

Tuberous Sclerosis Complex

Multisystem hamartoma syndrome • mTOR dysregulation

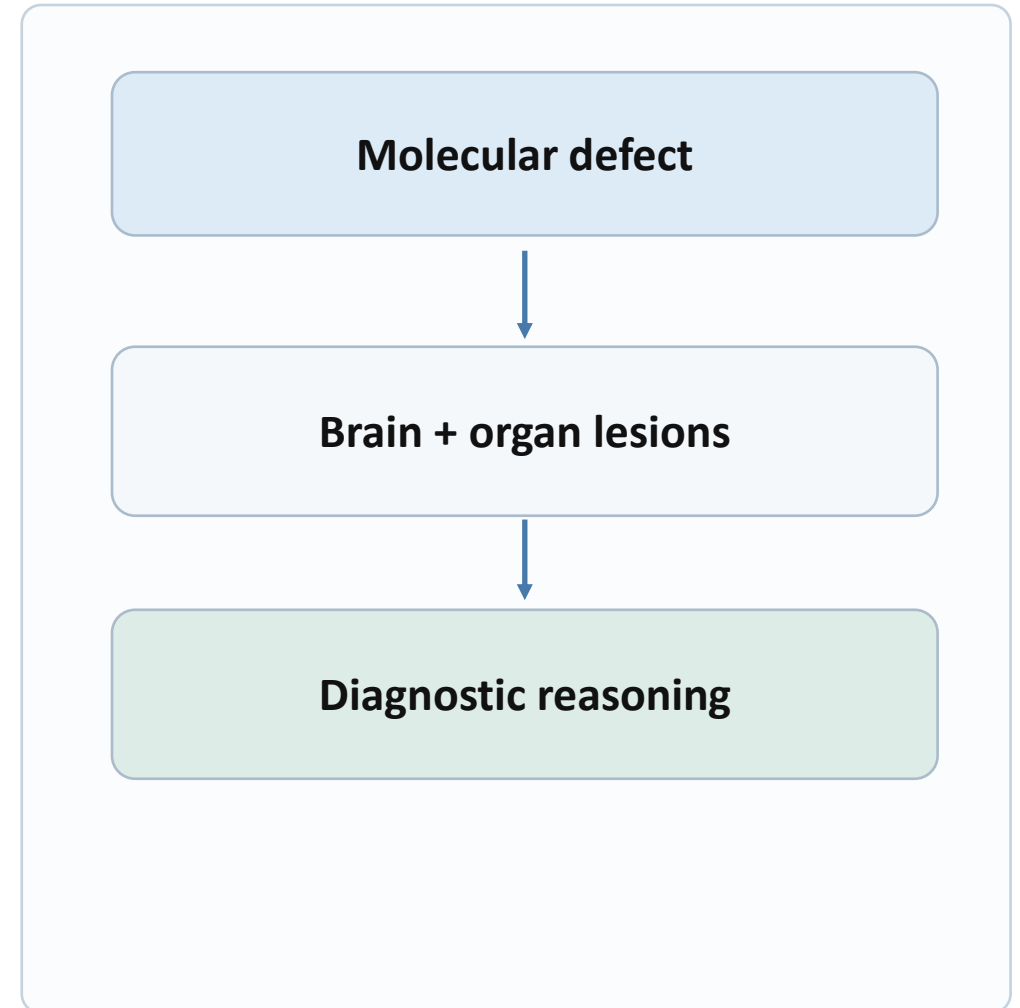
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Learning objectives

- Map the lesions of TSC to organ systems and symptoms.
- Explain TSC1/TSC2–hamartin/tuberin control of mTOR.
- Recognize cortical tubers, subependymal nodules and SEGA.
- Apply contemporary diagnostic and surveillance principles.



TSC is a multisystem hamartoma syndrome

- Autosomal dominant disorder with variable clinical expression.
- Characteristic hamartomas and benign neoplasms affect brain and extracranial tissues.
- Seizures and neurodevelopmental difficulties frequently dominate recognition.

CNS

Tuber • SEN • SEGA

Skin

Macules • fibromas

Kidney

AML • cysts

Other

Heart • retina • lung

TSC belongs to familial tumor syndromes

- Inherited syndromes can predispose to specific tissue growths.
- TSC is defined by distinctive CNS lesions and multisystem findings.
- The underlying defect affects growth regulation rather than a single organ.

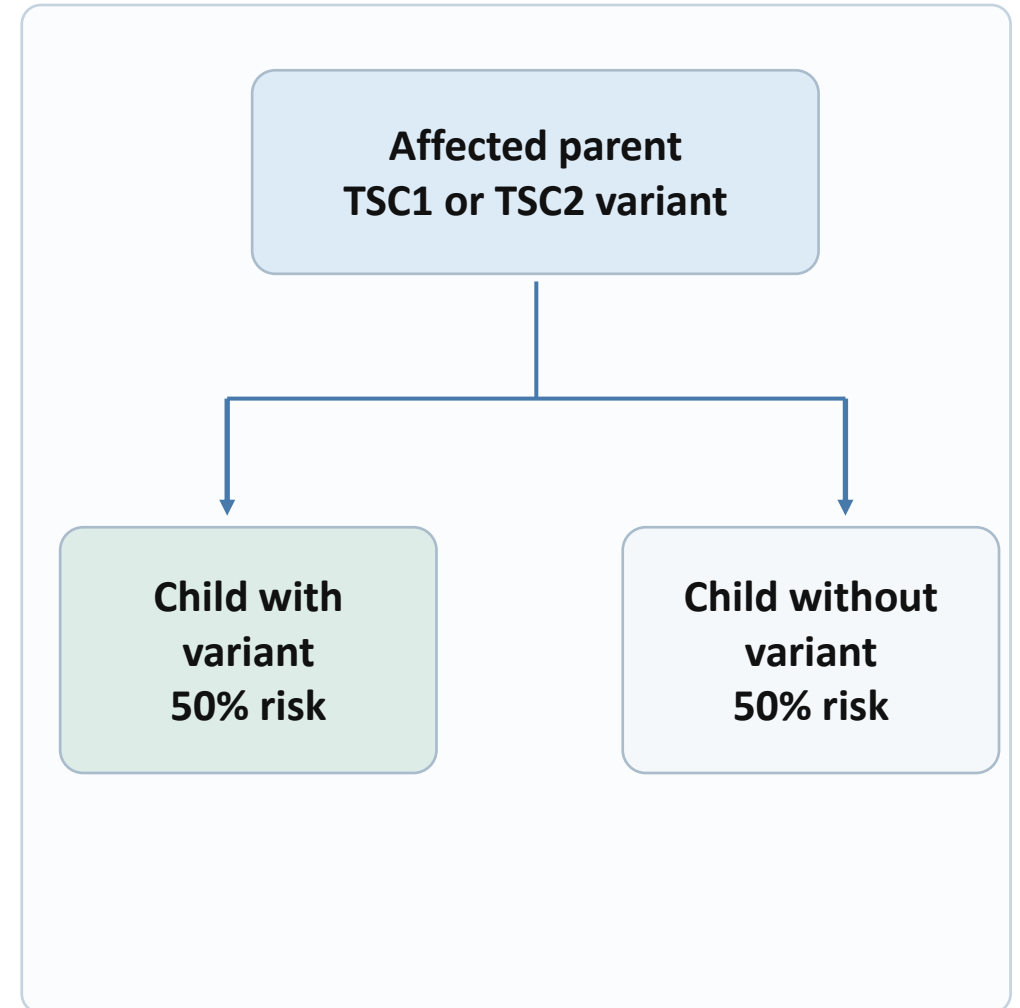
Familial tumor syndrome

Hamartomas + neoplasms

CNS and multiple organ sites

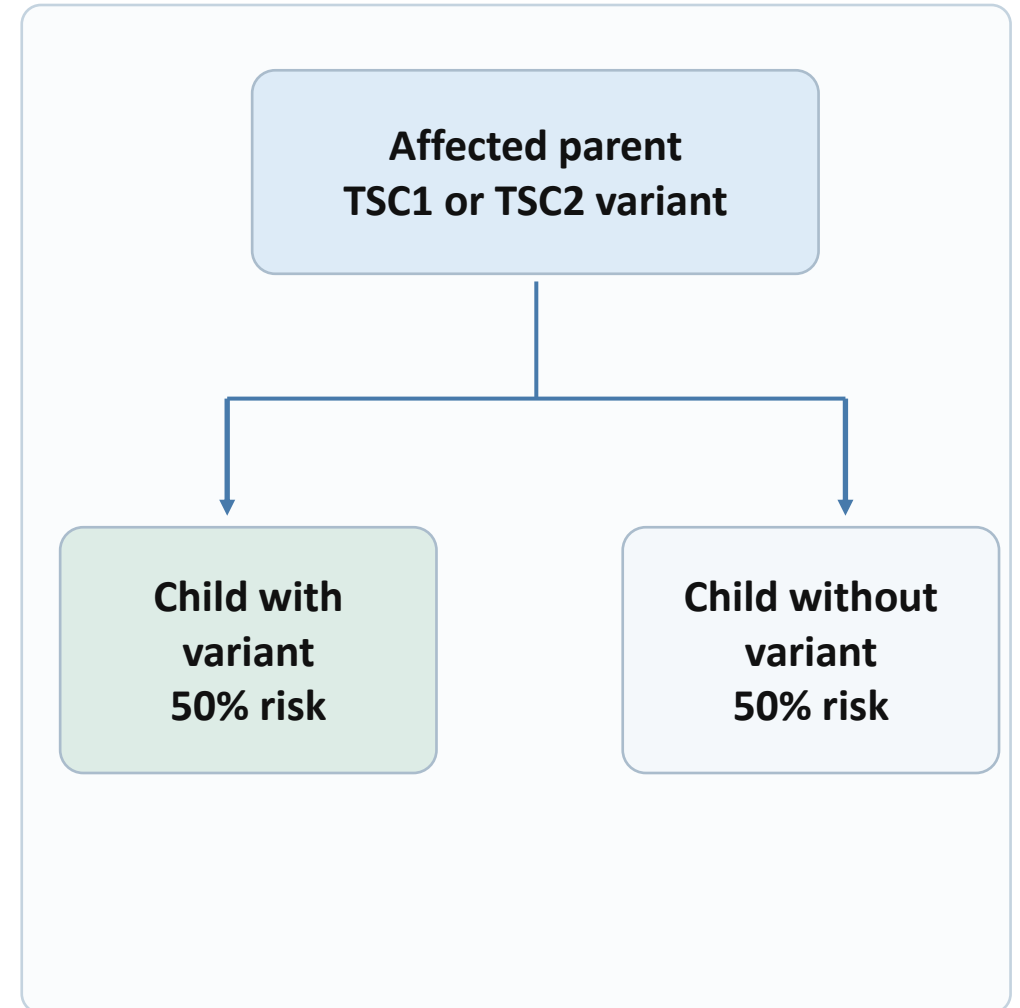
Frequency and population context

- A birth frequency of approximately 1 in 6,000.
- Both familial inheritance and apparently isolated presentations occur.
- Absence of an affected parent does not exclude TSC.



Inheritance: Autosomal dominant

- A heterozygous pathogenic variant can establish disease.
- Each child of an affected individual has a 50% transmission risk.
- GeneReviews reports approximately two thirds of cases result from de novo variants.



Phenotypic variability

- Clinical expression differs markedly between affected individuals.
- Different organ systems may come to attention at different ages.
- Normal findings in one organ do not exclude manifestations elsewhere.

Seizures and cognition

Renal / skin / cardiac signs

Variable timing and severity

Hamartoma and benign neoplasm: Distinct concepts

- A hamartoma is a disorganized growth of tissue components native to its site.
- Cortical tubers and subependymal nodules are hamartomatous CNS lesions.
- SEGA is designated a benign neoplasm, often associated with subependymal nodules.

Hamartoma

Disorganized native
tissue

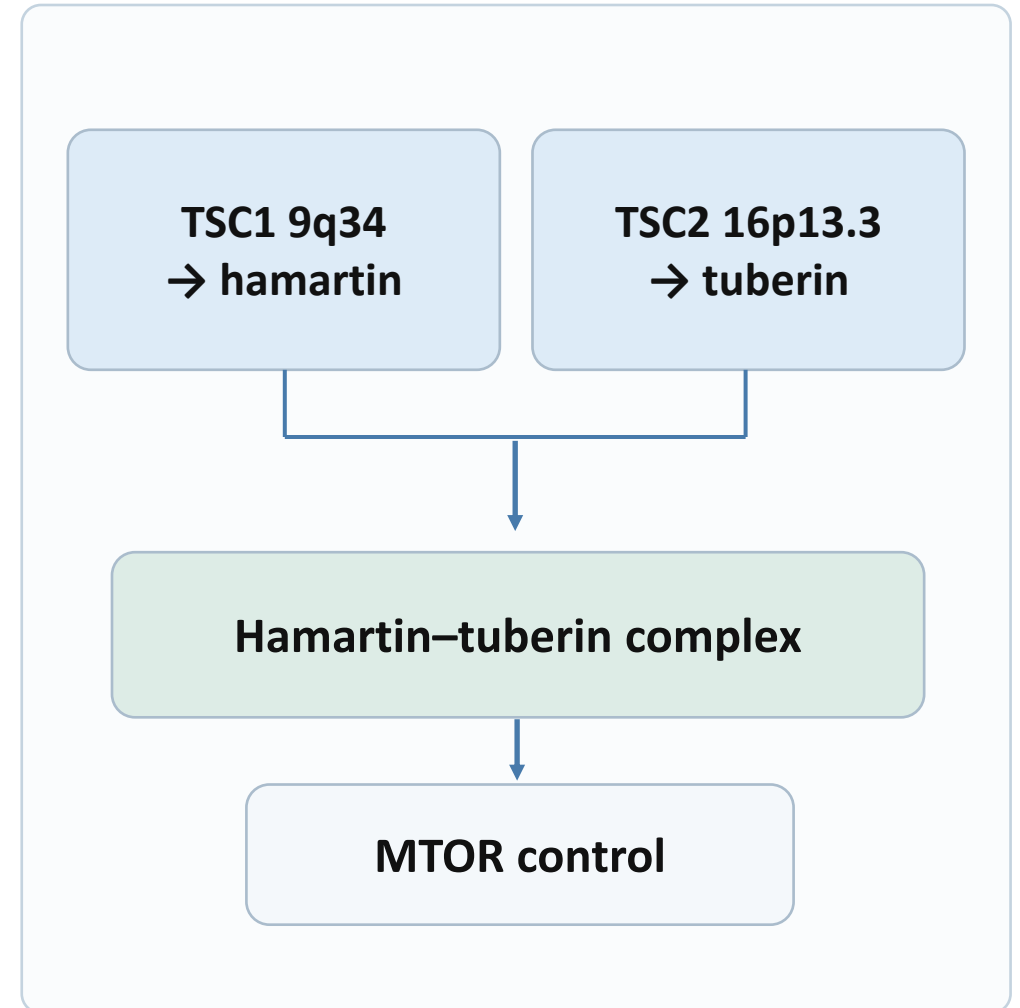
Benign neoplasm

Proliferative tissue
mass

Both may be clinically significant

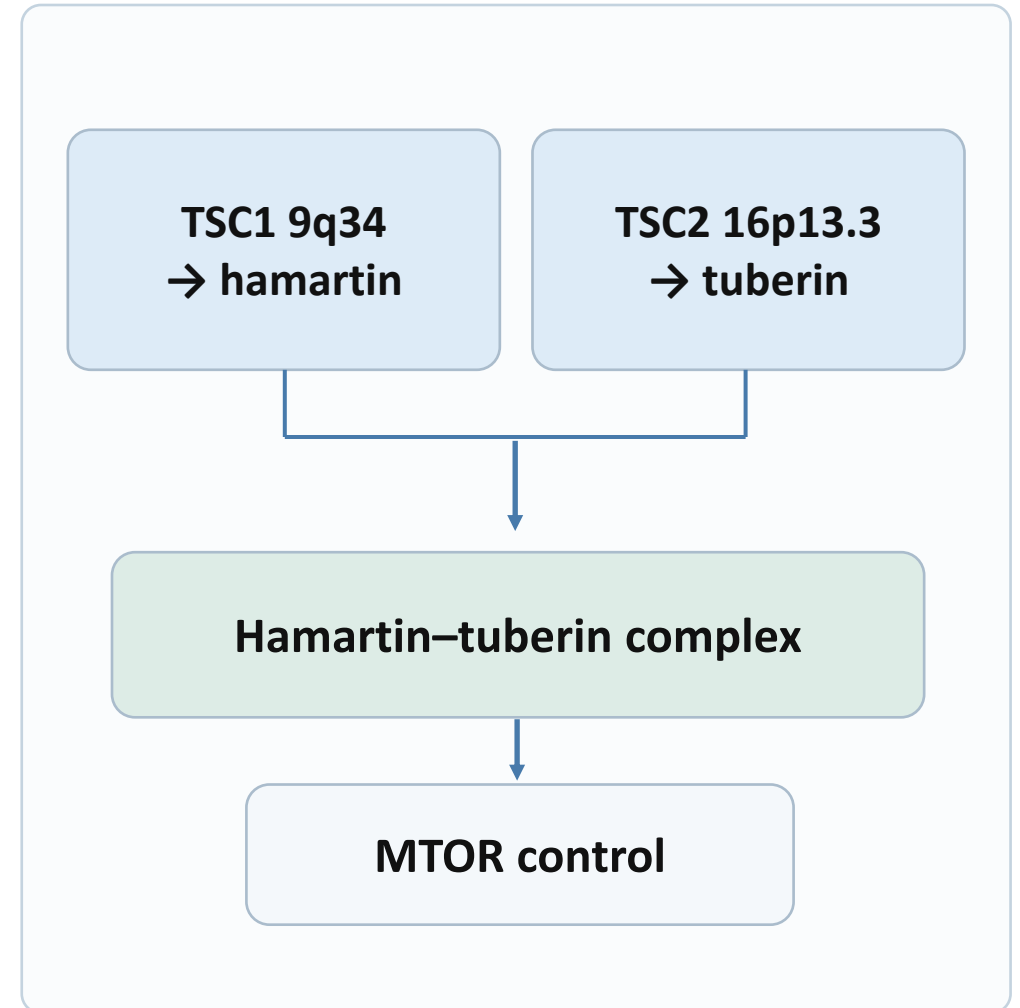
TSC1: The hamartin-encoding gene

- TSC1 maps to chromosome 9q34.
- Its protein product is hamartin.
- Hamartin acts together with tuberin in a growth-regulatory complex.



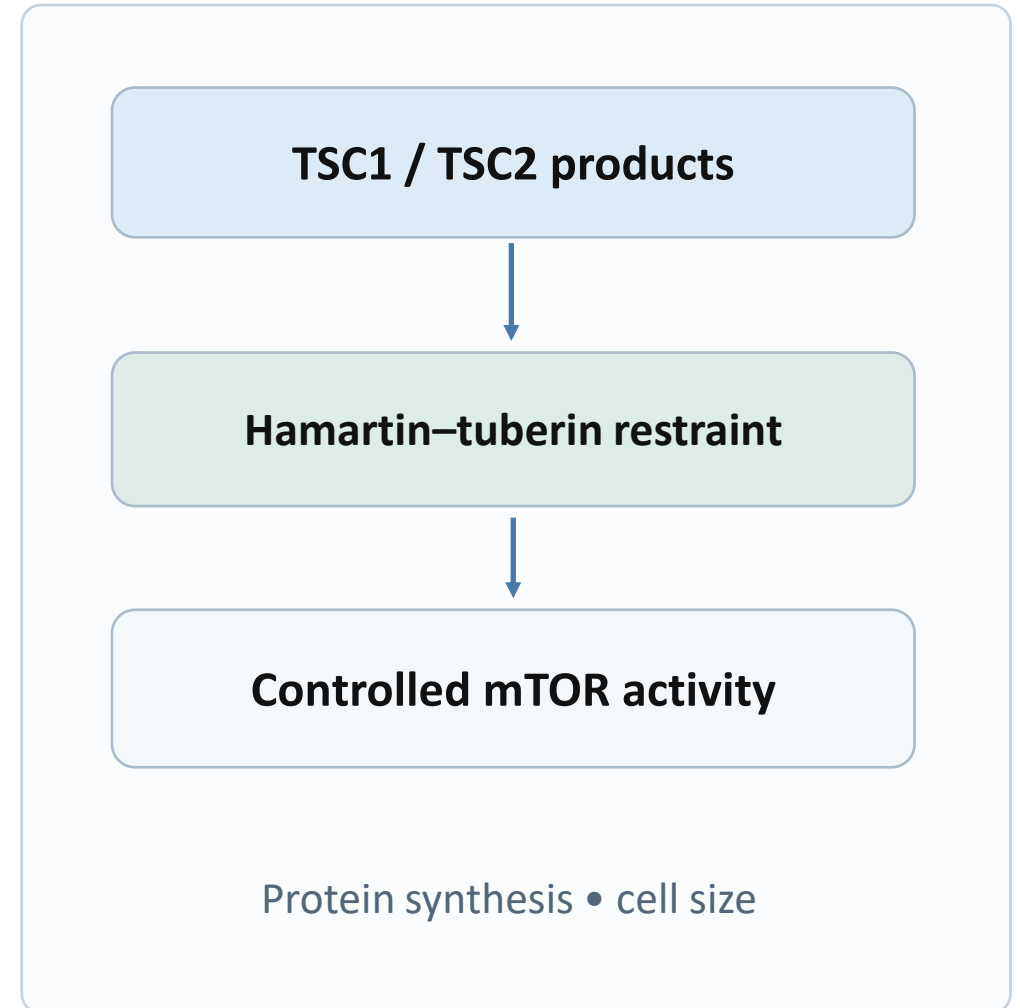
TSC2: The tuberin-encoding gene

- TSC2 maps to chromosome 16p13.3.
- Its protein product is tuberin.
- TSC2 as more commonly mutated than TSC1.



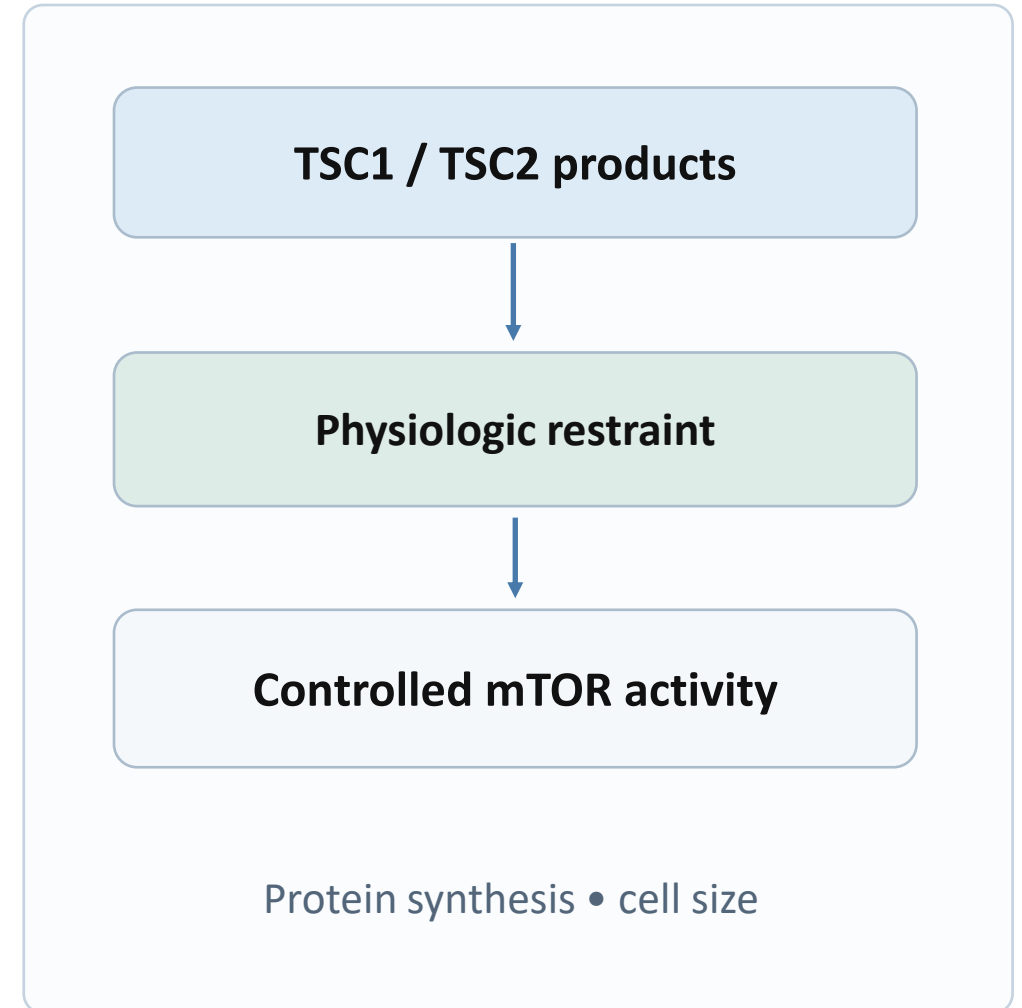
Hamartin and tuberin function together

- The two proteins operate as a functional inhibitory complex.
- An intact complex restrains mTOR kinase signaling.
- Pathogenic disruption releases this restraint on cell growth pathways.



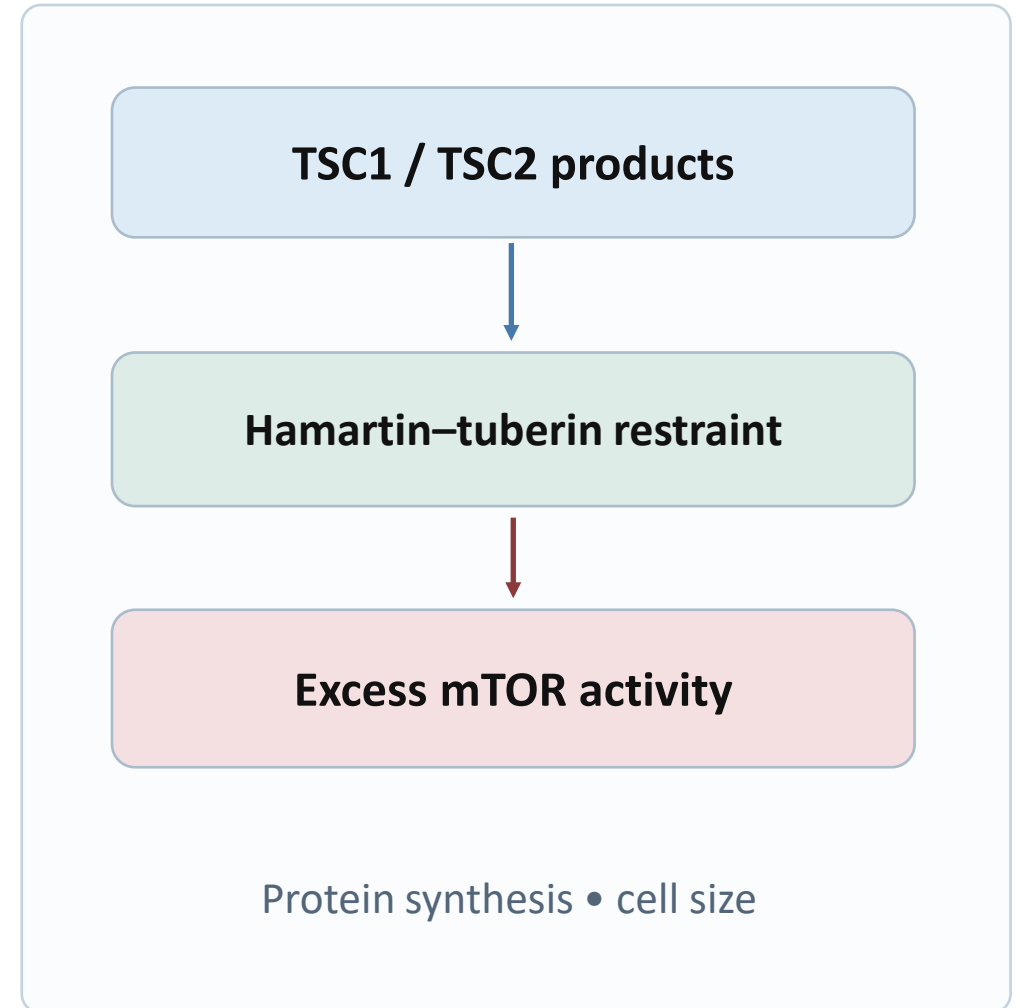
MTOR regulates anabolic metabolism

- MTOR is a kinase central to protein synthesis and cellular anabolism.
- Physiologic activity is controlled by upstream growth-regulatory signals.
- TSC1/TSC2 normally act as a brake on this pathway.



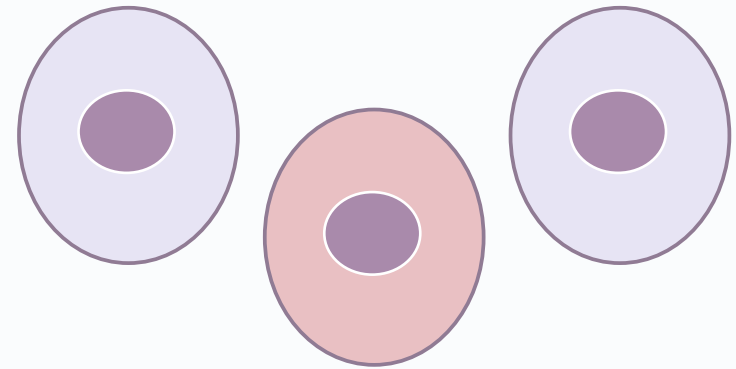
Loss of TSC restraint increases mTOR activity

- Pathogenic TSC1 or TSC2 alteration disrupts hamartin–tuberin control.
- MTOR signaling becomes excessive or inadequately regulated.
- Anabolic signaling contributes to abnormal cell size and tissue growth.



Why TSC cells can be unusually large

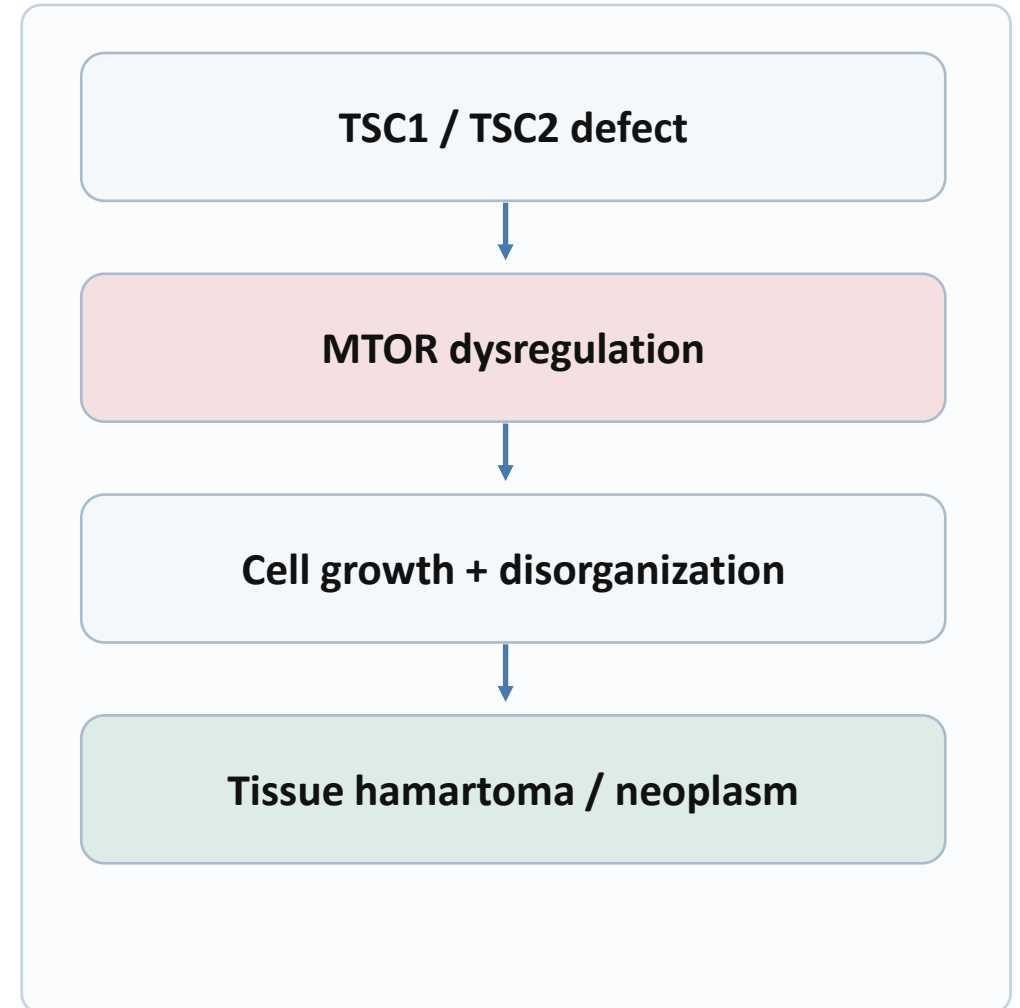
- MTOR participates in the control of cellular size.
- Large cells with abundant cytoplasm are characteristic in some TSC lesions.
- The voluminous cytoplasm of SEGA cells illustrates the molecular–morphologic link.



Large nucleus + voluminous cytoplasm

From variant to tissue phenotype

- Genetic alteration affects growth regulation in affected tissues.
- Disturbed cell size, organization and expansion help explain hamartomas.
- The brain expresses this disturbance as disorganized cortical and periventricular lesions.



Organ-system expression is heterogeneous

- CNS: Cortical tubers, subependymal nodules, SEGA.
- Other major sites: Skin, kidney, heart, retina and lung.
- A lesion in one system should trigger consideration of the full phenotype.

CNS

Tuber • SEN • SEGA

Skin

Macules • fibromas

Kidney

AML • cysts

Other

Heart • retina • lung

Three major CNS lesion classes

- Cortical tubers: Cortical hamartomas and frequent epileptogenic substrate.
- Subependymal nodules: Ventricular lining-associated hamartomas.
- SEGA: A benign neoplasm associated with ventricular outflow obstruction.

Cortex

Cortical tuber → Epilepsy

Ventricular wall

Subependymal nodule → Bulging nodules

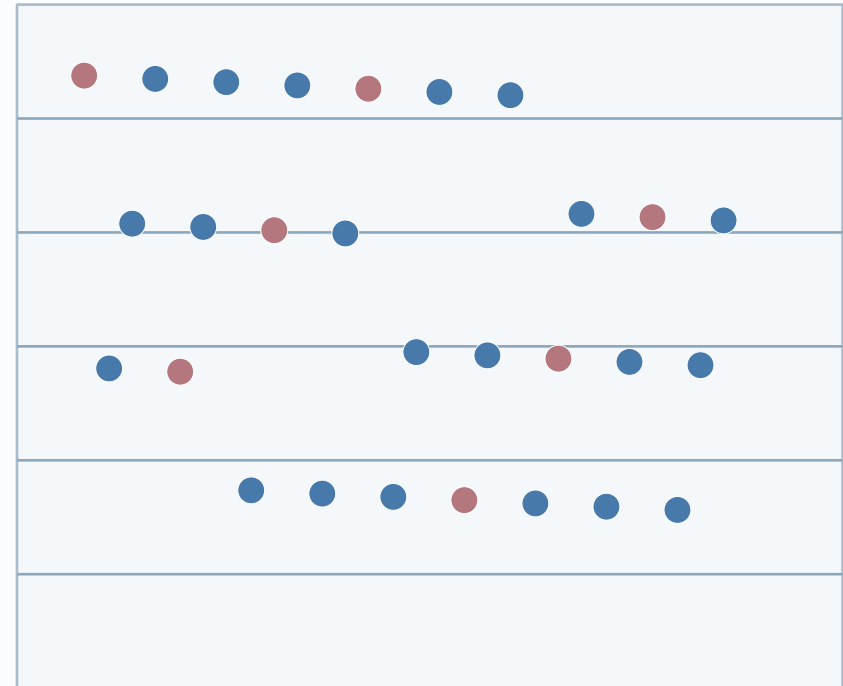
Ventricular growth

SEGA → CSF obstruction

Normal cortical architecture is laminated

- The cerebral cortex has an organized, layered neuronal arrangement.
- Laminar organization provides the reference for recognizing tuber dysplasia.
- TSC tubers lose the usual orderly pattern of cortical neurons.

Normal layered cortex



Cortical tuber: Disorganized cortex

- Neurons within tubers are haphazardly distributed.
- The usual cortical laminar organization is lost.
- Dysplastic cells may display mixed neuronal and astroglial morphology.

Cortical tuber (schematic)

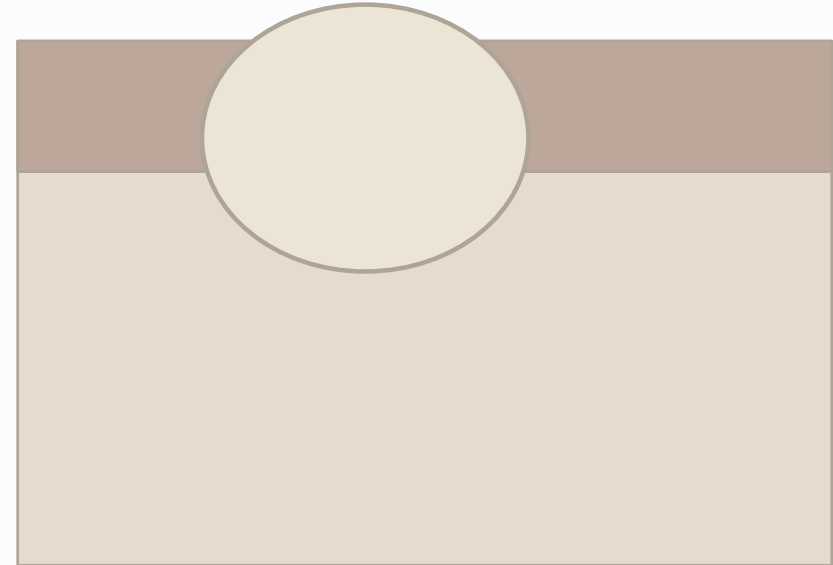


Disordered neurons / enlarged dysplastic cells

Gross pathology of a cortical tuber

- Tubers appear relatively firm compared with adjacent softer cortex.
- The name “tuber” reflects a potato-like firmness and appearance.
- The lesion represents a localized abnormality of cortical tissue organization.

Cortex in cross-section (schematic)



Firm tuber interrupts cortex

Neuronal elements within tubers

- Disordered neuronal arrangement is a defining microscopic feature.
- Abnormally enlarged neurons can occur among mixed dysplastic cell populations.
- The diagnostic context is cortical architectural disorganization, not a single isolated cell.

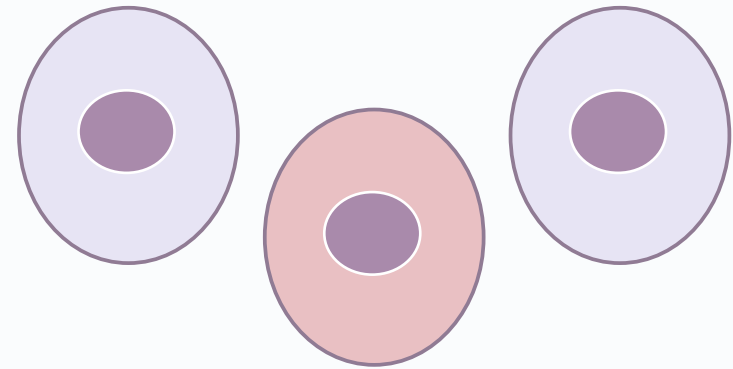
Cortical tuber (schematic)



Disordered neurons / enlarged dysplastic cells

Dysplastic cells cross morphologic categories

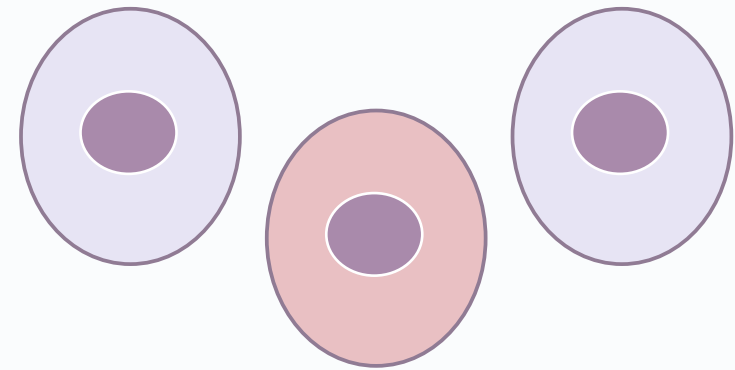
- Some cells look intermediate between neurons and astrocytes.
- Large vesicular nuclei with nucleoli resemble neuronal nuclei.
- Abundant eosinophilic cytoplasm resembles gemistocytic astrocytes.



Large nucleus + voluminous cytoplasm

Mixed neuronal–glial immunophenotype

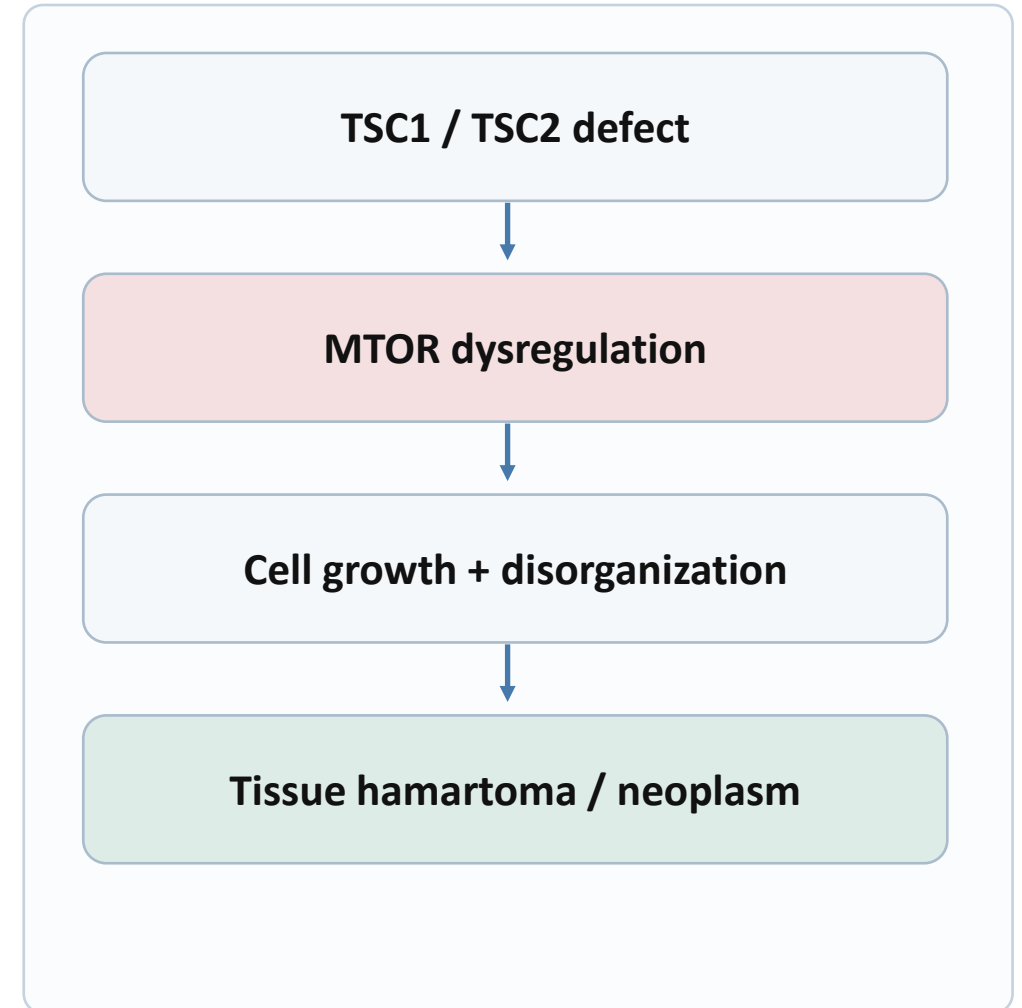
- Dysplastic tuber cells may express neurofilament proteins.
- Expression of GFAP can coexist in the same abnormal population.
- Dual lineage-associated staining supports mixed differentiation; Interpret with morphology.



GFAP + neurofilament expression

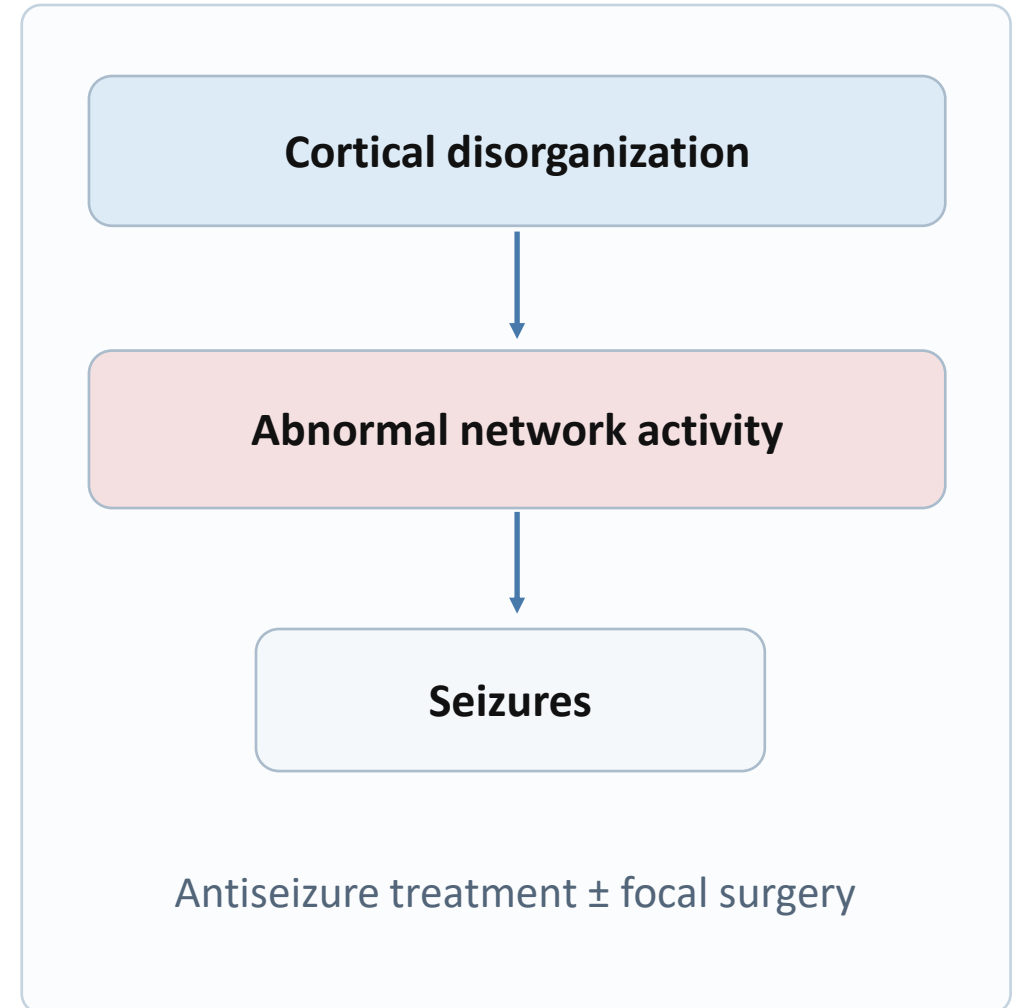
Molecular mechanism and cell morphology align

- Increased mTOR activity contributes to cell enlargement.
- Ballooned, cytoplasm-rich cells are a conspicuous pathologic correlate.
- Architecture and cellular composition together identify cortical hamartomas.



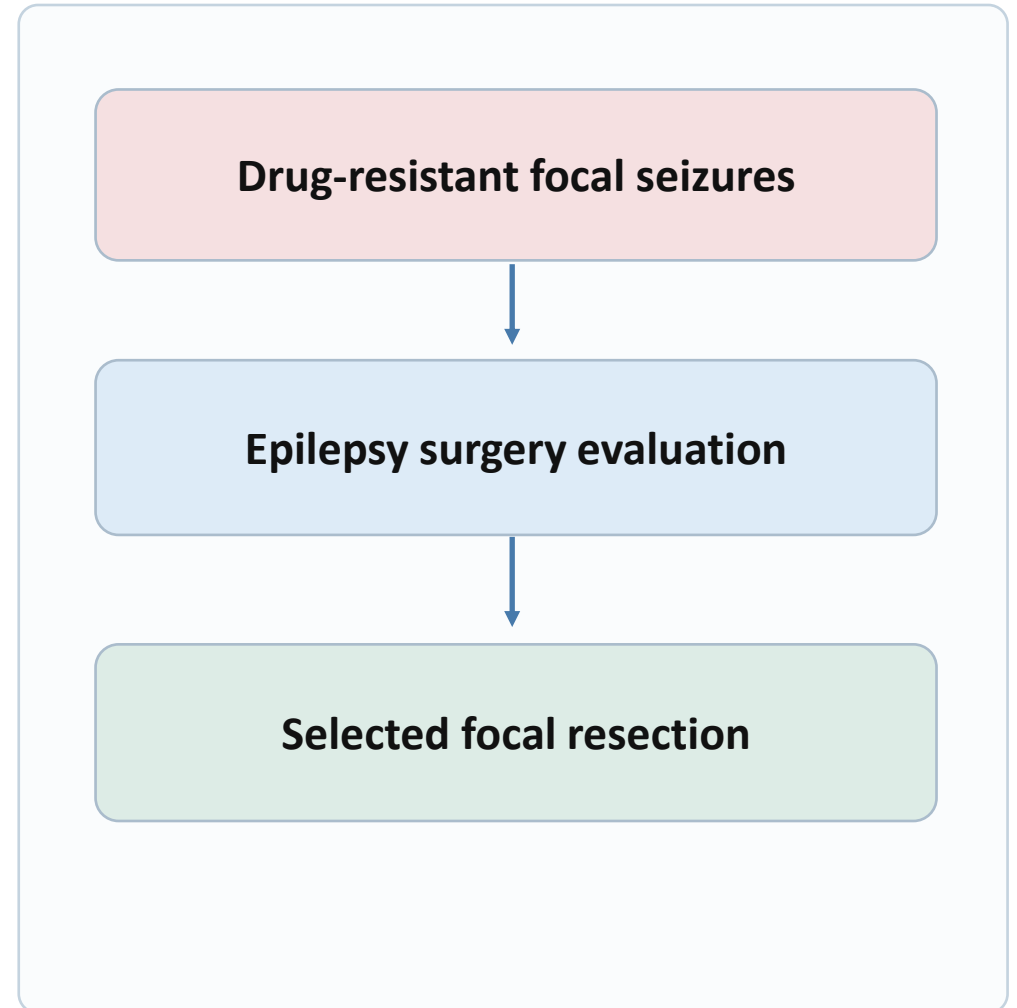
Cortical tubers can generate seizures

- Cortical tubers are often epileptogenic.
- Abnormal local cortical organization plausibly disrupts network function.
- Seizures may persist despite antiseizure medication.



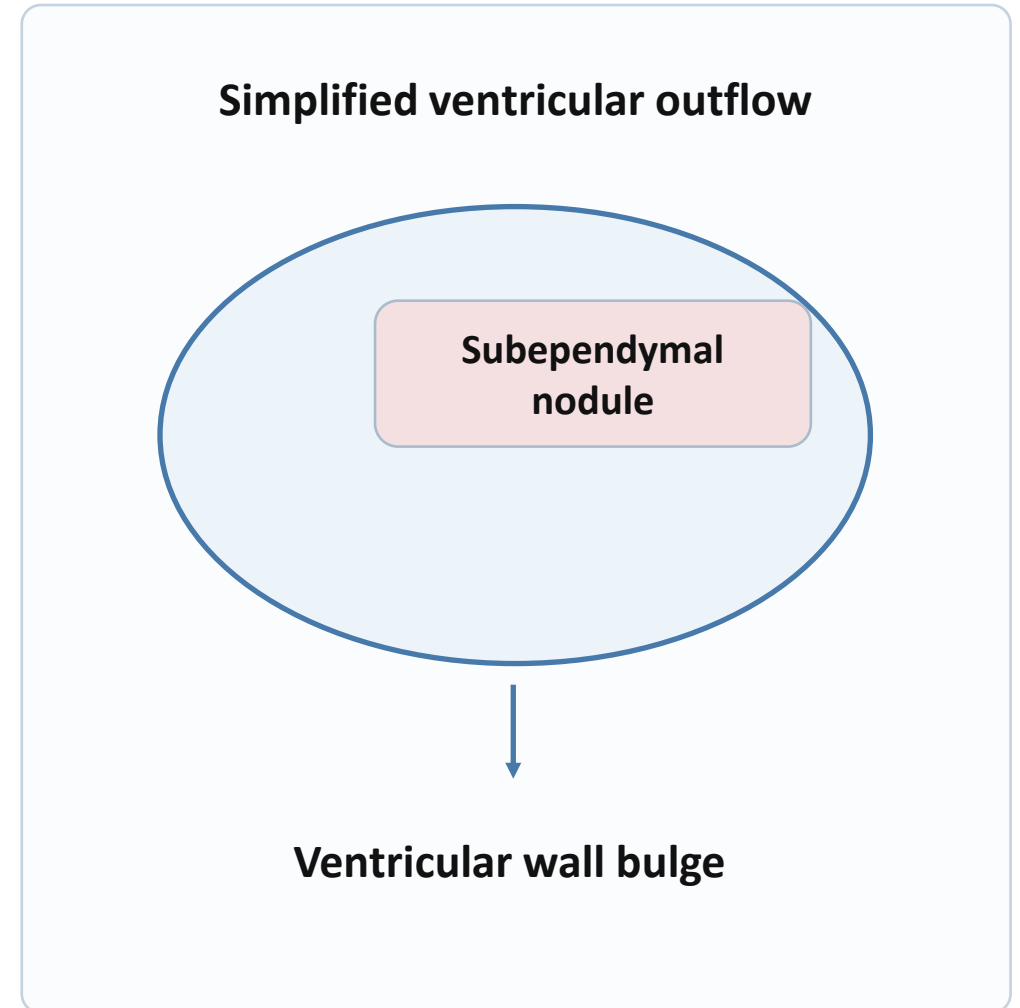
When surgery enters epilepsy care

- Medical treatment is the initial approach for many patients.
- Focal resection can be beneficial in appropriately selected drug-resistant cases.
- Referral to an experienced epilepsy surgery program is recommended.



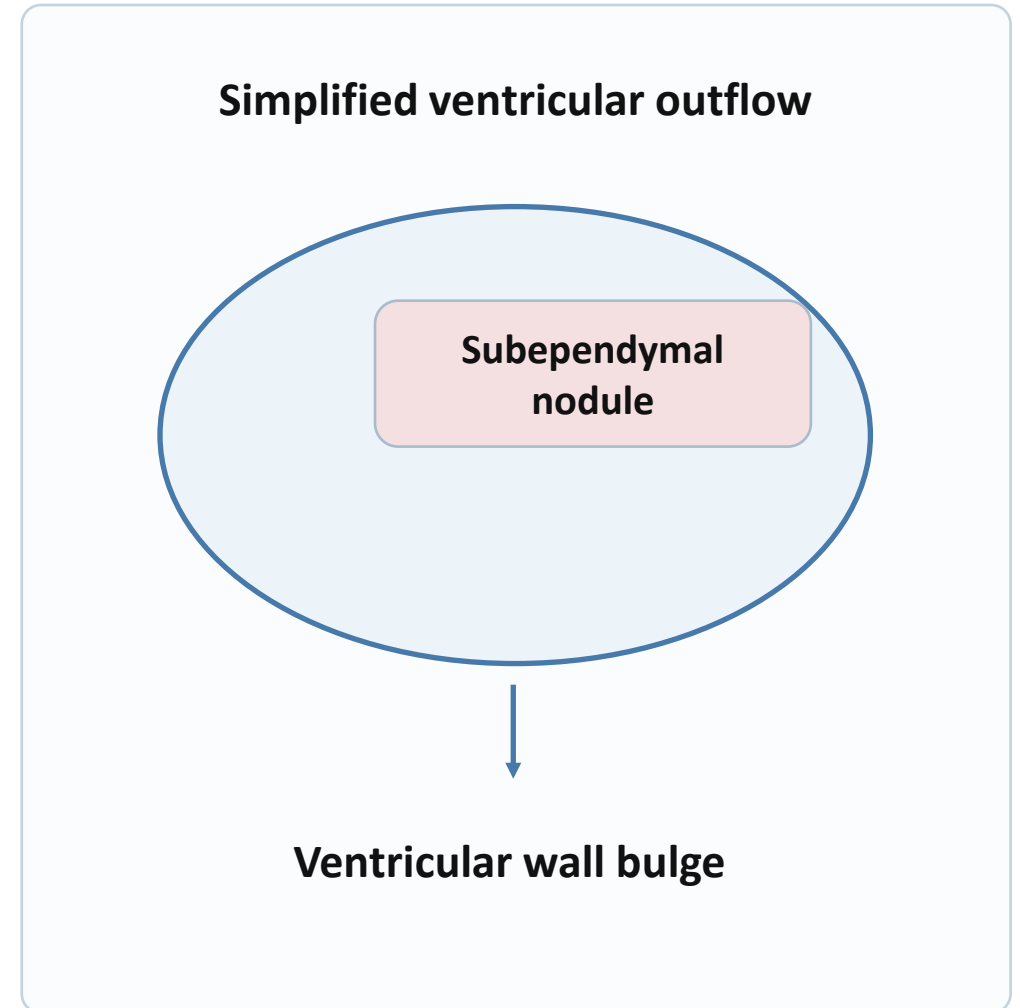
Subependymal nodules: Anatomic location

- Lesions cluster beneath the ventricular ependymal surface.
- They can project into the ventricular lumen.
- Their location contrasts with cortical parenchymal tubers.



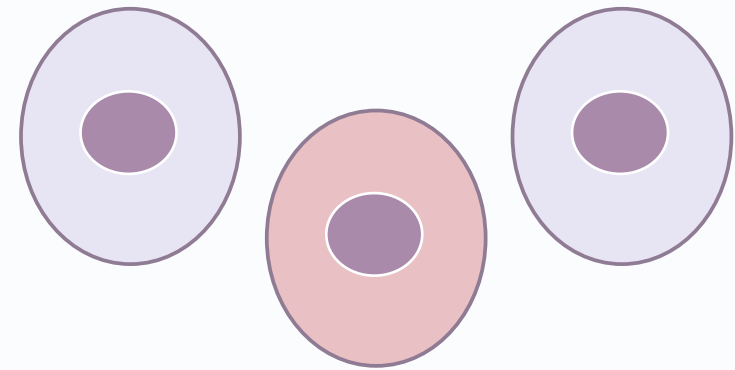
“Candle gutterings”: Gross description

- Small wax-like protrusions can bulge into the ventricular system.
- The appearance historically prompted the phrase “candle gutterings.”
- This describes subependymal nodules, not the cortical tubers.



Subependymal nodule histology

- Hamartomatous tissue contains large astrocyte-like cells.
- These cells are concentrated immediately beneath the ventricular lining.
- Histologic similarities exist between nodules and SEGA.



Large nucleus + voluminous cytoplasm

SEGA is a related but larger neoplasm

- Subependymal giant cell astrocytoma is classified as benign.
- An apparent relationship to hamartomatous nodules.
- Larger size and growth create clinically important mass effects.

Cortex

Cortical tuber → Epilepsy

Ventricular wall

Subependymal nodule → Bulging nodules

Ventricular growth

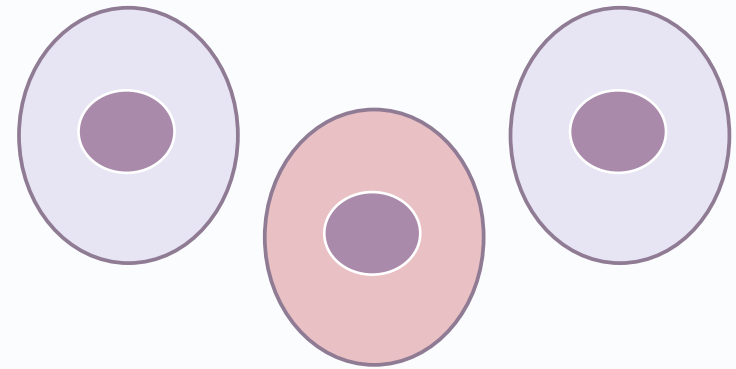
SEGA → CSF obstruction

Subependymal nodules versus SEGA

Feature	Subependymal nodule	SEGA
Nature	Hamartoma	Benign neoplasm
Site	Beneath ependyma	Ventricle-associated
Size / effect	Small protruding nodule	Larger mass; may obstruct CSF
Morphology	Large astrocyte-like cells	Related giant-cell morphology

SEGA histology mirrors the growth defect

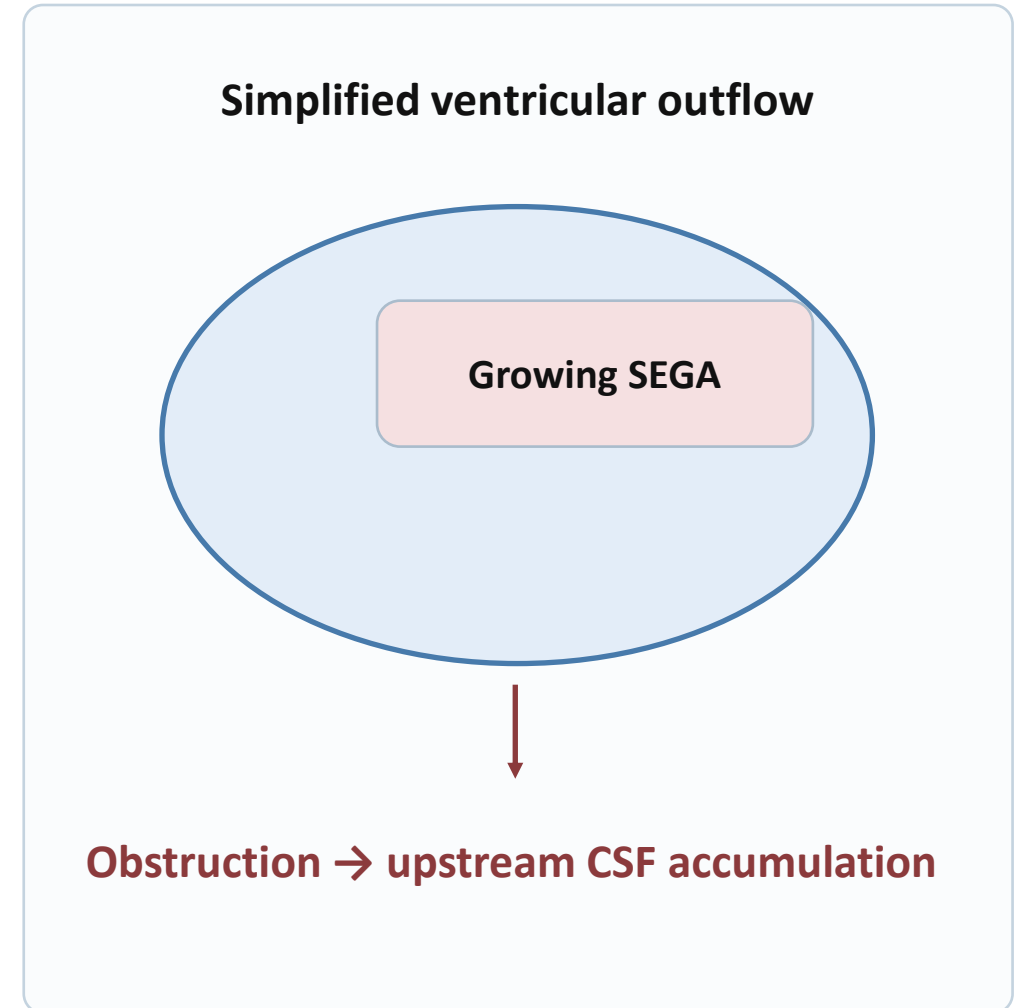
- Prominent giant or astrocyte-like cells with abundant cytoplasm.
- Histologic overlap with subependymal nodules is expected.
- Tumor location and clinical behavior are essential to interpretation.



Large nucleus + voluminous cytoplasm

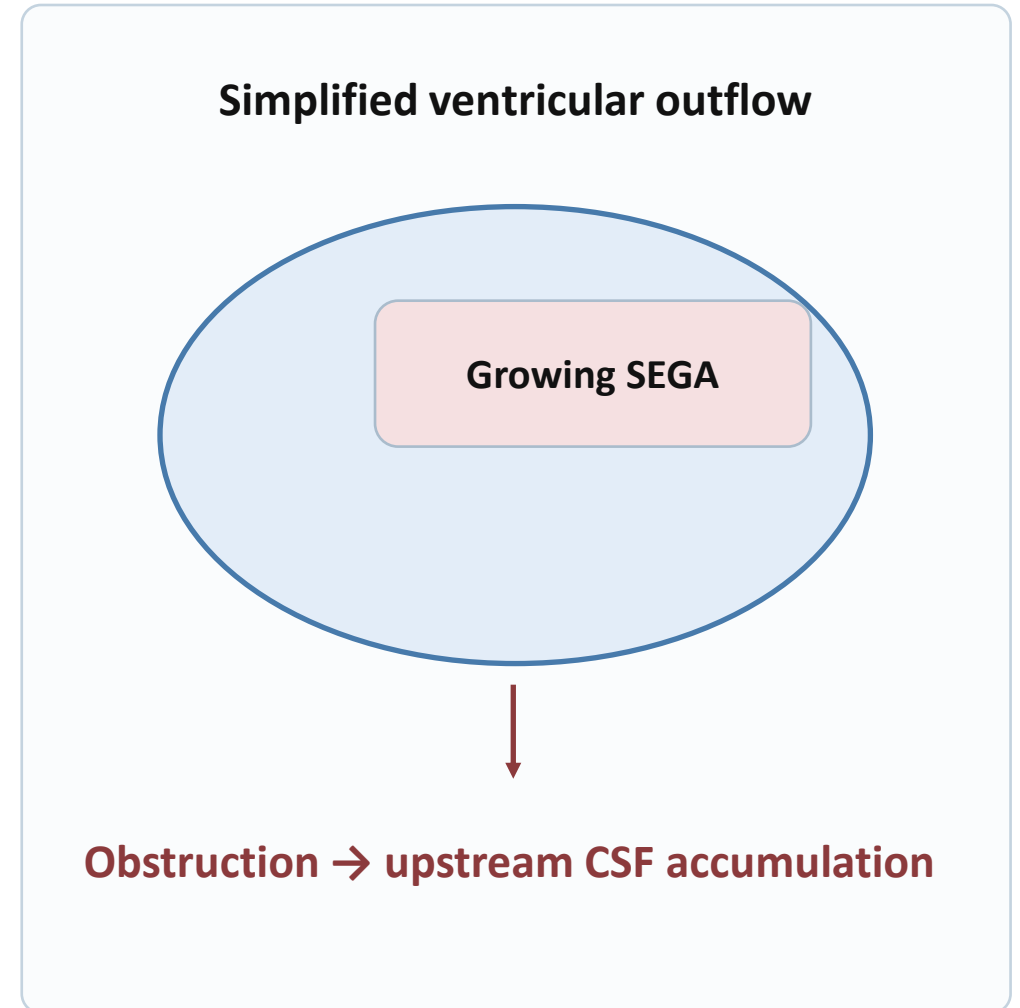
How SEGA produces hydrocephalus

- A growing ventricular-region lesion narrows the CSF passage.
- Blocked CSF outflow produces upstream ventricular enlargement.
- Symptomatic obstruction requires prompt assessment and management.



Clinical consequences of ventricular obstruction

- Headache, vomiting and declining neurologic function warrant urgent evaluation.
- Obstructive hydrocephalus reflects mass effect, not malignant transformation.
- Brain imaging determines the presence and extent of ventricular obstruction.



CNS lesions: A practical localization map

- Cortical parenchyma → tubers and epilepsy.
- Ventricular wall → subependymal nodules.
- Ventricular growth/CSF pathway → SEGA and hydrocephalus.

Cortex

Cortical tuber → Epilepsy

Ventricular wall

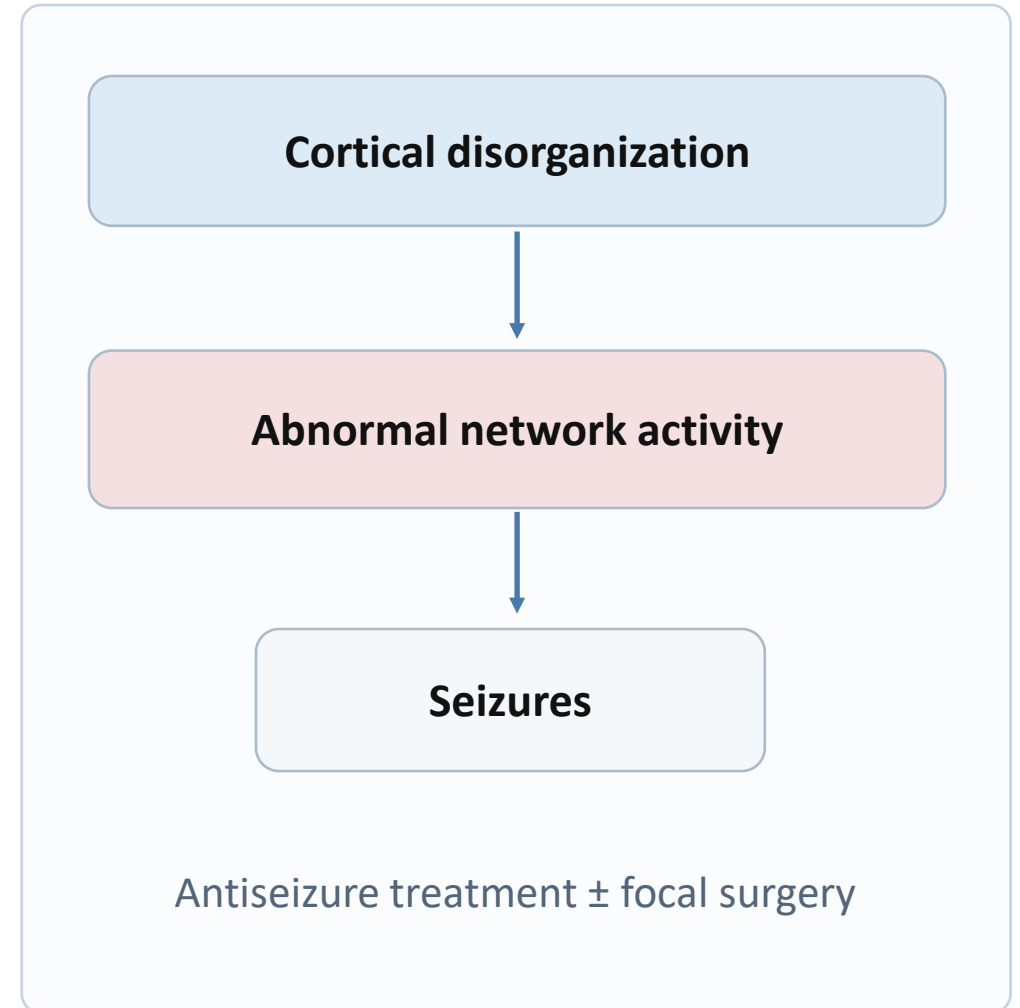
Subependymal nodule → Bulging nodules

Ventricular growth

SEGA → CSF obstruction

Seizures are a major clinical presentation

- Seizures are among the most frequent manifestations listed by Robbins.
- Infantile spasms and focal seizures warrant active recognition in infants with TSC.
- Clinical seizure evaluation should be paired with appropriate EEG assessment.



TSC-associated neuropsychiatric problems

- Autism and intellectual disability.
- The modern TAND framework also covers behavioral, psychiatric, learning and psychosocial domains.
- Symptoms require individual assessment; No single structural lesion predicts the entire profile.

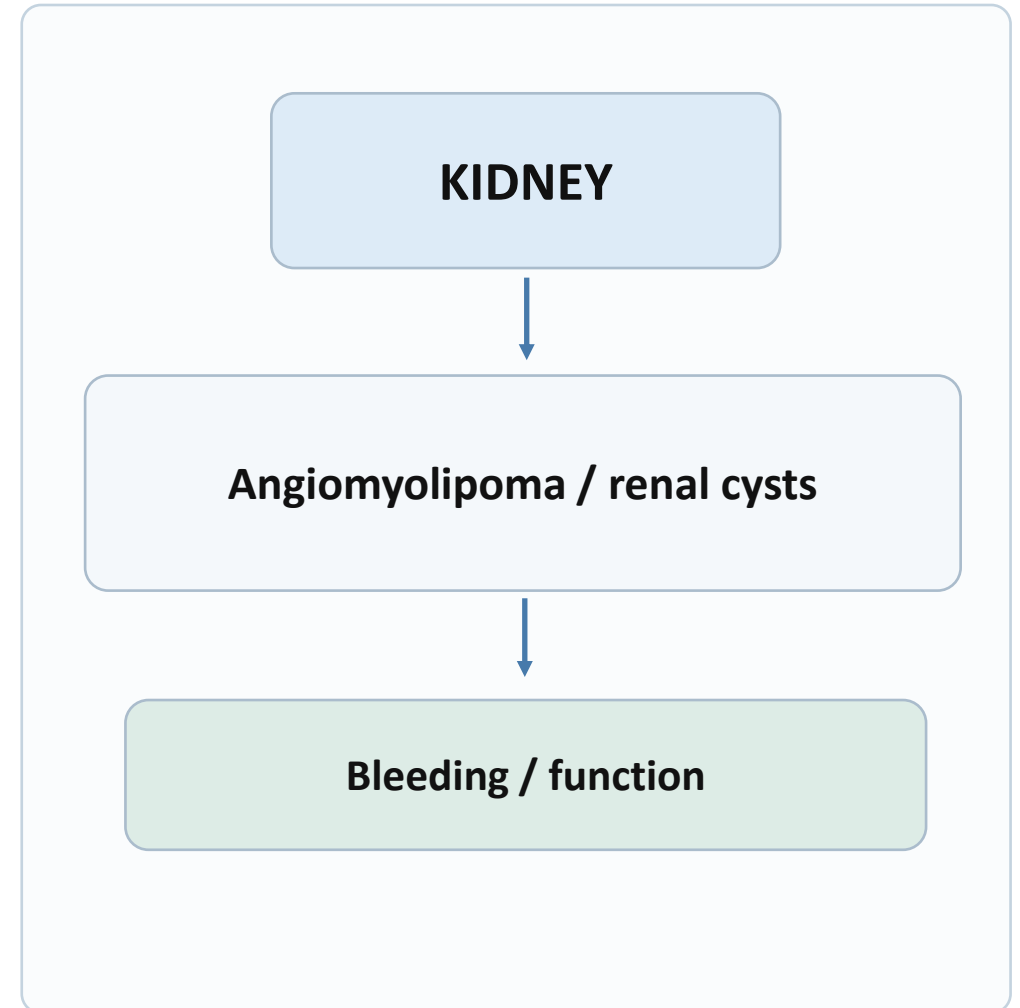
Seizures and cognition

Renal / skin / cardiac signs

Variable timing and severity

Renal angiomyolipomas

- Renal angiomyolipomas are major extracranial benign neoplasms in TSC.
- They can enlarge and become clinically significant through bleeding.
- Longitudinal kidney imaging and renal function assessment are important.



Cystic manifestations

- Cysts may involve kidneys, liver and pancreas.
- Renal cystic disease is monitored alongside angiomyolipomas.
- The presence of cysts broadens the phenotype beyond solid hamartomatous lesions.

CNS

Tuber • SEN • SEGA

Skin

Macules • fibromas

Kidney

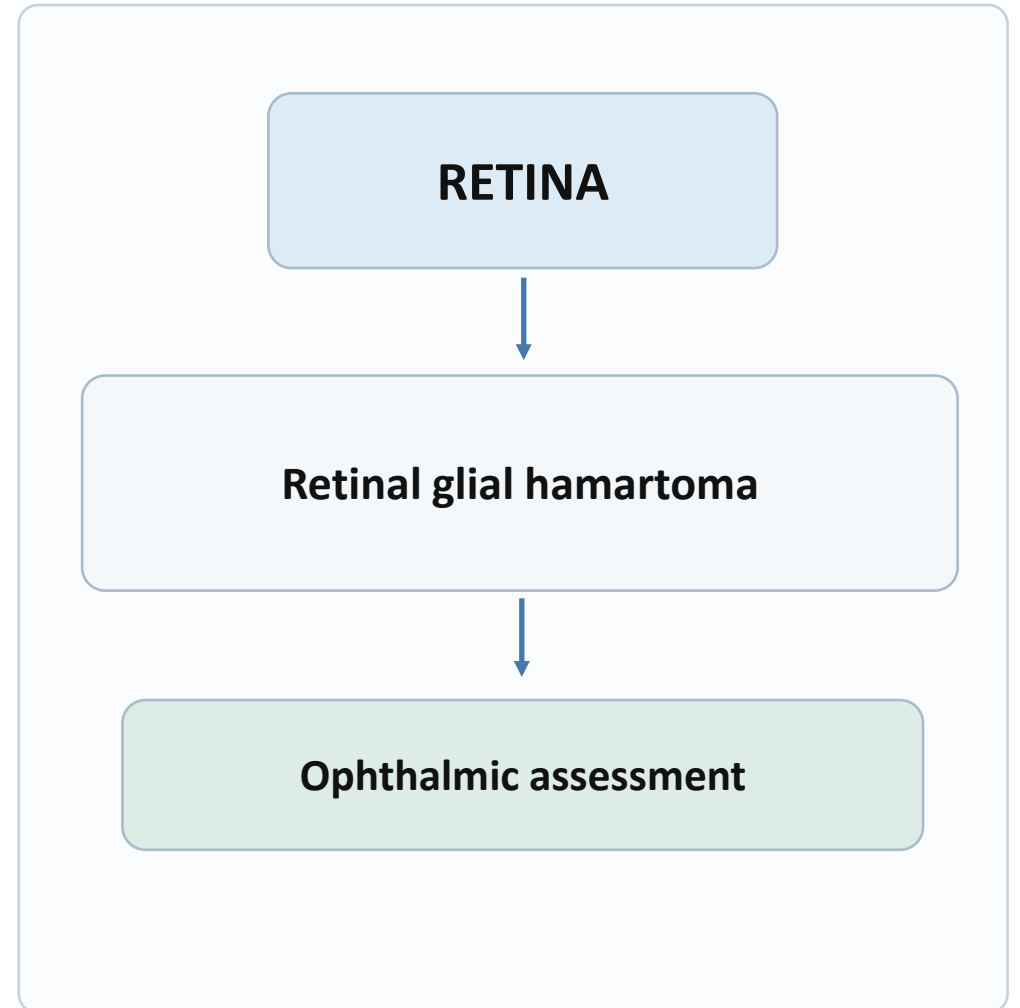
AML • cysts

Other

Heart • retina • lung

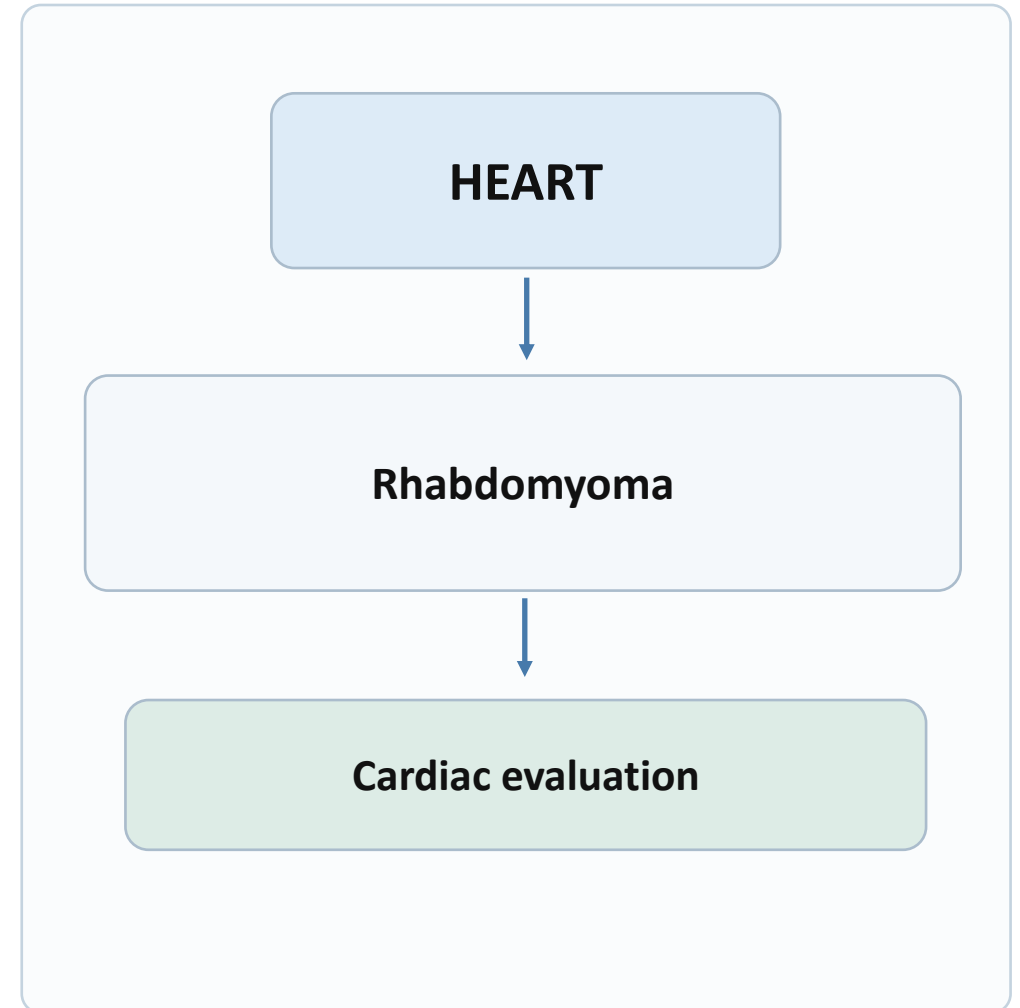
Retinal hamartomas

- Retinal glial or astrocytic hamartomas are a characteristic manifestation.
- Ophthalmologic examination contributes to clinical phenotyping.
- Retinal disease can be asymptomatic or affect vision depending on location.



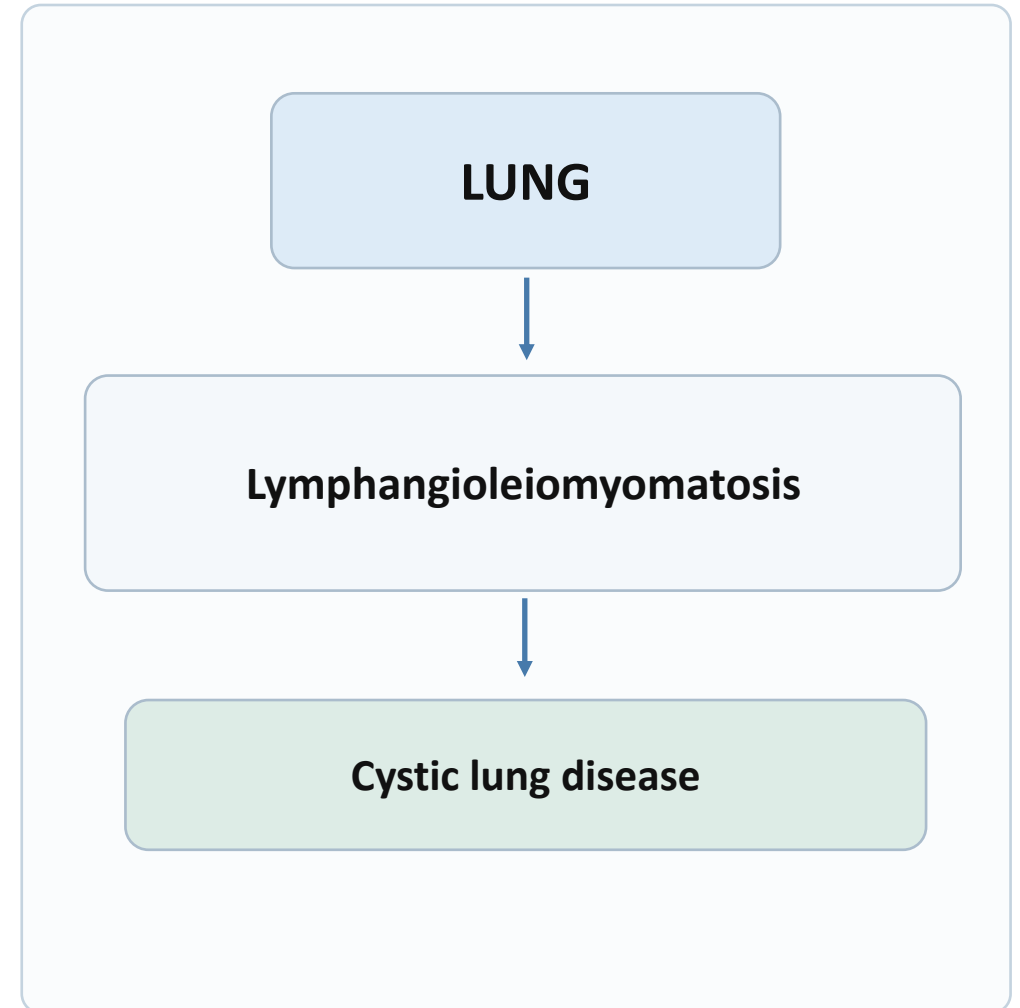
Cardiac rhabdomyomas

- Cardiac rhabdomyomas arise during childhood, sometimes recognized prenatally.
- They can be associated with rhythm or outflow problems when clinically significant.
- Echocardiographic surveillance is used until regression is documented.



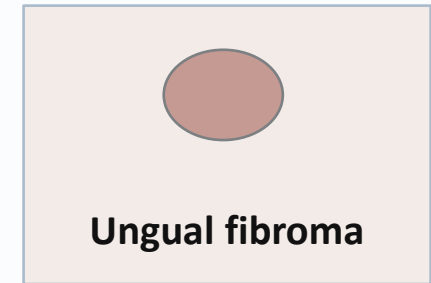
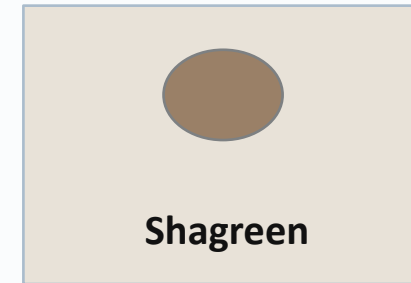
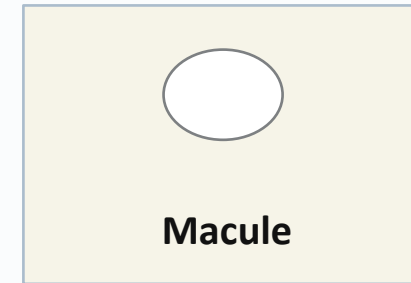
Pulmonary lymphangioleiomyomatosis

- LAM is a pulmonary manifestation of TSC.
- The disease is relevant particularly to adult women.
- Symptoms or CT evidence of cystic lung disease drive pulmonary evaluation.



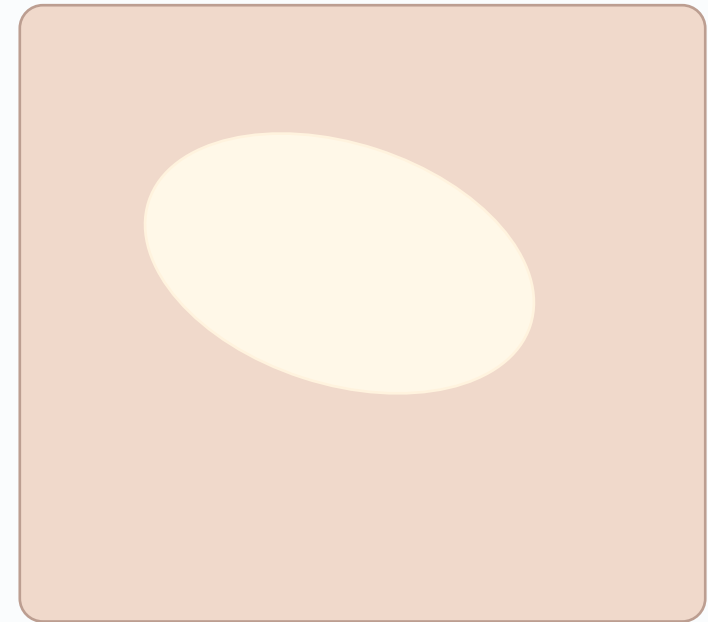
Cutaneous clues are highly informative

- Hypopigmented macules, angiofibromas, shagreen plaques and ungual fibromas.
- Cutaneous inspection is an accessible part of multisystem assessment.
- Several characteristic lesion types are included in formal diagnostic criteria.



Hypomelanotic “ash-leaf” macules

- These are localized hypopigmented skin lesions.
- Under the 2021 criteria, at least three macules ≥ 5 mm constitute a major feature.
- A single hypopigmented macule is not by itself diagnostic.

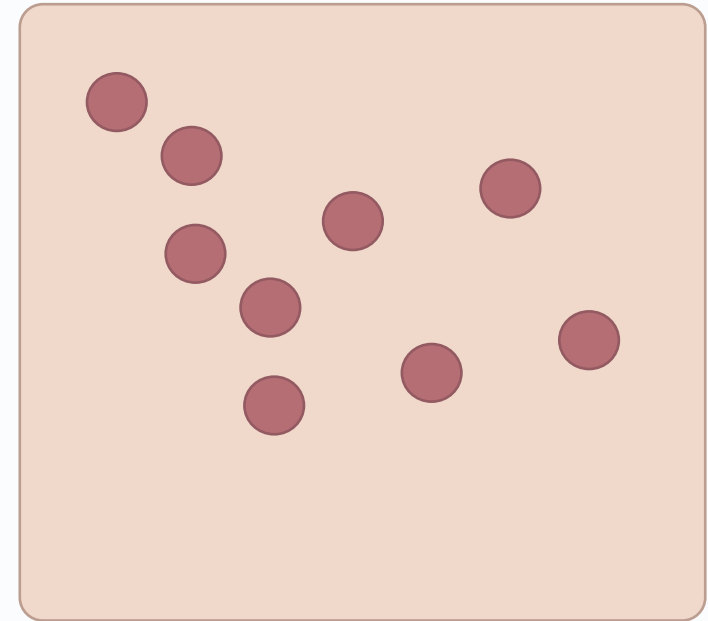


Hypopigmented area

Schematic

Facial angiofibromas

- Characteristic angiofibromas may develop on facial skin.
- The 2021 major criterion is at least three angiofibromas or a fibrous cephalic plaque.
- Their presence supports syndromic recognition, not a molecular diagnosis by itself.

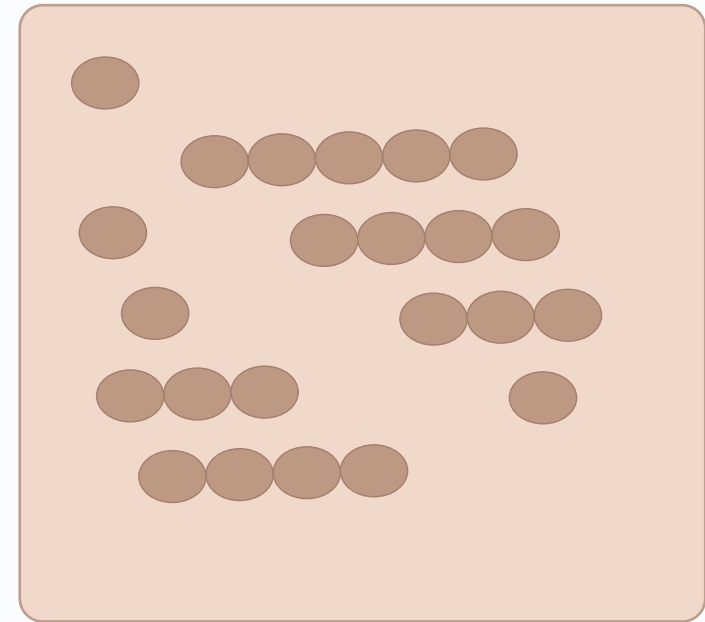


Multiple small facial papules

Schematic

Shagreen patches

- Localized leathery skin thickening.
- A shagreen patch is a major diagnostic feature in the 2021 consensus.
- This finding complements pigmentary and facial lesions.

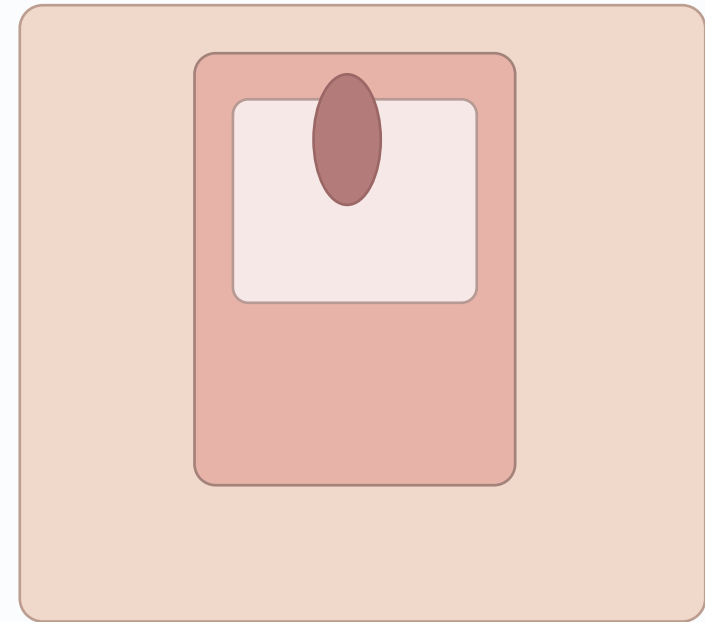


Leathery textured plaque

Schematic

Ungual fibromas

- Fibromas may develop around or beneath nails.
- At least two ungual fibromas constitute a 2021 major criterion.
- Distribution and number matter when applying diagnostic rules.



Periungual fibrous nodule

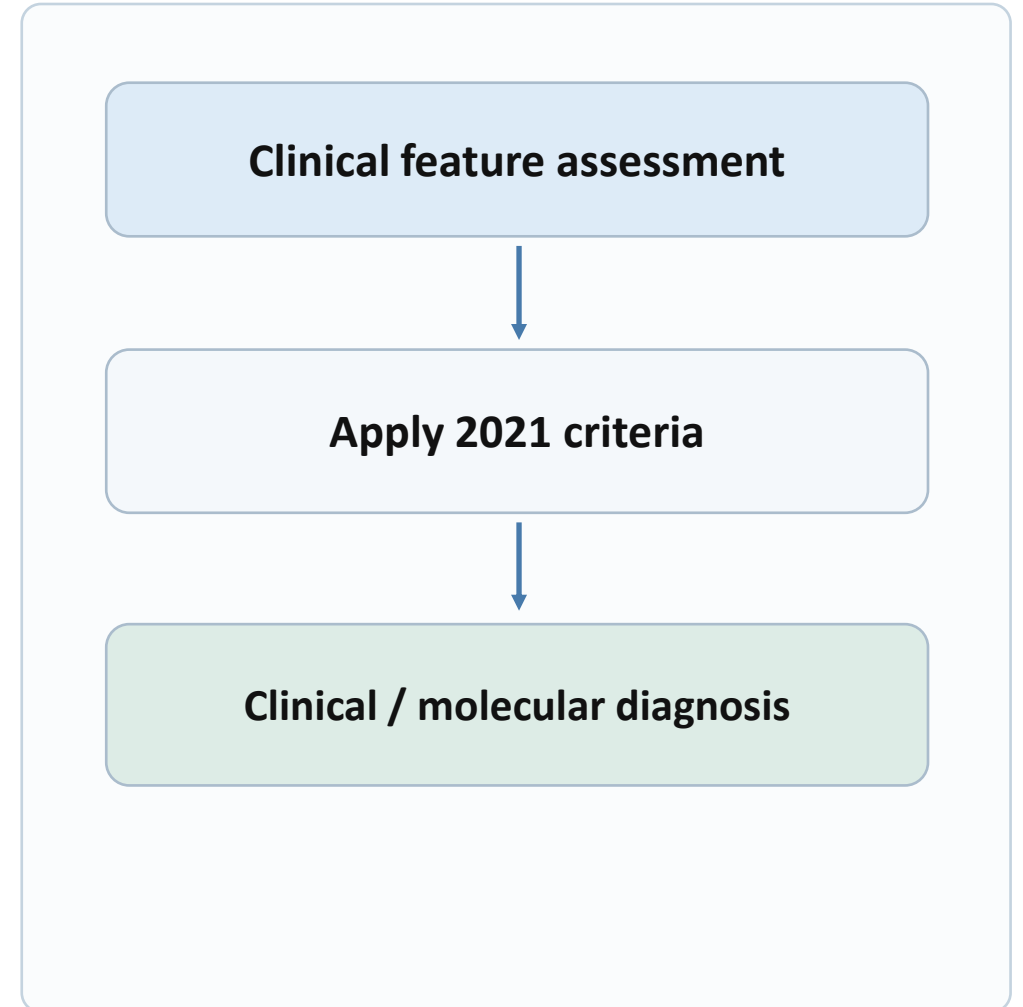
Schematic

Systems and their index lesions

System	Representative finding	Main concern
Brain	Tubers; SEN; SEGA	Seizures; CSF obstruction
Kidney	Angiomyolipoma; cysts	Bleeding; renal health
Heart	Rhabdomyoma	Cardiac effects
Lung	LAM	Cystic lung disease
Skin / eye	Distinctive lesions	Recognition / vision

Two complementary diagnostic routes

- Clinical diagnosis is based on combinations of major and minor features.
- Molecular diagnosis follows identification of a pathogenic TSC1 or TSC2 variant.
- The diagnostic rules shown here use the 2021 international consensus.



Major criteria: Skin and oral-region findings

- ≥ 3 hypomelanotic macules, each ≥ 5 mm.
- ≥ 3 angiofibromas or a fibrous cephalic plaque.
- ≥ 2 ungual fibromas; Shagreen patch.

Count the features correctly

Major versus minor distinction

Apply clinical diagnostic rule

Major criteria: CNS findings

- Multiple cortical tubers and/or radial migration lines.
- At least two subependymal nodules.
- Subependymal giant cell astrocytoma.

Count the features correctly

Major versus minor distinction

Apply clinical diagnostic rule

Major criteria: Other organ findings

- Multiple retinal hamartomas or cardiac rhabdomyoma.
- Pulmonary lymphangioleiomyomatosis.
- At least two renal angiomyolipomas.

Count the features correctly

Major versus minor distinction

Apply clinical diagnostic rule

Minor diagnostic criteria

- Confetti skin lesions or a retinal achromic patch.
- Dental enamel pits (≥ 3) or intraoral fibromas (≥ 2).
- Multiple renal cysts, nonrenal hamartomas or sclerotic bone lesions.

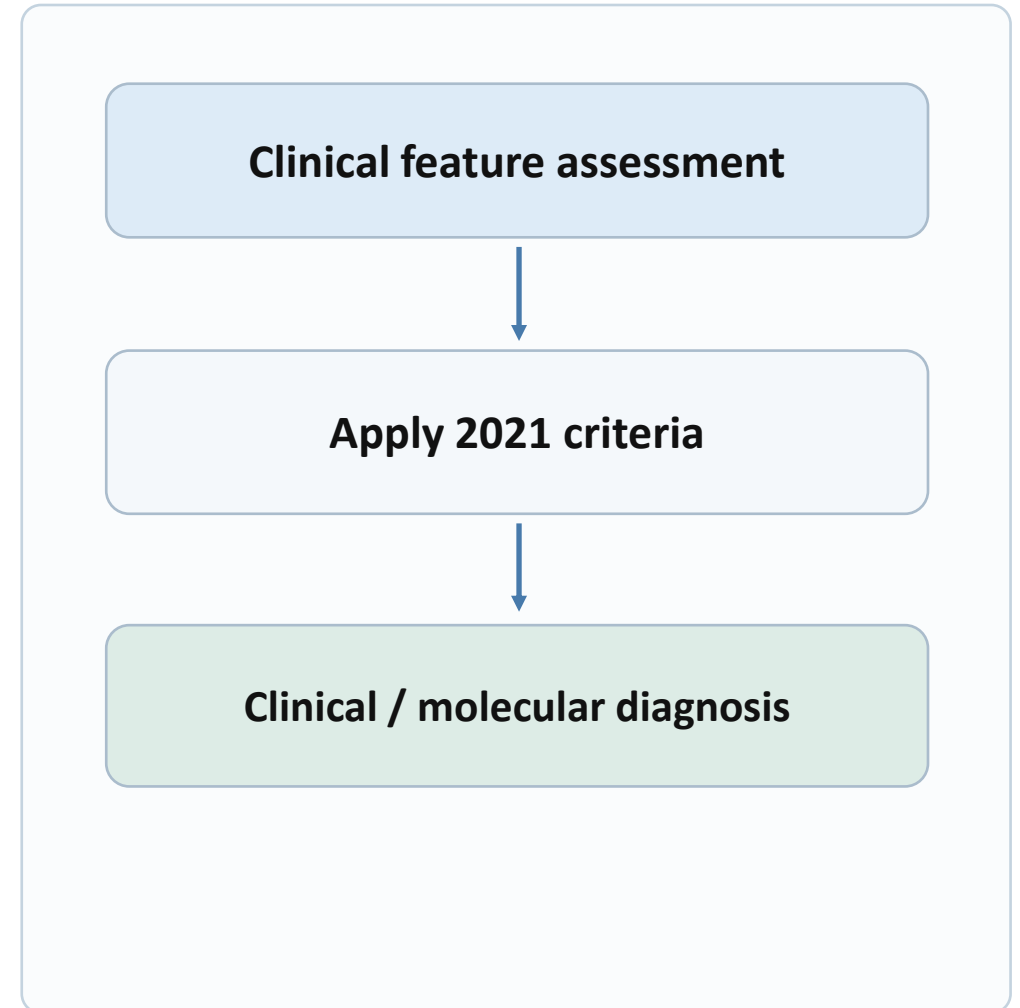
Count the features correctly

Major versus minor distinction

Apply clinical diagnostic rule

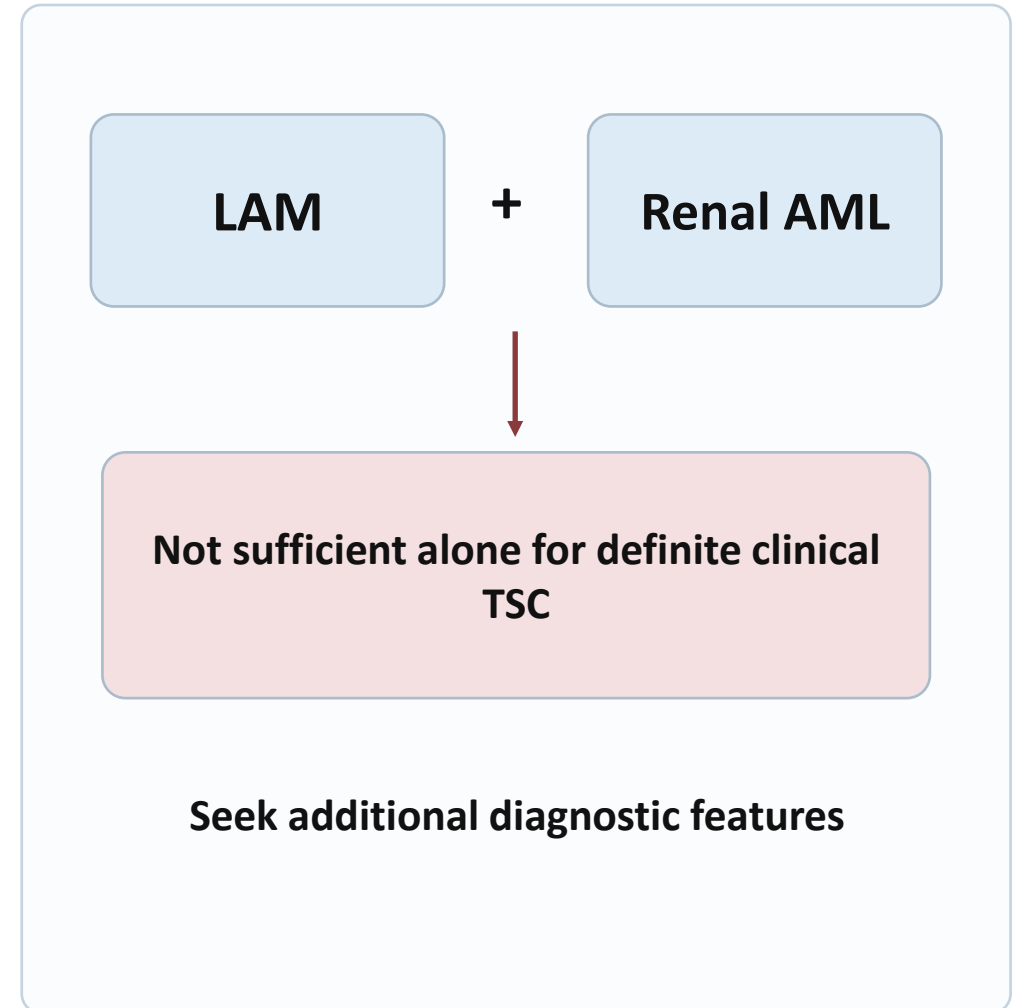
Definite versus possible clinical TSC

- Definite: Two major features, or one major plus two minor features.
- Possible: One major feature, or at least two minor features.
- Apply the specific exception for LAM plus angiomyolipomas.



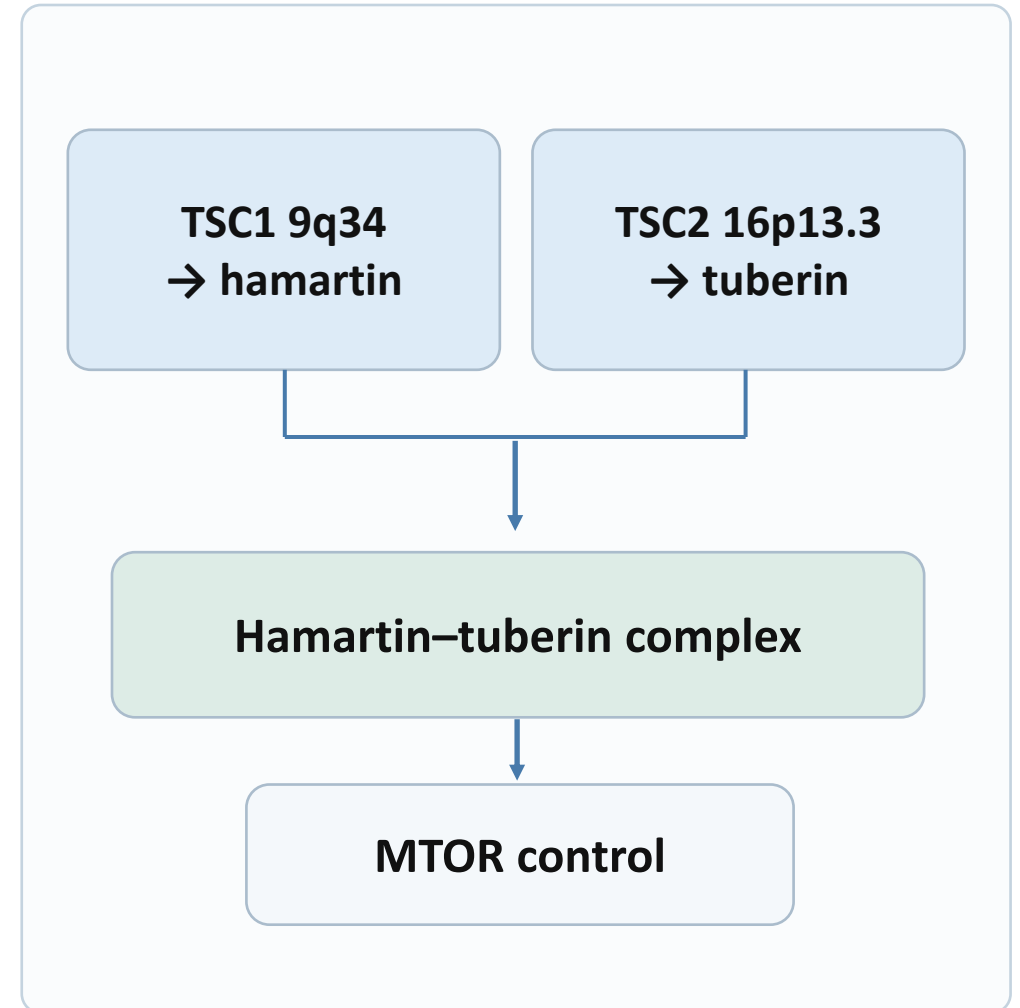
Important LAM + angiomyolipoma exception

- LAM and renal angiomyolipomas can occur together without other TSC findings.
- Those two major features alone do not establish definite clinical TSC.
- Additional features or molecular evidence are needed for definitive classification.



Interpreting TSC1/TSC2 genetic testing

- Pathogenic or likely pathogenic variants can establish molecular TSC.
- A variant of uncertain significance does not confirm or exclude TSC.
- If suspicion persists after negative routine testing, consider mosaicism in specialist evaluation.



Clinical workup: Assemble organ evidence

- Complete skin, dental and retinal examinations.
- Brain MRI for cortical and subependymal manifestations.
- Renal, cardiac and pulmonary assessment tailored to age and clinical context.

CNS

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Kidney

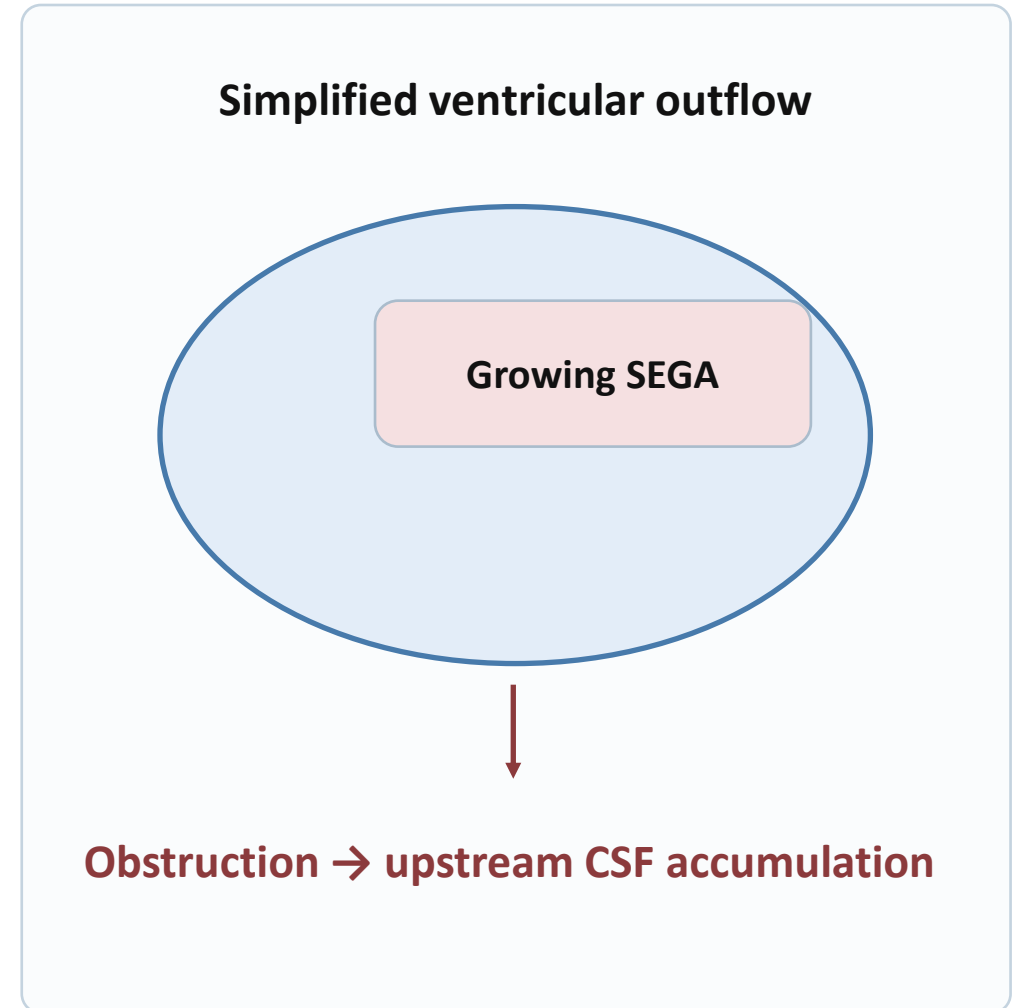
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Other

Heart • retina • lung

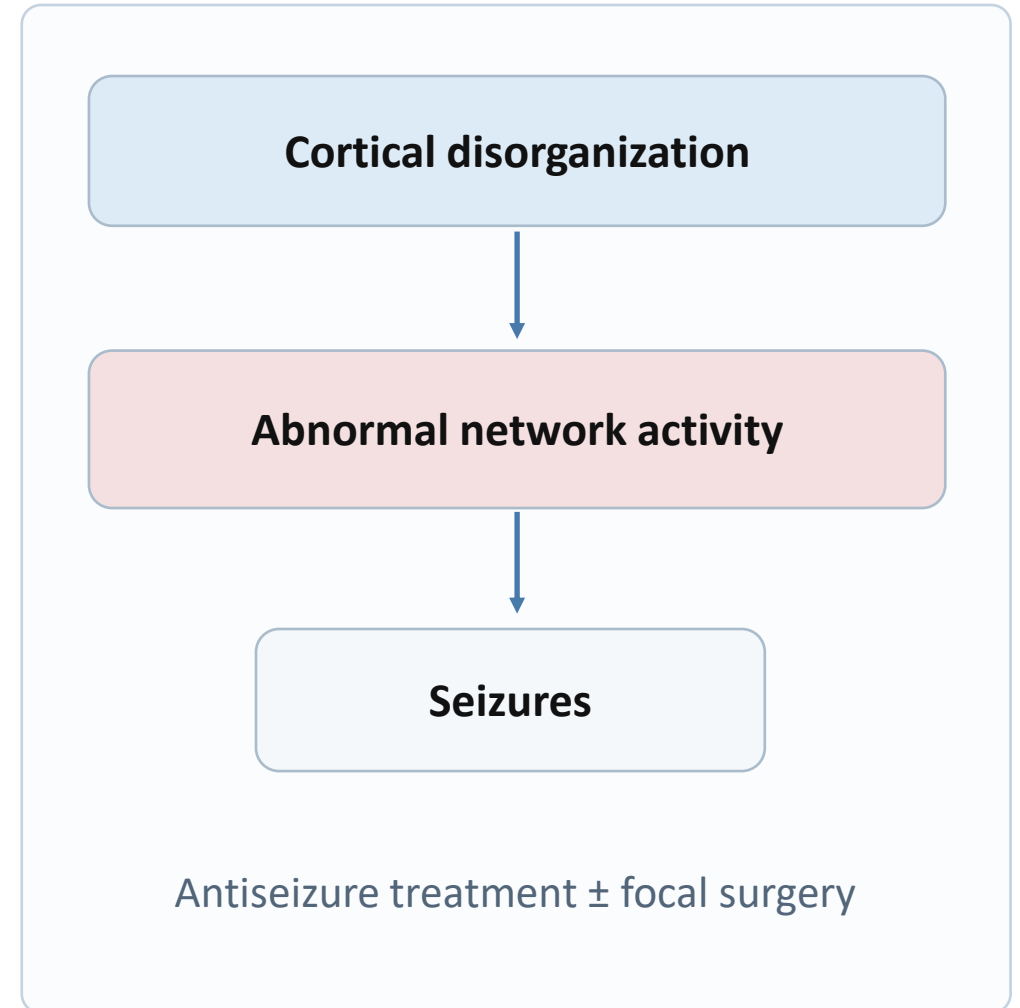
Neurologic surveillance follows SEGA risk

- Consensus recommends brain MRI every 1–3 years in asymptomatic patients younger than 25 years.
- Growing or symptomatic SEGA warrants more frequent evaluation.
- Surveillance seeks ventricular obstruction before acute deterioration.



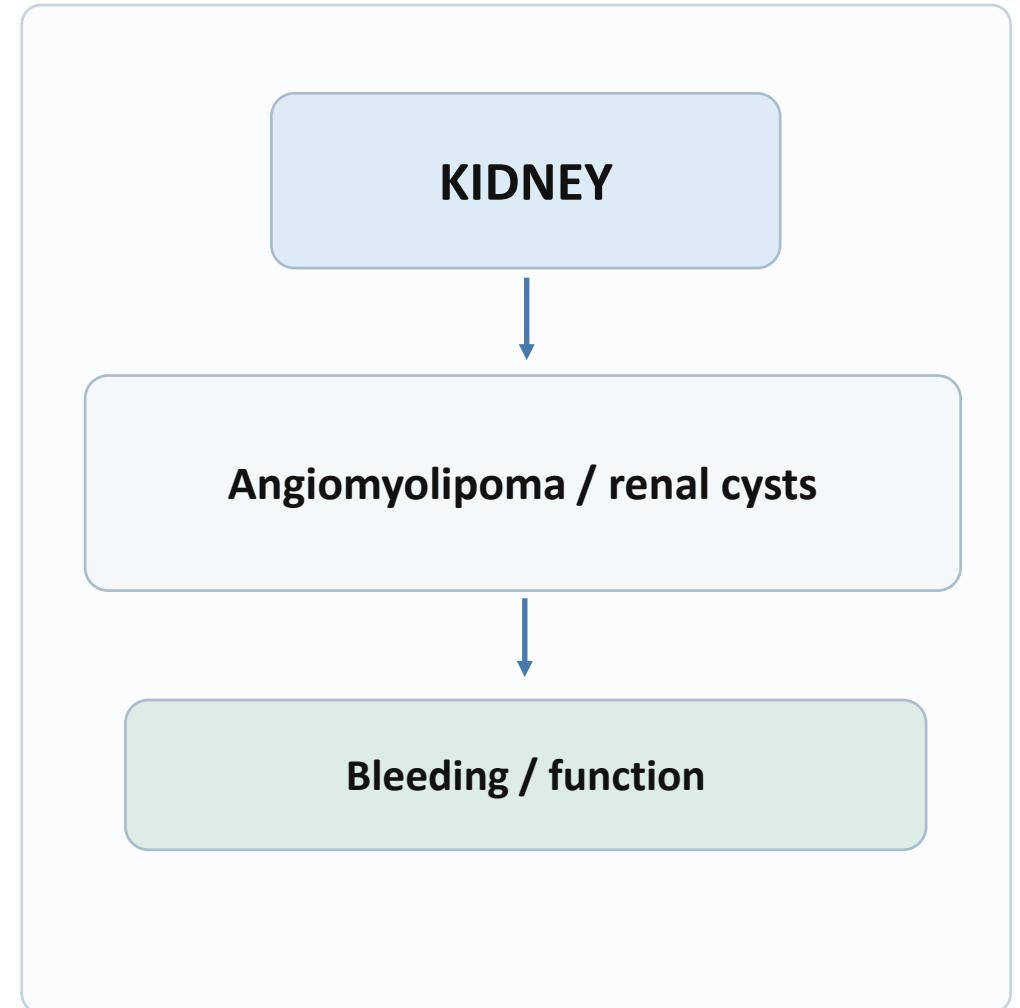
Epilepsy assessment begins early

- Teach families to recognize infantile spasms and focal seizures.
- Infant EEG surveillance and prompt evaluation are emphasized by consensus.
- Vigabatrin is first-line therapy for TSC-associated infantile spasms.



Renal surveillance is lifelong

- Abdominal MRI is recommended every 1–3 years for angiomyolipoma and cystic disease.
- Assess blood pressure and renal function at least annually.
- Acute angiomyolipoma hemorrhage requires an urgent kidney-sparing management strategy.



Other organ surveillance is targeted

- Cardiac rhabdomyomas: Childhood echocardiography until regression.
- Retinal lesions: Periodic specialist ophthalmic evaluation.
- LAM: Adult respiratory assessment and lung imaging according to sex, symptoms and findings.

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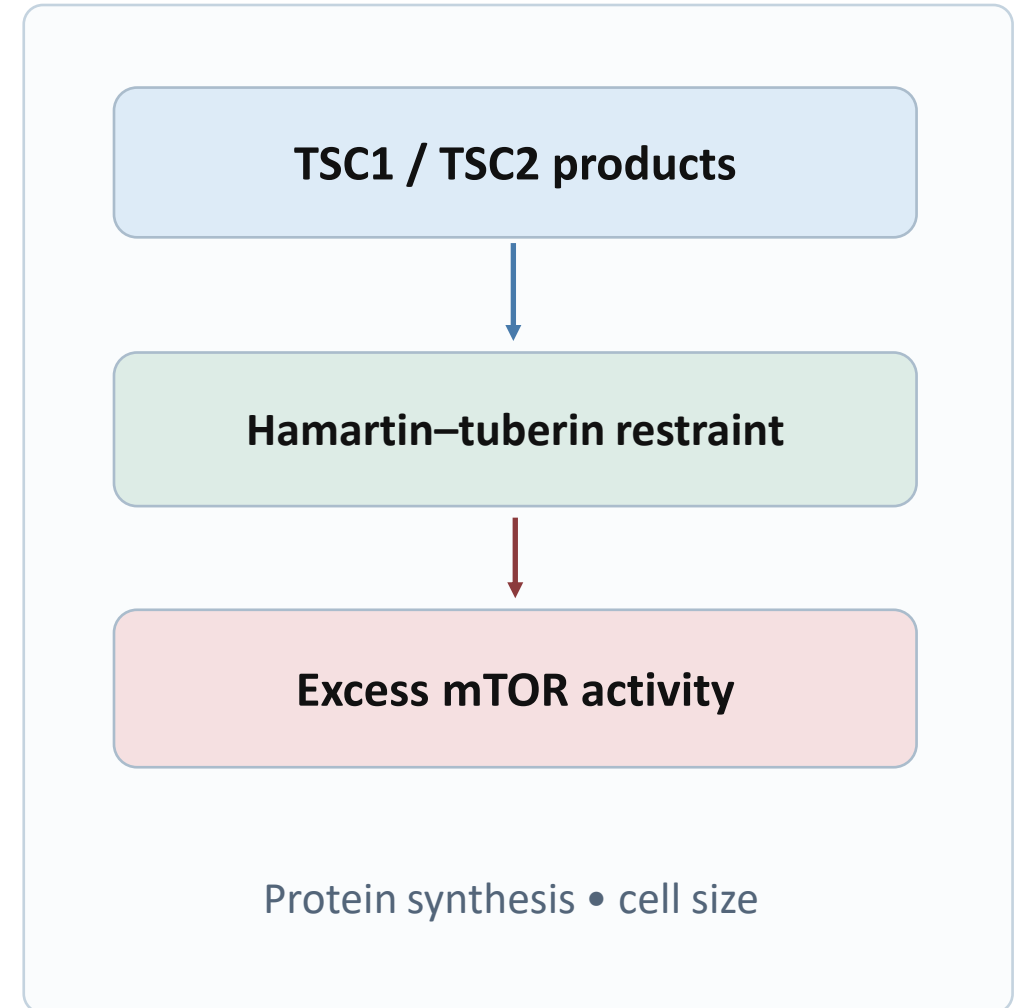
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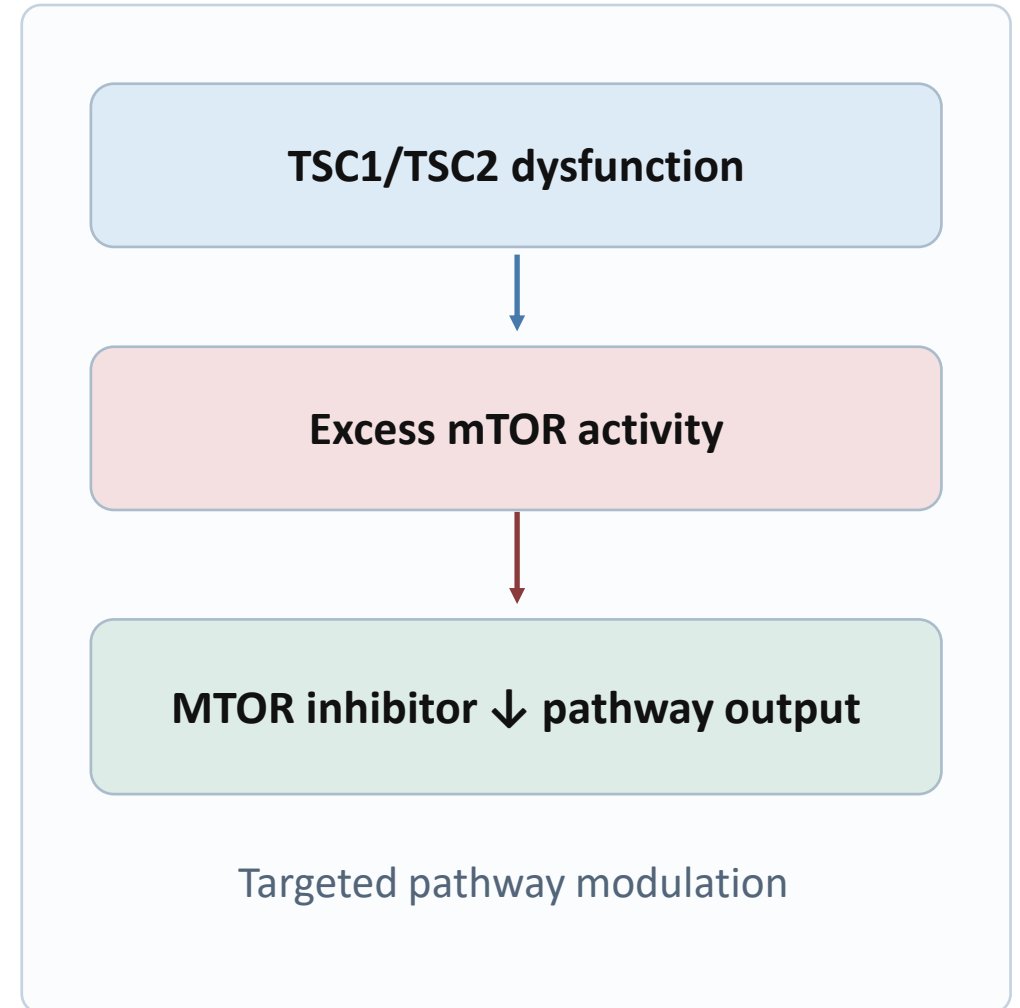
Management integrates symptoms and mechanism

- Antiseizure therapy addresses an important functional consequence.
- Surgery may treat drug-resistant seizures or obstructive SEGA.
- MTOR inhibitors target a growth-signaling mechanism shared across TSC lesions.



Why mTOR inhibitors are mechanistically rational

- The underlying TSC1/TSC2 defect removes restraint on mTOR signaling.
- Pharmacologic mTOR inhibition can reduce excessive anabolic drive.
- Therapeutic responses are lesion- and context-dependent, not a reversal of genotype.



SEGA treatment depends on clinical behavior

- Acutely symptomatic obstruction calls for urgent neurosurgical evaluation.
- For growing, otherwise asymptomatic SEGA, surgery or mTOR inhibition may be considered.
- Treatment planning balances lesion size, location, risks and follow-up feasibility.

SEGA: Assess growth and symptoms



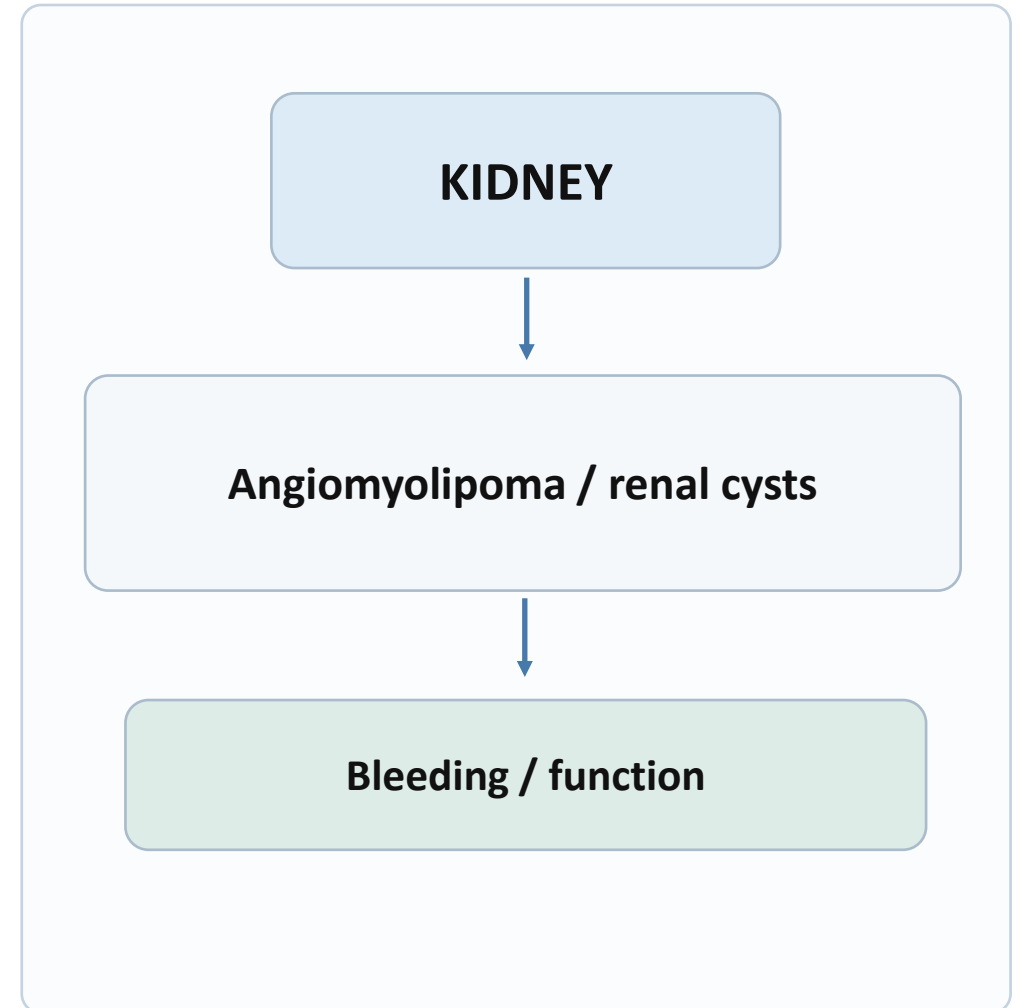
Acutely symptomatic obstruction

Urgent surgical assessment

**Growing asymptomatic SEGA: Surgery or
mTOR inhibitor**

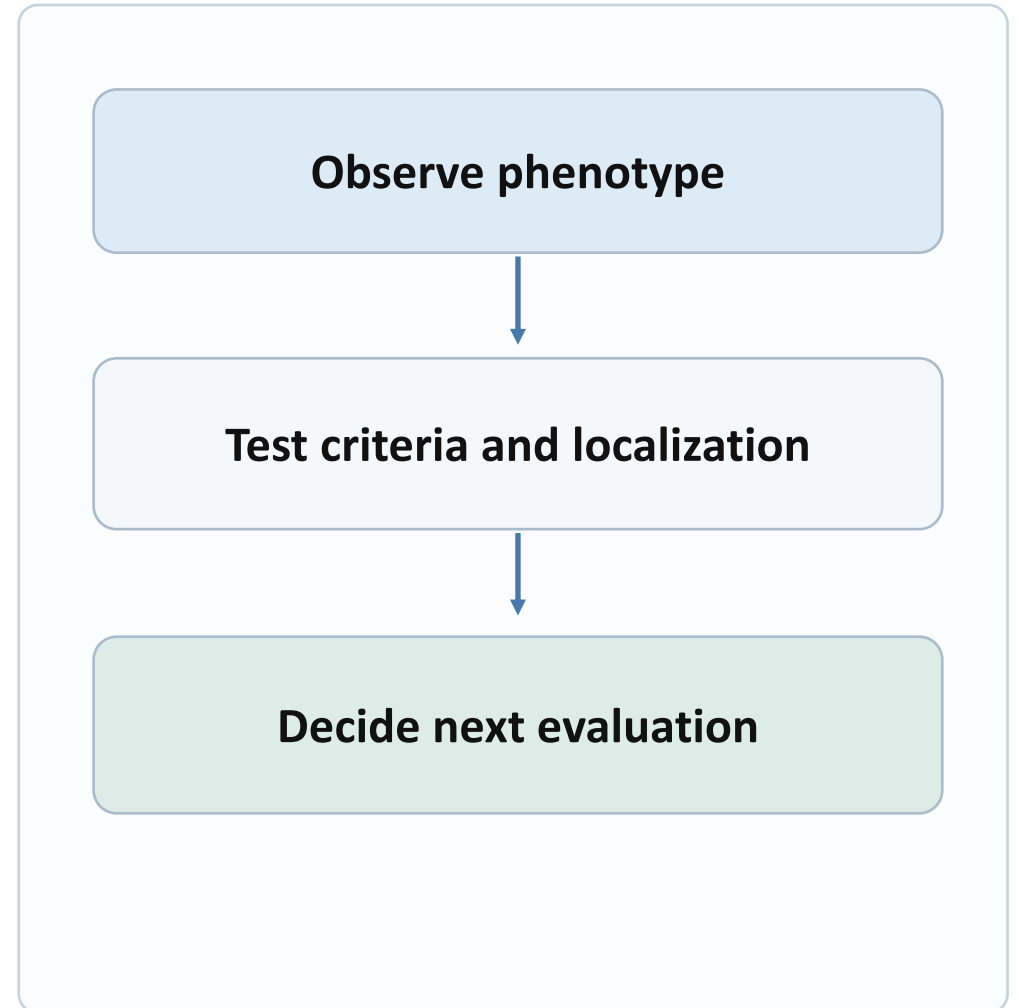
Renal lesion treatment: Protect kidney function

- Growing asymptomatic angiomyolipomas may be treated with mTOR inhibition.
- Acute hemorrhage is generally managed with selective embolization.
- Avoid routine nephrectomy when kidney-sparing approaches are feasible.



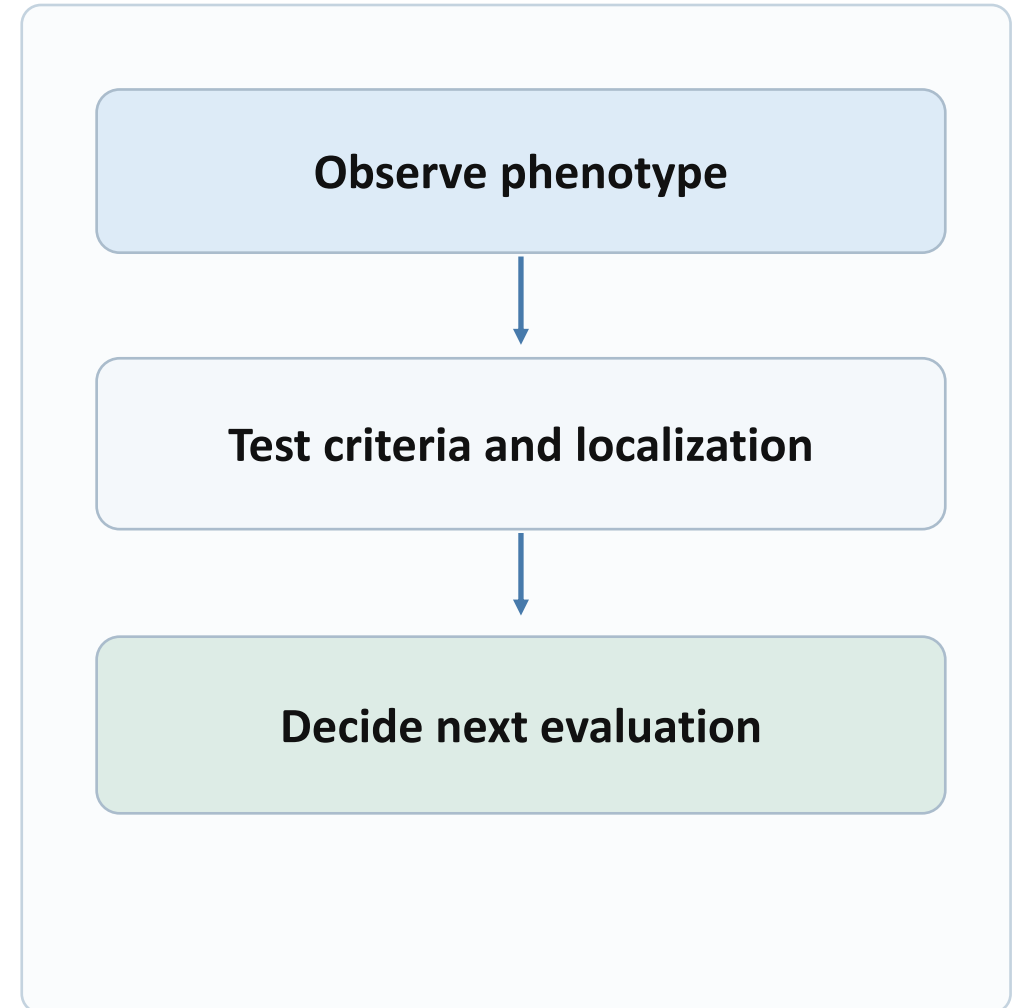
Case 1: Multiple clinical features

- An infant has multiple hypomelanotic macules and a cardiac rhabdomyoma.
- Two major clinical feature categories are present if macule count/size meet criteria.
- What tests identify the associated CNS and renal phenotype?



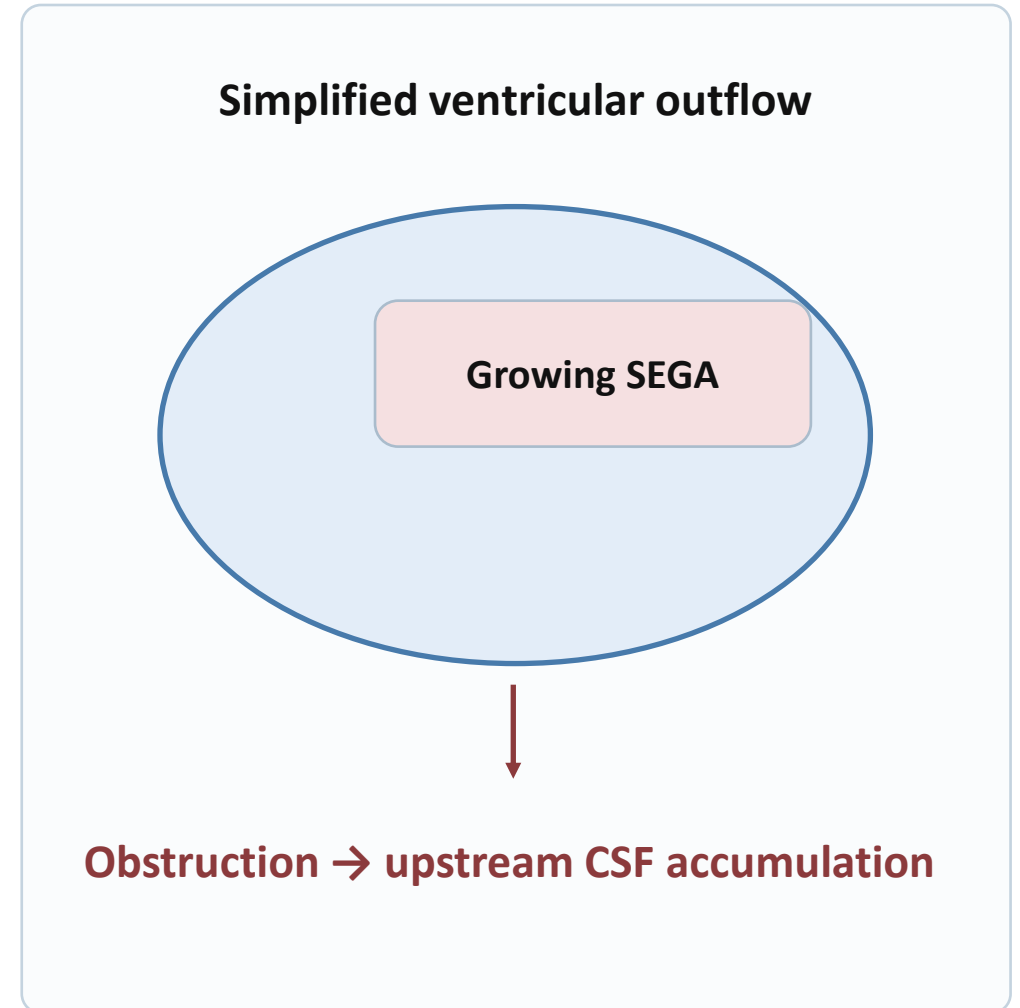
Case 1: Diagnostic reasoning

- Confirm ≥ 3 hypomelanotic macules, each ≥ 5 mm.
- Cardiac rhabdomyoma provides a separate major criterion.
- Brain MRI, renal imaging and specialist assessment complete initial phenotyping.



Case 2: Ventricular obstruction

- A patient with known TSC develops headache and vomiting.
- Brain MRI shows a growing lesion adjacent to a ventricular CSF channel.
- Recognize possible SEGA-associated obstructive hydrocephalus.



Case 2: Urgency and distinction

- Hydrocephalus is a mechanical complication of lesion location and growth.
- Benign histologic classification does not make the mass effect benign.
- Expedited neurosurgical assessment is required for symptomatic obstruction.

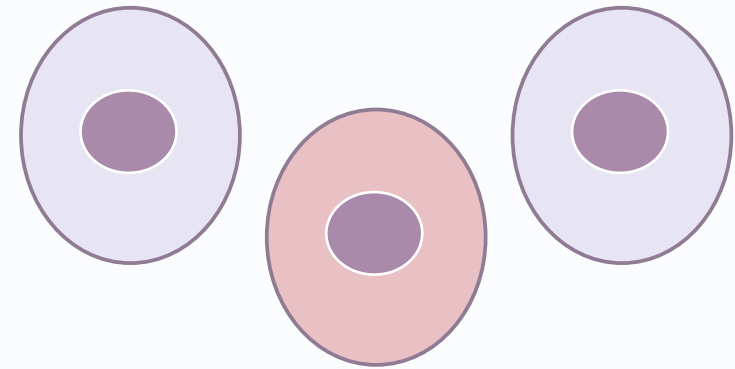
Potential urgent implication

Do not equate benign with harmless

Integrate anatomy and clinical signs

Case 3: Cortical epilepsy pathology

- An epilepsy resection contains disorganized neurons and giant dysplastic cells.
- Mixed neurofilament and GFAP expression is detected in characteristic cells.
- The combined architecture and immunophenotype support a cortical tuber.



GFAP + neurofilament expression

Differential: Familial CNS tumor syndromes

Feature	TSC	NF1	VHL
Key CNS lesion	Tubers / SEGA	Optic glioma	Hemangioblastoma
Skin clue	Macules; angiofibroma	Café-au-lait macules	Not defining here
Other lesion	Renal AML	Neurofibromas	Renal cell carcinoma

Morphology synthesis: Cortical versus ventricular

- Cortical tuber: Firm disorganized lamination and mixed dysplastic cells.
- Subependymal nodule: Small ventricular-surface hamartoma.
- SEGA: Larger related benign neoplasm with risk of obstruction.

Cortex

Cortical tuber → Epilepsy

Ventricular wall

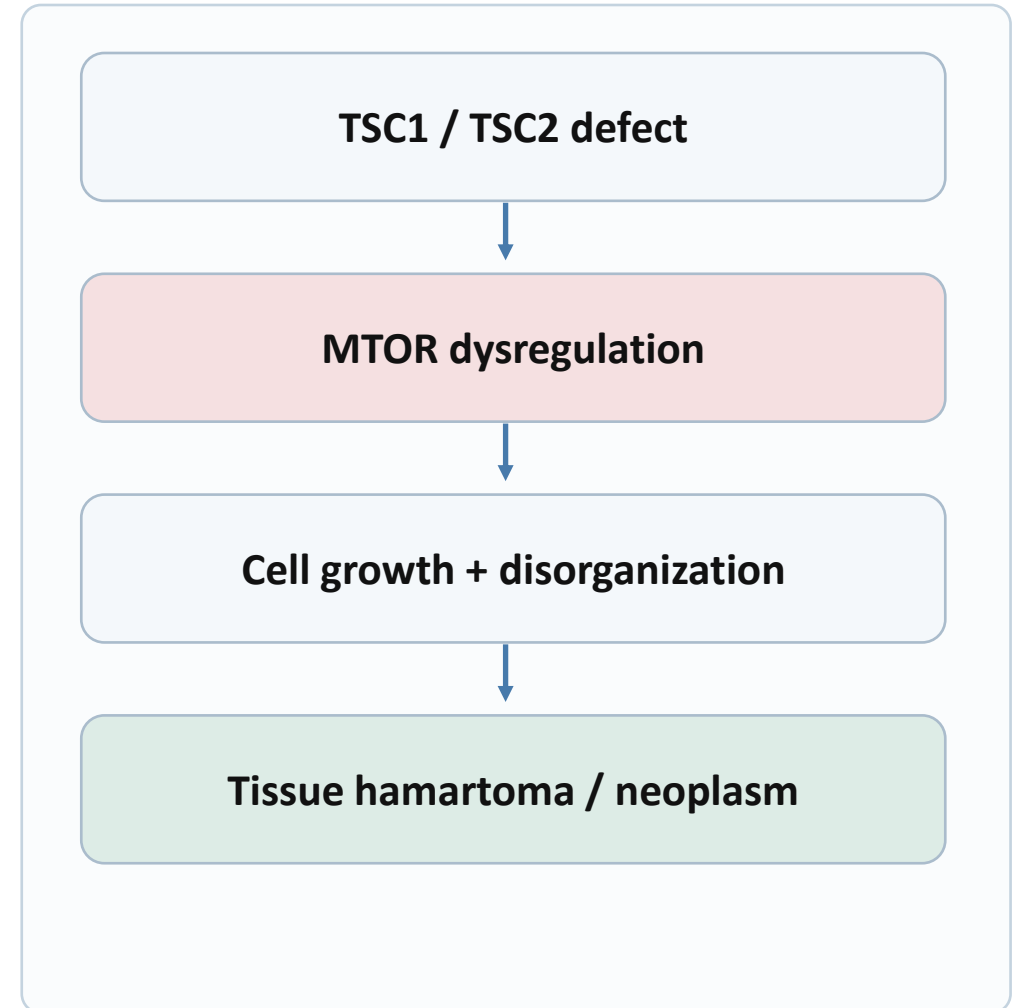
Subependymal nodule → Bulging nodules

Ventricular growth

SEGA → CSF obstruction

Clinicopathologic synthesis

- TSC1/TSC2 disruption links defective growth regulation to abnormal tissues.
- Tuber-associated epilepsy and SEGA-associated hydrocephalus reflect lesion localization.
- Multisystem surveillance follows from the distribution of pathology.



References

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