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Tuberous Sclerosis Complex

Synonym: Bourneville Disease

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Summary

Clinical characteristics

Tuberous sclerosis complex (TSC) involves abnormalities of the skin (hypomelanotic macules, confetti skin lesions, facial angiofibromas, shagreen patches, fibrous cephalic plaques, ungual fibromas); brain (subependymal nodules, cortical tubers, and subependymal giant cell astrocytomas [SEGAs], seizures, intellectual disability / developmental delay, psychiatric illness); kidney (angiomyolipomas, cysts, renal cell carcinomas); heart (rhabdomyomas, arrhythmias); and lungs (lymphangioleiomyomatosis [LAM], multifocal micronodular pneumonocyte hyperplasia). Central nervous system tumors are the leading cause of morbidity and mortality; renal disease is the second leading cause of early death.

Diagnosis/testing

The diagnosis of TSC is established in a proband with **one of the following**:

- Two major clinical features
- One major clinical feature and two or more minor features
- Identification of a heterozygous pathogenic variant in *TSC1* or *TSC2* by molecular genetic testing

Management

Treatment of manifestations: For enlarging SEGAs: mTOR inhibitors; neurosurgery when size causes life-threatening neurologic symptoms. For seizures: vigabatrin and other anti-seizure drugs, and on occasion, epilepsy surgery. For renal angiomyolipomas >4 cm, or >3 cm and growing rapidly: mTOR inhibitors are the recommended first line of therapy with secondary therapy options being embolization, renal sparing surgery, or ablative therapy. For facial angiofibromas: topical mTOR inhibitors. For symptomatic cardiac rhabdomyomas:

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surgical intervention or consideration of mTOR inhibitor therapy. For LAM: mTOR inhibitors. For TSC-associated neuropsychiatric disorder (TAND): refer to a suitable professional to provide appropriate treatment, which may include ABA therapy and consideration of medication for those with ADHD.

Prevention of secondary complications: For those on vigabatrin therapy, vision testing within four weeks of therapy initiation, at three-month intervals while on treatment, and three to six months after treatment is discontinued.

Surveillance: Brain MRI every one to three years in asymptomatic individuals with TSC younger than age 25 years to monitor for new occurrence of SEGAs; those with asymptomatic SEGA in childhood should continue to be imaged periodically in adulthood; for those with large or growing SEGA or SEGA causing ventricular enlargement, more frequent brain MRIs as deemed clinically appropriate; screening for TAND at least annually with comprehensive formal evaluation for TAND at key developmental time points; EEG in asymptomatic infants every six weeks up to age 12 months, every three months up to age 24 months, and in individuals with known or suspected seizure activity; MRI of the abdomen to assess for progression of angiomyolipoma and renal cystic disease every one to three years; assess renal function (glomerular filtration rate and blood pressure) at least annually; echocardiogram every one to three years in asymptomatic infants and children with cardiac rhabdomyomas until regression is documented; clinical screening for LAM symptoms (exertional dyspnea and shortness of breath) at each clinic visit in women older than age 18 years or those who report respiratory symptoms; high-resolution computed tomography (HRCT) every five to seven years through menopause in asymptomatic individuals at risk for LAM (adult females age >18 years) who have no evidence of lung cysts on baseline HRCT examination;for those with evidence of cystic lung disease consistent with LAM, follow-up scan intervals are determined on a case-by-case basis; annual dermatologic examination; dental examination every six months; annual ophthalmology evaluation.

Agents/circumstances to avoid: Smoking; estrogen use; nephrectomy.

Evaluation of relatives at risk: Identifying affected relatives enables monitoring for early detection of problems associated with TSC, which leads to earlier treatment and better outcomes.

Genetic counseling

TSC is inherited in an autosomal dominant manner. Two thirds of affected individuals have TSC as the result of a *de novo* pathogenic variant. The offspring of an affected individual are at a 50% risk of inheriting the pathogenic variant. If the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Consensus clinical diagnostic criteria for tuberous sclerosis complex (TSC) have been published [Northrup et al 2021] (full text).

Suggestive Findings

TSC **should be suspected** in individuals with either one major clinical feature or two or more minor features, as listed below.

Major features

- Angiofibromas (≥3) or fibrous cephalic plaque
- Cardiac rhabdomyoma
- Multiple cortical tubers and/or radial migration lines
- Hypomelanotic macules (≥3 macules that are at least 5 mm in diameter)

- Lymphangioleiomyomatosis (LAM) (See Clinical Diagnosis, *Note.)
- Multiple retinal nodular hamartomas
- Renal angiomyolipoma (≥2) (See Clinical Diagnosis, *Note.)
- Shagreen patch
- Subependymal giant cell astrocytoma (SEGA)
- Subependymal nodules (SENs) (≥2)
- Ungual fibromas (≥2)

Minor features

- Sclerotic bone lesions
- "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs)
- Dental enamel pits (>3)
- Intraoral fibromas (≥2)
- Multiple renal cysts
- Nonrenal hamartomas
- Retinal achromic patch

Establishing the Diagnosis

The clinical diagnosis of TSC can be **established** in a proband based on clinical diagnostic criteria [Northrup et al 2021] or the molecular diagnosis can be established in a proband with a heterozygous pathogenic (or likely pathogenic) variant in *TSC1* or *TSC2*.

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Clinical Diagnosis

A **definite** diagnosis of TSC **is established** in a proband with two major features (see *Note) or one major feature with two or more minor features.

*Note: The combination of LAM and angiomyolipomas without other features does not meet the clinical diagnostic criteria for a definite diagnosis.

Molecular Diagnosis

The molecular diagnosis of TSC is **established** in a proband by the identification of a heterozygous pathogenic variant in either *TSC1* or *TSC2* by molecular genetic testing (see Table 1), regardless of clinical findings.

Note: Clinical manifestations of TSC may develop over time and at various ages; therefore, the identification of a pathogenic variant in *TSC1* or *TSC2* is sufficient to make the diagnosis [Northrup et al 2021].

Molecular genetic testing approaches can include **concurrent gene testing** or use of a **multigene panel**:

- **Concurrent gene testing.** Perform sequence analysis and gene-targeted deletion/duplication analysis of *TSC1 and TSC2.*

  Note: If no pathogenic variant is identified, somatic mosaicism for a pathogenic variant should be considered [Qin et al 2010; Nellist et al 2015; Authors, personal observation]. For more information on somatic mosaicism as a cause of TSC click here (pdf).

- **A multigene panel** that includes *TSC1, TSC2* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause when the diagnosis of TSC is less certain in order to limit identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Tuberous Sclerosis Complex (TSC)

Gene [1, 2]	Proportion of TSC Attributed to Pathogenic Variants in Gene	Method	Proportion of Probands with a Pathogenic Variant [3] Detected by Gene, Family History, & Method	
			Familial cases	Simplex cases [4]
TSC1	~26% [5]	Sequence analysis [6, 7]	~9.8%	~15.5%
		Gene-targeted deletion/ duplication analysis [8]	~0.1% [9]	~0.5% [9]
TSC2	~69% [5]	Sequence analysis [6]	13.8%	~53%
		Gene-targeted deletion/ duplication analysis [8, 10]	~0.2% [9]	~2% [9]
Unknown	~5% [11, 12]	NA	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Simplex case = single occurrence in a family
5. Of the more than 10,000 individuals with TSC and their families in whom pathogenic variants have been identified, ~26% of probands had a pathogenic variant in *TSC1* and ~74% had a pathogenic variant in *TSC2* [Jones et al 1999, Dabora et al 2001, Au et al 2004, Sancak et al 2005, Au et al 2007, Tyburczy et al 2015] (see Table A, TSC databases).
6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
7. TSC1 pathogenic variants are primarily small deletions and insertions and pathogenic nonsense variants detected by sequence analysis.
8. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
9. Comparing methods to identify large (multi)exon/gene deletions in 65 individuals with TSC, Rendtorff et al [2005] concluded that multiple ligation-dependent probe amplification (MLPA) is more sensitive than Southern blot analysis and long-range PCR. Using MLPA, they identified large *TSC2* exon or whole-gene deletions in four of 15 families in which no pathogenic variant had been identified by sequence analysis and Southern blotting.
10. TSC2 pathogenic variants include significant numbers of large (exon and whole-gene) deletions and rearrangements that cannot be detected by sequence analysis of exons and thus require gene-targeted deletion/duplication analysis for detection.
11. Sancak et al [2005], Au et al [2007], Kwiatkowski [2010], Table A, TSC databases
12. Inferring from the 5% detection rate for somatic mosaicism [Kozlowski et al 2007, Qin et al 2010] among 15% of individuals with TSC who do not have a pathogenic variant identified in *TSC1* or *TSC2* by sequence analysis, the authors conclude that at least 1% of persons with TSC have somatic mosaicism for a *TSC1* or *TSC2* pathogenic variant [Author, personal observation].

Clinical Characteristics

Clinical Description

Tuberous sclerosis complex (TSC) exhibits both inter- and intrafamilial variability in clinical findings. Females tend to have milder disease than males [Sancak et al 2005, Au et al 2007]. Any organ system can be involved in TSC.

Skin

The skin is affected in virtually 100% of individuals with TSC. Skin lesions include: hypomelanotic macules (~90% of individuals), confetti skin lesions (frequency varies widely from 3% of children to ≤58% overall), facial angiofibromas (~75%), shagreen patches (~50%), fibrous cephalic plaques, and ungual fibromas (20% overall but ≤80% in older affected adults) [Northrup et al 2013]. Among the skin lesions, the facial angiofibromas cause the most disfigurement. None of the skin lesions results in serious medical problems.

Central Nervous System (CNS)

CNS tumors are the leading cause of morbidity and mortality in TSC. The brain lesions of TSC, including subependymal nodules (SENs), cortical tubers, and subependymal giant cell astrocytomas (SEGAs), can be distinguished with neuroimaging studies. SENs occur in 80% of individuals and cortical tubers in approximately 90%. SEGAs occur in 5%-15% of all individuals with TSC [Northrup et al 2013]. These giant cell astrocytomas may enlarge, causing pressure and obstruction and resulting in significant morbidity and mortality.

Seizures

More than 80% of individuals with TSC have been reported to have seizures, although this percentage may reflect ascertainment bias of more severely involved individuals. TSC is a known cause of infantile spasms. At least 50% of individuals have developmental delay or intellectual disability. The leading cause of premature death (32.5%) among individuals with TSC is a complication of severe intellectual disability (e.g., status epilepticus and bronchopneumonia) [Shepherd et al 1991].

TSC-Associated Neuropsychiatric Disorder (TAND)

TAND refers to the interrelated functional and clinical manifestations of brain dysfunction common in individuals with TSC, including behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial difficulties [de Vries 2010a]. Although more than 90% of children and adults with TSC will experience one or more TAND concerns in their lifetime, only 20% ever receive evaluation and intervention for them [Krueger 2013, de Vries et al 2015].

Autism spectrum disorder (ASD). Individuals with TSC are at high risk for ASD, with estimates running from 16% to 61% [Gillberg et al 1994, Bolton et al 2002, Wong 2006, de Vries et al 2007, Chung et al 2011, Numis et al 2011, Spurling Jeste et al 2014, Kingswood et al 2017], compared to a less than 2% risk in the general population (see Centers for Disease Control and Prevention: Autism Spectrum Disorder Data & Statistics). Signs of ASD in individuals with TSC emerge as early as age nine months [McDonald et al 2017]. Individuals with TSC who have subependymal giant cell astrocytomas are nearly twice as likely to have ASD [Kothare et al 2014], and treatment with everolimus has been found to reduce SEGA size, seizures, and features of ASD [Hwang et al 2016, Kilincaslan et al 2017]. Neurofunctional impairments closely associated with ASD, including impaired language pathways [Lewis et al 2013] and atypical face processing [Spurling Jeste et al 2014], have been noted in persons with TSC. Children with TSC and ASD are at higher risk for global cognitive impairment than are children with TSC who do not have ASD [Jeste et al 2008]. The ASD profile in toddlers with TSC has been found to have "complete convergence" with young children with nonsyndromic ASD [Jeste et al 2016].

Attention deficit hyperactivity disorder (ADHD) is another common (and potentially seriously debilitating) condition closely associated with TSC. Estimates of ADHD prevalence in individuals with TSC range from 21% to 50% [Gillberg et al 1994, Prather & de Vries 2004, Muzykewicz et al 2007, Kopp et al 2008, Chung et al 2011, Kingswood et al 2017]. Deficits in attention (particularly in dual-task performance), cognitive flexibility, and memory have also been noted in neuropsychological studies of children and adults with TSC [Ridler et al 2007, de Vries et al 2009, Tierney et al 2011, Curatolo et al 2015, de Vries et al 2015].

Learning and cognitive impairment. Individuals with TSC are at high risk for having intellectual disability, with prevalence rates estimated between 44% and 64% [Joinson et al 2003, Goh et al 2005, van Eeghen et al 2012].

- Approximately 36%-58% of children with TSC have serious academic difficulties (e.g., learning disabilities) requiring intervention [Curatolo et al 2015, de Vries 2010b, Kingswood et al 2017].
- The risk of learning and cognitive impairment increases significantly if seizure activity is not controlled. A number of investigations have demonstrated that a history of infantile spasms (IS) and/or poor seizure control in general is associated with lower intellectual ability [Joinson et al 2003, Goh et al 2005, Bolton et al 2015, Capal et al 2017]. In a small sample (n=6), Humphrey et al [2014] demonstrated a dramatic dose-dependent relationship between seizure activity and intellectual impairment: estimated intelligence quotient (IQ) dropped from 92 (prior to IS) to 73 (if IS duration was <1 month) to 62 (if IS duration was >1 month). These findings underscore the crucial need for adequate seizure control in individuals with TSC.

Disruptive behaviors and emotional problems are another cluster of debilitating conditions associated with TSC. Aggression has been noted in many individuals with TSC (13%-58%) [de Vries et al 2007, Kopp et al 2008, Staley et al 2008, Chung et al 2011, Eden et al 2014, Kingswood et al 2017, Wilde et al 2017] as has self-injurious behavior (27%-41%) [de Vries et al 2007, Eden et al 2014, Wilde et al 2017]. Individuals with TSC are also at high risk for anxiety (9%-48%) [de Vries et al 2007, Muzykewicz et al 2007, Kopp et al 2008, Chung et al 2011, Kingswood et al 2017] and depression (6%-43%) [de Vries et al 2015, Kingswood et al 2017].

Assessment. All individuals with TSC should be assessed for the presence of TAND, given that it has been closely associated with clinical outcome and quality of life [Krueger 2013]. The TAND Checklist [de Vries et al 2015], a simple paper-and-pencil screening questionnaire available at no cost, is a promising tool to address the significant gap between clinical need associated with TAND and those receiving intervention for these needs [de Vries et al 2015, Leclezio & de Vries 2015]. Given that unaddressed TAND concerns contribute significantly to poor outcome, and that individuals with TSC have a very high health care resource utilization [Lennert et al 2013, Rentz et al 2015], the importance of recognizing and addressing TAND concerns cannot be overestimated.

Kidneys

Renal disease is the second leading cause of early death (27.5%) in individuals with TSC [Shepherd et al 1991]. An estimated 80% of children with TSC have an identifiable renal lesion by a mean age of 10.5 years [Ewalt et al 1998].

Five different renal lesions occur in TSC: benign angiomyolipoma (70% of affected individuals); epithelial cysts (20%-30%) [Sancak et al 2005, Au et al 2007]; oncocytoma (benign adenomatous hamartoma) (<1%); malignant angiomyolipoma (<1%); and renal cell carcinoma (<3%) [Patel et al 2005].

Benign angiomyolipomas comprise abnormal blood vessels, sheets of smooth muscle, and mature adipose tissue. In children, angiomyolipomas tend to increase in size or number over time. Benign angiomyolipomas can cause life-threatening bleeding and can replace renal parenchyma, leading to end-stage renal disease (ESRD).

Renal cysts have an epithelial lining of hypertrophic hyperplastic eosinophilic cells. Some affected individuals have features of both TSC caused by deletion of *TSC2* and autosomal dominant polycystic kidney disease

(ADPKD) caused by deletion of *PKD1*. In these individuals, progressive enlargement of the cysts may compress functional parenchyma and lead to ESRD [Martignoni et al 2002]. Individuals with the *TSC2/PKD1* contiguous gene deletion syndrome are also at risk of developing the complications of ADPKD, which include cystic lesions in other organs (e.g., the liver) and Berry aneurysms.

Malignant angiomyolipoma and **renal cell carcinoma** (RCC) may result in death. Although rare, these two tumors are much more common in individuals with TSC than in the general population [Pea et al 1998]. It is estimated that 2%-5% of persons with TSC will develop RCC. The age of diagnosis of RCC in those with TSC is 28-30 years – much earlier than the age of diagnosis for sporadic RCC [Crino et al 2006, Borkowska et al 2011]. Note: Common imaging techniques may not distinguish fat-poor angiomyolipomas from RCC. Immunologic staining for HMB-45 for angiomyolipomas and cytokeratin for RCC is recommended.

Heart

Cardiac rhabdomyomas are present in 47%-67% of individuals with TSC [Jones et al 1999, Dabora et al 2001, Sancak et al 2005]. These tumors have been documented to regress with time and eventually disappear. The cardiac rhabdomyomas are often largest during the neonatal period. If cardiac outflow obstruction does not occur at birth, the individual is unlikely to have health problems from these tumors later. However, a small number of individuals have arrhythmias postulated to result from rests of persistent cells left after the rhabdomyomas regress. For information regarding treatment options for obstructive lesions, see Management.

Lung

Lymphangioleiomyomatosis (LAM) of the lung primarily affects women and has been estimated to occur in approximately 30%-40% of females with TSC; however, a recent study suggests that the diagnosis of LAM is age dependent and occurs in up to 80% of women with TSC by age 40 years [Adriaensen et al 2011]. Approximately 5%-10% of women with TSC present with symptomatic LAM [Henske et al 2016]. Cystic findings consistent with LAM are observed in 10%-12% of males with TSC [Northrup et al 2013].

- The mean age of diagnosis for LAM in those with TSC is 28 years, compared to 35 years for sporadic LAM.
- Individuals with TSC-associated LAM as well as sporadic LAM may present with shortness of breath or hemoptysis. Chest radiographs reveal a diffuse reticular pattern and CT examination shows diffuse interstitial changes with infiltrates and cystic changes. Pneumothorax and chylothorax may occur in individuals affected by LAM. Some individuals progress to respiratory failure and death.
- It is suggested that LAM associated with TSC is milder than sporadic LAM because persons with TSC and LAM account for only about 15% of registrants in the NHLBI LAM Foundation [McCormack 2008]. Furthermore, persons with TSC and LAM have less severe lung cysts than persons with sporadic LAM [Avila et al 2007].

Multifocal micronodular pneumonocyte hyperplasia (MMPH), characterized by multiple nodular proliferations of type II pneumocytes, was first described in association with TSC in 1991 [Popper et al 1991]. While MMPH does not have known prognostic or physiologic consequences, there have been at least two reports of respiratory failure associated with MMPH [Cancellieri et al 2002, Kobashi et al 2008]. The precise prevalence of MMPH in individuals with TSC is not known but may be as high as 40%-58% [Franz et al 2001, Muzykewicz et al 2009]. Males and females are equally likely to have MMPH, and it may occur in the presence or absence of LAM in persons with TSC. MMPH can be confused with atypical adenomatous hyperplasia, which is a premalignant lesion that is not clearly associated with TSC.

Eye

The retinal lesions of TSC include hamartomas (elevated mulberry lesions or plaque-like lesions) observed in 30%-50% of individuals with TSC. These lesions are relatively rare in the general population with a recent case series of 3573 healthy term newborns identifying only two with these lesions [Li et al 2013]. Achromic patches (similar to the hypopigmented skin lesions) have been noted to occur in 39% of individuals with TSC, while the general population incidence is 1:20,000 [Northrup et al 1993]. Although these lesions are usually asymptomatic, a few persons with TSC have had progressively enlarging retinal astrocytic hamartomas with total exudative retinal detachment and neovascular glaucoma [Shields et al 2004].

Extrarenal Angiomyolipomas (AMLs)

Although rare, extrarenal angiomyolipomas have been reported [Elsayes et al 2005]. In a retrospective study of sonographic and CT images, Fricke et al [2004] identified eight hepatic AMLs in 62 individuals with TSC (13%).

Neuroendocrine Tumors (NETs)

Dworakowska & Grossman [2009] summarized case reports of persons with TSC who had NETs; the majority of tumors were pituitary adenomas (ACTHoma and GHoma), parathyroid adenomas and hyperplasia, and pancreatic adenomas (insulinoma and islet cell neoplasm). More recently single case reports have included gastrinoma, pheochromocytoma, and carcinoids. Several individuals had a *TSC2* pathogenic variant and/or loss of heterozygosity in the islet cell neoplasms.

Phenotype Correlations by Gene

TSC2 pathogenic variants produce a more severe phenotype than *TSC1* pathogenic variants. A higher percentage of individuals with more severe features of TSC have a *de novo TSC2* pathogenic variant versus a *de novo TSC1* pathogenic variant [Au et al 2007]. Individuals representing simplex cases (i.e., a single occurrence in a family) are more likely to have a *TSC2* pathogenic variant, while those with familial TSC have an almost equal proportion of *TSC1* and *TSC2* pathogenic variants [Au et al 2007].

Individuals with a *TSC2* pathogenic variant are at greater risk for:

- Renal malignancy [Yang et al 2014]
- Intellectual disability[Kothare et al 2014]
- Autistic disorder, low IQ, and infantile spasms [Numis et al 2011]

Genotype-Phenotype Correlations

TSC2

- Females with pathogenic variants on the carboxy terminus of tuberin, the *TSC2* gene product, may have increased incidence and/or severity of lymphangioleiomyomatosis [Strizheva et al 2001].
- Some pathogenic *TSC2* missense variants – including but not limited to p.Arg622Trp, p.Arg905Gln, p.Ser1036Pro, p.Arg1200Trp, p.Gln1503Pro, p.Gly1579Ser, and p.Arg1713His (see Table 5) – are associated with milder disease phenotypes [Khare et al 2001, O'Connor et al 2003, Mayer et al 2004, Jansen et al 2006, Wentink et al 2012, Farach et al 2017, Fox et al 2017]. Many of the variants associated with a milder disease phenotype have been identified in individuals with a family history of TSC.
- Renal cystic disease may be more severe in individuals with small *TSC2* pathogenic variants (single- to few-base pair insertions, deletions, and single-nucleotide variants).

Penetrance

After detailed evaluation of each individual known to have a *TSC1* or *TSC2* pathogenic variant, the penetrance of TSC is now thought to be 100%. Rare instances of apparent non-penetrance have been reported; however, molecular studies revealed the presence of two different pathogenic variants in the family and the existence of germline mosaicism in others [Connor et al 1986, Webb & Osborne 1991, Rose et al 1999].

Nomenclature

Terms used in the past to describe findings in tuberous sclerosis that are now outdated or inappropriate but have not yet been eliminated from the medical literature include the following:

- **Adenoma sebaceum.** Used previously to describe facial lesions that are now better characterized as facial angiofibromas because the lesions have no "sebaceous" elements
- **Myomata.** Replaced by the more precise terms cardiac rhabdomyomas and cortical tubers
- **White ash leaf spots.** Used previously to describe the hypopigmented macules; now discouraged because the hypopigmented macules can be any shape or size. Hypopigmented macules of a certain size and shape are not more or less indicative of an association with tuberous sclerosis complex.
- **Epiloia.** Used to describe individuals with TSC and epilepsy

Prevalence

The incidence of TSC may be as high as 1:5,800 live births [Osborne et al 1991], but is generally estimated at between 1:6000 and 1:10,000 live births [Northrup et al 2021]. A high mutation rate (1:250,000 per gene per generation) is estimated [Sampson et al 1989].

Genetically Related (Allelic) Disorders

A contiguous gene deletion syndrome in which *PKD1* and the adjacent *TSC2* are disrupted by deletion has been described [Consugar et al 2008]. In individuals with this syndrome, the phenotype of tuberous sclerosis and severe polycystic kidney disease is usually evident in utero or is diagnosed in infancy.

Sporadic tumors (including pulmonary lymphangioleiomyomatosis, perivascular epithelioid cell tumors, urothelial carcinomas, and hepatocellular carcinomas) occurring as single tumors in the absence of any other findings of TSC harbor somatic variants in *TSC1* or *TSC* that are **not** present in the germline; thus, predisposition to these tumors is not heritable. For more details see Cancer and Benign Tumors.

Differential Diagnosis

Many of the features of TSC are nonspecific and can be seen as isolated findings or as a feature of another condition.

Skin

Hypopigmented macules have been observed in 0.8% of newborns in some studies and in most cases have no medical significance [Alper & Holmes 1983]. A study by Vanderhooft et al [1996] determined that three or more hypopigmented macules are much more likely to be seen in an individual who will be diagnosed with TSC. Other conditions with hypopigmented macules as part of the phenotype include vitiligo, nevus depigmentus, nevus anemicus, piebaldism, and Vogt-Koyanagi-Harada syndrome. Associated findings can usually distinguish these conditions from TSC.

Angiofibromas. A single facial angiofibroma or even two is not diagnostic of TSC (see Suggestive Findings). On physical examination, acne vulgaris, acne rosacea, or multiple trichoepithelioma (see *CYLD* Cutaneous Syndrome) can be mistaken for angiofibromas, but biopsy easily distinguishes among them.

The **shagreen patch** of TSC is quite specific based on location and appearance and was retained as a major diagnostic criteria for TSC. However, the diagnostic criteria has been updated to omit use of the term "connective tissue nevus" because this term encompasses a variety of skin lesions with excessive dermal connective tissue that are not necessarily associated with TSC.

Ungual fibromas can result from trauma, but generally traumatic ungual fibromas are single lesions and their presence can be explained (e.g., by a particular manner of holding a golf club). Two or more ungual fibromas are now required as a major clinical diagnostic criterion for TSC. Ungual fibromas must be distinguished from epithelial inclusion cysts, verruca vulgaris, and infantile digital fibromatosis.

Kidneys

Renal cysts are seen commonly in the population (1%-2%), but uncommonly in individuals younger than age 30 years [Northrup et al 1993].

Renal angiomyolipomas (AMLs) are rare tumors sometimes observed in individuals with no other medical problems. Studies have shown that such sporadic AMLs can have loss of heterozygosity for *TSC2*, leading to the conclusion that they occur as a result of loss of function of *TSC2* in individuals not affected with tuberous sclerosis complex.

Lungs

Some women who have lymphangioleiomyomatosis (LAM) also have renal angiomyolipomas but no other findings of TSC. These individuals do not transmit TSC or LAM to their offspring. Individuals with LAM and renal angiomyolipomas who have no other features of TSC do not meet diagnostic criteria for TSC [Northrup et al 2013].

Heart

Infants with cardiac rhabdomyomas have a 75%-80% chance of being affected with TSC. While cardiac rhabdomyomas can be observed as an isolated finding, this is unusual. Potentially, sporadically occurring cardiac rhabdomyomas could also have a mechanism similar to the sporadic AMLs described (see Kidneys).

Management

Consensus clinical management and surveillance recommendations for individuals with TSC have been published [Northrup et al 2021] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with tuberous sclerosis complex (TSC), the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended by the International Tuberous Sclerosis Consensus Conference [Northrup et al 2021] (full text).

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with TSC

System/Concern	Evaluation
Integument	Detailed dermatologic & dental exam

Table 2. continued from previous page.

System/Concern	Evaluation
Renal	• Blood pressure • Renal function; obtain a serum creatinine level to determine GFR. • MRI of abdomen to assess for angiomyolipoma & renal cysts
Central nervous system	• Brain MRI for tubers, SENs, migrational defects, SEGAs • Comprehensive eval for all levels of TAND • Parent/caregiver education & training about TAND to ensure families are monitoring for emerging TAND manifestations [1] • Baseline EEG while awake & asleep; if abnormal or if TAND is present: 24-hr video EEG to assess for subclinical seizure activity • During infancy, educate parents to recognize infantile spasms even if none have occurred at time of 1st diagnosis.
Ophthalmology	Complete ophthalmologic eval, incl dilated fundoscopy to assess for retinal lesions & visual field defects
Cardiology	• Echocardiogram in pediatric age group (esp if age <3 yrs) • EKG in all ages to assess for underlying conduction defects
Pulmonary	• Baseline chest CT in all females, & in symptomatic males, starting at age 18 yrs & older • Baseline PFT & 6-min walk test in those w/evidence of cystic lung disease c/w LAM on screening chest CT • In adults, inquire about tobacco exposure, manifestations of connective tissue disease, signs of chyle leak, & other pulmonary manifestations. [2] • Adult males, if symptomatic, should also undergo PFT.
Skin	Perform detailed clinical dermatologic exam.
Teeth	Perform detailed clinical dental inspection.
Other	Consultation w/clinical geneticist and/or genetic counselor

CT = computed tomography; c/w = consistent with; GFR = glomerular filtration rate; PFT = pulmonary function test/ing; SEGAs = subependymal giant cell astrocytomas ; SENs = subependymal nodules; TAND = TSC-associated neuropsychiatric disorder
1. For example, signs and symptoms of autism spectrum, language, attention-deficit/hyperactivity and anxiety disorders
2. Including dyspnea, cough, and spontaneous pneumothorax

Treatment of Manifestations

Subependymal giant cell astrocytomas (SEGAs). Early identification of an enlarging giant cell astrocytoma permits medical therapy with mTOR inhibitors [Krueger et al 2010], which may obviate the need for neurosurgical intervention in many individuals. However, neurosurgery may still be indicated when the size of the SEGA causes life-threatening neurologic symptoms.

Seizures. Early control of seizures is thought to prevent subsequent epileptic encephalopathy and reduce cognitive behavioral consequences [Bombardieri et al 2010]. The efficacy of different treatments for infantile spasms varies among individuals; however a retrospective review found that vigabatrin controlled infantile spasms in 73% of children with TSC [Camposano et al 2008] (see Prevention of Secondary Complications). An ongoing study (see ClinicalTrials.gov) is prospectively investigating the effect of early vigabatrin treatment on developmental outcomes in babies with TSC-associated infantile spasms.

The seizures in TSC may be resistant to polydrug therapy with anticonvulsants. A number of small studies have reported excellent results after epilepsy surgery.

- Jarrar et al [2004] found that unifocal-onset seizures and mild to no developmental delay at the time of surgery predict an excellent long-term outcome.

- Romanelli et al [2004] discussed the use of electroencephalographic techniques, functional neuroimaging, and invasive cortical mapping to aid the surgeon in evaluating options for surgical resection in individuals with TSC who have multifocal epileptogenic zones.
- Kagawa et al [2005] found that increased radiolabeled alpha-methyl-L-tryptophan uptake on PET scans identifies epileptogenic tubers with 83% accuracy, thus enhancing successful epilepsy surgery.
- Weiner et al [2006] used a three-staged bilateral surgical approach in 22 persons with TSC. They suggest that this approach can help identify both primary and secondary epileptogenic zones in young persons with multiple tubers.

Initial case reports suggested a potential for mTOR inhibitors to help in the treatment of intractable epilepsy in individuals with TSC [Krueger et al 2013]. The EXIST-3 clinical trial [French et al 2016] confirmed the benefit of these therapies; EXIST-3 received FDA approval (4/10/18) as adjunctive treatment of TSC-associated partial-onset seizures.

Renal angiomyolipoma

- For asymptomatic, growing angiomyolipoma measuring >4 cm in diameter or >3 cm and growing rapidly, treatment with an mTOR inhibitor is currently recommended as the most effective first-line therapy in the short term [Davies et al 2011, Bissler et al 2013]. The demonstrated tolerability to date is far preferable to the renal damage caused by angiomyolipoma progression or surgical and embolitic/ablative therapies, though studies are still needed to confirm long-term benefits and safety [Krueger et al 2013].
- Selective embolization followed by corticosteroids, kidney-sparing resection, or ablative therapy for exophytic lesions is acceptable second-line therapy for asymptomatic angiomyolipomas [Bissler et al 2002].
- For acute hemorrhage, embolization followed by corticosteroids is more appropriate [Mourikis et al 1999]. Nephrectomy is to be avoided because of the high incidence of complications and increased risk for future renal insufficiency and end-stage renal failure, and the poor prognosis that results from chronic kidney disease.

Facial angiofibromas. Topical mTOR inhibitor formulations have been shown to be efficacious in the treatment of facial angiofibromas.

Cardiac rhabdomyomas. Previous standard of care for the treatment of newborns with cardiac rhabdomyomas resulting in life-threatening complications (i.e., outflow tract obstruction) was surgery. There have now been several reports of off-label use of mTOR inhibitors to treat cardiac rhabdomyomas in infants with TSC with encouraging results [Dogan et al 2015, Goyer et al 2015, Mlczoch et al 2015]. These reports indicate that mTOR inhibitors may be a better alternative than surgery for clinically significant cardiac rhabdomyomas.

LAM. Trials have demonstrated efficacy of mTOR inhibitors for LAM [McCormack et al 2011]. The FDA approved use of mTOR inhibitors for treatment of the lung issues in people with TSC (5/28/15). Official guidelines for diagnosis and management of LAM have been published [McCormack et al 2016, Gupta et al 2017].

TAND. Refer to a suitable professional to provide appropriate treatment, which may include ABA therapy for autism spectrum disorders and consideration of medication for those with features of ADHD.

Prevention of Secondary Complications

For those on vigabatrin therapy, vision testing is recommended within four weeks of treatment initiation, every three months during therapy, and three to six months after treatment is discontinued because of the risk for peripheral visual field restriction (Sabril® prescribing information).

Surveillance

The following routine monitoring is recommended for individuals with TSC (adapted from Northrup et al [2021], Table 3).

Central nervous system

- Obtain MRI of the brain every one to three years in asymptomatic (i.e., having no CNS-related symptoms) individuals with TSC younger than age 25 years to monitor for new occurrence of SEGA. Those with asymptomatic SEGA in childhood should continue to be imaged periodically as adults to ensure that there is no growth.
- In affected individuals with large or growing SEGA causing ventricular enlargement who are still asymptomatic, brain MRI scans should be performed more frequently and these individuals and their families should be educated regarding the potential for new symptoms.
- Perform screening for TAND features at least annually using validated screening tools such as the TAND Checklist. Screening may be done more frequently depending on clinical needs. When any concerns are identified on screening, proceed to further evaluations by appropriate professionals to diagnose and treat the relevant TAND manifestation(s).
- Perform comprehensive formal evaluation for TAND at key developmental points: infancy (0-3 years), preschool (3-6 years), pre-middle school (6-9 years), adolescence (12-16 years), early adulthood (18-25 years), and as needed thereafter.
- Obtain routine EEG in asymptomatic infants with TSC every six weeks up to age 12 months and every three months up to age 24 months, as abnormal EEG frequently precedes onset of clinical seizures.
- Obtain routine EEG in individuals with known or suspected seizure activity. The frequency of routine EEG should be determined by clinical need.

Renal

- Obtain MRI of the abdomen to assess for progression of angiomyolipomas and renal cystic disease every one to three years throughout the lifetime of the affected individual.
- Assess renal function (including determination of GFR) and blood pressure at least annually.

Cardiac

- In asymptomatic infants and children with documented cardiac rhabdomyomas, obtain an echocardiogram every one to three years until regression of the cardiac rhabdomyomas is documented.
- More frequent or advanced diagnostic assessment may be required for symptomatic individuals.

Pulmonary

- Perform clinical screening (targeted history) for LAM symptoms including exertional dyspnea and shortness of breath at each clinic visit for women older than age 18 years or those who report respiratory symptoms. Counseling regarding smoking risk and estrogen use should be reviewed at each clinic visit for individuals at risk for LAM.
- Obtain a high-resolution computed tomography (HCRT) of the lungs every five to seven years through menopause in asymptomatic individuals at risk for LAM who have no evidence of lung cysts on baseline HRCT. For individuals with evidence of cystic lung disease consistent with LAM on screening chest CT, follow-up scan intervals should be determined on a case-by-case basis depending on the individual circumstances (e.g., presence or absence of symptoms, ability to perform reliable PFTs, pre-existing use of mTORis for other TSC indications, treatment response or the lack thereof, or development of other pulmonary complications).

Skin. Perform detailed clinical dermatologic inspection/exam annually.

Dental. Perform detailed clinical dental inspection/exam at minimum every six months and panoramic radiographs by age seven years, if not performed previously.

Ophthalmologic. Perform annual ophthalmologic evaluation in all affected individuals, even if there were no previously identified ophthalmologic lesions or vision symptoms at the baseline evaluation.

Agents/Circumstances to Avoid

Avoid the following:

- Smoking
- Estrogen use in adolescent and adult females
- Nephrectomy (See Treatment of Manifestations, **Renal angiomyolipoma**.)

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from surveillance and early treatment. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- If the pathogenic variant in the family is not known, physical examination and imaging studies (skin examination, retinal examination, brain imaging, and renal ultrasound examination) to assess for the clinical features of TSC (see Diagnosis).

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

In general, women with epilepsy or a seizure disorder from any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication during pregnancy reduces this risk. However, exposure to anti-seizure medication may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from anti-seizure medication exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of anti-seizure medication to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given anti-seizure drug during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for more information on medication use during pregnancy.

Therapies Under Investigation

Many clinical trials are assessing the effect of drug therapy on the manifestations of TSC (see ClinicalTrials.gov).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Tuberous sclerosis complex (TSC) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About one third of individuals diagnosed with TSC have an affected parent.
- Two thirds of individuals with TSC have the disorder as the result of a *de novo TSC1* or *TSC2* pathogenic variant.
- Recommendations for the clinical and genetic evaluation of parents of a child with an apparent *de novo* pathogenic variant include the following:
  - Targeted molecular genetic testing if the pathogenic variant has been identified in the child
  - If the pathogenic variant has not been identified in the child, skin examination, retinal examination, brain imaging, and renal ultrasound examination of the parents to determine their clinical status
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Germline mosaicism studies are typically limited to families with two or more affected children and unaffected parents. Of 120 such families, Rose et al [1999] identified six (5%) with molecularly confirmed germline mosaicism. Of these, one pathogenic variant was in *TSC1* and five in *TSC2;* pathogenic variants included missense and nonsense variants and a one-nucleotide insertion or deletion.
- The family history of some individuals diagnosed with TSC may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the recognition of symptoms, or late onset of the disorder in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent is affected or has the known *TSC1* or *TSC2* familial pathogenic variant, the risk to the sibs is 50%.
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent or the parents have not been tested for the pathogenic variant but are clinically unaffected, the risk to sibs of being affected is low (~1%-2%) but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with tuberous sclerosis has a 50% chance of inheriting the *TSC1* or *TSC2* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected or has the familial pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the *TSC1* or *TSC2* pathogenic variant in the family.

Considerations in families with apparent *de novo* pathogenic variant. When neither parent of a proband with TSC has the pathogenic variant or clinical evidence of the disorder, the *TSC1* or *TSC2* pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies

- **Molecular genetic testing.** Once the *TSC1* or *TSC2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for TSC are possible.
- **Fetal imaging studies.** For families in which a pathogenic variant has not been identified, high-resolution ultrasound examination for tumors is possible; however, its sensitivity is unknown. Fetal MRI may be of use in the evaluation of TSC in fetuses at 50% risk.

  Note: The cardiac tumors are generally not detected until the third trimester.

Low-risk pregnancies. When cardiac lesions consistent with rhabdomyoma are identified on fetal ultrasound examination, the risk to the fetus with no known family history of TSC of having TSC is 75%-80% [Northrup et al 2013].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Medical Home Portal**
  Tuberous Sclerosis Complex (TSC)
- **MedlinePlus**
  Tuberous sclerosis

- **NCBI Genes and Disease**
  Tuberous sclerosis
- **Tuberous Sclerosis Alliance**
  Phone: 800-225-6872; 301-562-9890
  Email: info@tsalliance.org
  www.tsalliance.org
- **American Epilepsy Society**
  www.aesnet.org
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **The LAM Foundation**
  Phone: 513-777-6889; 877-287-3526
  Email: info@thelamfoundation.org
  www.thelamfoundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Tuberous Sclerosis Complex: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TSC1	9q34.13	Hamartin	Tuberous sclerosis database (TSC1)	TSC1	TSC1
TSC2	16p13.3	Tuberin	Tuberous sclerosis database (TSC2)	TSC2	TSC2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Tuberous Sclerosis Complex (View All in OMIM)

191092	TSC COMPLEX SUBUNIT 2; TSC2
191100	TUBEROUS SCLEROSIS 1; TSC1
605284	TSC COMPLEX SUBUNIT 1; TSC1
613254	TUBEROUS SCLEROSIS 2; TSC2

Molecular Pathogenesis

Hamartin and tuberin form heterodimers, suggesting that they act in concert to regulate cell growth and proliferation [Plank et al 1998, van Slegtenhorst et al 1998, Han & Sahin 2011]. Tuberin and hamartin were shown to be key regulators of the AKT/mTOR signaling pathway and to participate in several other signaling pathways including the MAPK, AMPK, b-catenin, calmodulin, CDK, autophagy, and cell cycle pathways [Kozma & Thomas 2002, Astrinidis et al 2003, El-Hashemite et al 2003, Harris & Lawrence 2003, Yeung 2003, Au et al 2004, Birchenall-Roberts et al 2004, Li et al 2004, Mak & Yeung 2004, Zhang et al 2013]. The hamartin tuberin complex can also regulate mTORC2 complex activity that affects cytoskeleton formation and AKT

activation [Han & Sahin 2011]. These observations are consistent with more signaling pathway kinases targeting tuberin than hamartin to destabilize the tuberin-hamartin complex, thereby releasing suppression of mTOR functions allowing protein translation, cell growth, and proliferation.

Most *TSC1* pathogenic variants and 70% of *TSC2* pathogenic variants are predicted to result in a loss of functional protein products. Subsequent loss of function leads to uncontrolled cell growth and cell proliferation resulting in the formation of hamartias (a focal malformation consisting of disorganized arrangement of tissue types that are normally present in the anatomic area) and hamartomas [Au et al 2004].

Additionally, because tuberin and hamartin are subjected to multiple cell signaling pathway regulation, the quantity and quality of both somatic pathogenic variants and environmental factors targeting these pathways are expected to modify disease expression in individuals who have only one normal germline copy of *TSC1* or *TSC2*.

A pathogenic variant is defined as a variant that clearly inactivates the function of the TSC1 or TSC2 proteins (i.e., out-of-frame indel or nonsense variant), prevents protein synthesis (i.e., large genomic deletion), or is a pathogenic missense variant whose effect on protein function has been established by functional assessment (see LOVD Database – TSC1, LOVD Database – TSC2, Hoogeveen-Westerveld et al [2012], and Hoogeveen-Westerveld et al [2013]). Other *TSC1* or *TSC2* variants whose effects on function are less certain do not meet the criteria for diagnosis of TSC.

TSC1

Gene structure. *TSC1* is approximately 50 kb in size and the longest transcript variant (NM_000368.4), comprising 23 exons. The first two exons are noncoding. Exon 5 and exon 12 are alternatively spliced, producing shorter transcript variants. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Almost all *TSC1* pathogenic variants are predicted to cause truncation of the hamartin protein; the location of the *TSC1* pathogenic variant does not appear to associate with disease severity. Approximately 650 unique *TSC1* pathogenic variants have been identified in more than 1,950 individuals/families with *TSC1*-related TSC (Table A). Most pathogenic variants are unique, but a few are known to recur, including those in specific codons of exon 15. Other pathogenic variants are scattered throughout the exons and splice sites. A small percentage of pathogenic missense variants have been identified and located mostly in the region encoding the N-terminal of hamartin [Choi et al 2006, Lee et al 2007, Mozaffari et al 2009, Nellist et al 2009, Hoogeveen-Westerveld et al 2012].

Pathogenic variant types by percentage are shown in Table 3.

Table 3. Types of Pathogenic Variants Observed in *TSC1* (n=651)

Type	Percent of All *TSC1* Pathogenic Variants [1]
Small deletions and insertions	57.8%
Nonsense	22.7%
Splice	10.9%
Large deletions and rearrangements	2.9%
Missense [2]	5.7%

1. Estimated percentages from LOVD

2. A small percentage of missense variants have been identified in *TSC1* with demonstrated functional loss by in vitro assays [Choi et al 2006, Lee et al 2007, Mozaffari et al 2009, Nellist et al 2009, Hoogeveen-Westerveld et al 2012].

For more information, see Table A.

Normal gene product. The gene has no known structural homologies to other known gene families.

The protein product, hamartin, has one transmembrane domain and two coiled-coil domains. The first coiled-coil domain is necessary for protein-protein interactions between hamartin and tuberin. A second coiled-coil domain peptide, encoded by exons 17 to 23, interacts with tuberin to stabilize the tuberin-hamartin complex. Other domains are responsible for interacting with cytoskeletal ERM proteins, small G-protein Rho, cell division protein kinases, and I kappa kinase β (IKK-β). A study of the crystal structures of hamartin has mapped most of the pathogenic missense variants to the inside of the folded hamartin N-terminal globular structure and suggested that these variants may destabilize the globular structure of hamartin, leading to dissociation of the tuberin-hamartin complex [Sun et al 2013].

A major function of hamartin is to stabilize the hamartin tuberin complex to facilitate the GTPase-activating function of tuberin in the complex [Han & Sahin 2011]. In addition, hamartin interacts with the ezrin-radxin-moesin (ERM) family of actin-binding proteins [Lamb et al 2000] and hamartin also regulates the cell cycle through interaction with CDK [Astrinidis et al 2003]. Growth of neurites, synapse formation, and axon development are also regulated by hamartin [Floricel et al 2007, Knox et al 2007]. Hamartin was suppressed by TNFα-activated IKK-β phosphorylation at amino acid residue Ser511 resulting in dissociation of tuberin hamartin complex, activating S6Kinase and VEGF production [Lee et al 2007]. A recent study demonstrated that hamartin can facilitate molecular chaperone heat-shock protein 90 (Hsp90) to mediate correct folding of tuberin and prevent tubulin from ubiquitination and proteasomal degradation [Woodford et al 2017].

Abnormal gene product. See Molecular Pathogenesis.

TSC2

Gene structure. *TSC2* is approximately 50 kb in size; the longest transcript variant NM_000548.3 comprises 42 exons. A noncoding exon 1a has recently been identified in addition to at least six alternatively spliced transcripts. Exons 25 and 31 are alternatively spliced. The 3′ ends of *TSC2* and *PKD1* overlap with three base pairs, explaining how *TSC2/PKD1* contiguous gene syndrome occurs when a large deletion spans both genes. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 1,900 unique *TSC2* pathogenic variants distributed throughout the gene have been identified in more than 5,800 individuals/families with *TSC2*-related TSC. Approximately 33% of *TSC2* pathogenic variants are located in exons 32-41 (and associated splice sites) that encode the carboxy domain of tuberin consisting of several important functional motifs (e.g., GAP domain, estrogen receptor- and calmodulin-binding domains, and multiple signal pathway kinase targets).

Pathogenic variant types by percentage are shown in Table 4.

Missense variants account for approximately 26% of all *TSC2* pathogenic variants with approximately 50% concentrated in the carboxy domain. Missense variants are rarely the direct target of kinases: only two missense variants at the Tyr1571 residue are the predicted target of tyrosine kinase [Hoogeveen-Westerveld et al 2013].

Table 4. Types of Pathogenic Variants Observed in *TSC2* (n=1947)

Type	Percent of All *TSC2* Pathogenic Variants [1]
Small deletions and insertions	~37.7%
Missense	~25.7%
Nonsense	~14.5%
Splice	~16.6%
Large deletions and rearrangements [2]	~5.4%

1. Estimated percentages from LOVD

2. Approximately 5% of *TSC2* pathogenic variants are large deletions or rearrangements; 4.5% are partial-gene deletions and 0.5% whole-gene deletions. Approximately half of all larger gene deletions involve both *TSC2* and *PKD1*.

For more information, see Table A.

Table 5. *TSC2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1864C>T	p.Arg622Trp [1]	NM_000548.3 NP_000539.2
c.2714G>A	p.Arg905Gln [1]	
c.3106T>C	p.Ser1036Pro [1]	
c.3598C>T	p.Arg1200Trp [1]	
c.4508A>C	p.Gln1503Pro [1]	
c.4735G>A	p.Gly1579Ser [1]	
c.5138G>A	p.Arg1713His [1]	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Genotype-Phenotype Correlations.

Normal gene product. The gene product, tuberin, has GTPase-activating protein functions as a major regulator of small G-protein Rheb and the mTORC1 downstream signaling pathway on protein translation and cell growth and proliferation [Inoki et al 2003]. Tuberin also functions to regulate other small G-proteins such as Rap1a and Rab5 [Xiao et al 1997]. Activity of tuberin is suppressed by AKT and ERK2 and activated by GSK3 and AMPK [Han & Sahin 2011]. See Molecular Pathogenesis.

Abnormal gene product. See Molecular Pathogenesis.

Cancer and Benign Tumors

Pulmonary lymphangioleiomyomatosis (LAM). DNA extracted from lung tissue of some individuals with sporadic LAM harbors pathogenic variants in *TSC2* or *TSC1* not present in the germline [Smolarek et al 1998, Carsillo et al 2000, Sato et al 2002]. Tuberin is strongly expressed in LAM tissues [Johnson et al 2002]. A recent study demonstrated that not all the cells in sporadic LAM nodules contained pathogenic *TSC1* or *TSC2* variants; the range was 4%-60% [Badri et al 2013].

Perivascular epitheloid cell tumors (PEComa). In some PEComa, reported loss of either *TSC2* or *TSC1* [Pan et al 2008] is evidence to support an oncogenic lineage of PEComa and angiomyolipomas in TSC. Six of 11 PEComas studied showed partial to complete responses to mTOR inhibitors [Dickson et al 2013].

Urothelial carcinomas. A significant proportion of urothelial carcinomas were found to have a loss-of-function somatic pathogenic variant in *TSC1* and some had a somatic pathogenic variant in *TSC2* [Pymar et al 2008, Sjödahl et al 2011]. These findings suggest that a significant proportion of urothelial carcinomas may respond to mTORC1 inhibitors.

Hepatocellular carcinomas. Recent reports showed that approximately 10%-20% of hepatocellular carcinomas are associated with loss-of-function somatic pathogenic variants in *TSC2* and suggested that these carcinomas may respond to mTORC1 inhibitors [Huynh et al 2015, Cho et al 2016].

Chapter Notes

Revision History

- 9 December 2021 (ma) Revision: incorporated updated TSC diagnostic criteria and management guidelines from the 2021 International TSC Consensus Group
- 16 April 2020 (ma) Revision: correction to pdf
- 12 July 2018 (sw) Comprehensive update posted live
- 3 September 2015 (me) Comprehensive update posted live
- 23 November 2011 (me) Comprehensive update posted live
- 7 May 2009 (me) Comprehensive update posted live
- 5 December 2005 (me) Comprehensive update posted live
- 27 September 2004 (cd) Revision: FISH clinically available for *TSC2* deletions
- 29 August 2003 (me) Comprehensive update posted live
- 3 December 2002 (bp) Revisions
- 18 April 2001 (me) Comprehensive update posted live
- 13 July 1999 (pb) Review posted live
- 5 February 1999 (hn) Original submission

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