

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB

Gender:

Female

Patient Identifiers: 01234567890ABCD, 012345

Visit Number (FIN): 01234567890ABCD

Collection Date: 00/00/0000 00:00

Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication

ARUP test code 2007370

Periodic Fever Panel Specimen

whole blood

Periodic Fever Panel Interp

Positive

INDICATION FOR TESTING

Suspected familial Mediterranean fever syndrome.

RESULT

Two pathogenic variants were detected in the MVK gene.

PATHOGENIC VARIANT

Gene: MVK (NM_000431.2)

Nucleic Acid Change: c.803T>C; Heterozygous

Amino Acid Alteration: p.Ile268Thr

Inheritance: Autosomal Recessive

PATHOGENIC VARIANT

Gene: MVK (NM_000431.2)

Nucleic Acid Change: c.1129G>A; Heterozygous

Amino Acid Alteration: p.Val377Ile

Inheritance: Autosomal Recessive

INTERPRETATION

Two pathogenic variants, c.803T>C; p.Ile268Thr, and c.1129G>A; p.Val377Ile, were detected in the MVK gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic MVK variants are inherited in an autosomal recessive manner, and are associated with hyper-IgD syndrome (MIM: 260920) and mevalonic aciduria (MIM: 610377). If these variants are located on opposite chromosomes, this result is consistent with a diagnosis of hyper-IgD syndrome or mevalonic aciduria.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:

The MVK c.803T>C; p.Ile268Thr variant (rs104895304) is reported in the literature in the homozygous and compound heterozygous state in multiple individuals affected with hyperimmunoglobulinemia D syndrome (HIDS) and mevalonate kinase-associated periodic fever syndromes (Cuisset 2001, Dunn 2018, Hinson 1999, Houten 1999, Steiner 2011, Thors 2014). This variant is reported in Clinvar (Variation ID: 11932), and is found in the general population with an overall allele frequency of 0.016% (44/282850 alleles) in the Genome Aggregation Database. The isoleucine at codon 268 is moderately conserved,

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and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. Functional analyses of the variant protein show reduced expression and enzymatic activity (Cuisset 2001, Hinson 1999, Houten 1999). Based on available information, this variant is considered to be pathogenic.

The MVK c.1129G>A;p.Val377Ile variant (rs28934897) is described in the medical literature in both the homozygous and compound heterozygous state in individuals with hyperimmunoglobulin D syndrome (HIDS) with reduced mevalonate kinase activity and has been implicated as the most common pathogenic HIDS variant (Houten 1999, Houten 2003). The variant is listed in the ClinVar database (Variation ID: 11929) and in the Genome Aggregation Database with an allele frequency of 0.16% (438/275368 alleles). Considering available information, this variant is classified as pathogenic.

RECOMMENDATIONS

Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic MVK variants (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS

Likely benign and benign variants are not included in this report.

REFERENCES

Cuisset et al. Molecular analysis of MVK mutations and enzymatic activity in hyper-IgD and periodic fever syndrome. *Eur J Hum Genet.* 2001 9(4):260-6.

Dunn K et al. Mevalonate kinase deficiency presenting as recurrent rectal abscesses and perianal fistulae. *Ann Allergy Asthma Immunol.* 2018 Feb;120(2):214-215.

Hinson DD et al. Identification of a mutation cluster in mevalonate kinase deficiency, including a new mutation in a patient of Mennonite ancestry. *Am J Hum Genet.* 1999 Aug;65(2):327-35.

Houten SM et al. Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinemia D and periodic fever syndrome. *Nat Genet.* 1999 22(2):175-7.

Houten SM et al. Carrier frequency of the V377I (1129G>A) MVK mutation, associated with Hyper-IgD and periodic fever syndrome, in the Netherlands. *Eur J Hum Genet.* 2003 11(2):196-200.

Steiner LA et al. Perinatal onset mevalonate kinase deficiency. *Pediatr Dev Pathol.* 2011 Jul-Aug;14(4):301-6.

Thors et al. Periodic fever in MVK deficiency: a patient initially diagnosed with incomplete Kawasaki disease. *Pediatrics.* 2014 133(2):e461-5.

This result has been reviewed and approved by Pinar Bayrak-Toydemir, M.D., Ph.D.

BACKGROUND INFORMATION: Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Periodic fever syndromes, also called autoinflammatory disorders, are a group of disorders which often present with recurrent inflammatory symptoms such as fever. The etiology of periodic fever syndromes is broad and includes infectious diseases, neoplastic conditions, inflammatory disorders, autoimmune conditions, and hereditary conditions. Conditions tested with this panel include familial Mediterranean fever (FMF) syndrome (MEFV gene), cyclic neutropenia and severe congenital neutropenia (ELANE gene), Majeed syndrome (LPIN2

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gene), hyperimmunoglobulinemia D syndrome (HIDS) (MVK gene), mevalonate kinase-associated periodic fever syndrome (MVK gene), familial cold autoinflammatory syndrome (FCAS) (NLRP3 gene, NLRP12 gene), Muckle-wells syndrome (NLRP3 gene), neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA) (NLRP3 gene), Blau syndrome/pediatric granulomatous arthritis (NOD2 gene), pyogenic sterile arthritis pyoderma gangrenosum acne (PAPA) (PSTPIP1 gene), autoinflammatory syndrome, familial, Behcet-like (TNFAIP3 gene), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) (TNFRSF1A gene).

EPIDEMIOLOGY: The prevalence varies by condition and ethnicity.

INHERITANCE: Autosomal recessive for MEFV, MVK, LPIN2; autosomal dominant for TNFAIP3, TNFRSF1A, NOD2, NLRP12, NLRP3, ELANE, and PSTPIP1.

GENES TESTED: ELANE**, LPIN2, MEFV, MVK, NLRP12**, NLRP3, NOD2**, PSTPIP1, TNFAIP3**, TNFRSF1A

** - Deletion/duplication detection is not available for this gene.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable form of a periodic fever syndrome. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

Single exon deletions/duplications will not be called for the following exons:
LPIN2(NM_014646) 13,16;MVK(NM_000431) 11;PSTPIP1(NM_001321136) 2;PSTPIP1(NM_003978) 10;TNFRSF1A(NM_001346092) 6

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Periodic Fever Panel Specimen	19-326-402587	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Periodic Fever Panel Interp	19-326-402587	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical