Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: arup, arup

**Patient: FMF NGS, EXAMPLE**

| | |
|---|---|
| **DOB** | |
| **Sex:** | Male |
| **Patient Identifiers:** | 36419 |
| **Visit Number (FIN):** | 36738 |
| **Collection Date:** | 2/23/2022 07:44 |

## Familial Mediterranean Fever (MEFV) Sequencing

ARUP test code 3004434

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|---|---|
| FMF Specimen | Whole Blood |
| FMF Interp | Positive |

INDICATION FOR TESTING
Suspected diagnosis of familial Mediterranean fever

RESULT
Two apparent copies of a pathogenic variant were detected in the MEFV gene.

PATHOGENIC VARIANT
Gene: MEFV (NM_000243.2)
Nucleic Acid Change: c.2080A>G; homozygous
Amino Acid Alteration: p.Met694Val
Inheritance: Autosomal recessive

INTERPRETATION
Two apparent copies of a pathogenic variant, c.2080A>G; p.Met694Val, were detected in the MEFV gene by massively parallel sequencing. Although copy number cannot be determined by this assay, large deletions/duplications have never been reported in the MEFV gene; therefore, this result is predicted to represent homozygosity for the identified variant. This molecular result is consistent with a diagnosis of familial Mediterranean fever (FMF).

No additional pathogenic variants were identified in the MEFV gene by massively parallel sequencing. Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

Evidence for variant classification: The MEFV c.2080A>G; p.Met694Val variant (rs61752717) has been published as a common familial Mediterranean fever (FMF) pathogenic variant (The International FMF Consortium, 1997; Touitou, 2001). Functional analysis of the variant protein shows diminished capacity to suppress IL-8 secretion in synovial cell cultures (Sugiyama, 2014). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 2538) and is seen in the general population at an overall frequency of 0.03% (74/277222 including 1 homozygote) in the Genome Aggregation Database. Additionally, another variant at this codon (Met694Ile) has been reported in individuals with FMF and is considered pathogenic (Sugiyama, 2014). Based on the available information, this variant is considered pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management.

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

At-risk family members should be offered targeted sequencing for the identified pathogenic MEFV variant (Familial Mutation, Targeted Sequencing; ARUP test code 2001961). This individual's reproductive partner should be offered carrier screening for FMF.

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

REFERENCES
The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell. 1997;90:797-807.

Sugiyama R et al. Defect of suppression of inflammasome-independent interleukin-8 secretion from SW982 synovial sarcoma cells by familial Mediterranean fever-derived pyrin mutations. Mol Biol Rep. 2014;41(1):545-53.

Touitou I. The spectrum of Familial Mediterranean Fever (FMF) mutations. Eur J Hum Genet. 2001;9(7):478-483.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Familial Mediterranean Fever (MEFV) Sequencing

CHARACTERISTICS: Familial Mediterranean fever (FMF) is a genetic condition characterized by recurrent but short-lived attacks of fever, abdominal pain, joint pain, and/or skin rashes. Symptoms and frequency of these attacks are highly variable. Renal amyloidosis is another common complication in untreated individuals and may be the only manifestation in some patients.

CAUSE: Pathogenic germline variants in the MEFV gene

INHERITANCE: Autosomal recessive although some heterozygous individuals may have symptoms

CLINICAL SENSITIVITY: 75-90%

GENE TESTED: MEFV (NM_000243)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted MEFV gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. Human genome build 19 (Hg 19) was used for data analysis.

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

LIMITATIONS: A negative result does not exclude a diagnosis of familial Mediterranean fever. This test only detects variants within the coding regions and intron-exon boundaries of the MEFV gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA)

mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

| Procedure | Accession | Collected | Received | Verified/Reported |
|---|---|---|---|---|
| FMF Specimen | 22-054-100680 | 2/23/2022 7:44:00 AM | 2/23/2022 7:44:54 AM | 2/23/2022 7:48 00 AM |
| FMF Interp | 22-054-100680 | 2/23/2022 7:44:00 AM | 2/23/2022 7:44:54 AM | 2/23/2022 7:48 00 AM |

END OF CHART