

Familial Mediterranean Fever (*MEFV*) Sequencing

TO CONFIRM DIAGNOSIS OF FAMILIAL MEDITERRANEAN FEVER (FMF) OR CARRIER STATUS

Disease Overview

- Familial Mediterranean fever (FMF) is a recessive autoinflammatory disease commonly found in Mediterranean populations.
- FMF is characterized by recurrent short episodes of inflammation, fever, abdominal pain, chest pain, joint pain, skin eruption, and amyloidosis.
- Manifestations generally appear in childhood. Onset is rare after age 30.
- Minimum criteria for clinical diagnosis of FMF includes fever plus at least one major symptom (e.g., abdominal pain, chest pain, joint pain, or skin eruption) and one minor symptom (e.g., increased erythrocyte sedimentation rate, leukocytosis, or elevated serum fibrinogen concentration).
- Amyloidosis is the most severe complication of FMF and leads to end-stage renal disease.
- Abdominal pain or attacks occur in approximately 90–95 percent of affected individuals and start with a sudden onset of fever and pain affecting the entire abdomen.
- Colchicine treatment is used to prevent renal amyloidosis. Episodes of fever and inflammation are typically treated with non-steroidal anti-inflammatory drugs (NSAIDs).

Epidemiology

- As many as one in 1,000 individuals of Armenian, Arab, and Turkish descent have FMF.
- Carrier frequencies among commonly affected populations: North African Arabs (1:100); North African Jews, Iraqi Jews, Armenians, and Turks (1:3 to 1:7); and Ashkenazi Jews (1:5).

Genetics

- Autosomal recessive inheritance.
- Mutations in the *MEFV* gene are known to cause FMF. However, other genes may be involved as some affected patients do not have identifiable *MEFV* mutations.
- Affected individuals are usually compound heterozygous and carry two distinct *MEFV* mutations.
- Approximately 80 *MEFV* mutations have been reported; the majority are located in exon 10.
- Some genotype/phenotype correlations exist for *MEFV*.
 - Homozygotes for the common p.Met694Val mutation are more likely to develop amyloidosis. Patients may develop amyloidosis without having inflammatory attacks. Colchicine treatment is necessary to prevent renal amyloidosis.

Indications for Ordering

- To confirm a diagnosis of FMF in a symptomatic patient.
- Diagnostic or carrier testing in individuals with a family history of FMF.
- Carrier testing for the reproductive partner of an individual who is a carrier of, or affected with, FMF.
- To guide appropriate drug therapy (response to colchicine therapy differs for some mutations).

Additional Ordering Note

For optimal test interpretation, please submit a Patient History for FMF Form detailing clinical findings, family history, and ethnicity.

Interpretation

- The detection of two pathogenic *MEFV* gene mutations on opposite chromosomes predicts FMF.
- When one or no *MEFV* mutations are detected in a clinically affected individual, medical management should rely on clinical findings.
- When one pathogenic *MEFV* mutation is detected in a clinically unaffected individual, the individual is predicted to be at least a carrier.
- *MEFV* mutations of unknown clinical significance may be detected by this assay.

Methodology

- Bidirectional sequencing of the entire *MEFV* coding region and intron-exon boundaries.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity is approximately 80 percent.

Limitations

- Rare diagnostic errors can occur due to primer-binding site mutations.
- Regulatory region, intronic mutations, and large deletions/duplications will not be detected.
- Mutations in genes other than *MEFV* will not be detected.

Related Tests

- Sedimentation Rate, Westergren (0040325)
- Fibrinogen (0030130)
- White Blood Cell Count (0040320)

References

- Online Mendelian Inheritance in Man: #249100, Familial Mediterranean Fever. <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=249100> (accessed on June 18, 2009).
- Online Gene Tests: Familial Mediterranean Fever. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=fmf> (accessed on June 18, 2009).
- Touitou I. Familial Mediterranean Fever. Orphanet encyclopedia, May 2003. <http://www.orpha.net/data/patho/Pro/en/MediterraneanFeverFamilial-FRenPro920.pdf> (accessed on December 10, 2009).
- Lidar M and Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. Neth J Med 2007;65(9):318–24.

Test Information

2002658 Familial Mediterranean Fever (*MEFV*) Sequencing

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.