



# Tuberous Sclerosis Complex (TSC)

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## First description and alternative names

Even though earlier cases exist, the first detailed description of the disorder was by Désiré-Magloire Bourneville, a French Physician, in 1880 when he described the case of a young girl with severe intractable epilepsy, intellectual disability and a 'confluent vesiculo-papular eruption on her nose, cheeks and forehead'. Neuropathology showed white, potato-like growths in the brain, referred to by Bourneville as 'tuberous sclerosis of the cerebral convolutions'. The term *tuberous sclerosis complex* was introduced by Moolten in 1942 to describe the multi-system nature of the disorder. The abbreviation TSC is used (Kwiatkowski et al., 2010).

## Genetics and Molecular Biology

Occurs as a spontaneous mutation in 70% of cases. Autosomal dominantly inherited in the remaining 30% of familial cases. The disorder is associated with mutations in one of two genes, *TSC1* (on 9q34) or *TSC2* (on 16p13.3). The TSC1-2 protein complex acts as an intracellular complex that links a number of intracellular signalling pathways including the AMPK pathway, the MAPK pathway and the PI3K pathway. The TSC1-2 complex functions upstream of mTOR (mammalian Target Of Rapamycin). TSC mutations causes mTOR overactivation, leading to dysregulation of cell growth, proliferation and various other fundamental neurobiological processes (de Vries, 2010, Kwiatkowski et al., 2010). mTOR inhibitors have been approved by the FDA and EMA for the treatment of SEGA and angiomyolipoma associated with TSC. Clinical trials are underway of neurological and neuropsychiatric features of TSC (Curatolo, Moavero & de Vries, 2015)

## Incidence/prevalence

Birth incidence of about 1 in 5,800 (Osborne et al, 1991).

## Physical features and natural history

Wide variability of expression. The previously used "diagnostic triad" (of epilepsy, intellectual disability and characteristic facial skin lesions) is seen in only about 30% of people with the disorder. TSC is multi-system and can include hamartomatous growths affecting the brain, skin, kidneys, heart, eyes, teeth, lungs and other organs. About 80% of affected people have a lifetime history of epilepsy. Diagnosis is based on meeting clinical criteria for the disorder (Northrup, Krueger et al., 2013). Mutations are identified in 80-90% of individuals with clinically confirmed TSC.

TSC is not an inevitably declining condition and any deterioration in physical, neurocognitive and behavioural profile should be further investigated. Life expectancy is influenced by the degree of physical and neurological involvement. Intractable seizures, brain tumours (SEGAs – subependymal giant cell astrocytomas) and renal failure secondary to angiomyolipomas may be causes of death.

## Behavioural and psychiatric characteristics

Tuberous Sclerosis is associated with a wide range of behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial difficulties. The term TAND (TSC-Associated Neuropsychiatric Disorders) has been introduced as a summary term for all the bio-psycho-social aspects of the disorder (de Vries et al., 2015) and a TAND Checklist has been developed to aid clinical teams to screen for

TAND (de Vries et al., 2015; Leclezio et al., 2015) TSC is associated with high rates of various disruptive behaviours, sleep problems and self-injurious behaviours. Developmental disorders including autism and autism spectrum disorders (ASD) in 40-50%, ADHD and attention-related disorders in 30-50% and intellectual disability in ~50% of individuals. TSC is one of the medical conditions most commonly associated with ASD. In adolescents and adults, very high rates of anxiety and mood-related disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology (de Vries et al., 2015; Kwiatkowski et al., 2010).

### **Neuropsychological characteristics**

Global intellectual abilities show a bimodal distribution in TSC. 30% of individuals with TSC have profound global intellectual disability (IQ equivalent <20) and do not show significant developmental gains over time. The remaining 70% fall on a normal distribution curve, shifted to the left. In clinical practice, more than 50% of individuals with TSC will have global intellectual abilities in the normal range. There are, however, high rates of specific neuropsychological deficits in those with normal global intellectual abilities. Specific deficits are most prominent in attentional, executive and visuo-spatial skills. These specific cognitive deficits may be associated with significant scholastic difficulties and impair functional abilities in daily life (de Vries et al., 2015; Kwiatkowski et al., 2010; Tierney et al., 2011).

### **Available guidelines for behavioural assessment/treatment/management**

- International consensus guidelines were drawn up for the assessment of cognitive and behavioural problems in TSC (de Vries et al., 2005). These were revised and are augmented by the new guidelines on screening and assessment (Krueger, Northrup et al., 2013) and by the TAND Checklist (de Vries et al., 2015; Leclezio et al., 2015)
- There are currently no TSC-specific treatments available for the neuropsychiatric manifestations of TSC. Clinicians should therefore use evidence-based interventions as for the general population.
- Targeted treatments using mTOR inhibitors are currently in clinical trials for the neurocognitive and neurodevelopmental features of TSC (Curatolo, Moavero & de Vries, 2015), but these are not at present recommended outside clinical trials.
- The diagnostic criteria and management guidelines for TSC were revised in 2012 and were published in 2013 (Northrup, Krueger et al., 2013; Krueger, Northrup et al., 2013).

### **Useful websites/associations for more information**

- [www.tuberous-sclerosis.org](http://www.tuberous-sclerosis.org) [UK user/carer organization]
- [www.tsalliance.org](http://www.tsalliance.org) [USA user/carer organization]

### **References**

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