# AN INTRODUCTION TO

# TSC

*(Tuberous Sclerosis Complex)*

Tuberous Sclerosis Alliance

# Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder that can affect multiple organ systems. Care for an individual with TSC may require ongoing treatment involving medical specialists, allied healthcare specialists, and those skilled in educational and psychological care. As such, it is important for individuals with TSC, their family and/or caregivers to educate themselves about the disease and to facilitate communication between the healthcare providers and other professionals with whom they interact.

This brochure explains the clinical manifestations of TSC and its variable features; outlines some of the commonly needed medical tests and their purpose; and helps individuals cope with the diagnosis. There is a very strong bond within the TSC community, and the Tuberous Sclerosis Alliance exists to provide the guidance, support, services and networking to improve the lives of those affected by TSC.

***This brochure is intended to provide basic information about TSC. It is not intended to, nor does it, constitute medical or other advice. Readers are warned not to take any action with regard to medical treatment or otherwise based on the information in this brochure without first consulting a physician. The Tuberous Sclerosis Alliance does not promote or recommend any treatment, therapy, institution, or healthcare plan.***

# Contents



# What is TSC?

Tuberous sclerosis complex (TSC), or tuberous sclerosis (TS), is a genetic disorder that affects many organs and causes tumors in the skin, kidney, brain, heart, eyes, lungs, teeth or oral cavity, and other organs[1]. Individuals with TSC may be initially diagnosed because of involvement in any or all of these organs, often depending on the age at which a person receives the diagnosis. The severity of TSC can range from mild to severe, even within the same family if more than one person has TSC.

The diagnosis of TSC and further evaluation of people at risk for TSC involve careful examination of the skin, heart, eyes, brain, lungs and kidneys, as well as genetic testing. It is important to know the disorder's manifestations and to follow the recommendations for screening and evaluating TSC.

Population-based studies suggest a prevalence of 1 in 9,000 individuals in the general population, but its incidence has been estimated to be 1 in 6,000 live births. It is estimated that at least 50,000 Americans and 1 million individuals worldwide have TSC. TSC shows no gender bias and occurs in all races and ethnic groups.

Individuals of all ages may receive the diagnosis of TSC depending on the manifestations they have. The diagnosis of TSC may occur after the development of facial angiofibromas in an adolescent, because of the presence of heart tumors (cardiac rhabdomyomas) in a newborn or the onset of kidney problems in an adult. However, in the majority of cases, the diagnosis of TSC comes after the start of seizures.

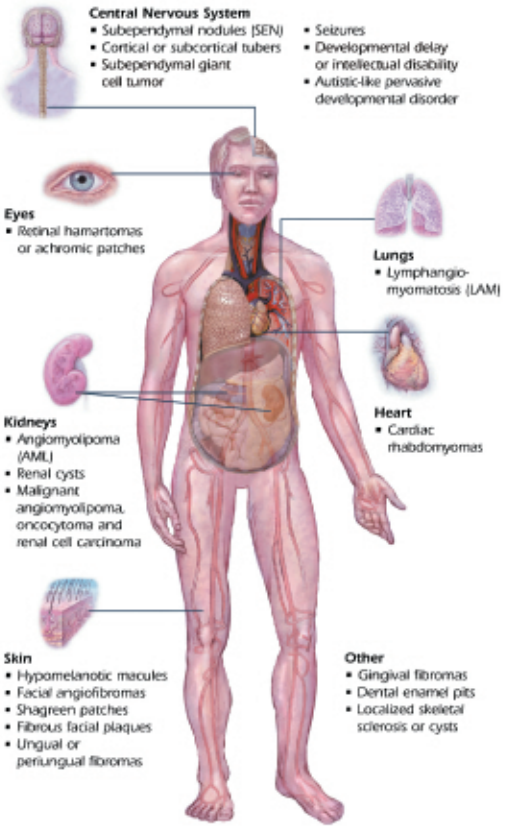
# How Is Tsc Diagnosed?

Clinical diagnosis of TSC is based on a careful physical exam in combination with imaging studies. The specific studies to be performed depend on the age of the individual who is suspected to have TSC. Magnetic resonance imaging (MRI) may be used to image the brain to look for tubers and other brain involvement. Computed tomography (CT) of the lungs, liver and kidneys may show tumors and/or cysts in those organs. Doctors should carefully examine the skin for the wide variety of skin features, such as fibromas found on the fingernails and toenails, dental pits and/or gum fibromas found on examination of the mouth. A Wood's lamp or ultraviolet light may be useful for locating the hypomelanotic macules (areas of the skin that are lighter than the surrounding, normal skin), which can be hard to see on infants and individuals with pale or fair skin. The eyes should be examined for abnormalities of the retina. The heart should also be examined using both imaging methods and electrocardiograms.

The diagnostic criteria and recommendations for testing and follow-up for TSC were published following the TSC Concensus Conference[2,3] and still apply today[1]. Genetic testing for TSC can now be used to diagnose and/or confirm a clinical diagnosis of TSC[4]. There is no single clinical feature absolutely specific to the condition. In addition, many features of TSC, such as seizures and intellectual disability, are seen in individuals *without* TSC. Therefore, a constellation of features is necessary for the clinical diagnosis, with certain features contributing more heavily to the diagnosis, and an increasing number of features making the clinical suspicion of TSC more likely.

# What Are The Clinical Features Of TSC?

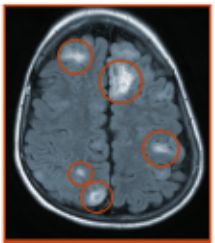
TSC can affect any or all systems of the body, causing a variety of signs and symptoms. Which features of TSC are present may also depend on the age of the individual who is being clinically evaluated or for whom genetic testing is being sought. Features of TSC are most commonly seen in the skin, brain, kidneys, heart, eyes and lungs. Additional features have been reported in multiple other organ systems including the gums, teeth, bones, liver, pancreas, and reproductive organs.




# Brain and Neurological Function

Several types of brain abnormalities may be seen in individuals with TSC, including cortical tubers, subependymal nodules, and subependymal giant cell tumors (SGCT). Some individuals will have all of these changes, whereas others will have none. The vast majority of individuals with TSC however, will have one of these abnormalities.

## *Cortical tubers*



*Multiple Cortical Tubers shown on MRI.*

Cortical tubers are best visualized using MRI of the brain. The cortical tuber, for which TSC was originally named, is a disorganized area of the brain that contains abnormal cells. Some individuals with TSC will have numerous tubers, whereas others will not have any. The tubers are more difficult to see in an infant's brain than in a more mature brain, but

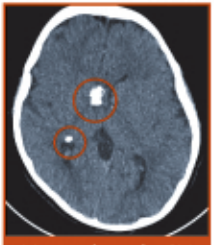
it is still possible to image the tubers in a newborn. Tubers and/or the brain area surrounding a tuber play a role in the development of seizures in individuals with TSC. However, recent studies have shown that there may also be numerous scattered abnormal cells throughout the brain of an individual with TSC, and the role of these cells in seizure development is not clear.

## Subependymal nodules

Subependymal nodules (SENs) are small accumulations of cells that are located on the walls of the cerebral ventricles (the spaces in the brain that contain cerebrospinal fluid [CSF]). The nodules often accumulate calcium, and are then easily identified on CT imaging of the brain.

## Subependymal giant cell tumor (SGCT)

This type of non-cancerous brain tumor develops in approximately 15% of individuals with TSC. A SGCT does not usually grow until later childhood, teenage and young adult ages, and the chance for its growth greatly decreases after the mid-20s. If a SGCT grows large enough, it can block the flow of CSF inside the ventricles of the brain causing hydrocephalus. With this condition, pressure will build up within the brain resulting in symptoms that may include vomiting, nausea, headache and changes in appetite, behavior and mood. Should this occur, the tumor will need treatment with either surgery or the FDA-approved drug Afinitor. SGCTs are also called subependymal giant cell astrocytomas (SEGAs). Since the SGCT is a benign tumor, radiation should never be used to treat this type of brain tumor.



*Tumors shown by CT scan with contrast.*

An MRI study should be performed at the time of diagnosis of TSC to get a baseline image, and then every 1 to 3 years (as determined by the individual with TSC and his or her family and physician). If a SGCT is identified, an MRI should be performed every 3 to 6 months to monitor its growth, and treated if the tumor continues to grow or if the individual becomes symptomatic. Some physicians believe that it is advantageous to treat or to have the SGCT removed

when it is small and has not had an opportunity to invade the surrounding brain tissue.

## Neurological involvement

Epilepsy, intellectual disabilities (mild to severe), and psychiatric and behavioral problems are the most common neurological manifestations in TSC. Individuals with milder forms of TSC commonly have little or no neurological impairment, although they may still have minor learning disabilities and/or mental health issues.

## Epilepsy/seizure disorders

Seizures remain one of the most common neurological features of TSC, occurring in 60% to 90% of individuals with TSC. Some infants will be diagnosed with TSC after they begin having a type of seizure called infantile spasms. Older children and adults may develop multiple types of seizures including generalized, complex partial and other focal seizures. More than 50% of individuals with TSC who have epilepsy will not respond to standard antiepileptic medications and have intractable epilepsy. Techniques can be used to identify the specific area where the seizures begin (called the seizure focus) and improved neurosurgical techniques used to remove that specific area of the brain. Although not all individuals with TSC who undergo brain surgery for epilepsy are seizure-free, many cases result in a significant improvement in seizure frequency and/or severity.

## Intellectual disability

Approximately 45% to 60% of individuals with TSC have intellectual disabilities, although the degree of intellectual dysfunction ranges from very mild to severe. Some children appear to develop normally until the onset of seizures, when their progress slows or they actually lose developmental milestones. Individuals whose seizures continue unchecked even after treatment (intractable seizures) have a higher likelihood of intellectual impairment.

While most individuals with TSC who have intellectual disabilities also have epilepsy, many individuals with TSC that have seizures do not have significant intellectual disabilities. Some individuals with TSC may have mild learning disabilities that are essential to consider when early interventions, school programs, or career choices are being made.

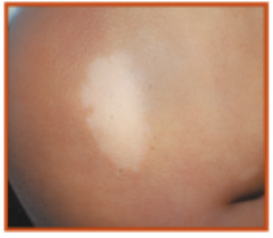
## *Psychiatric and behavioral problems*

Psychiatric and behavioral disorders are common in individuals with TSC and include autism spectrum disorder (ASD), pervasive developmental disorders (PDD), attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), depression, anxiety disorder, bipolar disorder and/or aggressive behavior. Risk factors for ASD, PDD, AD/HD and aggressive behavior include intellectual disability and seizures early in life, especially infantile spasms. Therefore, infants suspected of having TSC are at risk for the development of these diagnoses and should be evaluated by the appropriate healthcare providers.

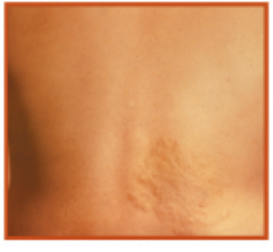
Experts recommend that all children diagnosed with TSC have a thorough neuropsychological evaluation at the time of diagnosis so that early intervention can be implemented. A consensus on the initial neuropsychological evaluation and subsequent follow-up was published in 2005 and includes recommendations for an initial evaluation and follow-up testing at times of school transition and/or as needed based on the needs of the individual with TSC[5].

## Skin

Skin lesions resulting from TSC include the following:



***Hypomelanotic macules*** are flat areas of skin that appear lighter than the surrounding skin. They can be any size or shape or may be the classic "ash-leaf" shape (as called in older literature). The skin cells in this area of the skin contain less pigment, so the area appears lighter than the surrounding skin.

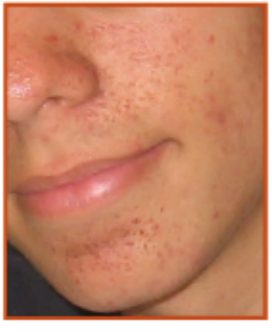


***The shagreen patch*** is a patch of skin that is similar in color to surrounding skin but may be tough and dimpled like an orange peel. The shagreen patch is usually found on the lower back and

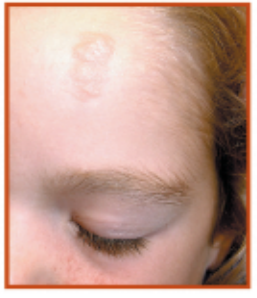
nape of the neck, but they may also be seen on other parts of the body.

***Periungual or subungual fibromas*** are small fibrous growths that appear around the fingernails or toenails and are usually not seen until adult life.

***Facial angiofibromas***, are benign tumors of the face that often appear across the checks and nose and on the chin. They are initially small reddish spots or bumps that may increase in size with age. Facial angiofibromas are rarely present at birth, but often appear as the child reaches 4 or 5 years of age or older. Some individuals with TSC will never develop this manifestation of the disease.



***A forehead plaque*** is similar to the angiofibroma but is found on the forehead and scalp. These flesh-colored plaques are soft or compressible or doughy to hard lesions.



At the initial examination, a physician will use a Wood's lamp (an ultraviolet light) to better visualize the hypomelanotic macules especially on infants and people with very pale skin. The skin should be carefully examined for other manifestations of TSC as well.

## Kidney

Renal (kidney) angiomyolipomas (AMLs) are non-cancerous tumors, and are the most common type of kidney lesion in TSC. AMLs occur in 70% to 80% of adults and older children with TSC. These tumors begin to grow in childhood in many individuals with TSC, but usually grow very slowly and may not

be problematic until young adulthood. Individuals with TSC should have their kidneys imaged at the time of diagnosis and then every one to three years as long as the individual shows no symptoms of kidney involvement. Once kidney involvement is identified, imaging should be performed on an annual basis. MRI is the best imaging technique for renal involvement. AMLs larger than 4 cm are more likely to cause symptoms such as hematuria (blood in the urine) because they often have abnormal blood vessels in them. AMLs may be treatable through a procedure called embolization in which the blood supply to the tumor is blocked.

Surgery is sometimes necessary to remove the AML as well as all or part of the kidney, depending on how large the AML has grown. If the AMLs are smaller than 4 cm, they should be closely monitored. Blood pressure should be monitored at each visit to the physician because it can be the first sign of increasing kidney involvement. Other signs to watch for are blood in the urine and complaints of abdominal or flank (the side of the body between the pelvis or hop and the last rib) pain. The use of urine and blood tests to monitor kidney function is not acceptable for individuals with TSC because they may have extensive involvement due to AMLs and still have normal test results.

Another common finding in individuals with TSC is renal cysts. Many individuals with TSC will have single cysts in one or both kidneys. These cysts are usually not clinically significant, and cause the individual with TSC no problems.

Some individuals with TSC will also have polycystic kidney disease (PKD). The TSC2 gene is located next to one of the genes for PKD on chromosome 16, so large deletions of this chromosome sometimes results in part of both the TSC2 and PKD genes being deleted. This then results in an individual with both diseases, and usually these children are born with PKD. PKD is characterized by polycystic kidneys, or kidneys that have multiple cysts. These cysts grow and multiply over time, also causing the mass of the kidney to increase. Ultimately, the diseased kidney shuts down causing end-stage renal disease for which dialysis and transplantation are the only forms of treatment.

## Heart

Cardiac (heart) rhabdomyomas (non-cancerous tumors) usually form in the heart of infants with TSC and are at their largest size at the time of birth. The incidence of these tumors in TSC has been reported to vary from 47% to 67%. An echocardiogram (ultrasound of the heart) is very important to determine the size and location of the cardiac rhabdomyomas, as well as cardiac function. The vast majority of cardiac rhabdomyomas spontaneously shrink and essentially disappear, but a few individuals with TSC will have long-term heart rhythm problems (arrhythmias) that will need to be monitored throughout their lives.

## Eye

Benign tumors and depigmented patches may occur inside the eyes of individuals with TSC, but they rarely cause any visual loss or problem. An eye exam at the time of diagnosis is recommended, and then follow-up as needed by an ophthalmologist familiar with TSC manifestations.

## Lung

Lung involvement is far more common in women with TSC than men. The average age of onset is during the childbearing years, although lung involvement can occasionally occur in teenagers or women with TSC who are in their 20s, as well as in postmenopausal women. This evidence suggests that lung involvement in TSC could be estrogen-related. However, a very small number of men with lung disease have been reported. Many women who have lung involvement due to TSC have lymphangioleiomyomatosis (LAM), a degenerative cystic disease of the lungs. The first symptoms of lung involvement in an individual with TSC may be shortness of breath after mild exercise, cough, or spontaneous pneumothorax (a collection of air or gas in the chest causing the lung to collapse). Progression of such lung involvement to pulmonary failure can sometimes occur, and some individuals may require lung transplantation.

Recent studies have shown that around 40% of women with TSC have LAM, but the lung involvement tends to be mild and most commonly does not produce symptoms.

It is recommended that women with TSC have a high-resolution chest CT scan (not a regular X-ray) sometime around 18 years of age or at the time of diagnosis of TSC for adult women. A high-resolution CT scan of the lung is superior to a regular X-ray because the early signs of lung involvement may easily be missed on an X-ray. If pulmonary involvement is noted, cigarette smoking and estrogen containing medications should be avoided, and chest CT scans and pulmonary function tests repeated at regular intervals. The individual should be followed closely by a pulmonologist familiar with TSC and LAM.

## Teeth and Oral Cavity

Oral involvement in TSC can include gum fibromas and dental pits. The fibromas appear as overgrowth of the gums and can be quite extensive, although this finding is not common in individuals with TSC.

Dental pits can be observed in both primary and adult teeth; the incidence in individuals who are 11 years old and older is 100%, while it is 76% in individuals younger than 11. The pits are seen on both the front and back surfaces of the teeth, which are areas that do not normally develop cavities. The dental pits can be revealed using a dental plaque-disclosing stain. Examination of the teeth is noninvasive and can usually be performed by a dental hygienist or other healthcare provider. Meticulous dental hygiene, including regular brushing and flossing, is an important aspect in preventative care for individuals with TSC.

## Other Organ Systems

Cysts and AMLs similar to those found in the kidneys have been observed in other organs such as the adrenal gland, liver, lung, ovary and pancreas. These lesions are usually asymptomatic and do not require treatment. If they are symptomatic, they should be treated by the appropriate specialist and be removed if they are enlarging.

# Genetics of Tsc

Genes are the biochemical instructions found inside the cell, not unlike the programs found inside computers. Human beings have 22 pairs of chromosomes, as well as a pair of sex chromosomes. Females have two X chromosomes and males have an X and a Y chromosome. Our genes come in pairs, with one copy inherited from the mother and the other from the father. All people have variations in their genes – some of which cause diseases and others increase risk for developing some diseases, and some variations cause no problems at all. Some of these variations have been passed down from one parent, and some variations are unique to individual human beings.

TSC is caused by a change or variation (called a mutation when it causes disease) in either the TSC1 gene on chromosome 9 or the TSC2 gene on chromosome 16. TSC is an autosomal dominant genetic disorder. This means that an individual with TSC has a mutation in either of the TSC genes that then causes the disease. Many genetic disorders such as TSC can be sporadic, or occur for the first time in a family. Such sporadic occurrences are the result of a new genetic mutation and account for approximately 60% of all cases of TSC. The remaining 40% of cases are the result of a TSC gene containing a mutation being passed along (inherited) from either the mother or the father to their child. Individuals with TSC have a 50% chance of passing their condition on to each of their children. The ability to differentiate between an inherited and sporadic occurrence of TSC sometimes relies on a thorough evaluation of the family members of the individual with TSC. This may involve evaluation of the parents, as well as some or all of the siblings.

There are no known cases of an individual having a mutation in both genes, and TSC does not skip a generation. It is possible for a member of the family to have such a mild case of TSC as to seem unaffected. It is still unclear whether the severity of an individual's TSC can be predicted by knowing their exact mutation, but preliminary evidence suggests that mutations in TSC2 tend to produce more symptoms with increased severity than mutations in TSC1[4]. Further studies are underway to clarify this issue.

Significant progress in understanding the function(s) of the TSC genes has translated into clinical trials to test medications for their ability to stop tumor growth. The TSC genes work together as a complex in a specific signaling pathway in cells that regulate cell growth. Ongoing basic and clinical research are rapidly moving toward additional clinical trials and hopefully to the day when the symptoms of TSC can be prevented.

# Genetic Testing of TSC

Genetic testing allows the individual with TSC, family members and healthcare provider to know exactly what mutation in either the TSC1 or TSC2 gene caused TSC. This information may be helpful for a number of reasons. In some cases, the identification of a TSC1 or TSC2 mutation will facilitate a definite genetic diagnosis of TSC in an individual who has not yet developed enough symptoms for a clinical diagnosis. While a negative DNA test result cannot rule out a diagnosis of TSC, a positive result confirms the diagnosis. In other cases, an individual may have a definite diagnosis of TSC, and family members may wish to know their own genetic status without undergoing extensive clinical evaluations. Upon identifying the TSC mutation in the individual with a definite diagnosis of TSC, any other family member can be easily tested to determine whether he or she is also affected. In addition, the availability of DNA mutation results makes reproductive decision-making possible.

Despite advancing knowledge about TSC mutations, it is not possible to predict the severity of symptoms in a person with a new diagnosis of TSC. A person can have TSC and have very few or mild symptoms, while a family member with TSC can have more severe or extensive symptoms. It is thought, however, that most people who have a TSC mutation will have some signs or symptoms if examined carefully by a physician familiar with the diagnosis of TSC. The distinction between sporadic TSC and familial (or inherited) TSC is important, as it affects the

risk that other persons in the family are affected. Therefore, immediate family members of a person newly diagnosed with TSC should be thoroughly examined.

Another factor that complicates the genetics of TSC is germline mosaicism. Germline mosaicism occurs when an individual has cells in his or her germline (egg or sperm cells) that carry a genetic mutation, but not in cells in other parts of the body. While quite rare, individuals with germline mosaicism may have one or more children with TSC but not have any clinical symptoms of TSC. Given the complicated nature of TSC genetics, all families who have an affected relative with TSC should receive a referral to a genetic counselor or geneticist to discuss their unique genetic risk to either have TSC or to have a child with TSC.

## Genetic Counseling

Genetic counselors are individuals who are trained in both genetics and counseling and work as part of the healthcare team. Genetic counselors offer individuals with TSC and their families information about the genetic nature of their condition and the risk for other family members to also have TSC. They also assist couples with making decisions about having children. The goal of genetic counseling is to ensure that the family understands the genetic implications of the diagnosis and to help individuals with TSC and their families make informed medical and personal decisions.

**For more information on obtaining the molecular diagnostic genetic test for TSC contact Athena Diagnostics at 1-800-394-4493, or visit www.athenadiagnostics.com**

***To locate a genetic counselor near you, contact:***

- **The National Society of Genetic Counselors at www.nsgc.org;**
- **Your state department of public health and ask for genetic services; or**
- **A comprehensive TSC Clinic.**

# Information And Support


When you or a member of your family receives the diagnosis of TSC, it is likely that this will be the first time you have heard the name of this rare genetic disorder. If you are a parent, you may ask yourself, "Did I do something to cause this?" or "Did I pass this disorder on to my child?" You may have fears for the future. These are feelings commonly felt by parents as they learn to cope with this diagnosis.

If you are diagnosed with TSC as an adult, you may wonder how this will impact your life and the lives of your family, how it will affect your health and where you can find information and support.

Individuals with TSC and their families learn about the disease and how it will affect their lives in many different ways. Some individuals want to have all of the information they can get their hands on so they know all the possible issues they will have to face in the future. Others prefer to take it one step at a time and only access the information they need for their immediate issues. There is no one right way, and every one does this at their own speed and in their own way.

One of the most frustrating things about TSC is that you never know what the next day may bring. Some have described it as feeling like walking through a minefield because you never know when the next crisis will occur. Because TSC is so variable, it is not possible to predict how an individual will be affected by TSC. The uncertainty is sometimes difficult to deal with and can cause a great deal of stress for individuals and their families. Support from your family and friends, and open and honest communication will provide strength for the whole family so that the individual with TSC will have the support he or she needs. Participating in a TSC support group may also be helpful for everyone involved.

## Tuberous Sclerosis Alliance

The Tuberous Sclerosis Alliance (TS Alliance) acts as a clearinghouse for individuals with TSC, their families, caregivers, educators and healthcare providers seeking the most up-to-date information about TSC. The TS Alliance also provides resource information on many aspects of healthcare, treatment, education and other challenges that may be encountered by individuals with TSC. The organization also serves to connect individuals throughout the nation and beyond, creating a network of informed constituents, educators and healthcare providers. Because TSC is often difficult to diagnose and proper management of TSC is essential to optimum health, the TS Alliance continues to focus on educating the general public and healthcare providers about the issues involved with a diagnosis of TSC.

By producing informative brochures, Information Sheets on the various manifestations of TSC, and other resources, the TS Alliance strives to educate individuals


with TSC, their families, care providers, educators and healthcare providers on identification and diagnosis of TSC, the latest in treatment protocols, and other issues related to TSC. *Perspective*, the organization's quarterly magazine, provides current news about the TS Alliance, research updates, government relations' actions and special events.

A continuously updated Web site serves as the primary source of information to a worldwide community of healthcare providers and individuals with TSC and their families seeking up-to-date information about TSC, while also serving as a networking tool for individuals and families to unite together to provide support and information through various online discussion groups.

The TS Alliance offers qualified staff members who can provide critical service to individuals with TSC, their families and caregivers. Services provided include one-on-one support/guidance, information about specific aspects of TSC, and referral to appropriate community resources as needed. Recognizing that TSC impacts each individual in a unique way, the TS Alliance offers tailored information and services to those who contact the organization in need of assistance. The TS Alliance teaches advocacy

skills essential for each individual with TSC to obtain the services needed to maximize his or her quality of life.

An extensive network comprised of dedicated volunteers across the country donates their time, talent and energy to support the TS Alliance. The TS Alliance Volunteer Outreach Program implemented through the volunteer networks nationwide includes the Support Network, Matching Program, Outreach and Awareness Program, and Community Fund Raising. These programs enable volunteers to create awareness of TSC in their communities, to establish peer connections and to participate in fund-raising events and campaigns.

The TS Alliance also offers local help across the country through local volunteer branches called Community Alliances. These Community Alliances provide support groups, help raise funds through special events and work with local healthcare providers to increase awareness of TSC.

**To contact the TS Alliance call 1-(800)225-6872, e-mail info@tsalliance.org or visit www.tsalliance.org**

# Commonly Asked Questions

**Q What is the life expectancy of an individual with TSC?**

**A** With ever-improving medical care and recognition of the potential severe consequences of many of the manifestations of TSC, most people with TSC will live a normal life span. However, complications in some organs such as the kidneys, lungs and brain can lead to severe difficulties and even death if left untreated or if mistreated. Sudden unexpected death due to epilepsy (SUDEP) has also been reported in TSC, as has death due to untreated cardiac rhabdomyomas in infants with TSC. To reduce these dangers, it is important for individuals with TSC to follow the recommended screening guidelines to identify potential complications, and be followed closely throughout their lives.

**Q Is my child with TSC at risk for a developmental disability?**

**A** Childen with TSC have a higher than normal risk of developmental delay, autism spectrum disorder or pervasive developmental disorder and should be evaluated as early as possible by trained healthcare professionals. Early intervention can be key to optimal development for children with TSC. Approximately 40% of individuals with TSC will require support throughout their lives, but many will go on to lead independent lives.

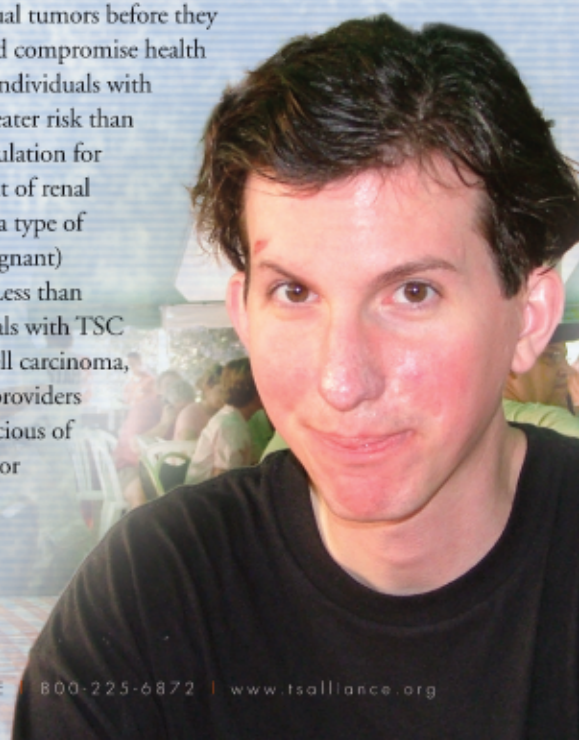
**Q If an individual with TSC who is mildly affected has a child, will that child also be mildly affected?**

**A** People with mild cases of TSC can have a child who is more severely affected. In fact, some people are so mildly affected that they may go undiagnosed until

their more severely affected child receives a diagnosis of TSC or other medical issues lead to a diagnosis of TSC.

**Q Are the tumors cancerous?**

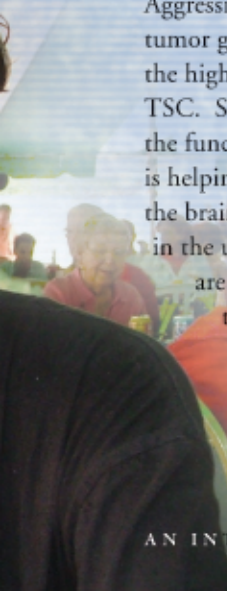
A The tumors resulting from TSC are benign or non-cancerous, but may still cause problems. Tumors that grow in the brain can block the flow of cerebrospinal fluid (CSF) in the ventricles in the brain. This can lead to behavioral changes, nausea, headaches or a number of other symptoms. In the heart, the tumors are usually at their largest at birth, and then decrease in size as the individual gets older. These heart tumors (cardiac rhabdomyomas) can cause problems at birth if they are blocking the flow of blood or causing severe arrhythmia problems. Tumors in the eyes are not as common, but can present problems if they block too much of the retina. In about one third of women with TSC, tumor cells in the lung can cause damage to the lung leading to shortness of breath and sometimes to leakage of air into the chest cavity and lung collapse. Renal AMLs can become so large that they eventually take over the entire normal kidney and cause severe dysfunction. In the past, the individual with TSC was left alone until they developed kidney failure. Today, doctors are more aggressive and use embolization to block the blood flow to the tumor or remove individual tumors before they get too large and compromise health kidney tissue. Individuals with TSC are at a greater risk than the general population for the development of renal cell carcinoma, a type of cancerous (malignant) kidney tumor. Less than 2% of individuals with TSC develop renal cell carcinoma, but healthcare providers should be suspicious of any kidney tumor that has a very low fat content based on



MRI imaging. These abnormalities must be evaluated further to determine if the tumor is an AML or a renal cell carcinoma.

**Q Since there is no cure, what can be done?**

A Early intervention is helping to diminish developmental delays in individuals with TSC. Aggressive treatment of all symptoms of TSC, including tumor growth, seizures and mental illness will provide the highest quality of life possible for individuals with TSC. Surgery to remove tumors is helping to preserve the function of affected organs. Improved technology is helping to pinpoint and remove the exact portions of the brain stimulating seizures. Significant advancements in the understanding of the functions of the TSC genes are bringing new and improved therapeutic options that are currently being tested in clinical trials. Each day brings us closer to finding improved treatments and a cure for TSC.



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# Appendix

## Revised Diagnostic Criteria for Tuberous Sclerosis Complex

| MAJOR FEATURES | |
|---|---|
| 1 | Facial angoifibromas or forehead plaque |
| 2 | Non-traumatic ungula or periungual fibroma |
| 3 | Hypomelanotic macules (more than three) |
| 4 | Shagreen patch (connective tissue nevus) |
| 5 | Multiple retinal nodular hamartomas |
| 6 | Cortical tuber[a] |
| 7 | Subependymal nodule |
| 8 | Subependymal giant cell astrocytoma |
| 9 | Cardiac rhabdomyoma, single or multiple |
| 10 | Lymphangioleiomyomatosis[b] |
| 11 | Renal angiomyolipoma[b] |

| MINOR FEATURES | |
|---|---|
| 1 | Multiple randomly distributed pits in dental enamel |
| 2 | Hamartomatous rectal polyps[c] |
| 3 | Bone cysts[d] |
| 4 | Cerebral white matter migration lines[a,d,e] |
| 5 | Gingival fibromas |
| 6 | Non-renal hamartoma[c] |
| 7 | Retinal achromic patch |
| 8 | "Confetti" skin lesions |
| 9 | Multiple renal cysts[c] |

**Definite TSC:** Either 2 major features or 1 major feature with 2 minor features

**Probable TSC:** One major feature and one minor feature

**Possible TSC:** Either 1 major feature or 2 or more minor features

[a] When cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of TSC.

[b] When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of TSC should be present before a definitive diagnosis is assigned.

[c] Histologic confirmation is suggested.

[d] Radiographic confirmation is sufficient

[e] One panel member recommended three or more radial migration lines constitute a major feature.

# Diagnostic and Surveillance Screening in TSC

| | "Asymptomatic" parent, child or 1st degree relative at time of diagnosis of affected individual | Suspected case or initial diagnostic evaluation | CHILD | | ADULT | |
|---|---|---|---|---|---|---|
| | | | Known case, no symptoms | Known case, symptoms or findings previously documented | Known case, no symptoms | Known case, symptoms or findings previously documented |
| Examination of the Eye | ✗ | ✗ | — | ✗ | — | ✗[d] |
| Brain MRI | ✗[a] | ✗ | ✗[b] | ✗ | ✗[c] | ✗[e] |
| Brain EEG | — | —[d] | — | ✗[e] | — | ✗[e] |
| Cardiac EKG and ECHO | —[f] | ✗ | — | ✗[g] | — | ✗[e] |
| Renal MRI | ✗[b] | ✗ | ✗[i] | ✗[g] | ✗[b] | ✗[g] |
| Dermatologic Screen | ✗ | ✗ | — | ✗[e] | — | ✗[e] |
| Pulmonary CT | — | — | — | ✗[e] | ✗[j] | ✗[e] |

*a* With a negative physical examination, MRI and/or CT is recommended
*b* Every 1 to 3 years
*c* Probably less frequently than in children
*d* Unless seizures are suspected, generally not useful in diagnosis
*e* As clinically indicated
*f* Unless needed for diagnosis
*g* Every 6 months to 1 year until tumor shrinks or the size stabilizes
*h* Ultrasound was previously recommended due to cost and ease of use, but more recent studies recommend use of MRI to provide more detail than ultrasound and to avoid X-rays utilized in CT
*i* Every 3 years until adolescence
*j* For women at age 18

Modified from Hyman, MH, Whittemore, VH (2000) National Institutes of Health Consensus Conference: Tuberous Sclerosis Complex. *Arch Neurol* 57:662-665

# Glossary

**AD/HD (attention-deficit/hyperactivity disorder)** is generally considered to be a developmental disorder, largely neurological in nature. The disorder is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity. Science recognizes three subtypes of AD/HD (inattentive, hyperactive-impulsive, and combined).

**Autism Spectrum Disorder** Autism is a complex brain disorder that inhibits a person's ability to communicate and develop social relationships and is often accompanied by extreme behavioral challenges. Autism Spectrum Disorders are diagnosed in one in 160 children in the United States.

**Benign Tumors** Non-cancerous growths. Most forms of benign tumors do not metastasize (spread to and grow in a distant focus in normal tissues elsewhere in the body).

**Cancer** Cancer develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all start because of out-of-control growth of abnormal cells.

**Cardic Rhabdomyoma** A benign tumor composed of muscle tissue that occurs in the heart.

**CT (computerized tomography)** A technique for creating images of the internal structures of the body. CT scans are formed from computerized imagery of many highly precise X-rays.

**Cyst** A closed sac containing fluid or semisolid material, developing abnormally in a body cavity or structure. Cysts can be damaging to surrounding tissue.

**Dermatologist** A healthcare provider specializing in disorders of the skin.

**Developmental Delay** Delay in the normal cognitive and/or physical development of a child.

**Early Intervention** A federally mandated, state administered program that provides interventions for children age 0 – 3 years who have or who are at risk of having developmental delays. The programs usually include various therapies (physical, occupational, speech, etc.).

**ECG, or EKG, Electrocardiogram** A recording created by an instrument called an electrocardiograph showing a record of the electric activity of the heart. This noninvasive procedure shows if there are abnormal cardiac electric impulses and/or rhythms.

**Epilepsy** When a person has had two or more seizures that have not been provoked by specific events such as trauma, infection, fever or chemical change, he or she is considered to have epilepsy.

**Facial Angiofibromas** A benign tumor of the face composed mainly of blood vessels and fibrous tissue. Angiofibromas initially appear as pink or red bumps and can form a butterfly shaped distribution around the nose, cheeks and chin.

**Genetic Counselor** A counselor who specializes in genetic disorders. Genetic counselors help individuals with genetic diseases and their families make medical and personal decisions based on their genetic information.

**Genetic Disorder** A disease or condition caused by an absent or defective gene or abnormal chromosome.

**Hamartoma** A common benign tumor in an organ composed of tissue elements normally found at that site but that are growing in a disorganized mass.

**Hypopigmentation** Skin abnormality featuring less color, or pigment, than normal. In TSC, hypopigmentation appears in the form of spots, or hypopigmented macules, on any part of the body. These spots are benign and pose no physical threat.

**Infantile Spasms** A severe type of seizure that typically occurs between the ages of two months and two years, although most children who develop this type of seizure are around 6 months old. It is identified by sudden myoclonic jerks, flexing of the body and neck and stiffening of the limbs. Each of these seizures lasts a very short time, but can occur in long or short clusters. If left untreated, infantile spasms can have a devastating effect on a child's intellectual development.

**Lymphangioleiomyomatosis or LAM** This is a lung disease that is caused by mutations in the TSC genes that can occur in individuals with TSC, primarily women, or in sporadic cases. Cystic lung destruction leads to loss of lung function in LAM.

**Malignant Tumor** A cancerous tumor.

**Metastasis** Sometimes abbreviated Mets, is the spread of cancer from its primary site to other places in the body (e.g., brain, liver).

**MRI, Magnetic Resonance Imaging** A noninvasive system producing images of brain tissues by using radio waves and strong magnetic fields. MRI can detect tumors, tubers and other soft tissue abnormalities.

**Neurologist** A healthcare provider who specializes in the function and disorders of the nervous system.

**Neurosurgery** Any surgery that involves the brain, the nerves or the spinal column. Neurosurgery of the brain may be performed in an attempt to control seizures, to remove a brain tumor or to alleviate the pressure from hydrocephalus.

**Ophthalmologist** A healthcare provider who specializes in the functions and disorders of the eyes.

**Polycystic Kidney Disease (PKD)** Polycystic means multiple cysts. In effect, PKD denotes multiple cysts on each kidney. These cysts grow and multiply over time, also causing the mass of the kidney to increase. Ultimately, the diseased kidney shuts down causing end-stage renal disease for which dialysis and transplantation are the only forms of treatment. PKD comes in two forms. Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common, affecting 1-in-400 to 1-in-500 adults. Autosomal Recessive Polycystic Kidney Disease (ARPKD) is far less common, affecting 1-in-10,000 at a far younger age, including newborns, infants and children.

**Seizure** In normal brain function, tiny electrical charges pass from nerve cells in the brain to the rest of the body. A seizure occurs when the normal pattern is interrupted by sudden and unusually intense bursts of electrical energy that

# Glossary

may cause strange sensations, emotions, behaviors or convulsions, muscle spasms and loss of consciousness. These unusual bursts are called seizures.

**Shagreen Patch** Abnormal patches of skin resembling an orange peel, usually found on the lower back or the back of the neck. Shagreen patches may be present on other parts of the body as well.

**Subependymal Giant Cell Tumor (SGCT)** A benign tumor found in the brain of individuals with TSC. SGCTs typically grow near or in the ventricles and can cause hydrocephalus (increased pressure in the brain) if they block the flow of cerebrospinal fluid (CSF).

**Subependymal Nodule** A non-cancerous nodule (collection of cells) located along the edge of the brain's ventricles. Subependymal nodules can grow into subependymal giant cell tumors, and some subependymal nodules become calcified (filled with a calcium deposit).

**Tuber** An area of the brain that contains a disorganized collection of abnormal cells; usually found in the outer layers of the brain called the cortex, but can be found in deeper areas of the brain.

**Tumor** Tumor is primarily used to denote abnormal growth of tissue. This growth can be either malignant or benign.

**Ungual Fibromas** Benign fibrous tumors found in the areas around the fingernails and toenails.

**Wood's Lamp** An ultraviolet light used to detect hypopigmented macules in TSC, and used to diagnose other skin and scalp diseases.


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