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

Gene/Protein/Ref Seq ID	Associated Syndromes	Inheritance	Age of Onset	Clinical Features	Analyzed by
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 • 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 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

Gene/Protein/Ref Seq ID	Associated Syndromes	Inheritance	Age of Onset	Clinical Features	Analyzed by
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 1 NM_001065	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