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.

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

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