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
  - Heterozygotes 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