PRIMEVIEW

TUBEROUS SCLEROSIS COMPLEX

nature REVIEWS DISEASE PRIMERS

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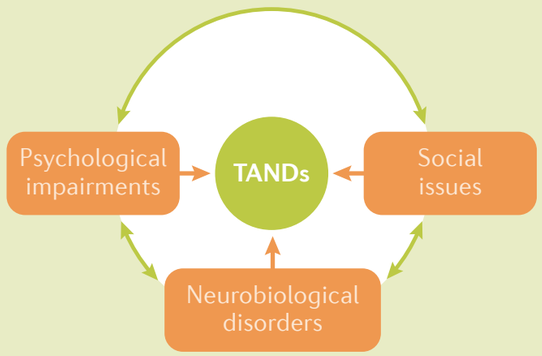
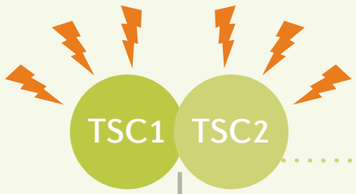
Tuberous sclerosis complex (TSC) is a rare autosomal dominant disorder caused by loss-of-function mutations in either of the tumour-suppressor genes *TSC1* or *TSC2*. The disease manifests as benign tumours in various organs and was named for the fibrous root-shaped growths or 'tubers' that form in the brains of patients.

MANAGEMENT

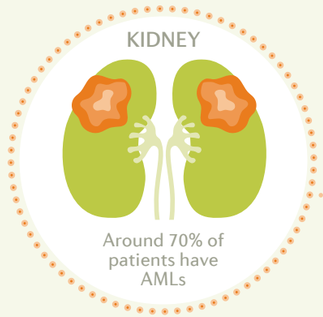
Although TSC can affect multiple organs and systems — including the lungs, kidneys, heart, skin, central nervous system, liver, gums and teeth — the manifestations of the disease vary widely between patients, even between those in the same family. Management strategies, therefore, need to be specifically tailored to individual patients. For example, epilepsy often occurs in infants with TSC and is treated according to standard practice, which usually involves the GABA transaminase inhibitor vigabatrin. In addition, mTOR inhibitors have been approved for the treatment of renal angiomyolipomas (AMLs), pulmonary lymphangioleiomyomatosis (LAM) and subependymal giant cell astrocytomas (SEGAs), and clinical guidelines recommend topical mTOR inhibitor therapy for angiofibromas. Management of TSC-associated neuropsychiatric disorders (TANDs) should involve multidisciplinary teams across health, educational and social agencies.

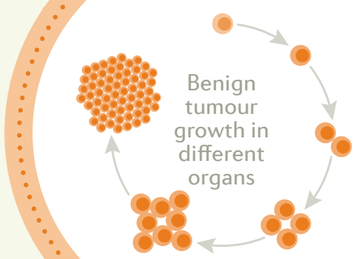


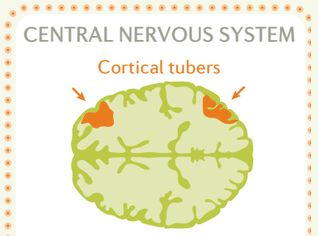
MECHANISMS

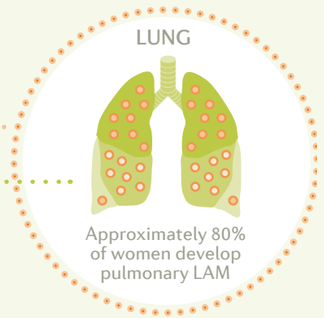


Together, TSC1 and TSC2 inhibit signalling through mTOR complex 1 (mTORC1). According to the 'two-hit' model, TSC is caused by a germline mutation (inherited or *de novo*) in *TSC1* or *TSC2*, followed by a somatic mutation in the second allele that results in increased mTORC1 signalling.









LAM is a progressive destructive lung disease, almost all cases of which occur in women. Although the reason for this sex preponderance is unknown, data suggest that the development and/or spread of LAM cells might be driven by female sex hormones.

OUTLOOK

The success of mTOR inhibitors for treating AMLs, LAM and SEGAs has spurred interest in using these drugs to prevent manifestations of TSC before they arise. Indeed, given that TSC is often diagnosed perinatally, early treatment might prevent epilepsy, benign tumour growth and aspects of TANDs. Studies in mice have demonstrated that prenatal treatment with mTOR inhibitors produces developmental defects, indicating that, if preventive treatment is to succeed, research will need to identify an ideal treatment 'window' that is late enough to ensure normal development but early enough to prevent disease onset.

DIAGNOSIS

In the absence of clear genetic findings, TSC is diagnosed using a combination of different clinical and radiographic characteristics. As the symptoms of TSC vary widely from patient to patient, no single combination of features defines TSC. Rather, clinicians use a scoring system that includes major and minor manifestations to diagnose the disease.

A definitive TSC diagnosis can be made on the basis of genetic findings alone if a loss-of-function mutation is identified in *TSC1* or *TSC2*

QUALITY OF LIFE

TSC is a multisystem and chronic disease that imparts high morbidity and considerable mortality, even though most patients with TSC have near-normal lifespans. Along with substantial implications for patient quality of life, the lifelong manifestations and management requirements of the disease often place considerable strains on family members, caregivers and service providers.

Although the effects of long-term mTOR inhibitor therapy for TSC are not yet known, the use of these agents for other diseases suggests that adverse effects might include stomatitis, wound-healing complications, metabolic defects, delayed sexual maturity and infertility

Designed by Laura Marshall

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