ARUP LABORATORIES
800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Tracy I. George, MD, Chief Medical Officer

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/17/1995
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Familial Mediterranean Fever (MEFV) Sequencing

ARUP test code 2002658

FMF FGS Specimen	Whole Blood	
Familial Mediterranean Fever (MEFV) Int	**Positive**	*

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

TEST PERFORMED - 2002658
TEST DESCRIPTION - Familial Mediterranean Fever (MEFV) Sequencing
INDICATION FOR TEST - Not Provided

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

DNA VARIANT
Classification: Pathogenic
Gene: MEFV
Nucleic Acid Change: c.2080A>G; Homozygous
Amino Acid Alteration: p.Met694Val

INTERPRETATION
Two apparent copies of a pathogenic variant, c.2080A>G; p.Met694Val, were detected in the MEFV gene. Sequence analysis is unable to detect large deletions; therefore, this individual either has two copies of the identified variant or a single copy of the variant and a large deletion on the opposite chromosome. Parental testing could determine which of the above scenarios is correct. Homozygosity for p.Met694Val is consistent with a clinical diagnosis of familial Mediterranean fever (FMF).

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 above information, this variant is considered pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members, ideally beginning with the parents, 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
Reference Sequence: GenBank # NM_000243.2 (MEFV)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. 1997 Cell. 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 Jan;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 Steven Steinberg, Ph.D.

Background Information for Familial Mediterranean Fever (MEFV) Sequencing:

Characteristics: Recurrent episodes of inflammation, fever, abdominal pain, chest pain, joint pain, skin eruptions and the development of renal amyloidosis.
Prevalence: 1 in 1,000 worldwide.
Inheritance: Primarily autosomal recessive; some activating mutations appear to be autosomal dominant.
Cause: Pathogenic MEFV gene mutations.
Clinical Sensitivity: Approximately 80 percent.
Methodology: Bidirectional sequencing of the entire MEFV coding region and intron-exon boundaries.
Analytical Sensitivity and Specificity: 99 percent.
Limitations: Diagnostic errors can occur due to rare sequence variations. Regulatory region, intronic mutations and large deletions/duplications will not be detected.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online at www.aruplab.com.

See Compliance Statement C: www.aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
FMF FGS Specimen	20-127-401992	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Familial Mediterranean Fever (MEFV) Int	20-127-401992	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