Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Cancer Prone Disease Section

Mini Review

Tuberous sclerosis (TSC)

Julie Steffann, Arnold Munnich, Jean-Paul Bonnefont

INSERM U393, Groupe Hospitalier Necker-Enfants Malades, Tour Lavoisier 2, 149 rue de Sèvres, 75743 Paris Cedex15, France (JS, AM, JPB)

Published in Atlas Database: June 2002

Online updated version: http://AtlasGeneticsOncology.org/Kprones/TuberSclerosID10014.html
DOI: 10.4267/2042/37912

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
- Lymphangiomyomatosis
- Renal angiomyolipoma

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 angiomyolipomas, often multiple and bilateral, (75% of children withTSC). occasionnally (< 2-3%), turn into renal carcinomaonly 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 lymphangiomyomatosis 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 disjonction (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-moiesin 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.
Fonctions: 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 occuring animal model of TSC, has an autosomal dominant trait of renal cell carcinoma caused by a germline mutation in the rat TSC2 gene.

Mutations

Germinal: 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.

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This article should be referenced as such:

Steffann J, Munnich A, Bonnefont JP. Tuberous sclerosis (TSC). Atlas Genet Cytogenet Oncol Haematol. 2002; 6(4):311-312.