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 and Deletion/Duplication 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

- Aksentijevich 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 2016 Dec 15]. 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