

Tuberous Sclerosis Complex (often referred to as TSC or TS) is a genetic condition, meaning that it is caused by an alteration (or change) in a gene. Genes are the instructions for the normal growth and maintenance of our bodies. Each of us has thousands of genes, and each gene is responsible for the direction of a specific protein or component of our bodies. A gene that carries an alteration is unable to instruct the body to grow correctly, causing a disruption in normal development and functioning.

## Tuberous Sclerosis Complex genes

Changes in one of two genes, TSC1 and TSC2, have been identified as causes for TSC.

All genes, including those involved in TSC, come in pairs, with one copy inherited from (or passed down by) the mother, and the other copy inherited from the father. In some genetic conditions, like TSC, an alteration in one copy of the gene is enough to cause the condition.

These conditions are called dominant conditions because the change in one copy “dominates” over the other copy, causing the condition and its symptoms.

## Dominant inheritance

Approximately 33 percent, or one-third, of people with TSC inherits it from a parent who also has TSC. This occurs via dominant inheritance.

When you have children, you pass on one copy of each of your gene pairs to the child, and your partner passes on one copy. The passage of one gene copy from each parent ensures that the child is a genetic “mix” of both parents. If a parent has TSC and passes on the copy of the gene with the TSC change, then the child will also have TSC.

If the parent passes on the copy of the gene without the change, the child will not have TSC. Thus, there is a 50 per cent chance with each pregnancy for a parent with TSC to have a child with TSC. This is true regardless of the sex of the parent or the sex of the child.

## New (sporadic) occurrence of TSC

In the remaining 66 percent, or two-thirds, of people with TSC, neither parent shows any symptoms or signs of TSC. It appears that one of

the normal genes from either parent changes to the altered form, leading to a new (or sporadic) occurrence of TSC in the child.

Normally, these parents do not have another child with TSC because the change was sporadic, not inherited. However, some families have more than one child with TSC, even though neither parent showed symptoms or findings of TSC. New alterations of all sorts of genes happen at the complicated time of conception.

## Mosaicism

Mosaicism is a term used to describe when a genetic alteration does not occur in all body cells. The proportion of normal to abnormal cells will determine the severity of the disorder.

Occasionally (2%) couples who have no apparent sign of TSC go on to have a further child with TSC i.e that the alteration may just be present in either the ovaries or the testes. This is called germline mosaicism (previously called gonadal mosaicism). It is not possible to test for mosaicism with the present technology.

## Diagnosis

The diagnosis of TSC is usually made according to accepted clinical diagnostic criteria. Two genes associated with TSC Complex have been identified: TSC2 (encoding tuberlin) and TSC1 (encoding hamartin). Molecular genetic diagnosis of TSC by analysis of a blood sample is now available but because the genes are unusually large and complex the analysis may take up to a year.

The genetic mutation can be identified in about eighty per cent of cases. Identification of the family-specific mutation enables early pre-natal diagnosis by chorion villus biopsy for couples who wish to take this step. You will need to be referred to a geneticist to discuss this possible option.

A small proportion of patients with TSC also have Polycystic Kidney disease. This is because the PKD1 gene that they have their genetic status determined by an unequivocal blood test. This is a more simple approach than by conventional clinical and radiographic tests.

## Prenatal diagnosis

Where a prospective parent has TSC, and the gene alteration which has caused this has already been identified, DNA based prenatal diagnosis is very reliable. The same is true for clinically unaffected couples who have an affected child, if they are concerned about the small recurrence risk posed by (gonadal) germline mosaicism (about two per cent).

In families where the mutation cannot yet be identified, an ultrasound scan can be done at eighteen to twenty weeks to which may diagnose heart tumours if present; with a further scan at twenty-two to twenty-three weeks to confirm the diagnosis.

## Genetic Testing

Situations in which molecular genetic testing is appropriate in persons / families with, or at risk of, TSC Complex include:  
Genetic counselling

Detection of a mutation in one or two TSC genes in the affected member of a family means that relatives at risk can have their genetic status determined by an unequivocal blood test. This is a more simple approach than by conventional clinical and radiographic tests.

## Clinical diagnostic uncertainty

Detection of a mutation in one of the two TSC genes in a person presenting with one or more features suggestive of TSC Complex, but which do not fulfil

the accepted clinical diagnostic criteria for the disorder, can clarify the person's status. However, a negative gene test result doesn't help much and so this approach requires careful consideration.

If you feel that you need a Genetics Consultation in the UK, you should contact your family doctor (GP) or, if you are being seen in a hospital speak to your specialist, who will be able to refer you to your Regional Genetics Service.

## Useful resources:

The TSA's TSC Advisers can offer information, advice and advocacy.

**[www.tuberous-sclerosis.org](http://www.tuberous-sclerosis.org)**

British Society of Human Genetics has a list of the UK regional genetics centres and information on genetic counselling

**[www.bshg.org.uk/for\\_patients/for\\_patients.htm](http://www.bshg.org.uk/for_patients/for_patients.htm)**

The Genetics Alliance UK has a wide range of genetics fact sheets

**Telephone:** 020 7704 3141

**[www.geneticalliance.org.uk/publications\\_patients.htm](http://www.geneticalliance.org.uk/publications_patients.htm)**

Contact a family: UK-wide charity providing advice, information and support to the parents of all disabled children

**Telephone:** 0808 808 3555

**[www.cafamily.org.uk](http://www.cafamily.org.uk)**

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Further information on TSC and the work of the Tuberous Sclerosis Association can be obtained from our website at: **[www.tuberous-sclerosis.org](http://www.tuberous-sclerosis.org)**

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