Periodic Fever Syndromes Panel

PANEL GENE LIST

ELANE (ELA2), LPIN2, MEFV, MVK, NLRP3 (CIAS1), PSTPIP1, TNFRSF1A

CLINICAL FEATURES

Familial Mediterranean fever (FMF) is caused by pathogenic variants in the MEFV gene. It typically presents in childhood or adolescence with periodic attacks of acute fever and localized inflammation lasting from one to three days. Intervals between attacks vary from days to months, and onset may be precipitated by physical or emotional stress. Abdominal symptoms, pleural involvement, arthralgias and arthritis are common. Leukocytosis, accelerated ESR, and progressive amyloidosis also affect many patients. Erysipeloid erythema, when present, usually involves the lower extremities. Most patients are responsive to colchicine treatment.

TNF-Receptor-Associated Periodic Syndrome (TRAPS) is caused by pathogenic variants in the *TNFRSF1A* gene. It usually presents in childhood with periodic fevers that last from a few days to several weeks. Fevers are accompanied by abdominal pain, diarrhea/constipation, pleuritis, arthralgias, myalgias, conjunctivitis, and/or periorbital edema. Tender, migratory, erythematous skin lesions also occur. Patients with TRAPS generally do not respond to treatment with colchicine, although corticosteroids relieve symptoms in some cases and effective treatment with etanercept has been reported.

Mevalonate kinase deficiency (MKD) exists as two types: hyperimmunoglobulinemia D syndrome (HIDS) and the more severe mevalonic aciduria (MVA). MKD disorders are caused by pathogenic variants in the MVK gene. HIDS usually presents in childhood, often before one year of age. Attacks typically last from three days to a week, often with a one to two month interval between them. Attacks are characterized by high spiking fever, abdominal pain, vomiting, diarrhea, headache, arthralgias, and swollen, tender lymph nodes. Red macules of the skin and aphthous ulcers may also be observed. Many patients have nondestructive recurrent arthritis, especially of the larger joints, and many younger patients exhibit splenomegaly. Constitutively elevated serum IgD levels (>100 U/mL; 14.1 mg/dL) are observed in the majority of patients but are not required for the diagnosis. Most patients are not responsive to colchicine, but treatment with corticosteroids, anakinra, and etanercept may be effective. Patients with the more severe type, MVA, have symptoms at all times. Individuals with MVA typically have a small, elongated head, profound developmental delay, and eye problems (uveitis, blue sclera, retinitis pigmentosa and cataracts). Those less severely affected may have, myopathy and short stature later in life. Severely affected cases may live only into early childhood while those with milder forms may have a normal life expectancy.

Muckle-Wells Syndrome (MWS), Familial Cold Autoinflammatory Syndrome (FCAS), and Chronic Infantile Neurologic Cutaneous and Articular (CINCA) Syndrome/ Neonatal Onset Multisystem Inflammatory Disease (NOMID) are systemic inflammatory diseases caused by pathogenic variants in the *NLRP3 (CIAS1)* gene. They are characterized by intermittent episodes of fever, urticarial rash, arthralgias, and abdominal pain. In FCAS, the symptoms are precipitated by exposure to cold. In both MWS and CINCA/NOMID, progressive sensorineural hearing loss is common, while chronic meningitis, uveitis, optic disc edema, developmental delay, and a characteristic deforming arthropathy (bony overgrowth) is observed only in CINCA/NOMID. Renal and systemic amyloidosis is a major cause of morbidity in MWS and FCAS. Treatment with anakinra typically results in improvement of symptoms.

207 Perry Parkway, Gaithersburg, MD 20877 • T: (888) 729-1206, (301) 519-2100 • F: (201) 421-2010 • support@genedx.com • GeneDx.com

Severe congenital neutropenia (SCN) and cyclic neutropenia (CN) are disorders of neutrophil production caused by pathogenic variants in the *ELANE* gene. Both disorders lead to lifelong problems with recurrent infections. CN is characterized by very low, non-oscillating neutrophil counts with normal hemoglobin and platelet levels. The bone marrow shows a selective defect in neutrophil formation with promyelocytic maturation arrest. Typical infections include omphalitis, pneumonia, sinusitis, and gingivitis. CN typically follows a 3-week cycle of neutropenia, fever, and mouth ulcers. The diagnosis is usually made in infancy, and infections may lessen in severity with age.

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is an autoinflammatory disorder caused by pathogenic variants in the *PSTPIP1* gene. It results in recurrent, destructive, early-onset inflammation of the joints, skin and muscle that occurs without discernible infection. Biopsies of synovial tissue show massive polymorphonuclear, neutrophil-rich infiltrates without immunoglobulin or complement deposits. The episodic inflammatory arthritis typically does not resolve spontaneously and must be treated with intraarticular steroids or surgical drainage of the infiltrate. Some affected individuals have expanding inflammatory, ulcerative skin lesions (pyoderma gangrenosum) and/or severe acne conglobata consisting of many painful abscesses and draining sinuses that heal with scarring. Pathergy (injection site abscess) is also common.

Majeed syndrome is caused by pathogenic variants in the *LPIN2* gene. Patients develop chronic recurrent multifocal osteomyelitis (CRMO) prior to two years of age that results in several episodes per month of high fever, severe pain, and soft tissue swelling. The CRMO often leads to delayed bone age, growth failure, and flexion contractures. Patients also have congenital dyserythropoietic anemia leading to hypochromic, microcytic anemia with onset in the first year of life. Transient inflammatory dermatosis, often manifesting as Sweet syndrome, is also common. In the neonatal period, hepatomegaly, neutropenia, and cholestatic jaundice may occur, but these symptoms are typically transient.

INHERITANCE/GENETICS

FMF: autosomal recessive
TRAPS: autosomal dominant
MKD: autosomal recessive
MWS, FCAS, and CINCA/NOMID: autosomal dominant
SCN and CN: autosomal dominant
PAPA syndrome: autosomal dominant
Majeed syndrome: autosomal recessive.

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing (NGS). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants. Alternative sequencing methods are used to analyze or confirm regions with inadequate sequence data by NGS. Reportable variants include

pathogenic variants, likely pathogenic variants, and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions, or rearrangements greater than 10 base pairs, or low-level mosaicism.

TEST SENSITIVITY

FMF: The sensitivity of *MEFV* variant analysis depends on ethnic background, but overall an estimated 70-80% of patients with a clinical diagnosis of FMF have at least one identifiable variant in the MEFV gene.[1,2] Of note, although FMF is an autosomal recessive disorder, approximately 30% of individuals have only a single identifiable *MEFV* variant.[4] Approximately 80 variants have been reported to date, the majority of which are missense variants located in exon 10. Certain variants occur in high frequency in specific ethnic populations due to a founder effect. The two most common variants among American patients are V726A and M694V.

TRAPS: Variants in *TNFRSF1A* account for approximately 32% to 50% of familial cases of TRAPS, while only 2% to 10% of sporadic cases have an identifiable variant in this gene.[3,5,6] Overall, approximately 8% of patients with a periodic fever syndrome who do not carry a *MEFV* variant associated with FMF are expected to harbor a variant in *TNFRSF1A*.[5] The vast majority of variants identified to date are missense changes in exons 2, 3, and 4, which code for the extracellular domains of the TNF receptor 1A. Variants near splice junction sites have also been reported.

HIDS: Previous studies have identified variants in the *MVK* gene in 52-100% of patients with a clinical diagnosis of HIDS.[7,8] In an Italian population, 11% of individuals with undiagnosed periodic fevers had a variant in the *MVK* gene.[9] The majority of variants are missense variants. The V377I variant occurs on >50% of *MVK* disease alleles in patients with HIDS and is especially common in individuals of Dutch ancestry, while the I268T variant has been found on >15% of *MVK* disease alleles.

MWS, FCAS, and CINCA/NOMID: In the largest cohort of patients reported to date, variants in the *NLRP3 (CIAS1)* gene were identified in greater than 88% of patients with FCAS, ~75% of patients with MWS, and 51% of patients with CINCA/NOMID.[10] Almost all reported variants are missense changes in exon 3 that are expected to affect the secondary structure, function, or protein-protein interaction of the cryopyrin molecule.

Cyclic Neutropenia (CN): *ELANE (ELA2)* variants have been identified 44-100% of patients with CN, as well as in the non-cyclic disorder Severe Congenital Neutropenia (SCN), i.e., the autosomal dominant type of Kostmann Syndrome.[11,12,13] Both disorders are associated with the production of stable neutrophil elastase proteins of near-normal sequence resulting from missense variants, small deletions, use of alternate splice sites, and distal truncations. For SCN, standard sequencing of *ELANE* is recommended for better coverage of novel deletions.

PAPA syndrome: Two gain-of-function variants, A230T and E250Q, have been published in association with PAPA syndrome, both of which co-segregate with the disorder in multi-generational families.[14,15] Two additional missense variants, E250K and D266N, have been identified in individuals with PAPA syndrome (Infevers database, personal communication). Due to scarcity of scientific data, it is currently unknown what proportion of individuals with a clinical diagnosis of PAPA syndrome carry variants in the *PSTPIP1* gene.

Majeed syndrome: As Majeed syndrome is a very rare disorder, the sensitivity of testing for variants in the *LPIN* gene is currently not well established. To date, variants have been identified in 3 of 3 families presenting with CRMO and microcytic CDA.[16]

REFERENCES:

1. Aksentijevich et al., (1999) Am J Hum Genet 64:949-962.
2. Touitou (2001) Eur J Hum Genet 9:473-483.
3. Aksentijevich et al., (2001) Am J Hum Genet 69:301
4. Booty et al., (2009) Arth Rheum 60:1851-1861.
5. Dode et al., (2002) Arth Rheum 46:2181-2188.
6. Aganna et al., (2003) Arth Rheum 48:2632-2644.
7. Cuisset et al., (2001) Eur J Hum Genet 9:260-266.
8. Mandey et al., (2006) Hum Mutat 27:796-802.
9. D'Osualdo et al., (2005) Eur J Hum Genet 13:314-320.
10. Aksentijevich et al., (2007) Arth Rheum 56:1273-1285.
11. Dale et al., (2000) Blood 96:2317-2322.
12. Bellanne-Chantelot (2004) Blood 103: 4119-4125.
13. Horwitz, M. (1999) Nat Gen 23:433-436.
14. Wise et al., (2002) Hum Mol Genet 11:961-969.
15. Shoham et al., (2003) PNAS 100:13501-13506. Infevers: an online database for autoinflammatory mutations. Copyright. Available at http://fmf.igh.cnrs.fr/ISSAID/infevers/ Accessed 01/16/09.
16. El-Shanti et al., (2007) Clin Ortho Rel Res 462:11-19