

Familial Mediterranean Fever (*MEFV*)

Indications for Ordering

- To confirm a diagnosis of familial Mediterranean fever (FMF) in a symptomatic individual
- 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 pathogenic variants)

Test Description

Bidirectional sequencing of the entire *MEFV* coding region and intron/exon boundaries

Tests to Consider

Primary test

[Familial Mediterranean Fever \(*MEFV*\) Sequencing 2002658](#)

- Preferred test for suspected FMF

Related tests

Initial testing for minor criteria

- [Sedimentation Rate, Westergren \(ESR\) 0040325](#)
- [Fibrinogen 0030130](#)
- [White Blood Cell Count 0040320](#)

[Periodic Fever Syndromes Panel, Sequencing 7 Genes and Deletion/Duplication, 6 Genes 2007370](#)

- Includes *ELANE*, *LPIN2*, *MEFV*, *MVK*, *NLRP3*, *PSTPIP1*, and *TNFRSF1A* genes
- May be used as initial test to identify genetic cause of FMF, or as a second test after normal *MEFV* sequencing
- Sequencing and deletion/duplication also orderable as separate tests

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence

- Up to 1/1,000 in individuals of Armenian, Arab, and Turkish descent
- Carrier frequencies among commonly affected populations
 - North African Arabs – 1/100
 - North African Jews, Iraqi Jews, Armenians, and Turks – 1/3 to 1/7
 - Ashkenazi Jews – 1/5

Age of onset – generally childhood, rare onset after age 30

Symptoms/diagnostic criteria

Fever plus at least one major symptom AND one minor symptom

- Major symptoms
 - Abdominal pain
 - Sudden onset of diffuse pain
 - Occurs in 90-95% of FMF individuals
 - Chest pain
 - Joint pain
 - Skin eruption
 - Amyloidosis
 - Most severe complication
 - Leads to end-stage renal disease
- Minor symptoms
 - Increased ESR
 - Leukocytosis
 - Elevated serum fibrinogen

Genetics

Gene – *MEFV*

Inheritance – mostly autosomal recessive

- Most affected individuals have two *MEFV* pathogenic variants
- Some activating variants can cause FMF in a heterozygous individual, appearing autosomal dominant

Variants

- ~80 reported, most located in exon 10
 - Most common pathogenic variant is p.Met694Val
- Some genotype/phenotype correlations exist
 - Homozygotes for p.Met694Val pathogenic variant have higher risk for amyloidosis
 - Individuals with certain pathogenic variants may respond differently to colchicine

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – ~80% (Aksentijevich, 1999; Shohat, 2014; Touitou, 2001)
- Analytical sensitivity/specificity – 99%

Results

- Two pathogenic *MEFV* variants detected
 - Individual is predicted to be affected with FMF
- One or no pathogenic *MEFV* variants detected in a clinically affected individual
 - May have FMF – medical management should rely on clinical findings
 - Some affected individuals may not have two detectable pathogenic variants
 - Carriers of some pathogenic variants may manifest symptoms
- One or no pathogenic *MEFV* variants detected in a clinically unaffected individual
 - Predicted to be at least a carrier
- No pathogenic *MEFV* variants detected in a clinically unaffected individual
 - Neither a carrier nor affected
- Inconclusive
 - *MEFV* variants of unknown clinical significance may be detected

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not detected
 - Regulatory region and intronic variants
 - Large deletions/duplications
 - Variants in genes other than *MEFV*

References

- Aksemitjevich I, Torosyan Y, et al. Mutation and haplotype studies of familial Mediterranean fever reveal new ancestral relationships and evidence for a high carrier frequency with reduced penetrance in the Ashkenazi Jewish population. *Am J Hum Genet.* 1999;64:949–962
- Shohat M, Halpern GJ. Familial Mediterranean Fever. 2000 Aug 8 [Updated 2014 Jun 19]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016
- Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. *Eur J Hum Genet.* 2001;9:473-483