TUBEROUS SCLEROSIS COMPLEX

ΟΖΩΔΗΣ ΣΚΛΗΡΥΝΣΗ

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Για την παρούσα εκδήλωση έλαβα χρηματική αμοιβή από την Novartis Hellas

An orphan disease is defined as a condition that affects fewer than 200,000 people nationwide.

- *Tuberculous meningitis*
- *Tuberculous uveitis*
- *Tuberous sclerosis*
- *Tuberous sclerosis type 1*
- *Tuberous sclerosis type 2*
- *Tubulointerstitial nephritis and uveitis*
- *Tucker syndrome*
- *Tuffli Laxova syndrome*

Tuberous Sclerosis Complex

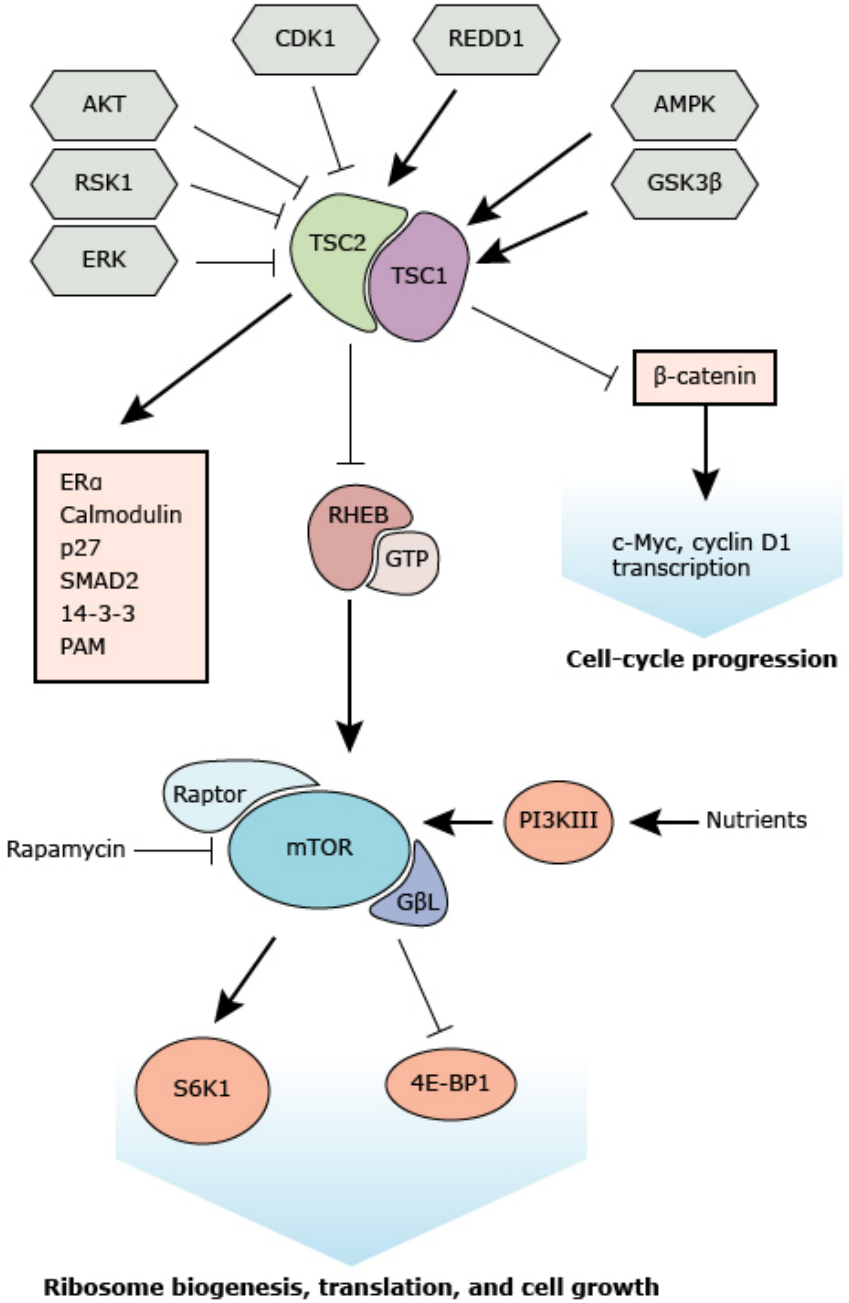
- Tuberous sclerosis complex is an autosomal dominant genetic disorder
- Approximately 1 in 5000 to 10,000 live births
- Caused by a mutation in either the TSC1 gene or the TSC2 gene
- Only 7 to 37 percent of newly diagnosed cases have a family history of TSC

Explanations for the apparently nonfamilial cases

- De novo mutation in the egg or sperm prior to fertilization.
- Somatic mosaic where a subset of somatic and germ cells carry the mutation
- Mutation occurred during the child's development and after fertilization
- Although penetrance is complete, TSC is highly variable in its expression

TSC Genes

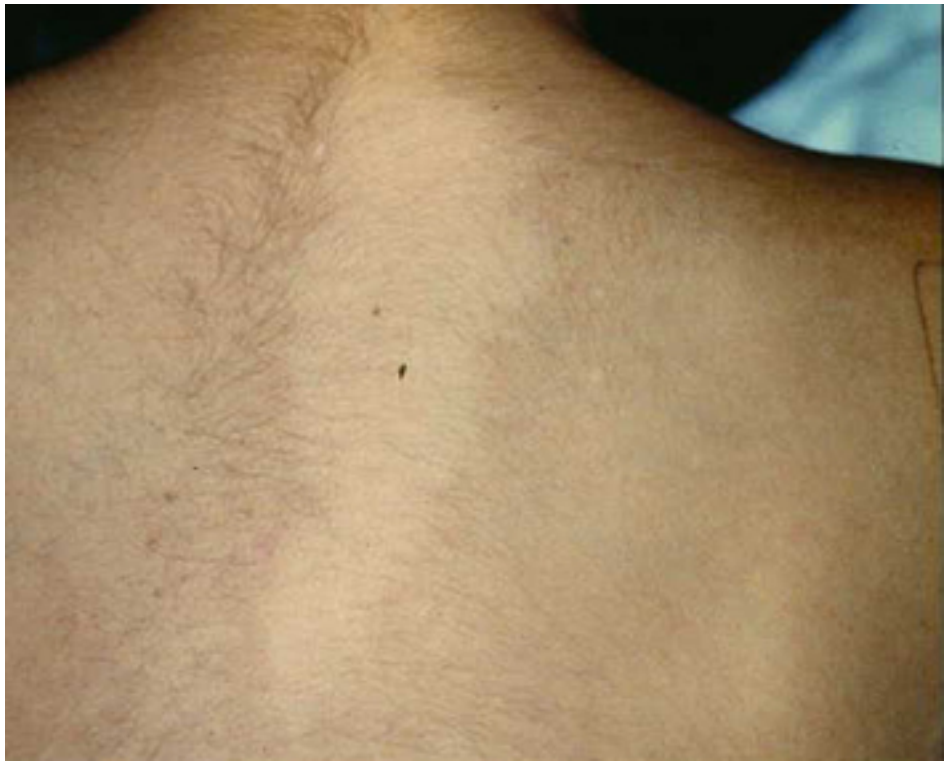
- The TSC1 gene maps to chromosome 9q34 and encodes a protein termed hamartin
- The TSC2 gene maps to chromosome 16p13.3 and encodes a protein termed tuberin
- Both these proteins form a complex with each other and are widely expressed in normal tissues
- TSC genes function as tumor suppressor genes, because stimulate the intrinsic activity of GTPases and inactivate GTP-binding proteins, such as ras superfamily, which control cell cycle


CDK1
REDD1
AKT
AMPK
RSK1
GSK3β
ERK
TSC2
TSC1
β-catenin
ERα
Calmodulin
p27
SMAD2
14-3-3
PAM
RHEB
GTP
c-Myc, cyclin D1
transcription
Cell-cycle progression
Raptor
PI3KIII
Nutrients
Rapamycin
mTOR
GβL
S6K1
4E-BP1
Ribosome biogenesis, translation, and cell growth

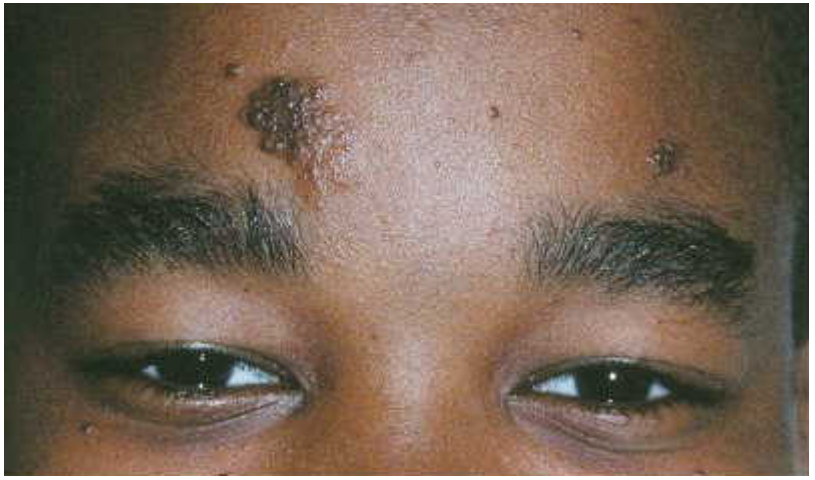
Tuberous sclerosis complex (TSC)

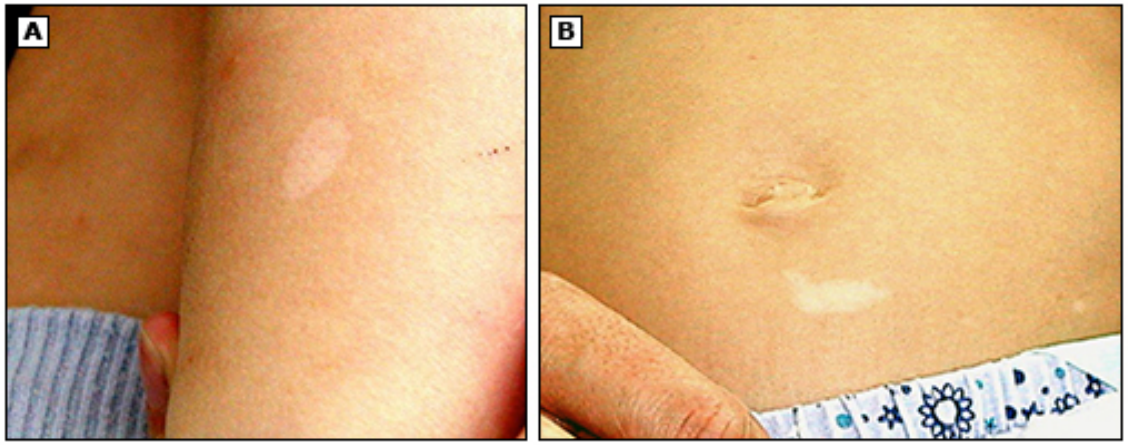
- Pleomorphic features involving many organ systems
  - Brain (most have epilepsy, >50% have cognitive deficits, learning disabilities, autism, behavioral problems, and psychosocial difficulties)
  - eyes (retinal hamartomas)
  - heart (rhabdomyomas typically multifocal)
  - lung (lymphagioleiomyomatosis)
  - liver,
  - kidney (amgiomyolipoma, cycts)
  - skin (nearly all patients have one or more of the skin lesions)
- Increased risk of malignancy

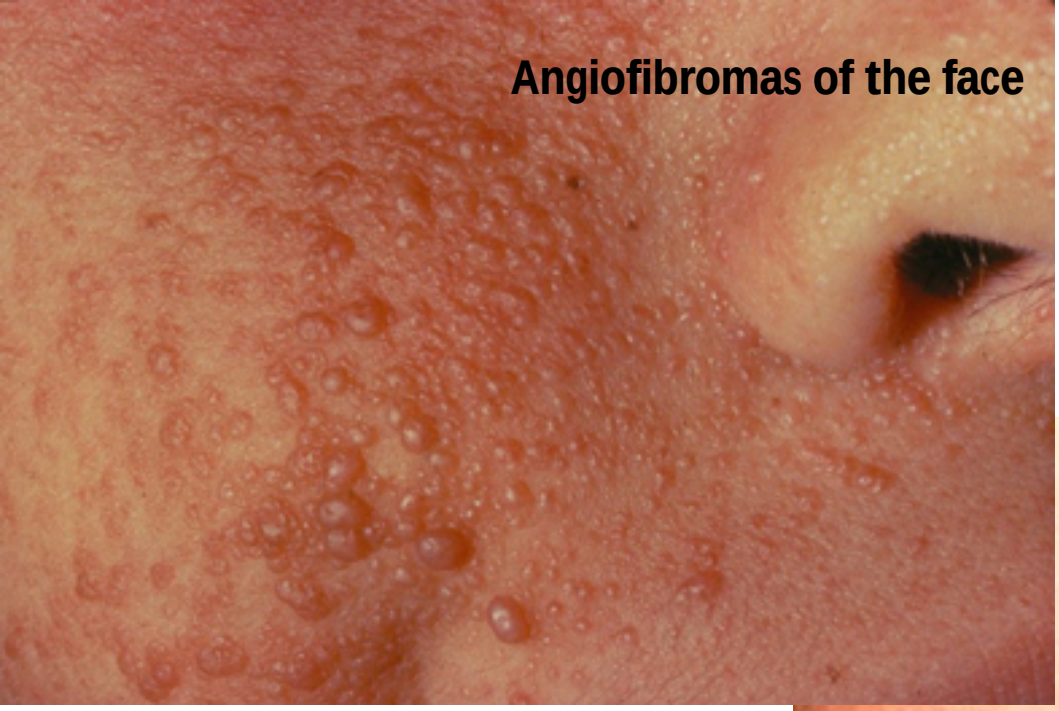
Hypomelanotic macule on the torso

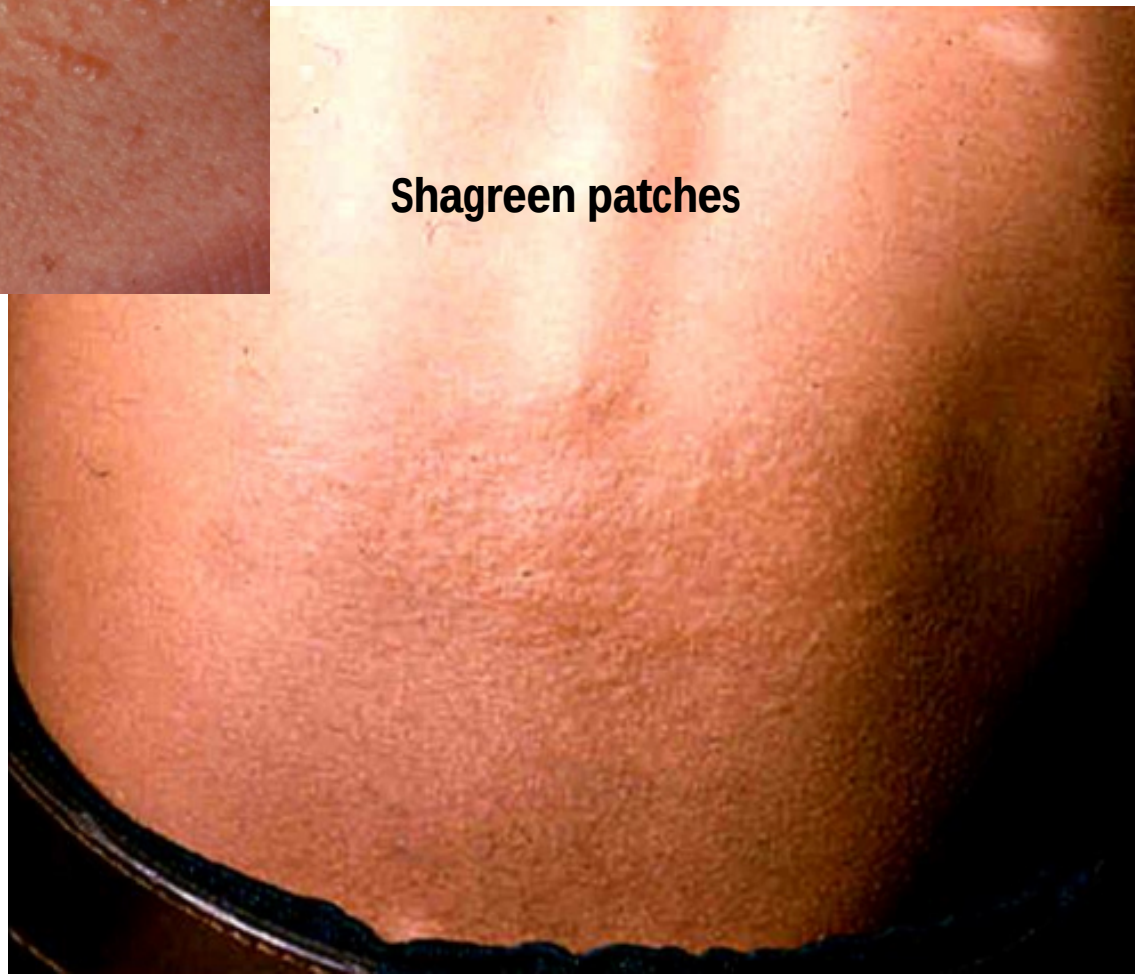


Forehead fibrous plaque

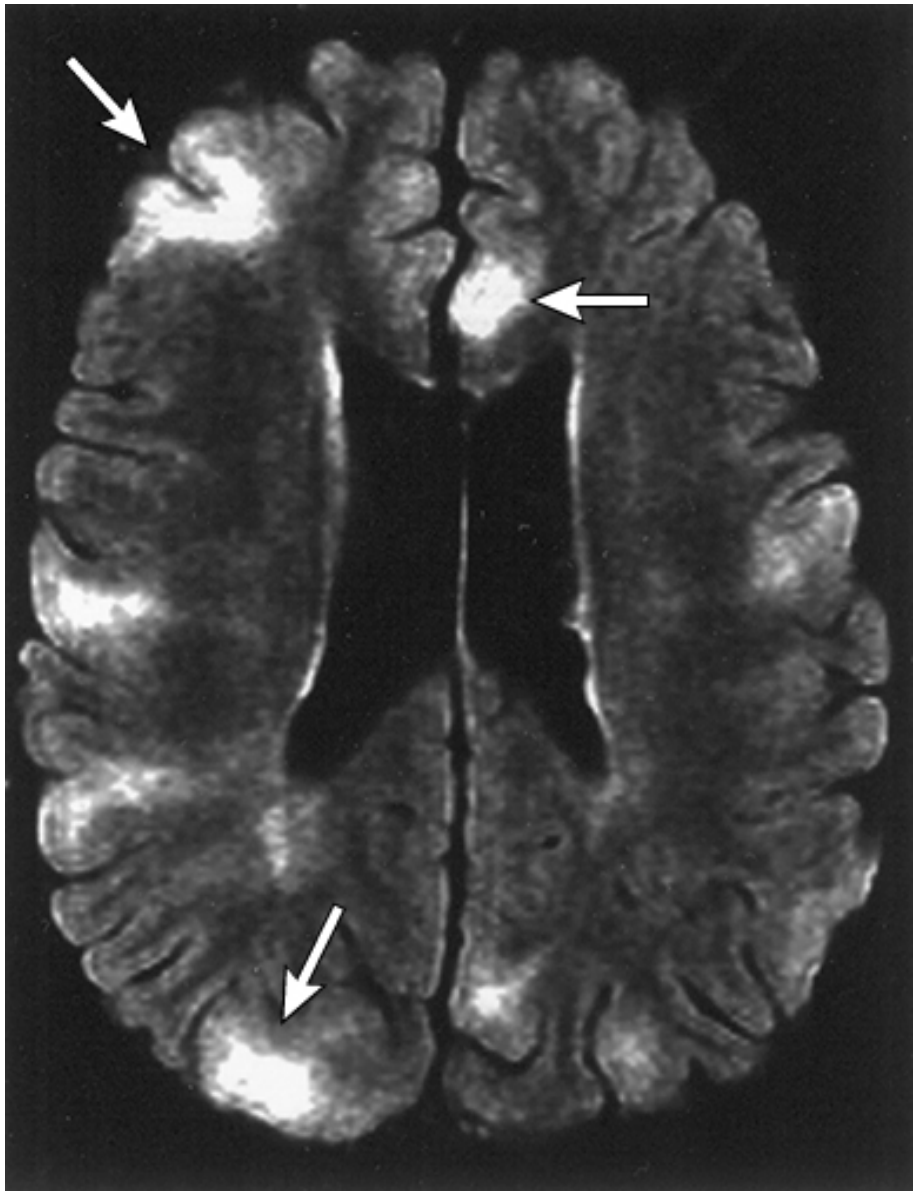




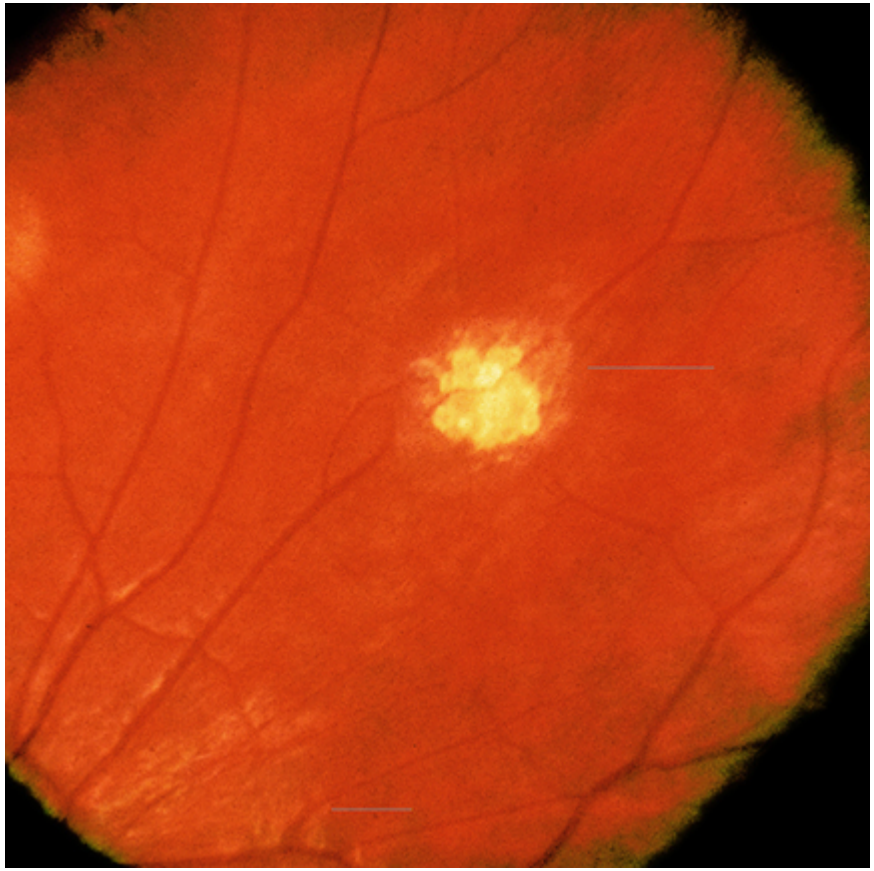

Angiofibromas of the face


Shagreen patches

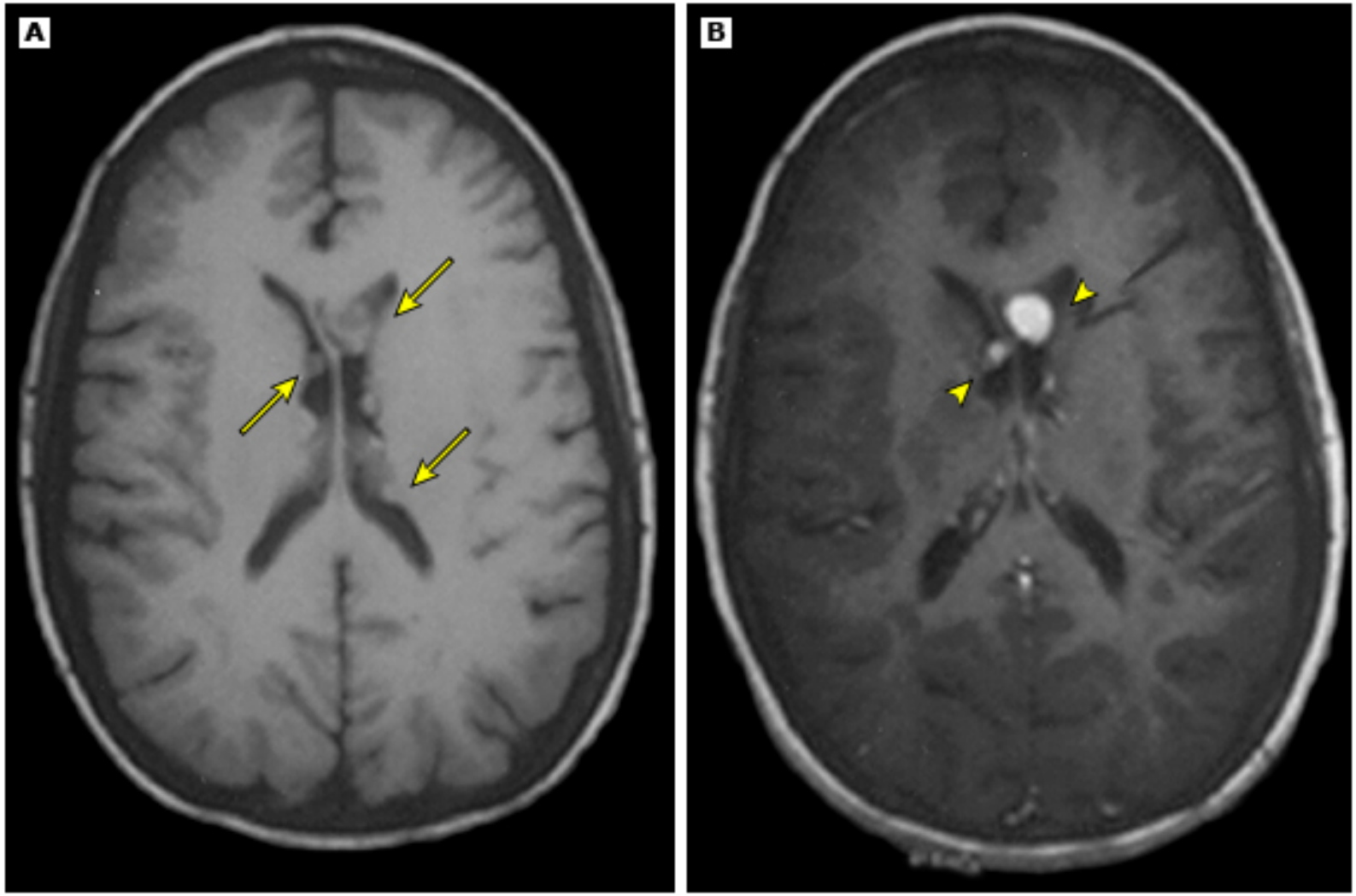

Ungual fibromas



Cortical glioneuronal hamartomas, also known as tubers (arrows).



Small, multinodular, calcified astrocytic hamartoma of the retina.



(A)Multiple subependymal nodules within the lateral ventricles (arrows).
(B) Two nodules enhance with gadolinium (subependymal giant cell astrocytomas).

ΔΙΑΓΝΩΣΤΙΚΑ ΚΡΙΤΗΡΙΑ TSC

Major features
1. Facial angiofibromas or forehead plaque
2. Nontraumatic ungual or periungual fibroma
3. Hypomelanotic macules (three or more)
4. Shagreen patch (connective tissue nevus)
5. Multiple retinal nodular hamartomas
6. Glioneuronal hamartoma (cortical tuber)*
7. Subependymal nodule
8. Subpendymal giant cell atrocytoma
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangioleiomyomatosis•
11. Renal angiomyolipoma•

Minor features
1. Multiple, randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps$^{\Delta}$
3. Bone cysts$^{\diamond}$
4. Cerebral white matter radial migration lines$^{*\diamond\S}$
5. Gingival fibromas
6. Nonrenal hamartoma$^{\Delta}$
7. Retinal achromic patch
8. "Confetti" skin lesions
9. Multiple renal cysts$^{\Delta}$

Definite tuberous sclerosis complex:
Either two major features or one major feature plus two minor features
Probable tuberous sclerosis complex:
One major plus one minor feature
Possible tuberous sclerosis complex:
Either one major feature or two or more minor features

Roach ES et al. J Child Neurol 1998; 13:624.


ΕΥΧΑΡΙΣΤΩ!