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Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication

Periodic fever syndromes are a varied group of autoinflammatory disorders characterized by recurrent episodes of fever that lack an infectious cause. They include familial Mediterranean fever (FMF), cyclic neutropenia, tumor necrosis factor receptor associated periodic syndrome (TRAPS), Muckle-Wells syndrome, and Hyper-IgD syndrome (HIDS). Genetic testing can confirm diagnosis or be used to determine whether individuals with a family history of a periodic fever syndrome may be carriers.

DISEASE OVERVIEW

- For specific disease descriptions, refer to the Genes Tested 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

Indications for Ordering

- Confirm diagnosis of a periodic fever syndrome in a symptomatic individual
- Diagnostic or carrier testing in individuals with a family history of a periodic fever syndrome

Epidemiology

Prevalence varies by condition and ethnicity.

Inheritance

- Autosomal dominant – *ELANE, NLRP12, NLRP3, NOD2, PSTPIP1, TNFAIP2, TNFRSF1A*
- Autosomal recessive – *LPIN1, MEFV, MVK*

TESTS TO CONSIDER

Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication 2007370
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

- Preferred test to confirm a diagnosis of a periodic fever syndrome.
- Predictive diagnostic or carrier testing in individuals with a family history of a periodic fever syndrome.

Familial Mediterranean Fever (MEFV) Sequencing 2002658
Method: Polymerase Chain Reaction/Sequencing

Preferred test when clinical symptoms are suspicious for FMF.

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

Recommended test for a known familial sequence variant previously identified in a family member.

TEST DESCRIPTION

See Genes Tested table for genes included in the panel.

Clinical Sensitivity

Variable, dependent on specific disorder

Limitations

- A negative result does not exclude a heritable form of a periodic fever syndrome.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *ELANE, NLRP12, NOD2, TNFAIP3*
  - Noncoding transcripts

- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:
    - *LPIN2* (NM_014646) 13, 16; *MVK* (NM_000431) 11; *PSTPIP1* (NM_001321136) 2; *PSTPIP1* (NM_003978) 10; *TNFRSF1A* (NM_001346092) 6

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are 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

Genes Tested

Gene	MIM Number	Disorder	Inheritance	Age of Onset	Clinical Symptoms
ELANE	130130	Cyclic neutropenia	AD	Infancy	Fever and malaise Mouth ulcers Cyclic neutropenia Chronic and severe infections
		Severe congenital neutropenia 1	AD	Infancy	Fever Inflammation of gums and skin Decreased levels of neutrophils Chronic and severe infections
LPIN2	605519	Majeed syndrome	AR	Before 2 years	Recurrent fever episodes Chronic recurrent multifocal osteomyelitis (CRMO) Congenital dyserythropoietic anemia Sweet syndrome –painful bumps and blisters Contractures Growth retardation
MEFV	608107	Familial Mediterranean fever (FMF)	AD and AR	Before 10 years	Recurrent fever episodes Painful inflammation in abdomen, chest, and joints Erysipelas-like rash on lower legs
MVK	251170	Porokeratosis 3	AD	Between 3rd-4th decade of life	Annular skin plaques surrounded by distinctive keratotic rim Fluctuate seasonally

Gene	MIM Number	Disorder	Inheritance	Age of Onset	Clinical Symptoms
		Hyper-IgD syndrome (HIDS)	AR	Infancy	Periodic high fevers Abdominal and joint pain Headache Skin lesions Hepatomegaly and/or splenomegaly Elevated immunoglobulin D
		Mevalonic aciduria	AR	Infancy	Hepatosplenomegaly Abdominal and joint pain Skin rashes Failure to thrive Developmental delay and progressive ataxia Progressive vision problems
NLRP12	609648	Familial cold autoinflammatory syndrome 2 (FCAS2)	AD	First year of life to middle age	Episodic and recurrent rash Urticaria Arthralgia Myalgia Abdominal and/or thoracic pain
NLRP3	606416	Familial cold autoinflammatory syndrome 1 (FCAS1)	AD	Before age 10	Recurrent episodes of nonpruritic urticaria rash Episodes triggered by exposure to cold Lowgrade fever and malaise Sweating, headaches, and nausea
		Keratoendothelitis fugax hereditaria	AD	Between ages 4-12 years	Periodic inflammation of corneal endothelium Redness of the eye, pain, and photophobia Blurry vision
		Muckle-Wells syndrome	AD	Infancy to early childhood	Recurrent rashes Intermittent fevers Joint pain Recurrent conjunctivitis Progressive hearing loss Amyloidosis
		Neonatal onset multisystem inflammatory disease (NOMID)/CINCA syndrome	AD	Infancy	Skin rash typically present at birth Chronic meningitis Headaches, seizures, and vomiting Intellectual disability and developmental delay Hearing and vision loss Joint inflammation and cartilage overgrowth Short stature Contractures

Gene	MIM Number	Disorder	Inheritance	Age of Onset	Clinical Symptoms
		Deafness, autosomal dominant 34, with or without inflammation	AD	Childhood	Postlingual sensorineural hearing loss Episodic urticaria Periodic fever Renal amyloidosis
NOD2	605956	Blau syndrome	AD	Early childhood; usually before age 4	Granulomatous dermatitis Arthritis Uveitis Nephritis; chronic kidney failure
PSTPIP1	606347	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne	AD	Childhood	Pyogenic arthritis Pyoderma gangrenosum Severe cystic acne
TNFAIP3	191163	Autoinflammatory syndrome, familial, Behcet-like	AD	First or second decade of life	Mucosal ulcers (particularly in oral and genital areas) Skin rash Uveitis Polyarthritis
TNFRSF1A	191190	Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) (aka periodic fever, familial)	AD	Childhood	Recurrent fever Sterile peritonitis/pleuritis Abdominal pain Myalgia Leukocytosis Elevated erythrocyte sedimentation rate

AD, autosomal dominant; AR, autosomal recessive

REFERENCES

Bodar EJ, Drenth JP, van der Meer JW, Simon A. Dysregulation of innate immunity: hereditary periodic fever syndromes. Br J Haematol. 2009; 144(3): 279-302. PubMed

Dale D, Makaryan V. ELANE-Related Neutropenia. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews, University of Washington, 1993-2018. Seattle, WA [Last Update: Aug 2018; Accessed: Nov 2018]

Goldfinger S. The inherited autoinflammatory syndrome: a decade of discovery. Trans Am Clin Climatol Assoc. 2009; 120: 413-8. PubMed

Goldsmith DP. Periodic fever syndromes. Pediatr Rev. 2009; 30(5): e34-41. PubMed

Shohat M. Familial Mediterranean Fever. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews, University of Washington, 1993-2018. Seattle, WA [Last Update: Dec 2016; Accessed: Nov 2018]

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