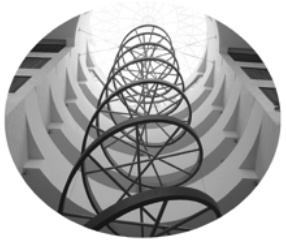
Malattia Policistica e Sclerosi Tuberosa: dal Gene alla Terapia



Division of Genetics and Cell Biology
San Raffaele Scientific Institute

Divisione di Genetica e Biologia Cellulare
Ospedale San Raffaele/Istituto Telethon Dulbecco

28° Congresso Nazionale della Società Italiana di Nefrologia Pediatrica

Milano, 24 Ottobre, 2012

1) Polycystic Kidney Diseases:

- Autosomal Dominant (ADPKD) also called the “adult form”
- Autosomal Recessive (ARPKD) also called “of the Child”

Recently, patients carrying hypomorphic mutations of the ADPKD gene in homozygosity were also identified!! No time to talk about this today

2) Tuberous Sclerosis Complex (TSC):

- 80% of patents develop renal angiomyolipoma, 20% develop cysts
- PKD1/TSC2 Contiguous genes Syndrome: severe PKD

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

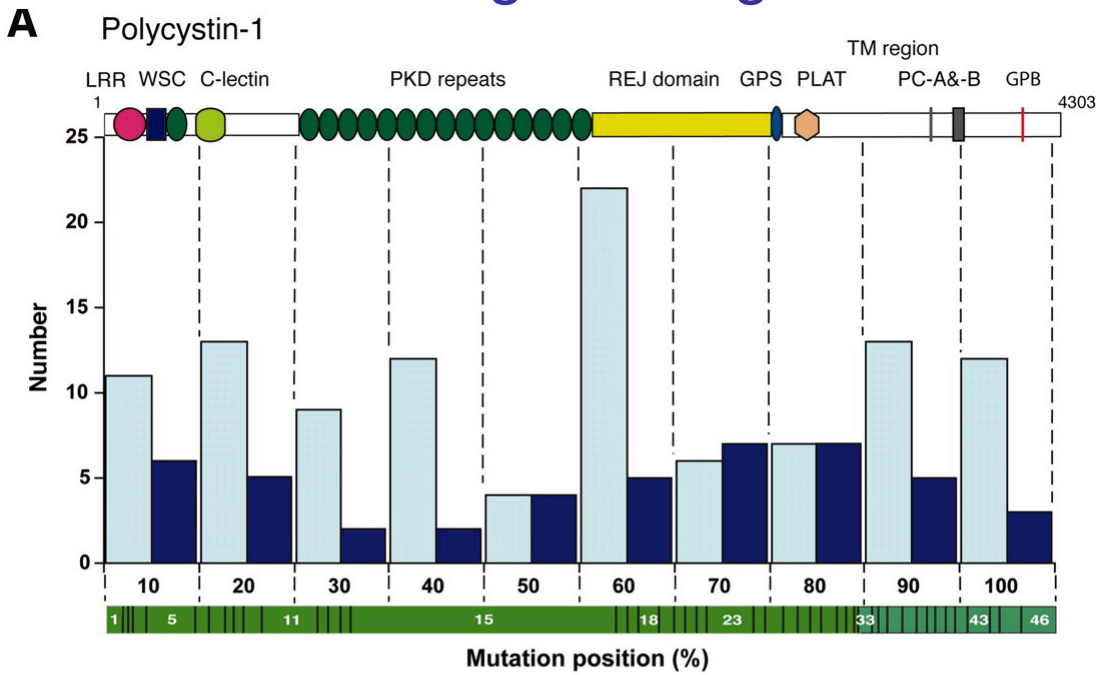
- **1/500-1/1000** of the general population
- Characterized by **bilateral renal cysts formation.**
- Systemic Disease:
  liver and pancreatic cysts.
  Cardiovascular defects**, Intracranial** and **aortic aneurysms.**
- Important cause of End Stage Renal Disease (ESRD), which occurs by age 50 in 50% of the patients (but a significant fraction is already present in infants)

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Mutations of 2 genes:

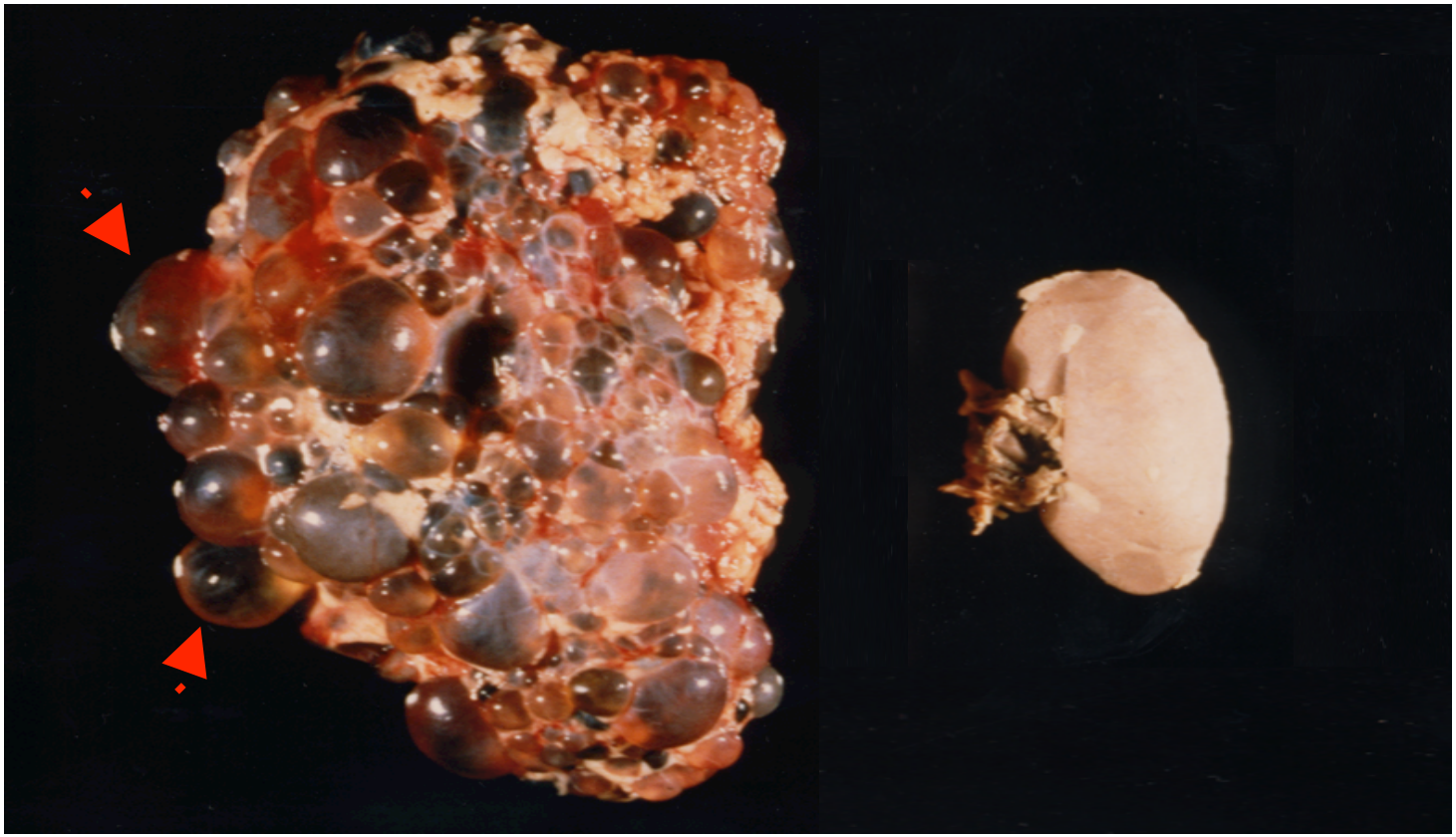
- PKD1 ⟶ 85% of all cases, chromosome 16p13.3
- PKD2 ⟶ 15% of cases, chromosome 4q22

ADPKD è dovuta a mutazioni loss-of-function disperse lungo i due geni



Rossetti et al, *J Am Soc Nephrol*, 2007

End Stage Polycystic Kidney (ADPKD)



PKD Foundation, www.pkdcure.com

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

- **1/10,000-1/40,000** of the general population
- Characterized by **bilateral renal cysts formation.**
- **Liver cysts (hepatomegaly)** are always present, but might not be yet visible at birth
- **Severe Hypertension**
- **Oligohydramnios** causing **pulmonary hypoplasia** is a frequent cause of death at birth (secondary)
- **Neonatal/infant** presentation in the majority of cases, but it can present in late childhood and adults

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Mutations of a Single gene:

- PKHD1 ⟶ chromosome 6p21

A very large gene which, undergoing a number of alternative splicing and having mutations dispersed all along the gene

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

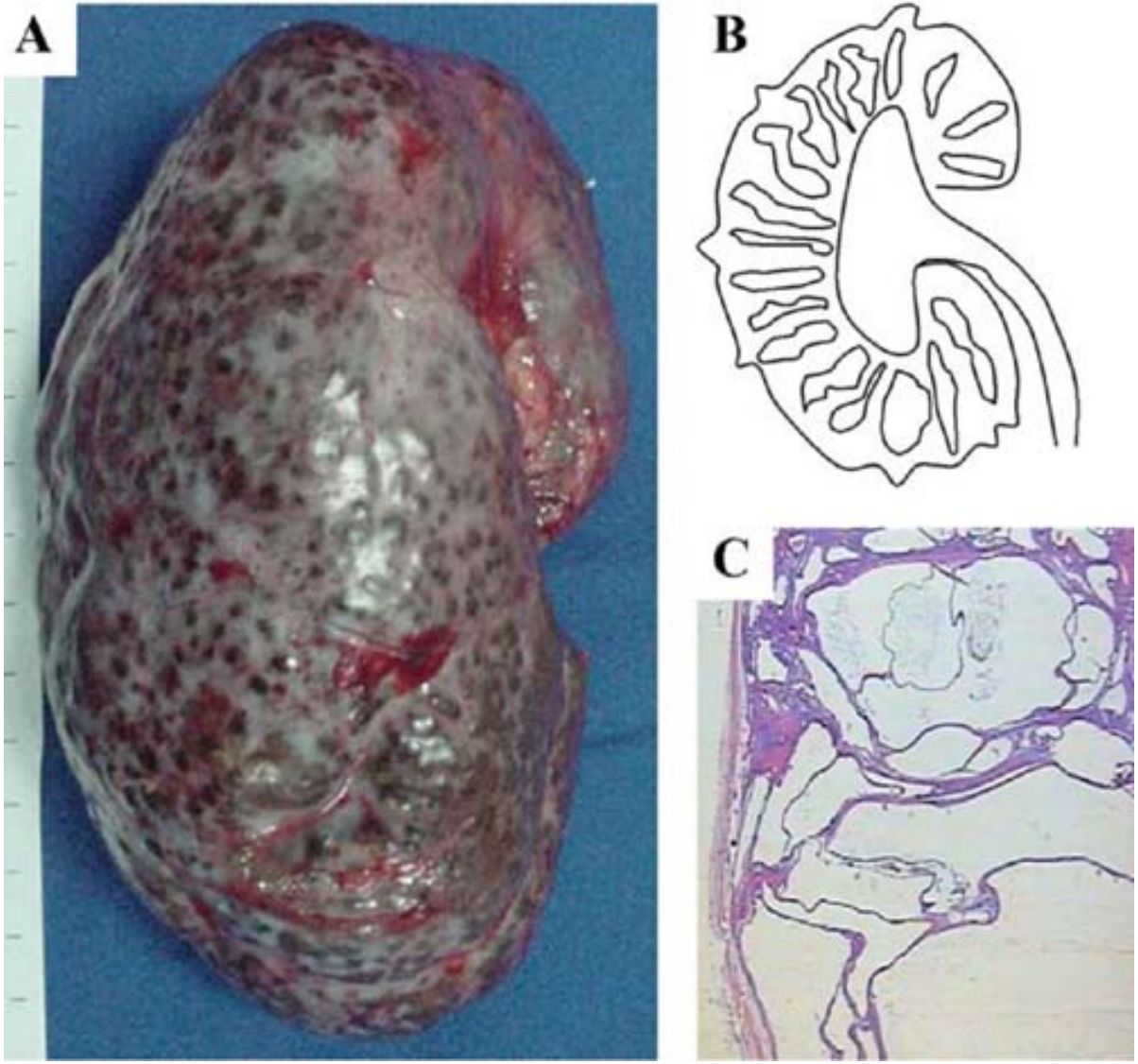
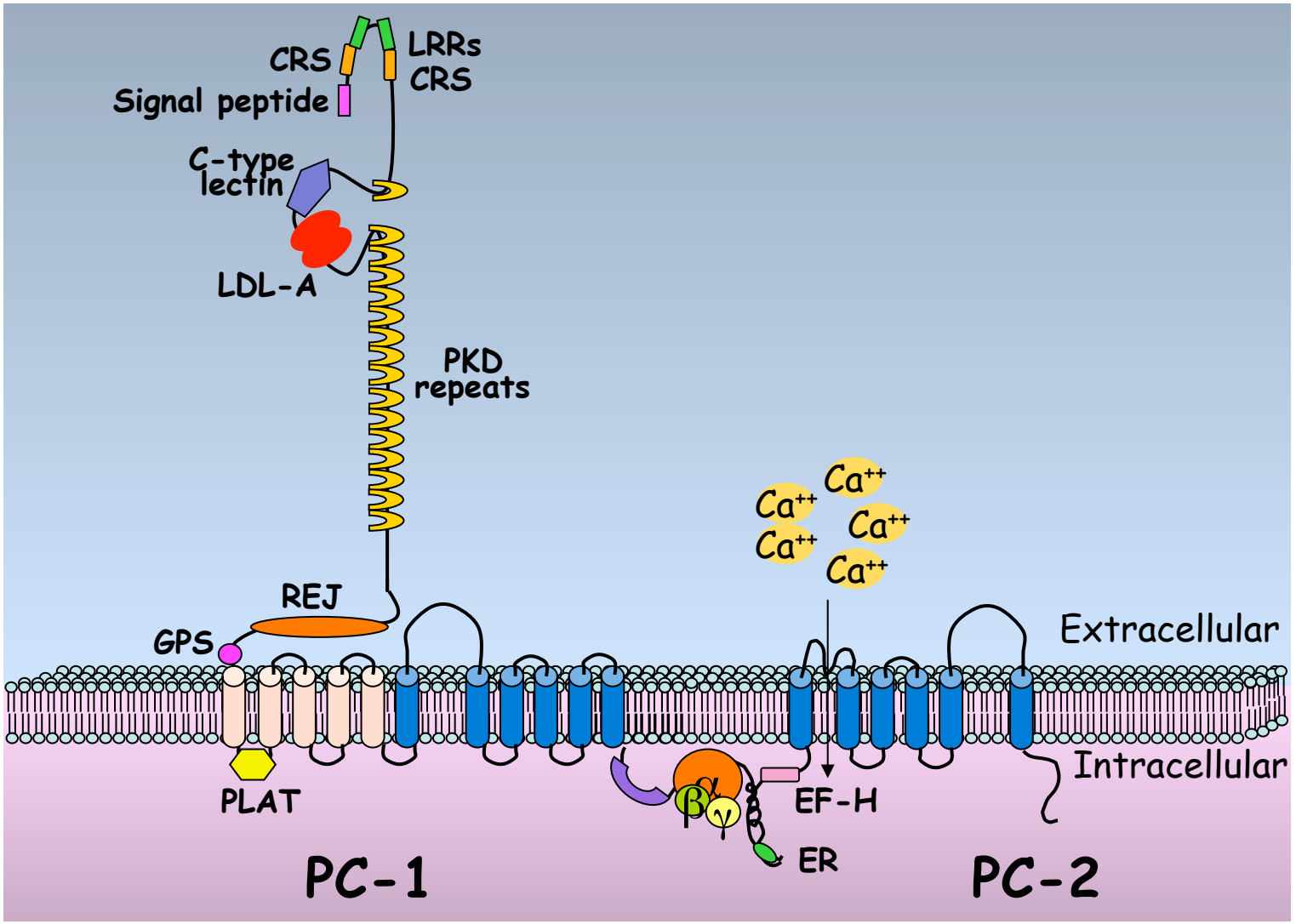


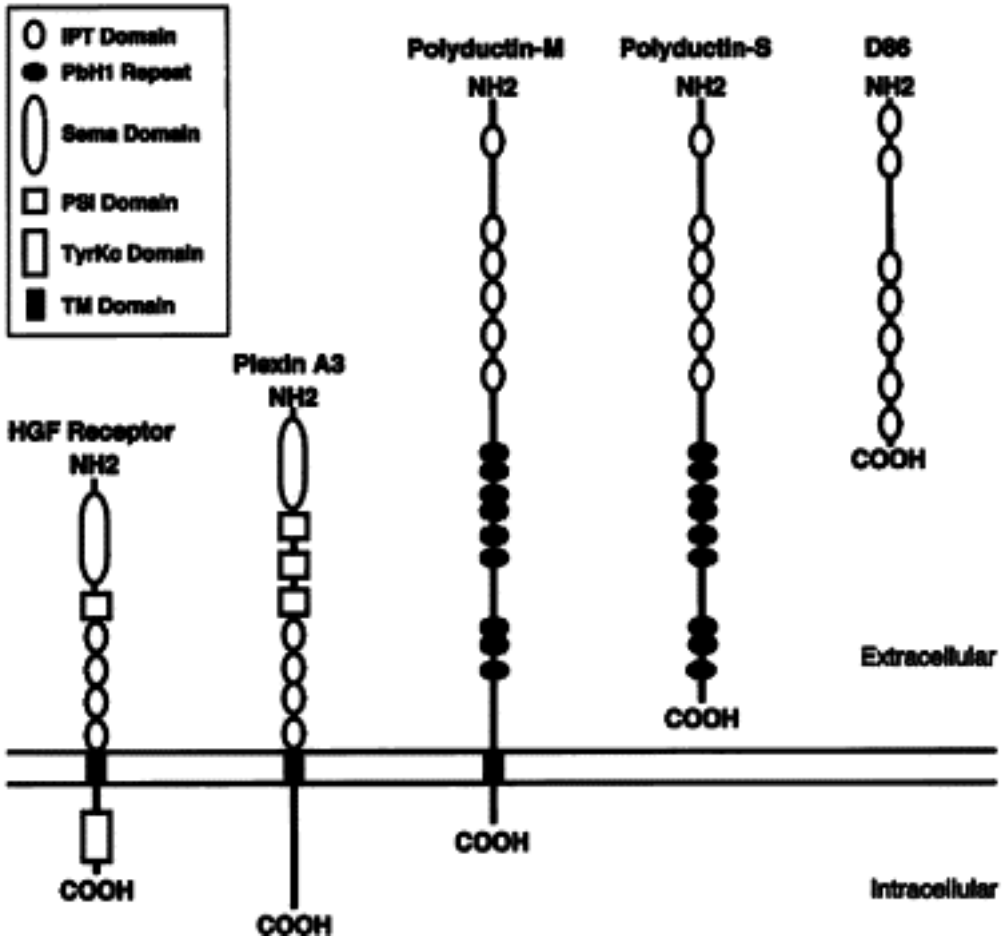
Figure 1. Renal pathology of autosomal recessive polycystic kidney disease. A, Kidney of a 2-year-old ARPKD-affected child.

L.F. Menezes and L.F. Onuchic.. Braz J Med Biol Res 2006; 39: 1537-1548.

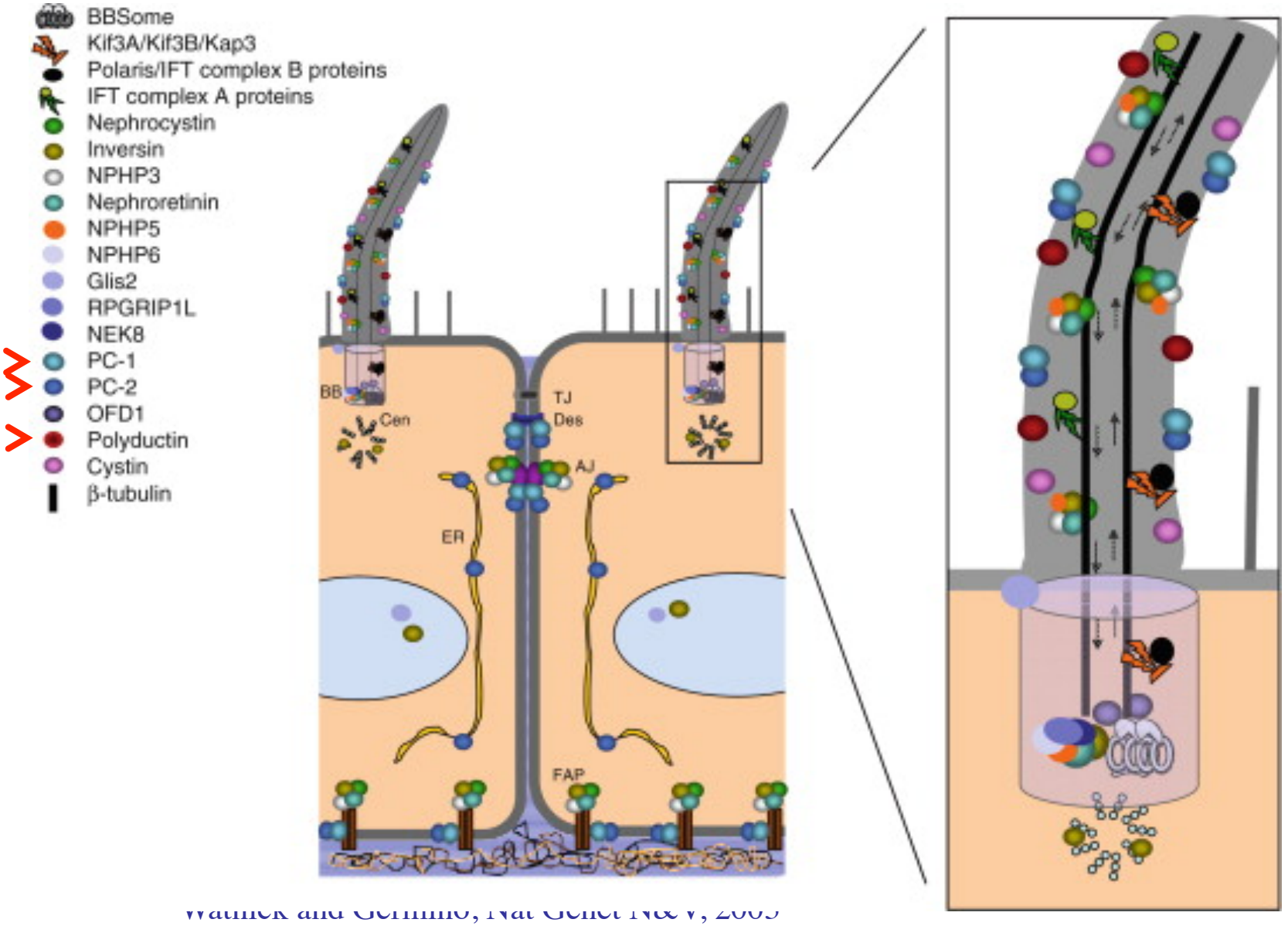
Polycystins Structure



Polyductin/Fibrocystin



The “Cystoproteins”-Cilia Connection: Sensing Flow to Maintain the Tubular Diameter?



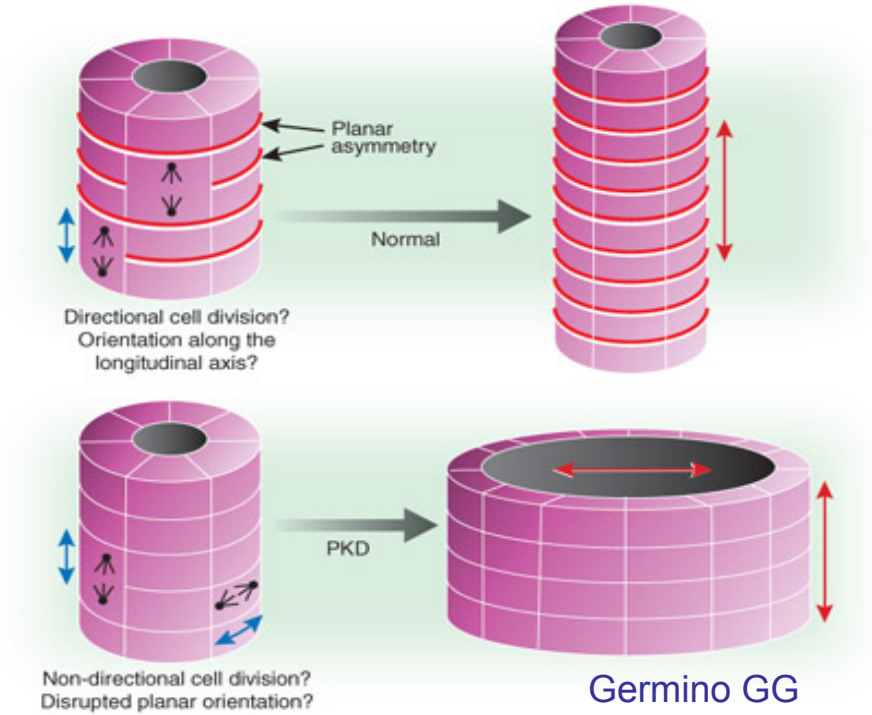
Wathek and Germino, Nat Genet N&V, 2005

The Planar Cell Polarity (PCP) Hypothesis, I
oriented cell division

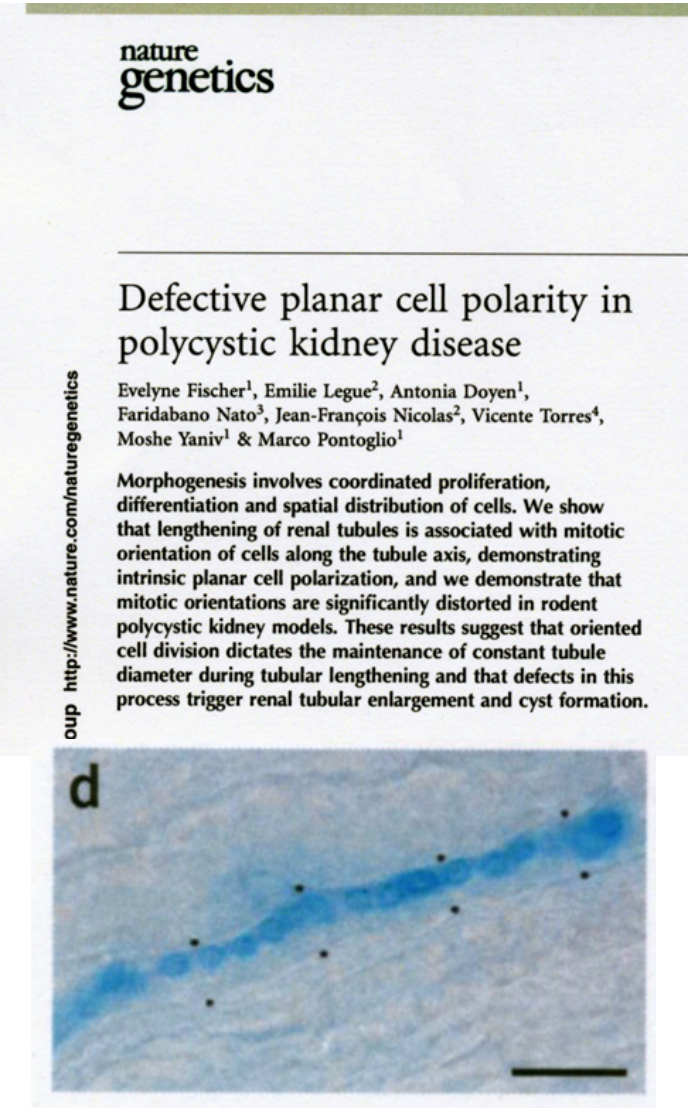
nature genetics

Inversin, the gene product mutated in nephronophthisis type II, functions as a molecular switch between Wnt signaling pathways

Matias Simons[1,6], Joachim Gloy[1,6], Athina Ganner[1], Axel Bullerkotte[1], Mikhail Bashkurov[1], Corinna Krönig[1], Bernhard Schermer[1], Thomas Benzing[1], Olga A Cabello[2], Andreas Jenny[3], Marek Mlodzik[3], Bozena Polok[4], Wolfgang Driever[4], Tomoko Obara[5] & Gerd Walz[1]



Germino GG
Nat Genet N&V, 2005

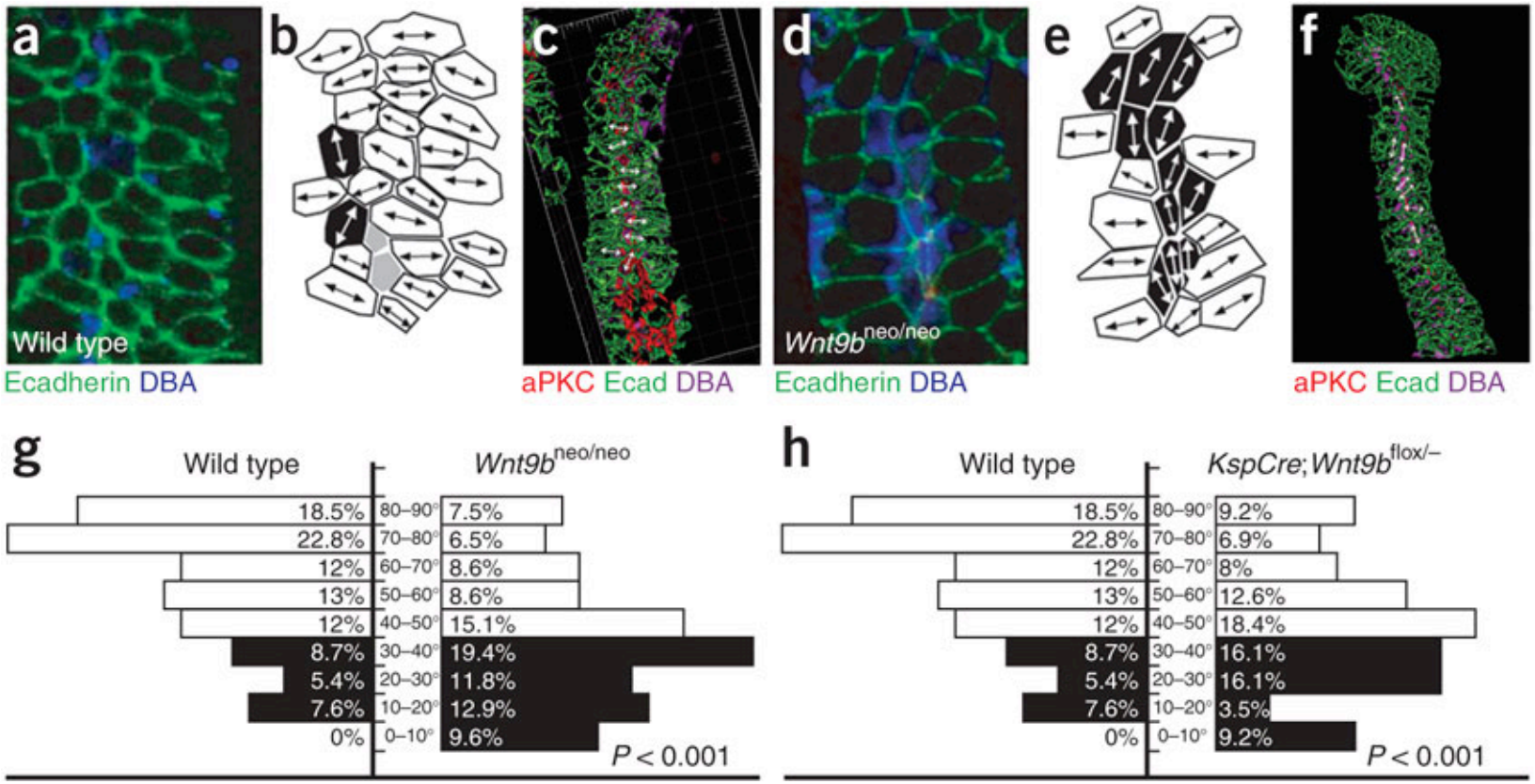


The Planar Cell Polarity (PCP) Hypothesis, II
convergent extension movements

nature genetics

Wnt9b signaling regulates planar cell polarity and kidney tubule morphogenesis

Courtney M Karner[1,2], Rani Chirumamilla[1,2], Shigehisa Aoki[1,3], Peter Igarashi[1,4], John B Wallingford[5] & Thomas J Carroll[1,2]

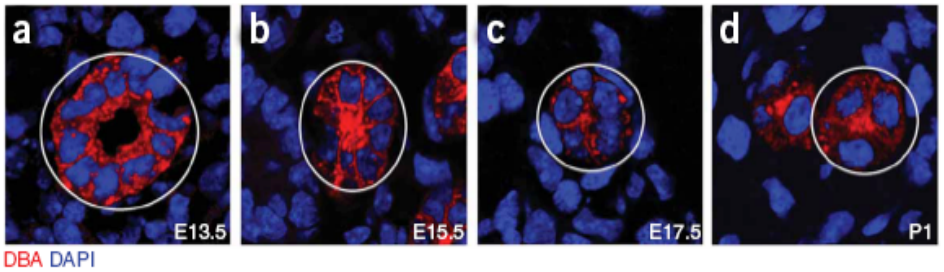


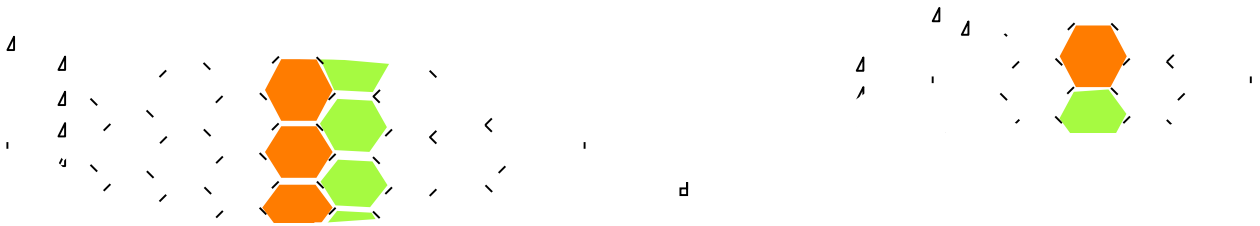
Planar polarity in the developing kidney: convergent extension

nature genetics

Wnt9b signaling regulates planar cell polarity and kidney tubule morphogenesis

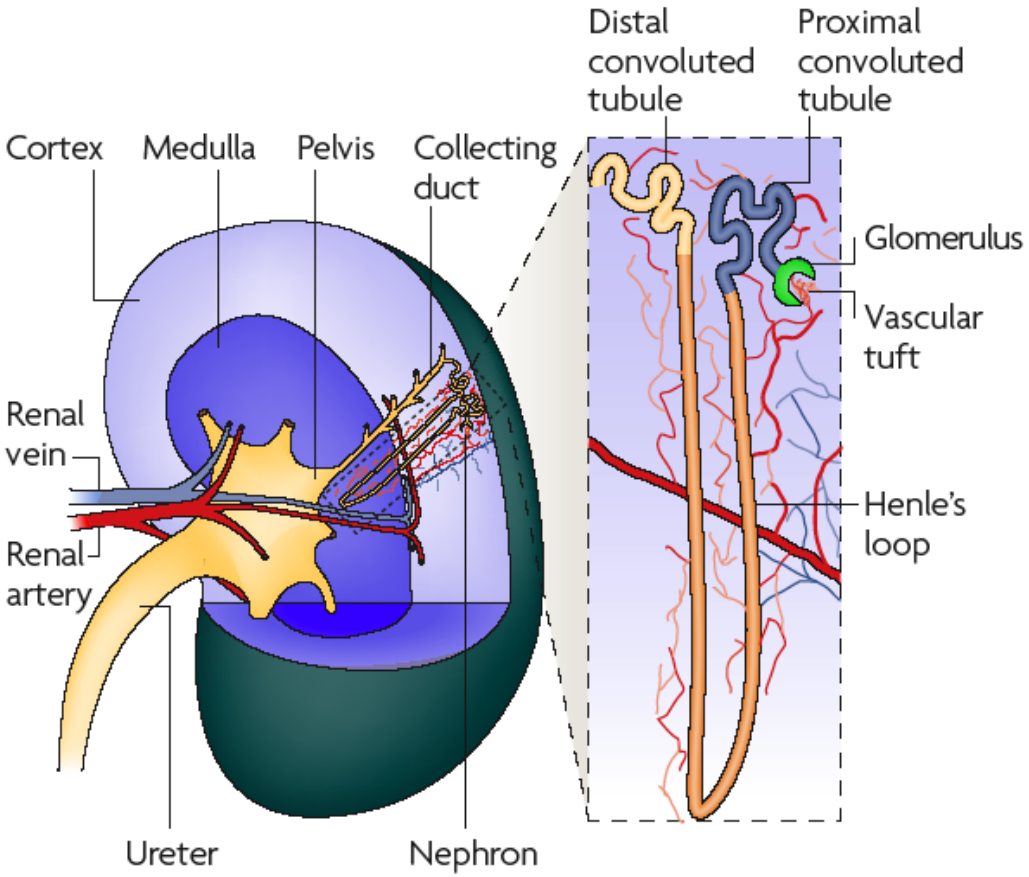
Courtney M Karner[1,2], Rani Chirumamilla[1,2], Shigehisa Aoki[1,3], Peter Igarashi[1,4], John B Wallingford[5] & Thomas J Carroll[1,2]

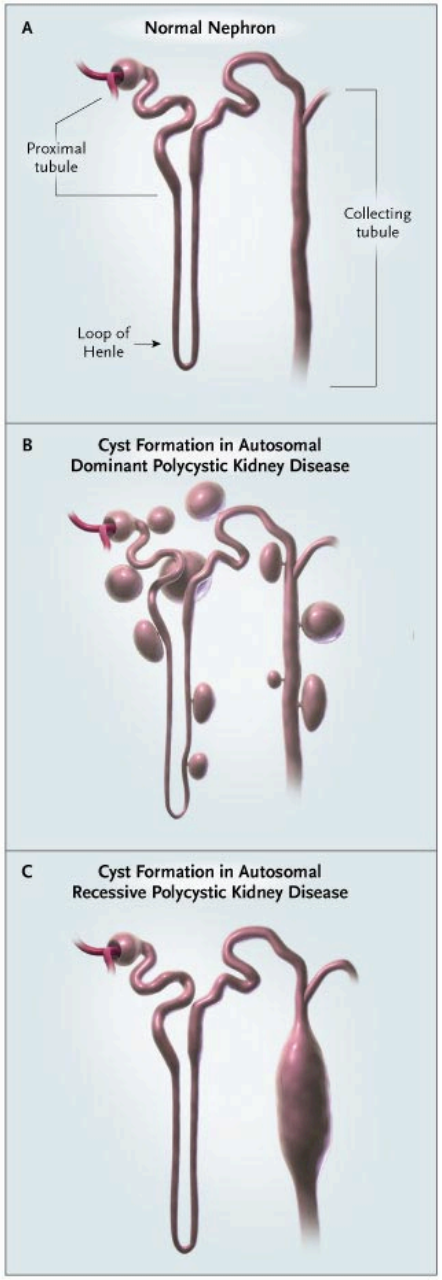


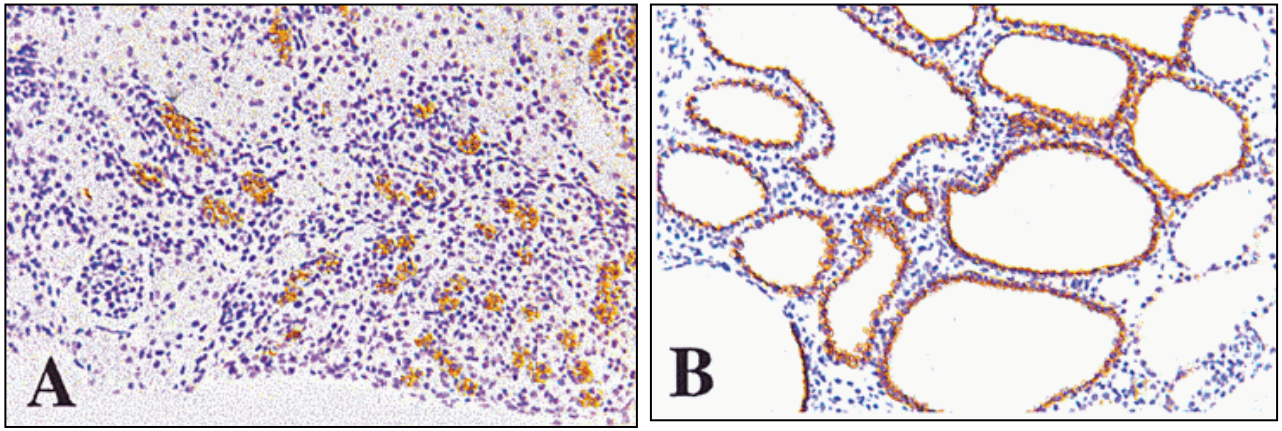


Important to note that the role of primary cilia in embryonic cyst formation has been challenged and it is possible that **this process might NOT be cilia-dependent**

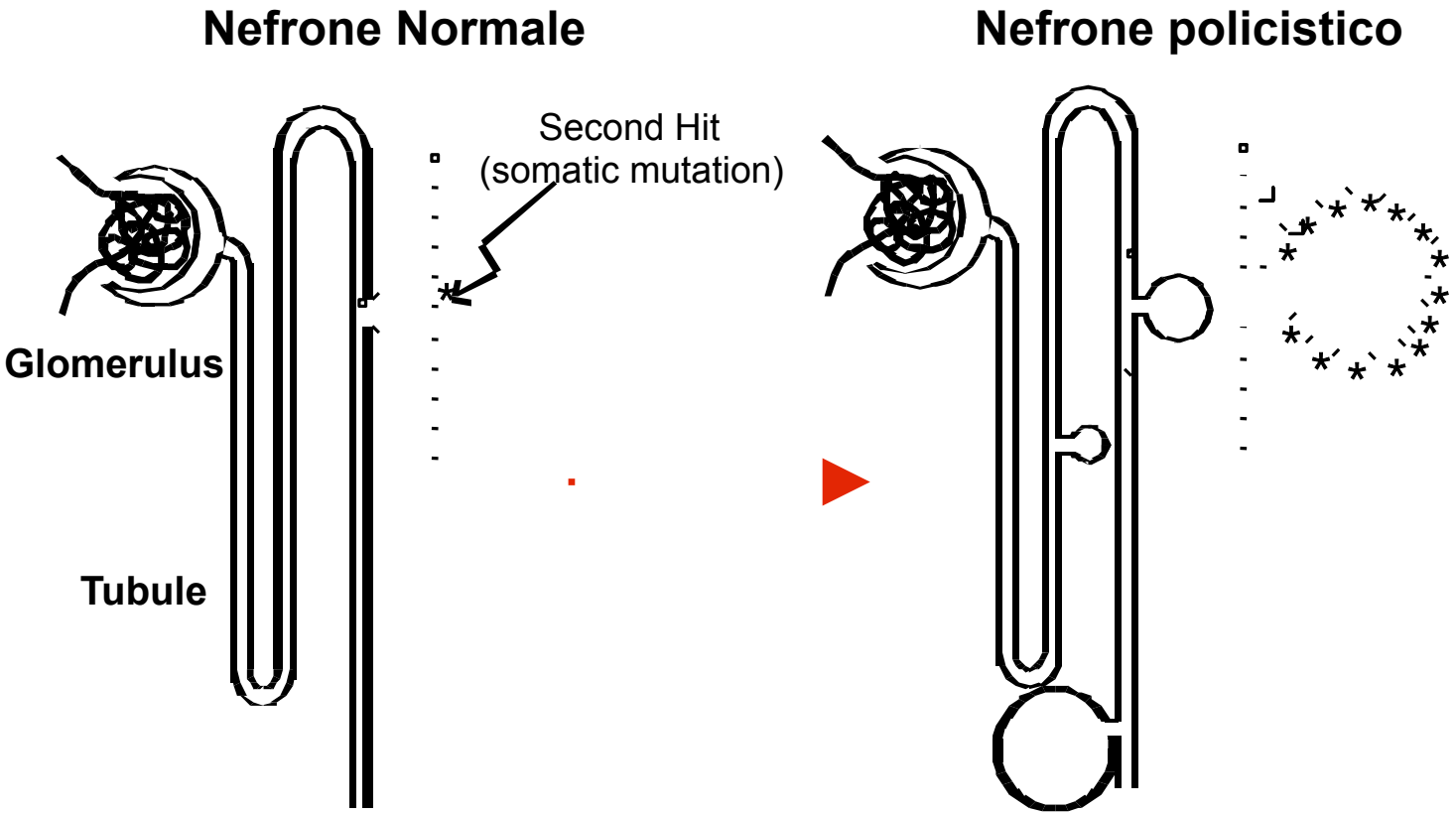
Polycystic Kidney Diseases





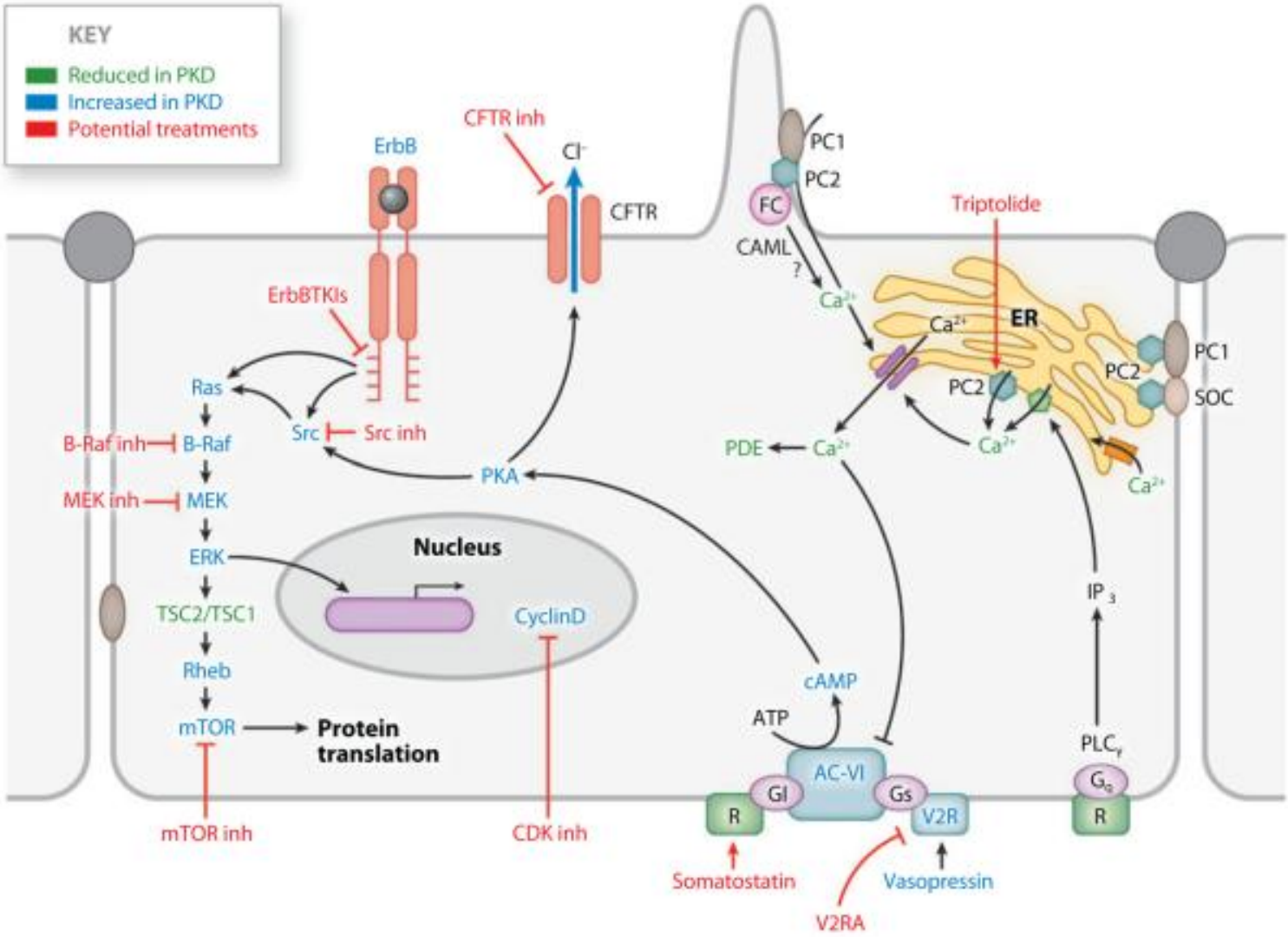


Two-hit model of cystogenesis in ADPKD



Qian F et al, Cell 87: 979-87, 1996

Cascate aumentate o diminuite nel rene policistico e potenzialmente utilizzate come targets terapeutici (primari or secondari?)



Torres V and Harris P Annu Rev Med 2009

Trials with Vasopressin receptor antagonists

CJASN Clinical Journal of the American Society of Nephrology

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Institution: FONDAZIONE CENTRO S RAFFAELE

Tolvaptan in Autosomal Dominant Polycystic Kidney Disease: Three Years' Experience

Eiji Higashihara*†, Vicente E. Torres*‡, Arlene B. Chapman§, Jared J. Grantham‖, Kyongtae Bae¶, Terry J. Watnick**, Shigeo Horie††, Kikuo Nutahara†, John Ouyang‡‡, Holly B. Krasa‡‡, Frank S. Czerwiec‡‡, for the TEMPO$_4$2 and 156-05-002 Study Investigators

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This Article

Published online before print September 2011, doi: 10.2215/CJN.03530411
CJASN October 2011 vol. 6 no. 10 2499-2507

Abstract *Free*

ADPKD cyst growth progresses more slowly with tolvaptan than in historical controls

very strong side effects (thirst and abnormally frequent urination)

The Tuberous Sclerosis Complex (TSC)

-Autosomal Dominant Genetic disease with an incidence of 1/6000

-**2 genes** causing the tuberous sclerosis clinical phenotype, **TSC1 (approx 15%) and TSC2 (Approx 75%)**.

-Hamartomas, often due to **Loss of heterozygosity (LOH)** for TSC1 and/or TSC2.

- Neurological disorder: mental retardation and seizures

Main Manifestations:

Facial Angiofibromas
Hypomelanotic macules
Cortical Tubers
Subependymal nodules
Giant Cell Astrocytomas
Cardiac Rhabdomas

Renal:

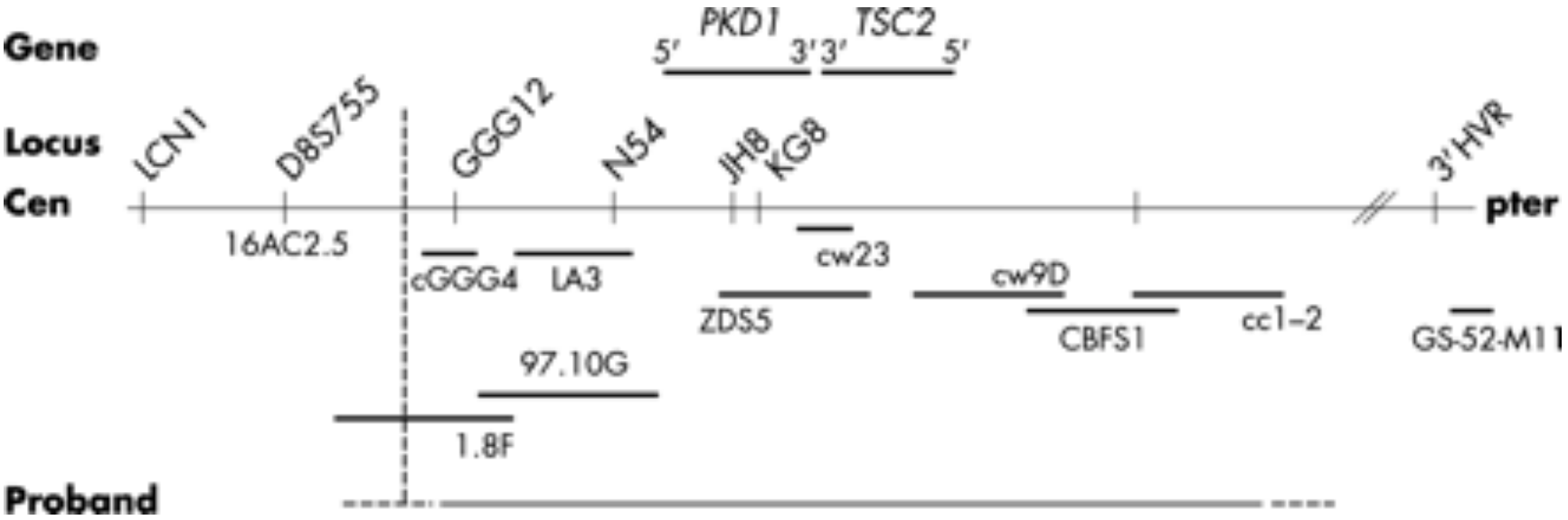
Almost all Patients have a renal manifestation:
80% benign Angyomyolipomas
Sporadic Renal Cysts Formation
Malignant Angiomyolipomas
Renal Cell Carcinoma

-About 20% of patients have **multiple and bilateral renal cysts formation**

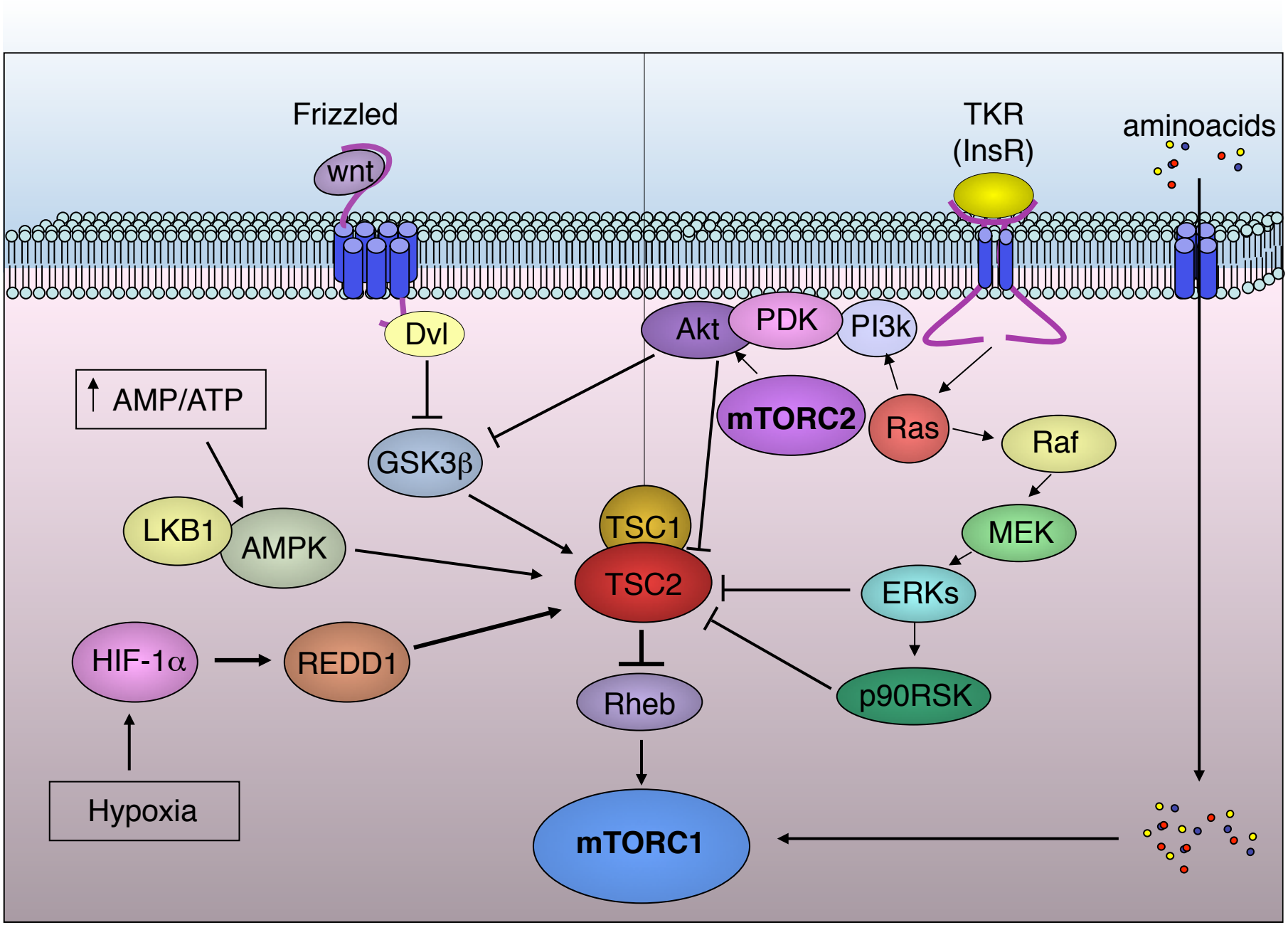
The PKD/TSC Contiguous Syndrome

-A PKD/TSC contiguous syndrome caused by large deletions of Chromosome 16 has been reported

-Patients manifest a **VERY SEVERE** Polycystic Kidney Disease

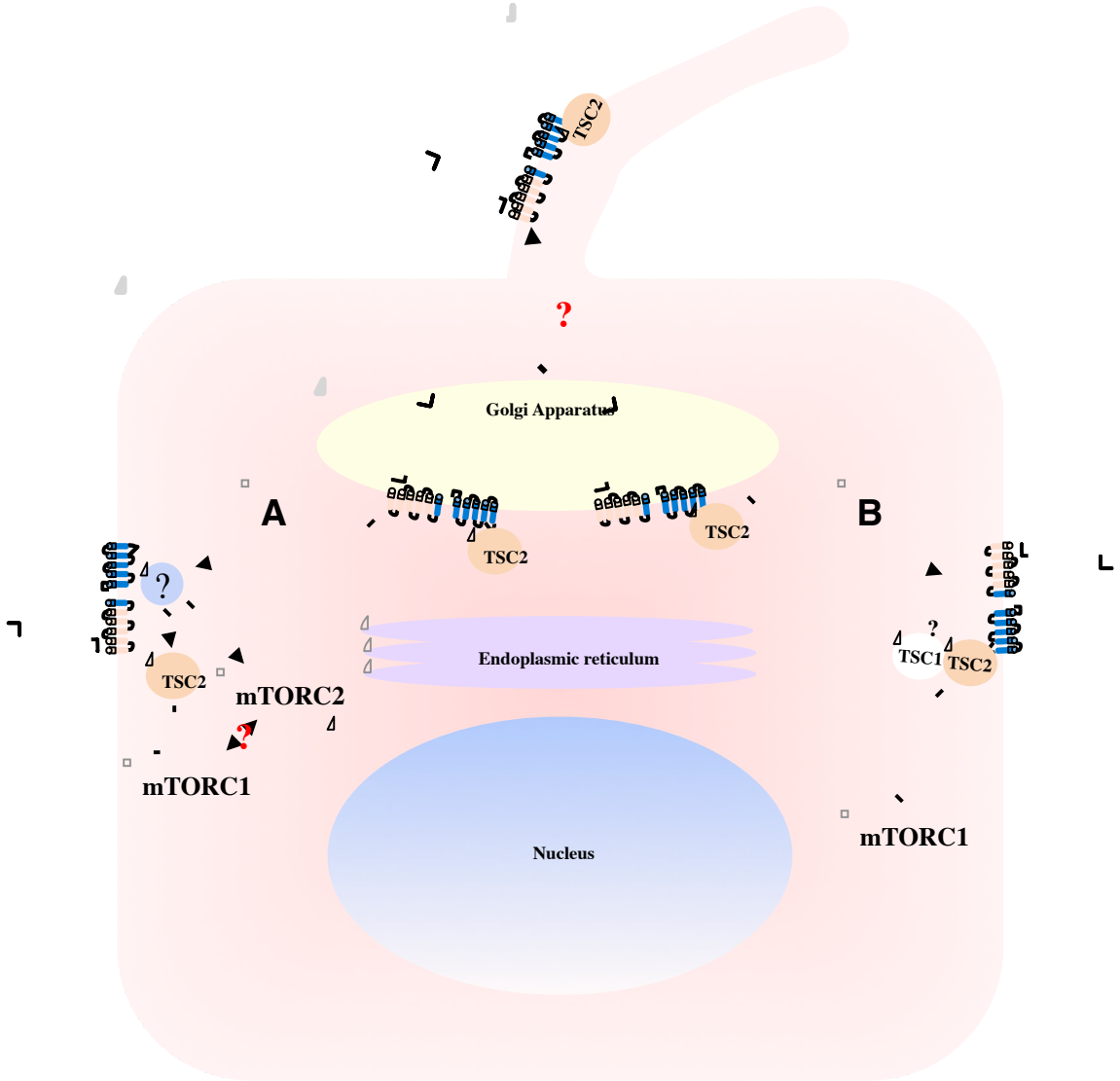


The Tuberous Sclerosis Complex (TSC) proteins regulate mTORC1



Torres, Boletta et al, CJASN, 2010

TSC and PKD co-operate somehow in regulating mTORC1?



A. Boletta, Pathogenetics, 2009

Evidence from pre-clinical animal models seemed to suggest that rapamycin might be a good treatment for PKD

Table 2. Summary of mTOR activation and sensitivity to mTOR inhibition in polycystic kidney rodent models

Rodent Model	Affected Protein	mTOR Activation in Kidneys?	Drug Treatment	Effective?	Reference
Han:SPRD rat (Cy/+ rat)	SamCystin (mutant protein)	Yes	SRL (0.2 mg/kg/d, IP)	Yes	Tao *et al.* (69)
			SRL (2 mg/kg/d, oral)	Yes	Wahl *et al.* (70)
			EVL (3 mg/kg/d, oral)	Yes	Wu *et al.* (72)
			SRL (0.2 mg/kg/d, IP)	Yes (long term)	Zafar *et al.* (73)
			SRL (2 mg/kg/d, oral)	Yes	Zhang *et al.* (71)
Pkd1 mouse model	Polycystin-1 (conditional, knockout)	Yes	SRL (5 mg/kg/d, IP)	Yes	Shillingford *et al.* (80)
Pkd2 mouse model	Polycystin-2	Yes (liver)	SRL (1.5 mg/kg/d, IP)	Yes (liver)	Spirli *et al.* (81)
MAL-transgenic mouse	MAL/VIP17 (overexpression)	Yes	ND	ND	Shillingford *et al.* (47)
orpk-rescue mouse	Polaris (re-expression of Polaris in hypomorphic mutant)	Yes	SRL (5 mg/kg/d, IP)	Yes	Shillingford *et al.* (47)
bpk mouse	Bicaudal-C (mutant protein)	ND	SRL (5 mg/kg/d, IP)	Yes	Shillingford *et al.* (47)
			SRL (1.67 mg/kg/d, IP)	Yes	
pcy mouse	Nephrocystin-3	Yes	SRL (3 mg/kg/d, oral)	Yes (late phase)	Gattone *et al.* (76)
		ND	SRL (5 mg/kg/d, IP)	Yes	Reichardt (77)
Folliculin KO mouse	FLCN (kidney-specific, conditional KO)	Yes	SRL (2 mg/kg/d, IP)	Yes	Baba *et al.* (46)

EVL, everolimus; IP, intraperitoneal; KO, knockout; ND, not determined; SRL, sirolimus.

Torres, Boletta et al, CJASN, 2010

…But unfortunately, the results from the first clinical trials were a cold shower…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease

Gerd Walz, M.D., Klemens Budde, M.D., Marwan Mannaa, M.D., Jens Nürnberger, M.D., Christoph Wanner, M.D., Claudia Sommerer, M.D., Ulrich Kunzendorf, M.D., Bernhard Banas, M.D., Walter H. Hörl, M.D., Ph.D., Nicholas Obermüller, M.D., Wolfgang Arns, M.D., Hermann Pavenstädt, M.D., Jens Gaedeke, M.D., Martin Büchert, Ph.D., Christoph May, Ph.D., Harald Gschaidmeier, Ph.D., Stefan Kramer, Ph.D., and Kai-Uwe Eckardt, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sirolimus and Kidney Growth in Autosomal Dominant Polycystic Kidney Disease

Andreas L. Serra, M.D., Diane Poster, M.D., Andreas D. Kistler, M.D., Fabienne Krauer, B.S., Shagun Raina, M.S., James Young, Ph.D., Katharina M. Rentsch, Ph.D., Katharina S. Spanaus, M.D., Oliver Senn, M.D., M.P.H., Paulus Kristanto, Ph.D., Hans Scheffel, M.D., Dominik Weishaupt, M.D., and Rudolf P. Wüthrich, M.D.

- No improve of the kidney function
- High drop-out rate: heavy side effects

Aknowledgements

Current Lab members:

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Marco Chiaravalli
Chiara De Pascalis
Gianfranco Distefano
Monika Pema
Isaline Rowe

Past Lab members:
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