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.

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%\textsuperscript{2,3}

Analytic Sensitivity
For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate\textsuperscript{a} (%)</th>
<th>Analytic Sensitivity (PPA) 95% Credibility Region\textsuperscript{a} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99</td>
<td>96.9-99.4</td>
</tr>
<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
</tr>
<tr>
<td>Deletions 11-44 bp</td>
<td>&gt;99</td>
<td>87.8-100</td>
</tr>
<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
</tr>
<tr>
<td>Insertions 11-23 bp</td>
<td>&gt;99</td>
<td>62.1-100</td>
</tr>
</tbody>
</table>

\textsuperscript{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

<table>
<thead>
<tr>
<th>Variant(s) Detected</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two pathogenic variants detected in the \textit{MEFV} gene</td>
<td>Consistent with a diagnosis of FMF</td>
</tr>
<tr>
<td>No pathogenic variants detected in the \textit{MEFV} gene</td>
<td>Decreases the likelihood of, but does not exclude, a diagnosis of FMF</td>
</tr>
<tr>
<td>One pathogenic variant detected in the \textit{MEFV} gene</td>
<td>At least a carrier of FMF</td>
</tr>
<tr>
<td></td>
<td>Some individuals with only one detected variant may have clinical features. Medical management should rely on clinical findings.</td>
</tr>
<tr>
<td>One or more variant(s) of unknown clinical significance detected in the \textit{MEFV} gene</td>
<td>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.</td>
</tr>
</tbody>
</table>

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


Additional Resources