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Patient Report

Patient Age/Gender: 36 hours Female

Specimen Collected: 08-Dec-20 12:49

Tuberous Sclerosis Complex |Received: 08-Dec-20 12:49 Report/Verified: 08-Dec-20 12:59

	Result	Units	Reference Interval
Tuberous Sclerosis Specimen	Whole Blood		
Tuberous Sclerosis Interp	Positive f1 i1		

Result Footnote

f1: Tuberous Sclerosis Interp

Section 79-1 of New York State Civil Rights Law requires informed consent be obtained from patients (or their legal guardians) prior to pursuing genetic testing. These forms must be kept on file by the ordering physician. Consent forms for genetic testing are available at www.aruplab.com. Incidental findings are not reported unless clinically significant but are available upon request.

INDICATION FOR TESTING
Confirm Diagnosis

RESULT
One pathogenic variant was detected in the TSC1 gene.

PATHOGENIC VARIANT
Gene: TSC1 (NM_000368.4)
Nucleic Acid Change: c.2818C>T
Amino Acid Alteration: p.Gln940Ter
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.2818C>T; p.Gln940Ter, was detected in the TSC1 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic TSC1 variants are inherited in an autosomal dominant manner, and are associated with tuberous sclerosis complex (TSC). The 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 TSC1 c.2818C>T; p.Gln940Ter variant, to our knowledge, has not been reported in the medical literature or in gene-specific databases. This variant is also absent from general population databases (1000 Genomes Project, Exome Variant Server, and Genome Aggregation Database), indicating it is not a common polymorphism. This variant induces an early termination codon in the C-terminal putative coiled-coil domain and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Variants that introduce premature termination codons are responsible for the majority of TSC1-associated tuberous sclerosis (Curatolo, 2015). 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 should be offered testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

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

Result Footnote

f1: Tuberous Sclerosis Interp
REFERENCES
Curatolo et al. Genotype/Phenotype Correlations in Tuberous Sclerosis Complex. Semin Pediatr Neurol. 2015; 22(4):259-73.

This result has been reviewed and approved by [redacted]

Test Information

i1: Tuberous Sclerosis Interp
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.

Test Information

i1: Tuberous Sclerosis Interp

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.