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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/4/2019
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication

ARUP test code 3002100

Tuberous Sclerosis Specimen	Whole Blood
Tuberous Sclerosis Interp	Positive

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

INDICATION FOR TESTING
Suspected diagnosis of Tuberous Sclerosis Complex (TSC).

RESULT
One pathogenic variant was detected in the TSC2 gene.

PATHOGENIC VARIANT
Gene: TSC2 (NM_000548.4)
Nucleic Acid Change: c.855C>G; Heterozygous
Amino Acid Alteration: p.Tyr285Ter
Inheritance: Autosomal Dominant

INTERPRETATION
One copy of a pathogenic variant, c.855C>G; p.Tyr285Ter, was detected in the TSC2 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic TSC2 variants are inherited in an autosomal dominant manner, and are associated with tuberous sclerosis complex (TSC). Future offspring of this individual have a 50 percent chance of inheriting the pathogenic variant.

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 TSC2 c.855C>G; p.Tyr285Ter variant is reported in an individual with a clinical diagnosis of TSC (Yang 2017). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Loss of function TSC2 variants are a known pathogenic mechanism (Northrup 1999). Based on available information, this variant is considered 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 TSC2 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not reported.

REFERENCES
Northrup H et al. Tuberous Sclerosis Complex. 1999 Jul 13 (Updated 2020 Apr 16). In: Adam MP et al., editors. GeneReviews (Internet). Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1220/
Yang G et al. Phenotypic and genotypic characterization of Chinese children diagnosed with tuberous sclerosis complex. Clin Genet. 2017 May;91(5):764-768.

This result has been reviewed and approved by [redacted]

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BACKGROUND INFORMATION: Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Tuberous sclerosis complex (TSC) is a multisystem, genetic disorder causing numerous benign tumors, as well as intellectual and developmental disabilities. Tumors can occur in the skin, brain, kidneys, and other organs, and can lead to significant health complications and may be life threatening.
PREVALENCE: 1 in 6,000 individuals
CAUSE: Pathogenic germline variants in TSC1 and TSC2
INHERITANCE: Autosomal dominant; approximately 66 percent are de novo
PENETRANCE: Complete penetrance with variable expressivity
CLINICAL SENSITIVITY: 95 percent
GENES TESTED: TSC1, TSC2
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 targeted genes. Human genome build 19 (Hg 19) was used for data analysis.
ANALYTICAL SENSITIVITY/SPECIFICITY: 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 diagnosis of TSC. 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 1 kb 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 mosaic or 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: TSC2 (NM_000548) 17,29,41

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Tuberous Sclerosis Specimen	21-003-108179	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Tuberous Sclerosis Interp	21-003-108179	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