Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication

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Tuberous sclerosis complex (TSC) is a multisystem, genetic disorder causing numerous benign tumors as well as cognitive and developmental disabilities. Tumors can occur in the skin, brain, kidneys, and other organs, and can lead to significant health complications. TSC may be life threatening. Nearly all affected individuals have skin findings that develop early in life, which can include pigmentary changes, thickened skin, growths in the nails, and facial angiofibromas. Changes in cognitive ability are common and can present in a variety of ways, including autism spectrum disorder, behavioral change, and cognitive disability. Seizures occur in more than 80% of affected individuals. TSC may be suspected prenatally due to the presence of a fetal cardiac rhabdomyoma, the most common cardiac tumor seen on ultrasound.[1]

Disease Overview

Diagnostic Criteria

- TSC should be suspected in individuals with either one major feature or two or more minor features.
- A definitive diagnosis is established by any of the following:
  - The presence of two major features
  - One major feature with two or more minor features
  - Identification of a pathogenic variant in either *TSC1* or *TSC2* by molecular genetic testing

Major Features	Minor Features
Angiofibromas or a fibrous cephalic plaque	"Confetti" skin lesions
Cardiac rhabdomyoma	Dental enamel pits
Cortical dysplasias	Intraoral fibromas
Hypomelanotic macules	Multiple renal cysts
Lymphangioleiomyomatosis (LAM)	Nonrenal hamartomas
Multiple retinal nodular hamartomas	Retinal achromic patch
Renal angiomyolipoma	
Shagreen patch	
Subependymal giant cell astrocytoma	
Subependymal nodules	
Ungual fibromas	

Sources: Northrup, 2021[1]; Northrup, 2013[2]

Genetics

Genes Tested

TSC1 and *TSC2*

Prevalence

1 in 6,000 individuals[3]

Featured ARUP Testing

Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication 3002100

Method: Massively Parallel Sequencing

Preferred DNA test to confirm clinical diagnosis of TSC

Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication, Fetal 3002096

Method: Massively Parallel Sequencing

- Use to confirm diagnosis of TSC in a fetus with suspected cardiac rhabdomyoma on ultrasound
- Use to confirm diagnosis in a fetus at risk for TSC based on a positive family history

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Etiology

Pathogenic variants in either the *TSC1* or *TSC2* gene

Inheritance

- Autosomal dominant
- Approximately 66% are de novo

Genotype-Phenotype Correlation

TSC2 pathogenic variants produce a more severe phenotype and are more likely to be sporadic (de novo) than *TSC1* variants. Individuals with *TSC2* variants are at a greater risk for renal malignancy, cognitive disability, autism spectrum disorder, and infantile spasm. However, there is variable expressivity and clinical overlap between *TSC1* and *TSC2* variants.

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

95% for TSC[1]

- *TSC1*: Approximately 26%
- *TSC2*: Approximately 69%
- Unknown: Approximately 5%

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [Single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Significance
Positive	One *TSC1* or *TSC2* pathogenic variant detected	Consistent with a diagnosis of TSC
Negative	No *TSC1* or *TSC2* pathogenic variants detected	Diagnosis of TSC is unlikely but not excluded
Uncertain	*TSC1* or *TSC2* variant of unknown clinical significance detected	It is unknown whether variant is benign or pathogenic

Limitations

- A negative result does not exclude a diagnosis of TSC.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massive parallel sequencing
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive or homologous regions
  - Low-level somatic variants

References

1. Northrup H, Koenig MK, Pearson DA, et al. Tuberous sclerosis complex. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2022. [Revised: Dec 2021; Accessed: Jun 2022]

2. Northrup H, Krueger DA; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. 2013;49(4):243-254.

3. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann N Y Acad Sci*. 1991;615:125-127.

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com