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Patient Report

Patient Age/Sex: Male

Specimen Collected: 09-Jun-22 11:36

Tuberous Sclerosis Complex, Fetal | Received: 09-Jun-22 11:36 Report/Verified: 09-Jun-22 11:44

Procedure	Result	Units	Reference Interval
Tuberous Sclerosis Fetal Interp	Positive [f1]		
Tuberous Sclerosis Fetal Specimen	Cultured CVS		
Maternal Contamination Study Fetal Spec	Fetal Cells [f2]		
Maternal Contam Study, Maternal Spec	Whole Blood [i1]		

Result Footnote

f1: Tuberous Sclerosis Fetal Interp
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.
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

Result Footnote

f1: Tuberous Sclerosis Fetal Interp
(800) 242-2787, extension 2141, prior to specimen submission.

COMMENTS
Likely benign and benign variants are not reported.

REFERENCES
Curatolo, et al. Genotype/phenotype correlations in tuberous sclerosis complex. Semin Pediatr Neurol. 2015;22(4):259–73.
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% 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.

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

Result Footnote

f1: Tuberous Sclerosis Fetal Interp
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. 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.

f2: 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.

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.