TUBEROUS SCLEROSIS COMPLEX

An Introduction to TSC

Tuberous Sclerosis Alliance of India

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.

ABOUT

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 strong bond within the TSC community, and the Tuberous Sclerosis Alliance of India exists to provide the guidance, support, services and networking to improve the lives of those affected by TSC.

INTENTION

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 within this brochure without first consulting a physician. The Tuberous Sclerosis Alliance of India does not promote or recommend any treatment, therapy, institution, or healthcare plan.

Contents

Tuberous Sclerosis Complex (TSC) is a genetic disorder that affects many organs and causes non-malignant tumors in the skin, kidney, brain, heart, eyes, lungs, teeth or oral cavity, and other organs.

WHAT IS 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. It is estimated that TSC affects 1 in 6,000 live births. Nearly 1 million people worldwide are estimated to have TSC, with approximately 1,50,000 in the United States. TSC shows no gender bias and occurs in all races and ethnic groups.

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 ranges from mild to severe, even within the same family if more than one person has TSC.

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.

The diagnostic criteria and recommendations for testing and follow-up for TSC were updated in 2012 at the second TSC Clinical Consensus Conference held in Washington, DC, and were published in 2013. Genetic testing for TSC can now be used to diagnose and/or confirm a clinical diagnosis.

DIAGNOSIS

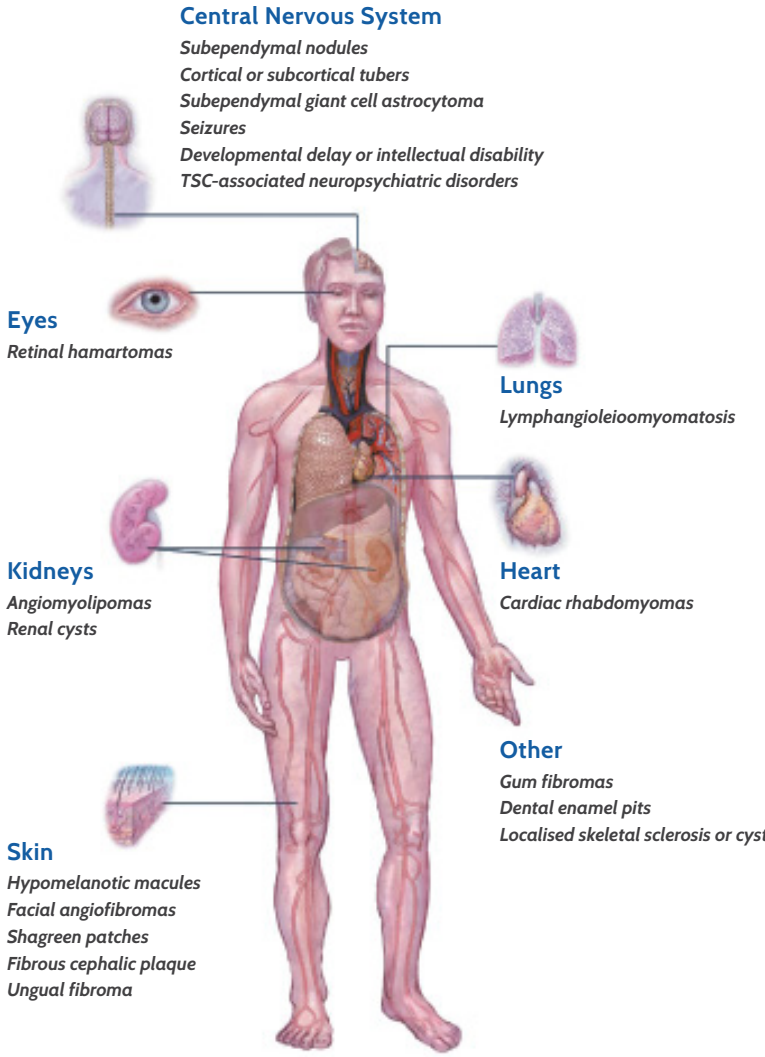
Clinical diagnosis of TSC is based on a careful physical exam in combination with imaging studies. The specific studies to be performed depend on the age of the individual who is suspected to have TSC. Computed tomography (CT) or magnetic resonance imaging (MRI) may be used to image the brain to look for tubers and other brain involvement. A high resolution CT (HRCT) of the lungs or MRI of the liver and kidneys may show tumors and/or cysts in those organs.

No single clinical feature is absolutely specific to TSC. Features like seizures and intellectual disability, are also seen in individuals without TSC. Therefore, a constellation of features is necessary for a clinical diagnosis, with certain features contributing more heavily, and an increasing number of features making the clinical suspicion of TSC more likely.

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 retina abnormalities. The heart should also be examined using an echocardiogram (ultrasound of the heart) and EKG (electrocardiogram, or ECG) to detect cardiac rhabdomyomas.

WE ARE DEDICATED TO FINDING A CURE FOR TSC, AND IMPROVING THE LIVES OF THOSE AFFECTED

Clinical Features of Tuberous Sclerosis Complex

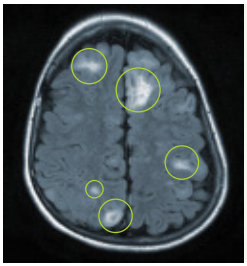


BRAIN & NEUROLOGICAL FUNCTION

Several types of brain abnormalities may be seen in individuals with TSC, including cortical tubers, subependymal nodules, and subependymal giant cell astrocytoma (SEGA). 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.

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 individual's age who is being clinically evaluated or for whom genetic testing is being sought.

TSC features are most commonly seen in the skin, brain, kidneys, heart, eyes and lungs. Additional features have also been reported in multiple other organ systems including gums, teeth, bones, liver, pancreas and reproductive organs.



Multiple cortical tubers shown on MRI.

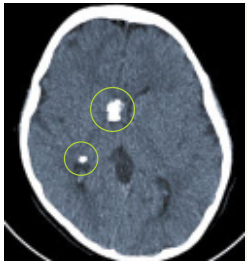
Cortical tubers

These 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 have several tubers, while others do not have any. 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.



Tumours shown by CT scan with contrast.

Subependymal giant cell astrocytoma (SEGA)

This type of non-cancerous brain tumor develops in 5% to 15% of individuals with TSC and may be detected during pregnancy or at birth. SEGA growth is most common during childhood, teenage and young adult ages, and the chance for its growth greatly decreases after the mid-20s. 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 until the age of 25 years. Follow-up scans frequency should be determined by the physician based on various clinical factors such as the previously described symptoms. Similarly, a follow-up scan should be performed more frequently than annually if a SEGA has increased in size between consecutive imaging studies.

If a SEGA 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 may have to be removed surgically. Since the SEGA is a benign tumor, radiation should never be used to treat this type of brain tumor.

Prospective clinical trials have shown SEGA shrinkage with oral administration of mTOR inhibitors such as everolimus and sirolimus. Common side effects associated with this medical therapy include stomatitis (mouth sores) and upper respiratory infections. Recurrence of tumor growth has been reported when mTOR inhibitor therapy is stopped. It is important to discuss the risks and benefits of surgery compared to mTOR inhibitor therapy with the doctor.

Neurological involvement

Epilepsy, intellectual disabilities (mild to severe), and psychiatric and behavioural 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 85% 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.

TSC-associated neuropsychiatric disorders (TAND)

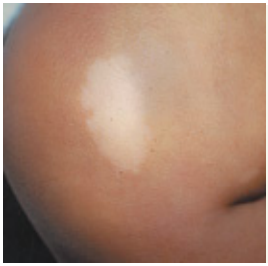
TSC is associated with a wide range of cognitive, behavioural, and psychiatric manifestations. TAND is a new terminology proposed to describe the interrelated functional and clinical manifestations of brain dysfunction in TSC, including aggressive behaviors, autism spectrum disorders (ASD), intellectual disabilities, psychiatric

disorders, neuropsychological deficits, as well as school and occupational difficulties. TSC is the genetic disorder most commonly associated with ASD, and suggestions of language and communication difficulties, reciprocal social interaction difficulties, and unusual patterns of behavior and play should trigger a careful developmental evaluation as soon as they are noted.

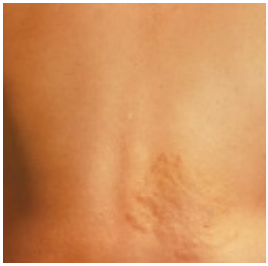
Experts at the 2012 TSC Clinical Consensus Conference recommended all individuals be screened for TAND upon diagnosis and at least annually. More detailed evaluations should follow from screening. Every individual with TSC should also have a comprehensive formal evaluation at key developmental timepoints (i.e., infancy, toddler, pre-school, early school years, middle school years, adolescence, adults).

SKIN

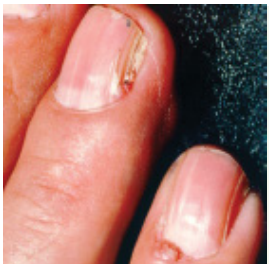
Skin lesions resulting from TSC include the following:



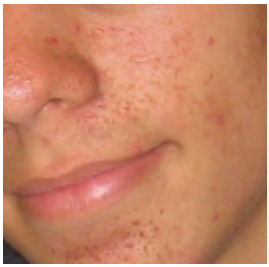
Hypomelanotic macules are flat areas of skin that appear lighter than the surrounding skin. They can be any size or shape or may be the classic "ash-leaf" shape (as called in older literature). The skin cells in this area of the skin contain less pigment, so the area appears lighter than the surrounding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



The shagreen patch is a patch of skin 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.

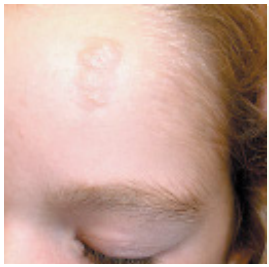


Ungual fibromas
are small fibrous growths that appear around the fingernails or toenails and are usually not seen until adult life. Surgical excision or laser ablation may be used to remove these lesions.



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.

There are several surgical approaches used to treat angiofibromas, including the use of lasers. There is evidence that medical treatments may also be effective. Many studies have shown that topical rapamycin treatment can be promising for the treatment for angiofibroma7.



Fibrous cephalic
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, the doctors may 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 are non-cancerous tumors and are the most common type of kidney lesion in TSC. Angiomyolipomas 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 throughout his/her lifetime.

MRI is the best imaging technique for renal involvement. Angiomyolipomas 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. Angiomyolipomas may be treatable through a procedure called embolization in which the blood supply to the tumor is blocked.

mTOR inhibitors are now the standard of care for preventative treatment of enlarging angiomyolipomas to prevent future bleeding and other problems. This is because of the high recurrence and re-bleeding rate following embolization and the success of mTOR inhibitor trials.

Selective embolization remains a feasible second line alternative and is still the first line treatment for angiomyolipomas that are actively bleeding. When feasible, selective embolization is preferred to surgical intervention. Although surgery is sometimes necessary to remove the angiomyolipoma, nephrectomy (removal of a kidney) should be avoided.

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 sufficient for individuals with TSC because they may have extensive involvement due to angiomyolipomas and still have normal test results.

Another common finding is renal cysts. Many individuals with TSC will have single cysts in one or both kidneys. Unless they grow to occupy a large portion of the kidney, cysts usually do not require treatment. A relatively small number of individuals with TSC 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 result in part of both the TSC2 and PKD genes being deleted.

An individual with both genes affected will have 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 and to assess 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 with TSC, as well as in postmenopausal women. This 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, by age 40, around 80% of women with TSC have cysts in the lung, but not all of them will have LAM symptoms. It is recommended that women with TSC have a high-resolution chest computed tomography (HRCT) (not a regular x-ray) sometime around 18 years of age or at the time of diagnosis of TSC for adult women.

HRCT 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 HRCT, pulmonary function tests, and 6-minute walk test should be 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 is not common in individuals with TSC. Dental pits occur in about 7% of the general population and 90% of those with TSC.

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. Meticulous dental hygiene, including regular brushing and flossing, is an important aspect in preventative care for individuals with TSC.

OTHER ORGAN SYSTEMS

Cysts and angiomyolipomas 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.

Biopsy of a suspicious lesion is recommended only when the lesion is unusually large, growing, causing symptoms, or exhibiting other suspicious characteristics. If they are symptomatic, they should be treated by the appropriate specialist and be removed if medically necessary.


WE PROVIDE
INFORMATION
AND SUPPORT
FOR PEOPLE WITH
TSC AND THEIR
FAMILIES

Genetics of Tuberous Sclerosis Complex

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 an individual with TSC has a mutation in one copy of either of the TSC genes that then causes the disease. Many genetic disorders such as TSC can be sporadic, meaning the disorder has not previously occurred in that family. Such sporadic occurrences are the result of a new genetic mutation and account for approximately two-thirds of all cases of TSC.

The remaining one-third 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. and to impact the neurologic features of TSC, including seizures and cognition. 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 moving rapidly forward, hopefully to the day when the symptoms of TSC can be prevented.

Genes are 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.

Individuals with TSC have a 50% chance of passing their condition on to each of their children. If parents are unaffected, the chance of a sibling of someone diagnosed with TSC also having TSC is approximately 1% to 2%. 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 with 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. At this point, the severity or risk of specific TSC features cannot be predicted by knowing an individual's genetic mutation.

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 and to impact the neurologic features of TSC, including seizures and cognition. 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 moving rapidly forward, hopefully to the day when the symptoms of TSC can be prevented.

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.

GENETIC TESTING OF TSC

Genetic testing allows individual with TSC, family members and healthcare providers to know exactly what mutation in either the TSC1 or TSC2 gene caused TSC. This information is helpful for a number of reasons. In some cases, the identification of a TSC1 or TSC2 mutation facilitates a definite genetic diagnosis of TSC in an individual who has not yet developed enough symptoms for a clinical diagnosis. In approximately 15% of individuals with TSC, no mutation is identified in either TSC1 or TSC2.

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 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 her or his 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 without any clinical symptoms. Given the complicated nature of TSC genetics, families with an affected relative 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.

Several laboratories in the India offer clinical genetic testing for TSC when ordered by a doctor. Test panels and pricing vary, so it is important for your doctor to select the lab that offers the appropriate test.

GENETIC COUNSELING

Genetic counselors are individuals trained in genetics and counseling and work as part of a healthcare team. They offer individuals and their families information on the genetic nature of the condition and the risk that other family members may also have TSC. They also assist couples in decisions about having children. The goal of 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.


WE'LL GIVE
EVERYTHING
BUT UP.

Information and Support

When you or a member of your family receives the diagnosis of TSC, it is likely the first time you will 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 anyone learning 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 his or her own speed and in his or her own way.

One of the most frustrating things about TSC is one can not anticipate what the next day may bring. Some have described it as feeling like walking through a minefield, because they 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, along with open and honest communication, will provide strength for the whole family so the individual with TSC will have the support he or she needs. Participating in a TSC peer support opportunities may also be helpful for everyone involved.

ABOUT THE TUBEROUS SCLEROSIS ALLIANCE OF INDIA

The Tuberous Sclerosis Alliance of India (TS Alliance of India) was founded in 2018 by parents and caregivers in India coming together to provide fellowship, generate awareness, pursue more knowledge and provide hope to those that shared the common bond of tuberous sclerosis complex. These goals still drive the organization today. Our mission is to ensure caregivers and TSC individuals are informed, empowered and connected for better management of TSC.

Because TSC is often difficult to diagnose and proper management is essential to optimum health, the TS Alliance of India offers a wide range of audio, digital, print and video materials to educate the general public and healthcare providers about the issues involved with a diagnosis of TSC.

The TS Alliance of India provides information, access to resources and a place for hope for those affected by tuberous sclerosis complex. We strive to fulfil our mission to improve quality of life for individuals and families:
- Provide information to caregivers, patients, hospitals, schools and other involved institutions about TSC.
- Educate caregivers and patients about management of TSC
- Organize events, seminars and conferences to interact with professionals.
- Create a support system in the form of online networks as well as city chapters to share experiences and TSC best management practices.
- Advocate to improve access to best clinical practices; and
- Support TSC research activity in India.

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Resource materials
are available on our website at
www.tsa-india.org

FAQs

What is the life expectancy of an individual with TSC?
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.

Is my child with TSC at risk for a developmental disability?
Children with TSC have a higher-than-average 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 the 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.

If an individual with TSC who is mildly affected has a child, will that child also be mildly affected?
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 until additional medical issues lead to a diagnosis.

Are the tumors cancerous?
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 behavioural 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 block the flow of blood or cause arrhythmias. Tumors in the eyes are not common, but they can present problems if they block too much of the retina. In some women with TSC, cysts or tumor cells in the lung can cause damage to the lung leading to shortness of breath and sometimes lung collapse. Renal angiomyolipomas occur in approximately 80% of individuals with TSC and can become so large they impair kidney function or rupture and cause significant bleeding.

Since there is no cure, what can be done?

Early diagnosis and intervention can help diminish developmental delays in individuals with TSC. Aggressive treatment of all symptoms of TSC, including tumor growth, seizures and cognitive challenges, will provide the highest quality of life possible for individuals with TSC. Surgery can help 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. Each day brings us closer to improved treatments and a cure for TSC.

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Diagnostic Criteria for Tuberous Sclerosis Complex[1]

MAJOR FEATURES	MINOR FEATURES
Hypomelanotic macules (>3, at least 5-mm diameter)	"Confetti" skin lesions
Angiofibromas (>3) or fibrous cephalic plaque	Dental enamel pits (>3)
Ungual fibromas (>2)	Intraoral fibromas (>2)
Shagreen patch	Retinal achromatic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasias *	Nonrenal hamartomas
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis (LAM) †	
Angiomyolipomas (>2) †	

Definite diagnosis
Two major features or one major feature with >2 minor features.

Possible diagnosis
Either one major feature or >2 minor features.

1 Northrup H, Krueger DA, on behalf of the International Tuberous Sclerosis Complex Consensus Group 2013). Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference Pediatr Neurol 49: 243-254.

** Includes tubers and cerebral white matter radial migration lines.*

† A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

Surveillance Recommendations

	FOR NEWLY DIAGNOSED OR SUSPECTED TSC
CENTRAL NERVOUS SYSTEM OR BRAIN	
Brain MRI with and without gadolinium	Yes
Electroencephalogram (EEG)	Yes; if abnormal, follow-up with 24-hour video EEG
TAND checklist	Yes
Comprehensive evaluation for TAND	If warranted by TAND checklist analysis
Counsel parents of infants	Educate parents to recognize infantile spasms
EYES, TEETH, SKIN	
Complete eye exam with dilated fundoscopy	Yes
Detailed dental exam	Yes
Panoramic radiographs of teeth	If age 7 or older
Detailed skin exam	Yes
HEART	
Fetal echocardiography	Only if rhabdomyomas identified by prenatal ultrasound
Echocardiogram	Yes in children, especially if younger than 3 years
Electrocardiogram (ECG/EKG)	Yes
KIDNEY	
Blood pressure Yes Annually	Yes
Abdominal MRI Yes Every 1-3 years	Yes
Glomerular filtration rate (GFR) test	Yes
LUNG	
Clinical screening for LAM symptoms	Yes
Pulmonary function test and 6-min walk test*	In all females age 18 or older; in adult males only if symptomatic
High resolution computed tomography (HRCT) of chest	In all females age 18 or older; in adult males only if symptomatic
Counsel on risks of smoking and estrogen use	In adolescent and adult females
GENETICS	
Genetics consultation	Obtain 3-generation family history

FOR ONGOING MANAGEMENT OF TSC

Every 1-3 years up to age 25; periodically as adults if SEGAs present in childhood
Routine EEG at a frequency determined by clinical need; video EEG when seizure occurrence is unclear or when unexplained behavioural or neurological changes occur
At least annually at each clinical visit
At key developmental time points: years 0-3, 3-6, 6-9, 12-16, 18-25, and as needed thereafter

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Annually if lesions or symptoms identified at baseline
Every 6 months
At age 7 if not performed previously
Annually

Every 1- 3 yr if rhabdomyoma present in asymptomatic children; more frequently in symptomatic individuals
Every 3-5 yr; more frequently if symptomatic

Annually
Every 1-3 years
Annually

At each clinic visit
Annually if lung cysts detected by HRCT

Every 2-3 yr if lung cysts detected on HRCT; otherwise every 5-10 yr

At each clinic visit for individuals at risk of LAM

Offer genetic testing and counseling if not done previously in individuals of reproductive age

Glossary

Attention-deficit hyperactivity disorder
ADHD 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 ADHD (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 behavioural challenges.

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.

Cardiac 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 impair the function of surrounding tissue.

Dermatologist
Healthcare provider specializing in skin disorders.

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 to 3 years who have or who are at risk of having developmental delays. The programs usually include various therapies (physical, occupational, speech, etc.).

Echocardiogram
A non-invasive test that uses high frequency sound waves (ultrasound) to produce an image of the heart.

EKG (electrocardiogram or ECG)
This non-invasive recording of the electric activity of the heart shows if there are abnormal cardiac electrical 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 angiofibroma
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 trained healthcare professional educated in providing genetic risk and diagnostic information. 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 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 2 months and 2 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.

Laser ablation
This is procedure uses a high energy pulse of light, which produces heat to remove tissue.

Lymphangioleiomyomatosis or LAM
LAM is a lung disease 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
The spread of cancer from its primary site to other places in the body (e.g., brain, liver).

Magnetic resonance imaging (MRI)
A non-invasive 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 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 astrocytoma (SEGA)
A benign tumor found in the brain of individuals with TSC. SEGAs 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 SEGAs, 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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