# Tuberous Sclerosis

Tuberous Sclerosis is a multisystem disorder with a highly variable clinical presentation. The high degree of variability has led to the condition now being called tuberous sclerosis complex (TSC).

## Epidemiology

- Incidence is ~ 1/10 000
- Male = Female

## Genetics

- Autosomal Dominant inheritance.
- TSC1 on chromosome 9q; 75% cases; encodes hamartin.
- TSC2 on chromosome 16; 25% cases encodes tuberin.
- Hamartin and tuberin dimerise to form a tumor supressor that acts as an inhibitor of the mTOR pathway which is critical in cell cycle growth and proliferation.
- Over 60% of cases are due to a new spontaneous mutation.
- Penetrance is 100% but with variable severity.
- A small minority of patients have a contiguous deletion involving TSC2 and the adjacent ADPKD gene on chromosome 16. This subset of patients often develop early onset renal cystic disease and hypertension. Approximately 5% of these patients go on to develop end stage renal failure.

## Clinical presentation

- The most common presentation is in childhood with epilepsy [90%] or developmental delay [80%] or infantile spasms [30%]
- Up to 50% of affected individuals may also have normal intelligence.
- Increasing numbers are being diagnosed in adulthood.

## Physical signs

- Facial angiofibromas or forehead plaques
- Ungal fibromas
- Hypopigmented macules
- Shagreen patch

## Diagnosis

Diagnostic criteria have been developed for TSC which require 2 major features or one major and 2 minor features.

### Major clinical diagnostic features

- Developmental delay
- Epilepsy
- Subependymal nodules/ hamartomas /cortical tubers
- Periventricular calcification
- Facial angiofibromas or forehead plaques
- Ungal fibromas
- Hypopigmented macules
- Shagreen patch
- Renal angiomyolipomas
- Cardiac rhabdomyoamas (as neonates) [30-70%]

### Minor clinical diagnostic features

- Renal cysts [40%]
- Dental Pits
- Bone cysts
- Rectal polyp hamartomas
- Retinal hamartomas
- Hepatic hamartomas [15%]

### Genetic testing

- Gene mutations are found in ~80% patients fulfilling diagnostic criteria.

Molecular DNA analysis is available for:

- Borderline cases where there is a known family mutation
- pre-natal testing
- predictive testing

## Complications

- Sporadic mutation patients with TSC1 mutations have a milder condition compared to TSC2 patients. Otherwise there is little difference between the genotypes in their complication rates.

The lesions of TSC are often asymptomatic but the main complications are:

- Intractable seizures
- Severe developmental delay
- Intracranial hypertension secondary to subependymal giant cell astrocytomas
- Enlarging renal angiomyolipomas and haematuria
- Cystic lung disease (lymphangiomyomatosis) in women



## Treatment

Annual systems review is directed towards preventative management in the following systems:

- Neurological
- Ophthalmological
- Cardiac
- Dermatological
- Developmental
- Renal

### Genetic counselling

- If parent affected, recurrence risk is 50% for each offspring
- If parent unaffected or *de novo* mutation, recurrence risk is less than 1%

### Differential Diagnosis TSC (BOX)

- Isolated cardiac rhadomyomas: 30-80% diagnosed prenatally will have TSC
- Periventricular heterotopia: rare X-linked disorder associated with normal intelligence, seizures and non-calcified periventricular nodules.
- Isolated renal angiomyolipomas, usually unilateral and more common in females

Pictures
Sahgreen patch
ungal fibroma
Facial rash
Dental pits
Aml angio
CT of brain