Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication

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Periodic fever syndromes are a varied group of autoinflammatory disorders characterized by recurrent episodes of fever that lack an infectious cause. These syndromes 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 a diagnosis or be used to determine whether individuals with a family history of a periodic fever syndrome may be carriers.

Featured ARUP Testing

Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication 2007370

Method: Massively Parallel Sequencing

- 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

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

- For specific disease descriptions, refer to the Genes Tested table.
- Attacks often begin with a prodromal phase, with symptoms such as fatigue, malaise, and headache.
- Inflammatory symptoms (eg, fever, pain, rash) follow the prodromal phase.
- Symptoms usually resolve spontaneously.
- Individuals are generally asymptomatic between attacks, though in some severe cases, inflammatory symptoms may not completely resolve between attacks.
- Depending on the specific syndrome, symptoms may be triggered by exposure to cold or trauma.

Indications for Ordering

- Use to 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

Prevalence

Varies by condition and ethnicity.

Inheritance

See the Genes Tested table.

Test Description

See the Genes Tested table for genes included in the panel.

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.

- Enriched DNA is sequenced by massively parallel sequencing (MPS), also known as next generation sequencing (NGS), followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and, in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

Variable, dependent on specific disorder

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] Deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] Duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

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 and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Large duplications less than three exons in size
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes or repetitive/homologous regions

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)	AR and AD	Typically before 10 years for AR FMF Milder/AD forms may not present until adulthood	Recurrent fever episodes Painful inflammation in abdomen, chest, and joints Erysipelas-like rash on lower legs
	608068	Acute febrile neutrophilic dermatosis	AD	Childhood	Recurrent fever Acute onset of painful skin lesions Arthralgia and myalgia
MVK	251170	Porokeratosis 3	AD	Between 3rd-4th decade of life	Annular skin plaques surrounded by distinctive keratotic rim Fluctuate seasonally
		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

AD, autosomal dominant; AR, autosomal recessive

Gene	MIM Number	Disorder	Inheritance	Age of Onset	Clinical Symptoms
					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 Low-grade fever and malaise Sweating, headaches, and nausea
		Keratoendotheliitis 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
		Deafness, autosomal dominant 34, with or without inflammation	AD	Childhood	Postlingual sensorineural hearing loss Episodic urticaria Periodic fever

AD, autosomal dominant; AR, autosomal recessive

Gene	MIM Number	Disorder	Inheritance	Age of Onset	Clinical Symptoms
					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