Tuberous sclerosis (TSC)

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Identity

Alias
Bourneville disease; Epiloia

Inheritance
Frequency: 1/6000-1/10000 birth. First genetic cause of epilepsy associated with mental retardation = epiloia. 2/3 of cases are sporadic, 1/3 are inherited.

Genetic heterogeneity: two genes, TSC1 and TSC2, account for the majority of cases. Somatic mosaicism has been reported in association with a milder form of the disease. Germinal mosaicism has been described and must be taken into account for genetic counselling. Autosomal dominant with almost complete penetrance but variable expressivity.

Clinics

Note
Disability in TSC patients most often results from the involvement of brain. Two types of lesions are static (hamartias); cortical tubers, and subcortical heterotopic nodules, whereas subependymal nodules are often progressive (hamartoma), hence the term subependymal giant cell astrocytoma.

Phenotype and clinics

The definition of the tuberous sclerosis complex requires either two major features or one major feature plus two minor features.

Major features:
- Facial angiofibromasor forehead plaque
- Non traumatic ungual or periungual fibroma
- Hypomelanotic macules (three or more)
- Shagreen patch ( connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma, single or multiple
- Lymphangioleiomyomatosis
- Renal angiomylipoma

Minor features:
- Multiple, randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- “confetti ” skin lesions
- Multiple renal cysts

Neoplastic risk

Renal angiomylipomas, often multiple and bilateral, (75% of children with TSC). occasionally (< 2-3%), turn into renal carcinoma only later in life.

Cardiac rhabdomyomas, often congenital, tend to regress in infancy, remain identical in same size through out childhood and can then either again regress or progress (girls) in adolescence.

Brain tumors, (incidence 5-14%), are mostly (>90%) subependymal giant cell astrocytomas, or ependymomas.

Hamartomas also occur in liver, spleen, and various tissues.

Pulmonary lymphangioleiomyomatosis is a destructive lung disease characterized by a diffuse hamartomatous proliferation of smooth muscle cells in lungs.
**Cytogenetics**

**Inborn conditions**
Increased frequency of premature centromere disjunction (PCD) in cultured fibroblasts, especially for chromosome 3.

**Cytogenetics of cancer**
No special feature.

**Genes involved and proteins**

**Note**
Two genes are involved, TSC1 and TSC2. The patients with TSC1 mutations would have a milder form of the disease, compared to those with TSC2 mutations.

**TSC1**

**Location**
9q34

**Note**
Accounts for about 50% of TSC patients.

**DNA/RNA**
Description: 23 exons.

**Protein**
Note: Tumor suppressor.
Description: Hamartin and tuberin cohybridize in vivo. Hamartin is a growth inhibitory protein, affecting cell proliferation via deregulation of G1 phase, possibly by regulating cellular adhesion through ezrin-radixin-moesin family proteins and the small GTP-binding protein RHO.

**TSC2**

**Location**
16p13

**Note**
Accounts for about 50% of TSC patients.

**DNA/RNA**
Description: 41 exons.

**Protein**
Note: Tumor suppressor.
Functions: as a GTPase activating protein which activates the Ras-related family of small GTP-binding proteins such as Rap1 and Rab5. Inhibits the G1/S transition and promotes entry to the G0 phase. The Eker rat, a naturally occurring animal model of TSC, has an autosomal dominant trait of renal cell carcinoma caused by a germline mutation in the rat TSC2 gene.

**Mutations**
Germline: Most TSC1 and TSC2 mutations are truncating mutations. Both large deletions and missense mutations are not uncommon at TSC2 locus, whereas most TSC1 mutations are small truncating lesions.

Somatic: Loss of heterozygosity has been described in some tumor types, such as angiomyolipomas, giant cell astrocytomas, or rhabdomyomas, but is rare in cortical tubers.

**References**


**This article should be referenced as such:**