

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

Physician: Doctor, Example

Patient: Patient, Example

DOB: 1/3/2025
Gender: Female
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

RESULT
One pathogenic variant was detected in the TSC2 gene.

PATHOGENIC VARIANT
Gene: TSC2 (NM_000548.3)
Nucleic Acid Change: Deletion of exons 17-30; Heterozygous
Inheritance: Autosomal Dominant

INTERPRETATION
According to the information provided to ARUP, this individual has cardiac rhabdomyomas and subependymal nodules. One pathogenic variant, deletion of exons 17-30, were detected in the TSC2 gene by massively parallel sequencing-based deletion/duplication analysis and confirmed by exon-level microarray. Pathogenic TSC2 variants are inherited in an autosomal dominant manner and are associated with tuberous sclerosis complex (TSC). Therefore, this result is consistent with a diagnosis of TSC. Guidelines from the National Comprehensive Cancer Network (NCCN) and International Tuberous Sclerosis Consensus Conference are available for medical management in heterozygous individuals (NCCN Guidelines, Northrup 2021). This individual's future offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The TSC2 deletion of exons 17-30, to our knowledge, is not reported in the medical literature or gene specific databases. This deletion is also absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This is a multi-exon deletion, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Other protein-truncating deletions in this region have been described in individuals affected with tuberous sclerosis complex (Reyna-Fabian 2020, Rosengren 2020, Savini 2020). Based on available information, this deletion is classified as pathogenic.

RECOMMENDATIONS
Genetic consultation, including a discussion of medical screening and management, is indicated. At-risk family members should be offered testing for the identified pathogenic variant.

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

COMMENTS

Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations: None

REFERENCES

National Comprehensive Cancer Network. Hereditary Renal Cell Carcinoma Guideline (2.2024):
www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
Northrup H et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. *Pediatr Neurol*. 2021 Oct;123:50-66. PMID: 34399110.
Reyna-Fabian ME et al. First comprehensive TSC1/TSC2 mutational analysis in Mexican patients with Tuberous Sclerosis Complex reveals numerous novel pathogenic variants. *Sci Rep*. 2020 Apr 20;10(1):6589. PMID: 32313033.
Rosengren T et al. Mutational analysis of TSC1 and TSC2 in Danish patients with tuberous sclerosis complex. *Sci Rep*. 2020 Jun 18;10(1):9909. PMID: 32555378.
Savini MN et al. Electro-clinical and neurodevelopmental outcome in six children with early diagnosis of tuberous sclerosis complex and role of the genetic background. *Ital J Pediatr*. 2020 Mar 27;46(1):36. PMID: 32216820.

This result has been reviewed and approved by [REDACTED]

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% are de novo

PENETRANCE: Complete penetrance with variable expressivity

CLINICAL SENSITIVITY: 95%

GENES TESTED: TSC1, TSC2

METHODOLOGY: Probe hybridization-based 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 to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. 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. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

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



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. 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. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. 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. The U.S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Tuberous Sclerosis Specimen	25-006-401477	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Tuberous Sclerosis Interp	25-006-401477	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