



Tuberous Sclerosis Complex

Synonym: Bourneville Disease

Hope Northrup, MD, FACMG,¹ Mary Kay Koenig, MD,² Deborah A Pearson, PhD,³ and Kit Sing Au, PhD¹

Created: July 13, 1999; Revised: December 9, 2021.

Summary

Clinical characteristics

Tuberous sclerosis complex (TSC) involves abnormalities of the skin (hypomelanotic macules, confetti skin lesions, facial angiofibromas, shagreen patches, fibrous cephalic plaques, unguinal 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 (lymphangiomyomatosis [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:

Author Affiliations: 1 Department of Pediatrics Division of Medical Genetics McGovern Medical School University of Texas Health Science Center at Houston Houston, Texas; Email: hope.northrup@uth.tmc.edu; Email: kit-sing.au@uth.tmc.edu. 2 Division of Child and Adolescent Neurology Department of Pediatrics McGovern Medical School University of Texas Health Science Center at Houston Houston, Texas; Email: mary.k.koenig@uth.tmc.edu. 3 Department of Psychiatry and Behavioral Sciences Division of Child and Adolescent Psychiatry McGovern Medical School University of Texas Health Science Center at Houston Houston, Texas; Email: deborah.a.pearson@uth.tmc.edu.

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)

- Lymphangiomyomatosis (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 Proband with a Pathogenic Variant ³ Detected by Gene, Family History, & Method	
			Familial cases	Simplex cases ⁴
<i>TSC1</i>	~26% ⁵	Sequence analysis ^{6, 7}	~9.8%	~15.5%
		Gene-targeted deletion/duplication analysis ⁸	~0.1% ⁹	~0.5% ⁹
<i>TSC2</i>	~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 unguis 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 SEGAs 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

Lymphangiomyomatosis (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 pneumocyte 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 tuberlin, 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 lymphangiomyomatosis, 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 *TSC2* 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 depigmentosus, 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 unguinal fibromas are single lesions and their presence can be explained (e.g., by a particular manner of holding a golf club). Two or more unguinal 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 lymphangiomyomatosis (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	<ul style="list-style-type: none"> • Blood pressure • Renal function; obtain a serum creatinine level to determine GFR. • MRI of abdomen to assess for angiomyolipoma & renal cysts
Central nervous system	<ul style="list-style-type: none"> • 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 manifestations¹ • 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 funduscopy to assess for retinal lesions & visual field defects
Cardiology	<ul style="list-style-type: none"> • Echocardiogram in pediatric age group (esp if age <3 yrs) • EKG in all ages to assess for underlying conduction defects
Pulmonary	<ul style="list-style-type: none"> • 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 (HRCT) 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
<i>TSC1</i>	9q34.13	Hamartin	Tuberous sclerosis database (TSC1)	TSC1	TSC1
<i>TSC2</i>	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 <i>TSC1</i> 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-radixin-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 [Florice et al 2007, Knox et al 2007]. Hamartin was suppressed by TNF α -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 <i>TSC2</i> 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 lymphangiomyomatosis (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, Sjødahl 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

References

Published Guidelines / Consensus Statements

- Gupta N, Finlay GA, Kotloff RM, Strange C, Wilson KC, Young LR, Taveira-DaSilva AM, Johnson SR, Cottin V, Sahn SA, Ryu JH, Seyama K, Inoue Y, Downey GP, Han MK, Colby TV, Wikenheiser-Brokamp KA, Meyer CA, Smith K, Moss J, McCormack FX; ATS Assembly on Clinical Problems. Lymphangioleiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. an official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2017;196:1337–48. PubMed PMID: 29140122.
- McCormack FX, Gupta N, Finlay GR, Young LR, Taveira-DaSilva AM, Glasgow CG, Steagall WK, Johnson SR, Sahn SA, Ryu JH, Strange C, Seyama K, Sullivan EJ, Kotloff RM, Downey GP, Chapman JT, Han MK, D'Armiento JM, Inoue Y, Henske EP, Bissler JJ, Colby TV, Kinder BW, Wikenheiser-Brokamp KA, Brown KK, Cordier JF, Meyer C, Cottin V, Brozek JL, Smith K, Wilson KC, Moss J; ATS/JRS Committee on Lymphangioleiomyomatosis. Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management. Available [online](#). 2016. Accessed 6-28-22.
- Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, Frost MD, Fuchs Z, Gosnell ES, Gupta N, Jansen AC, Jóźwiak S, Kingswood JC, Knilans TK, McCormack FX, Ponders A, Roberds SL, Rodriguez-Buritica DF, Roth J, Sampson JR, Sparagana S, Thiele EA, Weiner HL, Wheless JW, Towbin AJ, Krueger DA, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Available [online](#). 2021. Accessed 6-28-22.

Literature Cited

- Adriaensen ME, Schaefer-Prokop CM, Duyndam DA, Zonnenberg BA, Prokop M. Radiological evidence of lymphangioleiomyomatosis in female and male patients with tuberous sclerosis complex. *Clin Radiol.* 2011;66:625–8. PubMed PMID: 21459371.
- Alper JC, Holmes LB. The incidence and significance of birthmarks in a cohort of 4,641 newborns. *Pediatr Dermatol.* 1983;1:58–68. PubMed PMID: 6679890.

- Astrinidis A, Senapedis W, Coleman TR, Henske EP. Cell cycle-regulated phosphorylation of hamartin, the product of the tuberous sclerosis complex 1 gene, by cyclin-dependent kinase 1/cyclin B. *J Biol Chem*. 2003;278:51372–9. PubMed PMID: 14551205.
- Au KS, Williams AT, Gambello MJ, Northrup H. Molecular genetic basis of tuberous sclerosis complex: from bench to bedside. *J Child Neurol*. 2004;19:699–709. PubMed PMID: 15563017.
- Au KS, Williams AT, Roach ES, Batchelor L, Sparagana SP, Delgado MR, Wheless JW, Baumgartner JE, Roa BB, Wilson CM, Smith-Knuppel TK, Cheung MY, Whittemore VH, King TM, Northrup H. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. *Genet Med*. 2007;9:88–100. PubMed PMID: 17304050.
- Avila NA, Dwyer AJ, Rabel A, Moss J. Sporadic lymphangiomyomatosis and tuberous sclerosis complex with lymphangiomyomatosis: comparison of CT features. *Radiology*. 2007;242:277–85. PubMed PMID: 17105849.
- Badri KR, Gao L, Hyjek E, Schuger N, Schuger L, Qin W, Chekaluk Y, Kwiatkowski DJ, Zhe X. Exonic mutations of TSC2/TSC1 are common but not seen in all sporadic pulmonary lymphangiomyomatosis. *Am J Respir Crit Care Med*. 2013;187:663–5. PubMed PMID: 23504366.
- Birchenall-Roberts MC, Fu T, Bang OS, Dambach M, Resau JH, Sadowski CL, Bertolette DC, Lee HJ, Kim SJ, Ruscetti FW. Tuberous sclerosis complex 2 gene product interacts with human SMAD proteins. A molecular link of two tumor suppressor pathways. *J Biol Chem*. 2004;279:25605–13. PubMed PMID: 15066998.
- Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, Nonomura N, Brakemeier S, de Vries PJ, Whittemore VH, Chen D, Sahmoud T, Shah G, Lincy J, Lebowhl D, Budde K. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2013;381:817–24. PubMed PMID: 23312829.
- Bissler JJ, Racadio J, Donnelly LF, Johnson ND. Reduction of post-embolization syndrome after ablation of renal angiomyolipoma. *Am J Kidney Dis*. 2002;39:966–71. PubMed PMID: 11979340.
- Bolton PF, Clifford M, Tye C, Maclean C, Humphrey A, le Marechal K, Higgins JNP, Neville BGR, Rijdsdijk F, Yates JRW, et al. Intellectual abilities in tuberous sclerosis complex: risk factors and correlates from the Tuberous Sclerosis 2000 Study. *Psychol Med*. 2015;45:2321–31. PubMed PMID: 25827976.
- Bolton PF, Park RJ, Higgins JN, Griffiths PD, Pickles A. Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex. *Brain*. 2002;125:1247–55. PubMed PMID: 12023313.
- Bombardieri R, Pinci M, Moavero R, Cerminara C, Curatolo P. Early control of seizures improves long-term outcome in children with tuberous sclerosis complex. *Eur J Paediatr Neurol*. 2010;14:146–9. PubMed PMID: 19369101.
- Borkowska J, Schwartz RA, Kotulska K, Jozwiak S. Tuberous sclerosis complex: tumors and tumorigenesis. *Int J Dermatol*. 2011;50:13–20. PubMed PMID: 21182496.
- Camposano SE, Major P, Halpern E, Thiele EA. Vigabatrin in the treatment of childhood epilepsy: a retrospective chart review of efficacy and safety profile. *Epilepsia*. 2008;49:1186–91. PubMed PMID: 18479386.
- Cancellieri A, Poletti V, Corrin B. Respiratory failure due to micronodular type II pneumocyte hyperplasia. *Histopathology*. 2002;41:263–5. PubMed PMID: 12207789.
- Capal JK, Bernardino-Cuesta B, Horn PS, Murray D, Byars AW, Bing NM, Kent B, Pearson DA, Sahin M, Krueger DA, et al. Influence of seizures on early development in tuberous sclerosis complex. *Epilepsy Behav*. 2017;70:245–52. PubMed PMID: 28457992.

- Carsillo T, Astrinidis A, Henske EP. Mutations in the tuberous sclerosis complex gene TSC2 are a cause of sporadic pulmonary lymphangiomyomatosis. *Proc Natl Acad Sci U S A*. 2000;97:6085–90. PubMed PMID: 10823953.
- Cho J, Lee J, Kim J, Kim ST, Lee S, Kim SY, Ha SY, Park CK, Lim HY. Loss of tuberous sclerosis complex 2 (TSC2) as a predictive biomarker of response to mTOR inhibitor treatment in patients with hepatocellular carcinoma. *Transl Oncol*. 2016;9:466–71. PubMed PMID: 27751352.
- Choi JE, Chae JH, Hwang YS, Kim KJ. Mutational analysis of TSC1 and TSC2 in Korean patients with tuberous sclerosis complex. *Brain Dev*. 2006;28:440–6. PubMed PMID: 16554133.
- Chung TK, Lynch ER, Fiser CJ, Nelson DA, Agricola K, Tudor C, Franz DN, Krueger DA. Psychiatric comorbidity and treatment response in patients with tuberous sclerosis complex. *Ann Clin Psychiatry*. 2011;23:263–9. PubMed PMID: 22073383.
- Connor JM, Stephenson JB, Hadley MD. Non-penetrance in tuberous sclerosis. *Lancet*. 1986;2:1275. PubMed PMID: 2878149.
- Consugar MB, Wong WC, Lundquist PA, Rossetti S, Kubly VJ, Walker DL, Rangel LJ, Aspinwall R, Niaudet WP, Ozen S, David A, Velinov M, Bergstralh EJ, Bae KT, Chapman AB, Guay-Woodford LM, Grantham JJ, Torres VE, Sampson JR, Dawson BD, Harris PC, et al. Characterization of large rearrangements in autosomal dominant polycystic kidney disease and the PKD1/TSC2 contiguous gene syndrome. *Kidney Int*. 2008;74:1468–79. PubMed PMID: 18818683.
- Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med*. 2006;355:1345–56. PubMed PMID: 17005952.
- Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. *Lancet Neurol*. 2015;14:733–45. PubMed PMID: 26067126.
- Dabora SL, Jozwiak S, Franz DN, Roberts PS, Nieto A, Chung J, Choy YS, Reeve MP, Thiele E, Egelhoff JC, Kasprzyk-Obara J, Domanska-Pakiela D, Kwiatkowski DJ. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. *Am J Hum Genet*. 2001;68:64–80. PubMed PMID: 11112665.
- Davies DM, de Vries PJ, Johnson SR, McCartney DL, Cox JA, Serra AL, Watson PC, Howe CJ, Doyle T, Pointon K, Cross JJ, Tattersfield AE, Kingswood JC, Sampson JR. Sirolimus therapy for angiomyolipoma in tuberous sclerosis and sporadic lymphangiomyomatosis: A Phase 2 trial. *Clin Cancer Res*. 2011;17:4071–81. PubMed PMID: 21525172.
- de Vries PJ. Neurodevelopmental, psychiatric, and cognitive aspects of tuberous sclerosis complex. In: Kwiatkowski DJ, Whittemore VH, Thiele EA, eds. *Tuberous Sclerosis Complex: Genes, Clinical Features, and Therapeutics*. Weinheim, Germany: Wiley-Blackwell; 2010a:229267.
- de Vries PJ. Targeted treatments for cognitive and neurodevelopmental disorders in tuberous sclerosis complex. *Neurotherapeutics*. 2010b;7:275–82. PubMed PMID: 20643380.
- de Vries PJ, Gardiner J, Bolton PF. Neuropsychological attention deficits in tuberous sclerosis complex (TSC). *Am J Med Genet A*. 2009;149A:387–95. PubMed PMID: 19215038.
- de Vries PJ, Hunt A, Bolton PF. The psychopathologies of children and adolescents with tuberous sclerosis complex (TSC): a postal survey of UK families. *Eur Child Adolesc Psychiatry*. 2007;16:16–24. PubMed PMID: 17268883.
- de Vries PJ, Whittemore VH, Leclizio L, Byars AW, Dunn D, Ess KC, Hook D, King BH, Sahin M, Jansen A. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. *Pediatr Neurol*. 2015;52:25–35. PubMed PMID: 25532776.

- Dickson MA, Schwartz GK, Antonescu CR, Kwiatkowski DJ, Malinowska IA. Extrarenal perivascular epithelioid cell tumors (PEComas) respond to mTOR inhibition: clinical and molecular correlates. *Int J Cancer*. 2013;132:1711–7. PubMed PMID: 22927055.
- Dogan V, Yesil S, Kayali S, Beken S, Ozgur S, Ertugrul I, Bozkurt C, Orun UA, Karademir S. J Regression of symptomatic multiple cardiac rhabdomyomas associated with tuberous sclerosis complex in a newborn receiving everolimus *Trop Pediatr* 2015;61:74-7
- Dworakowska D, Grossman AB. Are neuroendocrine tumours a feature of tuberous sclerosis? A systematic review. *Endocr Relat Cancer*. 2009;16:45–58. PubMed PMID: 18978035.
- Eden KE, de Vries PJ, Moss J, Richards C, Oliver C. Self-injury and aggression in tuberous sclerosis complex: cross syndrome comparison and associated risk markers. *J Neurodev Disord*. 2014;6:10. PubMed PMID: 24822087.
- El-Hashemite N, Zhang H, Henske EP, Kwiatkowski DJ. Mutation in TSC2 and activation of mammalian target of rapamycin signalling pathway in renal angiomyolipoma. *Lancet*. 2003;361:1348–9. PubMed PMID: 12711473.
- Elsayes KM, Narra VR, Lewis JS Jr, Brown JJ. Magnetic resonance imaging of adrenal angiomyolipoma. *J Comput Assist Tomogr*. 2005;29:80–2. PubMed PMID: 15665688.
- Ewalt DH, Sheffield E, Sparagana SP, Delgado MR, Roach ES. Renal lesion growth in children with tuberous sclerosis complex. *J Urol*. 1998;160:141–5. PubMed PMID: 9628635.
- Farach LS, Gibson WT, Sparagana SP, Nellist M, Stumpel CT, Hietala M, Friedman E, Pearson DA, Creighton SP, Wagemans A, Segel R, Ben-Shalom E, Au KS, Northrup H. TSC2 c.1864C>T variant associated with mild cases of tuberous sclerosis complex. *Am J Med Genet A*. 2017;173:771–5. PubMed PMID: 28211972.
- Florice F, Higaki K, Maki H, Nanba E, Ninomiya H, Ohno K. Antisense suppression of TSC1 gene product, hamartin, enhances neurite outgrowth in NGF-treated PC12h cells. *Brain Dev*. 2007;29:502–9. PubMed PMID: 17376623.
- Fox J, Ben-Shachar S, Uziel S, Svirsky R, Saitsu H, Matsumoto N, Fattal-Valevski A. Rare familial TSC2 gene mutation associated with atypical phenotype presentation of tuberous sclerosis complex. *Am J Med Genet A*. 2017;173:744–8. PubMed PMID: 28127866.
- Franz DN, Brody A, Meyer C, Leonard J, Chuck G, Dabora S, Sethuraman G, Colby TV, Kwiatkowski DJ, McCormack FX. Mutational and radiographic analysis of pulmonary disease consistent with lymphangiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. *Am J Respir Crit Care Med*. 2001;164:661–8. PubMed PMID: 11520734.
- French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, Curatolo P, de Vries PJ, Dlugos DJ, Berkowitz N, Voi M, Peyrard S, Pelov D, Franz DN. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet*. 2016;388:2153–63. PubMed PMID: 27613521.
- Fricke BL, Donnelly LF, Casper KA, Bissler JJ. Frequency and imaging appearance of hepatic angiomyolipomas in pediatric and adult patients with tuberous sclerosis. *AJR Am J Roentgenol*. 2004;182:1027–30. PubMed PMID: 15039181.
- Gillberg IC, Gillberg C, Ahlsén G. Autistic behaviour and attention deficits in tuberous sclerosis: a population-based study. *Dev Med Child Neurol*. 1994;36:50–6. PubMed PMID: 8132114.
- Goh S, Kwiatkowski DJ, Dorer DJ, Thiele EA. Infantile spasms and intellectual outcomes in children with tuberous sclerosis complex. *Neurology*. 2005;65:235–8. PubMed PMID: 16043792.
- Goyer I, Dahdah N, Major P. Use of mTOR inhibitor everolimus in three neonates for treatment of tumors associated with tuberous sclerosis complex. *Pediatr Neurol*. 2015;52:450–3. PubMed PMID: 25682485.

- Gupta N, Finlay GA, Kotloff RM, Strange C, Wilson KC, Young LR, Taveira-DaSilva AM, Johnson SR, Cottin V, Sahn SA, Ryu JH, Seyama K, Inoue Y, Downey GP, Han MK, Colby TV, Wikenheiser-Brokamp KA, Meyer CA, Smith K, Moss J, McCormack FX, et al. Lymphangiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. an official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2017;196:1337–48. PubMed PMID: 29140122.
- Han JM, Sahin M. TSC1/TSC2 signaling in the CNS. *FEBS Lett*. 2011;585:973–80. PubMed PMID: 21329690.
- Harris TE, Lawrence JC Jr. TOR signaling. *Sci STKE*. 2003;2003:re15. PubMed PMID: 14668532.
- Henske EP, Jóźwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. *Nat Rev Dis Primers*. 2016;2:16035. PubMed PMID: 27226234.
- Hoogeveen-Westerveld M, Ekong R, Povey S, Karbassi I, Batish SD, den Dunnen JT, van Eeghen A, Thiele E, Mayer K, Dies K, Wen L, Thompson C, Sparagana SP, Davies P, Aalfs C, van den Ouweland A, Halley D, Nellist M. Functional assessment of TSC1 missense variants identified in individuals with tuberous sclerosis complex. *Hum Mutat*. 2012;33:476–9. PubMed PMID: 22161988.
- Hoogeveen-Westerveld M, Ekong R, Povey S, Mayer K, Lannoy N, Elmslie F, Bebin M, Dies K, Thompson C, Sparagana SP, Davies P, van Eeghen AM, Thiele EA, van den Ouweland A, Halley D, Nellist M. Functional assessment of TSC2 variants identified in individuals with tuberous sclerosis complex. *Hum Mutat*. 2013;34:167–75. PubMed PMID: 22903760.
- Humphrey A, MacLean C, Ploubidis GB, Granader Y, Clifford M, Haslop M, Neville BG, Yates JR, Bolton PF, et al. Intellectual development before and after the onset of infantile spasms: a controlled prospective longitudinal study in tuberous sclerosis. *Epilepsia*. 2014;55:108–16. PubMed PMID: 24417555.
- Huynh H, Hao HX, Chan SL, Chen D, Ong R, Soo KC, Pochanard P, Yang D, Ruddy D, Liu M, Derti A, Balak MN, Palmer MR, Wang Y, Lee BH, Sellami D, Zhu AX, Schlegel R, Huang A. Loss of tuberous sclerosis complex 2 (TSC2) is frequent in hepatocellular carcinoma and predicts response to mTORC1 inhibitor everolimus. *Mol Cancer Ther*. 2015;14:1224–35. PubMed PMID: 25724664.
- Hwang SK, Lee JH, Yang J, Lim CS, Lee JA, Lee YS, Lee K, Kaang BK. Everolimus improves neuropsychiatric symptoms in a patient with tuberous sclerosis carrying a novel TSC2 mutation. *Mol Brain*. 2016;9:56. PubMed PMID: 27216612.
- Inoki K, Li Y, Xu T, Guan KL. Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. *Genes Dev*. 2003;17:1829–34. PubMed PMID: 12869586.
- Jansen AC, Sancak O, D'Agostino MD, Badhwar A, Roberts P, Gobbi G, Wilkinson R, Melanson D, Tampieri D, Koenekoop R, Gans M, Maat-Kievit A, Goedbloed M, van den Ouweland AM, Nellist M, Pandolfo M, McQueen M, Sims K, Thiele EA, Dubeau F, Andermann F, Kwiatkowski DJ, Halley DJ, Andermann E. Unusually mild tuberous sclerosis phenotype is associated with TSC2 R905Q mutation. *Ann Neurol*. 2006;60:528–39. PubMed PMID: 17120248.
- Jarrar RG, Buchhalter JR, Raffel C. Long-term outcome of epilepsy surgery in patients with tuberous sclerosis. *Neurology*. 2004;62:479–81. PubMed PMID: 14872037.
- Jeste SS, Sahin M, Bolton P, Ploubidis GB, Humphrey A. Characterization of autism in young children with tuberous sclerosis complex. *J Child Neurol*. 2008;23:520–5. PubMed PMID: 18160549.
- Jeste SS, Varcin KJ, Hellemann GS, Gulsrud AC, Bhatt R, Kasari C, Wu JY, Sahin M, Nelson CA. Symptom profiles of autism spectrum disorder in tuberous sclerosis complex. *Neurology*. 2016;87:766–72. PubMed PMID: 27440144.
- Johnson SR, Clelland CA, Ronan J, Tattersfield AE, Knox AJ. The TSC-2 product tuberin is expressed in lymphangiomyomatosis and angiomyolipoma. *Histopathology*. 2002;40:458–63. PubMed PMID: 12010366.

- Joinson C, O'Callaghan FJ, Osborne JP, Martyn C, Harris T, Bolton PF. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. *Psychol Med.* 2003;33:335–44. PubMed PMID: 12622312.
- Jones AC, Shyamsundar MM, Thomas MW, Maynard J, Idziaszczyk S, Tomkins S, Sampson JR, Cheadle JP. Comprehensive mutation analysis of TSC1 and TSC2-and phenotypic correlations in 150 families with tuberous sclerosis. *Am J Hum Genet.* 1999;64:1305–15. PubMed PMID: 10205261.
- Kagawa K, Chugani DC, Asano E, Juhász C, Muzik O, Shah A, Shah J, Sood S, Kupsky WJ, Mangner TJ, Chakraborty PK, Chugani HT. Epilepsy surgery outcome in children with tuberous sclerosis complex evaluated with alpha-[11C]methyl-L-tryptophan positron emission tomography (PET). *J Child Neurol.* 2005;20:429–38. PubMed PMID: 15971355.
- Khare L, Strizheva GD, Bailey JN, Au KS, Northrup H, Smith M, Smalley SL, Henske EP. A novel missense mutation in the GTPase activating protein homology region of TSC2 in two large families with tuberous sclerosis complex. *J Med Genet.* 2001;38:347–9. PubMed PMID: 11403047.
- Kilincaslan A, Kok BE, Tekturk P, Yalcinkaya C, Ozkara C, Yapici Z. Beneficial effects of everolimus on autism and attention-deficit/hyperactivity disorder symptoms in a group of patients with tuberous sclerosis complex. *J Child Adolesc Psychopharmacol.* 2017;27:383–8. PubMed PMID: 27797585.
- Kingswood JC, d'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R, Cottin V, Curatolo P, Dahlin M, de Vries PJ, Feucht M, Fladrowski C, Gislimberti G, Hertzberg C, Jozwiak S, Lawson JA, Macaya A, Nabbout R, O'Callaghan F, Benedik MP, Qin J, Marques R, Sander V, Sauter M, Takahashi Y, Touraine R, Youroukos S, Zonneberg B, Jansen AC. Tuberous Sclerosis registry to increase disease Awareness (TOSCA)–baseline data on 2093 patients. *Orphanet J Rare Dis.* 2017;12:2. PubMed PMID: 28057044.
- Knox S, Ge H, Dimitroff BD, Ren Y, Howe KA, Arsham AM, Easterday MC, Neufeld TP, O'Connor MB, Selleck SB. Mechanisms of TSC-mediated control of synapse assembly and axon guidance. *PLoS One.* 2007;2:e375. PubMed PMID: 17440611.
- Kobashi Y, Sugui T, Irei T, Nakata M, Oka M. Clinicopathological analysis of multifocal micronodular pneumocyte hyperplasia associated with tuberous sclerosis in Japan. *Respirology.* 2008;13:1076–81. PubMed PMID: 18699800.
- Kopp CM, Muzykewicz DA, Staley BA, Thiele EA, Pulsifer MB. Behavior problems in children with tuberous sclerosis complex and parental stress. *Epilepsy Behav.* 2008;13:505–10. PubMed PMID: 18602868.
- Kothare SV, Singh K, Chalifoux JR, Staley BA, Weiner HL, Menzer K, Devinsky O. Severity of manifestations in tuberous sclerosis complex in relation to genotype. *Epilepsia.* 2014;55:1025–9. PubMed PMID: 24917535.
- Kozłowski P, Roberts P, Dabora S, Franz D, Bissler J, Northrup H, Au KS, Lazarus R, Domanska-Pakiela D, Kotulska K, Jozwiak S, Kwiatkowski DJ. Identification of 54 large deletions/duplications in TSC1 and TSC2 using MLPA, and genotype-phenotype correlations. *Hum Genet.* 2007;121:389–400. PubMed PMID: 17287951.
- Kozma SC, Thomas G. Regulation of cell size in growth, development and human disease: PI3K, PKB and S6K. *Bioessays.* 2002;24:65–71. PubMed PMID: 11782951.
- Krueger DA. Management of CNS-related disease manifestations in patients with tuberous sclerosis complex. *Curr Treat Options Neurol.* 2013;15:618–33. PubMed PMID: 23852707.
- Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, Wilson KA, Byars A, Sahmoud T, Franz DN. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N Engl J Med.* 2010;363:1801–11. PubMed PMID: 21047224.
- Krueger DA, Wilfong AA, Holland-Bouley K, Anderson AE, Agricola K, Tudor C, Mays M, Lopez CM, Kim M-O, Franz DN. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. *Ann Neurol.* 2013;74:679–87. PubMed PMID: 23798472.

- Kwiatkowski DJ. Genetics of tuberous sclerosis complex. In: Kwiatkowski DJ, Whitemore VH, Thiele EA, eds. *Tuberous Sclerosis Complex: Genes, Clinical Features, and Therapeutics*. Weinheim: Wiley-Blackwell; 2010:29-57
- Lamb RF, Roy C, Diefenbach TJ, Vinters HV, Johnson MW, Jay DG, Hall A. The TSC1 tumour suppressor hamartin regulates cell adhesion through ERM proteins and the GTPase Rho. *Nat Cell Biol*. 2000;2:281-7. PubMed PMID: 10806479.
- Leclezio L, de Vries PJ. Advances in the treatment of tuberous sclerosis complex. *Curr Opin Psychiatry*. 2015;28:113-20. PubMed PMID: 25602245.
- Lee DF, Kuo HP, Chen CT, Hsu JM, Chou CK, Wei Y, Sun HL, Li LY, Ping B, Huang WC, He X, Hung JY, Lai CC, Ding Q, Su JL, Yang JY, Sahin AA, Hortobagyi GN, Tsai FJ, Tsai CH, Hung MC. IKK beta suppression of TSC1 links inflammation and tumor angiogenesis via the mTOR pathway. *Cell*. 2007;130:440-55. PubMed PMID: 17693255.
- Lennert B, Farrelly E, Sacco P, Pira G, Frost M. Resource utilization in children with tuberous sclerosis complex and associated seizures: a retrospective chart review study. *J Child Neurol*. 2013;28:461-9. PubMed PMID: 22772159.
- Lewis WW, Sahin M, Scherrer B, Peters JM, Suarez RO, Vogel-Farley VK, Jeste SS, Gregas MC, Prabhu SP, Nelson CA 3rd, Warfield SK. Impaired language pathways in tuberous sclerosis complex patients with autism spectrum disorders. *Cereb Cortex*. 2013;23:1526-32. PubMed PMID: 22661408.
- Li LH, Li N, Zhao JY, Fei P, Zhang GM, Mao JB, Rychwalski PJ. Findings of perinatal ocular examination performed on 3573, healthy full-term newborns. *Br J Ophthalmol*. 2013;97:588-91. PubMed PMID: 23426739.
- Li Y, Corradetti MN, Inoki K, Guan KL. TSC2: filling the GAP in the mTOR signaling pathway. *Trends Biochem Sci*. 2004;29:32-8. PubMed PMID: 14729330.
- Mak BC, Yeung RS. The tuberous sclerosis complex genes in tumor development. *Cancer Invest*. 2004;22:588-603. PubMed PMID: 15565817.
- Martignoni G, Bonetti F, Pea M, Tardanico R, Brunelli M, Eble JN. Renal disease in adults with TSC2/PKD1 contiguous gene syndrome. *Am J Surg Pathol*. 2002;26:198-205. PubMed PMID: 11812941.
- Mayer K, Goedbloed M, van Zijl K, Nellist M, Rott HD. Characterization of a novel TSC2 missense mutation in the GAP related domain associated with minimal clinical manifestations of tuberous sclerosis. *J Med Genet*. 2004;41:e64. PubMed PMID: 15121792.
- McCormack FX, Gupta N, Finlay GR, Young LR, Taveira-DaSilva AM, Glasgow CG, Steagall WK, Johnson SR, Sahn SA, Ryu JH, Strange C, Seyama K, Sullivan EJ, Kotloff RM, Downey GP, Chapman JT, Han MK, D'Armiento JM, Inoue Y, Henske EP, Bissler JJ, Colby TV, Kinder BW, Wikenheiser-Brokamp KA, Brown KK, Cordier JF, Meyer C, Cottin V, Brozek JL, Smith K, Wilson KC, Moss J; ATS/JRS Committee on Lymphangiomyomatosis. Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangiomyomatosis Diagnosis and Management. *Am J Respir Crit Care Med*. 2016;194:748-61. PubMed PMID: 27628078.
- McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, Barker AF, Chapman JT, Brantly ML, Stocks JM, Brown KK, Lynch JP 3rd, Goldberg HJ, Young LR, Kinder BW, Downey GP, Sullivan EJ, Colby TV, McKay RT, Cohen MM, Korbee L, Taveira-DaSilva AM, Lee HS, Krischer JP, Trapnell BC; National Institutes of Health Rare Lung Diseases Consortium. MILES Trial Group. Efficacy and safety of sirolimus in lymphangiomyomatosis. *N Engl J Med*. 2011;364:1595-606. PubMed PMID: 21410393.
- McCormack FX. Lymphangiomyomatosis: a clinical update. *Chest*. 2008;133:507-16. PubMed PMID: 18252917.

- McDonald NM, Varcin KJ, Bhatt R, Wu JY, Sahin M, Nelson CA, Jeste SS. Early autism symptoms in infants with tuberous sclerosis complex. *Autism Research*. 2017;10:1981–1990. PubMed PMID: 28801991.
- Mlczoch E, Hanslik A, Luckner D, Kitzmüller E, Prayer D, Michel-Behnke I. Prenatal diagnosis of giant cardiac rhabdomyoma in tuberous sclerosis complex: a new therapeutic option with everolimus. *Ultrasound Obstet Gynecol*. 2015;45:618–21. PubMed PMID: 24913039.
- Mourikis D, Chatziioannou A, Antoniou A, Kehagias D, Gikas D, Vlahos L. Selective arterial embolization in the management of symptomatic renal angiomyolipomas. *Eur J Radiol*. 1999;32:153–9. PubMed PMID: 10632551.
- Mozaffari M, Hooegeveen-Westerveld M, Kwiatkowski D, Sampson J, Ekong R, Povey S, den Dunnen JT, van den Ouweland A, Halley D, Nellist M. Identification of a region required for TSC1 stability by functional analysis of TSC1 missense mutations found in individuals with tuberous sclerosis complex. *BMC Med Genet*. 2009;10:88. PubMed PMID: 19747374.
- Muzykewicz DA, Newberry P, Danforth N, Halpern EF, Thiele EA. Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis complex. *Epilepsy Behav*. 2007;11:506–13. PubMed PMID: 17936687.
- Muzykewicz DA, Sharma A, Muse V, Numis AL, Rajagopal J, Thiele EA. TSC1 and TSC2 mutations in patients with lymphangioleiomyomatosis and tuberous sclerosis complex. *J Med Genet*. 2009;46:465–8. PubMed PMID: 19419980.
- Nellist M, Brouwer RW, Kockx CE, van Veghel-Plandsoen M, Withagen-Hermans C, Prins-Bakker L, Hooegeveen-Westerveld M, Mrcsic A, van den Berg MM, Koopmans AE, de Wit MC, Jansen FE, Maat-Kievit AJ, van den Ouweland A, Halley D, de Klein A, van IJcken WF. Targeted Next Generation Sequencing reveals previously unidentified TSC1 and TSC2 mutations. *BMC Med Genet*. 2015;16:10. PubMed PMID: 25927202.
- Nellist M, van den Heuvel D, Schluep D, Exalto C, Goedbloed M, Maat-Kievit A, van Essen T, van Spaendonck-Zwarts K, Jansen F, Helderma P, Bartalini G, Vierimaa O, Penttinen M, van den Ende J, van den Ouweland A, Halley D. Missense mutations to the TSC1 gene cause tuberous sclerosis complex. *Eur J Hum Genet*. 2009;17:319–28. PubMed PMID: 18830229.
- Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, Frost MD, Fuchs Z, Gosnell ES, Gupta N, Jansen AC, Józwiak S, Kingswood JC, Knilans TK, McCormack FX, Pounders A, Roberds SL, Rodriguez-Buritica DF, Roth J, Sampson JR, Sparagana S, Thiele EA, Weiner HL, Wheless JW, Towbin AJ, Krueger DA, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. *Pediatr Neurol*. 2021;123:50–66. PubMed PMID: 34399110.
- Northrup H, Krueger DA, et al. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. 2013; 2013;49:243–54. PubMed PMID: 24053982.
- Northrup H, Wheless JW, Bertin TK, Lewis RA. Variability of expression in tuberous sclerosis. *J Med Genet*. 1993;30:41–3. PubMed PMID: 8423606.
- Numis AL, Major P, Montenegro MA, Muzykewicz DA, Pulsifer MB, Thiele EA. Identification of risk factors for autism spectrum disorders in tuberous sclerosis complex. *Neurology*. 2011;76:981–7. PubMed PMID: 21403110.
- O'Connor SE, Kwiatkowski DJ, Roberts PS, Wollmann RL, Huttenlocher PR. A family with seizures and minor features of tuberous sclerosis and a novel TSC2 mutation. *Neurology*. 2003;61:409–12. PubMed PMID: 12913212.
- Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann N Y Acad Sci*. 1991;615:125–7. PubMed PMID: 2039137.

- Pan CC, Chung MY, Ng KF, Liu CY, Wang JS, Chai CY, Huang SH, Chen PC, Ho DM. Constant allelic alteration on chromosome 16p (TSC2 gene) in perivascular epithelioid cell tumour (PEComa): genetic evidence for the relationship of PEComa with angiomyolipoma. *J Pathol.* 2008;214:387–93. PubMed PMID: 18085521.
- Patel U, Simpson E, Kingswood JC, Saggarr-Malik AK. Tuberose sclerosis complex: analysis of growth rates aids differentiation of renal cell carcinoma from atypical or minimal-fat-containing angiomyolipoma. *Clin Radiol.* 2005;60:665–73. PubMed PMID: 16038693.
- Pea M, Bonetti F, Martignoni G, Henske EP, Manfrin E, Colato C, Bernstein J. Apparent renal cell carcinomas in tuberous sclerosis are heterogeneous: the identification of malignant epithelioid angiomyolipoma. *Am J Surg Pathol.* 1998;22:180–7. PubMed PMID: 9500218.
- Plank TL, Yeung RS, Henske EP. Hamartin, the product of the tuberous sclerosis 1 (TSC1) gene, interacts with tuberin and appears to be localized to cytoplasmic vesicles. *Cancer Res.* 1998;58:4766–70. PubMed PMID: 9809973.
- Popper HH, Juettner-Smolle FM, Pongratz MG. Micronodular hyperplasia of type II pneumocytes--a new lung lesion associated with tuberous sclerosis. *Histopathology.* 1991;18:347–54. PubMed PMID: 2071093.
- Prather P, de Vries PJ. Behavioral and cognitive aspects of tuberous sclerosis complex. *J Child Neurol.* 2004;19:666–74. PubMed PMID: 15563012.
- Pymar LS, Platt FM, Askham JM, Morrison EE, Knowles MA. Bladder tumour-derived somatic TSC1 missense mutations cause loss of function via distinct mechanisms. *Hum Mol Genet.* 2008;17:2006–17. PubMed PMID: 18397877.
- Qin W, Kozlowski P, Taillon BE, Bouffard P, Holmes AJ, Janne P, Camposano S, Thiele E, Franz D, Kwiatkowski DJ. Ultra deep sequencing detects a low rate of mosaic mutations in tuberous sclerosis complex. *Hum Genet.* 2010;127:573–82. PubMed PMID: 20165957.
- Rendtorff ND, Bjerregaard B, Frödin M, Kjaergaard S, Hove H, Skovby F, Brøndum-Nielsen K, Schwartz M; Danish Tuberous Sclerosis Group. Analysis of 65 tuberous sclerosis complex (TSC) patients by TSC2 DGGE, TSC1/TSC2 MLPA, and TSC1 long-range PCR sequencing, and report of 28 novel mutations. *Hum Mutat.* 2005;26:374–83. PubMed PMID: 16114042.
- Rentz AM, Skalicky AM, Liu Z, Wheless JW, Dunn DW, Frost MD, Nakagawa J, Magestro M, Prestifilippo J. Tuberous sclerosis complex: a survey of health care resource use and health burden. *Pediatr Neurol.* 2015;52:435–41. PubMed PMID: 25771998.
- Ridler K, Suckling J, Higgins NJ, de Vries PJ, Stephenson CM, Bolton PF, Bullmore ET. Neuroanatomical correlates of memory deficits in tuberous sclerosis complex. *Cereb Cortex.* 2007;17:261–71. PubMed PMID: 16603714.
- Romanelli P, Verdecchia M, Rodas R, Seri S, Curatolo P. Epilepsy surgery for tuberous sclerosis. *Pediatr Neurol.* 2004;31:239–47. PubMed PMID: 15464634.
- Rose VM, Au KS, Pollom G, Roach ES, Prashner HR, Northrup H. Germ-line mosaicism in tuberous sclerosis: how common? *Am J Hum Genet.* 1999;64:986–92. PubMed PMID: 10090883.
- Sampson JR, Scahill SJ, Stephenson JB, Mann L, Connor JM. Genetic aspects of tuberous sclerosis in the west of Scotland. *J Med Genet.* 1989;26:28–31. PubMed PMID: 2918523.
- Sancak O, Nellist M, Goedbloed M, Elfferich P, Wouters C, Maat-Kievit A, Zonnenberg B, Verhoef S, Halley D, van den Ouweland A. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype--phenotype correlations and comparison of diagnostic DNA techniques in tuberous sclerosis complex. *Eur J Hum Genet.* 2005;13:731–41. PubMed PMID: 15798777.
- Sarma AK, Khandker N, Kurczewski L, Brophy GM. Medical management of epileptic seizures: challenges and solutions. *Neuropsychiatr Dis Treat.* 2016;12:467–85. PubMed PMID: 26966367.

- Sato T, Seyama K, Fujii H, Maruyama H, Setoguchi Y, Iwakami S, Fukuchi Y, Hino O. Mutation analysis of the TSC1 and TSC2 genes in Japanese patients with pulmonary lymphangiomyomatosis. *J Hum Genet.* 2002;47:20–8. PubMed PMID: 11829138.
- Shepherd CW, Gomez MR, Lie JT, Crowson CS. Causes of death in patients with tuberous sclerosis. *Mayo Clin Proc.* 1991;66:792–6. PubMed PMID: 1861550.
- Shields JA, Eagle RC Jr, Shields CL, Marr BP. Aggressive retinal astrocytomas in four patients with tuberous sclerosis complex. *Trans Am Ophthalmol Soc.* 2004;102:139–47. PubMed PMID: 15747752.
- Smolarek TA, Wessner LL, McCormack FX, Mylet JC, Menon AG, Henske EP. Evidence that lymphangiomyomatosis is caused by TSC2 mutations: chromosome 16p13 loss of heterozygosity in angiomyolipomas and lymph nodes from women with lymphangiomyomatosis. *Am J Hum Genet.* 1998;62:810–5. PubMed PMID: 9529362.
- Sjödahl G, Lauss M, Gudjonsson S, Liedberg F, Halldén C, Chebil G, Månsson W, Höglund M, Lindgren D. A systematic study of gene mutations in urothelial carcinoma; inactivating mutations in TSC2 and PIK3R1. *PLoS One.* 2011;6:e18583. PubMed PMID: 21533174.
- Spurling Jeste S, Wu JY, Senturk D, Varcin K, Ko J, McCarthy B, Shimizu C, Dies K, Vogel-Farley V, Sahin M, Nelson CA 3rd. Early developmental trajectories associated with ASD in infants with tuberous sclerosis complex. *Neurology.* 2014;83:160–8. PubMed PMID: 24920850.
- Staley BA, Montenegro MA, Major P, Muzykewicz DA, Halpern EF, Kopp CM, Newberry P, Thiele EA. Self-injurious behavior and tuberous sclerosis complex: frequency and possible associations in a population of 257 patients. *Epilepsy Behav.* 2008;13:650–3. PubMed PMID: 18703161.
- Strizheva GD, Carsillo T, Kruger WD, Sullivan EJ, Ryu JH, Henske EP. The spectrum of mutations in TSC1 and TSC2 in women with tuberous sclerosis and lymphangiomyomatosis. *Am J Respir Crit Care Med.* 2001;163:253–8. PubMed PMID: 11208653.
- Sun W, Zhu YJ, Wang Z, Zhong Q, Gao F, Lou J, Gong W, Xu W. Crystal structure of the yeast TSC1 core domain and implications for tuberous sclerosis pathological mutations. *Nat Commun.* 2013;4:2135. PubMed PMID: 23857276.
- Tierney KM, McCartney DL, Serfontein JR, de Vries PJ. Neuropsychological attention skills and related behaviours in adults with tuberous sclerosis complex. *Behav Genet.* 2011;41:437–44. PubMed PMID: 21191642.
- Tyburczy ME, Dies KA, Glass J, Camposano S, Chekaluk Y, Thorner AR, Lin L, Krueger D, Franz DN, Thiele EA, Sahin M, Kwiatkowski DJ. Mosaic and intronic mutations in TSC1/TSC2 explain the majority of TSC patients with no mutation identified by conventional testing. *PLoS Genet.* 2015;11:e1005637. PubMed PMID: 26540169.
- van Eeghen AM, Black ME, Pulsifer MB, Kwiatkowski DJ, Thiele EA. Genotype and cognitive phenotype of patients with tuberous sclerosis complex. *Eur J Hum Genet.* 2012;20:510–5. PubMed PMID: 22189265.
- van Slegtenhorst M, Nellist M, Nagelkerken B, Cheadle J, Snell R, van den Ouweland A, Reuser A, Sampson J, Halley D, van der Sluijs P. Interaction between hamartin and tuberin, the TSC1 and TSC2 gene products. *Hum Mol Genet.* 1998;7:1053–7. PubMed PMID: 9580671.
- Vanderhooft SL, Francis JS, Pagon RA, Smith LT, Sybert VP. Prevalence of hypopigmented macules in a healthy population. *J Pediatr.* 1996;129:355–61. PubMed PMID: 8804323.
- Webb DW, Osborne JP. Non-penetrance in tuberous sclerosis. *J Med Genet.* 1991;28:417–9. PubMed PMID: 1870099.
- Weiner HL, Carlson C, Ridgway EB, Zaroff CM, Miles D, LaJoie J, Devinsky O. Epilepsy surgery in young children with tuberous sclerosis: results of a novel approach. *Pediatrics.* 2006;117:1494–502. PubMed PMID: 16651302.

- Wentink M, Nellist M, Hoogeveen-Westerveld M, Zonnenberg B, van der Kolk D, van Essen T, Park SM, Woods G, Cohn-Hokke P, Brussel W, Smeets E, Brooks A, Halley D, van den Ouweland A, Maat-Kievit A. Functional characterization of the TSC2 c.3598C>T (p.R1200W) missense mutation that co-segregates with tuberous sclerosis complex in mildly affected kindreds. *Clin Genet*. 2012; 2012;81:453–61. PubMed PMID: 21332470.
- Wilde L, Eden K, de Vries P, Moss J, Welham A, Oliver C. Self-injury and aggression in adults with tuberous sclerosis complex: Frequency, associated person characteristics, and implications for assessment. *Research in Developmental Disabilities*. 2017;64:119–30. PubMed PMID: 28411579.
- Wong V. Study of the relationship between tuberous sclerosis complex and autistic disorder. *J Child Neurol*. 2006;21:199–204. PubMed PMID: 16901420.
- Woodford MR, Sager RA, Marris E, Dunn DM, Blanden AR, Murphy RL, Rensing N, Shapiro O, Panaretou B, Prodromou C, Loh SN, Gutmann DH, Bourboulia D, Bratslavsky G, Wong M, Mollapour M. Tumor suppressor Tsc1 is a new Hsp90 co-chaperone that facilitates folding of kinase and non-kinase clients. *EMBO J*. 2017;36:3650–65. PubMed PMID: 29127155.
- Xiao GH, Shoarinejad F, Jin F, Golemis EA, Yeung RS. The tuberous sclerosis 2 gene product, tuberin, functions as a Rab5 GTPase activating protein (GAP) in modulating endocytosis. *J Biol Chem*. 1997;272:6097–100. PubMed PMID: 9045618.
- Yang P, Cornejo KM, Sadow PM, Cheng L, Wang M, Xiao Y, Jiang Z, Oliva E, Jozwiak S, Nussbaum RL, Feldman AS, Paul E, Thiele EA, Yu JJ, Henske EP, Kwiatkowski DJ, Young RH, Wu CL. Renal cell carcinoma in tuberous sclerosis complex. *Am J Surg Pathol*. 2014;38:895–909. PubMed PMID: 24832166.
- Yeung RS. Multiple roles of the tuberous sclerosis complex genes. *Genes Chromosomes Cancer*. 2003;38:368–75. PubMed PMID: 14566857.
- Zhang J, Kim J, Alexander A, Cai S, Tripathi DN, Dere R, Tee AR, Tait-Mulder J, Di Nardo A, Han JM, Kwiatkowski E, Dunlop EA, Dodd KM, Folkerth RD, Faust PL, Kastan MB, Sahin M, Walker CL. A tuberous sclerosis complex signalling node at the peroxisome regulates mTORC1 and autophagy in response to ROS. *Nat Cell Biol*. 2013;15:1186–96. PubMed PMID: 23955302.

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.