Familial Mediterranean Fever (MEFV) Sequencing

Familial Mediterranean fever (FMF) is a genetic condition characterized by recurrent but short-lived attacks of fever, abdominal pain, joint pain, and/or skin rashes. Symptoms and frequency of these attacks are highly variable. Renal amyloidosis is a common complication in untreated individuals and may be the only manifestation in some patients.

Featured ARUP Testing

Familial Mediterranean Fever (MEFV) Sequencing 3004434

Method: Massively Parallel Sequencing

- Use to confirm a diagnosis of FMF in a symptomatic individual and to guide appropriate treatment options (response to colchicine differs for some pathogenic variants).
- May also be useful as a diagnostic or carrier test for individuals with a family history of FMF.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Common symptoms of FMF include:

- Recurrent fever
- Erysipelas-like erythema
- Acute attacks of abdominal pain with board-like rigidity of the abdominal muscles, rebound tenderness, abdominal distension, and loss of peristaltic sounds
- Acute attacks of arthritis, often with synovial effusion
- Acute attacks of pleuritis
- Type AA amyloidosis, leading to nephrotic syndrome and end-stage renal disease if untreated
- Increased erythrocyte sedimentation rate (ESR)
- Leukocytosis
- Elevated serum fibrinogen concentration

Treatment with colchicine can prevent inflammatory attacks and deposition of amyloid in affected individuals, although specific treatment recommendations vary based on the disease-causing variant(s) and clinical history.

Genetics

Gene

MEFV (NM_000243)

Incidence

FMF is common among ethnic groups in the Mediterranean region, including individuals with Ashkenazi Jewish, Armenian, Turkish, Arab, North African Jewish, and Iraqi Jewish ancestry. Incidences of 1 in 400 to 1 in 1000 have been reported in these regions.[1,2]

Inheritance

Autosomal recessive, although some heterozygous individuals may have symptoms

Genotype/Phenotype Correlations

- The most common severe variant in *MEFV* is p.Met694Val, which is almost always correlated with a severe disease course in homozygotes and a higher risk for amyloidosis compared with other variants.
- Most heterozygotes do not have symptoms, but autosomal dominant transmission of a milder phenotype with reduced penetrance has been reported in some families with severe *MEFV* variants such as p.Met694del and p.Ile692del.
- Milder variants such as p.Val726Ala have been associated with milder disease course or incomplete penetrance, with some homozygous or compound heterozygous individuals remaining asymptomatic.[2]
- Pathogenic variants are gain of function; loss of function variants are not a known disease mechanism.

Test Interpretation

Clinical Sensitivity

75-90%[2,3]

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%)	Analytic Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	>99	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	>99	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	>99	62.1-100

[a]The gene included on this test is a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Variant(s) Detected	Clinical Significance
Two pathogenic variants detected in the *MEFV* gene	Consistent with a diagnosis of FMF
No pathogenic variants detected in the *MEFV* gene	Decreases the likelihood of, but does not exclude, a diagnosis of FMF
One pathogenic variant detected in the *MEFV* gene	At least a carrier of FMF Some individuals with only one detected variant may have clinical features. Medical management should rely on clinical findings.
One or more variant(s) of unknown clinical significance detected in the *MEFV* gene	Inconclusive; based on currently available information, it is unknown whether the variant is disease-associated or benign. Medical management should rely on clinical findings. Surveillance of the literature for new information concerning the uncertain variant is recommended.

Limitations

- A negative result does not exclude a diagnosis of FMF.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene
  - Variants in the mitochondrial genome
  - Regulatory region and deep intronic variants
  - Large deletions/duplications (large deletions/duplications have not been reported as causative variants for FMF)
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

References

1. Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. *Eur J Hum Genet*. 2001;9(7):473-483.

2. Ben-Chetrit E, Touitou I. Familial Mediterranean fever in the world. *Arthritis Rheum*. 2009;61(10):1447-1453.

3. Shohat M. Familial Mediterranean fever. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last update: Dec 2016; Accessed: Oct. 2021]

Additional Resources

Booty MG, Chae JJ, Masters SL, et al. Familial Mediterranean fever with a single MEFV mutation: where is the second hit? *Arthritis Rheum*. 2009;60(6):1851-1861.

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