Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication

Indications for Ordering

- Confirm diagnosis of a periodic fever syndrome
- Diagnostic or carrier testing in individuals with a family history of a periodic fever syndrome
- Guide appropriate therapy

Test Description

- Massively parallel sequencing of all coding exons and exon/intron junctions in 7 genes
  - ELANE, LPIN2, MEFV, MVK, NLRP3, PSTPIP1, and TNFRSF1A
  - Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants; see below for further technical limitations
- Deletion/duplication analysis of 6 genes by comparative genomic hybridization (CGH) array
  - LPIN2, MEFV, MVK, NLRP3, PSTPIP1, and TNFRSF1A

Tests to Consider

Primary tests

Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication 2007370
- Most comprehensive test to identify causative periodic fever syndromes variants

Related tests

Initial testing for periodic fever syndromes
- Sedimentation Rate, Westergren (ESR) 0040325
- Fibrinogen 0030130
- White Blood Cell Count 0040320

Familial Mediterranean Fever (MEFV) Sequencing 2002658
- Preferred test for suspected familial Mediterranean fever

Disease Overview

- For specific disease descriptions, refer to table
- Attacks often begin with a prodromal phase
  - Symptoms – fatigue, malaise, headache
- Inflammatory symptoms follow prodromal phase
  - Symptoms – fever, pain, rash
  - Symptoms usually resolve spontaneously
- Individuals are generally asymptomatic between attacks
  - In some severe cases, inflammatory symptoms may not completely resolve between attacks
- Depending on specific syndrome, symptoms may be triggered by
  - Exposure to cold
  - Trauma

Genetics

For gene-specific information, refer to table

Test Interpretation

Results

- Positive
  - ELANE, NLRP3, PSTPIP1, or TNFRSF1A genes
    - One pathogenic variant predicts periodic fever syndrome
  - LPIN2, MEFV, or MVK genes
    - One pathogenic variant predicts carrier status
    - Two pathogenic variants predict periodic fever syndrome
    - Some activating variants in MEFV may cause symptoms without a second variant
- Negative
  - Absence of pathogenic variants in a clinically affected individual decreases the likelihood but does not exclude diagnosis of a periodic fever syndrome
- Inconclusive
  - Variants of unknown clinical significance may be identified in any of the seven genes examined
## Limitations
- Not detected
  - Regulatory region variants
  - Deep intronic variants
  - Breakpoints of large deletions and/or duplications
  - Copy number variants smaller than one kb (1,000 base pairs)
  - Large exonic deletions and/or duplications in the ELANE gene
- Exon 1 in each of the LPIN2, MEFV, MVK, NLRP3, PSTPIP1, and TNFRSF1A genes is not evaluated by CGH array

<table>
<thead>
<tr>
<th>Gene/Protein/Ref Seq ID</th>
<th>Associated Syndromes</th>
<th>Inheritance</th>
<th>Age of Onset</th>
<th>Clinical Features</th>
<th>Analyzed by</th>
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</table>
| **ELANE** *(ELA2)* neutrophil elastase protein NM_001972** | Severe congenital neutropenia | Autosomal dominant | During infancy | • Recurrent fever  
• Propharyngeal inflammation (including mouth ulcers)  
• Chronic and severe infections | Sequencing only |
| **LPIN2** lipin-2 NM_014646 | Majeed syndrome | Autosomal recessive | Before 2 years | • Cutaneous pustulosis  
• Sweet syndrome  
• Chronic recurrent multifocal osteomyelitis  
• Hepatosplenomegaly  
• Growth retardation  
• Contractures  
• Hypochromic microcytic dyserythropoietic anemia  
• More common in Arab ethnicities | Sequencing and CGH array |
| **MEFV** Pyrin NM_000243 | Familial Mediterranean fever (FMF) | Mostly autosomal recessive (rarely dominant) | Before 10 years | • Periodic acute fever  
• Sterile peritonitis  
• Erysipelas-like rash on lower legs  
• Oligoarthritis  
• Amyloidosis  
• Myalgia  
• Myopathy  
• Aseptic meningitis  
• More common in Armenian, Arab, Turkish, Italian, and Jewish ethnicities  
• Treated with daily colchicine | Sequencing and CGH array |
| **MVK** mevalonate kinase D syndrome (HIDS) Mevalonate kinase-associated periodic fever syndrome NM_000431 | Hyperimmunoglobulinemia D syndrome (HIDS)  
Mevalonate kinase-associated periodic fever syndrome | Autosomal recessive | Around 6 months | • Fever  
• Abdominal pain  
• Headaches  
• Cervical lymphadenopathy  
• Diarrhea  
• Maculopapular rash  
• Elevated immunoglobulin D  
• More common in Caucasians of western European ancestry | Sequencing and CGH array |
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<tr>
<td>NLRP3 (CIASI) NM_004895</td>
<td>Familial cold autoinflammatory syndrome (FCAS)</td>
<td>Autosomal dominant</td>
<td>Before 1 year</td>
<td>• Symptoms triggered by exposure to cold&lt;br&gt;• Urticarial-like rash&lt;br&gt;• Myalgia, arthralgia&lt;br&gt;• Nausea&lt;br&gt;• Headache&lt;br&gt;• Conjunctivitis&lt;br&gt;• More common in Caucasians of western European ancestry</td>
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<td>Muckle-Wells syndrome</td>
<td>Autosomal dominant</td>
<td>Before 20 years</td>
<td>• Urticarial-like rash&lt;br&gt;• Myalgia/arthritis&lt;br&gt;• Malaise&lt;br&gt;• Lancing limb pain&lt;br&gt;• Abdominal pain&lt;br&gt;• Deafness&lt;br&gt;• Headache&lt;br&gt;• Conjunctivitis&lt;br&gt;• Anemia of chronic illness&lt;br&gt;• Amyloidosis&lt;br&gt;• More common in Caucasians of western European ancestry</td>
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<tr>
<td>Neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA)</td>
<td>Autosomal dominant</td>
<td>Before 1 year</td>
<td>• Fever&lt;br&gt;• Urticarial-like rash&lt;br&gt;• Chronic meningitis&lt;br&gt;• Erosive arthritis, destructive arthropathy&lt;br&gt;• Hepatosplenomegaly&lt;br&gt;• Frontal bossing and digital clubbing&lt;br&gt;• Deafness&lt;br&gt;• Cerebral atrophy&lt;br&gt;• Developmental delay&lt;br&gt;• Optic neuritis, vision loss&lt;br&gt;• Anemia of chronic illness&lt;br&gt;• Amyloidosis&lt;br&gt;• More common in Caucasians of western European ancestry</td>
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<td>PSTPIP1 proline-serine-threonine phosphatase-interacting protein 1 (CD2-binding protein 1) NM_003978</td>
<td>Pyogenic sterile arthritis pyoderma gangrenosum acne (PAPA)</td>
<td>Autosomal dominant</td>
<td>Before 16 years</td>
<td>• Pyogenic sterile arthritis&lt;br&gt;• Pyoderma gangrenosum&lt;br&gt;• Cystic acne&lt;br&gt;• Sterile abscess&lt;br&gt;• Joint pain</td>
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<td>TNFRSF1A tumor necrosis factor receptor-associated periodic syndrome (TRAPS) NM_001065</td>
<td>Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)</td>
<td>Autosomal dominant</td>
<td>Before 20 years</td>
<td>• Fever&lt;br&gt;• Sterile peritonitis/pleuritis&lt;br&gt;• Large joint arthritis&lt;br&gt;• Severe deep muscle aches&lt;br&gt;• Abdominal pain&lt;br&gt;• Constipation/diarrhea&lt;br&gt;• Splenomegaly&lt;br&gt;• Anemia of chronic illness&lt;br&gt;• Periorbital edema&lt;br&gt;• Conjunctivitis&lt;br&gt;• Inguinal hernias in males&lt;br&gt;• Migratory erythematous rashes&lt;br&gt;• Amyloidosis&lt;br&gt;• More common in Caucasians of western European ancestry</td>
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