

This fact sheet describes the condition **tuberous sclerosis complex** and includes the symptoms, causes, and any treatment or testing that is available.

In summary

- Tuberous sclerosis complex (TSC) is a rare genetic condition affecting multiple parts of the body. It is named for characteristic hard (or sclerotic) root-like (tuberous) growths that occur in the brain
- The brain, skin, heart, kidneys, lungs, and eyes are all potentially impacted by the growth of largely benign (non-cancerous) tumours, with a small risk of malignancy
- TSC is caused by mutations in two genes – *TSC1* and *TSC2* – which are involved in regulating cell growth. When faulty, these genes lead to uncontrolled cell proliferation and the tumours characteristic of TSC
- TSC is inherited in an autosomal dominant pattern with offspring of an affected individual at 50% risk
- Many cases of TSC occur without any family history and may be due to spontaneous mutations that occur for the first time in an individual or due to mosaicism in a parent.

WHAT IS TUBEROUS SCLEROSIS COMPLEX?

Tuberous sclerosis complex (TSC) is a genetic condition characterised by non-cancerous growths (benign tumours or lesions) in various parts of the body and is named for the hard (or sclerotic) root-like (tuberous) growths that can occur in the brain. The characteristic signs and symptoms of TSC are listed below for each part of the body that may be affected:

Brain:

Several different types of non-cancerous growths may occur in the brain of individuals with TSC. **Subependymal nodules (SENs)** are tumours that grow in the fluid filled spaces in the brain known as the ventricles and occur in about 80% of people with TSC. If these grow longer than 1cm, they are called **subependymal giant cell astrocytomas (SEGAs)** and these are rarer, occurring in 5-15% of people. **Cortical dysplasias** are lesions composed of disorganised brain cells that did not develop correctly and occur in 90% of people. Other issues involving the brain may include epilepsy, developmental delay, and learning disabilities.

Skin:

Almost all individuals with TSC will have involvement of the skin, with multiple white patches (**hypopigmented macules**) often being the most obvious first sign of TSC. Other skin lesions include **facial angiofibromas**, which are small, red, benign lumps, often over the cheeks and nose.

These rarely cause problems or physical discomfort but can be a source of cosmetic concern.

Heart:

Rhabdomyomas are growths that occur in the heart muscle. They may be detected on a prenatal ultrasound scan in a baby before birth. These usually do not cause any medical problems and generally shrink with age. Very occasionally, surgery is required if the growth is blocking the blood flow.

Kidneys:

Cysts and growths can occur in the kidneys. The most common type of kidney (renal) growth is called an **angiomyolipoma** or **AML**. These can sometimes cause problems like bleeding, pain or renal dysfunction. There is a slightly increased risk of kidney cancer in people with TSC. A very small proportion of people with TSC also have another renal problem called polycystic kidney disease.

Lungs:

Cysts can occur in the lungs. This is known as **lymphangiomyomatosis (LAM)** of the lung. LAM may not cause any problems or may cause shortness of breath requiring medical attention. The radiological changes of LAM may be seen in about 30% of individuals with TSC, but symptomatic LAM is uncommon. Women of reproductive age are most commonly affected and are offered screening for this rare but potentially serious complication.

WHAT CAUSES TUBEROUS SCLEROSIS COMPLEX?

Our body is made up of millions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to function. These genes are packaged onto little long strands known as chromosomes.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

Eyes:

Benign tumours called **hamatomas** can occur at the back of the eye (retina). These generally do not affect vision.

Two genes are known to cause TSC – known as **TSC1** which produces the protein **hamartin** and **TSC2** which produces the protein **tuberin**. In individuals with TSC, one of these genes has a mutation that prevents it from working properly and is 'faulty'. The proteins produced from **TSC1** and **TSC2** are important for making sure that cells only grow as fast as they need to. If these proteins are not being produced correctly, some cells grow in an uncontrolled way forming the tumours seen in people with TSC.

HOW IS TUBEROUS SCLEROSIS COMPLEX INHERITED?

There are two copies of each of our genes, one inherited from our mother and the other from our father. In individuals with TSC, there is one working copy and one faulty copy of their TSC gene (either **TSC1** or **TSC2**). These faulty genes can be passed on to future generations in a pattern known as **autosomal dominant inheritance**.

In Figure 61.1, for every pregnancy in this situation there is a:

- 50% chance that a child, either male or female, will inherit only working copies of a gene from their parents and be healthy
- 50% chance that they will inherit one copy of the faulty gene, and one working copy and be affected with TSC
- A mother or a father can pass on an autosomal dominant condition and both male and female children may be affected.

In about 30% of individuals with TSC, the faulty gene was inherited from an affected parent (either the mother or the father) as shown in Figure 61.1. However, approximately 70% of individuals with TSC are the first person in their family to be affected.

In these individuals, TSC occurred due to a mutation in one copy of the **TSC1** or **TSC2** gene that arose during formation of the egg or sperm, during conception or shortly after. These changes that make one of the TSC gene copies faulty are called **spontaneous mutations**.

If the TSC gene became faulty shortly after conception, not all of the baby's cells may contain the mutation and this individual is said to be **mosaic** for the faulty TSC gene. They may experience milder symptoms because the faulty gene may not be present in all of the organs usually affected in TSC.

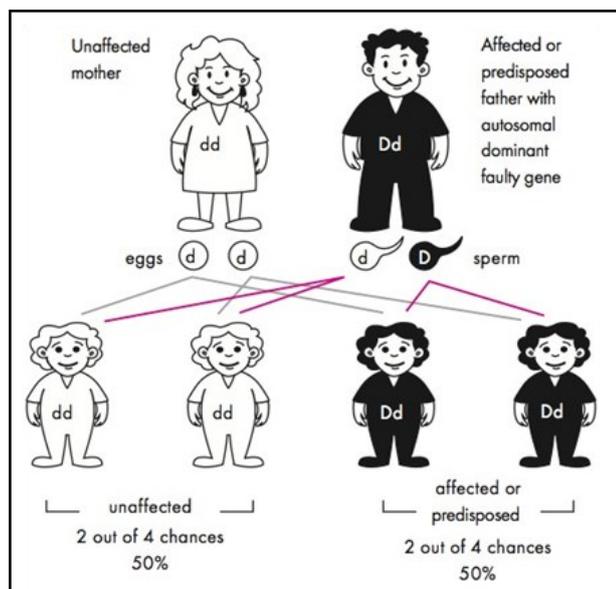


Figure 61.1: Autosomal dominant inheritance when one parent carries the autosomal dominant faulty gene copy. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.

The faulty gene might also not be in all the egg or sperm cells of an individual with mosaic TSC and therefore their chance of passing on the faulty gene is less than 50% but difficult to estimate accurately.

If a child of a parent who is mosaic for TSC inherits the faulty TSC gene copy, they may be more severely affected by TSC than their parent. This is because the child has the faulty gene in all the cells of their body, while their parent only has the faulty gene in some cells. That child also has a 50% chance of passing on the faulty gene copy to his or her children.

Because of the possibility that an unaffected parent of a child with TSC is mosaic for the faulty TSC gene only in their egg and sperm cells, the chance of having another child affected by TSC is estimated to be between 1% and 2%. The chance that a spontaneous mutation in the TSC gene would happen again in further pregnancies is low.

TSC does not 'skip generations' although sometimes the features of the condition are so subtle that individuals do not realise they have TSC. An assessment by a skin specialist (dermatologist), eye doctor (ophthalmologist) and genetics doctor (clinical geneticist) may be useful in either confirming or ruling out whether someone is affected by TSC.

IS THERE ANY TESTING OR TREATMENT AVAILABLE FOR TUBEROUS SCLEROSIS COMPLEX?

Clinical Testing

The diagnosis of TSC can be very complicated and involves a comprehensive assessment of any individual who has had one of the unusual tumours or lesions associated with the condition to determine whether they have any other signs of TSC. Testing looks at each of the organs potentially involved in TSC, and once a diagnosis is confirmed can help to determine the extent of symptoms and needs of the affected individual.

Genetic Testing

Genetic testing is available to try and identify the faulty gene causing TSC and may be used to confirm a suspected diagnosis of TSC. The first step is a **mutation search** in an individual with TSC to search for a mutation in *TSC1* or *TSC2*. If a mutation is identified, genetic testing can be offered to other family members, called **predictive testing**, to determine if they also have TSC. If a mutation cannot be found though, no further genetic testing can be offered in the family.

Prenatal testing and PGD

For couples where the familial mutation is identified, testing may be available during a pregnancy to determine whether or not the baby has inherited the mutation. It may also be possible to undergo pre-implantation genetic diagnosis (PGD) on an embryo created using in vitro fertilisation (IVF) to ensure that a child does not inherit the mutation. These options are best discussed and considered before pregnancy, when possible, in order to ensure all possible risks, benefits and outcomes can be explored.

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Treatment Options

There is no cure for TSC, but the symptoms can be treated and managed. Some promising new treatments known as **mTOR inhibitors** are becoming more readily available and can be discussed with your health professional. Regular surveillance to look for symptoms and early treatment are associated with better health and quality of life outcomes for people with TSC.