] While standard biochemical assays are not diagnostic, serum levels of fibrinogen, serum amyloid A, and C-reactive protein can be used to monitor disease course and response to treatment.[3] Genetic testing can confirm the diagnosis of FMF and, once the mutations causing FMF in a specific family have been identified, can also identify presymptomatic individuals among the patient's relatives. By distinguishing presymptomatic family members from heterozygous carriers, genetic testing can help to facilitate prophylactic treatment of presymptomatic individuals, while protecting heterozygous carriers from unnecessary lifelong preventive treatment.

For additional information, see Tables 1-2 below and references 1-5.

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Table 1: Disease Facts about FMF (based on references 1-5, unless otherwise noted)

Disease Fact	Familial Mediterranean Fever
MIM* number	249100
Estimated Prevalence	1:400 to 1:1000
Average Age at Diagnosis	Childhood to young adults
Typical Symptoms	Recurrent, short episodes of fever Abdominal, joint, or chest pain Rash on the ankles Increased erythrocyte sedimentation rate Elevated serum concentration of fibrinogen Amyloidosis
Therapy	Nonsteroidal anti-inflammatory drugs (NSAIDs) for febrile and inflammatory episodes Renal transplantation for end-stage renal disease Colchicine prophylactic treatment to reduce inflammatory attacks and prevent amyloidosis

**MIM: Mendelian Inheritance in Man, see http://www.ncbi.nlm.nih.gov/omim*

Table 2: Molecular Genetics of FMF (based on references 1-5, unless otherwise noted)

Gene (Protein)	Trans-mission	Mutation type	Penetrance	Comments
MEFV (Pyrin)	Autosomal recessive	Loss-of-function	80%	Among the five most common variants of *MEFV*, the penetrance of p. Met694Val is highest (99%) and p.Glu148Gln is least (55%).[5]

References

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