## Periodic Fever Syndromes

### 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
- 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 7 Genes and Deletion/Duplication, 6 Genes 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
    - 1 pathogenic variant predicts periodic fever syndrome
  - LPIN2, MEFV, or MVK genes
    - 1 pathogenic variant predicts carrier status
    - 2 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 7 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</th>
<th>Associated Syndromes</th>
<th>Inheritance</th>
<th>Age of Onset</th>
<th>Clinical Features</th>
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| **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 |
| | Cyclic neutropenia | Autosomal dominant | During infancy | - Cyclic neutropenia  
- Recurrent fever  
- Oropharyngeal inflammation (including mouth ulcers)  
- Abdominal pain  
- Chronic and severe infections | |
| **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  
- Erysipelias-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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| NLRP3 (CIASI) Cryopyrin NM_004895 | Familial cold autoinflammatory syndrome (FCAS) | Autosomal dominant | Before 1 year | • Symptoms triggered by exposure to cold  
• Urticarial-like rash  
• Myalgia, arthralgia  
• Nausea  
• Headache  
• Conjunctivitis  
• More common in Caucasians of western European ancestry | Sequencing and CGH array |
| Muckle-Wells syndrome | | Autosomal dominant | Before 20 years | • Urticarial-like rash  
• Myalgia/arthralgia/arthritis  
• Malaise  
• Lancing limb pain  
• Abdominal pain  
• Deafness  
• Headache  
• Conjunctivitis  
• Anemia of chronic illness  
• Amyloidosis  
• More common in Caucasians of western European ancestry | |
| Neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA) | | Autosomal dominant | Before 1 year | • Fever  
• Urticarial-like rash  
• Chronic meningitis  
• Erosive arthritis, destructive arthropathy  
• Hepatosplenomegaly  
• Frontal bossing and digital clubbing  
• Deafness  
• Cerebral atrophy  
• Developmental delay  
• Optic neuritis, vision loss  
• Anemia of chronic illness  
• More common in Caucasians of western European ancestry | |
| PSTPIP1 proline-serine-threonine phosphatase-interacting protein 1 [CD2-binding protein 1] NM_003978 | Pyogenic sterile arthritis pyoderma gangrenosum acne (PAPA) | Autosomal dominant | Before 16 years | • Pyogenic sterile arthritis  
• Pyoderma gangrenosum  
• Cystic acne  
• Sterile abscess  
• Joint pain | Sequencing and CGH array |
| TNFRSF1A tumor necrosis factor receptor-associated periodic syndrome (TRAPS) | Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) | Autosomal dominant | Before 20 years | • Fever  
• Sterile peritonitis/pleuritis  
• Large joint arthritis  
• Severe deep muscle aches  
• Abdominal pain  
• Constipation/diarrhea  
• Splenomegaly  
• Anemia of chronic illness  
• Periorbital edema  
• Conjunctivitis  
• Inguinal hernias in males  
• Migratory erythematous rashes  
• Amyloidosis  
• More common in Caucasians of western European ancestry | Sequencing and CGH array |