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# Insights into Tuberous Sclerosis Complex : From Genes to Clinics

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Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder caused by pathogenic variants of *TSC1* or *TSC2* genes, leading to dysregulation of the mammalian target of rapamycin (mTOR) pathway. This dysregulation results in the formation of organ-specific tumors and neurological manifestations such as seizures, intellectual disability, and developmental delays. These characteristic clinical features are crucial for diagnosis, and genetic testing is playing an increasingly significant role. Long-term disease monitoring and appropriate interventions by multidisciplinary experts, including the use of mTOR inhibitors and promising therapeutic agents based on disease pathomechanisms, are essential for effective TSC management and improved clinical outcomes.

**Key Words :** Tuberous sclerosis · Practice guideline · Genetics · Guideline.

## INTRODUCTION

Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome first described by von Recklinghausen in 1862 in a baby with cardiac myomas[97]. TSC is an autosomal dominant genetic disorder whose multiorgan manifestations have been documented in numerous studies beginning in 1880, when Bourneville[14] and Bourneville and Brissaud[15] identified 'tubers' of the brain, a discovery that gave rise to the name TSC[57,93]. Although the clinical spectrum varies widely among patients, hallmark features such as cortical tubers, facial angiofibromas, renal angiomyolipomas (AMLs), cardiac rhabdomyomas, and retinal hamartomas are commonly observed, forming the basis for a typical clinical diagnosis. The first diagnostic criteria were proposed in 1998 based on these characteristic symptoms[98]. With the advent of advanced molecular techniques, genetic testing was incorporated into the revised diagnostic criteria in 2012[87]. Given that the disease produces diverse tumors with varying prognoses, proactive tumor surveillance and appropriate management strategies are crucial.

TSC is caused by variants of *TSC1* or *TSC2* genes, which were identified in the 1990s[35,116]. These genes encode hamartin and tuberin, respectively, which together form the TSC complex, a key regulator of the mammalian target of the rapamycin complex 1 (mTORC1) pathway[111,127]. Dysregulation of the mTORC1 pathway, a well-established driver of tumor growth

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and related symptoms, has prompted extensive research into its detailed pathomechanisms and targeted therapies. Notably, several studies have demonstrated the efficacy of mammalian target of rapamycin (mTOR) inhibitors in reducing tumor size or improving clinical symptoms, thus providing diverse management options for TSC[7,41,42].

This review aims to provide a comprehensive overview of the pathophysiology, clinical manifestations, and advancements in the diagnosis and management of TSC, highlighting recent developments in therapeutic strategies and their implications for patient care. By integrating the current findings, this study seeks to elucidate the multifaceted nature of the TSC and its management, offering insights into standardized practices and future research directions.

## EPIDEMIOLOGY AND DISEASE BURDEN

TSC occurs across all races and sexes, with an estimated worldwide incidence of one in 6000–10000 newborns[58]. Its prevalence varies between four and eight per 100000 persons[19,37,107,121]. The increased use of genetic testing has likely improved diagnostic rates, although epidemiological studies post-2012, when revised diagnostic criteria, including genetic testing, were introduced, remain limited[86]. Epilepsy, a common manifestation of TSC, was reported to occur in 80–90% of all patients with TSC as of 2010; however, subsequent studies indicate a prevalence ranging from 30–70%, suggesting that genetic diagnosis has identified more patients with milder clinical symptoms[19,37,107].

TSC imposes a significant disease burden owing to its multisystem involvement and chronic complications. Epilepsy incurs high medical expenses and diminishes quality of life due to refractory seizures and neurocognitive impairment[19,23,107]. Additionally, multiple tumors, such as subependymal giant cell astrocytomas (SEGAs), renal AMLs and pulmonary lymphangioleiomyomatosis (LAM), further exacerbate morbidity[62]. Most patients with TSC have a normal life expectancy. However, some manifestations of TSC, epilepsy-related complications and renal involvement, may lead to serious complications and premature death[92]. Survival rates decrease with age, with 20-year and 50-year survival rates of 98.6% and 79.5%, respectively[18].

## PATHOPHYSIOLOGY

TSC is a genetic disorder caused by pathogenic variants of *TSC1* or *TSC2* genes, which encode hamartin and tuberin, respectively. They form a complex that functions as a GTPase-activating protein for Rheb, thereby inhibiting the mTORC1 pathway, which is a critical regulator of cell growth, proliferation, and metabolism[59,111]. Pathogenic variants of *TSC1* or *TSC2* disrupt the function of the TSC, leading to hyperactivation of mTORC1 signaling. This dysregulation results in abnormal cell growth and tumorigenesis in multiple organs, including the brain, kidneys, heart, retina, and skin. In the central nervous system, the mTORC1 pathway plays a critical role in synaptic plasticity, neuronal differentiation, and axonal growth. This dysregulation leads to abnormal neural connectivity and cortical dysplasia, which manifests as cortical tubers, subependymal nodules (SENs), and SEGAs[9,22,41,44]. These structural abnormalities result in epilepsy in patients with TSC along with persistent neural network hyperexcitability[110]. Cognitive impairment in TSC is thought to arise through similar mechanisms. Impaired neuronal migration and abnormal synaptic pruning during early development are major contributors. Dysregulated mTORC1 affects both excitatory and inhibitory synaptic transmission, leading to imbalanced neural circuits that result in early-onset developmental delay, autism spectrum disorder (ASD), and cognitive impairments. Neuroinflammation, mediated by microglial activation in response to cortical tubers, is another factor that contributes to neuronal dysfunction and cognitive decline[9,67,126].

## CLINICAL MANIFESTATIONS

TSC is characterized by the development of benign tumors in multiple organs including the brain, heart, eyes, lungs, kidneys, and skin. These tumors can lead to various complications, often necessitating medical or surgical interventions. Neurological manifestations are prominent and include epilepsy, global developmental delay, ASD, and cognitive decline, all of which significantly diminish the quality of life of the patients and their families.

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## CENTRAL NERVOUS SYSTEM INVOLVEMENT

### Epilepsy

Epilepsy is the most common neurological manifestation of TSC, affecting approximately 60–90% of patients[19,37,107]. Seizures often present as the initial symptom, with onset occurring before the age of 2 years in more than 80% of cases, although they can develop at any point during the disease course[19,55,81,112]. Patients may experience multiple seizure types, with focal seizures being the most prevalent, reported in 60–70% of cases, followed by epileptic spasms in 35–40% and generalized seizures in 10–20%[55,81,112]. Additionally, 20–50% of patients exhibit multiple seizure types, either simultaneously or sequentially[81,112].

Once seizures commence, antiseizure medications (ASMs) are considered. However, achieving seizure control is challenging, with varying outcomes among patients. Several studies have indicated that approximately 65–70% of patients fail to achieve a seizure-free state[81,112]. Epileptic spasms are often initially managed with medications such as vigabatrin and are usually controlled in over 50% of patients; however, some patients who become spasm-free subsequently develop other types of seizures that are often refractory to ASMs over time[26,56,81].

Genotype-phenotype correlations in TSC-related epilepsy revealed that mutations in *TSC2* are associated with a more severe phenotype, including earlier seizure onset and a higher incidence of refractory epilepsy, compared to *TSC1* mutations[23,25,90]. The increased severity of patients with *TSC2* variants is likely due to the greater impact of *TSC2* mutation, as tuberin plays an important role in regulating the mTORC1 pathway[28,113]. Cortical dysplasia is more extensive in patients with *TSC2* variants, which further contributes to epileptogenesis[2,113]. However, this genotype-phenotype correlation is not strict, and some patients who present with a mild phenotype and *TSC2* variants have been reported[28].

### TSC-associated neuropsychiatric disorders (TANDs)

TSC is often associated with a spectrum of neuropsychiatric disorders, collectively termed TANDs. TAND encompasses cognitive, behavioral, and psychiatric challenges, including early developmental delay, intellectual disability (affecting approximately 50% of patients), ASD (40–50%), attention-deficit/hyperactivity disorder, and anxiety disorders (30–60%)[19,32,49,88]. The severity of cognitive impairment and early developmental delays in patients with TSC is often correlated with early seizure onset, refractory epilepsy, and a higher burden of cortical tubers[10,90,125]. Moderate to severe cognitive impairment, frequently accompanied by refractory epilepsy, significantly diminishes quality of life. Mental health concerns, such as anxiety or depression, are prone to being overlooked compared to other physical symptoms. However, they are critical components that necessitate thorough evaluation and appropriate interventions to maintain and enhance quality of life.

TANDs also exhibit varying severities depending on the causative gene. ASD and intellectual disabilities are more prevalent in patients with *TSC2* variants, who also experience more behavioral and emotional problems. This correlation is linked to greater cortical tuber burden, disrupted synaptic plasticity, and increased neuroinflammation[31,34].

### Cortical tubers, SENs, and SEGAs

Cortical tubers, resulting from abnormal neuronal migration and differentiation during fetal brain development, are a hallmark of patients with TSC. Typically located in the cerebral cortex, these lesions are visible on brain magnetic resonance imaging (MRI) as hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery sequences (Fig. 1A)[23]. Cortical tubers are associated with various neurological manifestations including seizures and TANDs. Although these lesions are nonprogressive, they can serve as epileptogenic foci, making surgical resection a therapeutic option for patients with refractory epilepsy. The extent and distribution of tubers often correlate with the severity of these symptoms[113].

SENs are benign hamartomatous lesions that occur along the walls of the lateral ventricles, and are another hallmark of TSC. Histologically, these lesions are characterized by large, dysplastic astrocytes and calcification, making them visible on brain MRI as hyperintense lesions on T2-weighted sequences (Fig. 1B)[23]. SENs are usually asymptomati, but can transform into SEGAs if located near the foramen of Monro. Distinguishing SENs from SEGAs based solely on pathological findings can be challenging[12].

SEGAs are low-grade astrocytic tumors that arise from SENs and are typically located near the foramen of Monro (Fig. 1C). These tumors occur in approximately 5–15% of patients with TSC and are usually identified in childhood or adolescence, although fetal or infantile cases have also been reported[23,49]. SE-

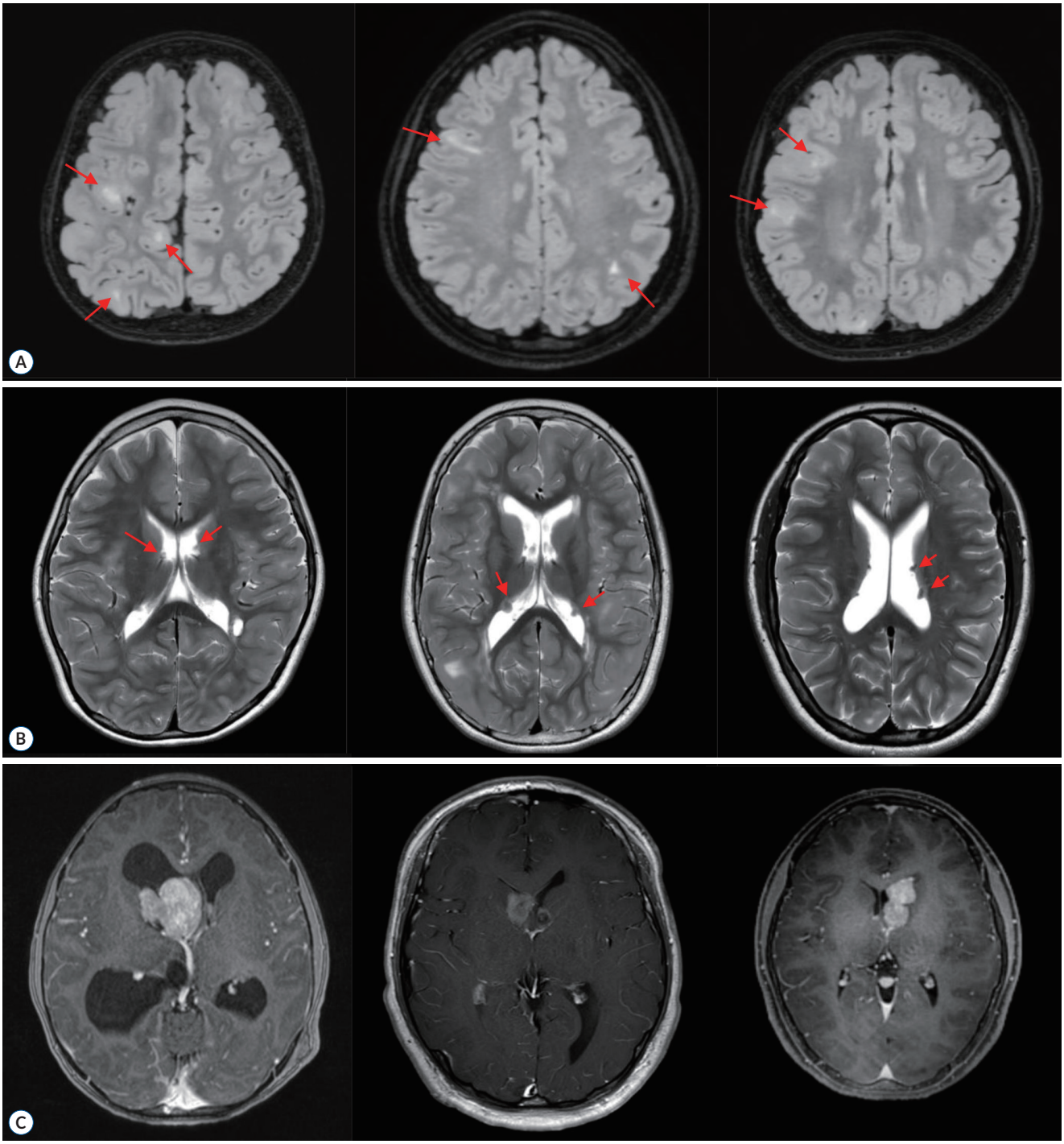


**Fig. 1.** Typical brain manifestations in TSC. A : T2-FLAIR MRI showing cortical tubers as hyperintense lesions within the cerebral cortex (arrows). B : T2-weighted MRI indicating a subependymal nodule along the lateral ventricles (arrows). C : Contrast enhanced T1-weighted MRI demonstrating a well-circumscribed, enhancing mass near the foramen of Monro, characteristic of subependymal giant cell astrocytoma. TSC : tuberous sclerosis complex, FLAIR : fluid-attenuated inversion recovery, MRI : magnetic resonance imaging.

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GAs are composed of multinucleated cells with astrocytic and neuronal characteristics, do not possess malignant potential, and tend to stabilize in size in adulthood[41]. Their growth can lead to cerebrospinal fluid obstruction, resulting in increased intracranial pressure, headache, papilledema, and hydrocephalus, often necessitating management strategies, such as surgery or mTOR inhibitors[23].

## CARDIOVASCULAR INVOLVEMENT

Cardiac rhabdomyomas are the most common primary cardiac tumors in children and serve as strong indicators of TSC. Approximately 70–90% of patients with cardiac rhabdomyomas are eventually diagnosed with TSC[13,47]. These tumors are often detected using ultrasonography (USG) during the fetal period, indicating their early development[47]. In most cases, patients with cardiac rhabdomyomas are asymptomatic. However, if a tumor obstructs blood flow, it can lead to cardiac dysfunction[3,54,109]. Heart failure associated with cardiac rhabdomyomas has been reported in about 2–5% of pediatric patients with TSC[65,85]. Arrhythmias are also commonly observed in patients with TSC and are linked to the location of specific tumors and associated nodal dysfunction or accessory pathways[52,69,76]. Medical treatment for heart failure or related arrhythmias may be required in some patients, depending on the severity of the symptoms. Active treatment of cardiac tumors is usually unnecessary because most tumors spontaneously regress over time[13,105].

## RENAL INVOLVEMENT

Renal involvement is observed in approximately 80% of patients with TSCs. Renal AMLs are the most prevalent manifestation, occurring in 70–80% of patients. These tumors are detected in less than 20% of patients under 2 years of age but in over 60% of patients under the age of 10 years[36]. The term angiomyolipoma reflects the pathological composition of these tumors, which include abnormal vasculatures, smooth muscle cells, and adipocytes[50,68,72]. Renal AMLs are often multiple and bilateral and tend to grow over time, which can result in flank pain and renal dysfunction. Additionally, their vascular components may cause spontaneous bleeding, which is a medical emergency requiring prompt management.

Renal cysts are the second most common kidney manifestation and are present in 15–50% of patients with TSC[21,96]. These cysts are considered to result from second hit mutations in *TSC1* or *TSC2* within renal epithelium, although further studies are required to conform this[71]. Renal cysts are usually small and asymptomatic in most cases, and the number of cysts is less than five in 45–65% of cases[17,96].

Renal cell carcinoma (RCC) occurs in 2–4% of patients with TSC[1,8,96]. The median age of onset of RCC in patients with TSC is in their forties, approximately 20 years earlier than in the general population. Some patients with TSC present with multiple bilateral RCCs, which often have distinct histopathologic features[115].

## PULMONARY INVOLVEMENT

The main pulmonary manifestation of TSC is LAM, a progressive cystic lung disease characterized by the abnormal proliferation of smooth muscle-like cells within the lungs. This leads to the cystic destruction of the lung parenchyma, airway obstruction, lymphatic involvement, and effusions[46]. LAMs occur exclusively in women with TSC, affecting 30–40% of females of reproductive age[46,63]. Clinically, patients with pulmonary LAM may present with a chronic cough, progressive dyspnea on exertion, recurrent pneumothorax, and pleural effusion. High-resolution computed tomography (HRCT) scans of the chest typically reveal diffuse, round, thin-walled cysts, which are considered the hallmarks of the disease. Elevated vascular endothelial growth factor-D (VEGF-D) levels can serve as a biomarker of pulmonary LAM. Once a patient is diagnosed with LAM, regular pulmonary function tests (PFTs) are strongly recommended to evaluate respiratory function and establish a management plan. Serial HRCT scans or measurements of VEGF-D levels can serve as alternative assessment tools for patients with cognitive impairments who cannot undergo PFT[46,63,87].

Multifocal micronodular pneumocyte hyperplasia (MMPH), is another pulmonary manifestation associated with TSC[87]. Characterized by nodular proliferation of type II pneumocytes, MMPH can occur in both men and women with TSC. It is considered a benign lesion and is rarely reported in patients with sporadic LAM. On imaging, MMPH appears as multiple

small nodules with ground-glass opacity, measuring up to 5 mm in diameter, distributed throughout the lungs[70,74]. While MMPH is generally asymptomatic, its recognition is important for differentiating it from other pulmonary nodular lesions, such as LAM[74,87].

## DERMATOLOGIC INVOLVEMENT

Patients with TSC exhibit various dermatological manifestations that differ across age groups. Nearly all patients have one or more cutaneous symptoms. Recognizing these features is crucial for the early diagnosis and management of TSC, as they often serve as visible indicators of the disease[87].

Hypomelanotic macules, also known as hypopigmented macules, are flat patches of skin lighter than the surrounding area. They vary in size and can appear anywhere on the body. More than 90% of patients with TSC display hypomelanotic macules, frequently observed within the first year of life[33,87]. These macules become less apparent with age.

Angiofibromas, formerly referred to as adenoma sebaceum, are observed in approximately 75% of patients aged between 2–5 years, and typically increase in number and size during adolescence[33,87]. These hamartomatous nodules are primarily distributed on the cheeks bilaterally, nasolabial folds, and chin[33,84]. They are often mistaken for simple acne, especially during adolescence, leading to cosmetic concerns; however, they do not require serious medical attention.

Shagreen patches are distinctive skin lesions present in approximately 50% of patients with TSC. Characterized by elevated and thickened patches of skin with rough and irregular textures, they are usually located on the trunk. A large shagreen patch is one of the main diagnostic criteria for TSC[87].

Additional dermatological manifestations include confetti skin lesions, which appear as numerous small hypopigmented macules typically over the distal extremities. This lesion is observed in approximately 3–28% of patients with TSC and is used as a minor diagnostic criteria[103,119].

Ungual fibromas commonly emerge after adolescence as benign fibrous lesions around the nail bed[33]. Although ungual fibromas are benign, their growth can cause pain or discomfort, sometimes necessitating surgical excision or laser therapy[33,84].

## OPHTHALMIC INVOLVEMENT

Retinal astrocytic hamartomas are observed in approximately 50% of patients with TSC. These lesions are one of the major diagnostic criteria for TSC[85]. Retinal hamartomas can be categorized into three phenotypes : flat and translucent lesions, nodular lesions, and transitional-type lesions. Most lesions remained stable over years, regardless of the lesion type and patients' age[53].

Ophthalmic findings other than retinal lesions have also been reported. Hamartomas can occur in the iris and ciliary epithelia. Hypopigmented sectoral lesions of the iris and ciliary body and colobomas have also been reported[53].

## OTHER FEATURES

In addition to the major manifestations described above, patients can may present with various minor symptoms owing to underlying disease pathomechanisms involving abnormal cell growth and metabolism. Symptoms include small dental pit depressions on the tooth surface and gingival fibromas, which are benign fibrous growths of the gum. Studies have reported that 69% of adult patients with TSC present with oral fibromas, primarily attached to or internal to the dental gingiva[105,106]. Additionally, bone cysts have been observed in some patients with TSC. Gastrointestinal hamartomatous polyps and lymphangiomas have been identified in some patients[87].

## DIAGNOSIS

The diagnosis of TSC integrates clinical symptoms and signs, imaging findings, and genetic testing. The first official diagnostic criteria were established by the International Tuberous Sclerosis Consensus Conference in 1998, focusing on major and minor clinical features identified through imaging and physical examination without incorporating genetic testing[98]. Advancements in imaging techniques, particularly MRI, have enhanced the detection of brain lesions associated with TSC, prompting further refinement of the diagnostic criteria[98,99,102]. In 2012, the criteria were revised to include genetic testing as a major diagnostic component, acknowledging the role of pathogenic variants in *TSC1* or *TSC2*[87]. The most recent update in 2021 reaf-

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firmed the importance of both clinical and genetic diagnostic criteria[86].

## DIAGNOSTIC CRITERIA UPDATES

According to the revised diagnostic criteria, the clinical diagnostic features included 11 major and seven minor features (Table 1)[86,87]. A definitive diagnosis of TSC can be made if the patient presents with two major features, or one major and two or more minor features. A possible diagnosis can be considered with one major feature or two or more minor features. Notably, the identification of a pathogenic variant in either *TSC1* or *TSC2* is sufficient for a definitive diagnosis of TSC, even in the absence of clinical features, provided that the variant has a clear pathogenic effect on function. Genetic testing is particularly useful for patients who do not fully meet clinical criteria. However, a negative genetic test does not rule out TSC, as approximately 10–15% of patients with TSC do not have detectable pathogenic germline variants in *TSC1* or *TSC2* through conventional genetic testing. This may be due to mosaic variants or variants in the deep intronic regions[45,94,115].

Although the diagnostic criteria have been revised over decades, achieving a definite diagnosis remains challenging in some cases. Studies have shown that up to 29% of patients may not meet the established diagnostic criteria[103]. Factors such as limited access to advanced imaging techniques or a lack of specialized expertise can contribute to the under-recognition of TSC in certain regions. Continued efforts to raise disease awareness and conduct organized studies are essential for address these challenges[49].

## TSC GENETICS AND MOLECULAR TESTING

TSC is caused by pathogenic variations in *TSC1* or *TSC2*, located on chromosomes 9q34 and 16p13, respectively[35,116]. Approximately 85% of patients clinically diagnosed with TSC have detectable *TSC1* or *TSC2* variants. *TSC1* variants are identified in approximately 15% and *TSC2* variants in 50–65% of patients[100,101]. These variants include missense mutations, nonsense mutations, small insertions/deletions (indels), and genomic deletions or duplications, with approximately 65–85% of identified variants reported as *de novo* cases[28,100,101]. Historically, Sanger sequencing has been the primary diagnostic method for detecting single-nucleotide variants, whereas techniques such as multiplex ligation-dependent probe amplification, gene-targeted microarray, or polymerase chain reaction have been employed to identify genomic deletions or duplications. Advancements in next-generation sequencing, particularly whole-genome sequencing, now allow for the simultaneous detection of all variant types, thereby enhancing diagnostic accuracy. The choice of diagnostic method varies across countries depending on test availability and cost-effectiveness. Although many patients can be diagnosed based solely on their clinical features, early genetic testing offers significant clinical benefits. It facilitates disease surveillance, enables preemptive management, and supports prenatal family counselling, all contributing to improved outcomes.

**Table 1.** Updated diagnostic criteria for tuberous sclerosis complex*

| |
|---|
| A. Genetic diagnostic criteria |
| a. The identification of pathogenic variants in *TSC1* or *TSC2* in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC) |
| b. A pathogenic variant is defined as follows : i) out-of-frame indel or nonsense variant that clearly inactivates the function of the TSC1 or TSC2 proteins, ii) genomic deletion which prevent protein synthesis, and iii) a missense variant whose effect on protein function has been established by functional assessment |
| c. Note that 10–25% of patients with TSC have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC or have any effect on the use of clinical diagnostic criteria to diagnosis TSC |
| B. Clinical diagnostic criteria |
| Major features: 1) hypomelanotic macules (≥3, at least 5 mm diameter); 2) angiofibromas (≥3) or fibrous cephalic plaque; 3) ungual fibromas (≥2); 4) shagreen patch; 5) multiple retinal hamartomas; 6) cortical dysplasias (includes tubers and cerebral white matter radial migration lines); 7) subependymal nodules; 8) subependymal giant cell astrocytomas; 9) cardiac rhabdomyomas; 10) lymphangioleiomyomatosis†; and 11) angiomyoliomas (≥2)† |
| Minor features : 1) confetti skin lesions; 2) dental enamel pits (>3); 3) intraoral fibromas (≥2); 4) retinal achromic patch; 5) multiple renal cysts; 6) nonrenal hamartomas; and 7) sclerotic bone lesions |

Definite diagnosis : two major features OR one major feature and ≥2 minor features. Possible diagnosis : one major feature OR ≥2 minor features. *This table is derived from the updated diagnostic criteria for tuberous sclerosis complex 2012, with minor revisions from the updated criteria in 2021[86,87]. †A combination of these two major features without other features does not meet criteria for a definite diagnosis

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**Table 2.** Surveillance and management recommendations for tuberous sclerosis complex*

| Organs or conditions | Surveillance recommendations | Management recommendations |
|---|---|---|
| Brain | 1. Neuroimaging<br>- Baseline brain MRI should be performed in all newly diagnosed patients, to look for tubers, SENs, and SEGAs<br>- Regular brain MRI every 1–3 years is recommended until age of 25 years, to monitor SEGAs<br>- If MRI is unavailable, CT can be an alternative option<br>2. Seizure monitoring<br>- Baseline EEG is recommended for infants with TSC, even a patient do not show clinical seizures<br>- In case where seizures are observed for the first time, a routine EEG should be performed initially<br>- A 24-hour video EEG monitoring can be considered if further evaluation is required<br>- Caregiver education is required regarding seizure patterns commonly occurring in infancy and childhood, such as epileptic spasms | 1. SEGA<br>- Surgical resection should be considered for acute symptomatic SEGAs<br>- mTOR inhibitors can be considered for growing but asymptomatic SEGAs<br>2. Epilepsy<br>- ASMs are treatments of choice for epilepsy<br>- Vigabatrin is the first-line therapy for epileptic spasm<br>- ACTH and corticosteroid can be considered as second-line therapies for epileptic spasm<br>- Choice of ASMs for other seizure types depends on seizure types and EEG findings<br>- Ketogenic diet and epileptic surgery (focal resection, vagus nerve stimulation, callosotomy, or deep brain stimulation) |
| TAND | 1. Perform baseline assessment for potential TAND manifestations. The TAND checklist is available online<br>2. Caregiver education and training about TAND manifestations, such as autism spectrum disorder, language disorders, attention-deficit/hyperactivity disorder, mood disorder | 1. Provide appropriate education and interventions for specific TAND manifestations |
| Kidney | 1. Renal imaging<br>- Regular renal imaging every 1–3 years is recommended for all patients, to screen for AMLs and cysts<br>- MRI is the preferred modality, but if it is unavailable, CT or USG can be considered as other screening tools<br>2. Renal function<br>- Baseline and annual evaluation for renal function is required : blood pressure, serum creatinine, estimated glomerular filtration rate, and/or cystatin C (specific examination items may be subject to change based on the experts' opinion) | 1. A mTOR inhibitor, everolimus, is recommended for AMLs >3 cm in diameter<br>2. If everolimus is unavailable, selective embolization or kidney sparing resection can be considered as second-line therapy for asymptomatic AMLs<br>3. Selective embolization followed by corticosteroid should be considered for acute symptomatic AMLs<br>4. The treatment of RCC follows similar principles to that of RCC in the general population; however, a kidney-sparing strategy should be prioritized whenever possible |
| Lung | 1. Baseline chest CT is recommended for all females and symptomatic males with TSC, to screen for LAM<br>2. Perform baseline and regular PFTs in patients whose chest CT imaging finds cystic lung disease suggesting LAM<br>3. For patients unable to perform PTFs, regular CT and serum VGEF level can be alternative tests for monitoring LAM | 1. Smoking cessation is recommended for all patients<br>2. Consider mTOR inhibitors for treatment of LAM in patients with decreased FEV1 values (<70% predicted), problematic chylous effusion, and rapidly progressive disease, indicated by symptoms or imaging<br>3. Pre-counselling for women with LAM regarding the risk of pregnancy and exogenous estrogen use. Avoid routine use hormonal therapy |
| Heart | 1. All patients under 3 years old should undergo baseline echocardiogram and ECG<br>2. For patients with confirmed cardiac rhabdomyoma, regular echocardiogram is recommended until the tumor regresses | 1. Active intervention for cardiac rhabdomyoma is not recommended for most patients<br>2. Medical treatment may be required for some symptomatic cases with cardiac rhabdomyoma; treatment options depend on the symptoms |
| Eye | 1. Baseline and regular ophthalmologic evaluation including fundoscopy is recommended for all patients | 1. Active treatment is not required for most of ophthalmic manifestations<br>2. Selective treatment can be required for some cases with aggressive ophthalmic lesions |
| Skin and teeth | 1. Baseline and regular dermatologic and dental examination should be performed | 1. Topical sirolimus can be provided for facial angiofibromas or other skin lesions |

**Table 2.** Continued

| Organs or conditions | Surveillance recommendations | Management recommendations |
|---|---|---|
| Genetic testing | 1. Genetic testing is recommended for all patients diagnosed with TSC or suspected of having TSC | 1. Obtain the extended pedigree, for three or more generations<br>2. Provide genetic counselling for family members and cascade screening<br>3. Prenatal counselling should be provided for family members who plan a pregnancy |

*This table is derived from updated diagnostic criteria for tuberous sclerosis complex 2012, with minor revision from updated criteria in 2021[86,87]. MRI : magnetic resonance imaging, SEN : subependymal nodule, SEGA : subependymal giant cell astrocytoma, CT : computed tomography, EEG : electroencephalogram, TSC : tuberous sclerosis complex, mTOR : mammalian target of rapamycin, ASM : antiseizure medication, ACTH : adrenocorticotropic hormone, TAND : TSC-associated neuropsychiatric disorder, AML : angiomyolipoma, USG : ultrasonography, RCC : renal cell carcinoma, LAM : lymphangioleiomyomatosis, PFT : pulmonary function test, VEGF-D : vascular endothelial growth factor-D, FEV1 : forced expiratory volume in one second, ECG : echocardiogram

## DISEASE SURVEILLANCE AND MANAGEMENT

TSC affect multiple organ systems in an age-dependent manner, and requires regular monitoring and a multidisciplinary approach for effective management. International guidelines for TSC have been published and are periodically updated to optimize disease surveillance and management[86,87]. Table 2 summarizes the disease surveillance and management of TSC.

## DISEASE SURVEILLANCE

### Central nervous system

Patients suspected of having TSC at any age should undergo brain MRI to evaluate cortical dysplasia, SENs, and, particularly, SEGAs, regardless of the presence of seizures or other focal neurological signs. Early detection facilitates prompt management and helps prevent complications[49,87]. The 2012 International Tuberous Sclerosis Complex Consensus Conference recommended routine neuroimaging every 1–3 years until 25 years of age to monitor the development of SEGAs, as early detection and treatment are associated with a favorable prognosis[30]. The imaging interval may be shortened if a SEGA shows growth between scans, or if related clinical symptoms emerge. Although brain MRI is the gold standard for evaluating structural lesions in TSC, computed tomography (CT) or brain USG can be considered when MRI is unavailable[49,87]. A SEGA identified during childhood in a patient with TSC can slowly grow over time after adulthood[87]. Additionally, recent studies have reported that SEGA may develop in adulthood[77]. Therefore, continued vigilance in monitoring is essential, even beyond the age of 25 years, especially if clinical symptoms suggest potential SEGA development.

Electroencephalograms (EEGs) are recommended for surveillance of all TSC cases. Epilepsy is one of the main manifestations of TSC and historically, EEGs were obtained following the onset of clinical seizures. However, recent guidelines advocate for baseline EEGs in all pediatric patients with TSC, irrespective of seizure history, due to the strong correlation between early seizure detection and improved neurological outcomes[11,19,24,64,87]. Infantile spasms are a common type of seizures in infants with TSC. Therefore, educating parents to recognize spasms is crucial. If a baseline EEG reveals abnormalities, particularly a hypsarrhythmic pattern, 24-hour video EEG

monitoring can provide further insights into under-recognized seizures that may require treatment. Recent studies have explored the additional benefits of preemptive treatment with vigabatrin in infants with TSC who exhibit epileptiform discharges on EEG[71]. One study indicated that such preventive treatment did not improve neurocognitive outcomes at 24 months, nor did it delay seizure onset and drug-resistant epilepsy[66]. In summary, while baseline and routine EEG monitoring are essential for early seizure detection and management in pediatric patients with TSC, the efficacy of preemptive vigabatrin treatment in improving long-term developmental and neurological outcomes remains uncertain[67,71,79].

Recognizing the importance of early detection and intervention for TAND, the 2012 TSC Consensus Conference guidelines recommended that all pediatric patients with TSC undergo baseline neurocognitive evaluations with regular follow-ups throughout childhood and adolescence. This proactive approach ensures that patients receive optimal educational support and specialized therapies tailored to their needs. A specific tool known as the TAND checklist has been developed[32]. This checklist was designed to help clinical teams, individuals with TSC, and their families to identify and prioritize neuropsychiatric concerns. It is freely accessible online in multiple languages, which makes it a valuable resource for diverse populations (https://tandconsortium.org/checklists/).

## Kidney

Regular renal imaging every 1–3 years is recommended for patients with TSC to screen for AMLs or renal cysts[86]. MRI is preferred because of its high resolution and lack of radiation exposure. If MRI is unavailable, USG or CT scans can be performed[49,87]. For patients with AMLs growing over time, more frequent imaging, every 6–12 months, is recommended to monitor tumor size and determine preemptive treatment. Additionally, the 2012 TSC Consensus Conference guidelines recommend baseline and annual screening of renal function using blood tests and blood pressure[86,87]. Renal function can be measured using serum creatinine levels, estimated glomerular filtration rate (eGFR), and cystatin C.

RCCs are usually detected by routine kidney evaluation[87]. However, confirmation of RCC is often challenging in imaging studies. Distinguishing RCC from renal AMLs is a critical component that is often challenging and necessitates regular imaging studies, with MRI being the preferred modality. However, in the case of fat-poor AMLs, which can be challenging to differentiate from RCC, a needle biopsy is indicated if the lesion exhibits a growth rate >5 mm/year and/or shows a poor response to mTOR inhibitors[8,87,114].

## Lung

Women with TSC are at a risk of developing LAM after adulthood. Annual examinations of the lungs and taking a history of respiratory symptoms, including dyspnea on exertion, shortness of breath, and hemoptysis, are recommended. Baseline chest HRCT scans should be performed in all women aged over 18 years and in symptomatic men with TSC[86,87]. A PFT is also recommended as a baseline test if the patient can perform it, although some patients may have difficulties undergoing PFTs because of cognitive impairment[49,87]. If an HRCT scan reveals normal lungs and there are no clinical symptoms, subsequent imaging can be conducted after 5–10 years. In contrast, if progressive cysts are detected, repeated imaging should be performed every 2–3 years with annual PFTs. The test interval can be shortened according to the degree of disease progression. Serum VEGF-D levels can serve as a biomarker for LAM development and progression[123,124]. Despite regular screening, there are currently no established guidelines for prevention or early treatment of LAM. Further studies using long-term clinical data may provide future perspectives regarding the use of mTOR inhibitors.

## Heart

Pediatric patients with TSC, especially those younger than 3 years of age, should undergo echocardiography and electrocardiography (ECG) to screen for cardiac rhabdomyomas and arrhythmias[87]. In cases of cardiac rhabdomyomas detected prenatally via fetal USG, repeated fetal and postnatal USG can be performed based on expert decisions. Routine echocardiography may not be necessary after adolescence if the patient has no suspicious cardiac symptoms or concerning medical history[87]. However, a baseline ECG is recommended because asymptomatic conduction defects can be present even in adults[87].

## Eye

Baseline ophthalmologic evaluation, including dilated fundoscopy, is recommended for all patients with TSC to screen for retinal astrocytic hamartomas or other ophthalmologic lesions[87]. Regular ophthalmologic evaluation is important for

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the early detection and management of the ocular manifestations of TSC.

### Skin and teeth

Dermatological and dental examinations should be performed at the baseline evaluation for all patients with TSC[87]. These examinations are crucial for identifying clinical diagnostic features such as facial angiofibromas, hypomelanotic macules, ungual fibromas, and dental pits, which are commonly associated with TSC. Although many dermatological and dental manifestations may not necessitate active treatment, their identification is essential for a definitive diagnosis. Additionally, recognizing these features, which can be identified by simple examinations, may provide clues for diagnosing family members with milder phenotypes, thereby facilitating appropriate family counselling and cascade screening.

### Genetic testing and counselling

Genetic testing is recommended for all patients with TSC to confirm the diagnosis and for family counselling[87]. If a patient does not fulfill the clinical criteria for a definite diagnosis, genetic testing can provide decisive information for accurate diagnosis. After the patient's diagnosis, physicians should obtain a three-generation family history and offer appropriate genetic counselling and cascade screening[86]. Since about one-third of TSC cases are familial, parental testing is strongly recommended particularly for family members who are considering pregnancy, as each pregnancy has a 50% chance of passing the condition to the child from mild symptomatic or asymptomatic parent.

### Other manifestations

In addition to the primary manifestations discussed above, patients with TSC can experience other presentations, such as gastrointestinal polyps, bone cysts, or aneurysms. However, the current evidence does not fully support routine screening and preemptive treatment for these conditions in asymptomatic patients[86]. Therefore, a case-by-case approach involving physical examination and a detailed history relating to these symptoms is necessary to identify symptoms and determine further specific investigations.

## MANAGEMENT

### Epilepsy

Epilepsy requires immediate treatment because seizure control correlates with developmental and cognitive outcomes in patients with TSC[71,79]. ASMs are the first-line treatment in patients with TSC, with the choice of ASM tailored to the patient's seizure type and EEG findings. In the case of epileptic spasms, which account for approximately 35–40% of all seizures in TSC, vigabatrin is the first treatment of choice. The efficacy of vigabatrin for TSC-associated epileptic spasms has been well documented[11,16,64,91]. If spasms remain uncontrolled after titration of vigabatrin up to 100–150 mg/kg/day, adrenocorticotropic hormone (ACTH) or prednisolone may be considered as adjunctive therapy[89]. Recent studies have suggested that preemptive vigabatrin treatment for patients with TSC reduces the risk of seizure occurrence and epileptic spasms, although further studies are required[71]. As vigabatrin, ACTH, and corticosteroid hormones are inappropriate for long-term use owing to their complications, including retinal toxicity, adrenal suppression, and growth retardation, rapid titration followed by discontinuation is required.

For other seizure types in patients with TSC, the ASMs that are usually selected first include valproate, levetiracetam, lamotrigine, and lacosamide for both focal and generalized seizures, whereas oxcarbazepine and carbamazepine are typically used for only focal seizures[102]. If a patient is refractory to multiple conventional ASMs, dietary intervention or epilepsy surgery should be considered. Recently, cannabidiol has also emerged as a treatment option for pharmacoresistant epilepsy in TSC. A ketogenic diet has been reported to be effective for both focal and generalized seizures, as well as refractory epileptic spasm, with complete seizure control or >50% seizure reduction observed in 25–33% of patients with TSC, without serious complications[38,122]. Surgical options for epilepsy include epileptogenic region resection, callosotomy, vagus nerve stimulation, or deep brain stimulation. Resection of epileptogenic foci has produced favorable outcomes, leading to seizure reduction in 25–80% of patients[61].

### Kidney

The 2012 TSC Consensus Conference guidelines recommend long-term monitoring and management of renal involvement. mTOR inhibitors, such as everolimus, are recommended as the

first-line treatment for asymptomatic but growing renal AMLs larger than 3 cm in diameter[87]. The extended EXIST-2 study demonstrated that 58% of the patients achieved a long-term reduction in tumor size without serious complications, including renal function impairment[5]. Although the standard everolimus dosage for adults is 5–10 mg/day, a continuous low dose (2.5 mg/day) of everolimus has also shown efficacy for tumor shrinkage, suggesting an alternative option for patients who experience complications from the recommended dose[29,120]. For patients with asymptomatic large AML where mTOR inhibitors are unavailable, second-line therapies, such as selective embolization followed by corticosteroids, kidney-sparing resection, or ablative therapy, can be considered[18,129]. If acute bleeding occurs due to AMLs, emergency embolization followed by corticosteroid therapy is preferred. Total nephrectomy should be avoided because of the increased risk of further renal impairment and poor prognosis[60,129].

The guidelines recommend an annual evaluation of renal function (using the eGFR), proteinuria, and blood pressure in patients with TSC. For patients with TSC and hypertension, inhibitors of the renin-aldosterone-angiotensin system, such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are recommended as first-line treatments. A recent study demonstrated that ACEIs and ARBs maintain long-term renal function and reduce AML formation in younger patients[104]. For some patients with TSC and renal failure, the administration of mTOR inhibitors has prevented AML bleeding and preserved renal function[4]. If a patient has end-stage renal disease, renal replacement therapy such as dialysis or organ transplantation may be considered.

Histologically proven RCC should be managed surgically, similar to RCC in the general population. Nonetheless, careful kidney-sparing strategies are essential because of the increased risk of multiple tumors and potential for future renal impairment in patients with TSC[78].

## Lung

In patients with TSC and suspected LAM identified through imaging studies, annual PFTs are recommended. The mTOR inhibitor sirolimus is recommended as the first-line therapy for LAM in patients with TSC[86]. However, there are no standardized international guidelines regarding the timing of treatment initiation. In practice, treatment decisions are made based on symptoms and test results under the guidance of a specialist. Treatment may be initiated in patients with a forced expiratory volume in one second (FEV1) of less than 70% of the predicted value, with or without worsening symptoms[77]. For patients unable to undergo PFTs because of cognitive impairment, rapidly progressing LAM documented by serial imaging or elevated serum VEGF-D levels can serve as alternative indicators for treatment[86,123,124]. Recent studies have also demonstrated the potential efficacy of everolimus in patients with TSC and LAM under different circumstances. The 2012 guidelines recommend continuing everolimus treatment for LAM in patients who are already receiving the drug for other indications such as AMLs, SEGA, or epilepsy[6,39,43,87].

As LAMs may rapidly progress during pregnancy, preemptive counselling should be provided to all female patients with LAM[20,48]. Lung transplantation can be considered[87].

## Skin

Various skin lesions have been reported in patients with TSC, and regular skin examinations are recommended. While most lesions are benign, they can cause pain, bleeding, and secondary infections depending on the lesion size[87]. Sun protection is recommended for all patients with TSC to prevent potential complications[87].

Topical sirolimus has been proven to be effective for facial angiofibromas and other skin lesions, with minimal complications[75,117,118]. Topical sirolimus should be applied once or twice daily at concentrations ranging 0.1–1%. Early initiation of treatment is preferred, as smaller and flatter lesions respond better, and long-term therapy is often required for maintenance[117,118].

Recent studies of oral mTOR inhibitors used for other organ involvement have shown additional improvements in TSC-associated skin lesions during treatment[27,40,83]. However, oral mTOR inhibitors are not recommended as primary or adjunctive treatments for TSC-associated skin lesions because of a lack of evidence. For severe or protruding lesions, surgical interventions, such as excision or laser therapy can be considered[86].

## Heart

Cardiac rhabdomyomas are typically identified in the fetal or neonatal period. Although most cardiac tumors are benign and regress spontaneously, regular echocardiography is recommended until the tumor has fully regressed. In most cases, active treatment is not required because these tumors are usually

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asymptomatic or result in only mild symptoms that resolve as the tumors regress. However, in some symptomatic cases, treatment may be necessary to manage the heart failure or arrhythmia. Initial treatment options typically include medical treatments, such as ACEIs, ARBs, or diuretics for heart failure, as well as antiarrhythmic agents. If a tumor obstructs blood flow, leading to severe hemodynamic compromise, surgical resection can be considered[51,86]. Recent studies have demonstrated the efficacy of mTOR inhibitors in reducing tumor size during both the prenatal and postnatal period[80,108]. However, mTOR inhibitors have not yet been included in the latest management guidelines for cardiac rhabdomyoma because of insufficient evidence[86].

### Eye

Retinal hamartomas are the most common ophthalmic manifestations of TSC. Although these lesions are typically asymptomatic and do not require specific treatment, aggressive lesions may result in vision loss[73,82,128]. In such cases, interventions to improve the clinical outcomes include laser therapy, photodynamic therapy, intravitreal anti-VEGF injections, intravitreal steroids, and surgery. Recent studies have demonstrated favorable responses to mTOR inhibitors for the treatment of symptomatic retinal hamartomas. However, further studies are required to establish standardized recommendations[86].

## mTOR INHIBITORS

As mentioned above, mTOR inhibitors have significantly advanced TSC management by targeting underlying pathomechanisms. Since the United States Food and Drug Administration approved everolimus for the treatment of SEGAs in 2010, it has been widely accepted as first-line or additive therapy for SEGAs, renal AMLs, and epilepsy[86,95]. Similarly, sirolimus, another mTOR inhibitor, has been approved for the treatment of LAM in Japan and the United States of America[86]. Although the use of mTORs has improved patient outcomes, ongoing research is exploring new therapeutic avenues and optimizing existing treatments to benefit individuals affected by this complex disorder. The latest research on mTOR inhibitors in TSC investigated prenatal treatments aimed at preventing lesion development, particularly in the central nervous system, with the hope of improving neurocognitive outcomes[94]. Additional research should focus on combination therapies with mTOR inhibitors and the identification of biomarkers to predict individual responses to these treatments with the goal of enhancing efficacy and minimizing adverse events[74].

## SUMMARY

TSC is a rare genetic disorder characterized by the growth of benign tumors in multiple organs, including the brain, kidneys, heart, eyes, lungs, and skin. It is caused by variants of *TSC1* or *TSC2*, leading to dysregulation of the mTOR pathway. The clinical features vary among patients and may include early-onset epilepsy, developmental delay, organ-specific tumors, and skin lesions. Early diagnosis and long-term monitoring by a multidisciplinary team are essential for effective treatment and an improved quality of life.

## AUTHOR'S DECLARATION

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

### Informed consent

This type of study does not require informed consent.

### Author contributions

Conceptualization : SYK; Writing - original draft : SYK; Writing - review & editing : SYK

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