Last Updated March 2020

Tuberous Sclerosis Complex (TSC): *TSC1* and *TSC2* Mutations

Tuberous Sclerosis Complex, or TSC, is an extremely variable disease that results in benign (non-cancerous) tumors forming throughout the body. The most common benign tumors occur in the skin, brain, kidneys, lungs, and heart. While most of these tumors are not cancerous, they may still cause organ dysfunction or other serious problems in the body, so early detection is important. TSC may also cause autism spectrum disorder and seizures. TSC is caused by a likely pathogenic or pathogenic mutation in either the *TSC1* or *TSC2* gene.

Features of TSC

This chart summarizes the features, both major and minor, of TSC. Presence of these features helps clinicians make a diagnosis of TSC, although genetic testing is utilized as well.

Major Features	**Minor Features**
1. Hypomelanotic macules (≥3. at least 5·mm diameter) **2.** Angiofibroma (≥3) or fibrous cephalic plaque **3.** Ungual fibromas (≥2) **4.** Shagreen patch **5.** Multiple retinal hamartomas **6.** Multiple cortical tubers and/or radial migration lines **7.** Subependymal giant cell astrocytoma (SEGA) **8.** Subependymal nodule (≥2) **9.** Cardiac rhabdomyoma **10.** Lymphangioleiomyomatosis (LAM)* **11.** Angiomyolipomas (>2)*	**1.** "Confetti" skin lesions **2.** Dental enamel pits (>3) **3.** Intraoral fibromas (≥2) **4.** Retinal achromatic patch **5.** Multiple renal cysts **6.** Nonrenal hamartomas **7.** Sclerotic bone lesions

- **Definite diagnosis of TSC:** Two major features or one major feature with 2 minor features.
    - **A combination of the two major clinical features LAM and angiomyolipomas without other features does not meet criteria for a Definite Diagnosis*
- **Possible diagnosis of TSC**: Either one major feature or > 2 minor features.

TSC Risks and Management Recommendations

A summary of the natural history and general management guidelines is included below for your information. The following recommendations are based on the 2012 International Tuberous Sclerosis Complex Conference (Krueger & Northrup, 2013) and the Tuberous Sclerosis Alliance.

Skin and Teeth: The skin is affected in virtually 100% of individuals with TSC. Skin lesions include: hypomelanotic macules (ash leaf patch) (90%); facial angiofibromas (75%); shagreen patches (50%); fibrous facial plaques and ungual fibromas (17-87%). Dental enamel pits are frequent.

- Surveillance: A detailed dermatologic exam at initial diagnosis and annual dermatologic examinations are recommended. A detailed dental examination at initial diagnosis (with panoramic x-rays by age 7 is recommended, and individuals with TSC should have regular dental examinations every 6 months.
- Treatment: Rapidly changing, disfiguring, or symptomatic lesions should be treated as appropriate for the lesion. Approaches include surgical excision, laser(s), or topical mTOR inhibitors may be beneficial.

Central Nervous System (CNS): CNS tumors are the leading cause of morbidity and mortality in TSC. Brain lesions include SENs, cortical tubers, SEGAs and can be distinguished with neuroimaging studies. SENs occur in 90% of individuals, cortical or subcortical tubers in 70%, and SEGAs in 6-14%. More than 80% of individuals with TSC have been reported to have seizures. Early-onset seizures and increased tuber burden are risk factors for cognitive impairment.

- Seizures: Early control of seizures is thought to prevent subsequent epileptic encephalopathy and reduce cognitive impairment. Parents should be trained to recognize symptoms of seizures. It is recommended that a baseline EEG be obtained at initial diagnosis. If this exam is abnormal, follow up 24-hour video EEG is recommended, and routine EEGs are recommended for individuals with seizures. Vigabatrin is recommended for infantile spasms. ACTH is a second line therapy. Epilepsy surgery should be considered when seizures cannot be otherwise managed, and it is recommended that this be performed at centers with expertise in TSC.
- Surveillance: MRI with and without gadolinium every 1-3 years for asymptomatic individuals under age 25. Individuals without SEGA by the age of 25 years do not require continued surveillance imaging. MRI should be done more frequently in symptomatic individuals. If MRI is not available, CT or head ultrasound (in infants) can be done but is not optimal. Early identification of an enlarging giant cell astrocytoma permits medical therapy with mTOR inhibitors which obviates the need for neurosurgical intervention in many individuals. Symptomatic SEGAs require surgical intervention.
- Evaluation/Intervention: A comprehensive multidisciplinary assessment for functional and clinical manifestations of brain dysfunction should be performed. This includes evaluation for aggressive behavior, autism spectrum disorder, neuropsychological deficits, and school/occupational functioning. Interventions should be developed for any specific areas of concern.

Kidneys: Renal disease is the second leading cause of early death. Approximately 80% of individuals with TSC have an identifiable renal lesion by age 10. Renal lesions include benign angiomyolipoma, epithelial cysts, oncocytoma, malignant angiomyolipoma, and renal cell carcinoma.

- Surveillance: Abdominal MRI and blood tests to determine glomerular filtration rate (GFR) is recommended at the time of diagnosis. MRI every 1-3 years, annual blood pressure monitoring and GFR are recommended.
- Surgery: It is recommended that persons with symptomatic angiomyolipomas greater than 3.5-4.0 cm be treated with mTOR inhibitor therapy. Selective embolization or kidney-sparing resection can be considered as a second line treatment.

Heart: Cardiac rhabdomyomas are present in 47-67% of individuals with TSC. These tumors have been documented to regress with time and eventually disappear. If cardiac outflow obstruction does not occur at birth, the individual is unlikely to have health problems from these tumors later.

- Surveillance: Echocardiography is recommended at initial diagnosis in individuals under age 3. ECG should be performed at all ages at initial diagnosis. Children with asyptomatic cardiac rhabdomyomas should be followed with echocardiography every 1-3 years, and asymptomatic patients of all ages should have an ECG every 3-5 years. Symptomatic patients may require more frequent imaging.

- Surgery: Surgical intervention immediately after birth is only necessary when cardiac outflow obstruction occur.

Lung: Lymphangiomyomatosis (LAM) of the lung (which primarily affects women) is estimated to occur in approximately 30%-40% of females and 10-12% of males with TSC. The mean age of diagnosis for TSC LAM is 28.

- Surveillance: A baseline pulmonary function test (PFT) and high-resolution chest computed tomography (HCRT) should be performed at the time of initial diagnosis in females over the age of 18 and in symptomatic males. HCRT should be repeated every 5-10 years if the initial screen was normal. Individuals with lung cysts should have annual PFT and HRCT every 2-3 years. Evaluation for exertional dyspnea and shortness of breath at each clinic visit is recommended.
- Treatment: LAM may be treated with mTOR inhibitors. Lung transplantation can be considered.
- Agents to Avoid: Smoking and estrogen use can complicate LAMs, and should be avoided.

Eye: The retinal lesions of TSC are hamartomas (elevated mulberry lesions or plaque-like lesions) and achromic patches (similar to the hypopigmented skin lesions) and may be present in up to 75% of affected individuals. Although these lesions are usually asymptomatic, complications with enlarging retinal astrocytic hamartomas have included retinal detachment and neovascular glaucoma.

- Surveillance: Opthalmologic examination including dilated fundoscopy is recommended at initial diagnosis, followed by annual ophthalmologic exams for symptomatic individuals.

Other Cancer Risks: Although rare, extrarenal angiomyolipomas have been reported in the liver. Case reports of persons with TSC have also documented pituitary adenomas, parathyroid adenomas and hyperplasia, pancreatic adenomas, gastrinoma, pheochromocytoma, and carcinoids.

Resources for Individuals with TSC

- Accurate information and a wide array of resources may be found on the TS Alliance's website: https://www.tsalliance.org/

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *TSC1* or *TSC2* gene mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.