Tuberous Sclerosis Complex

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. TSC may be life threatening. Nearly all affected individuals have skin findings that develop early in life and can include pigmentary changes, thickened skin, growths in the nails, and facial angiofibromas. Intellectual changes are common and can present in a variety of ways, including autism spectrum disorder, behavioral changes, and intellectual disability. Seizures occur in >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.

Disease Overview

Diagnostic Criteria

- A diagnosis of 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*[1] 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
LAM	Nonrenal hamartomas
Multiple retinal nodular hamartomas	Retinal achromic patch
Renal angiomyolipoma	
Shagreen patch	
Subependymal giant cell astrocytoma	
Subependymal nodules	
Ungual fibromas	

LAM, lymphangioleiomyomatosis

Prevalence

1 in 6,000 individuals[2]

Etiology

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

Tests to Consider

Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication 3002100

Method: Massively Parallel Sequencing/Genomic Microarray (Oligo-based Array)

Preferred DNA test to confirm clinical diagnosis of TSC

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

Method: Massively Parallel Sequencing/Genomic Microarray (Oligo-based Array)

- 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

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

- This is the recommended test for a known familial sequence variant previously identified in a family member.
- A copy of the family member's test result documenting the known familial variant is required.

Inheritance

- Autosomal dominant
- ~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, intellectual disability, autism spectrum disorder, and infantile spasm. However, there is variable expressivity and clinical overlap between *TSC1* and *TSC2* variants.

Test Description

Clinical Sensitivity

95%[3]

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

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
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massive parallel sequencing
  - Single exon deletions/duplications or deletions/duplications less than 1 kb by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications will not be called for the following exons:
    - TSC2 (NM_000548) 17, 29, 41

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

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

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

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

References

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

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

3. Northrup H, Koenig MK, Pearson DA, et al. Tuberous sclerosis complex. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Revision: Apr 2020; Accessed: Jun 2020]

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