

Specimen Collected: 08-Dec-20 12:52

Tuberous Sclerosis Complex, Fetal | Received: 08-Dec-20 12:52

Report/Verified: 08-Dec-20 13:12

Result	Units	Reference Interval
Maternal Contamination Study Fetal Cells ^{f1} Study Fetal Spec		
Maternal Contam Study, Whole Blood ⁱ¹ Maternal Spec		
Tuberous Sclerosis Fetal Specimen	Cultured Amnio	
Tuberous Sclerosis Fetal Interp	Positive ^{f2 i2}	

Result Footnote

f1: Maternal Contamination Study Fetal Spec

Single fetal genotype present; no maternal cells present. Fetal and maternal samples were tested using STR markers to rule out maternal cell contamination.

f2: Tuberous Sclerosis Fetal 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

Fetal cardiac rhabdomyoma

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 in this fetal sample. Pathogenic TSC1 variants are inherited in an autosomal dominant manner, and are associated with tuberous sclerosis complex (TSC). Therefore, this fetus is predicted to be affected.

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.

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H=High, i=Test Information, L=Low, t=Interpretive Text, @=Performing Lab

Unless otherwise indicated, testing performed at:

ARUP Laboratories

500 Chipeta Way, Salt Lake City, UT 84108

Laboratory Director: Tracy I. George, MD

ARUP Accession: 20-343-900159

Report Request ID: 13692274

Printed: 08-Dec-20 13:27

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Result Footnote

f2: Tuberous Sclerosis Fetal Interp

RECOMMENDATIONS

Genetics consultation is indicated. At-risk family members should be offered targeted testing for the identified pathogenic TSC1 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Because parental somatic or germline mosaicism for the identified TSC1 pathogenic variant cannot be excluded. The parents of this fetus should be offered prenatal diagnosis in future pregnancies (Familial Mutation, Targeted Sequencing, Fetal. ARUP test code 2001980).

For quality assurance purposes, ARUP Laboratories will confirm the above result at no charge following delivery. Order Confirmation of Fetal Testing and include a copy of the original fetal report (or the mother's name and date of birth) with the test submission. Please contact an ARUP genetic counselor at (800) 242-2787, extension 2141 prior to specimen submission.

COMMENTS

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

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: Maternal Contam Study, Maternal Spec

For quality assurance purposes, ARUP Laboratories will confirm the above result at no charge following delivery. Order Confirmation of Fetal Testing and include a copy of the original fetal report (or the mother's name and date of birth) with the test submission. Please contact an ARUP genetic counselor at (800) 242-2787 extension 2141 prior to specimen submission.

i2: Tuberous Sclerosis Fetal Interp

BACKGROUND INFORMATION: Tuberous Sclerosis Complex Panel,
Sequencing and Deletion/Duplication,
Fetal

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.

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Test Information

i2: Tuberos Sclerosis Fetal Interp

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 1kb 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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