Tuberous sclerosis complex

- A clinical and research update

Finbar O'Callaghan

Plan of talk

- Epidemiology & Genetics
- Clinical Overview
  - Epilepsy
  - SEGAs
  - Guidelines

- TSC signaling
- Pre-clinical studies of mTOR inhibition
- Clinical results of mTOR inhibition
- Current trials

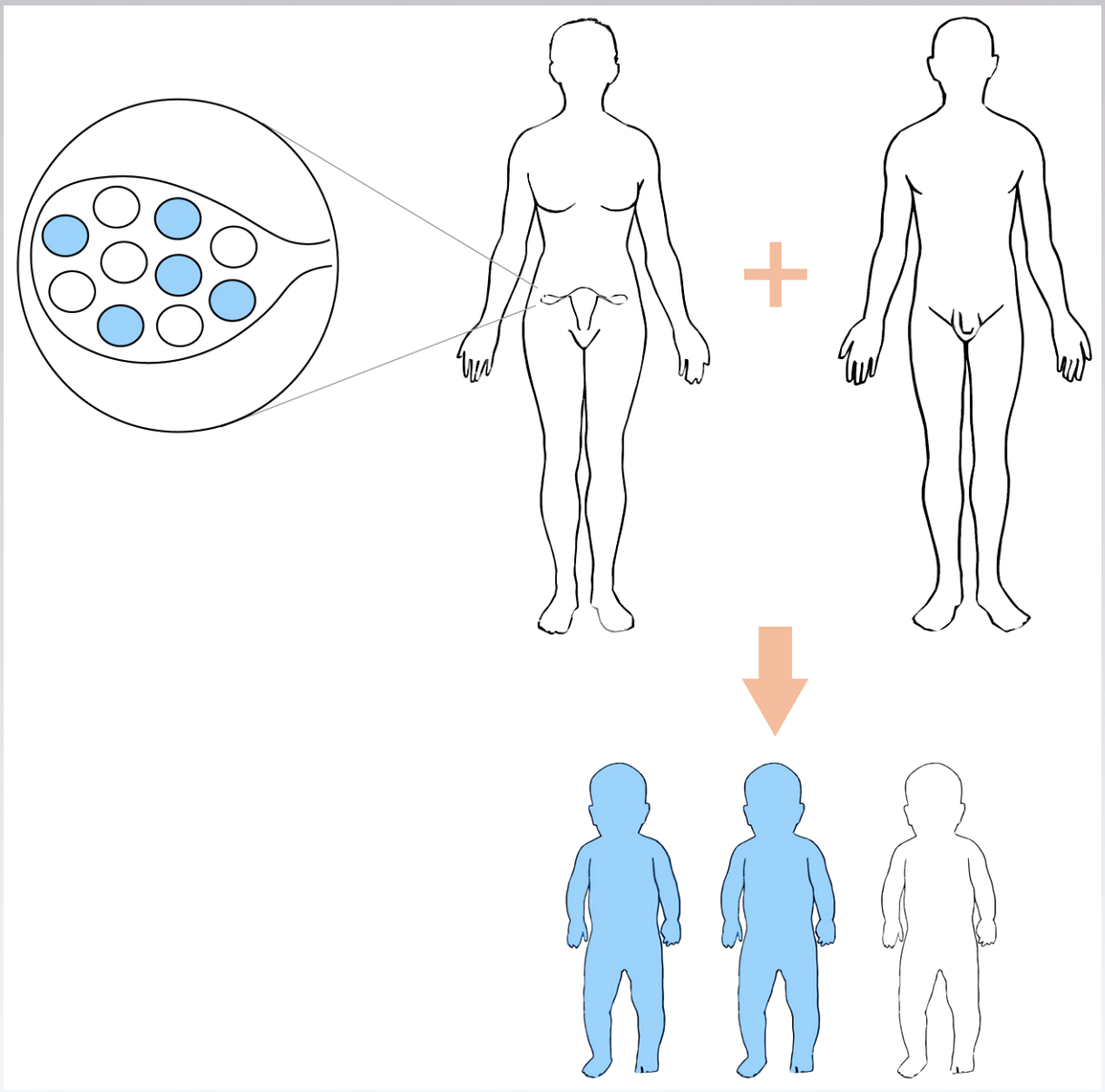
Epidemiology

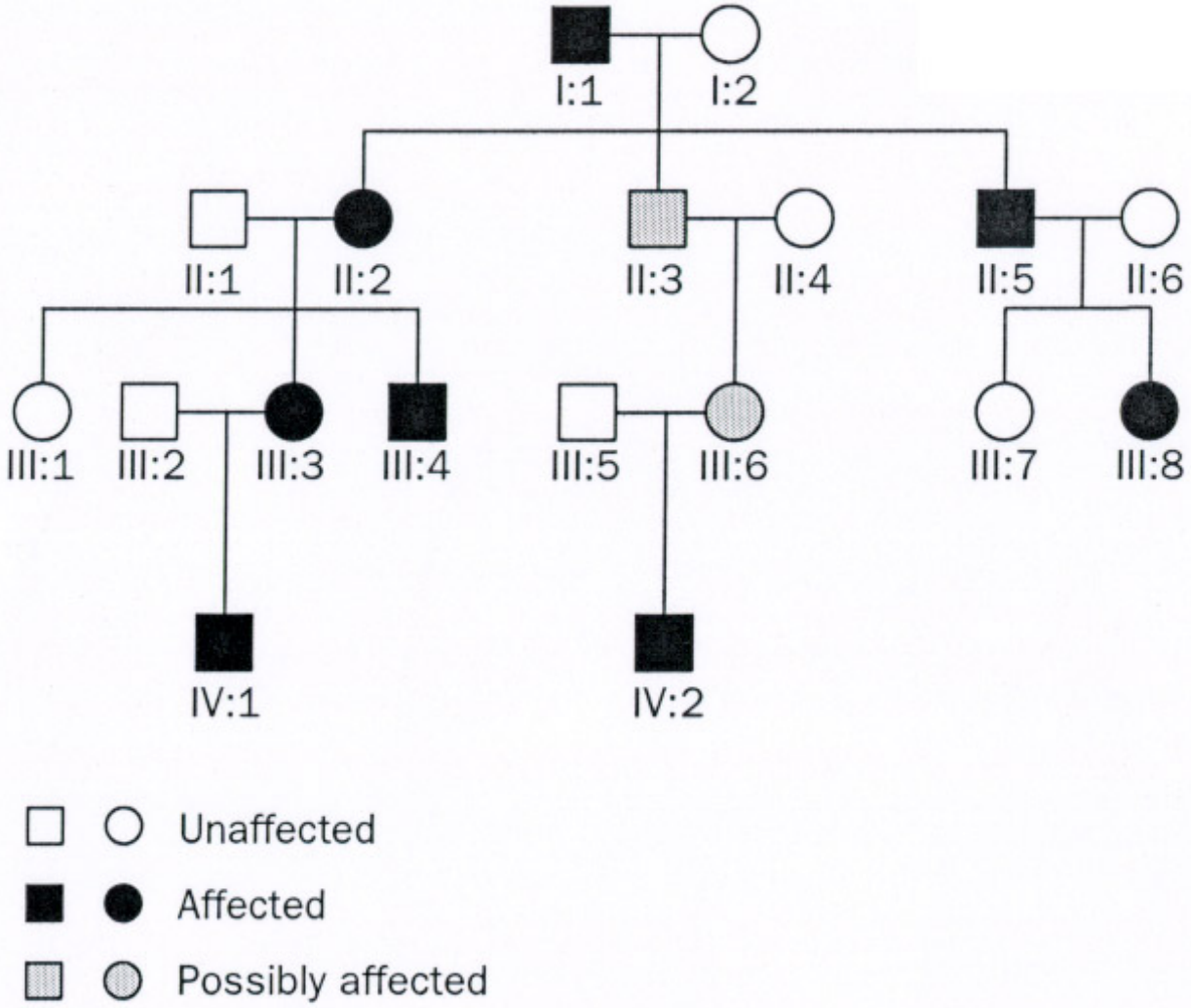
- Prevalence of 8.8 per 100,000 (95% CI 6.8 to 12.4)

O'Callaghan et al Lancet 1998 16;351(9114):1490

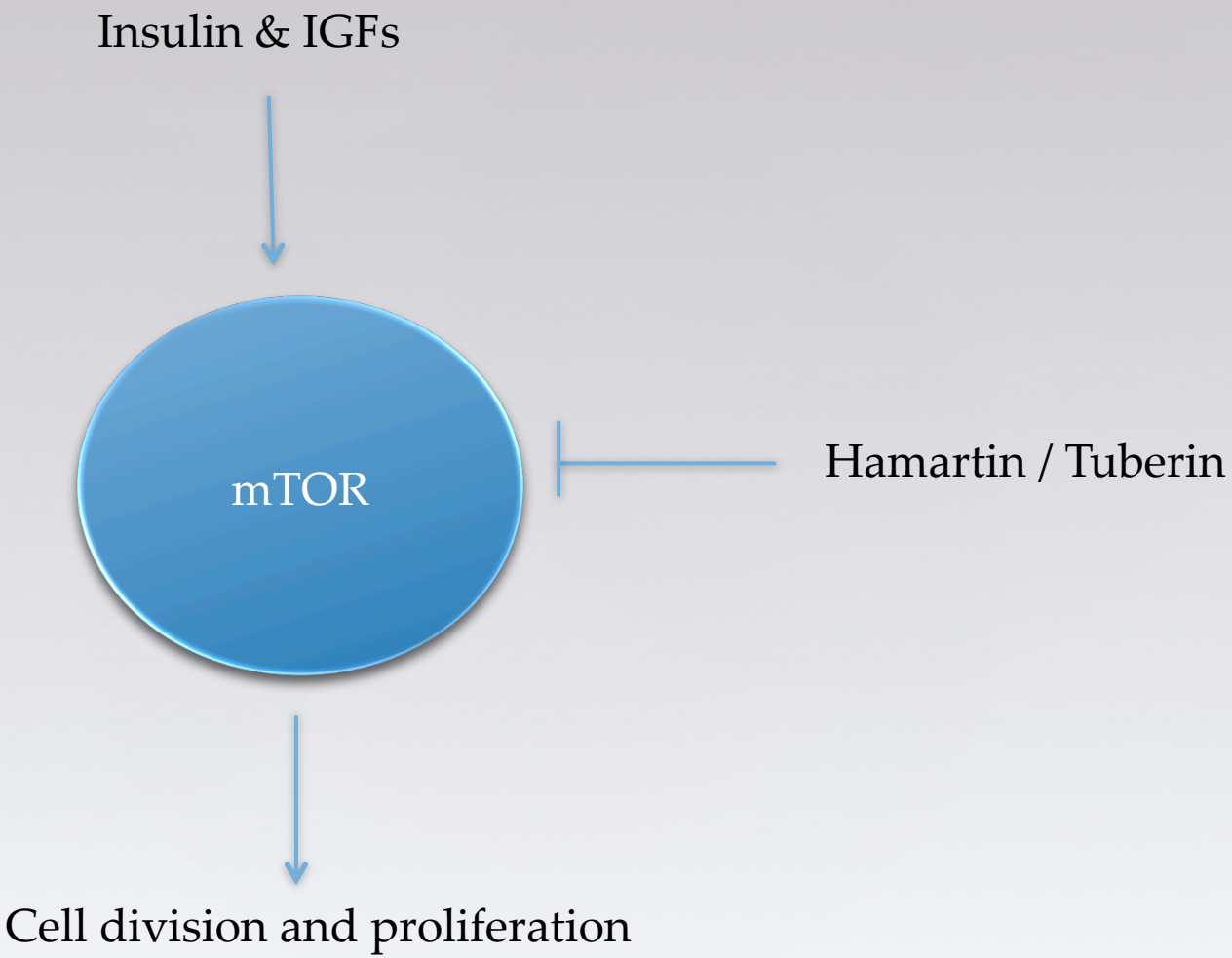
Basic Genetics of TSC

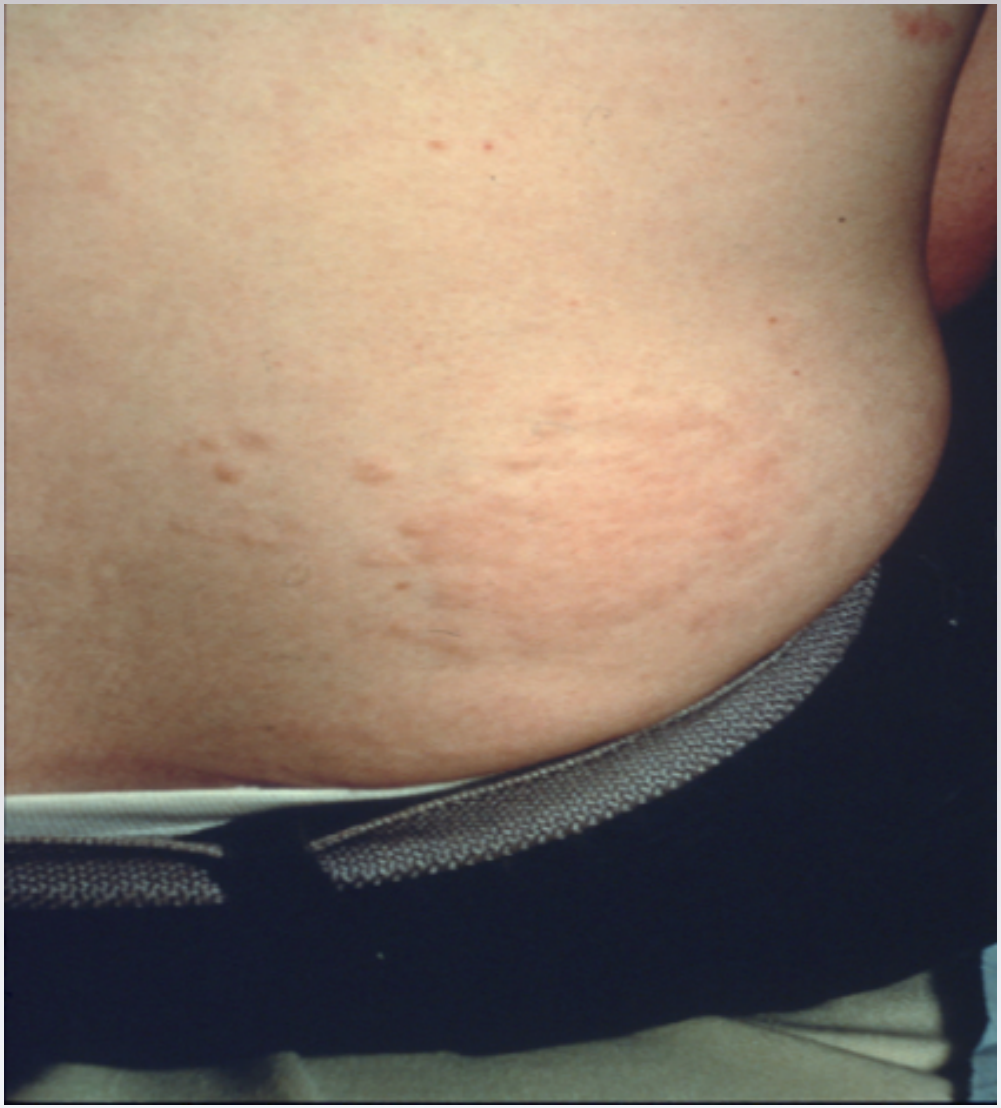
- Autosomal Dominant inheritance
- Genetic heterogeneity (TSC1 at 9q34 and TSC2 at 16p1)
- Tumour suppressor genes
- 60-70% sporadic mutations
- High Penetrance





Family tree of affected children

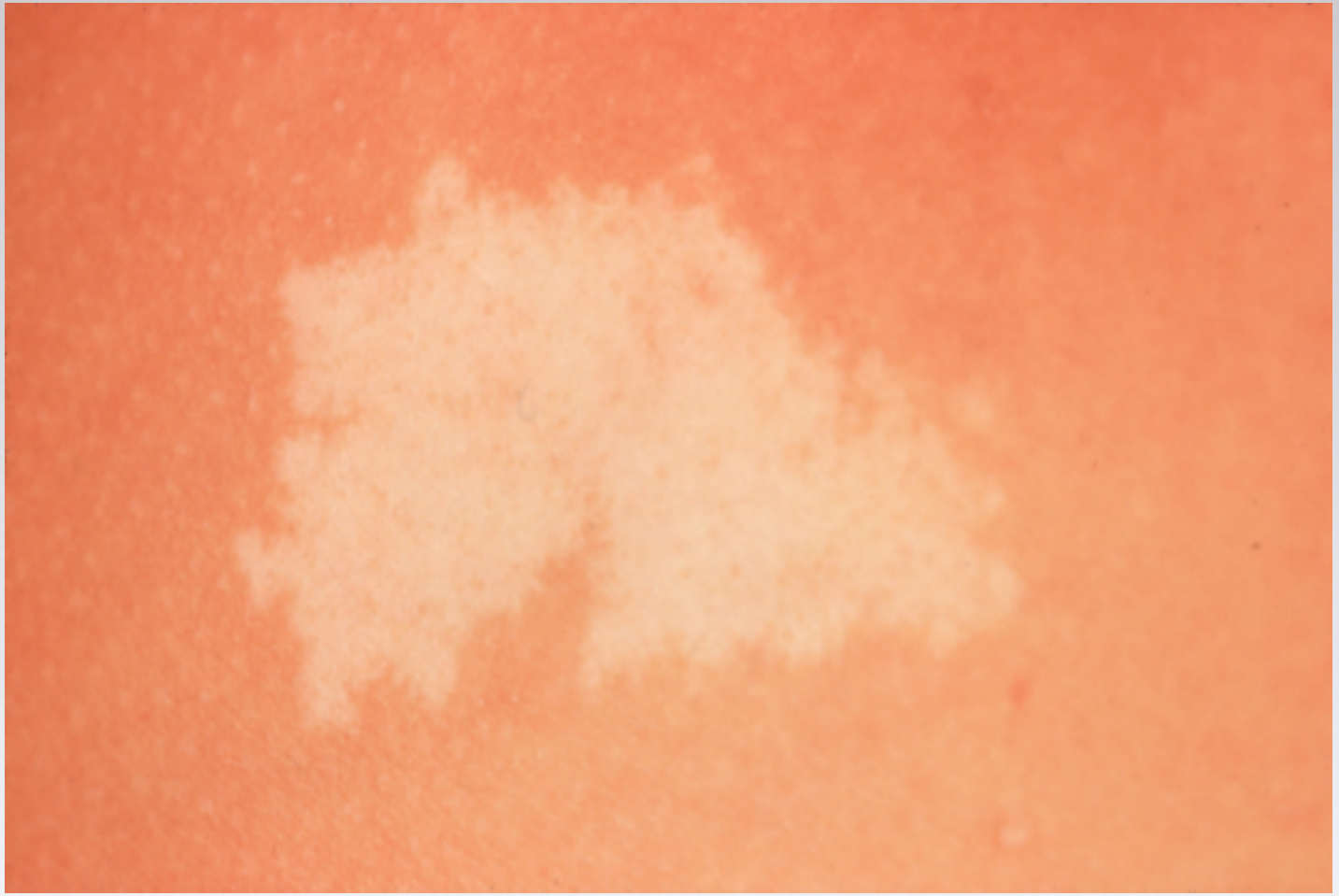

Insulin & IGFs
mTOR
Hamartin / Tuberin
Cell division and proliferation



Shagreen Patch

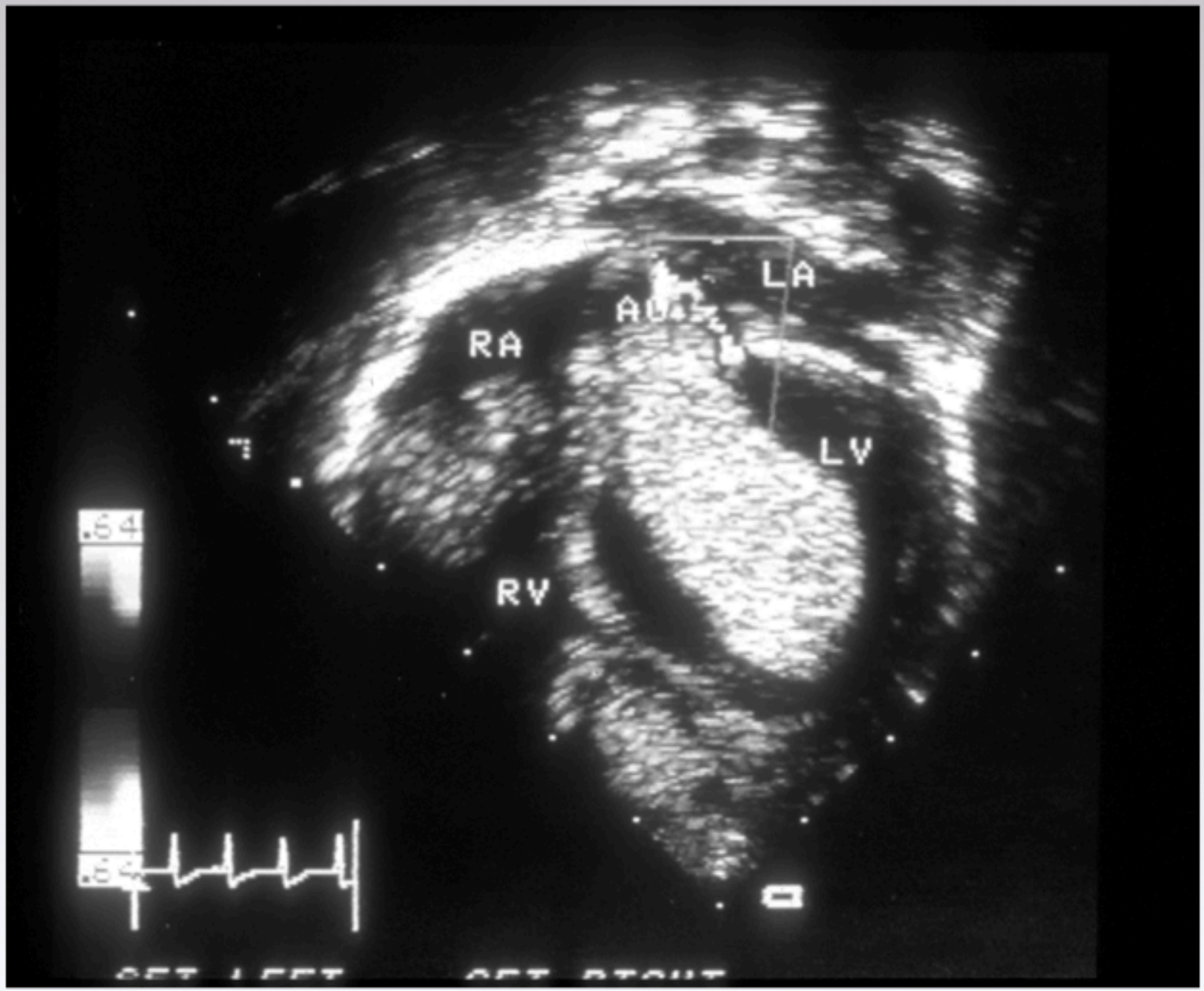
Ungual and Periungual Fibromas

1. Dack
2. Bissler. www.tsalliance.org/pages.aspx?content=498. 2010
3. Data provided by F O'Callaghan, The Institute of Child Health.



Condition	Prevalence in TSC
Hypomelanotic macules (ash-leaf spots)	87%–100%
Facial angiofibromas	70%–80%
Shagreen patches	20%–50%
Ungual or periungual fibromas	15%–52%
Fibrous facial plaques	~36%

1. Leung. *J Ped Health Care.* 2007;21:108-14.
2. Bissler. www.tsalliance.org/pages.aspx?content=498. 2010.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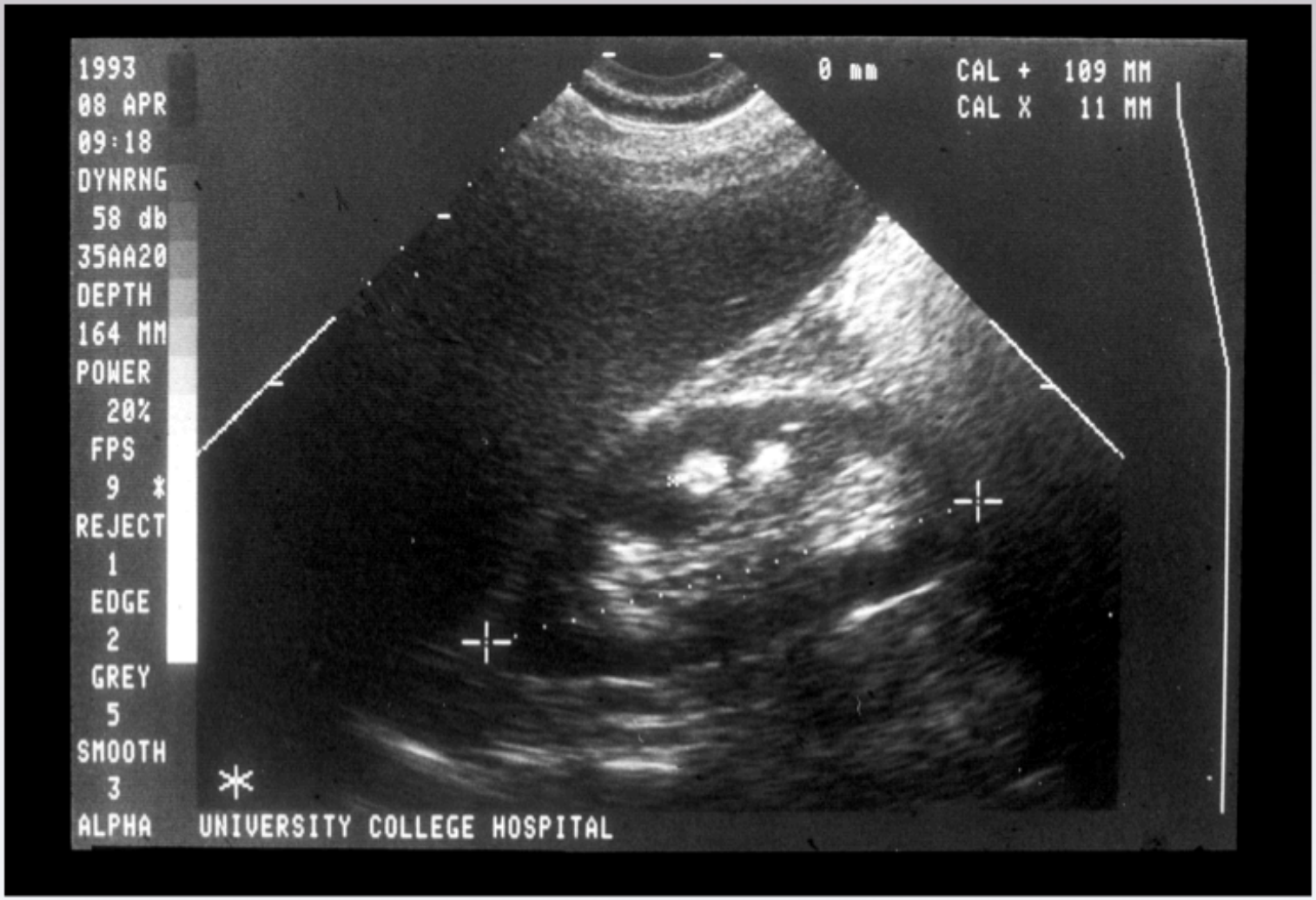
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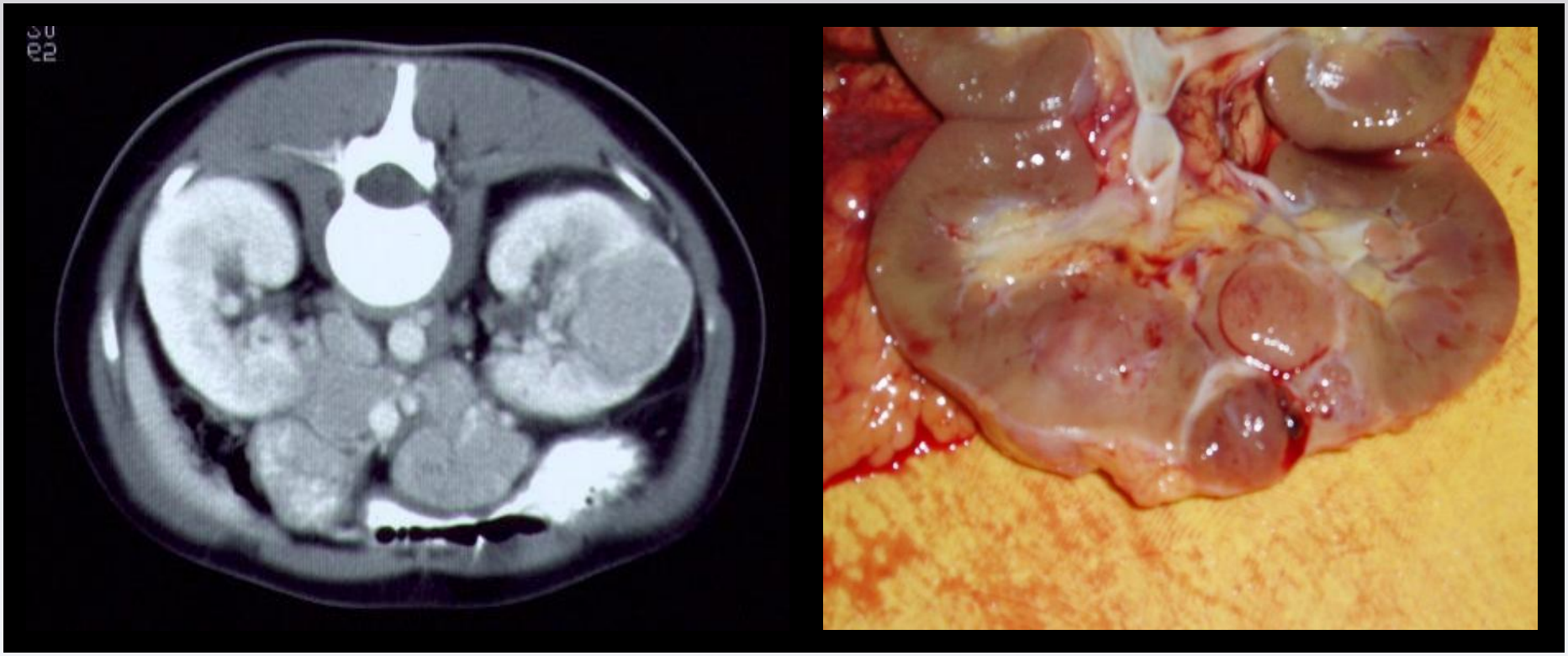
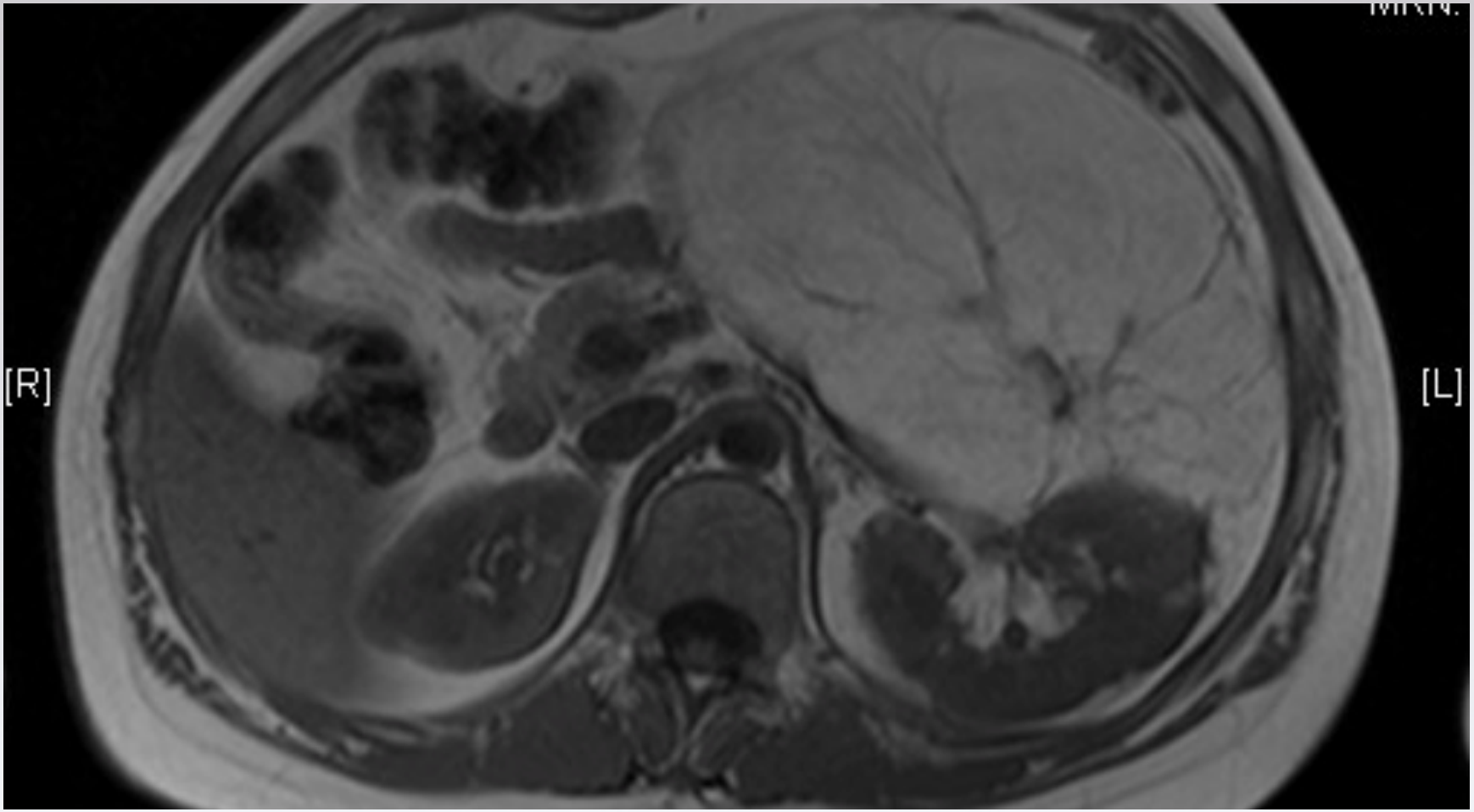
CAL X 11 MM
UNIVERSITY COLLEGE HOSPITAL

Angiomyolipomas

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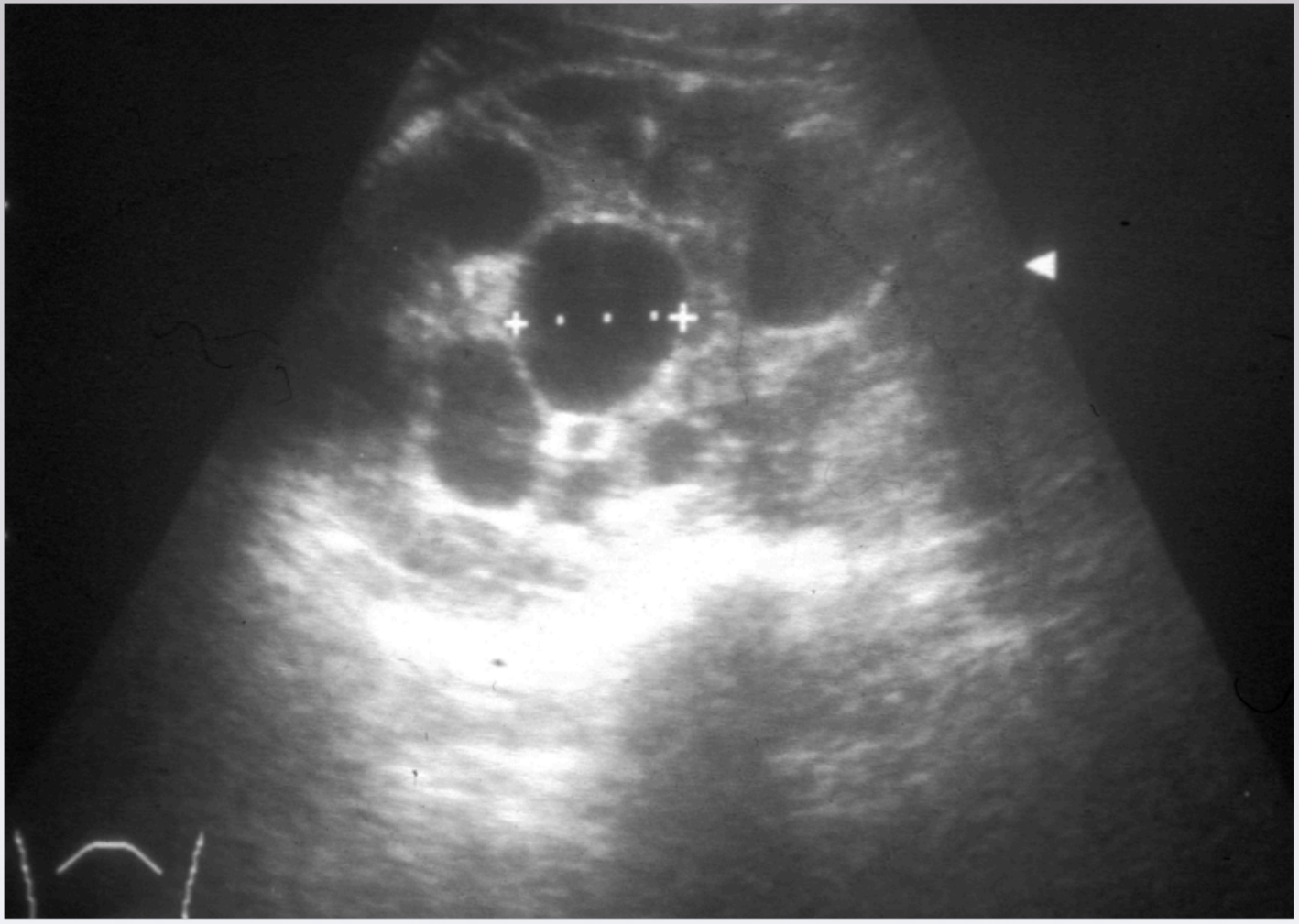

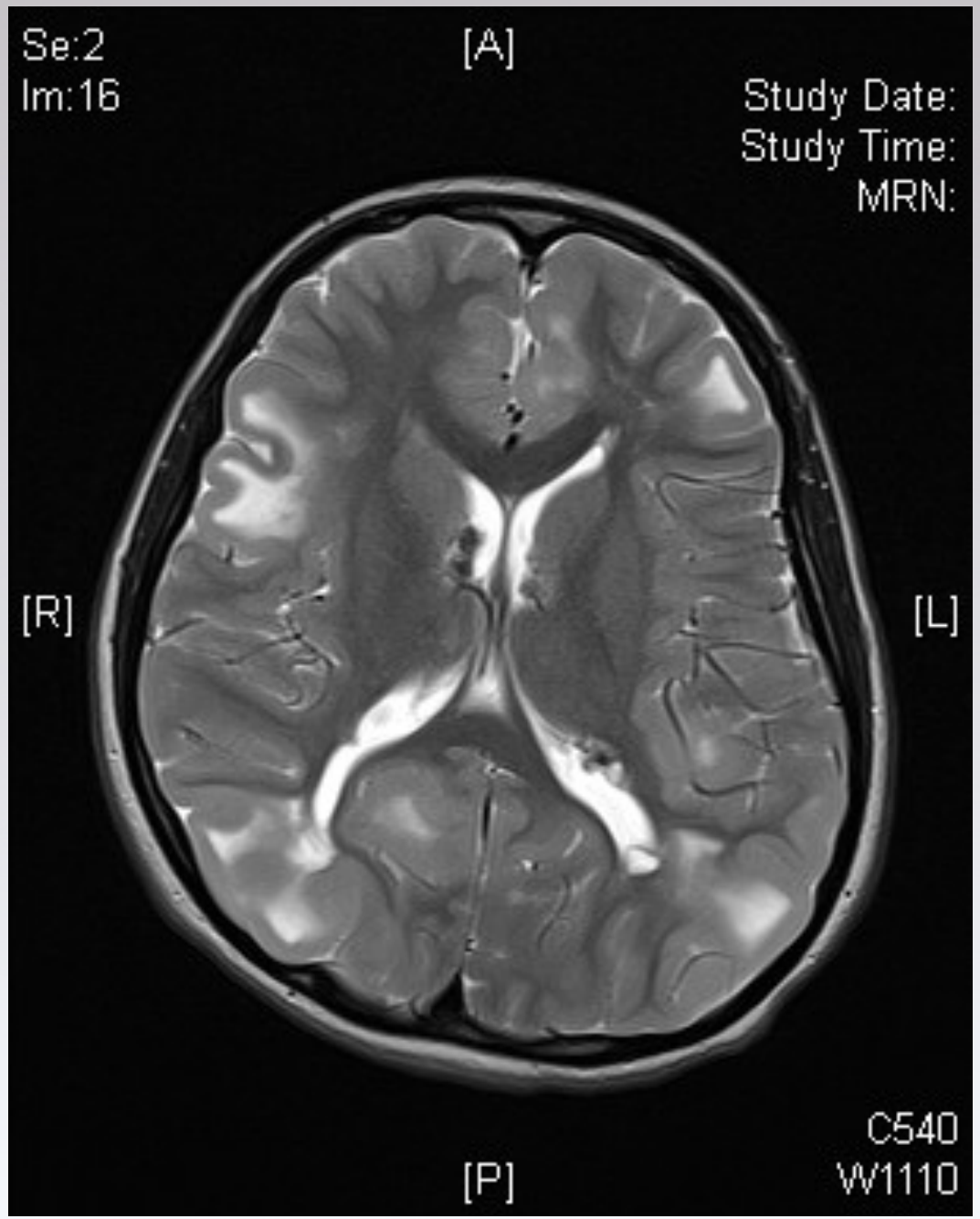
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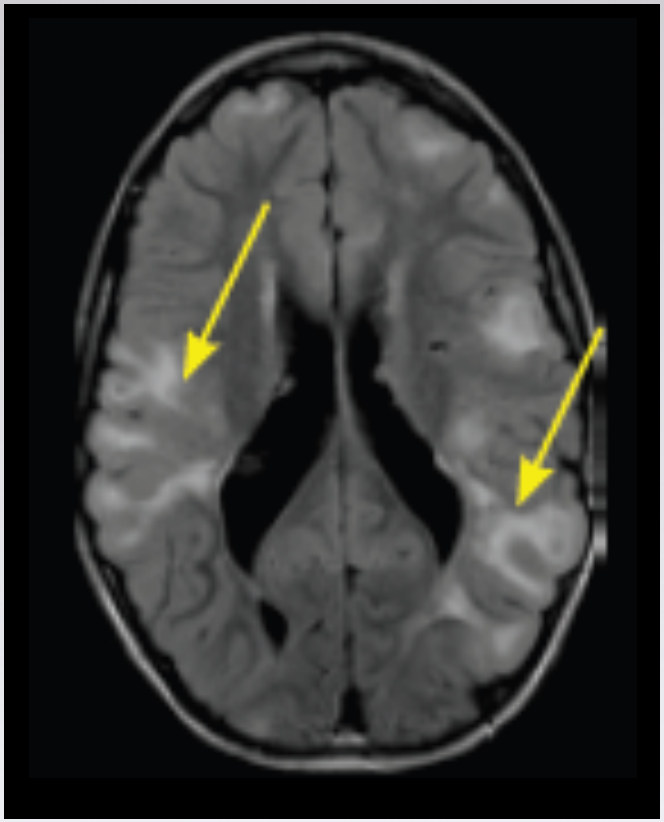
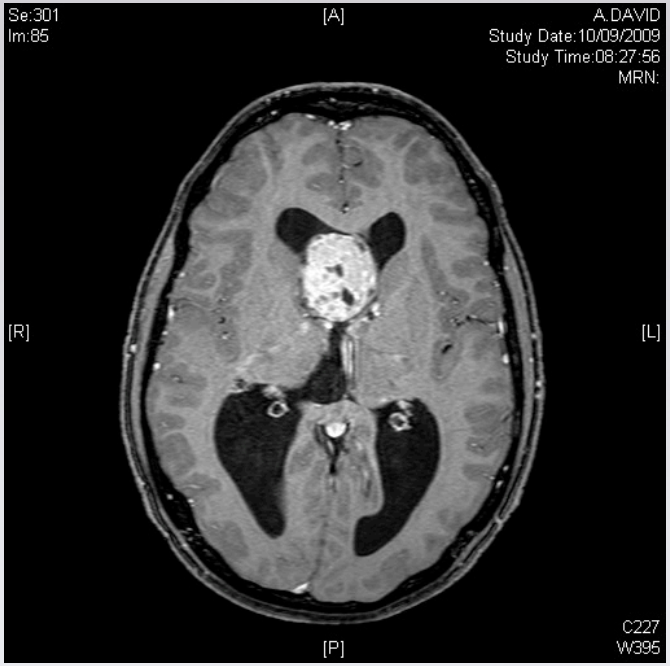
- Cortical tubers are collections of dysmorphic neurons, large astrocytes, and giant cells1,2
- Epilepsy occurs in over 90% of patients and is associated with the presence of cortical tubers2
- Behavioral and cognitive impairments are common in children with TSC, including such disorders as ASD (17%–68%) or ADHD (>50%)3



1. Crino. *N Engl J Med* 2006;355:1345-56.
2. Curatolo. *Eur J Paediatr Neurol.* 2002;6:15-23.
3. Kopp. *Epilepsy* Behav 2008;13:505-10.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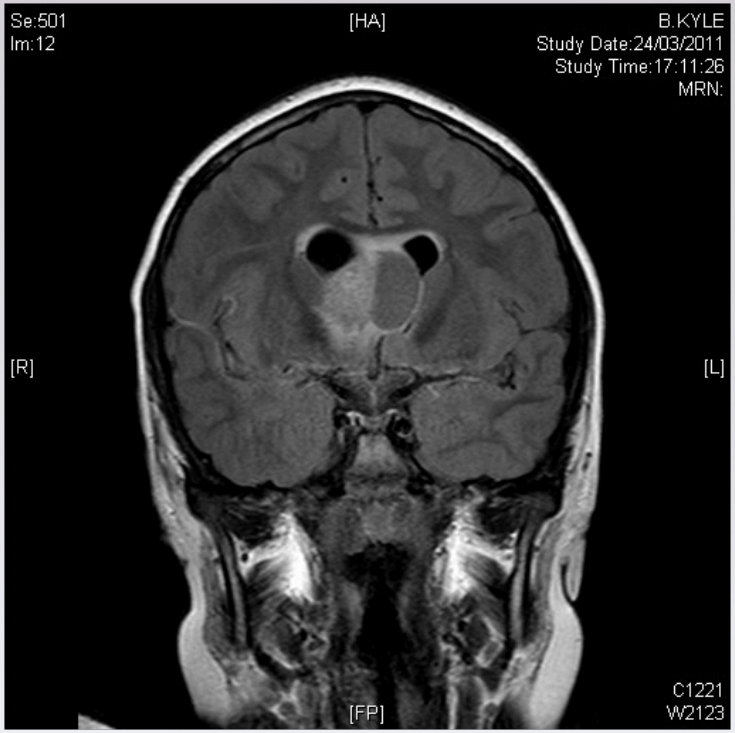
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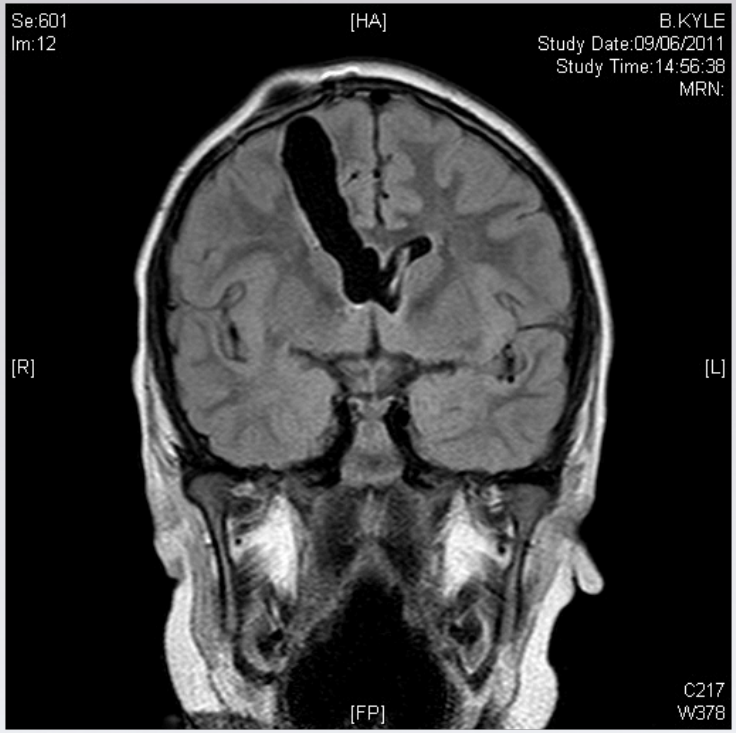
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Outcome of neurosurgery for SEGA

- 19 patients, 20 resections since 2000
- 18/19 complete macroscopic resection
- 1 incomplete, re-do op, progression of SEGA
- No progression/recurrence in 18/19
- 5/19 required CSF diversion
- No haemorrhagic/infective/neurological complications
- No deaths

Amin S et al. EJPN 2013 17(1):36-44

Tubers and epilepsy

- Epilepsy appears to come from tubers or perituberal areas
- Surgical removal can improve the epilepsy
- Increased excitation
  - Changes in glutamate receptors
- Decreased inhibition
  - Deficiency of: GABA-ergic interneurons, synthetic enzymes isoform GAD65 and GABA receptor sub-units alpha-1 and alpha-2
- Drug resistance
  - Multi-drug resistant proteins, MDR-1 and MRP-1, expressed in tubers

Seizure Onset and Intellectual Difficulties

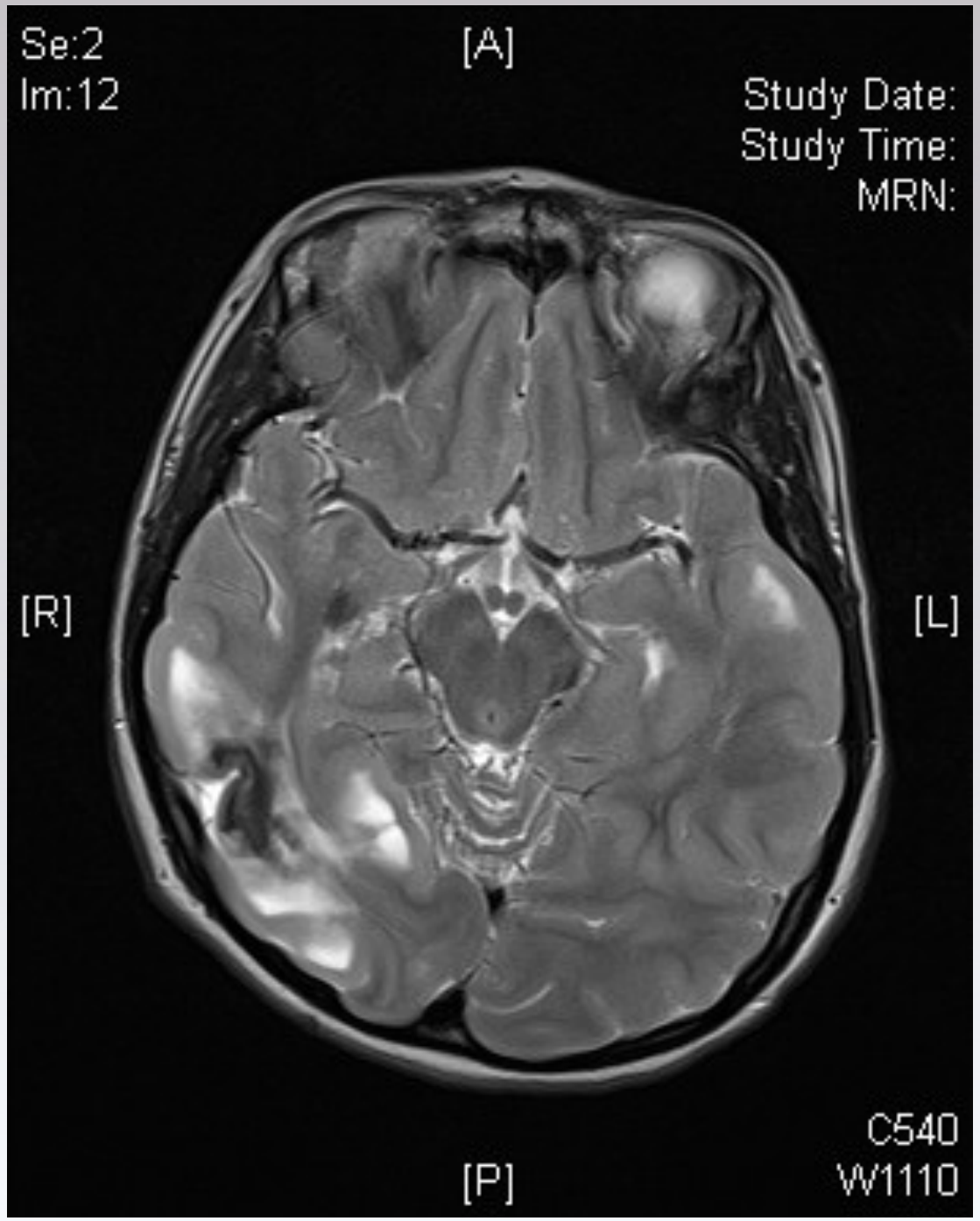
- Mean age (95% CI) of seizure onset in ID individuals = 6.6 months (5.1 to 8.1)
- Mean age of seizure onset in normal IQ patients = 70.2 months (44.4 to 95.9)

$P < 0.001$

Mayo clinic series

	Normal	Intellectual Disability
Seizures (n=129)	40 (31%)	89 (69%)
Without seizures (n=19)	19 (100%)	0 (0%)

1. Gomez MR, ed. Tuberous Sclerosis. 2nd ed. New York, NY; Raven Press:1988.
2. Jóźwiak S, et al. Epilepsia 2007;48:1632.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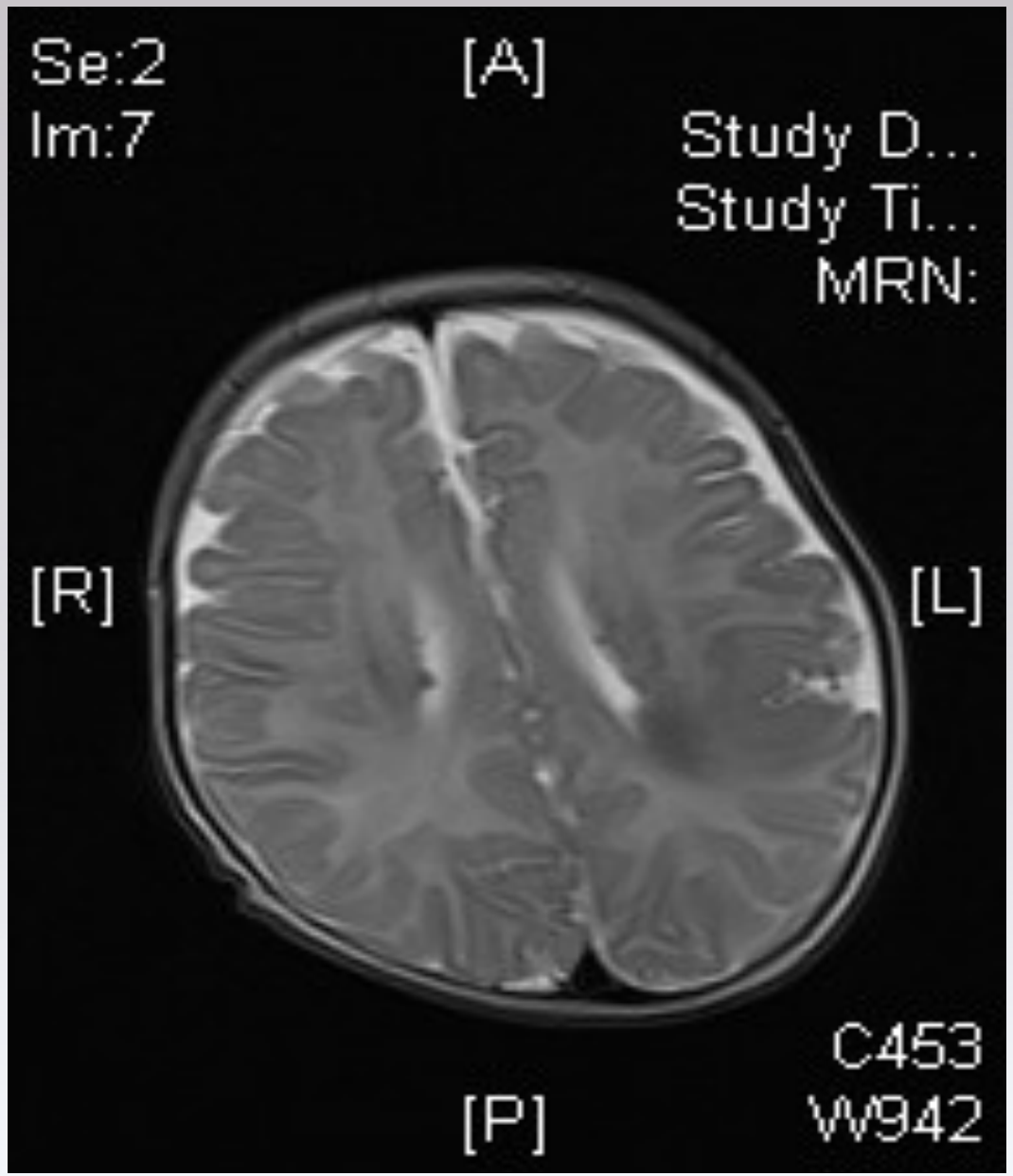
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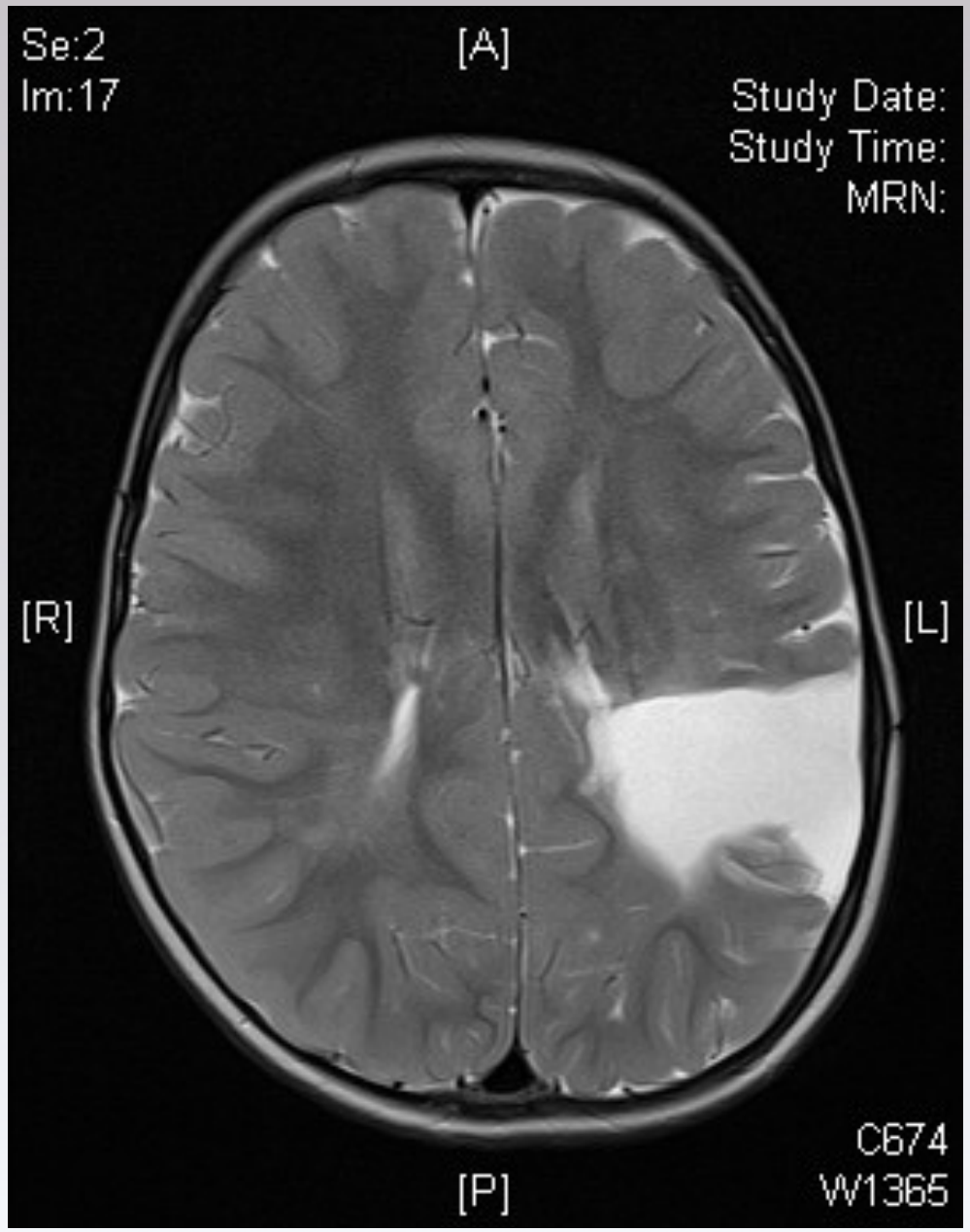
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Outcome of epilepsy surgery in TSC

- Systematic review by Jansen (Epilepsia 2007 48(8): 1477-84
- 177 TSC patients
- Seizure freedom in 101 (57%)
- Seizure frequency improved by > 90% in 32 (18%) patients

Guidelines

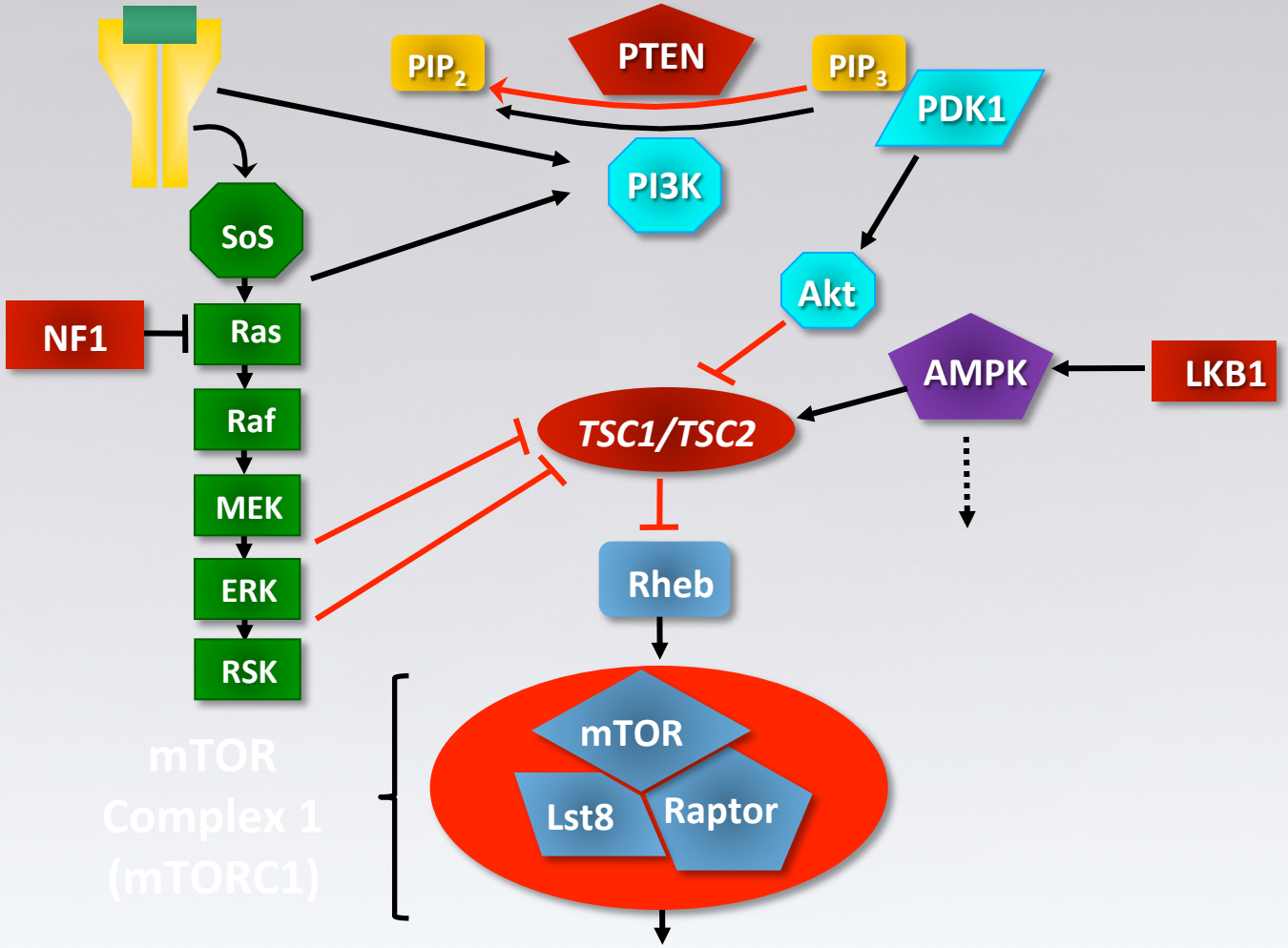
Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference

Darcy A. Krueger, MD, PhD[a,*] and **Hope Northrup, MD**[b] **on behalf of the International Tuberous Sclerosis Complex Consensus Group**

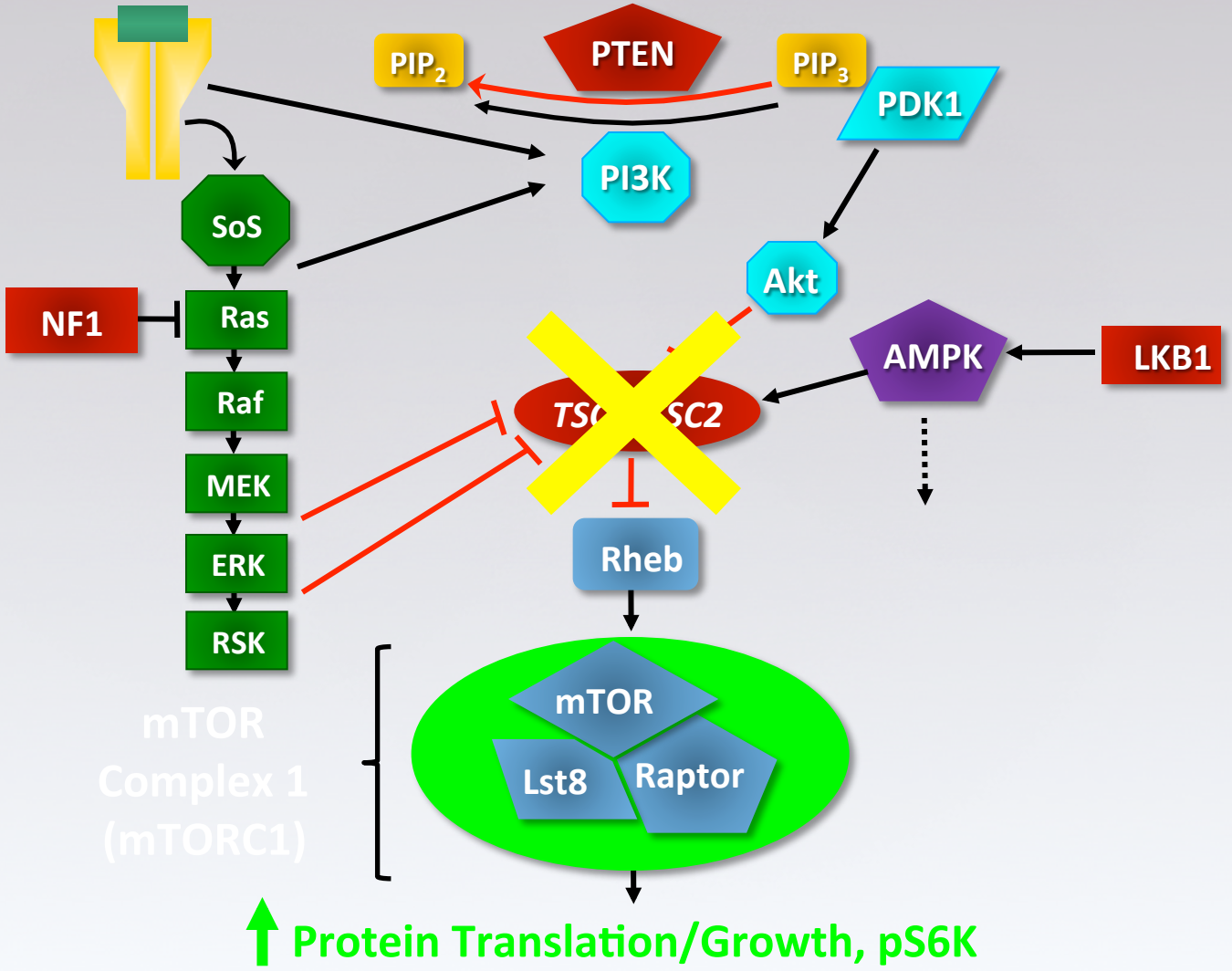
Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference

Hope Northrup, MD[a,*], **Darcy A. Krueger, MD PhD**[b], and **on behalf of the International Tuberous Sclerosis Complex Consensus Group**

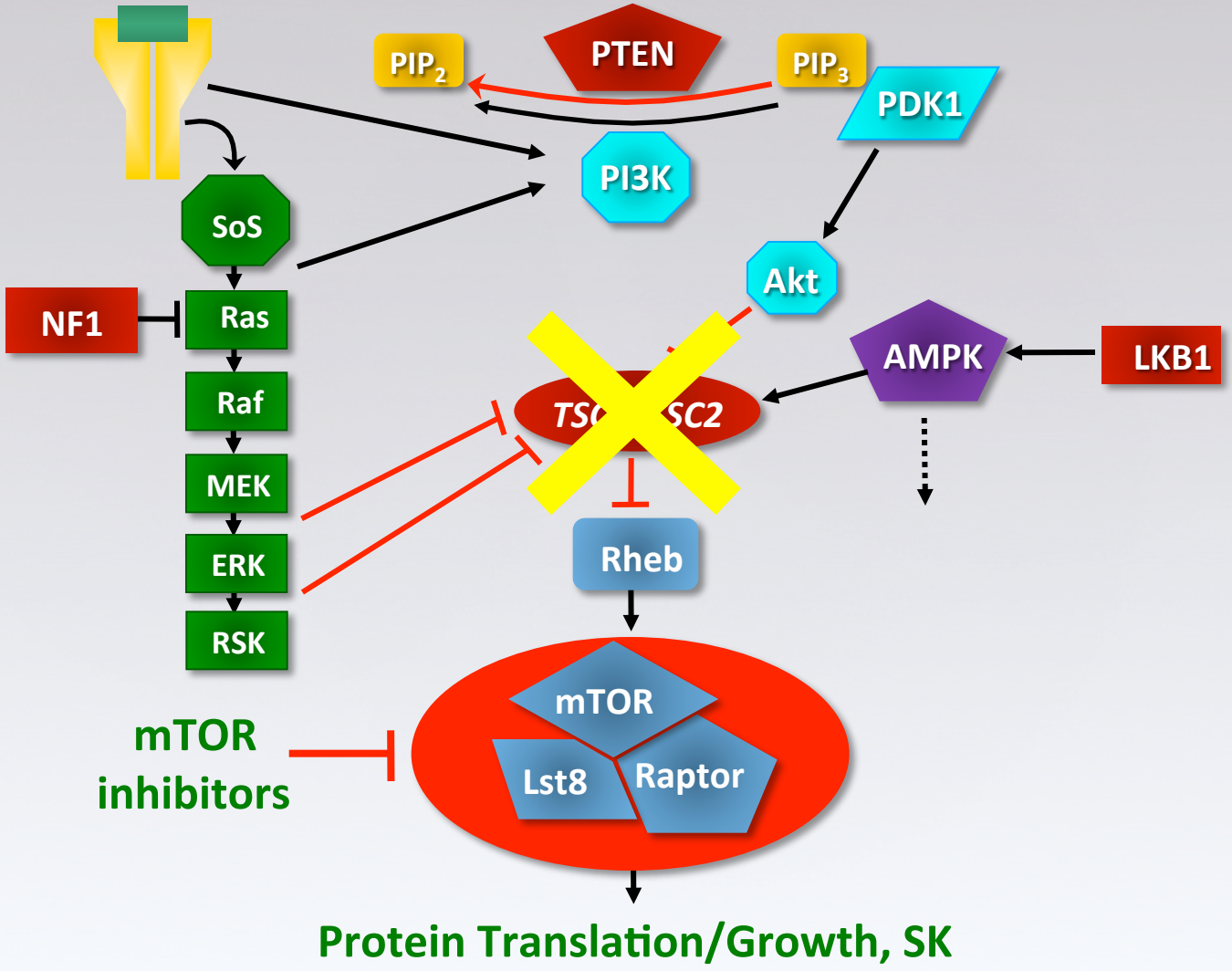
TSC1/2 Integrates Many Cell Signals



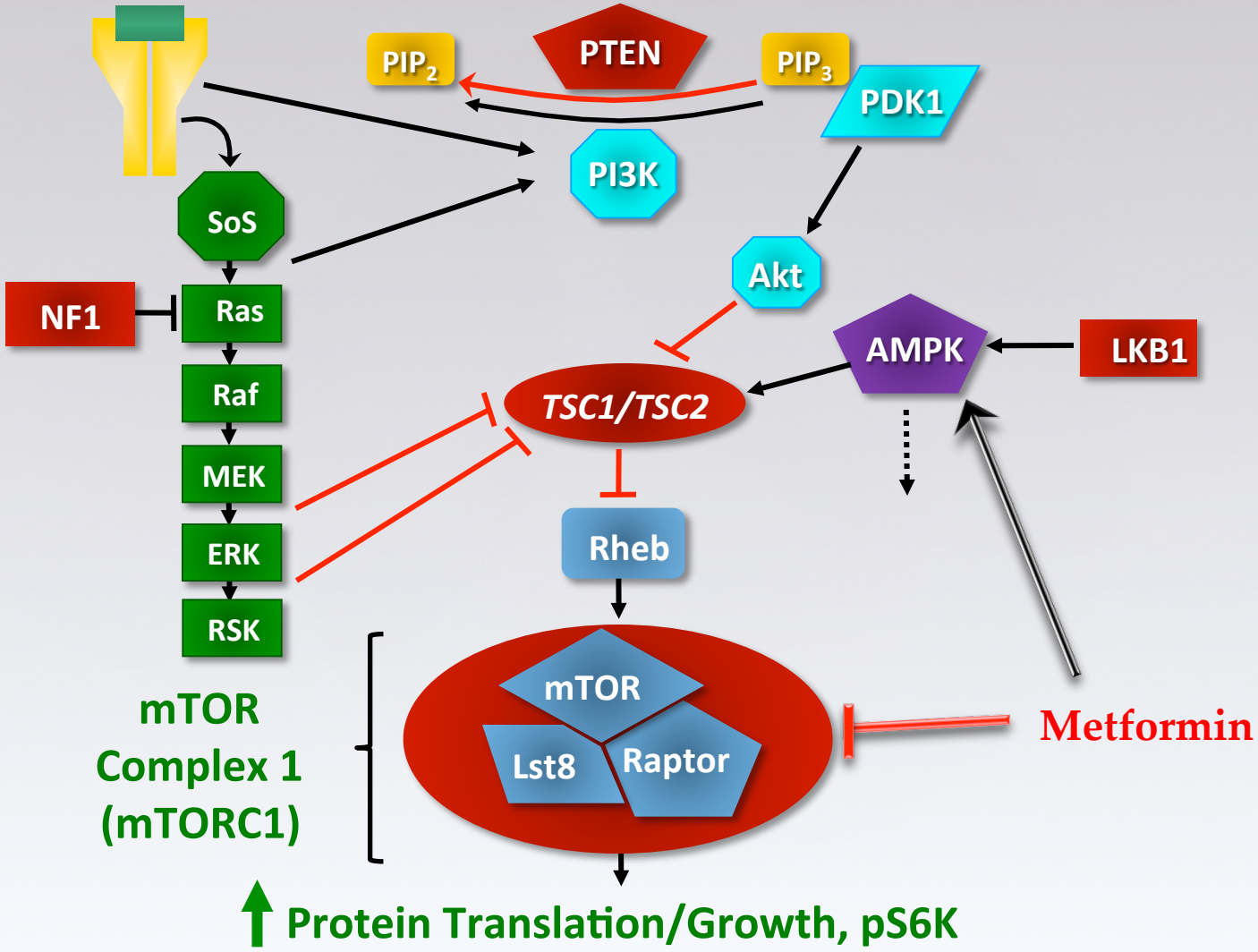
Mutation of *TSC1/2* and mTOR Activation



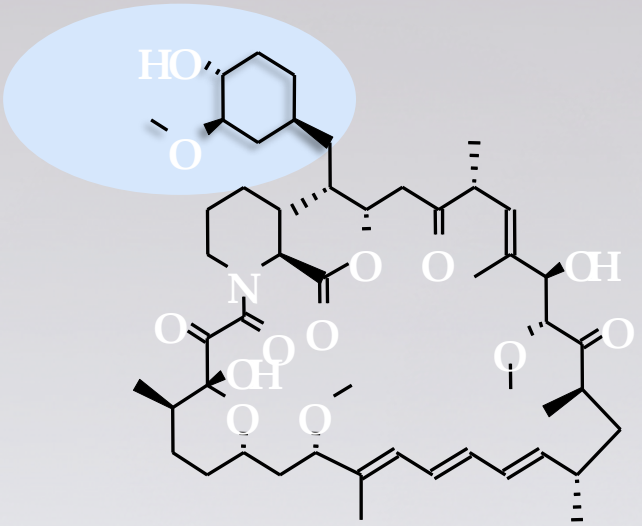
mTOR Inhibitors to Treat TSC?



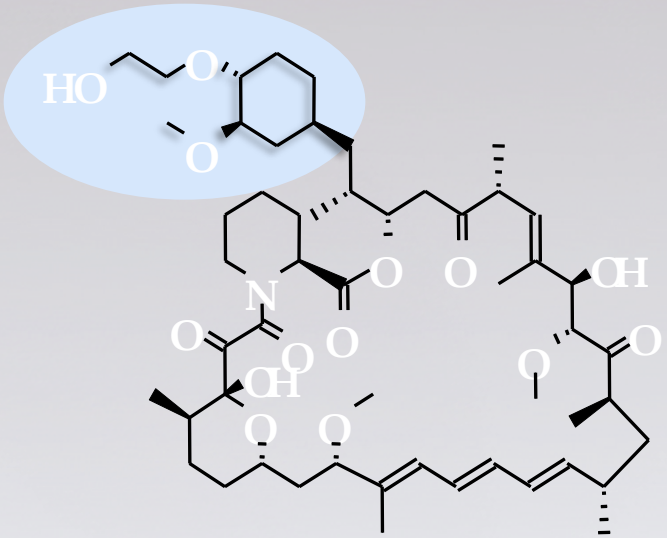
Metformin: Attenuates mTORC1 Signalling in Presence or Absence of *TSC1/2*



mTORC1 Inhibitors Investigated in TSC



Rapamycin

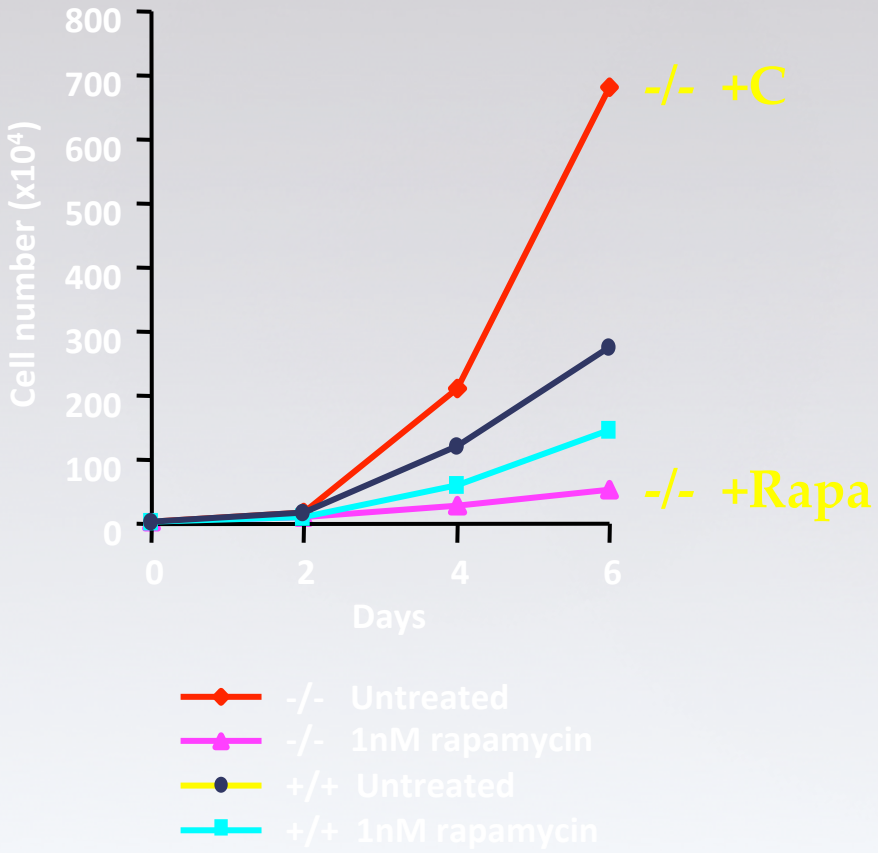


Everolimus

- Immunosuppression in transplant recipients
- Renal cell carcinoma
- Coronary artery stents
- Hundreds of trials in many indications
- Mouth ulcers/hyperlipidaemia/leuko-thrombocytopenia/ pneumonitis

Rapamycin Has a Selective Effect on *TSC2*-null Cell Proliferation

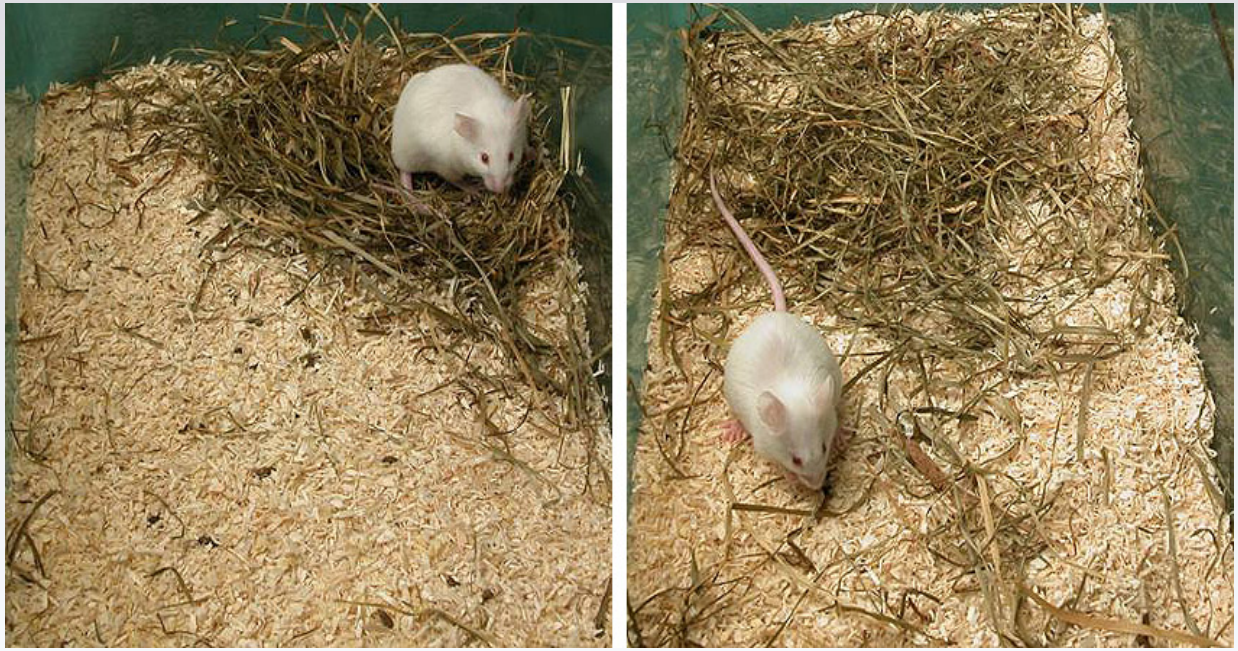
Proliferation assays in *TSC2*-/- MEFs



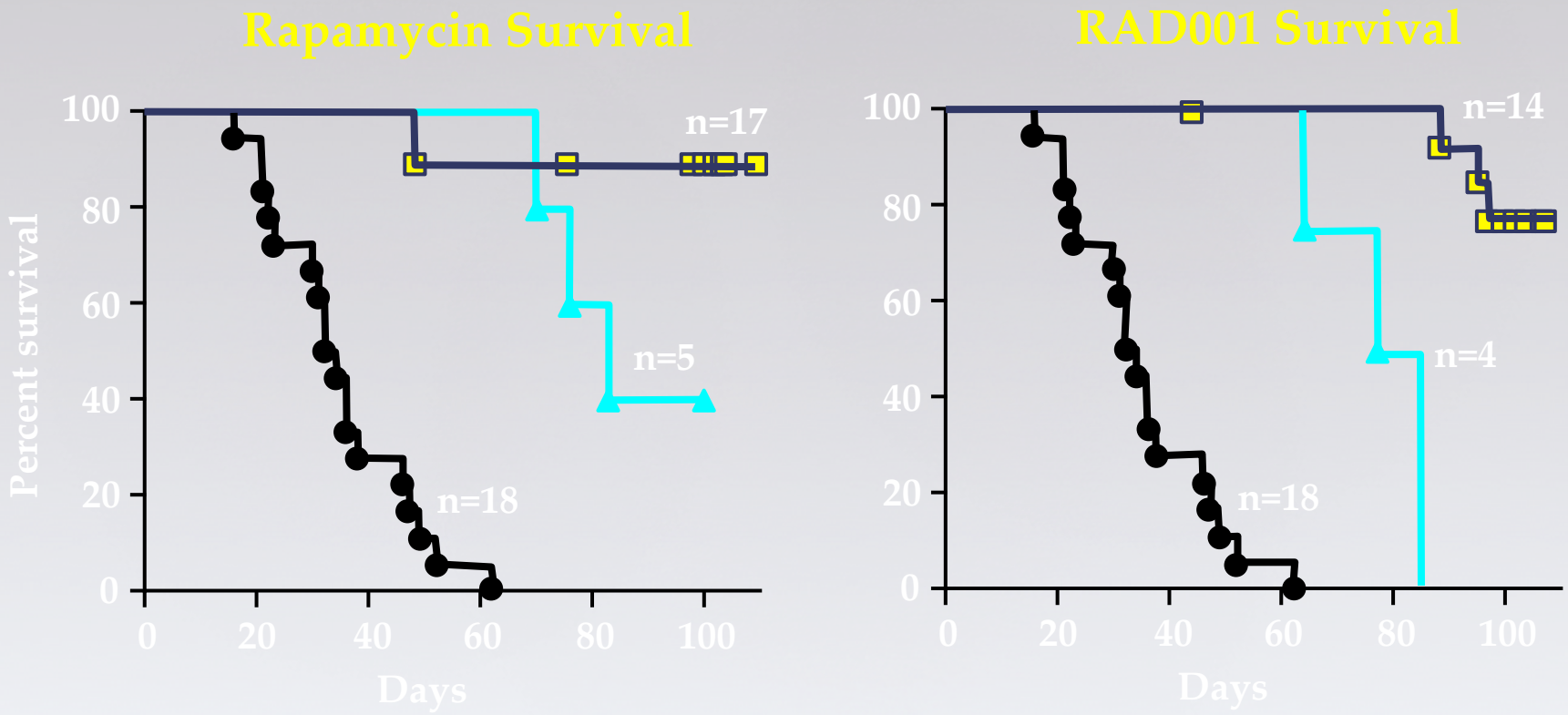
Courtesy of Dr R Lamb.

Preclinical Studies in *TSC1* and *TSC2* Transgenic Mouse Models: Brain

- TSC -/- conditional neuronal KO: enlarged brain, seizures, hypoactivity, early death
- TSC +/- constitutional heterozygotes: brain appears "normal", no seizures, BUT learning, memory, behavior/ socialization deficits

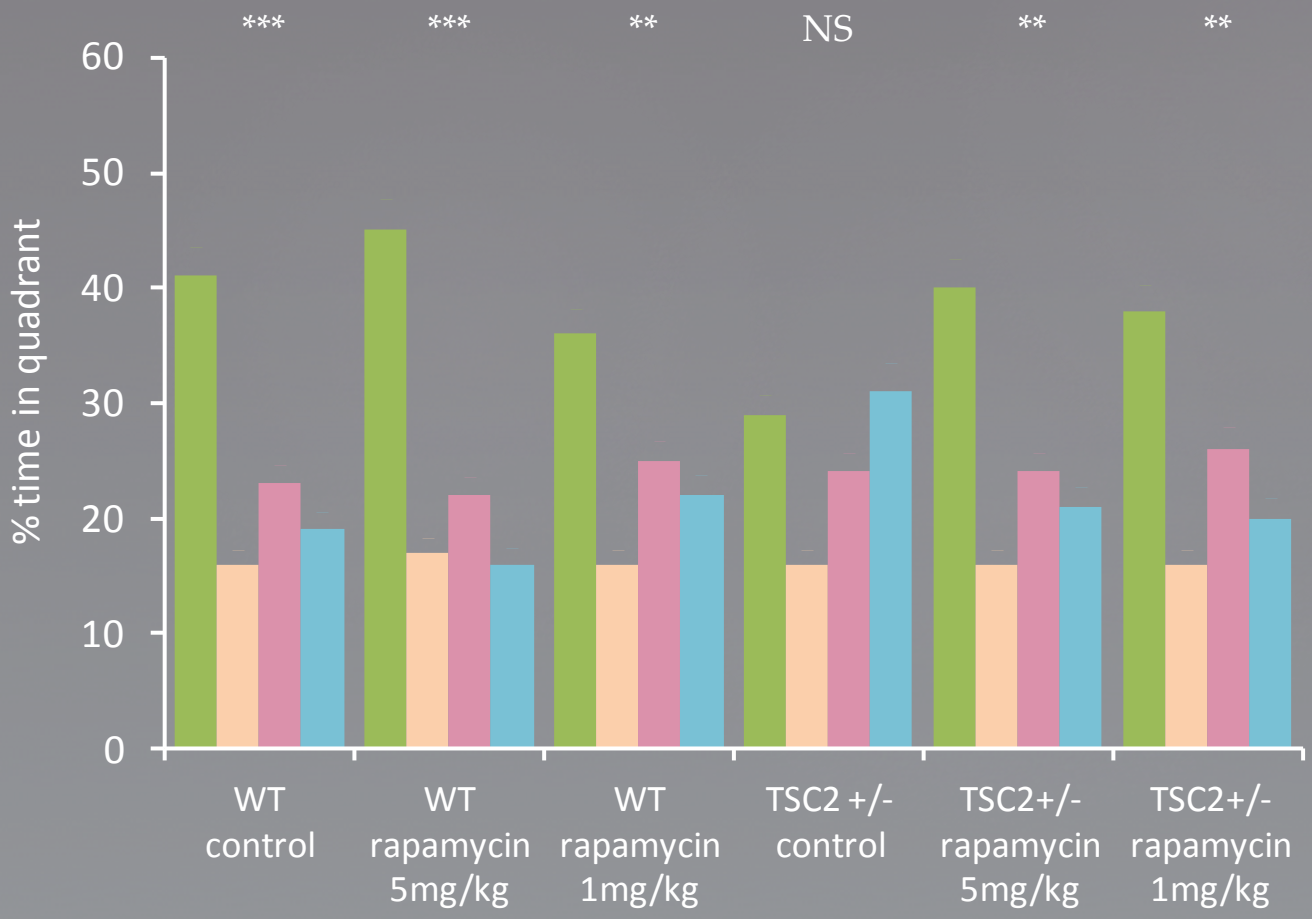


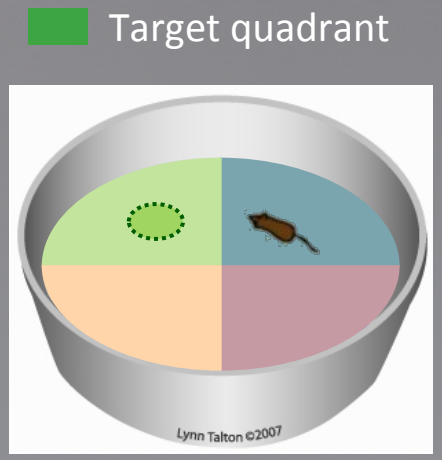
Conditional Neuronal *TSC1* Knockout: Rapamycin and Everolimus Increase Survival



Meikle L, et al. J Neurosci 2008;28:5422-32.

Rapamycin Reverses Spatial Learning Deficits in Heterozygous *TSC2*+/- Mice

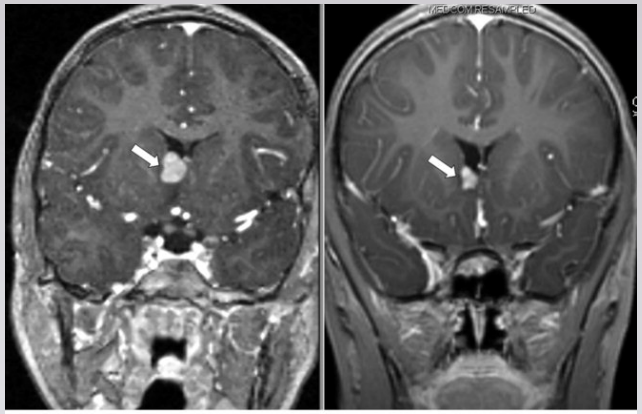


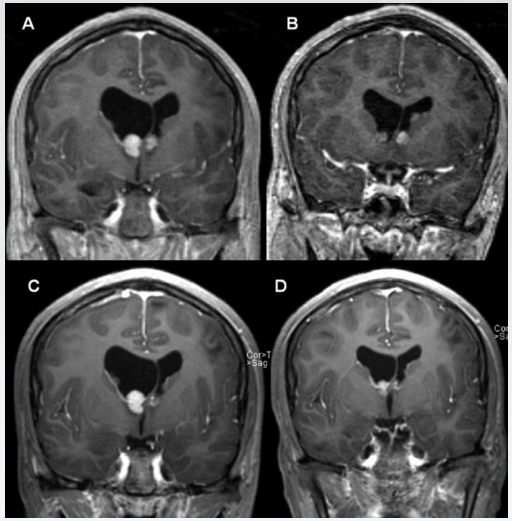


*P<0.05; **P<0.01; ***P<0.001

Ehninger, et al. Nature Med 2008;14:843-8.

Therapeutic use of mTOR inhibitors





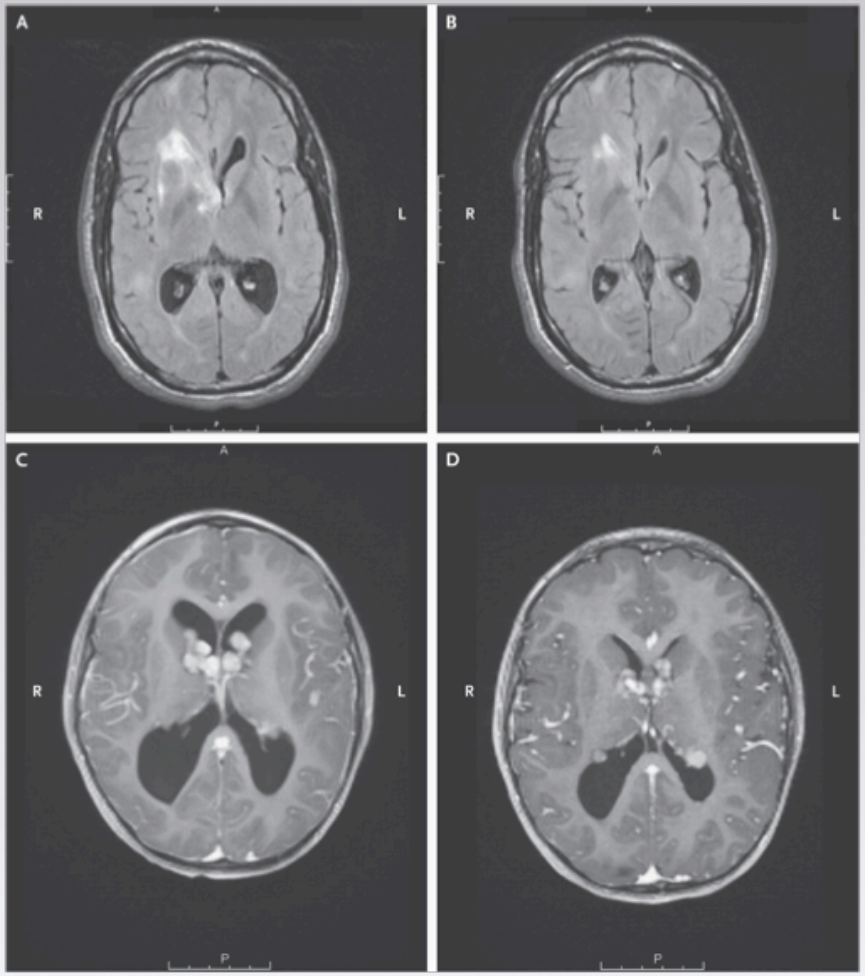
- First described by David Franz in Ann Neurol 59(3) 2006

5 patients: 4 with TSC and 1 with pilocytic astrocytoma. All lesions regressed

Also shrank renal AMLs and facial Lesions.

Franz also demonstrated rebound growth.

Effect of Everolimus on Subependymal Giant-Cell Astrocytoma (SEGA) in Two Patients.



Krueger DA et al. N Engl J Med 2010;363:1801-1811.

Open label study

28 patients

Comparison made With baseline after 6 months

30% + reduction in Tumour volume in 21 patients

Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial

David Neal Franz, Elena Belousova, Steven Sparagana, E Martina Bebin, Michael Frost, Rachel Kuperman, Olaf Witt, Michael H Kohrman, J Robert Flamini, Joyce Y Wu, Paolo Curatolo, Petrus J de Vries, Vicky H Whittemore, Elizabeth A Thiele, James P Ford, Gaurav Shah, Helene Cauwel, David Lebwohl, Tarek Sahmoud, Sergiusz Jozwiak

117 patients

2:1 randomisation everolimus:placebo

35% of patients in everolimus group had > 50% reduction in SEGA volume versus 0% in placebo group

No effect on epilepsy

Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial

John J Bissler, J Christopher Kingswood, Elżbieta Radzikowska, Bernard A Zonnenberg, Michael Frost, Elena Belousova, Matthias Sauter, Norio Nonomura, Susanne Brakemeier, Petrus J de Vries, Vicky H Whittemore, David Chen, Tarek Sahmoud, Gaurav Shah, Jeremie Lincy, David Lebwohl, Klemens Budde

118 patients

2:1 randomisation

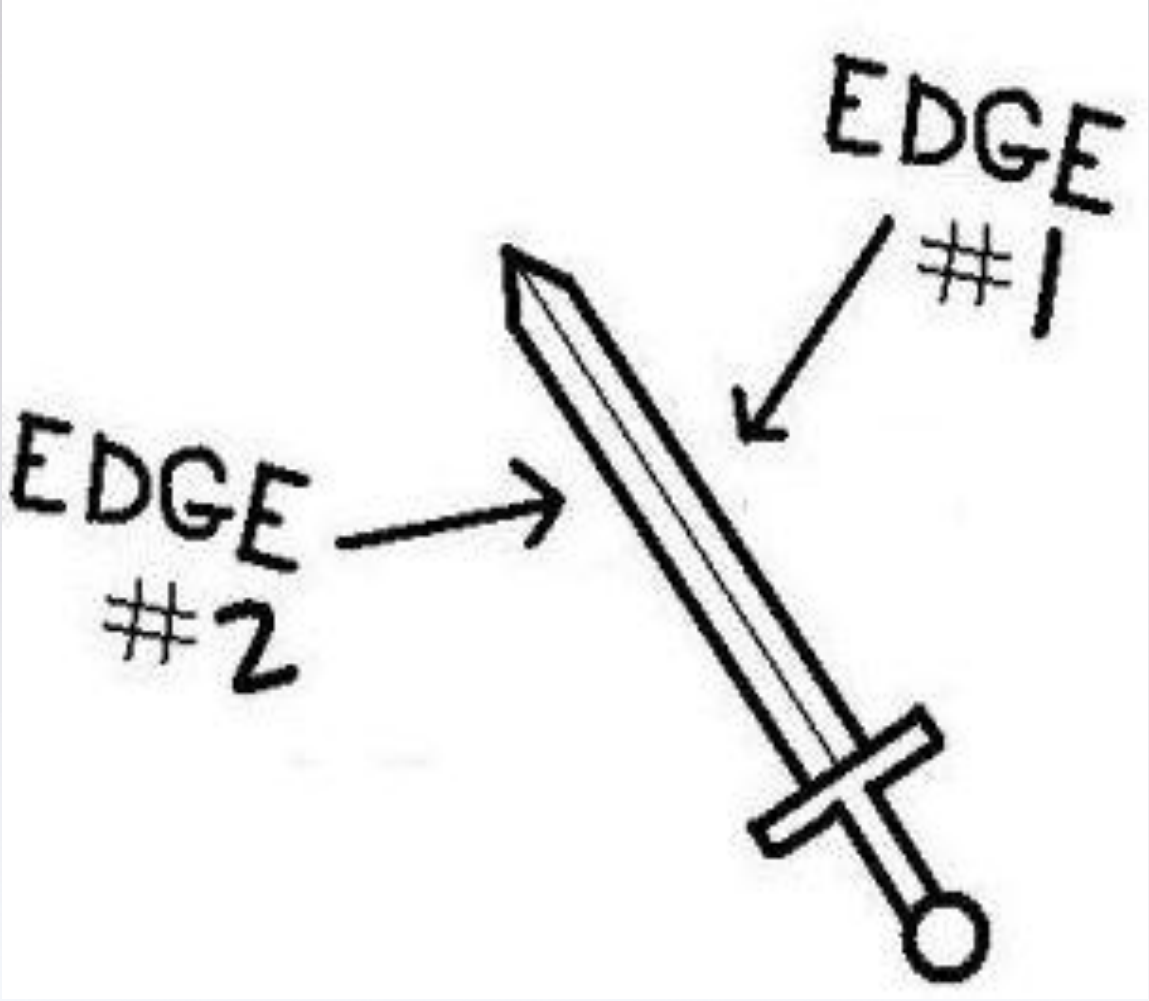
42% had >50% reduction in AML volume versus 0% on placebo

No effect on epilepsy

Current Trials

- EXIST-3
  - Placebo-controlled trial of everolimus in patients with intractable focal epilepsy
- MiTS (Metformin in TS)
  - Placebo-controlled trial of metformin in TS
  - Patients with angiomyolipomas of 1cm
  - Primary outcome = reduction in renal aml volume
  - Secondary outcomes incl epilepsy, SEGA

mTOR inhibition – a double-edged sword?



Regulation of cell death and epileptogenesis by the mammalian target of rapamycin (mTOR)

A double-edged sword?

Ling-Hui Zeng,[1] Sharon McDaniel,[2] Nicholas R. Rensing[2] and Michael Wong[2]

[1]Department of Pharmacy; Zhejiang University City College; Hangzhou, Zhejiang China; [2]Department of Neurology and the Hope Center for Neurological Disorders; Washington University School of Medicine; St. Louis, MO USA

- mTOR inhibition may prevent essential repair of brain in the context of brain injury

- Paradoxical effect of mTOR inhibitors in animal models of status epilepticus
    - Timing of administration

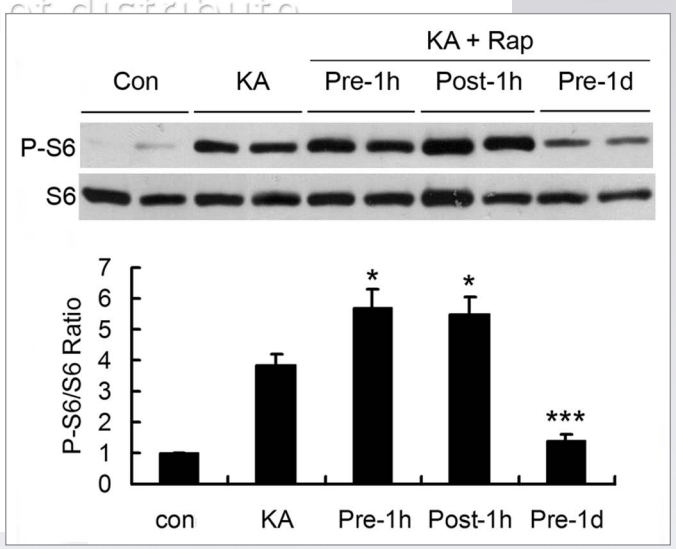


Figure 3. Rapamycin causes paradoxical exacerbation of kainate-induced mTOR activation when administered within one hour of kainate. Adult rats were injected with vehicle (Con), kainate (15 mg/kg, i.p.), or rapamycin (6 mg/kg) at different intervals before or after kainate. Kainate alone (KA) causes increased mTOR activation, as reflected by the ratio of phospho-S6 to total S6 expression measured 7 days after kainate injection, compared to vehicle (Con). Pretreatment with rapamycin one day prior to kainate inhibits the kainate-induced mTOR activation (Pre-1d). In contrast, rapamycin administered within one hour before (Pre-1 h) or after (Post-1 h) kainate causes a paradoxical increase in the kainate-induced mTOR activation. *$p < 0.05$, ***$p < 0.001$ by ANOVA, compared to the KA group.