Tuberous Sclerosis

U.S. DEPARTMENT OF HEALTH
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What is Tuberous Sclerosis?

Tuberous sclerosis (also called tuberous sclerosis complex, or TSC) is a rare, multi-system genetic disease that causes non-cancerous (benign) tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin. It usually affects the central nervous system and can result in a combination of symptoms including seizures, impaired intellectual development, autism, behavioral problems, skin abnormalities, and kidney disease.

The severity of symptoms varies widely. Symptoms range from mild—allowing people to live independent, productive lives—to more severe symptoms that can affect everyday life and even be life-threatening. Many people with TSC show evidence of the disorder in the first year of life. However, clinical features can be subtle initially, and many signs and symptoms take years to develop. As a result, TSC can be unrecognized or misdiagnosed for years.

The name tuberous sclerosis comes from the characteristic *tuber* or potato-like nodules in the brain, which calcify with age and become hard or *sclerotic*. TSC occurs in all races and ethnic groups, and in both genders.

What causes Tuberous Sclerosis?

TSC is caused by defects, or mutations, on two genes—TSC1 and TSC2. Only one of the genes needs to be affected for TSC to be present. The TSC1 gene is on chromosome 9 and produces a protein called *hamartin*. The TSC2 gene is on chromosome 16 and produces the protein *tuberin*. Scientists believe these proteins act as growth suppressors by inhibiting the activation of a protein called mTOR. Loss of regulation of mTOR occurs in cells lacking either hamartin or tuberin, and this leads to abnormal differentiation and development, and to the generation of enlarged cells, as are seen in TSC brain lesions.

Is TSC inherited?

Although some individuals inherit the disorder from a parent with TSC, most cases occur as sporadic cases due to new, spontaneous mutations in TSC1 or TSC2—meaning neither parent has the disorder or the faulty gene(s). Instead, a faulty gene first occurs in the affected individual.

In cases where TSC is inherited, only one parent needs to have the faulty gene in order to pass it on to a child (called autosomal dominant inheritance). If a parent has TSC, each child has a 50 percent chance of developing the disorder. Children who inherit TSC may not have the same symptoms as their parent and may have either a milder or a more severe form of the disorder.

In rare instances, people acquire TSC through a process called *gonadal mosaicism*. These individuals have parents with no apparent defects in the two genes that cause the disorder. Yet these parents can have a child with TSC because a portion of one of the parent's reproductive cells (sperm or eggs) can contain the genetic mutation without the other cells of the body being involved. In cases of gonadal mosaicism, genetic testing of a blood sample might not reveal the potential for passing the disease to offspring.

What are the signs and symptoms of TSC?

TSC can affect many different systems of the body, causing a variety of signs and symptoms that range from very mild to quite severe. Common symptoms include:

Benign tumors are most common in the brain, kidneys, heart, lungs, and skin. Cancerous tumors are rare in TSC and those that do occur primarily affect the kidneys.

Three types of brain lesions are seen in TSC:

- *cortical tubers*, for which the disease is named, generally form on the surface of the brain but may also appear in the deep areas of the brain
- *subependymal nodules (SEN)*, which form in the walls of the ventricles—the fluid-filled cavities of the brain, and
- *subependymal giant-cell astrocytomas (SEGA)*, which develop from SEN and grow such that they may block the flow of fluid within the brain—causing a buildup of fluid and pressure that can lead to headaches and blurred vision.

Tumors called cardiac *rhabdomyomas* are often found in the hearts of infants and young children with TSC, and they are often seen on prenatal fetus ultrasound exams. If the tumors are large or there are multiple tumors, they can block circulation and cause death. However, if they do not cause problems at birth—when in most cases they are at their largest size—they usually become smaller with time and do not affect the individual in later life.

Benign tumors called *phakomas* are sometimes found in the eyes of individuals with TSC, appearing as white patches on the retina. Generally, they do not cause vision loss or other vision problems, but they can be used to help diagnose the disease.

Additional tumors and cysts may be found in other areas of the body, including the liver, lung, and pancreas. Bone cysts, rectal polyps, gum fibromas, and dental pits may also occur.

Seizures affect most individuals with TSC at some point during their life. While some kinds of seizures caused by TSC result in obvious convulsive movements, others alter awareness, behavior, or postural tone without convulsions. Seizures also can be difficult to control by medication, and sometimes surgery or other measures are used.

Cognitive disabilities affect some people with TSC. Developmental delay occurs in about one-half to two-thirds of people with TSC. Delays range from mild learning disabilities to severe impairment.

Behavior problems, including aggression, sudden rage, attention deficit hyperactivity disorder, acting out, obsessive-compulsive disorder, and repetitive, destructive, or self-harming behavior occur in children with TSC and can be difficult to manage. About one-third of children with TSC meet criteria for autism spectrum disorder.

Skin abnormalities vary widely in individuals with TSC. Most cause no problems but are helpful in diagnosis. Some cases may cause disfigurement, necessitating treatment. The most common skin abnormalities include:

- *Hypomelanic macules* ("ash leaf spots"), which are white or lighter patches of skin that may appear anywhere on the body and are caused by a lack of skin pigment or melanin—the substance that gives skin its color.
- *Facial angiofibromas* (also called *adenoma sebaceum*) are reddish spots or bumps which appear on the face (sometimes resembling acne) and consist of blood vessels and fibrous tissue.
- *Forehead plaques* are raised, discolored areas on the forehead which are common and unique to TSC and may help doctors diagnose the disorder.
- *Shagreen patches* are areas of thick leathery, pebbly skin, usually found on the lower back or nape of the neck.
- *Ungual or subungual fibromas* are small fleshy tumors that grow around and under the toenails or fingernails and may need to be surgically removed if they enlarge or cause bleeding. These usually appear later in life, ages 20-50.

- Other skin features that are not unique to individuals with TSC, including *molluscum fibrosum* or skin tags, which typically occur across the back of the neck and shoulders; *café au lait spots* or flat brown marks; and *poliosis*, a tuft or patch of white hair that may appear on the scalp or eyelids.

Kidney problems such as *cysts* and *angiomyolipomas* (benign growths of fatty tissue and muscle cells) occur in an estimated 70 to 80 percent of individuals with TSC. They usually occur between ages 15 and 30.

- Cysts are usually small, appear in limited numbers, and most often cause no serious problems. A very small percent of individuals with TSC develop large numbers of cysts during childhood, which may lead to bleeding, anemia, and kidney failure.
- Angiomyolipomas are the most common kidney lesions in TSC and can be found in people without TSC. Angiomyolipomas caused by TSC are usually found in both kidneys and in most cases do not produce symptoms. However, they can sometimes grow so large that they cause pain or kidney failure. Bleeding from angiomyolipomas may also occur, causing both pain and weakness. If severe bleeding does not stop naturally, there may be severe blood loss, resulting in profound anemia and a life-threatening drop in blood pressure, warranting urgent medical attention.
- Other rare kidney problems include renal cell carcinoma, developing from an angiomyolipoma, and oncocytomas, benign tumors unique to individuals with TSC.

Lung lesions are present in about one-third of adult women with TSC and are much less commonly seen in men. Lung lesions include lymphangioleiomyomatosis (LAM) and multinodular multifocal pneumocyte hyperplasia (MMPH). LAM is a tumor-like disorder in which cells proliferate in the lungs, and there is lung destruction with cyst formation. A range of symptoms can occur with LAM, with many TSC individuals having no symptoms, while others suffer with breathlessness, which can progress and be severe. MMPH is a more benign tumor that occurs in men and women equally.

How is TSC diagnosed?

Diagnosing TSC is based upon clinical criteria. The first clue may be the presence of seizures or delayed development. In other cases, the first sign may be white patches on the skin (hypomelanotic macules) or the identification of cardiac tumor rhabdomyoma.

Diagnosis of the disorder is based on a careful clinical exam in combination with computed tomography (CT) or magnetic resonance imaging (MRI) of the brain—which may show tubers in the brain—and an ultrasound of the heart, liver, and kidneys, which may show tumors in those organs. Doctors should carefully examine the skin for the wide variety of skin features; the fingernails, and toenails for ungual fibromas; the teeth and gums for dental pits and/or gum fibromas; and the eyes for retinal lesions. A small hand-help lamp that uses black light, otherwise known as ultraviolet light, may show hypomelanotic macules which are sometimes hard to see on infants and individuals with pale or fair skin.

A doctor experienced in the diagnosis of TSC should evaluate a potential patient.

In infants, TSC may be suspected if the child has cardiac rhabdomyomas at birth or seizures (especially the kind called infantile spasms) in the first six months of life. With a careful examination of the skin and brain, it may be possible to diagnose TSC in a very young infant. However, many children are not diagnosed until later in life when their seizures begin and other symptoms such as facial angiofibromas appear.

How is TSC treated?

There is no cure for TSC, although treatment is available for a number of the symptoms. Antiepileptic drugs may be used to control seizures. Vigabatrin is a particularly useful medication in TSC and has been approved by the U.S. Food and Drug Administration (FDA) for treatment of infantile spasms in TSC, although it has significant side effects. The FDA has approved the drug everolimus (Afinitor®) to treat subependymal giant cell astrocytomas (SEGA brain tumors) and angiomyolipoma kidney tumors, in addition to intractable seizures (seizures not controlled well by medicine). Specific medications may be prescribed for behavior problems. Intervention programs including special school programs and various therapies (such as physical, occupational, and speech therapies) may benefit individuals with special needs and developmental issues. Surgery may be needed in case of complications connected to tubers, subependymal nodules, or

SEGA, as well as in risk of hemorrhage from kidney tumors. Respiratory insufficiency due to LAM can be treated with supplemental oxygen therapy or lung transplantation, if severe.

Because TSC is a lifelong condition, individuals need to be regularly monitored by a doctor to make sure they are receiving the best possible treatments. Due to the many varied symptoms of TSC, care by a clinician experienced with the disorder is recommended.

Basic laboratory studies have revealed insight into the function of the TSC genes and have led to use of rapamycin (mTOR) inhibitors and related drugs for treating some of the manifestations of TSC.

What is the prognosis?

The prognosis for individuals with TSC is highly variable and depends on the severity of symptoms. Those individuals with mild symptoms usually do well and have a normal life expectancy, while paying attention to TSC-specific issues. Individuals who are severely affected can suffer from severe intellectual disability and persistent epilepsy.

All individuals with TSC are at risk for life-threatening conditions related to the brain tumors, kidney lesions, or LAM. Continued monitoring by a physician experienced with TSC is important. With appropriate medical care, most individuals with the disorder can look forward to normal life expectancy.

What research is being done?

Within the Federal Government, the leading supporter of research on TSC is the National Institute of Neurological Disorders and Stroke (NINDS). NINDS, part of the National Institutes of Health (NIH), is responsible for supporting and conducting research on the brain and the central nervous system. NINDS conducts research in its laboratories at NIH and also supports studies through grants to major medical institutions across the country. Scientists hope knowledge gained from this research may improve diagnostic and genetic testing for TSC, and lead to new avenues of treatment, methods of prevention, and, ultimately, a cure.

The National Heart, Lung, and Blood Institute and the National Cancer Institute, also components of the NIH, support and conduct research on TSC.

NINDS-funded scientists are using animal or cell-based models to understand:

- the role of TSC1/TSC2 and the mTOR pathway in neurodevelopment,
- the mechanisms that lead to epilepsy and autism in TSC,
- shared mechanisms with related neuro-developmental disorders, and
- how TSC mutations contribute to cognitive dysfunction and intellectual disability.

In one NINDS-supported clinical trial researchers are studying the effectiveness of early intervention with vigabatrin, an antiseizure medication, on preventing seizures and improving neurocognitive outcomes in infants with TSC.

NIH's Rare Diseases Clinical Research Network (RDCRN) furthers medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment and data sharing. RDCRN includes the Developmental Synaptopathies Consortium which supports natural history, imaging, and biomarker identification for TSC and related neurodevelopmental disorders.

TSC research and planning efforts are coordinated through the Trans-NIH TSC Working Group, which includes representatives from NIH Institutes, the Tuberous Sclerosis Alliance, and the Department of Defense's Congressionally Directed Medical Research Programs. The goal of the group is to share advances in understanding disease pathology and treatment strategies and identify opportunities to support activities that will further research progress.

Where can I get more information?

For more information on neurological disorders or research programs funded by NINDs, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
800-352-9424
http://www.ninds.nih.gov

Information also is available from the following organizations:

Tuberous Sclerosis Alliance
801 Roeder Road, Suite 750
Silver Spring, MD 20910-4467
301-562-9890; 800-225-6872
http://www.tsalliance.org/

Epilepsy Foundation
8301 Professional Place West, Suite 230
Landover, MD 20785-7223
301-459-3700; 800-EFA-1000 (332-1000)
http://www.epilepsy.com

National Organization for Rare Disorders (NORD)
55 Kenosia Avenue
Danbury, CT 06810
203-744-0100;
Voice Mail: 800-999-NORD (6673)
https://rarediseases.org/

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