Tuberous Sclerosis Complex (TSC): Genetics and Care Guidelines

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Disclosure

• I am listed as an inventor on a patent application held by the Board of Regents of the University of Texas System for a topical composition of rapamycin for the treatment of facial angiofibromas
Objectives

- List and describe Major and Minor clinical features of TSC used to make a clinical diagnosis
- Describe genetic and molecular basis of TSC
- List current recommendations for surveillance and management for TSC
- Identify resources for families affected by TSC
Tuberous Sclerosis Complex (TSC)

- Autosomal dominant disorder in humans
- Develop hamartomas (benign tumors resulting from excessive growth of normal tissues)
- Most frequently affects: skin, brain, kidney, heart and eye
- Every tissue type of the body can be affected
Timeline of TSC Discoveries

- von Recklinghausen cardiac myomata in newborn
- Bourneville

1862

- Linkage to chromosome 9
- Genetic Heterogeneity

1879

- TSC2
- Insulin signaling pathway

1987

- TSC1
- mTOR

1993

- mTOR

1997

- Rapamycin tx for kidney and lung

2001

- Rapamycin trial for kidney and lung

2003

- Rapamycin tx for brain tumors

2006

- FDA approved therapies
- Many clinical trials

2008

- Many clinical trials

2012

- Many clinical trials

2018
Clinical Features of Tuberous Sclerosis

Skin Findings

Hypomelanotic macules

Facial angiofibromas
Clinical Features of Tuberous Sclerosis

Skin Findings

Ungual fibromas

Shagreen patches

Cephalic plaques
Clinical Features of Tuberous Sclerosis

Brain-Related System Findings

Subependymal glial nodules, Cortical tubers, SEGAs

Seizures, Intellectual disability/developmental delay, neuropsychiatric issues
Clinical Features of Tuberous Sclerosis

Kidney Findings

Angiomyolipomas, Renal Cell Carcinoma, Cysts
Clinical Features of Tuberous Sclerosis
Cardiac and Lung Findings

Cardiac rhabdomyoma on prenatal ultrasound

Lymphangioleiomyomatosis
Numerous clinical manifestations are associated with tuberous sclerosis complex (TSC). These include hypopigmented macules, subependymal nodules, epilepsy, facial angiofibromas, renal angiomyolipomas, cardiac rhabdomyomas, ungual fibromas, liver hamartomas, and retinal hamartomas. The prevalence of these manifestations varies throughout a patient's life, as illustrated in the graph.
## Causes of Premature Death in TSC Patients

<table>
<thead>
<tr>
<th>Count</th>
<th>Percentage</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>13/40</td>
<td>(32.5%)</td>
<td>Complications related to severe intellectual disability (status epilepticus: bronchopneumonia)</td>
</tr>
<tr>
<td>11/40</td>
<td>(27.5%)</td>
<td>Renal disease</td>
</tr>
<tr>
<td>10/40</td>
<td>(25%)</td>
<td>Brain tumors</td>
</tr>
<tr>
<td>4/40</td>
<td>(10%)</td>
<td>Lymphangioleimyomatosis</td>
</tr>
<tr>
<td>1/40</td>
<td>(2.5%)</td>
<td>Cardiac rhabdomyomas</td>
</tr>
<tr>
<td>1/40</td>
<td>(2.5%)</td>
<td>Thoracic aneurysm</td>
</tr>
</tbody>
</table>

40/355 (11.3%) Individuals with TSC Followed Long-Term
Diagnosis of TSC

• Diagnosing tuberous sclerosis complex (TSC) is a challenge\textsuperscript{1-3}
• TSC was underdiagnosed until the 1980s\textsuperscript{1}
  • Population prevalence of TSC was estimated to be between 1:100,000 and 1:200,000
• Current birth incidence of TSC is estimated to be between 1:6,000 to 1:10,000, with a population prevalence of approximately 1:20,000\textsuperscript{1}
• Two-thirds of patients have no parental history of TSC\textsuperscript{2}
• There is no single symptom in all patients, and none are absolutely pathognomonic\textsuperscript{3}

2012 Diagnostic Criteria Update: Clinical Diagnostic Criteria

**Major Features (11)**
1. Hypomelanotic macules (≥3, at least 5-mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias (≥3)*
7. SENs (≥2)
8. SEGAs
9. Cardiac rhabdomyoma
10. LAM†
11. Angiomyolipomas (≥2)†

**Minor Features (6)**
1. “Confetti” skin lesions
2. Dental enamel pits (≥3)
3. Intraoral fibromas (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartoma

- Includes tubers and cerebral white matter radial migration lines
- A combination of the 2 major clinical features (LAM and angiomyolipoma), without other features, does not meet criteria for a definite diagnosis.

Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference

Hope Northrup MD, Darcy A. Krueger MD PhD, on behalf of the International Tuberous Sclerosis Complex Consensus Group

Original Article

Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference

Darcy A. Krueger MD PhD, Hope Northrup MD, on behalf of the International Tuberous Sclerosis Complex Consensus Group

Original Article

Subependymal Giant Cell Astrocytoma: Diagnosis, Screening, and Treatment. Recommendations From the International Tuberous Sclerosis Complex Consensus Conference 2012

Jonathan Roth MD, E. Steve Roach MD, Ute Bartels MD, Sergiusz Jóźwiak MD, Mary Kay Koenig MD, Howard L. Weiner MD, David N. Franz MD, Henry Z. Wang MD

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www.tsalliance.org/consensus
Genetic Aspects of TSC

• Autosomal dominant inheritance

• Two-thirds of cases sporadic; one-third of cases familial

• Two known genes: \textit{TSC1} and \textit{TSC2}

• Variable expression

• Common in the population with approximately 1:6,000-10,000 individuals affected
TSC Genotype

~85-90% of affected individuals have identifiable TSC1 or TSC2 gene mutation
- TSC1 – over 95% protein truncating
- TSC2 – ~25% missense and ~70% protein truncating, ~5% large gene deletion/duplication

Remainder of mutations likely represent:
- Somatic mosaicism
- Mutations in unanalyzed gene regions
- Additional loci?
2012 Diagnostic Criteria Update: Genetic Diagnostic Criterion

- Most significant change in the diagnostic criteria
- Either a $TSC1$ or $TSC2$ pathogenic mutation is sufficient to make a definite diagnosis of TSC
- A pathogenic mutation is defined as:
  - A sequence variant that clearly inactivates the function of the TSC1 or TSC2 proteins
  - A mutation that prevents protein synthesis
  - A missense mutation whose effect on protein function has been established by functional assessment
- Other $TSC1$ or $TSC2$ variants, whose effect is less certain, do not meet these criteria and are not sufficient to make a definite diagnosis of TSC

10% to 15% of patients with TSC have no mutation identified (NMI) by conventional genetic testing; a normal result does not exclude TSC or have any effect on the use of clinical diagnostic criteria to diagnose TSC

Rapamycin

- Naturally occurring substance
- Discovered in 1965
- Binds mTOR and inhibits its action, thus preventing cell division and growth
- Also decreases levels of VEGF
Rapamycin

• Approved by the FDA in 1999 as an immunosuppressant drug to be used post renal transplant

• Side effect profile well defined:
  • Immunosuppression
  • Oral Ulcers
  • Skin Breakdown
  • Poor wound healing
  • Hyperlipidemia
  • Thrombocytopenia

- 1st report of use of rapamycin in TSC patients
- Showed regression of astrocytomas with low dose rapamycin
- Confirmed in subsequent case report by Koenig, Butler, & Northrup. (J Child Neurol 2008 Oct;23(10):1238-9.)
Figure 2. Case 1. Coronal T1 contrast-enhanced magnetic resonance imaging. Long-term follow-up: continued regression 20 months after starting rapamycin therapy, 8 months after therapy resumed. (Franz et al. Feb. 2006, Annals of Neurology)

A. Baseline

B. 2.5 months after rapamycin therapy

C. Recurrence after 8 months on rapamycin therapy, then 4 months without drug

D. 8 months after therapy resumed
Phase I-II Study of Everolimus in SEGA

Key Eligibility Criteria
- ≥3 yrs of age with TSC*
- Serial SEGA growth
- No signs of cerebral herniation or critical hydrocephalus

N=28

Baseline
- Physical exam
- MRI/MRS
- 24-hr video EEG

Everolimus 3 mg/m²/d, titrated to attain blood trough level 5-15 ng/mL

1 Mo
- Physical exam
- Hematology

2 Mos
- Physical exam
- Hematology

3 Mos
- Physical exam
- Hematology
- QOL
- MRI/MRS

6 Mos
- Physical exam
- Hematology
- QOL
- MRI/MRS
- Neuropsychology
- 24-hr video EEG

Primary endpoint: SEGA volume change between baseline and 6 mos

*Definitive diagnosis per modified Gomez criteria or positive results on genetic test.
†Upon completion of the core phase, pts can continue to receive everolimus if evidence of therapeutic benefit.

EEG=electroencephalography

Median reduction in SEGA volume at 6 mos was 0.80 cm³ ($P<0.001$)*

Responders (N)*:
- All pts (N): 28, 26, 27, 26, 18, 8
- Responders (N)*: 0, 65%, 78%, 77%, 67%, 75%

*By central review. Responders defined as pts demonstrating ≥30% reduction compared to baseline.

Median reduction in SEGA volume at 6 mos was 0.80 cm³ ($P<0.001$)*

Trials and Approval for Therapies in TSC

• Subependymal giant cell astrocytoma (SEGA)-October 2010
• Renal angiomyolipomas-April 2012
• Lymphangioleiomyomatosis-May 2015
• Intractable epilepsy in TSC patients-April 2018
• Trials assessing biomarkers for earlier interventions for seizures-ongoing
• Trials assessing cognitive outcomes-ongoing
• Trials working toward topical indication-ongoing
Surveillance and management recommendations for newly diagnosed or suspected tuberous sclerosis complex (TSC)

Genetics

- Obtain three-generation family history to assess for additional family members at risk of TSC
- Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed

Brain

- Perform magnetic resonance imaging (MRI) of the brain to assess for the presence of tubers, subependymal nodules (SEN), migrational defects, and subependymal giant cell astrocytoma (SEGA)
- Evaluate for TSC-associated neuropsychiatric disorder (TAND)
- During infancy, educate parents to recognize infantile spasms, even if none have occurred at time of first diagnosis
- Obtain baseline routine electroencephalogram (EEG). If abnormal, especially if features of TAND are also present, follow-up with a 24-hr video EEG to assess for subclinical seizure activity

Kidney

- Obtain MRI of the abdomen to assess for the presence of angiomyolipoma and renal cysts
- Screen for hypertension by obtaining an accurate blood pressure
- Evaluate renal function by determination of glomerular filtration rate (GFR)
Surveillance and management recommendations for newly diagnosed or suspected tuberous sclerosis complex (TSC)

Lung
- Perform baseline pulmonary function testing (pulmonary function testing and 6-minute walk test) and high-resolution chest computed tomography (HRCT), even if asymptomatic, in patients at risk of developing lymphangioleiomyomatosis (LAM), typically females 18 years or older. Adult males, if symptomatic, should also undergo testing
- Provide counsel on smoking risks and estrogen use in adolescent and adult females

Skin
- Perform a detailed clinical dermatologic inspection/exam

Teeth
- Perform a detailed clinical dental inspection/exam

Heart
- Consider fetal echocardiography to detect individuals with high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound
- Obtain an echocardiogram in pediatric patients, especially if younger than 3 yr of age
- Obtain an electrocardiogram (ECG) in all ages to assess for underlying conduction defects

Eye
- Perform a complete ophthalmologic evaluation, including dilated funduscopy, to assess for retinal lesions and visual field deficits
Surveillance and management recommendations for patients already diagnosed with definite or possible tuberous sclerosis complex (TSC)

Brain

- Obtain magnetic resonance imaging (MRI) of the brain every 1-3 yr in asymptomatic TSC patients younger than age 25 yr to monitor for new occurrence of subependymal giant cell astrocytoma (SEGA). Patients with large or growing SEGA, or with SEGA causing ventricular enlargement but yet are still asymptomatic, should undergo MRI scans more frequently and the patients and their families should be educated regarding the potential of new symptoms. Patients with asymptomatic SEGA in childhood should continue to be imaged periodically as adults to ensure there is no growth.

- Surgical resection should be performed for acutely symptomatic SEGA. Cerebral spinal fluid diversion (shunt) may also be necessary. Either surgical resection or medical treatment with mammalian target of rapamycin complex (mTOR) inhibitors may be used for growing but otherwise asymptomatic SEGA. In determining the best treatment option, discussion of the complication risks, adverse effects, cost, length of treatment, and potential impact on TSC-associated comorbidities should be included in the decision-making process.

- Perform screening for TSC-associated neuropsychiatric disorders (TAND) features at least annually at each clinical visit. Perform comprehensive formal evaluation for TAND at key developmental time points: infancy (0-3 yr), preschool (3-6 yr), pre-middle school (6-9 yr), adolescence (12-16 yr), early adulthood (18-25 yr), and as needed thereafter. Management strategies should be based on the TAND profile of each patient and should be based on evidence-based good practice guidelines/practice parameters for individual disorders (e.g., autism spectrum disorder, attention deficit hyperactivity disorder, anxiety disorder). Always consider the need for an individual educational program (IEP). Sudden change in behavior should prompt medical/clinical evaluation to look at potential medical causes (e.g., SEGA, seizures, renal disease).
Surveillance and management recommendations for patients already diagnosed with definite or possible tuberous sclerosis complex (TSC)

Brain

- Obtain routine electroencephalograph (EEG) in individuals with known or suspected seizure activity. The frequency of routine EEG should be determined by clinical need rather than a specific defined interval. Prolonged video EEG, 24 hr or longer, is appropriate when seizure occurrence is unclear or when unexplained sleep, behavioral changes, or other alteration in cognitive or neurological function is present.

- Vigabatrin is the recommended first-line therapy for infantile spasms. Adrenocorticotropic hormone (ACTH) can be used if treatment with vigabatrin is unsuccessful. Anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies. Epilepsy surgery should be considered for medically refractory TSC patients, but special consideration should be given to children at younger ages experiencing neurological regression and is best if performed at epilepsy centers with experience and expertise in TSC.

Eye

- Perform annual ophthalmologic evaluation in patients with previously identified ophthalmologic lesions or vision symptoms at the baseline evaluation. More frequent assessment, including those treated with vigabatrin, is of limited benefit and not recommended unless new clinical concerns arise.

Genetics

- Offer genetic testing and family counseling, if not done previously, in individuals of reproductive age or newly considering having children.
Surveillance and management recommendations for patients already diagnosed with definite or possible tuberous sclerosis complex (TSC)

**Kidney**
- Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1-3 yr throughout the lifetime of the patient.
- Assess renal function (including determination of glomerular filtration rate [GFR]) and blood pressure at least annually.
- Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy is to be avoided. For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first-line therapy. Selective embolization or kidney-sparing resection are acceptable second-line therapy for asymptomatic angiomyolipoma.

**Lung**
- Perform clinical screening for lymphangioleiomyomatosis (LAM) symptoms, including exertional dyspnea and shortness of breath, at each clinic visit. Counseling regarding smoking risk and estrogen use should be reviewed at each clinic visit for individuals at risk of LAM.
- Obtain high-resolution computed tomography (HRCT) every 5-10 yr in asymptomatic individuals at risk of LAM if there is no evidence of lung cysts on their baseline HRCT. Individuals with lung cysts detected on HRCT should have annual pulmonary function testing (pulmonary function testing and 6-min walk) and HRCT interval reduced to every 2-3 yr.
- mTOR inhibitors may be used to treat LAM patients with moderate to severe lung disease or rapid progression. TSC patients with LAM are candidates for lung transplantation but TSC comorbidities may impact transplant suitability.
Surveillance and management recommendations for patients already diagnosed with definite or possible tuberous sclerosis complex (TSC)

Skin

- Perform a detailed clinical dermatologic inspection/exam annually.
- Rapidly changing, disfiguring, or symptomatic TSC-associated skin lesions should be treated as appropriate for the lesion and clinical context, using approaches such as surgical excision, laser(s), or possibly topical mTOR inhibitor.

Teeth

- Perform a detailed clinical dental inspection/exam at minimum every 6 months and panoramic radiographs by age 7 yr, if not performed previously.
- Symptomatic or deforming dental lesions, oral fibromas, and bony jaw lesions should be treated with surgical excision or curettage when present.
TSC Centers of Excellence

• Scottish Rite Hospital for Children, Dallas, TX
• Cook Children’s Hospital, Fort Worth TX
• Dell Children’s Hospital, Austin, TX
• Texas Children’s Hospital, Houston, TX
• University of Texas, McGovern Medical School, Houston, TX

Recognized by the Tuberous Sclerosis Alliance as meeting criteria for designation as TSC Center of Excellence

https://www.tsalliance.org
Breakthroughs in TSC Biology

2018
TSC, a manageable chronic disease?

2006-2018
Clinical trials with mTOR inhibitors and other drugs using biomarkers

2002
*TSC1* and *TSC2* gene products, hamartin and tuberin, respectively, inhibit mTOR signaling

1997-2001
Mutational analysis of *TSC1* and *TSC2*; >3,600 unique *TSC1/2* allelic variants reported

1993-1997
Cloning of *TSC1* and *TSC2* genes