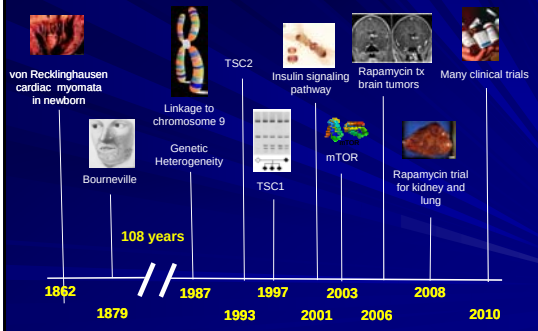
Tuberous Sclerosis Complex: From Bedside to Bench and Back Again

Hope Northrup, MD
Director, Division of Medical Genetics
Professor, Department of Pediatrics
The University of Texas Medical School at Houston

Timeline of TSC Discoveries



Tuberous Sclerosis Complex (TSC)

- Autosomal dominant disorder in humans
- Develop hamartomas (benign tumors resulting from excessive growth of normal tissues)
- Most frequently affects: skin, brain, kidney, heart and retina
- Every tissue type of the body can be affected

Clinical Features of Tuberous Sclerosis

Dermatologic Findings

Hypomelanotic macules

Facial angiofibromas

Clinical Features of Tuberous Sclerosis

Dermatologic Findings

Ungual fibromas

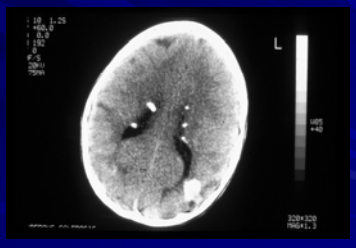
Shagreen patches

Fibrous facial plaques

Clinical Features of Tuberous Sclerosis

Central Nervous System Findings

Subependymal glial nodules, Cortical tubers, SEGAs



Seizures, Mental retardation/developmental delay

Clinical Features of Tuberous Sclerosis

Renal Findings

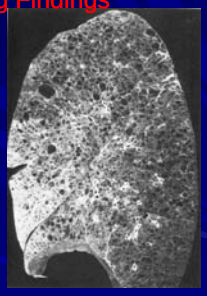
Angiomyolipomas, Cysts, RCCs

Clinical Features of Tuberous Sclerosis

Cardiac and Lung Findings

Lymphangioleiomyomatosis

Cardiac rhabdomyomas



Frequency of Disease Phenotype Observed Among TSC Patients

Phenotype	Frequencies
Cortical tuber	~90%
Facial angiofibroma	>80%
Renal angiomyolipoma	>80%
Subependymal nodule	~80%
Cardiac rhabdomyomas	~50%
Ungual/subungual fibroma	52~88%

Diagnostic Criteria for Tuberous Sclerosis Complex (1998)

11 Major Features

- Facial angiofibroma, forehead plaques (≥2)
- Nontraumatic ungual/periungual fibromas (>2)
- Hypomelanotic macules (≥ 3)
- Shagreen patch (>3)
- Multiple retinal nodular hamartomas
- Cortical tuber (>2)
- Subependymal nodule (>2)
- Subependymal giant cell astrocytoma (>2)
- Cardiac rhabdomyomas
- Lymphangiomyomatosis
- Renal angiomyolipomas

9 Minor Features

- Dental enamel pits (>3)
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines (>3)
- Gingival fibromas (>2)
- Nonrenal hamartomas
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts

Definite TSC: 2 major features or 1 major features with 2 minor features
Probable TSC: 1 major and 1 minor features
Possible TSC: either 1 major feature or ≥2 minor features
Other organs involved: liver, pancreas, thyroid, gonads, arteries, uterus etc.

Causes of Premature Death in TSC Patients

13/40	(32.5%)	Complications related to severe mental retardation (status epilepticus: bronchpneumonia)
11/40	(27.5%)	Renal disease
10/40	(25%)	Brain tumors
4/40	(10%)	Lymphangiomyomatosis
1/40	(2.5%)	Cardiac rhabdomyomas
1/40	(2.5%)	Thoracic aneurysm
40/355	(11.3%)	Individuals with TSC Followed Long-Term

Genetic Aspects of TSC in 1987

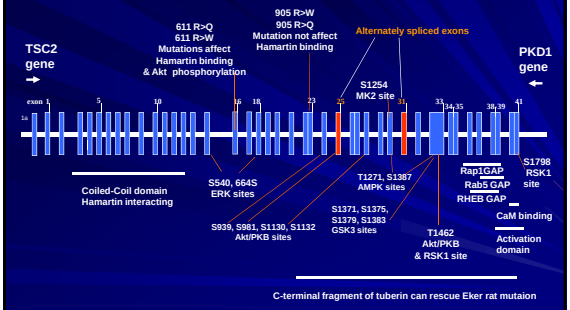
- Autosomal dominant inheritance
- Two-thirds of cases sporadic
- One-third of cases familial
- Variable expression
- Common in the population with approximately 1:6,000-10,000 individuals affected

Identification and characterization of the tuberous sclerosis gene on chromosome 16.

The European Chromosome 16 Tuberous Sclerosis Consortium

Cell 75: 1305 – 1315, 1993.

TSC2 Gene Structure and Functions

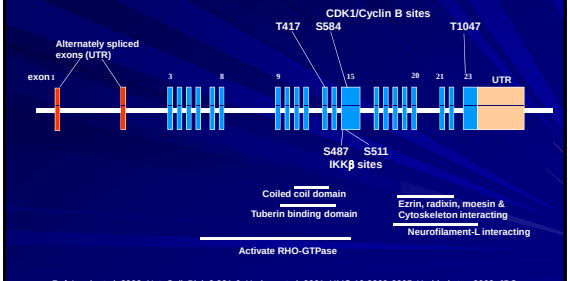


Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34.

van Slegtenhorst M, de Hoogt R, Hermans C, Nellist M, Janssen B, Verhoef S, Lindhout D, van den Ouweland A, Halley D, Young J, Burley M, Jeremiah S, Woodward K, Nahmias J, Fox M, Ekong R, Osborne J, Wolfe J, Povey S, Snell RG, Cheadle JP, Jones AC, Tachataki M, Ravine D, Sampson JR, Reeve MP, Richardson P, Wilmer F, Munro C, Hawkins TL, Sepp T, Ali JBM, Ward S, Green AJ, Yates JRW, Kwiatkowska J, Hanske EP, Short MP, Haines JH, Jozwiak S, Kwiatkowski DJ.

Science 277: 805 – 808, 1997.

TSC1 Gene Structure and Functions



Ref. Lamb et al. 2000. Nat. Cell. Biol. 2:281-6. Hodges et al. 2001. HMG 10:2899-2905. Haddad et a. 2002. JBC 277:44180-6.

TSC Genotype

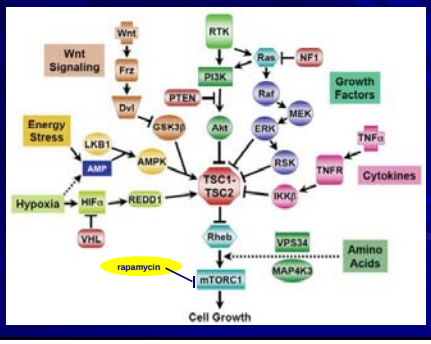
~85% of affected individuals have identifiable *TSC1* or *TSC2* gene mutation

- *TSC1* – over 95% protein truncating
- *TSC2* – ~25% missense and ~70% protein truncating, ~5% large gene deletion/duplication

Remainder of mutations likely represent:

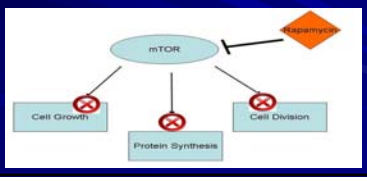
- Somatic mosaicism
- Mutations in unanalyzed gene regions
- Additional loci?

Pathways Involving TSC1/TSC2



Rapamycin

- Naturally occurring substance
- Discovered in 1965
- Binds mTOR and inhibits its action, thus preventing cell division and growth
- Also decreases levels of VEGF



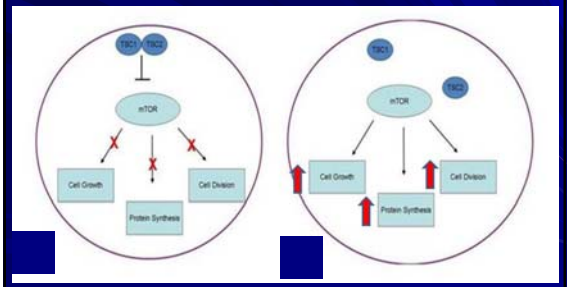
Rapamycin

- Approved by the FDA in 1999 as an immunosuppressant drug to be used post renal transplant
- Side effect profile well defined:
  - Immunosuppression
  - Oral Ulcers
  - Skin Breakdown
  - Poor wound healing
  - Hyperlipidemia
  - Thrombocytopenia

Therapy

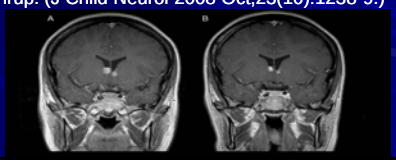
- Rapamycin-down-regulates mTOR activity
- Eker rat studies-rats with pituitary and renal tumors had improved clinical state and prolonged survival (Kenerson et al., 2005)

TSC & mTOR



Rapamycin causes regression of astrocytomas in tuberous sclerosis complex.
Franz DN, Leonard J, Tudor C, Chuck G, Care M, Sethuraman G, Dinopoulos A, Thomas G, Crone KR.
Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH 45229-3039, USA. david.franz@cchmc.org
Ann Neurol. 2006 Mar;59(3):490-8.

- 1st report of use of rapamycin in TSC patients
- Showed regression of astrocytomas with low dose rapamycin
- Confirmed in subsequent case report by Koenig, Butler, & Northrup. (J Child Neurol 2008 Oct;23(10):1238-9.)



A. Baseline

B. 2.5 months after rapamycin therapy

C. Recurrence after 8 months on rapamycin therapy, then 4 months without drug

D. 8 months after therapy resumed

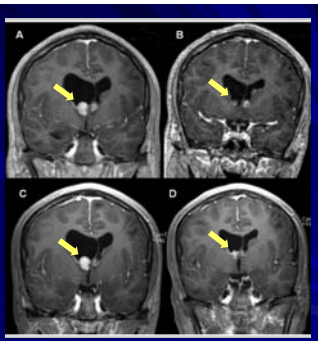
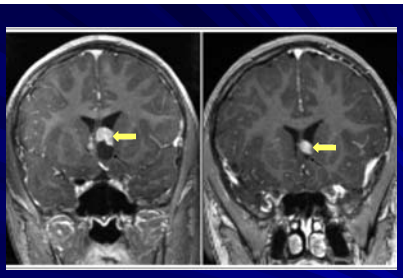


Figure 2. Case 1. Coronal T1 contrast-enhanced magnetic resonance imaging. Long-term follow-up: continued regression 20 months after starting rapamycin therapy, 8 months after therapy resumed. (Franz et al. Feb. 2006. Annals of Neurology. Articles online in advance of print)



Baseline
13.7 × 23.4mm
(volume, 3.4cc)

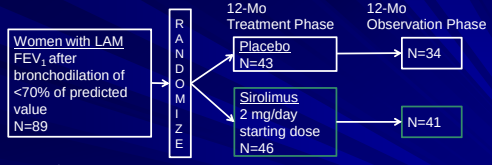
2.5 months Posttreatment
8.1 × 13.7mm
(volume, 1.7cc).

Figure 6. Case 5. Reduction in cystic (*black arrows*) and solid (*white arrows*) components of a giant cell astrocytoma following 2.5 months rapamycin therapy. (Left). (Right) Coronal T1 contrast-enhanced magnetic resonance imaging.
(Franz et al. Feb. 2006. Annals of Neurology. Articles online in advance of print)

Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphagioleiomyomatosis.
Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, Schmithorst VJ, Laor T, Brody AS, Bean J, Salisbury S, Franz DN.
Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
45229-3039, USA. John.bissler@cchmc.org
N Engl J Med. 2008 Jan 10;358(2):140-51.

- 24-month, nonrandomized, open-label trial to assess volume of AMLs and LAM in patients with TSC receiving oral rapamycin
  - 25 subjects
  - AMLs decreased in volume up to 30%
  - LAM patients had improvements in spirometric measurements

Safety and Efficacy of Sirolimus in LAM (MILES) Study Design



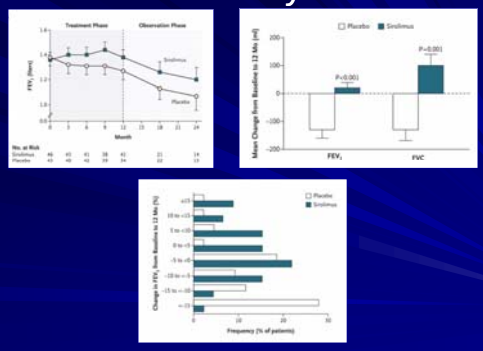
- Primary outcome: FEV_1 response
- Secondary outcomes: forced vital capacity response, lung volumes, distance covered on 6-min walk test, diffusing capacity CO, serum vascular endothelial growth factor-D levels, function, and QOL scores*

*St. George's Respiratory Questionnaire, Medical Outcomes Study 36-Item Short-Form Health Survey, Functional Performance Inventory, General Well-Being Questionnaire, EuroQOL visual-analogue scale

CO=carbon monoxide; QOL=quality of life.

McCormack. *N Eng J Med.* 2011;364(17):1595.

MILES: Efficacy Results



Reproduced with permission from McCormack. *N Eng J Med.* 2011;364(17):1595.

Rapamycin and facial angiofibromas in TSC

The mTOR inhibitor rapamycin significantly improves facial angiofibroma lesions in a patient with tuberous sclerosis
Hofbauer GF, Marcollo-Pini A, Corsenca A, Kistler AD, French LE, Wuthrich RP, Serra AL.
Department of Dermatology, University Hospital, Zurich, Switzerland. hofbauer@usz.ch
Br J Dermatol. 2008 Aug;159(2):473-5.

Topical rapamycin: a novel approach to facial angiofibromas in tuberous sclerosis.
Haemel AK, O'Brian AL, Teng JM.
Departments of Dermatology and Pediatrics, University of Wisconsin School of Medicine and Public Health, 1 S Park St, Seventh Floor, Madison, WI 53715. jteng@dermatology.wisc.edu.
Arch Dermatol. 2010 Jul;146(7):715-8.