Cystic kidney disease

The clinician’s perspective

George Reusz

First Department of Pediatrics

Semmelweis University

Outline

- Definitions, clinical presentation
- Pathophysiology of cyst formation
- Clinical implications, studies

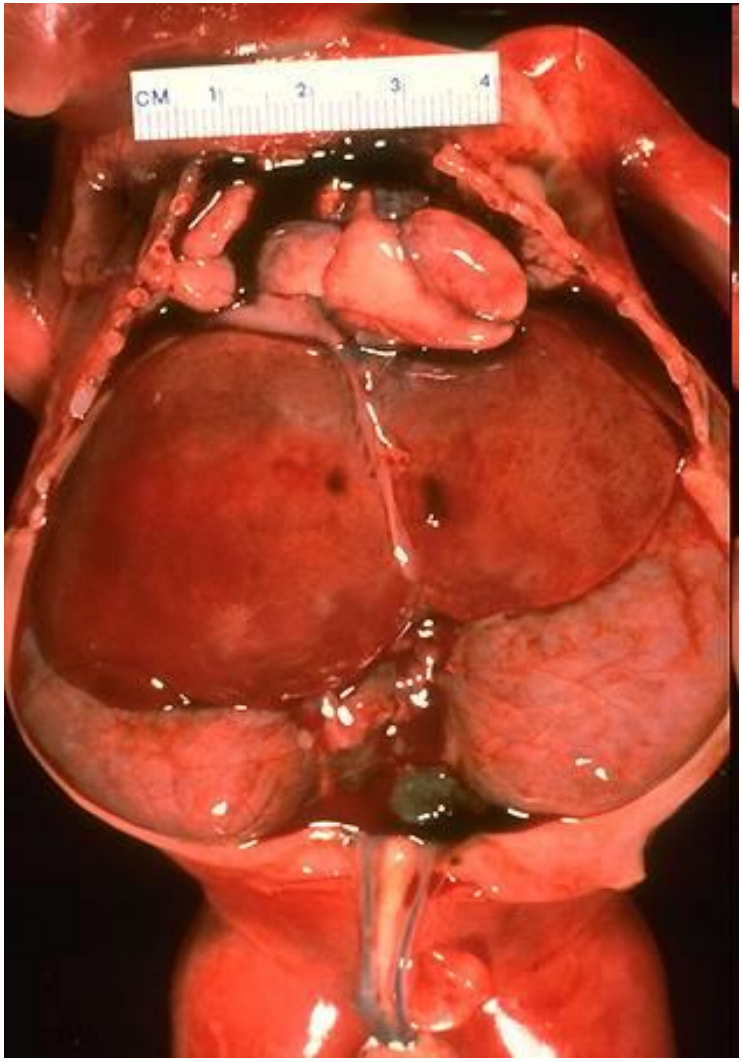
Hereditary polycystic diseases

- **Polycystic Kidney disease**
  - **(AD, AR)**
- **Juvenile nephronophtisis**
- **Cysts associated with multiple malformations**
  - **Autosomal dominant**
    - **Tuberous sclerosis**
    - **von Hippel–Lindau disease**
  - **X linked dominant**
    - **Orofaciodigital syndrome, type I**
  - **Autosomal recessive:**
    - **Meckel syndrome, asphyxiating thorax dystrophy of Jeune type,**
    - **Zellweger cerebrohepatorenal syndrome,**
    - **Goldston syndrome, etc. (glomerulocystic disease in most of the cases)**
  - **Chromosomal abnormalities**
    - **21 trisomy, 13 trisomy, 18 trisomy**

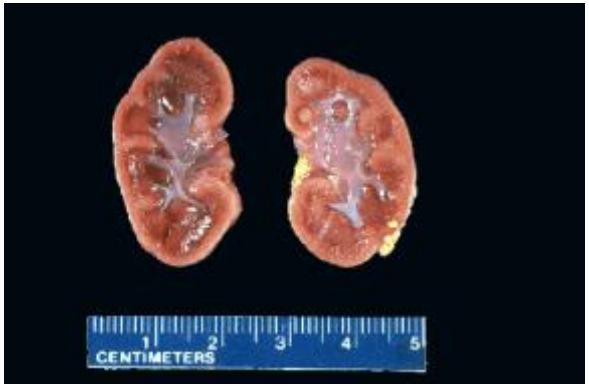
PKHD1
Carrier frequency 1:65
Incidence 1:15.000
ERDS in childhood
Collecting duct
Liver fibrosis

ARPKD

Enormous kidneys filling the abdomen
Preterm neonate (23. gestational week)
Respiratory distress, exitus lethalis



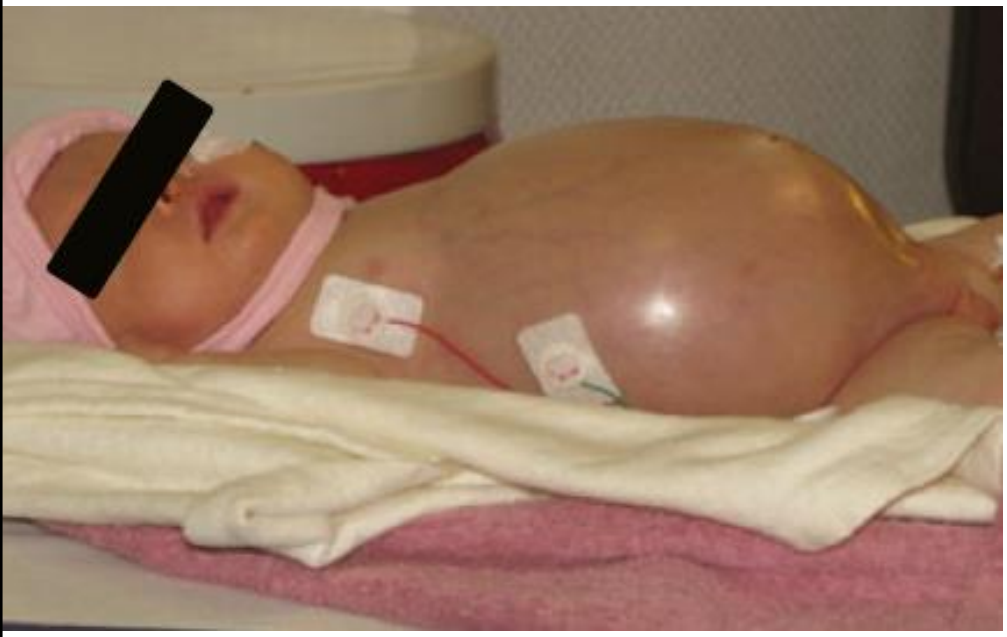
Normal kidney



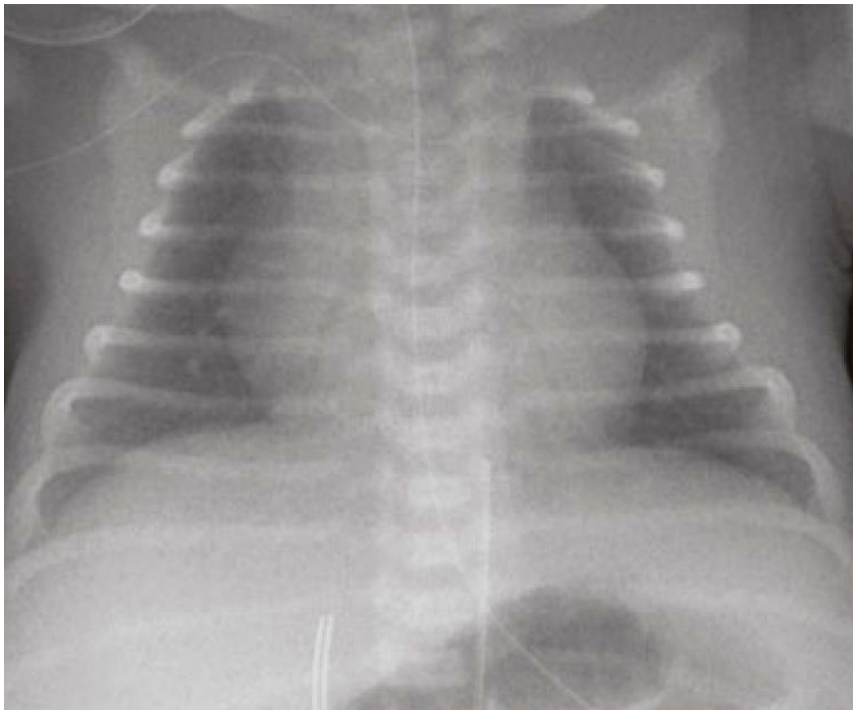
ARPKD kidney

Enlarged kidney no corticomedullary difference

Ten-day-old preterm infant (34th week) with autosomal recessive polycystic kidney disease

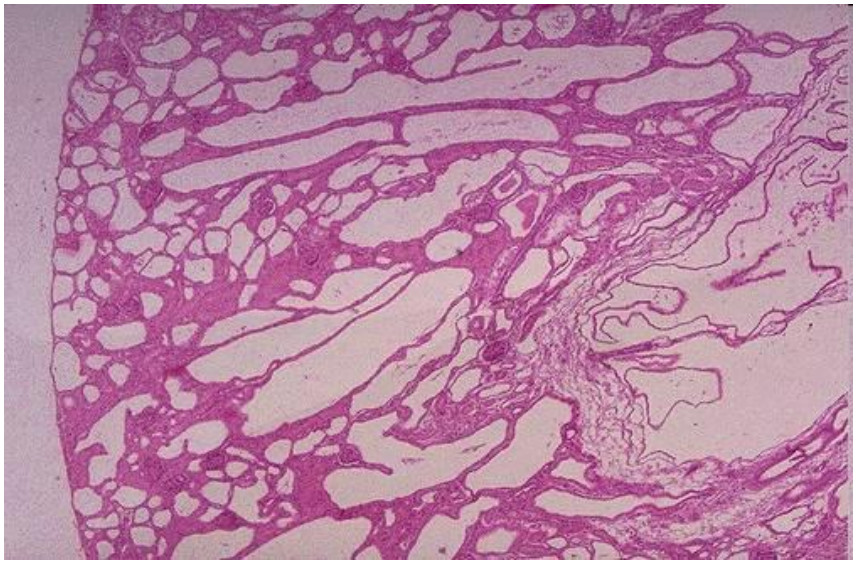


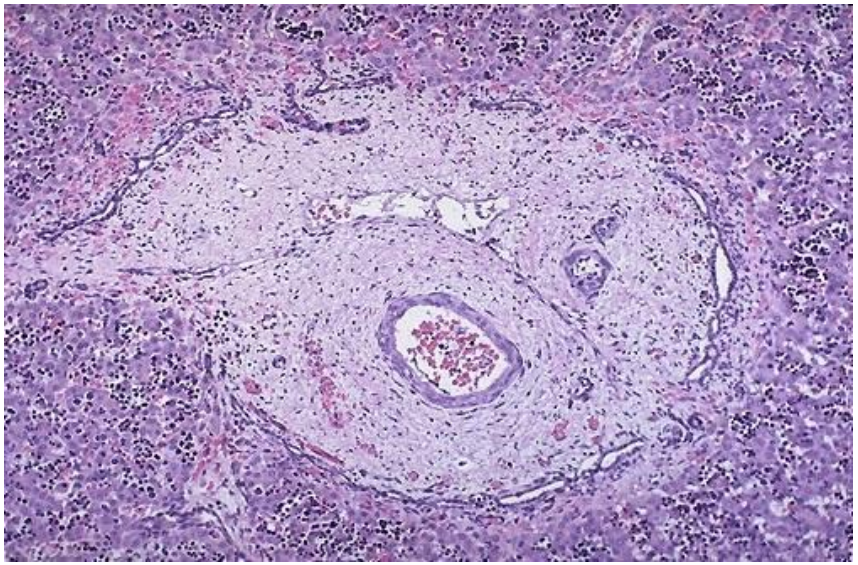
Pulmonary hypoplasia in ARPKD



Büscher R et al; Pediatr Nephrol, 2013; DOI 10.1007/s00467-013-2634-1

ARPKD





the kidney parenchyma is replaced by cysts

ARPKD: congenital liver fibrosis

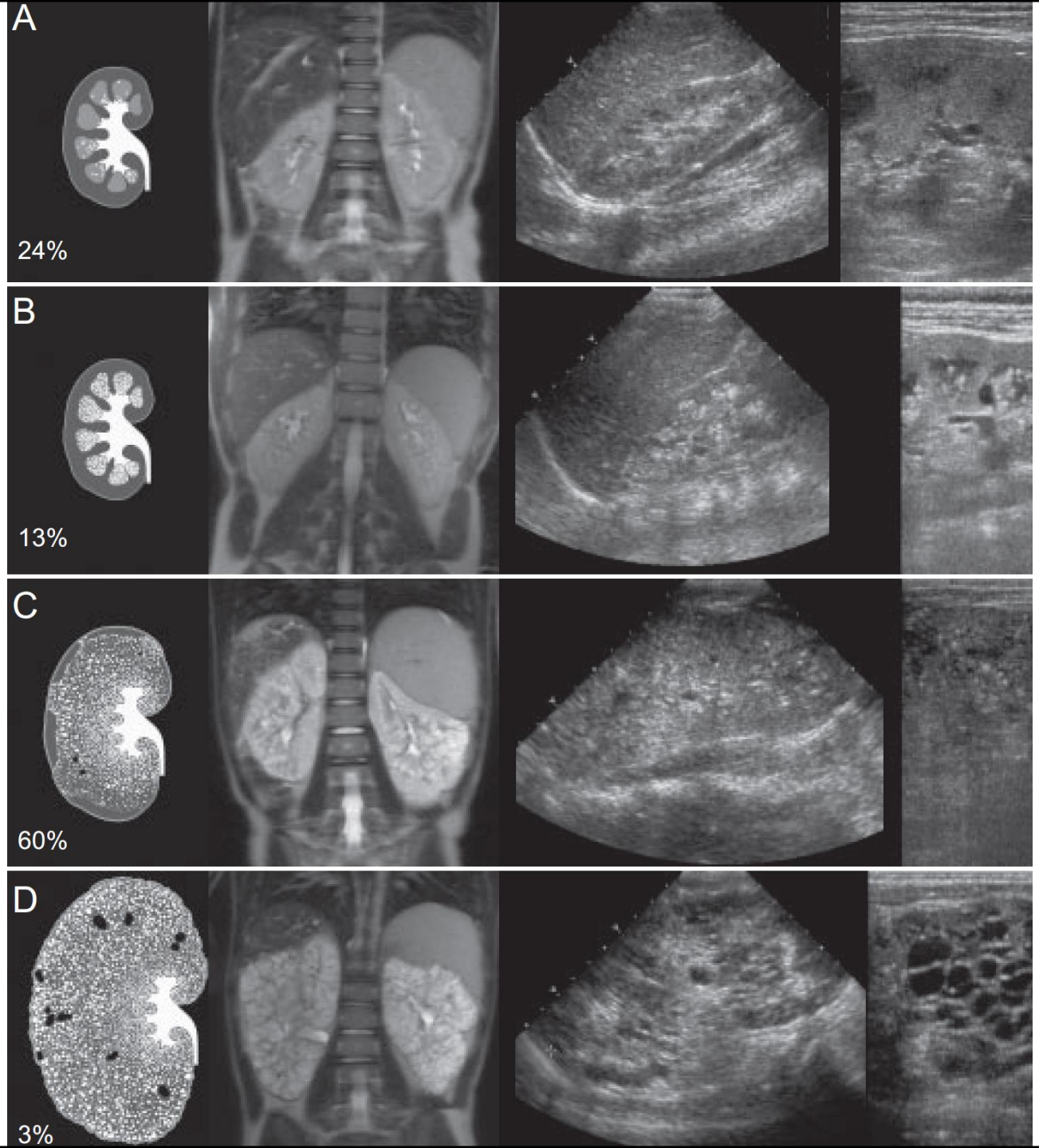
The defective fibrocystin (see later) is present in the kidney, the liver and the pancreas as well

Büscher R et al; Pediatr Nephrol, 2013; DOI 10.1007/s00467-013-2634-1

ARPKD

Principal consequences of renal manifestation

- Foetus (about 30% of the cases)
  - oligohydramnios, pulmonary hypoplasia, Potter sequence, IU death
- Newborn
  - **Severe CRF –** usually combined with respiratory distress
  - **Less severe CRF** - hypertension, electrolyte-, acid-base imbalance, failure to thrive
  - **Normal kidney function** and less severe manifestations
    - mild proteinuria, glucosuria, hyperphosphaturia, increased urinary excretion of magnesium)
  - Recurrent episodes of **UTI**
  - Kidney **function may recover with time**



Kidney ultrasound patterns in ARPKD

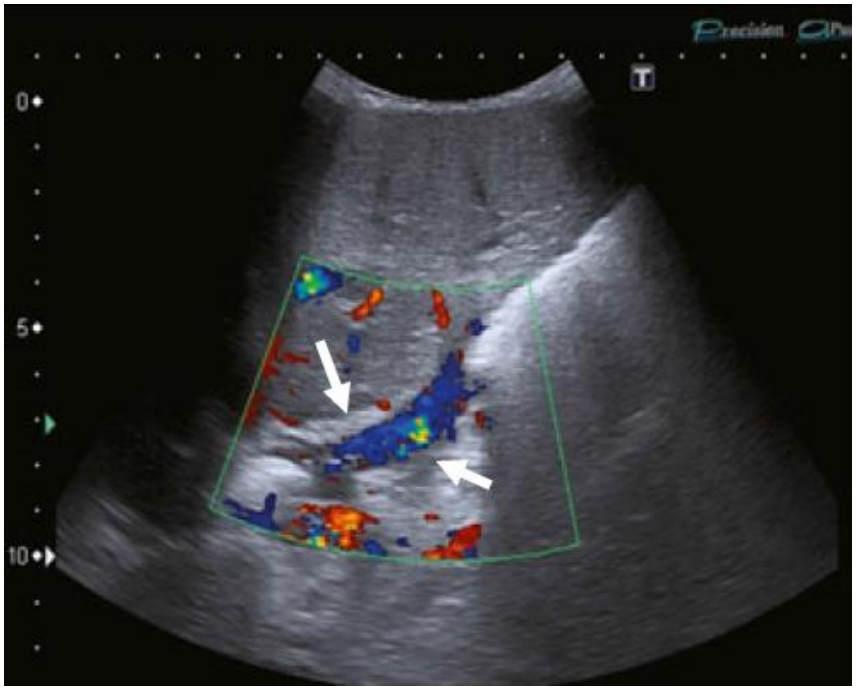
N=62

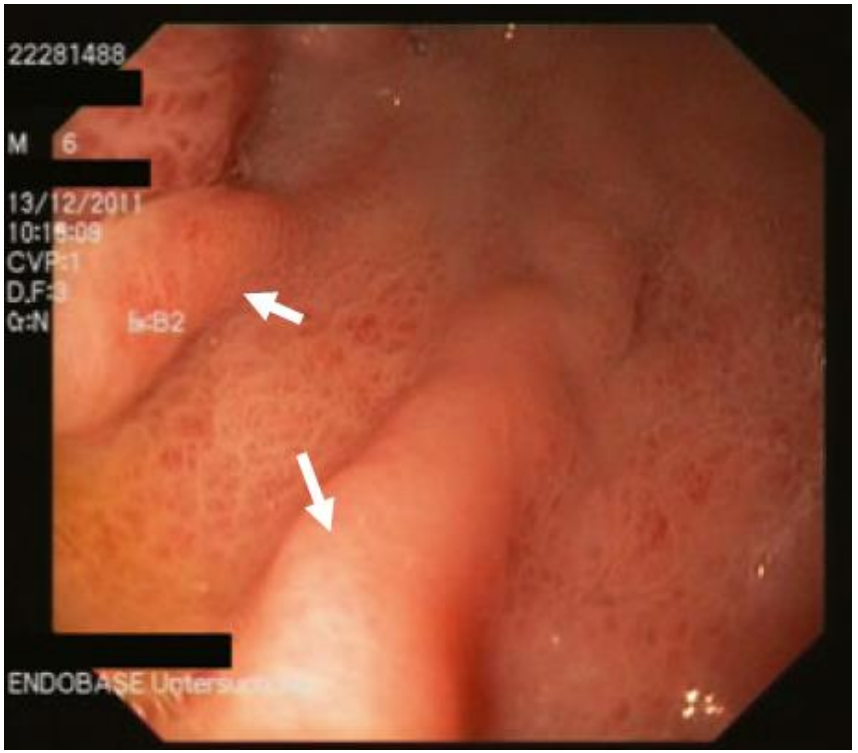
Clin J Am Soc Nephrol
5: 972–984, 2010

Principal extrarenal manifestations

- Hepatic fibrosis
  - May be present already at infancy
  - Dominantly vascular involvement (portal hypertension)
  - Parenchymal insufficiency later during the course
  - Severe adverse events
    - Bleeding from esophageal varices
    - Encephalopathy
  - Finally may need hepatic transplantation

Color Doppler ultrasound and endoscopy of a 8-year-old boy with ARPKD and esophageal and gastric varices

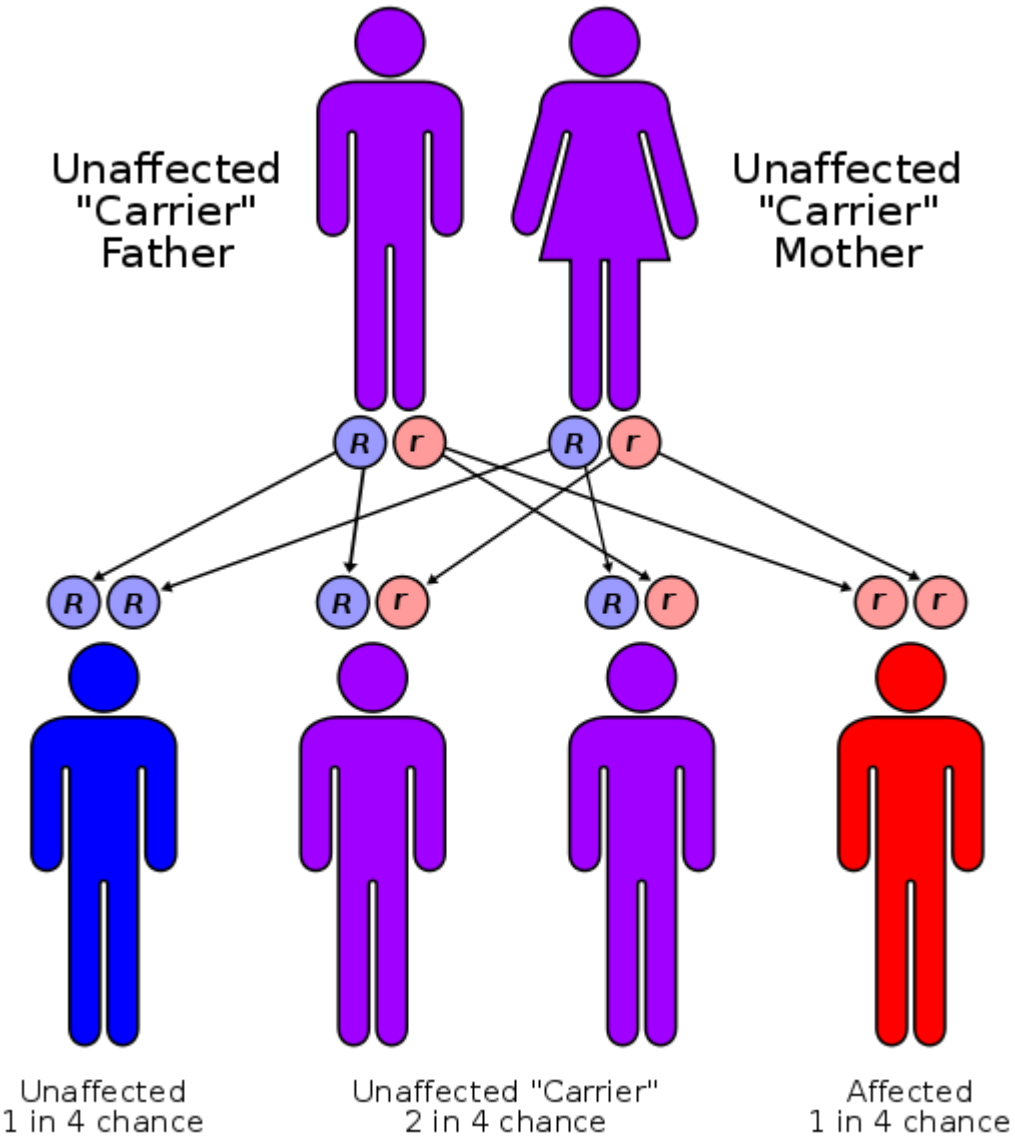




Büscher R et al; Pediatr Nephrol, 2013; DOI 10.1007/s00467-013-2634-1

Family counseling - genetic testing

- AR patter
- Preimplar laboratori n some
  - Linkage ilability of membe
  - Gene se ween 42 and 87 p
  - Targete tations that are spe ble in some laborato



ADPKD

PKD1>PKD2

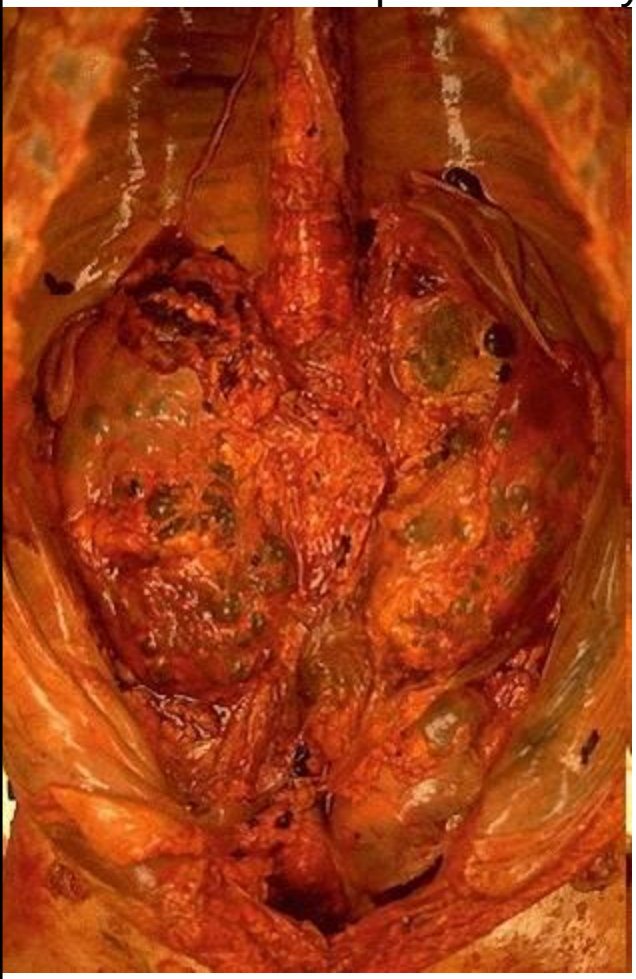
Incidence 1:500-1.000 (5% sporadic)

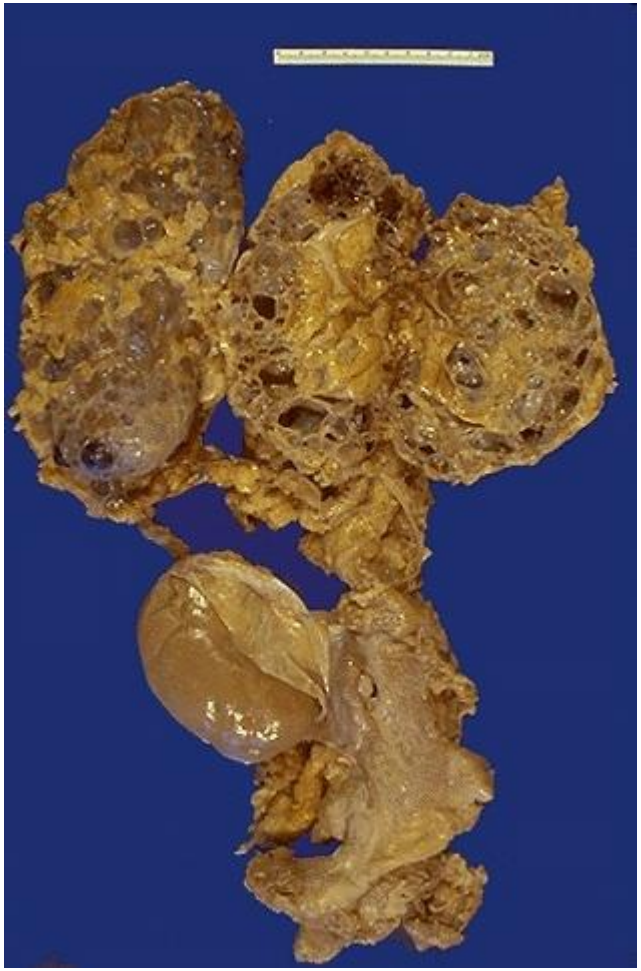
Fourth cause of ESRD

PKD1: ESRD at 54 y - PKD2 at 74 y

Collecting duct, distal nephron

Liver and pancreatic cysts





Enlarged kidneys filling the retroperitoneum and the abdominal cavity

The parenchyma is replaced by cysts

Principal consequences of renal manifestation

Hypertension

May be the first sign of disease

Hematuria

May be due to kidney stone formation or macro/micro trauma affecting one or multiple cysts

UTI

Infection of the cystic parenchyma may lead to abscess formation

Cyst rupture

Cysts subject to trauma may ruprute

Principal extrarenal manifestations

Hepatic and pancreatic cysts

Asymptomatic in many patients, but can expand and cause pain and infection; rarely massive PLD

Cardiac valvular abnormalities

Mitral, tricuspid and aortic valve prolapse and regurgitation

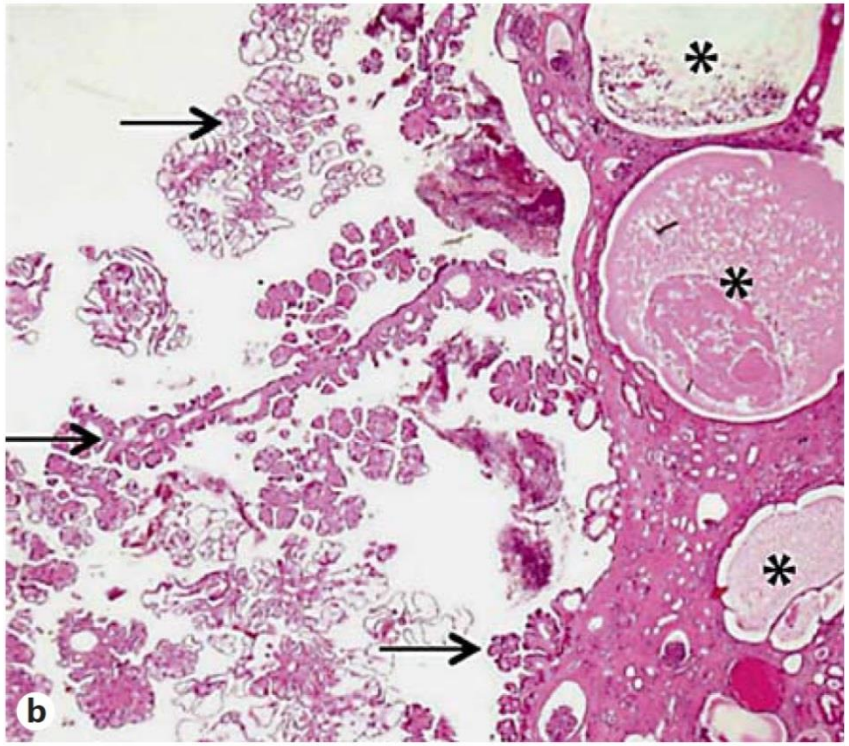
Intracranial aneurysms

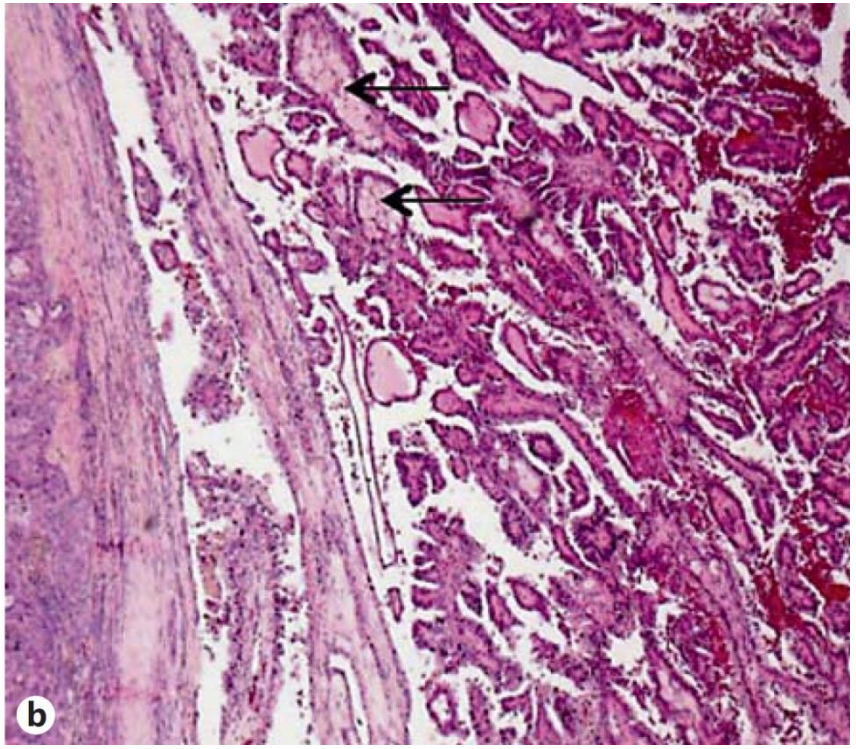
Low risk of rupture; size predictive. Found in approximately 5% of patients with no family history and about 22% of patients with family history of ICA or SAH

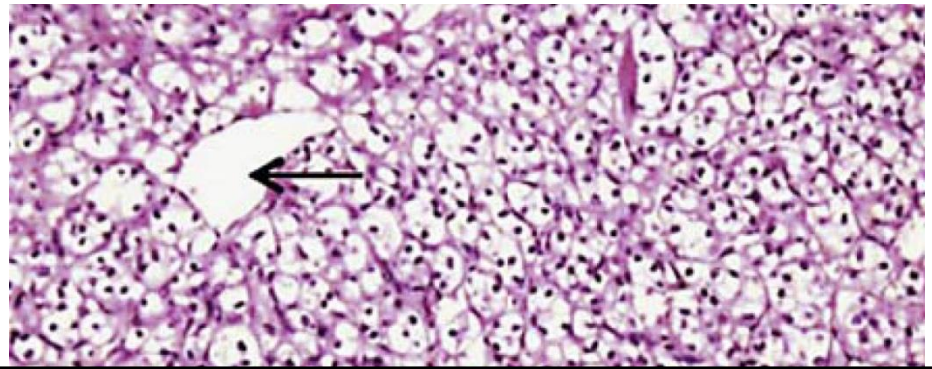
Seminal vesicle cysts

Found in 39-60% of men; undefined risk of infertility

ADPKD: Renal Neoplasias in Surgical Kidney Specimens







N=240
Malignancy: 12/240 =5% (8/12 on dialysis)
63% papillary 31% clear cell RCC
6% urothelial CC

Jilg CA et al: Nephron Clin Pract 2013;123:13–21

Presymptomatic diagnosis of ADKPD

- AD inheritence
- Selection of transplant donor within an ADPKD family
- Benefits
  - Earlier clinical intervention, i.e., for hypertension
- Potential adverse impact on insurability and employment
  - At this time, there is no specific therapy for ADPKD

- ?Prenatal diagnosis
- ?Preimplantation Genetic Diagnosis

US criteria for ADPKD in a PKD family

age	Number of cysts
< 30	At least 2 cysts in one or both kidneys
30-59	At least 2 cysts/kidney
>60	At least 4 cysts/kidney

At least one family member ESRD ≤ 55 years

JASN 20:205, 2009, JASN 20:1833, 2009

US criteria
or in a family with unknown genotype

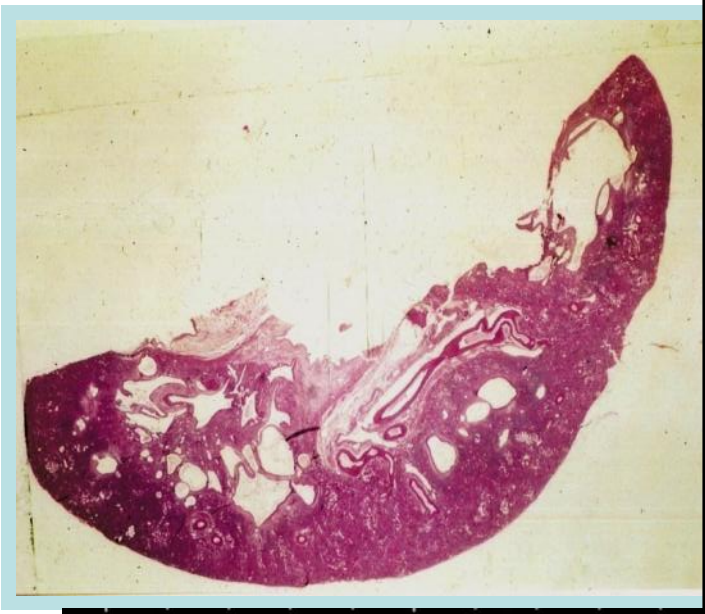
age	cysts
15-39	At least 3 cysts in one or both kidneys
40-59	At least 2 cysts/kidney
>60	At least 4 cysts/kidney
No ADPKD if:	
≥40	< 2 cysts

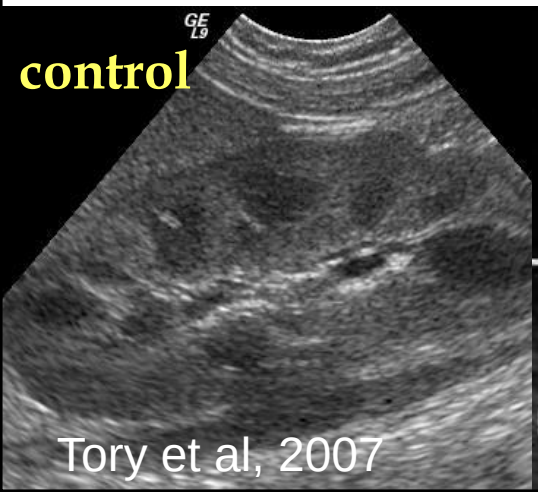
Nephronophthisis – macroscopic morphology

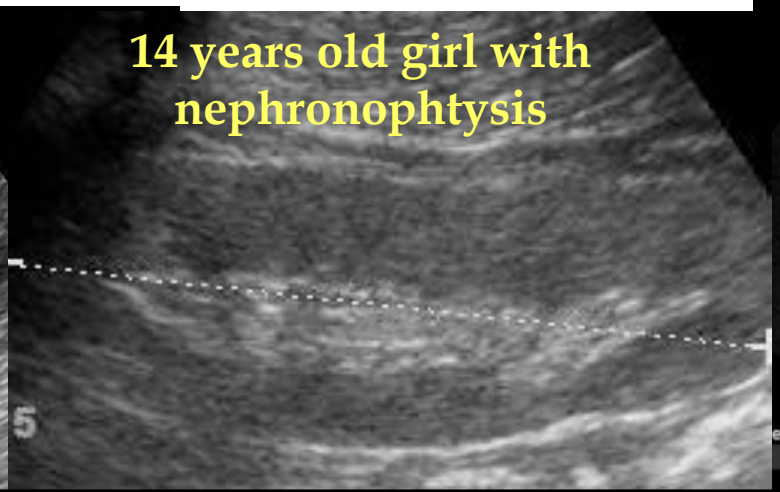
1. Dimension: in juvenile NPH the kindey is usually small, in the infantile type it may be enlarged (+2-3 SD)

2. Cysts: several cysts at the cortico-medullary boundary. Not a real „cystic” disease!

3. **Hyperechogenic**, the cortico-medullary boundary is blurred







Outline

- Definitions, clinical presentation
- Pathophysiology of cyst formation
- Clinical implications, studies

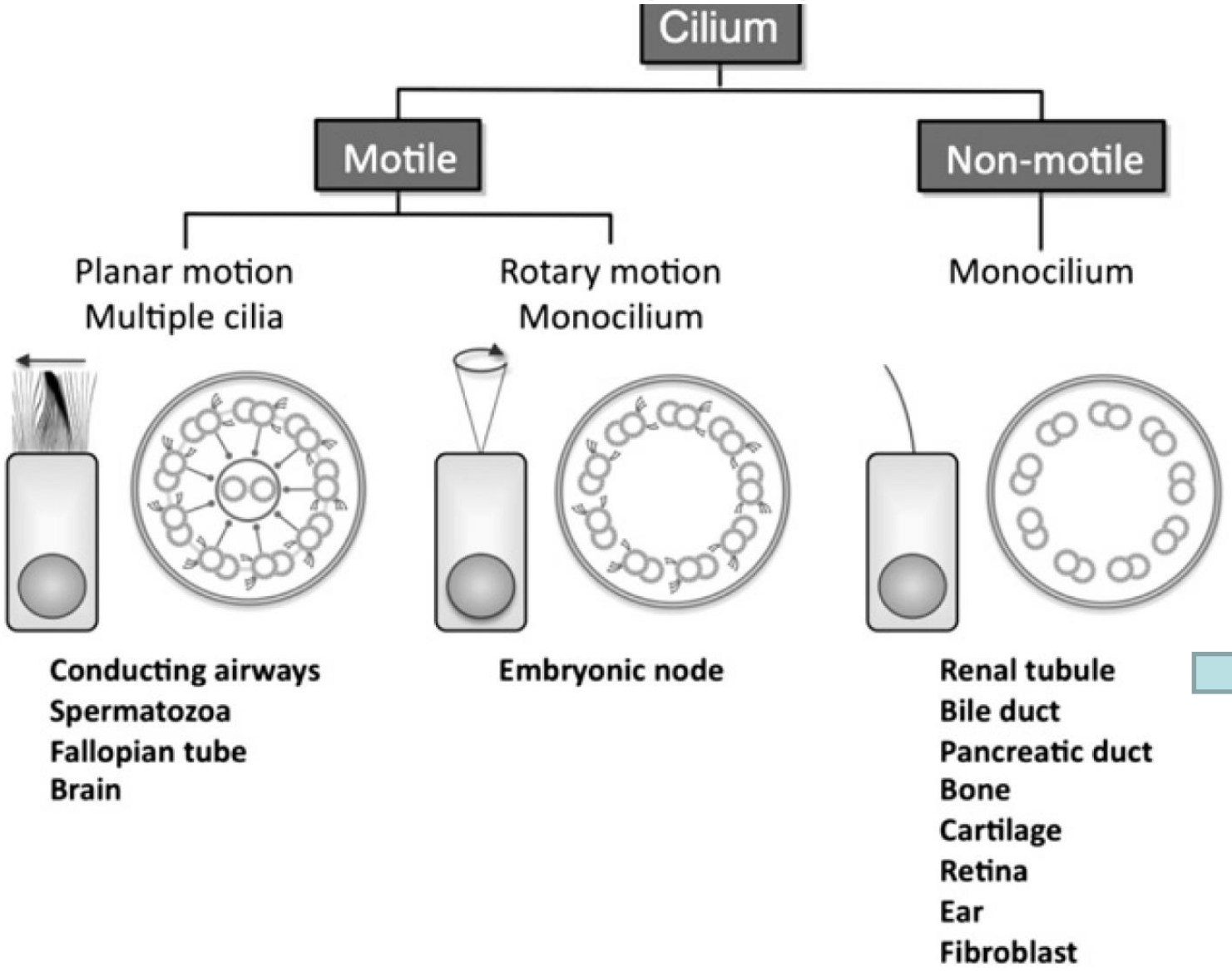
The Cilia Saga

Genes involved in hereditary cystic diseases:

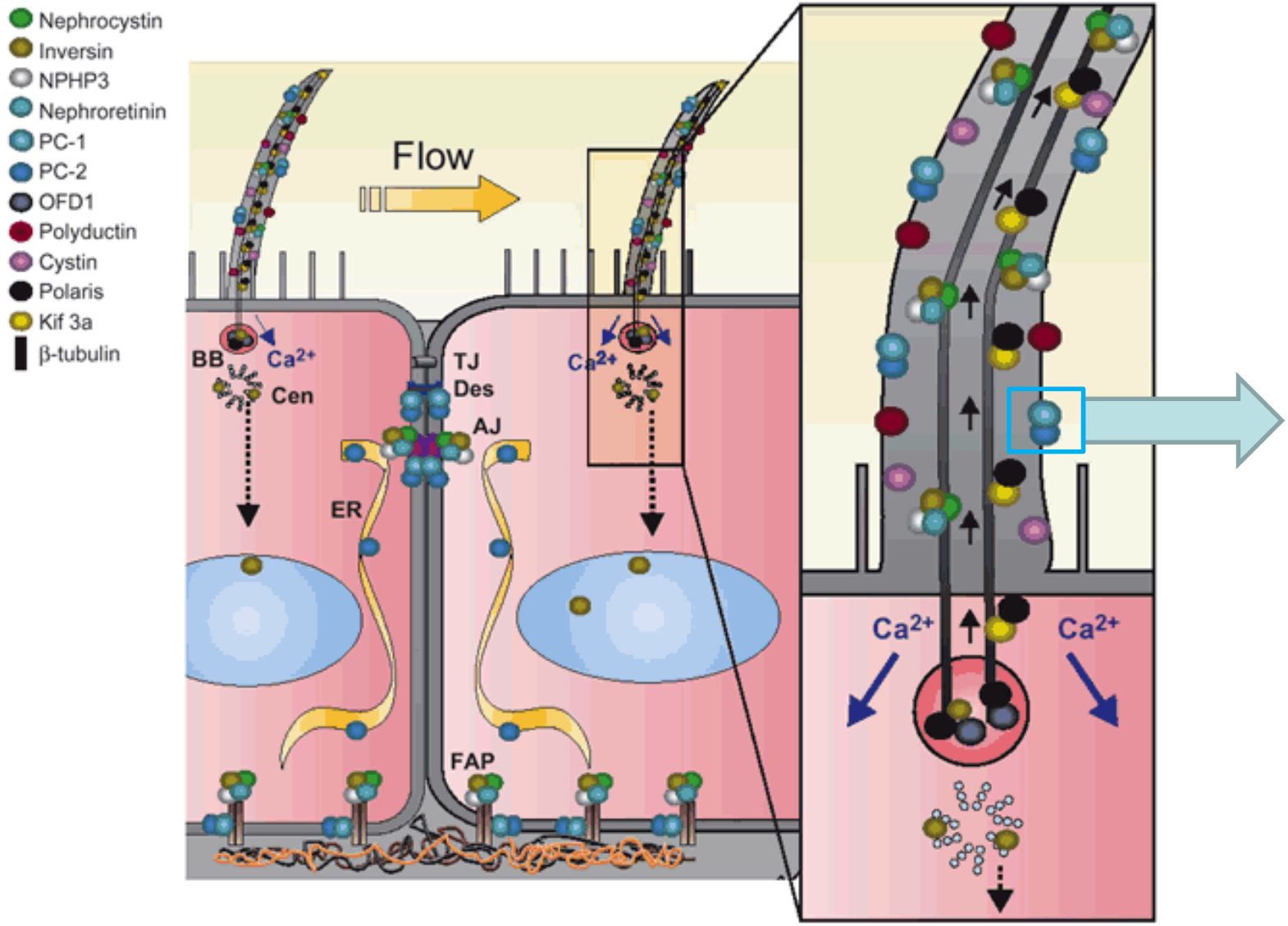
cystic deseases are caused by mutations in genes encoding for proteins involved in the function or structure of the cilia and/or the basal bodies

Ciliopathies: The Central Role of Cilia in a Spectrum of Pediatric Disorders

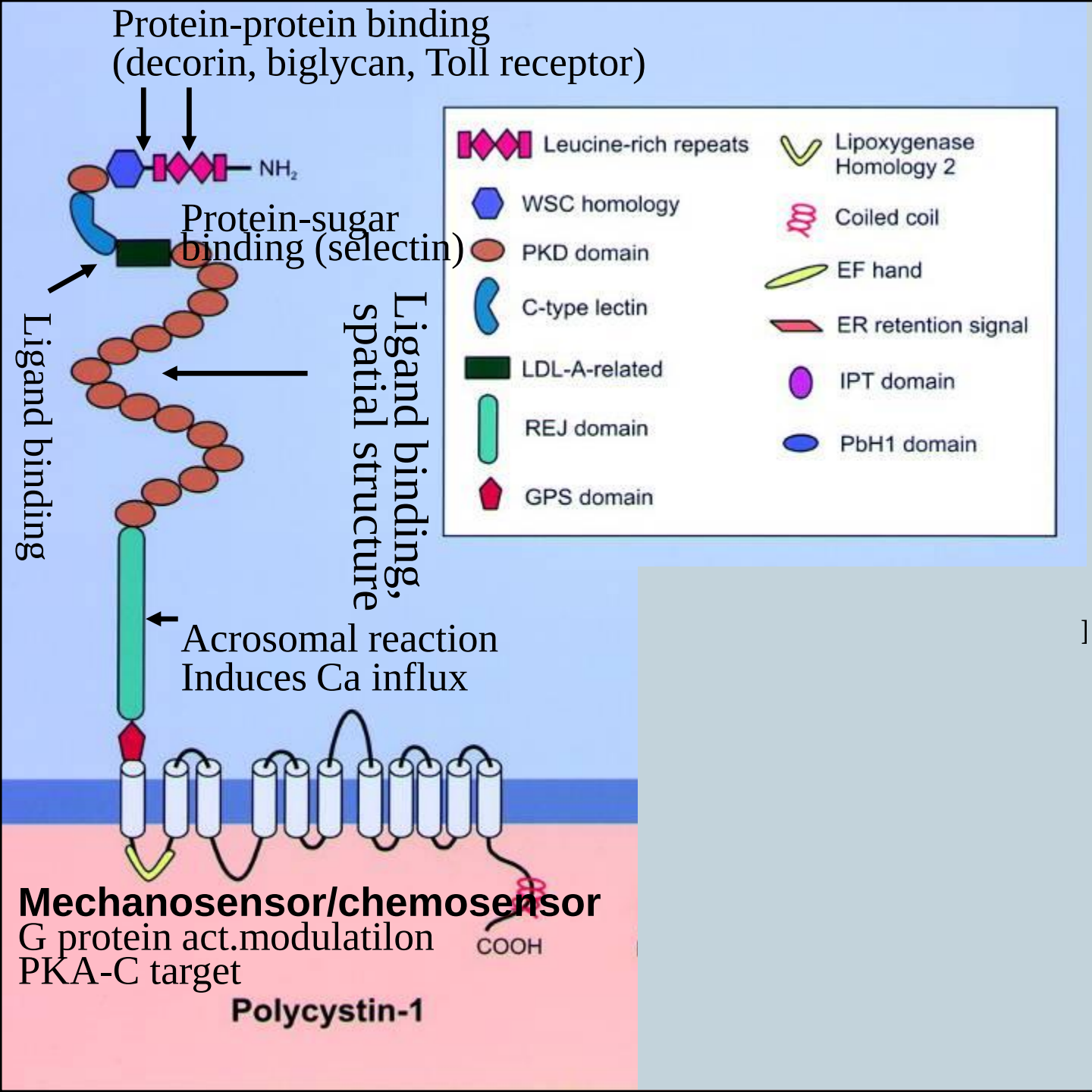
Thomas W. Ferkol, MD[1], and Margaret W. Leigh, MD[2]

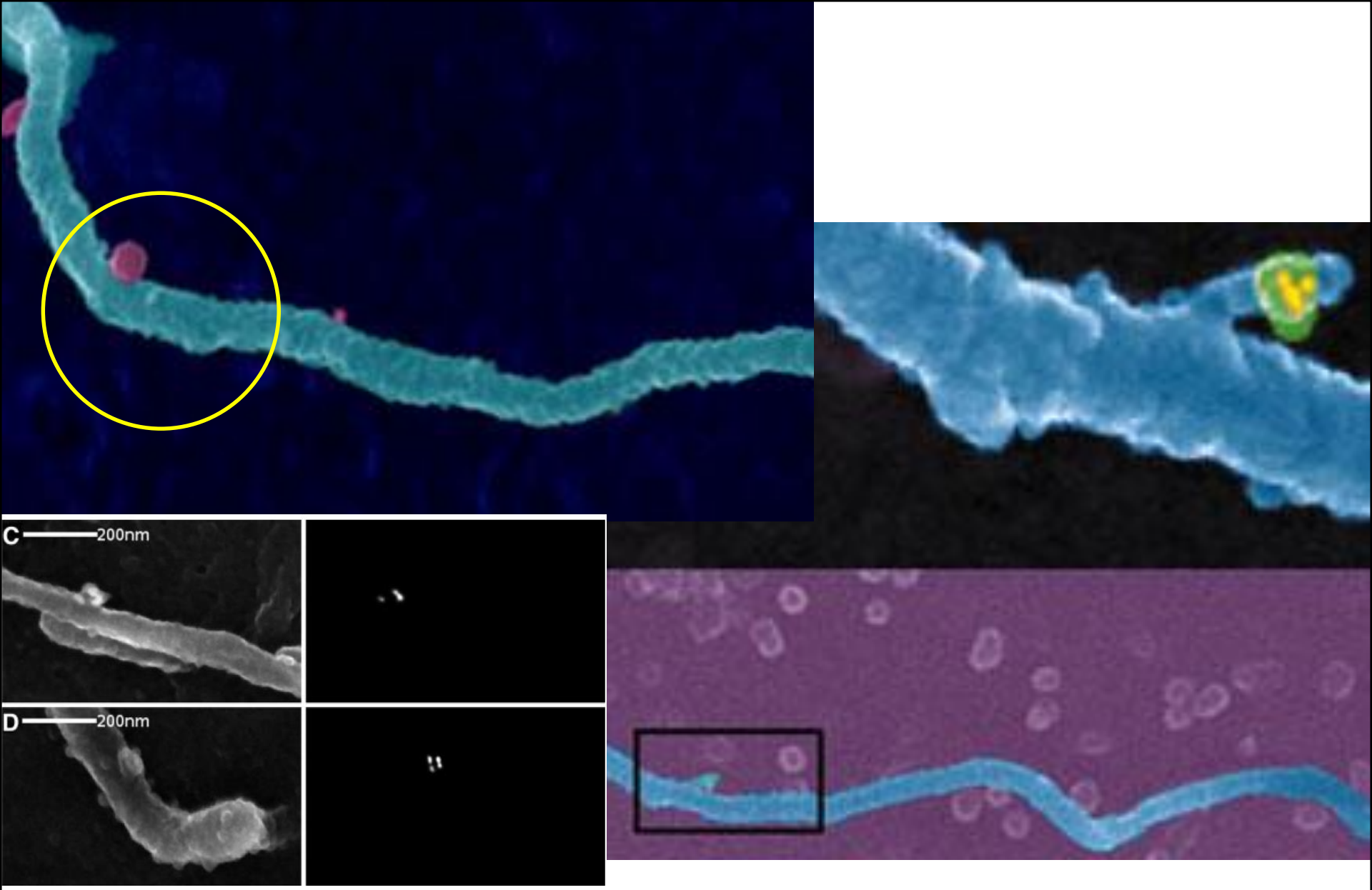


Ferkol TW and Leigh MW: The Journal of Pediatrics, 2012, 160: 366-371



Watnick T & Germino G: **From cilia to cyst***Nature Genetics* **34**, 355 - 356 (2003)


Protein-protein binding
(decorin, biglycan, Toll receptor)
NH2
Protein-sugar
binding (selectin)
Ligand binding
Ligand binding,
spatial structure
Acrosomal reaction
Induces Ca influx
Leucine-rich repeats
WSC homology
PKD domain
C-type lectin
LDL-A-related
REJ domain
GPS domain
Lipoxygenase
Homology 2
Coiled coil
EF hand
ER retention signal
IPT domain
PbH1 domain
Mechanosensor/chemosensor
G protein act.modulatilon
PKA-C target
COOH
Polycystin-1



Bakeberg JL, et al. Epitope-tagged Pkhd1 tracks the processing, secretion and localization of fibrocystin. JASN. 2011;22:2266

Unifying concept: the example of nephronophtisis

- Tubulointerstitial nephropathy
- Polyuria, polydipsia
- Anemia
- Normal blood pressure
- ESRD

- Further caracteristics
  - Multiple syndromes and type of inheritance
  - Joubert, Bardet Biedl
  - Associated anomalies
    - Liver,
    - CNS
    - Retina
    - Olfactory
    - (Hearing)
    - Situs inversus
    - Kartagener syndrome

Nephronophtysis

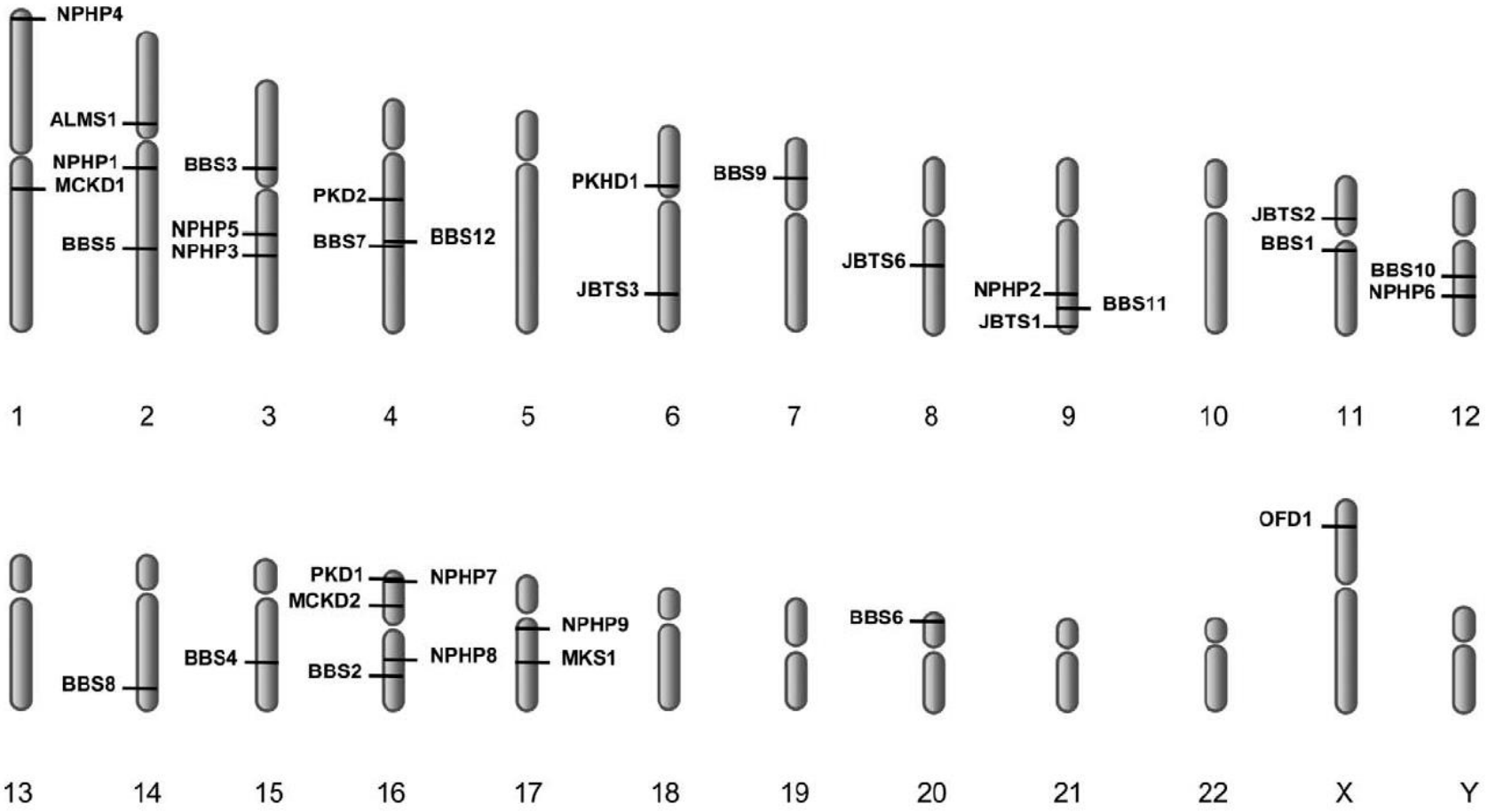
- diversity

Table 1 Genetic heterogeneity and overlap of nephronophthisis (NPH), Senior-Løken, Joubert, and Meckel-Gruber syndromes

Locus	Chromosome	Gene*	Clinical manifestations
NPHP1/SLSN1	2q13	*NPHP1* (nephrocystin-1)	Juvenile nph (mild JBTS, mild RP, Cogan)
NPHP2	9q31	*NPHP2/INVS* (Inversin)	Infantile nph (RP, liver fibrosis, HT)
NPHP3/SLSN3	3q22	*NPHP3* (nephrocystin-3)	Juvenile nph (liver fibrosis, RP)
NPHP4/SLSN4	1p36	*NPHP4* (nephrocystin-4 or nephroretinin)	Juvenile nph (Cogan, RP)
NPHP5/SLSN5	3q21	*NPHP5/IQCB1*	Juvenile nph + severe RP
NPHP6/SLSN6/JBTS5/ MKS4	12q21	*NPHP6/CEP290*	Juvenile nph + JBTS + severe RP, isolated RP, (MKS)
NPHP7	16p	*NPHP7/GLIS2*	Juvenile nph
NPHP8/JBTS7/MKS5	16q	*NPHP8/RPGRIP1L*	Juvenile nph + JBTS (MKS)
NPHP9	17q11	*NPHP9/NEK8*	Juvenile and infantile nph

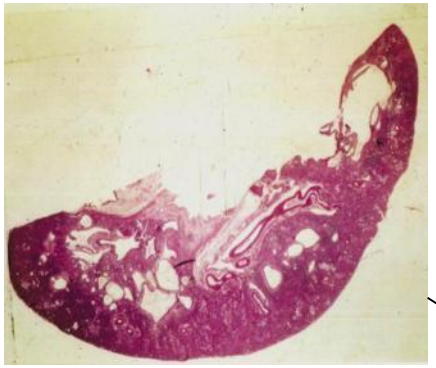
- … and ciliae

Cystic Diseases of the Kidney
Molecular Biology and Genetics



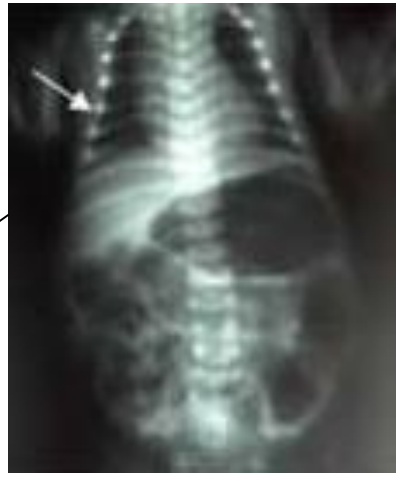
Constantinos Deltas, PhD; Gregory Papagregoriou, MRes
***Arch Pathol Lab Med.* 2010;134:569–582)**

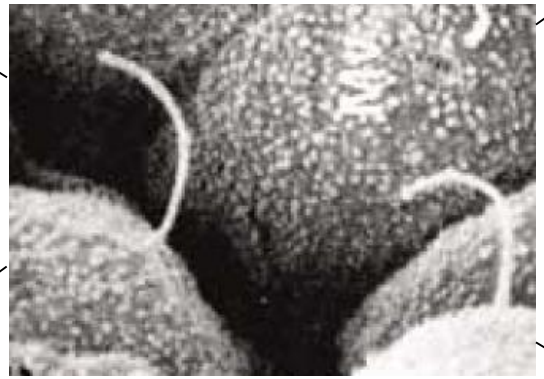
Ciliary proteins – the nephrocystins

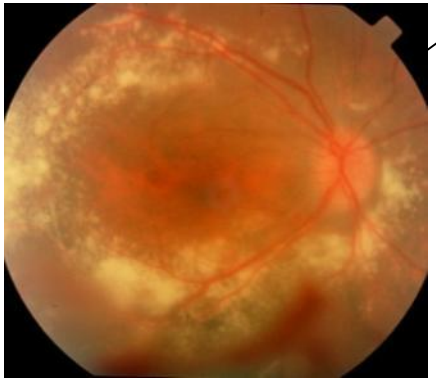


Nephrocystin 1-10

IFT-80



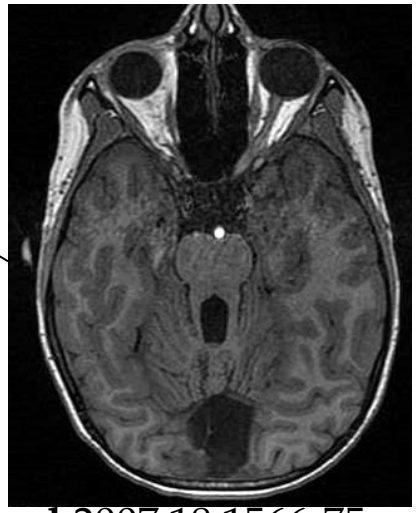




Nephrocystin 1,3,4,5,6,

RPGR, RPGRIP1

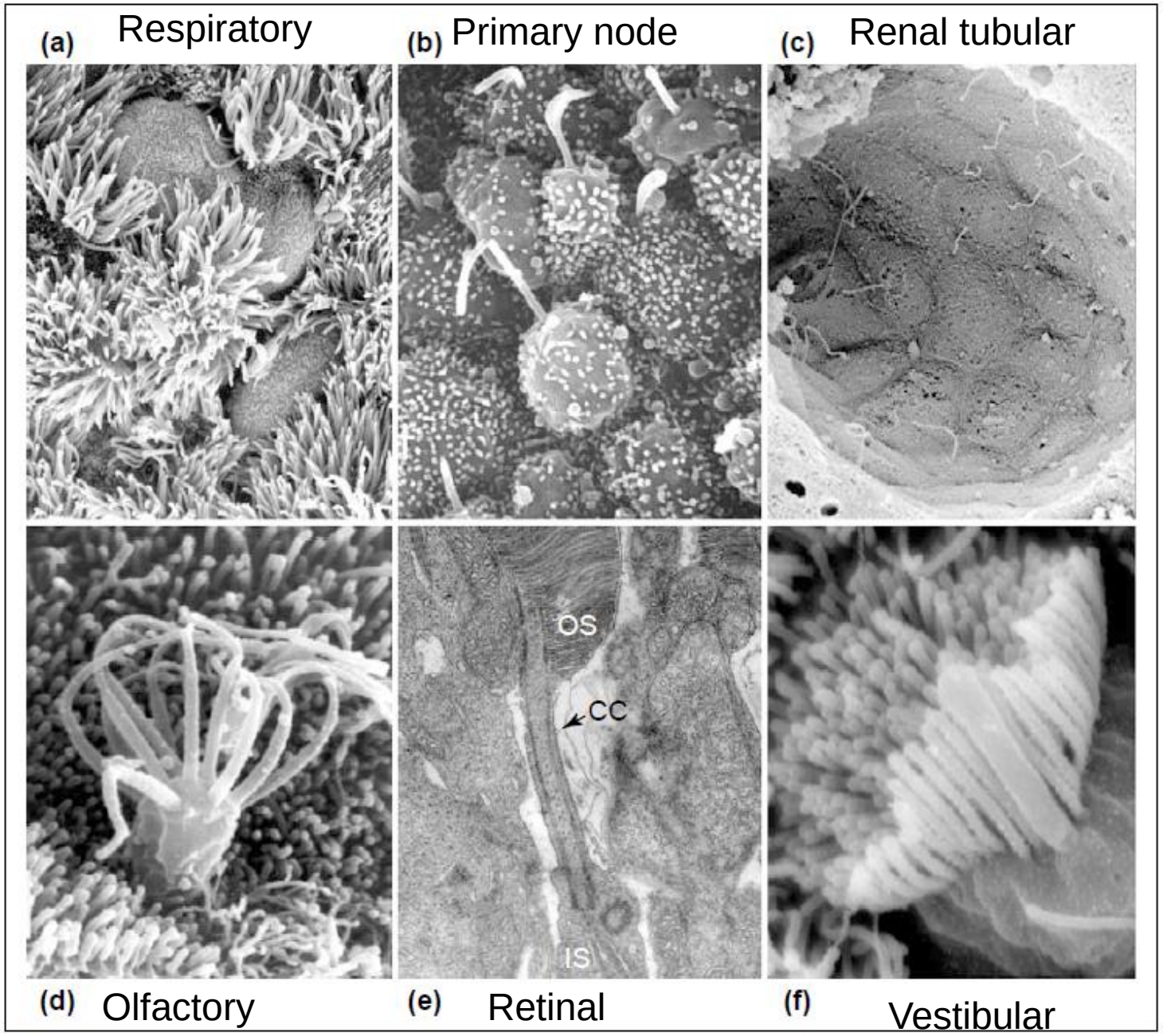
Nephrocystin 1,6,8, meckelin



Tory K et al. **J Am Soc Nephrol** 2007;18:1566-75.

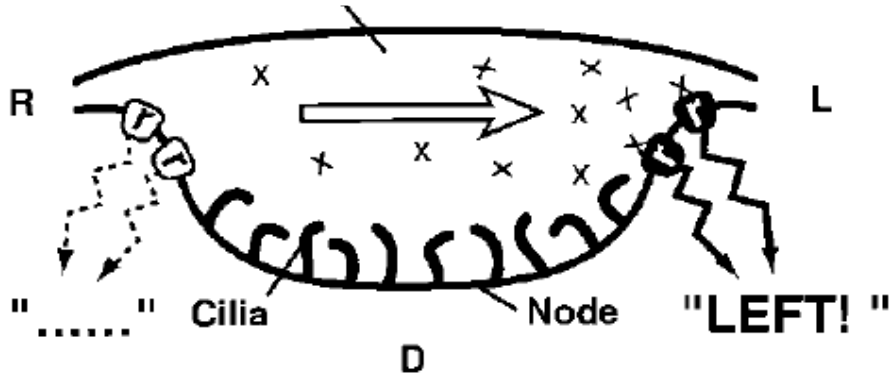
The concept

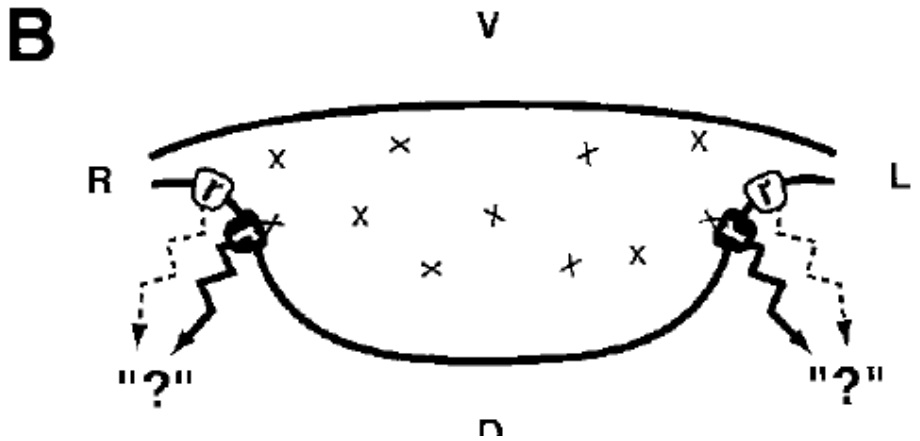
- Inherited cystic diseases are caused by:
  - a defect of proteins involved in the structure and/or the function of the ciliae
- Clinical signs and symptoms: depend on the distribution of the expression of the given protein in the different types of ciliae
  - Evolutionary examples
  - situs inversus, cartagener
  - nephronophtisis - overlaps



Current Opinion in Genetics & Development 2005, 15:308–314

Randomization of Left–Right Asymmetry due to Loss of Nodal Cilia Generating Leftward Flow of Extraembryonic Fluid in Mice Lacking KIF3B Motor Protein

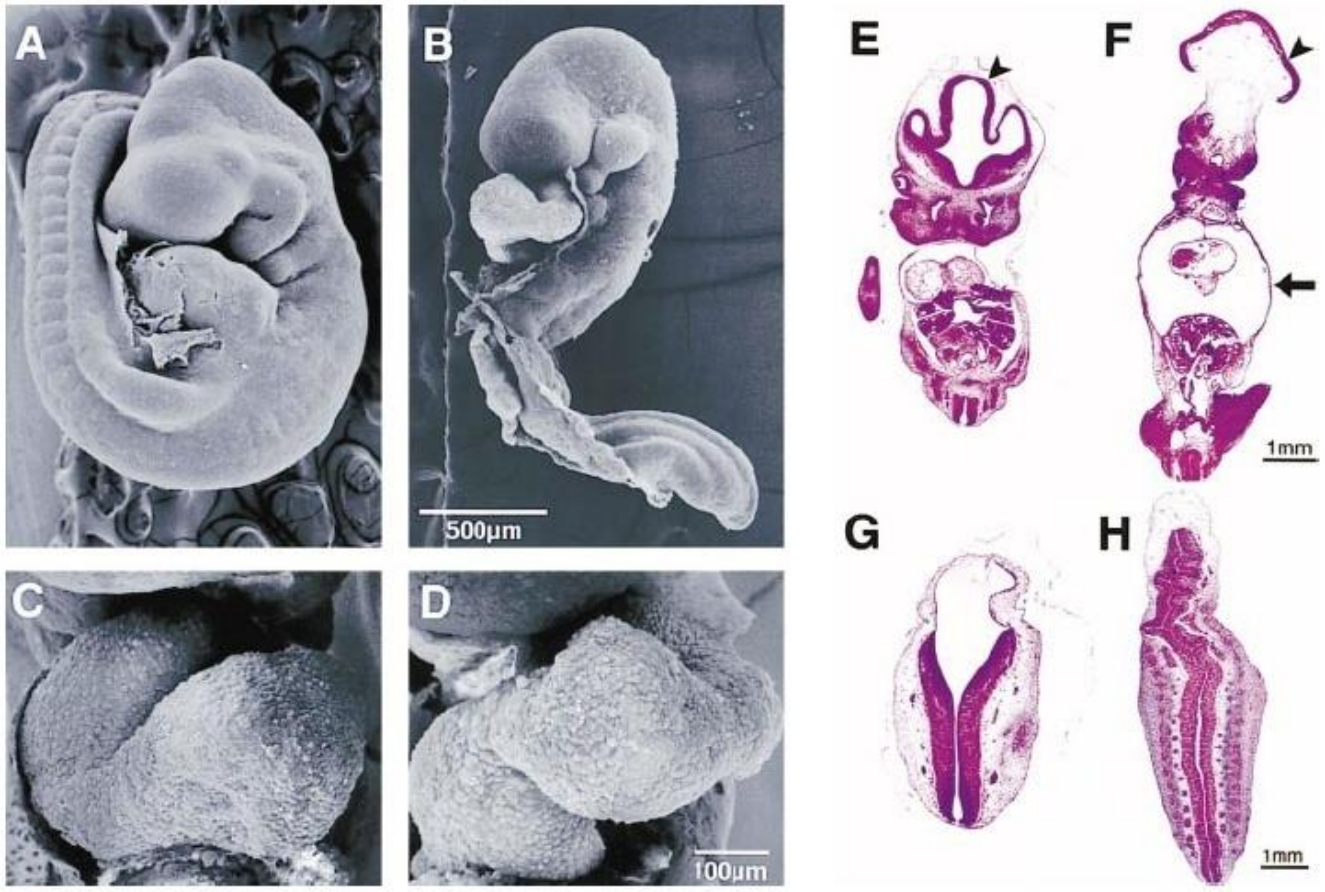




Shigenori Nonaka,

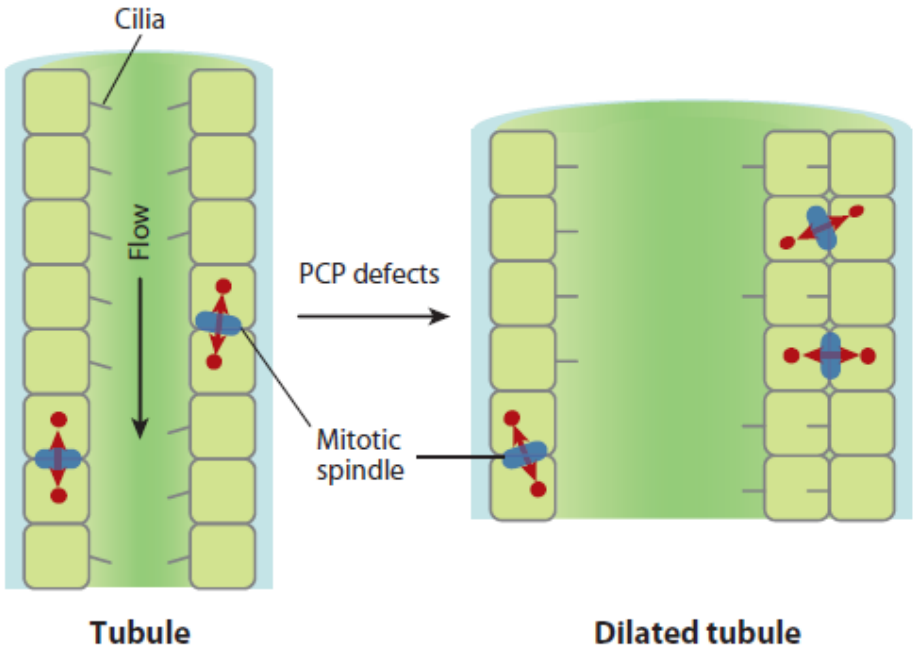
Cell, Vol. 95, 829–837, December 11, 1998, Copyright ©1998 by Cell Press

Randomization of Left–Right Asymmetry due to Loss of Nodal Cilia Generating Leftward Flow of Extraembryonic Fluid in Mice Lacking KIF3B Motor Protein



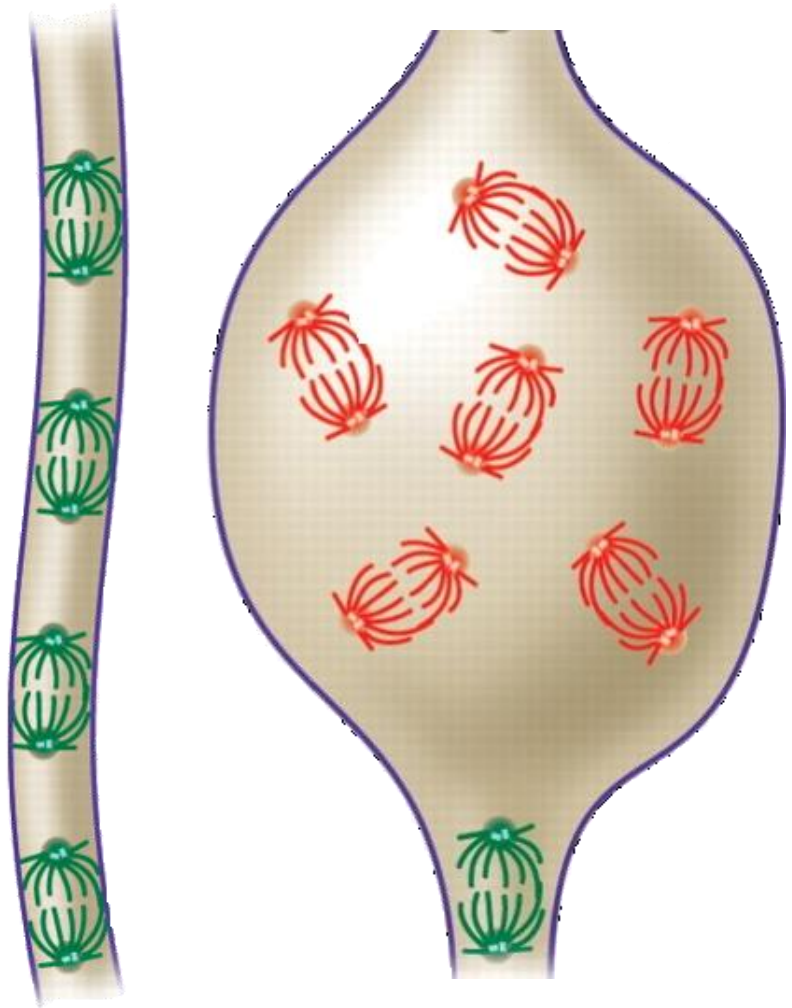
Cell, Vol. 95, 829–837, December 11, 1998, Copyright ©1998 by Cell Press

Ciliary disease and the kidney: „loss of orientation”



Annu. Rev. Physiol. 2009. 71:83–113

Loss of Planar Polarity: Cyst Initiation



Fischer, Nature Genetics, 38:21, 2006
Singla Science 313:629, 2006

CRITICAL THRESHOLD

ARPKD

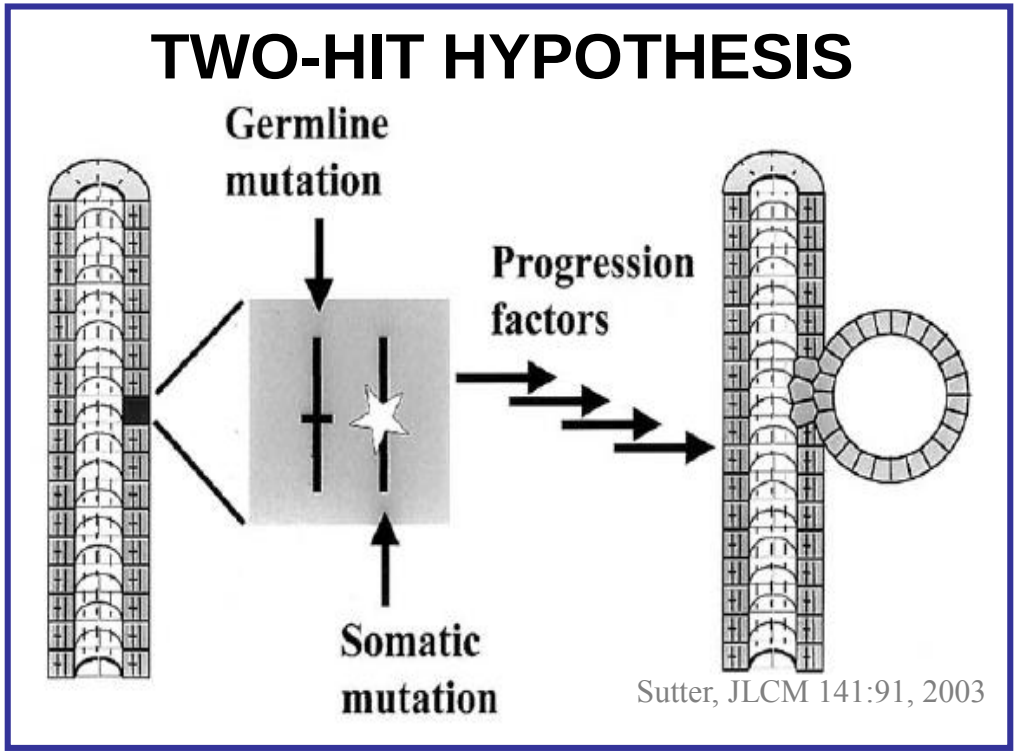
TWO INACTIVATING MUTATIONS

PERINATAL DEATH

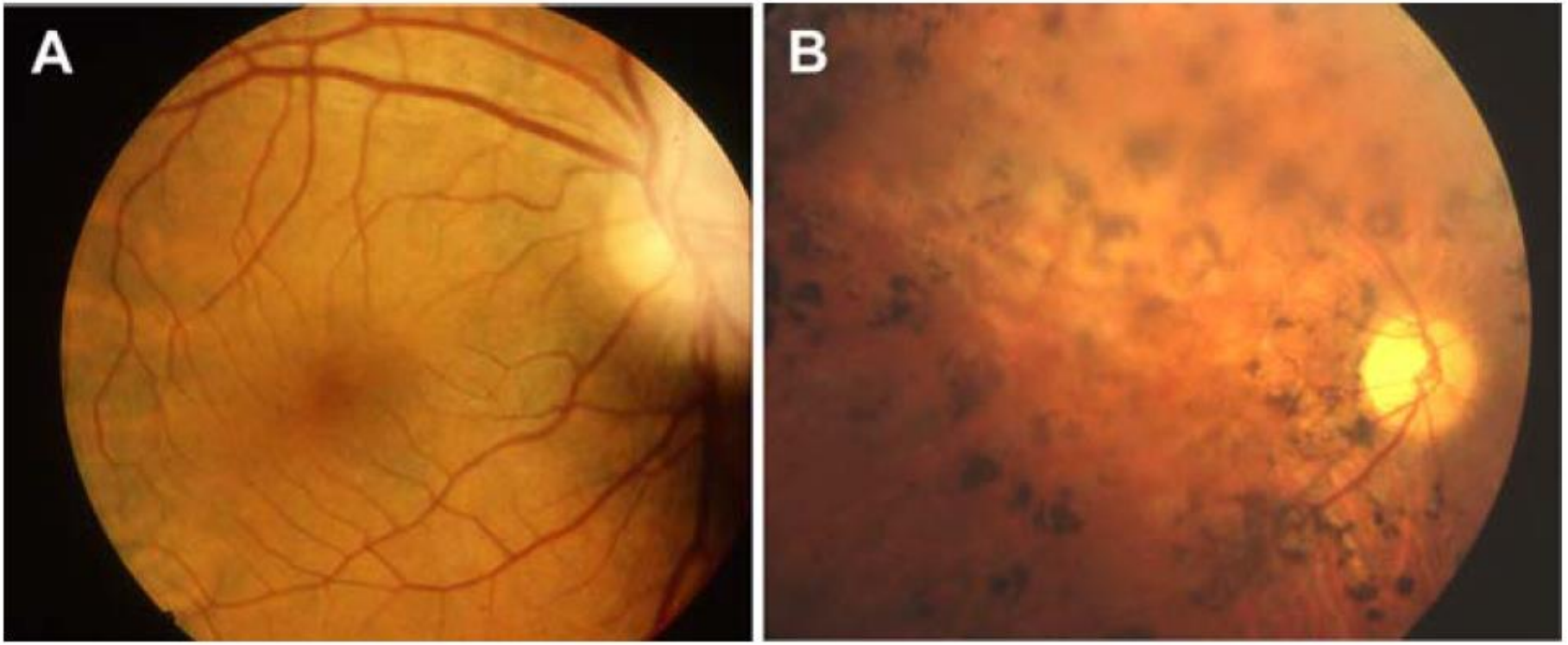
AT LEAST ONE MISSENSE MUTATION

LESS SEVERE PHENOTYPE

ADPKD



Ciliary disease and the retina: transport defect



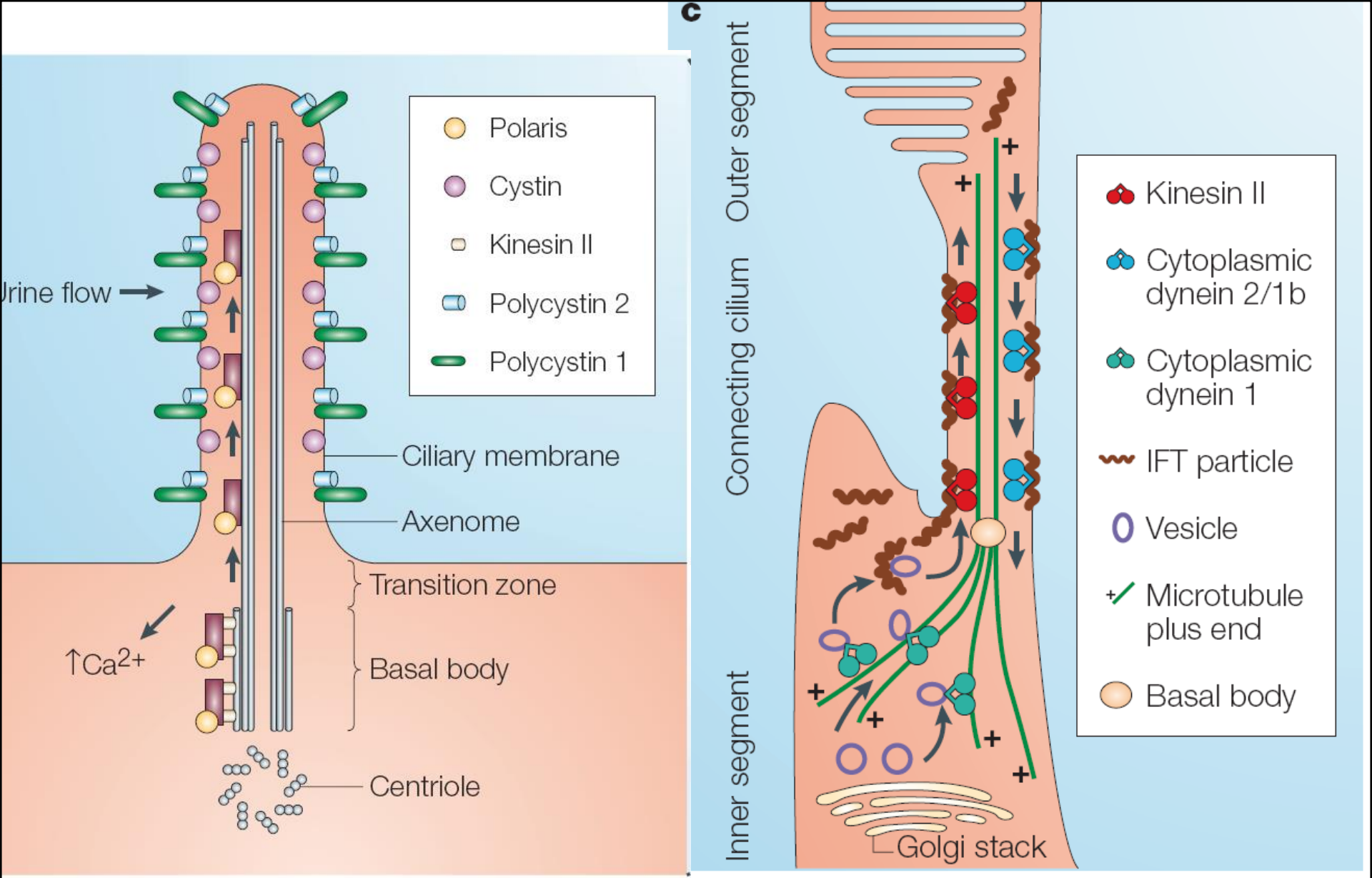
Nephronophthisis

Rémi Salomon · Sophie Saunier · Patrick Niaudet

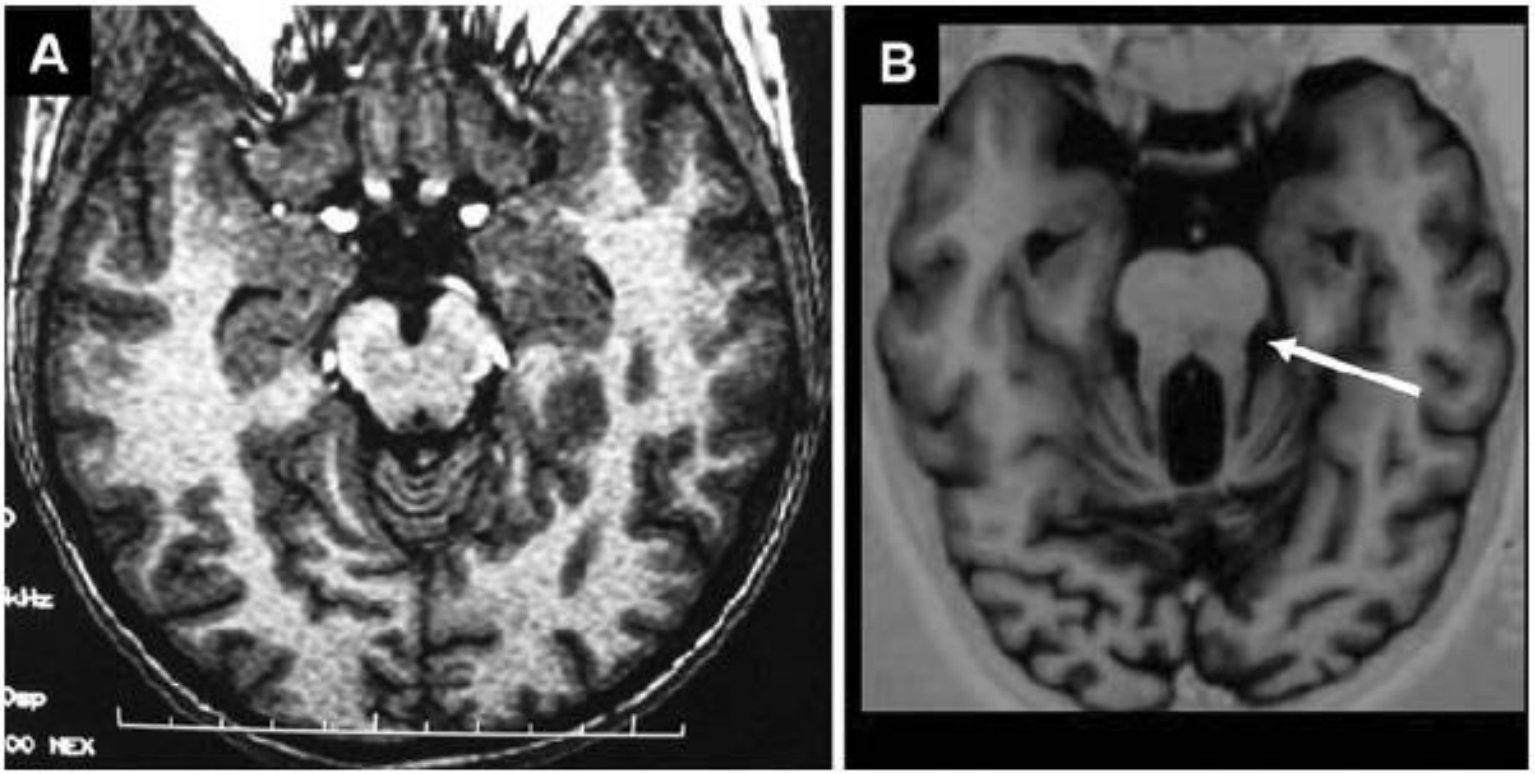
Pediatr Nephrol (2009) 24:2333–2344

Ophtalmoscopic examinations of a control subject (a) and an affected individual (b) showing typical retinitis pigmentosa fundus characterized by very thin retinal vessels, retinal pigment epithelium atrophy, abnormal pigmentary migrations, and pallor of the optic disk

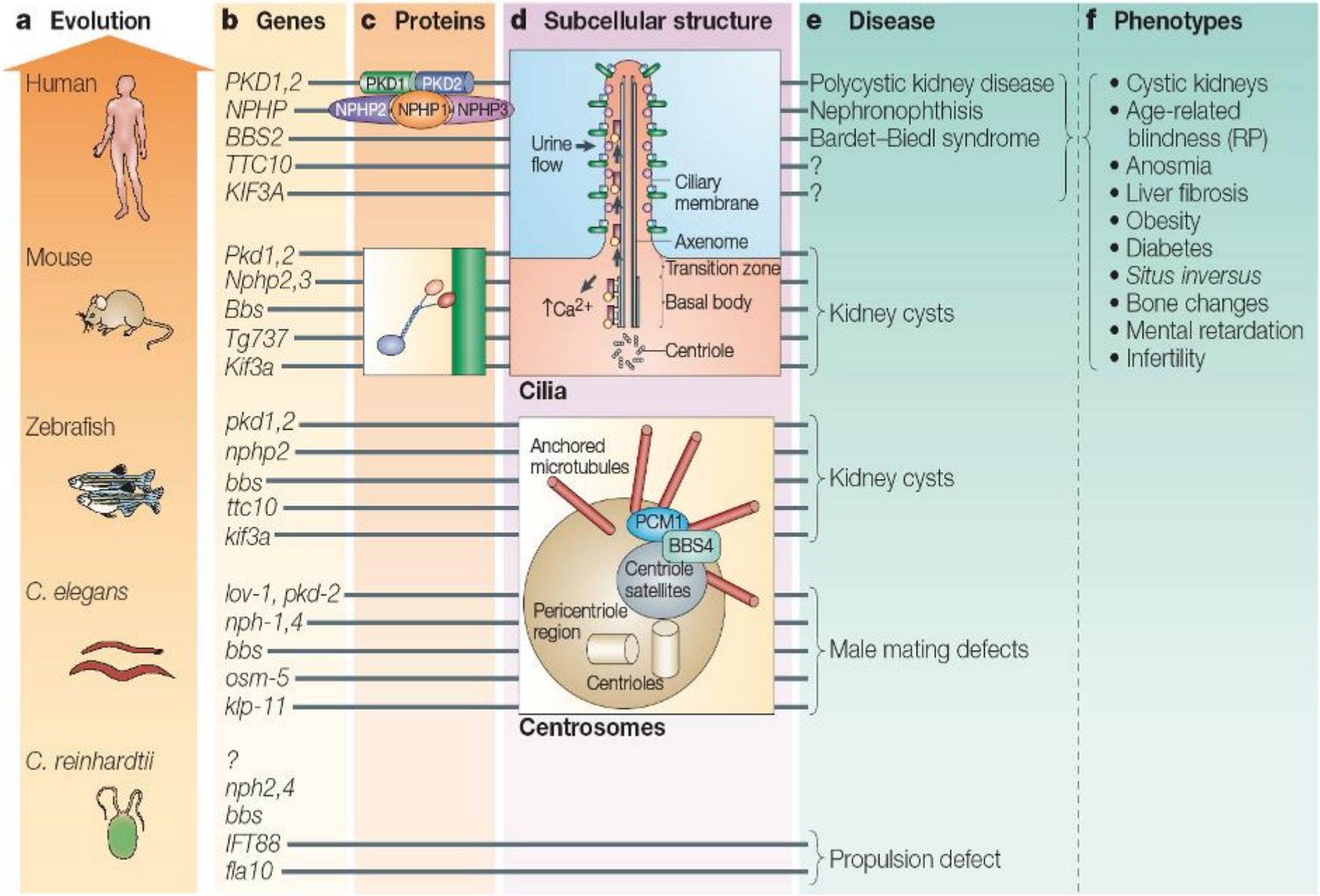
Retinitis pigmentosa


Polaris
Cystin
Kinesin II
Polycystin 2
Polycystin 1
Urine flow
Ciliary membrane
Axenome
Transition zone
Basal body
↑Ca2+
Centriole
c
Outer segment
Connecting cilium
Inner segment
Kinesin II
Cytoplasmic dynein 2/1b
Cytoplasmic dynein 1
IFT particle
Vesicle
Microtubule plus end
Basal body
Golgi stack

Ciliary disease and the central nervous system: defect of migration & orientation



Pediatr Nephrol (2009) 24:2333–2344


a Evolution
b Genes
c Proteins
d Subcellular structure
e Disease
f Phenotypes
Human
Mouse
Zebrafish
C. elegans
C. reinhardtii
PKD1,2
NPHP
BBS2
TTC10
KIF3A
Pkd1,2
Nphp2,3
Bbs
Tg737
Kif3a
pkd1,2
nphp2
bbs
ttc10
kif3a
lov-1, pkd-2
nph-1,4
bbs
osm-5
klp-11
?
nph2,4
bbs
IFT88
fla10
PKD1
PKD2
NPHP2
NPHP1
NPHP3
Urine flow
Ciliary membrane
Axenome
Transition zone
Basal body
Centriole
↑Ca2+
Cilia
Anchored microtubules
PCM1
BBS4
Centriole satellites
Pericentriole region
Centrioles
Centrosomes
Polycystic kidney disease
Nephronophthisis
Bardet–Biedl syndrome
?
?
Kidney cysts
Kidney cysts
Male mating defects
Propulsion defect
• Cystic kidneys
• Age-related blindness (RP)
• Anosmia
• Liver fibrosis
• Obesity
• Diabetes
• Situs inversus
• Bone changes
• Mental retardation
• Infertility

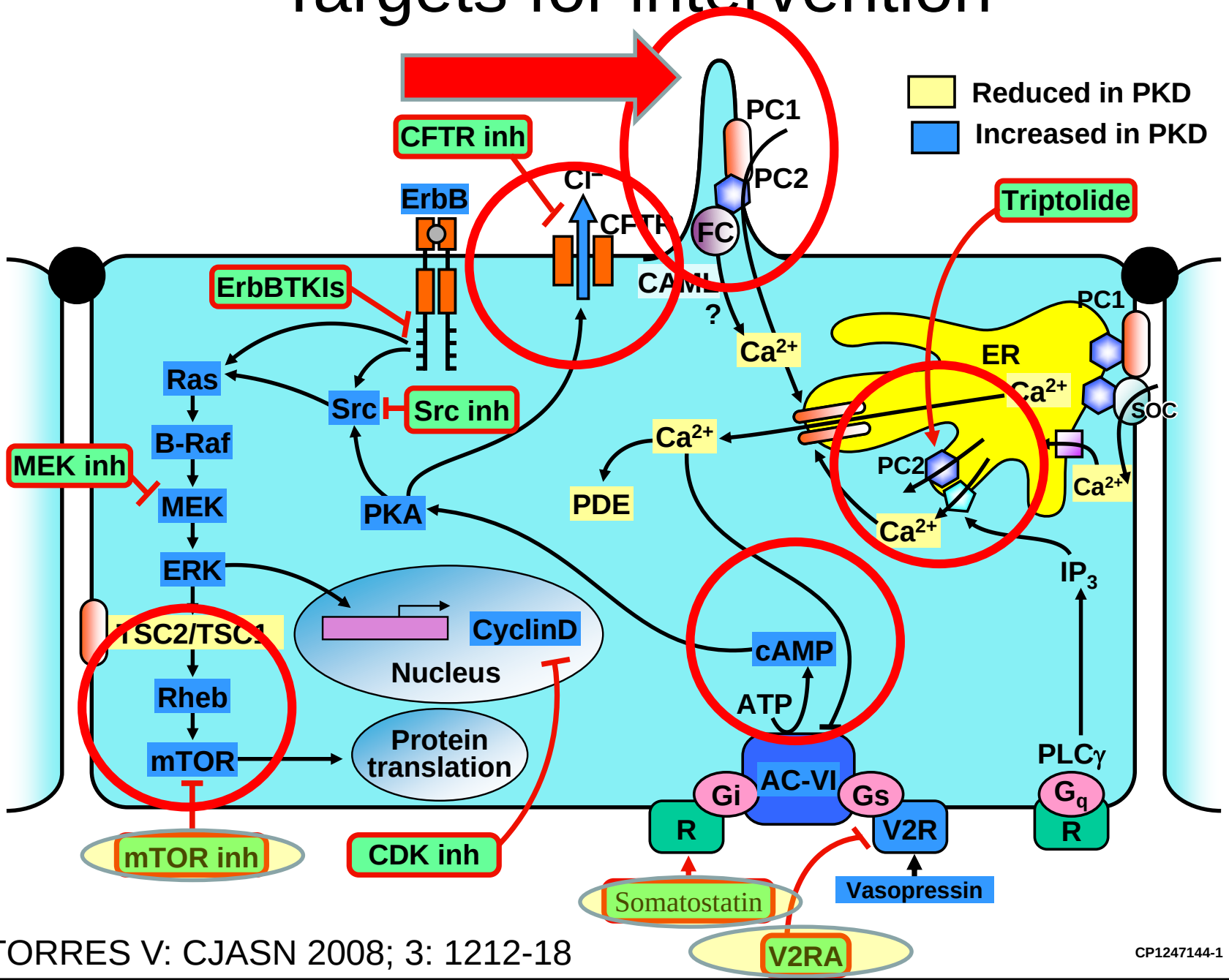
Outline

- Definitions, clinical presentation
- Pathophysiology of cyst formation
- Clinical implications, studies

Therapeutic perspective

Signalling pathways

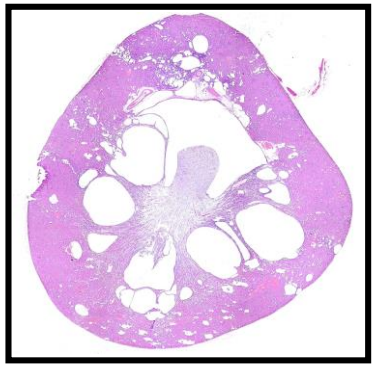
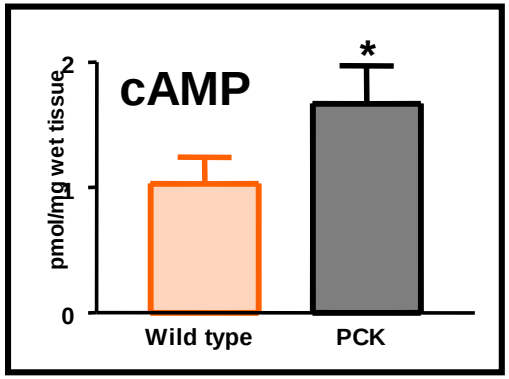
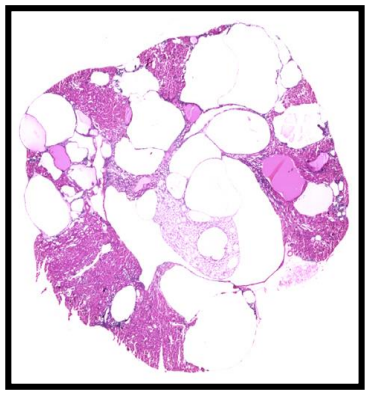
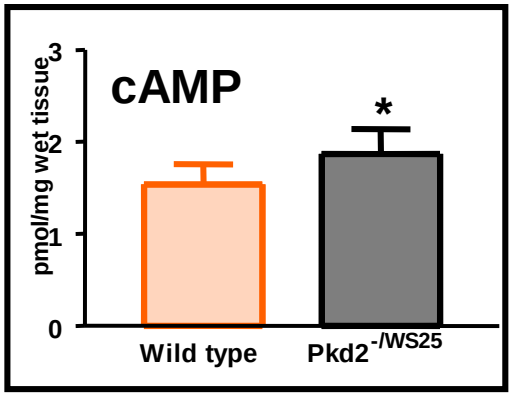
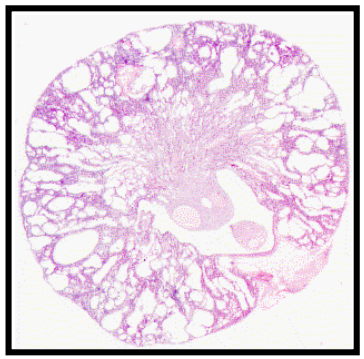
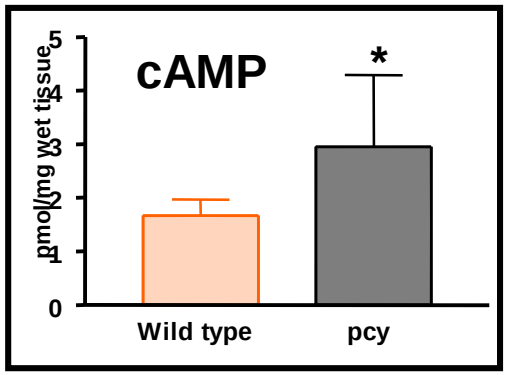
Targets for intervention



TORRES V: CJASN 2008; 3: 1212-18

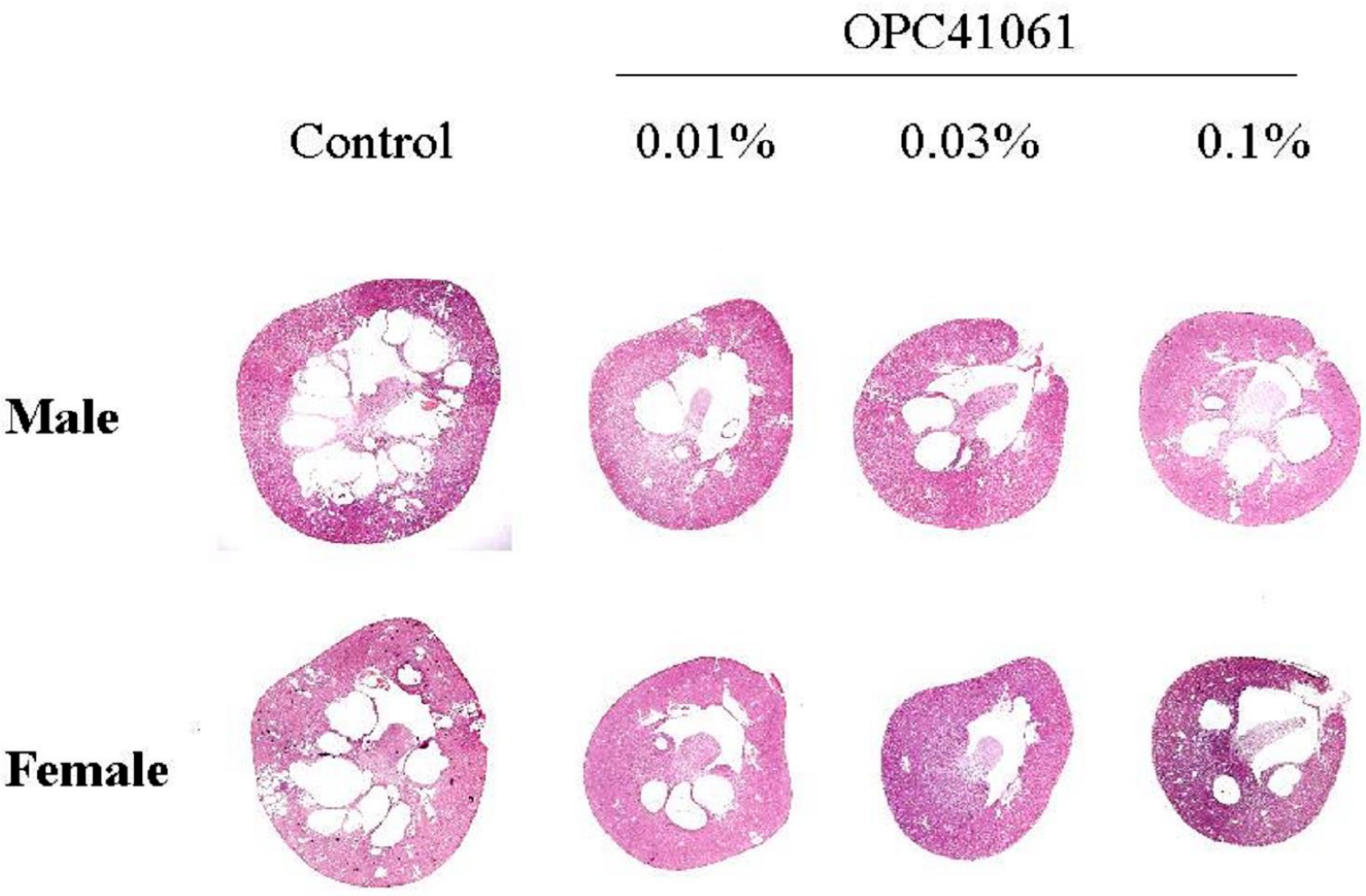
CP1247144-1

Human disease and animal homologues

Model			Human
PCK rat			**ARPKD**
Pkd2$^{WS25/-}$ mouse			**ADPKD**
***pcy* mouse**			**NPHP3**

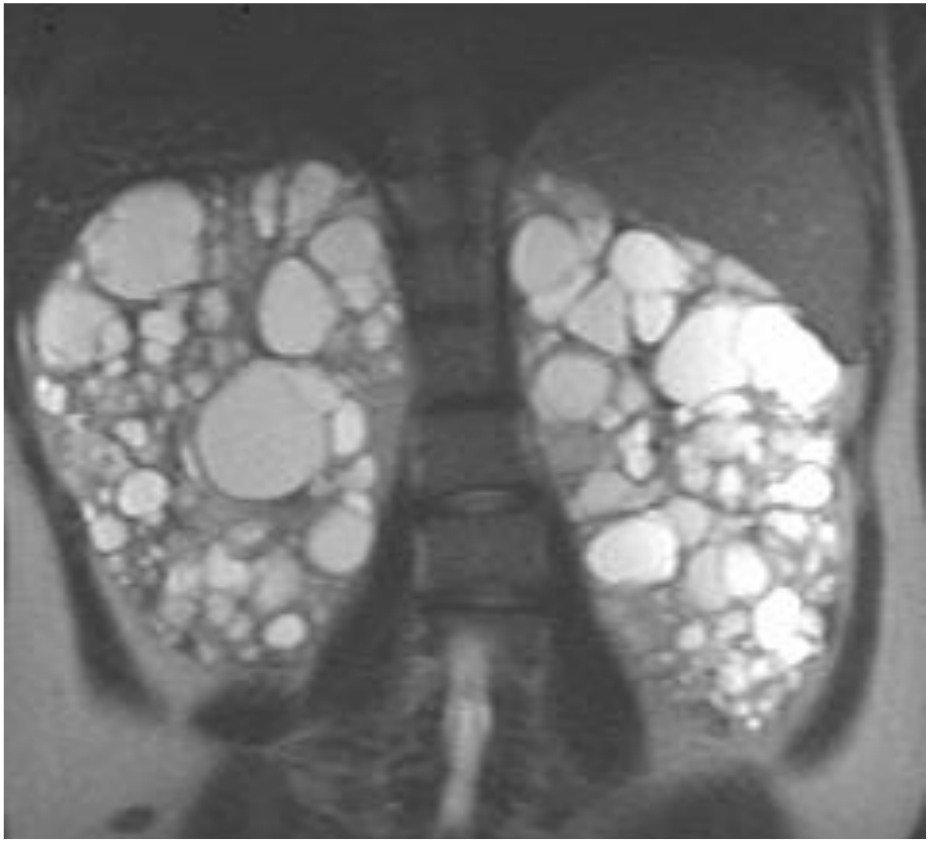
Torres V: 2007

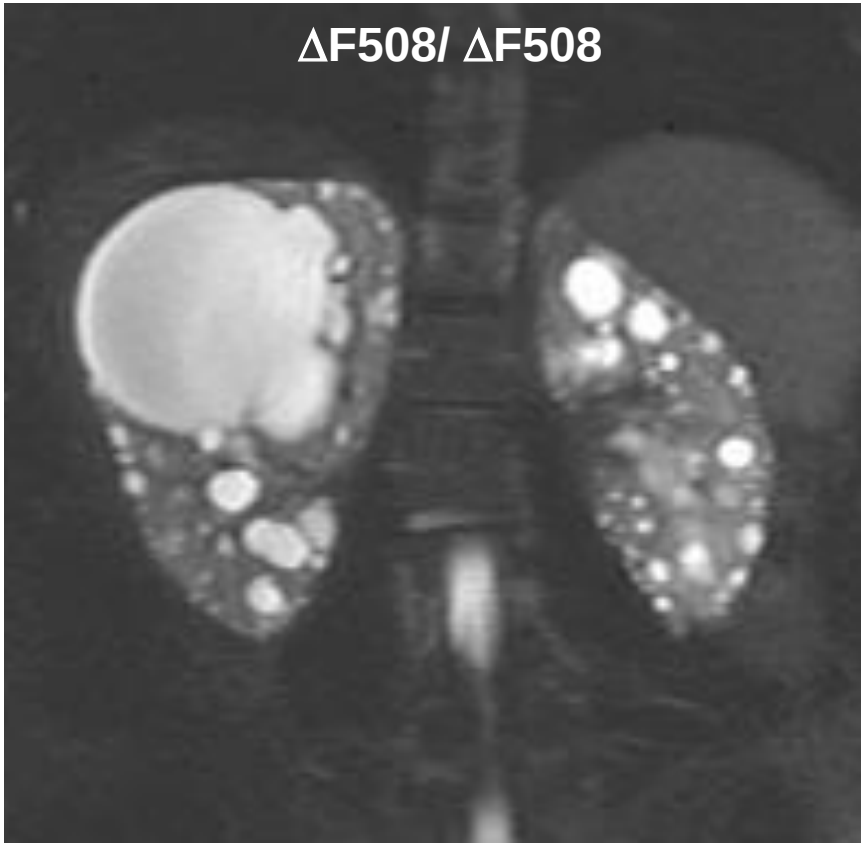
Vasopressin antagonists



Wang JASN 16:846, 2005

CFTR INHIBITION:
ADPKD COEXISTING WITH CYSTIC FIBROSIS
MILDER PHENOTYPE



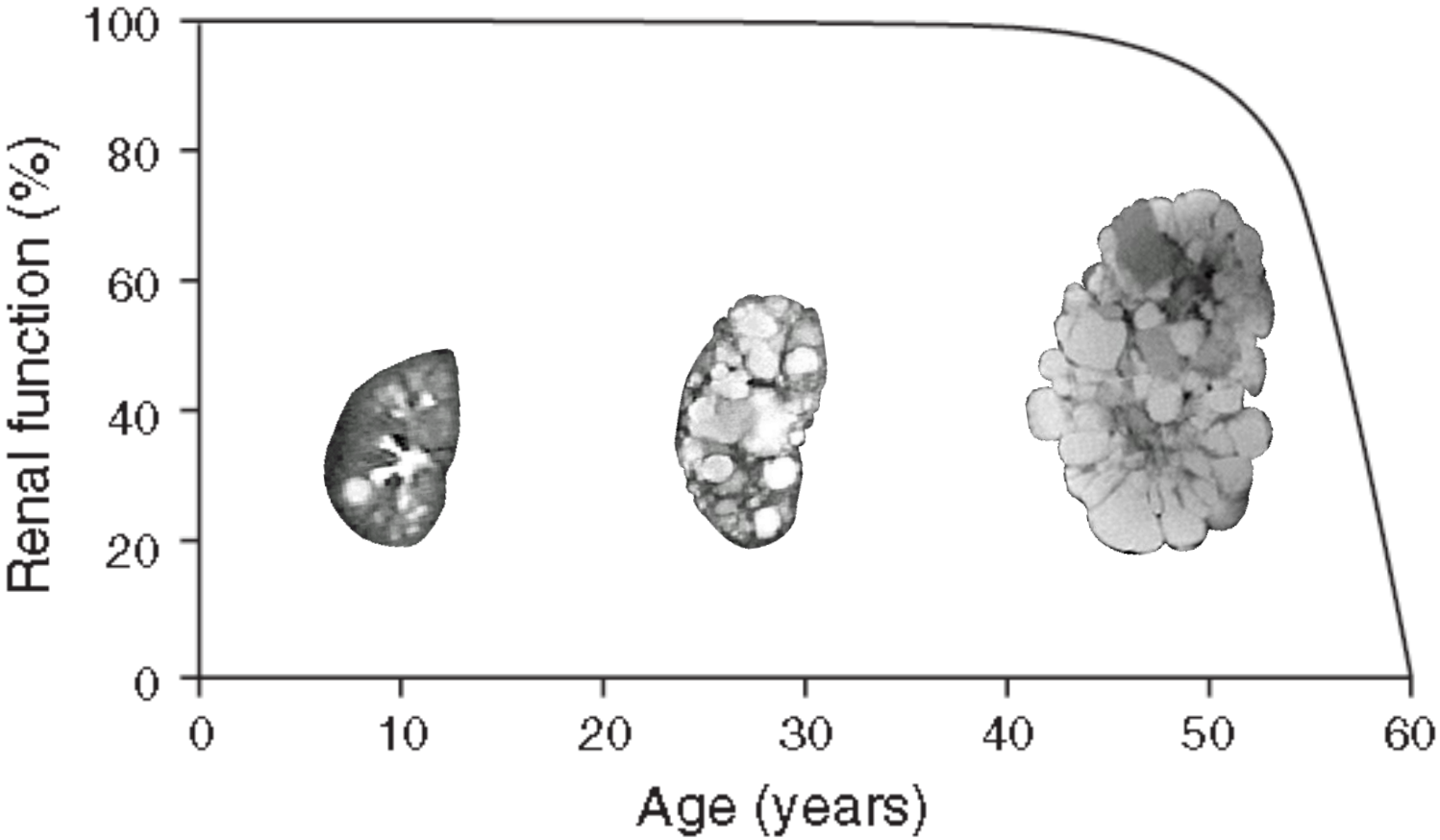


O'Sullivan. AJKD 32:976,1998
Xu. J Nephrol 19:529,2006

ADPKD: Clinical studies

- CRISP – morphology and function
- V2 receptor antagonists: tolvaptan
- Somatostatin analogues: octreotide, lanreotide
- mTOR inhibitors: sirolimus, everolimus
- ACEI & ACEI+ARB: lisinopril - telmisartan

Renal survival curve in ADPKD



long duration of intact renal function before loss of renal function or entry into ESRD

Chapman et al: Clin J Am Soc Nephrol 3: 1197–1204, 2008.

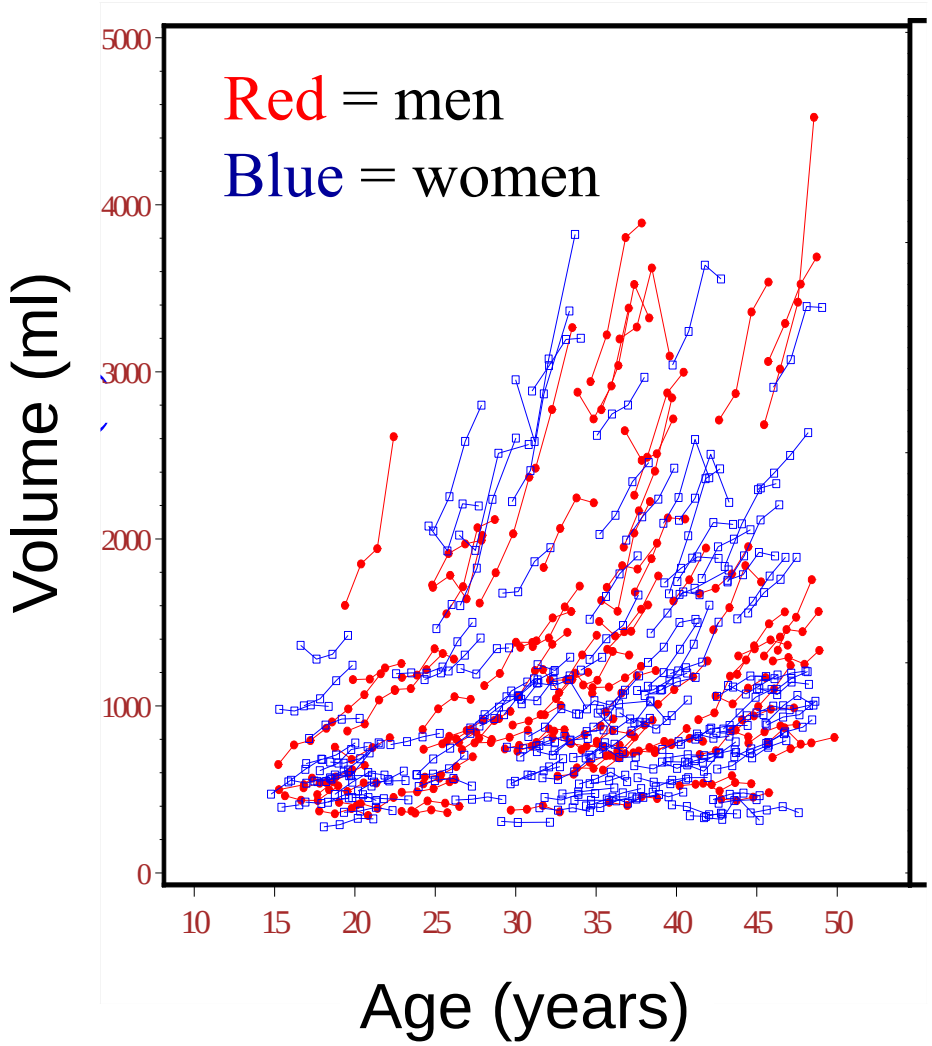
CRISP

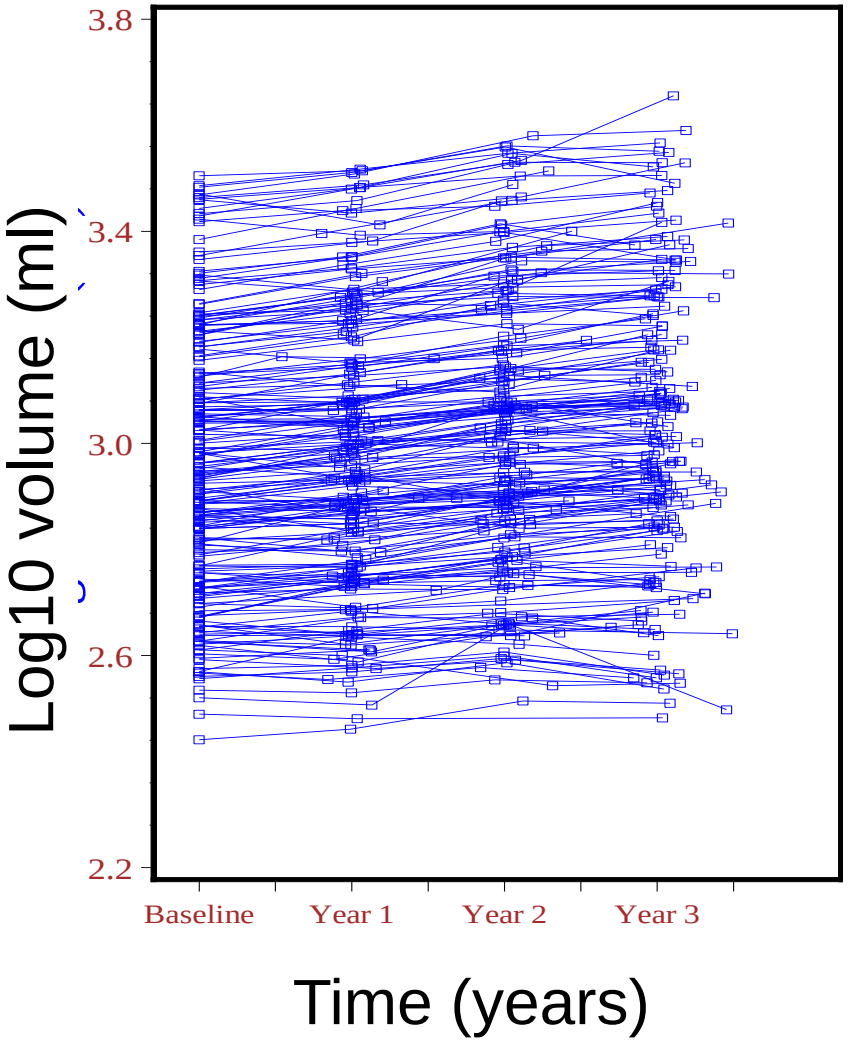
Consortium for Radiological Imaging in Studies of Polycystic Kidney Disease

- Need for a more sensitive tool than GFR to assess progression of ADPKD

- CRISP
  - Whether kidney/cyst volume changes
    - can be detected over a short period of time
    - and are associated with loss of renal function
  - Prospective observational study
  - Patients with eGFR >70 ml/min

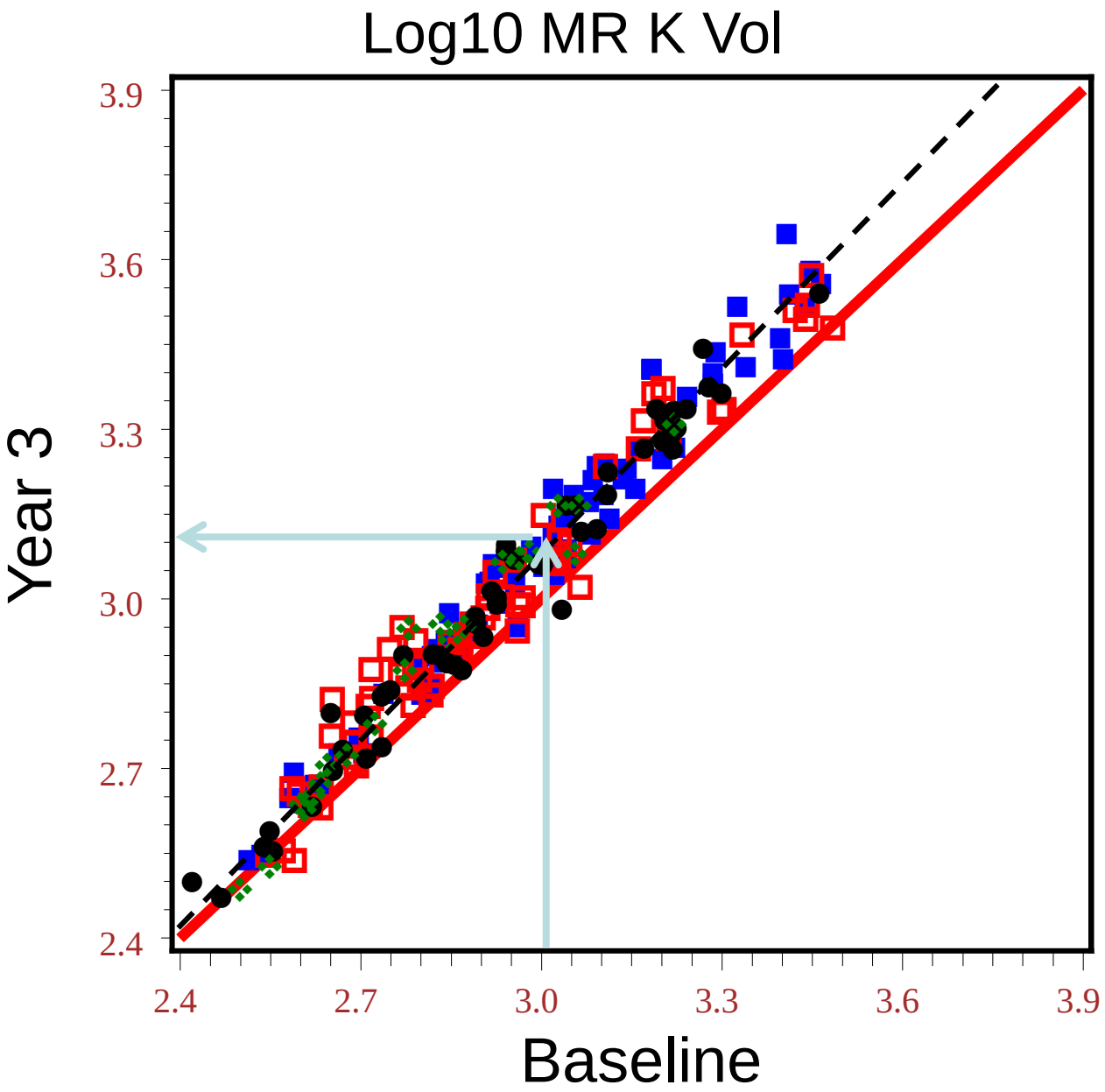
Kidney enlargement is detectable over a short period of time, it is continuous and relatively constant





Grantham NEJM 354:2122-2130, 2006

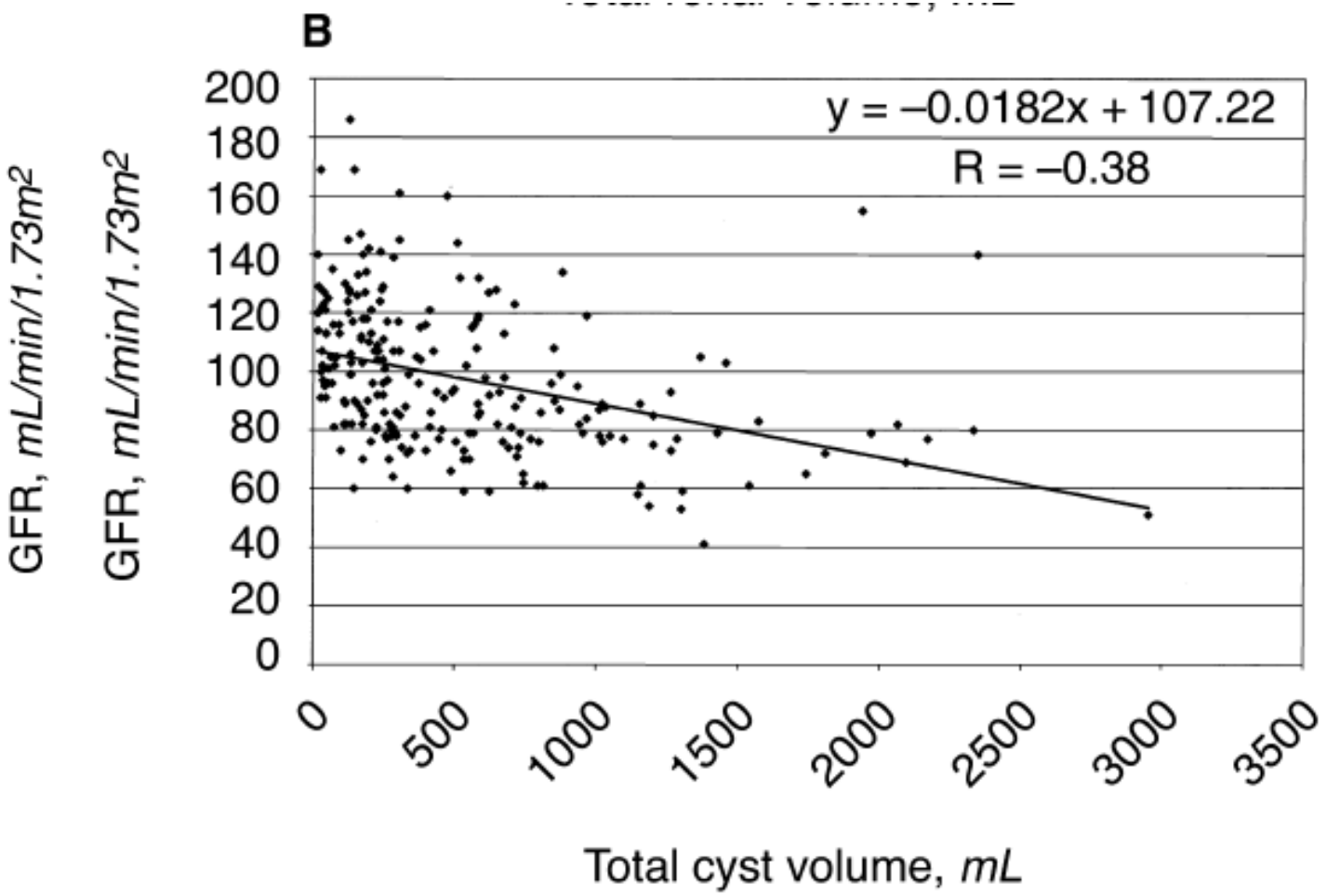
Renal volume predicts rate of enlargement



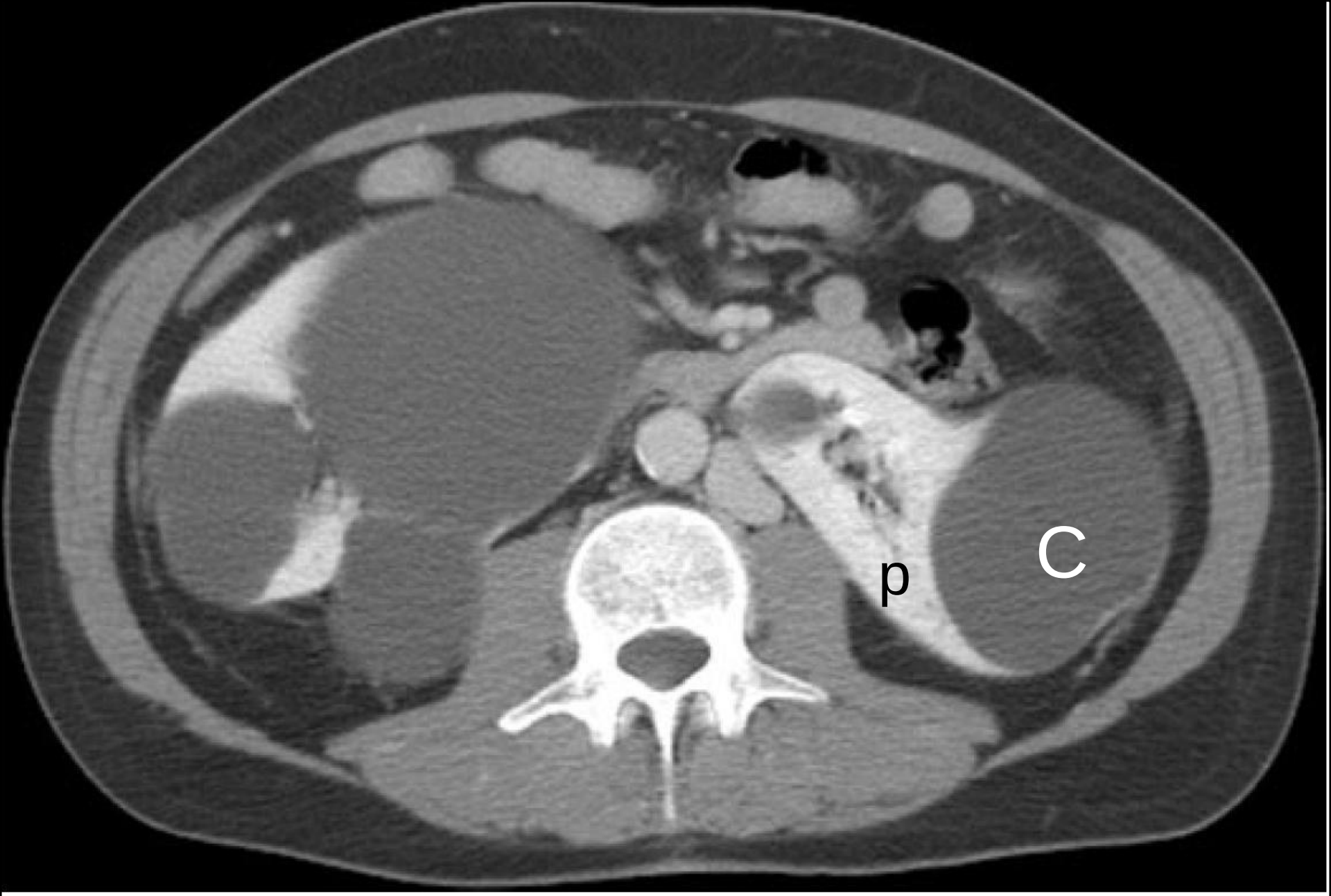
5.3 % average yearly increase in renal size

Grantham NEJM 354:2122-2130, 2006

Relationship between GFR and age adjusted renal volumes



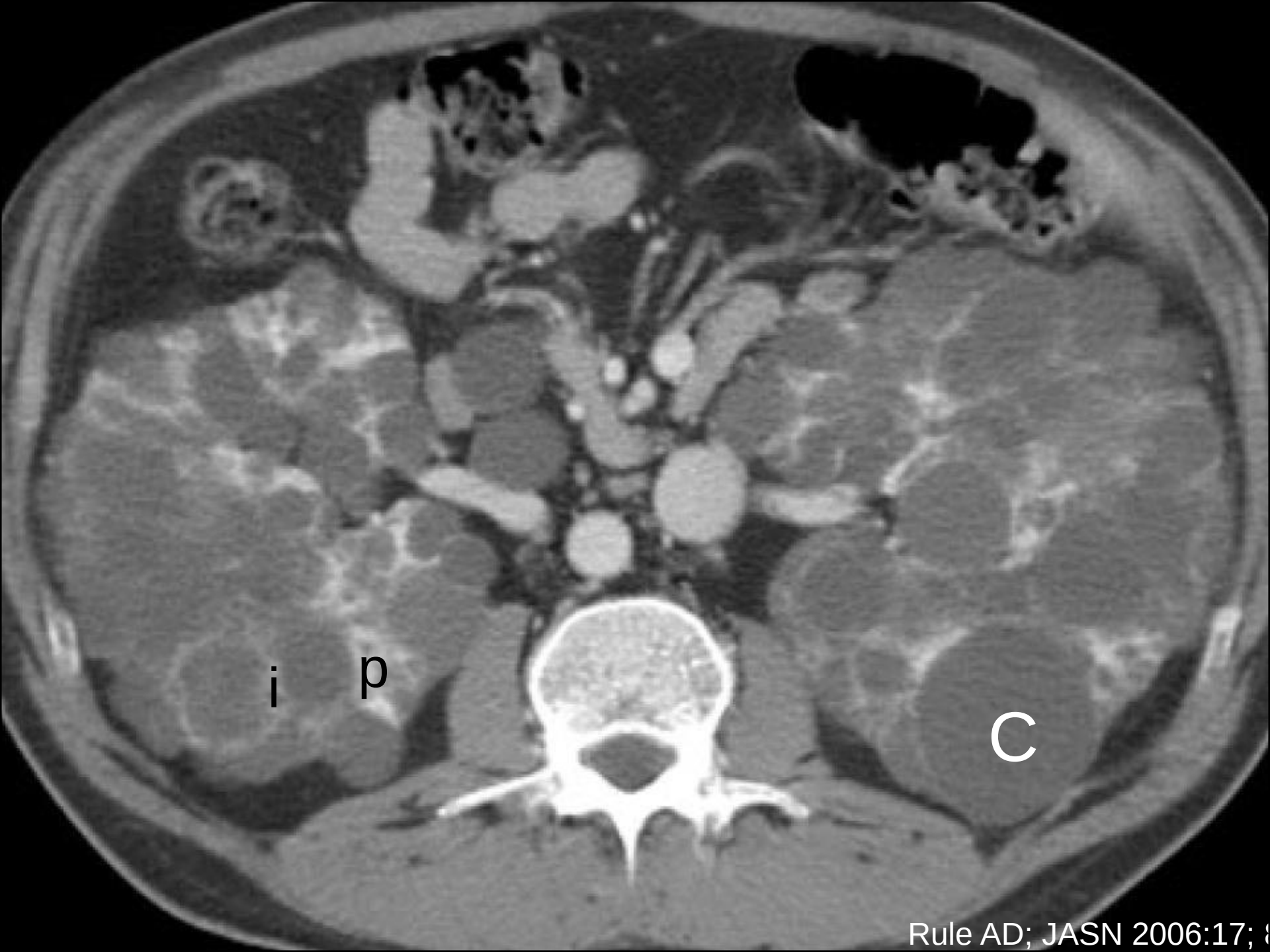
Chapman AD: Kidney International, Vol. 64 (2003), pp. 1035–1045



C=cyst P=parenchyma

CT

Rule AD; JASN 2006:17; 854-862



Rule AD; JASN 2006:17; 8

CRISP Conclusions

Kidney enlargement is

- Detectable over a short period of time
- A strong predictor of functional progression
- A surrogate endpoint “reasonably likely” to predict clinical benefit in clinical trials

CRISP conclusions

- Height adjusted total kidney volume (htTKV) at baseline >600 cm^3
  - 75% risk of developing CKD >III within 8 years
  - Every 100 cm^3 increment of baseline htTVK = OR 1.48x of reaching CKD>III
- Decline in function delayed
  - GFR: unchanged in the first 3 years
  - Decline by 10.6% and 22.3% by years 6 and 8

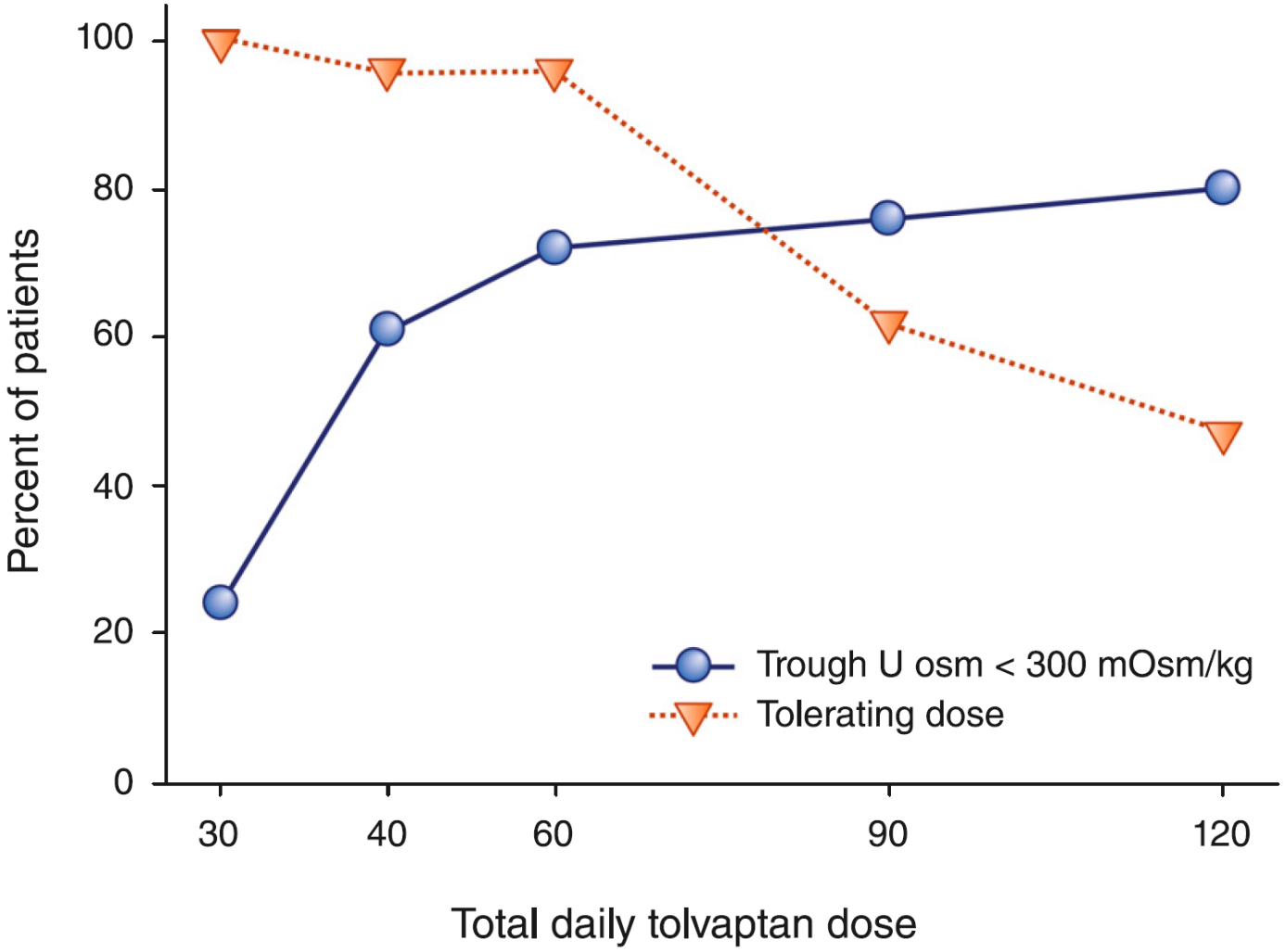
Interventional studies

V2 receptor antagonist

TEMPO

(Tolvaptan Eficacy and Safety in Management of PKD and Outcomes)

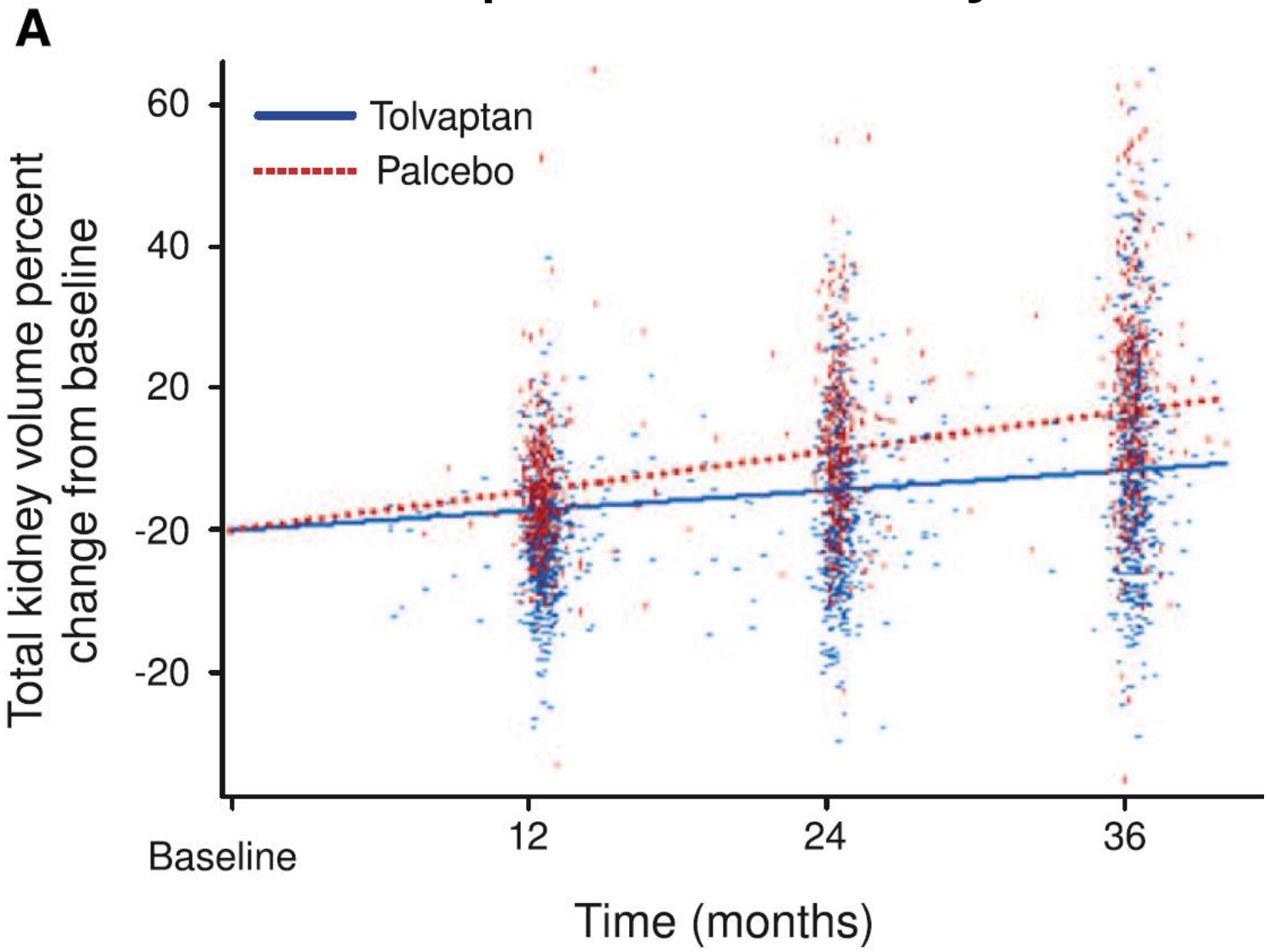
Tolerability and efficacy



Higashihara E et al. Clin J Am Soc Nephrol 2011; 6: 2499–2507

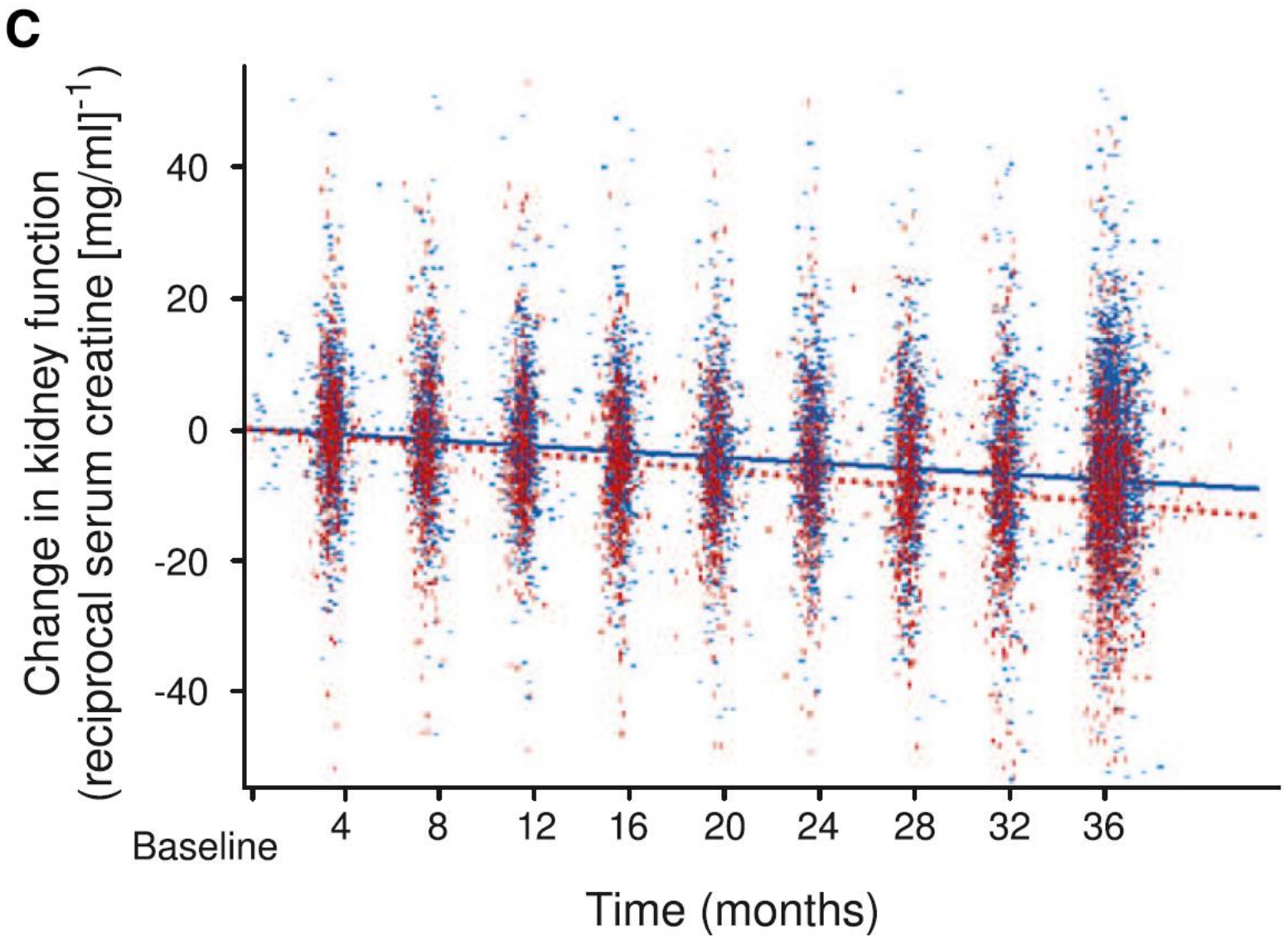
Torres VW, Harris PC: . J Am Soc Nephrol 25: 18–32, 2014

Effect of tolvaptan on kidney volume



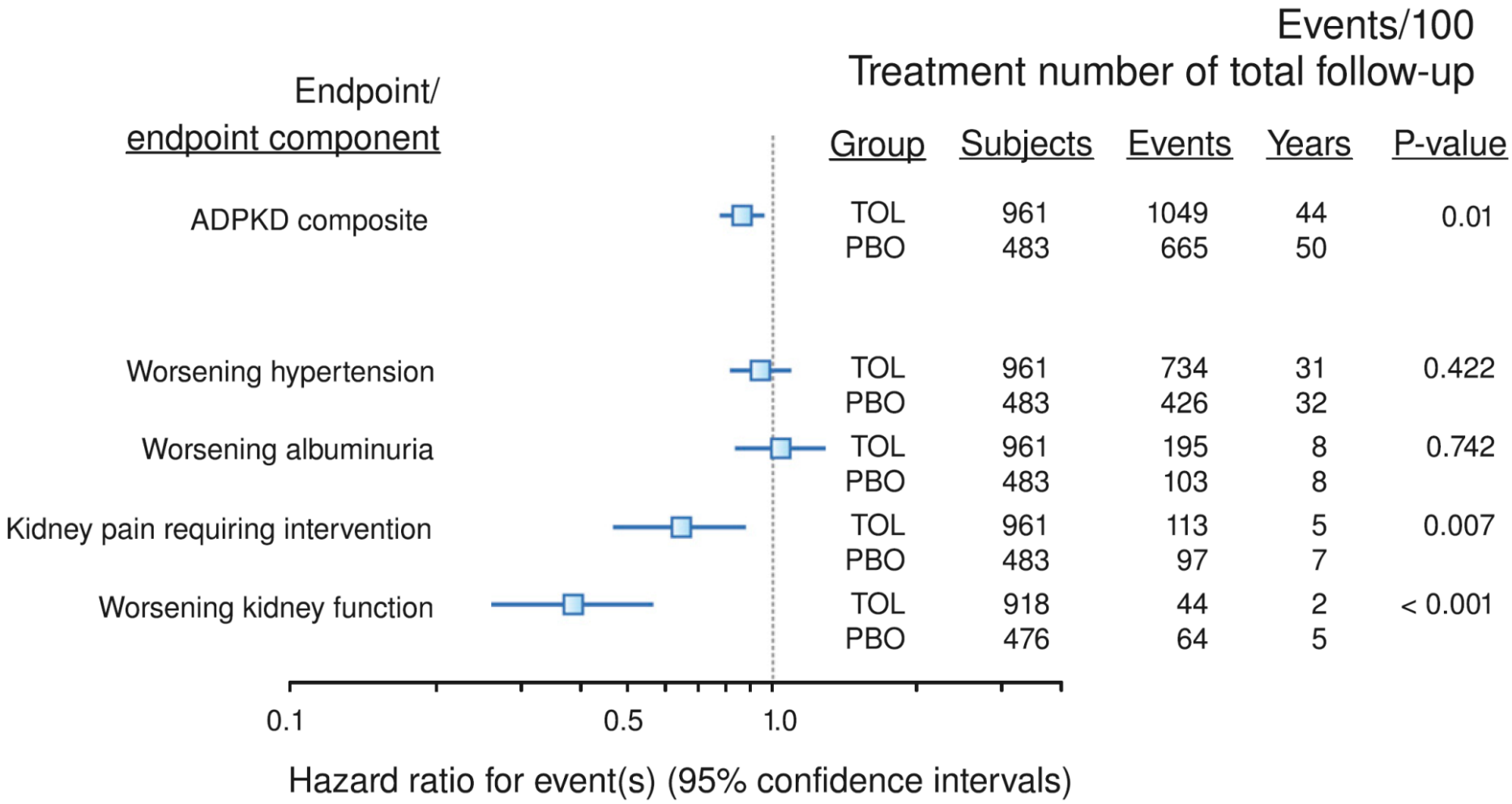
Torres VE et al. N Engl J Med 2012; 367: 2407–2418,

Effect of Tolvaptan on kidney function



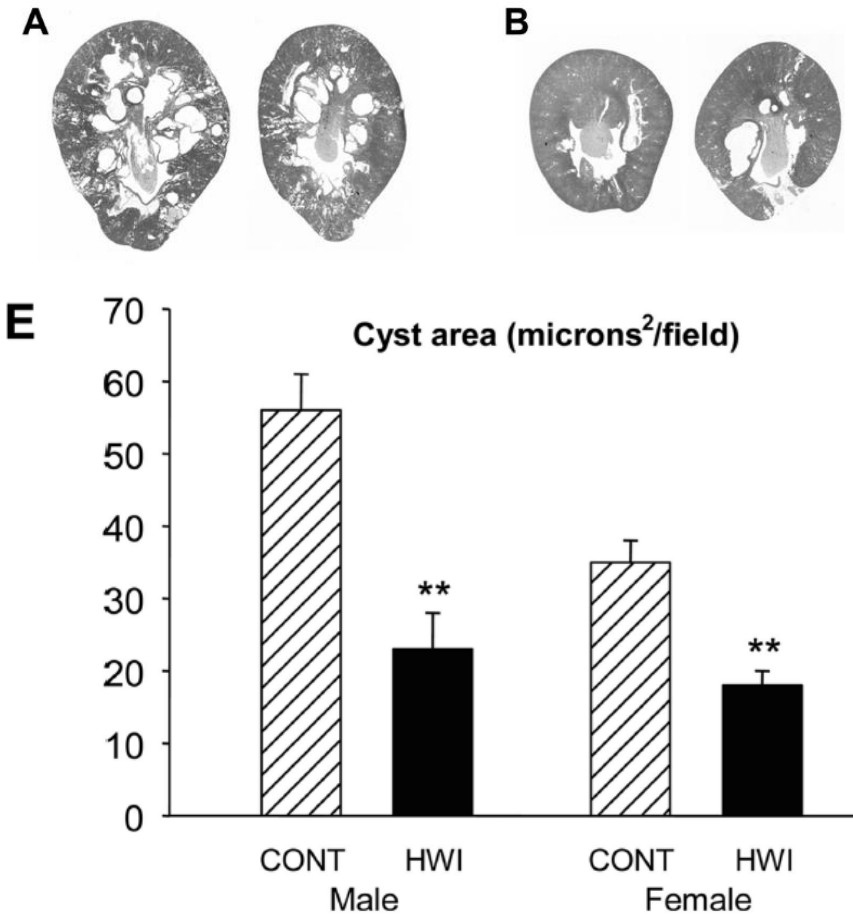
Torres VE et al. N Engl J Med 2012; 367: 2407–2418,

Effect of Tolvaptan in ADPKD



Torres VE et al. N Engl J Med 2012; 367: 2407–2418,

Increased Water Intake Decreases Progression of PKD the Rat

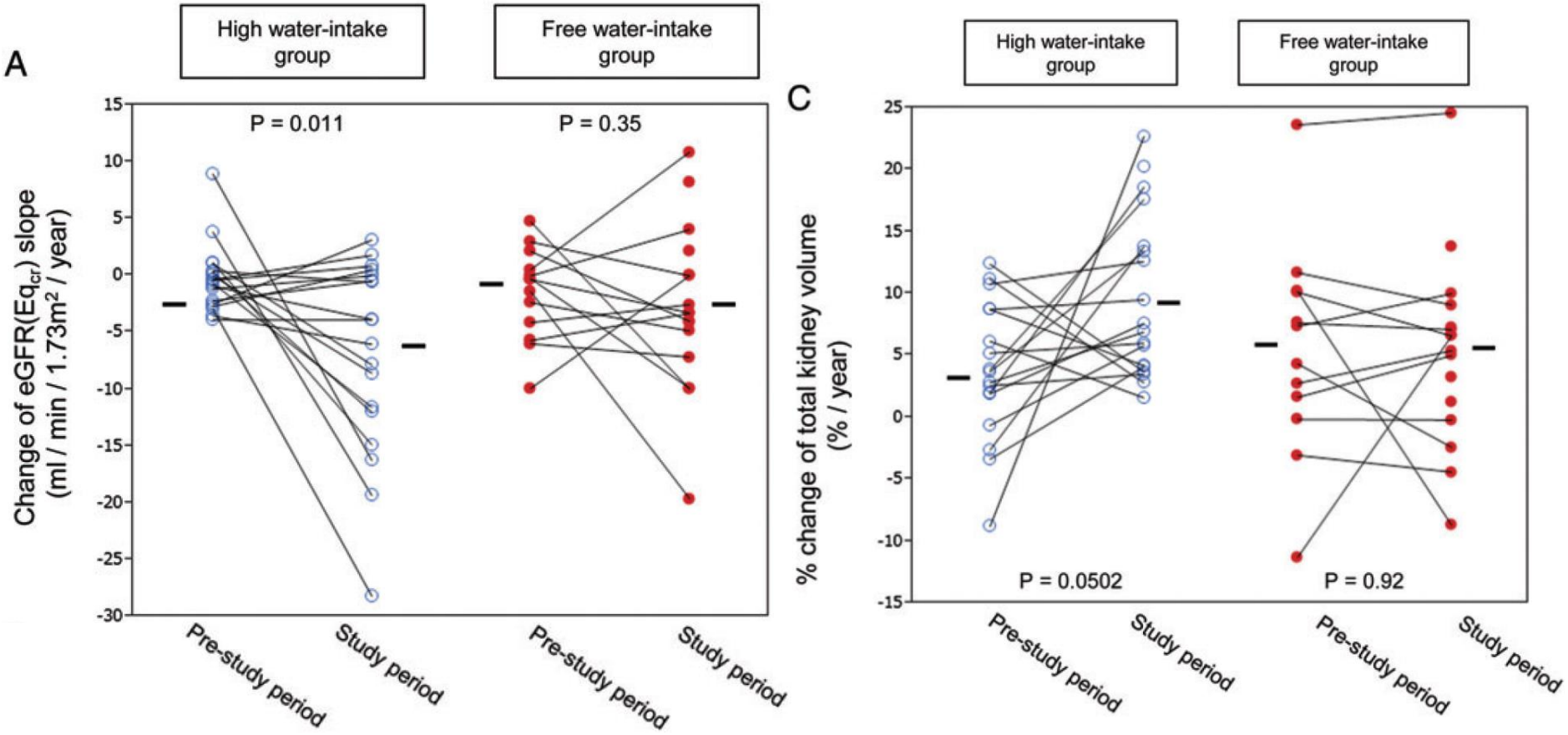


Nagao S et al: J Am Soc Nephrol 17: 2220–2227, 2006.

Does increased water intake prevent disease progression in autosomal dominant polycystic kidney disease?

ndt
Nephrology Dialysis Transplantation

Eiji Higashihara[1,2], Kikuo Nutahara[2], Mitsuhiro Tanbo[2], Hidehiko Hara[2], Isao Miyazaki[3], Kuninori Kobayashi[4] and Toshiaki Nitatori[3]



high water intake enhanced disease progression

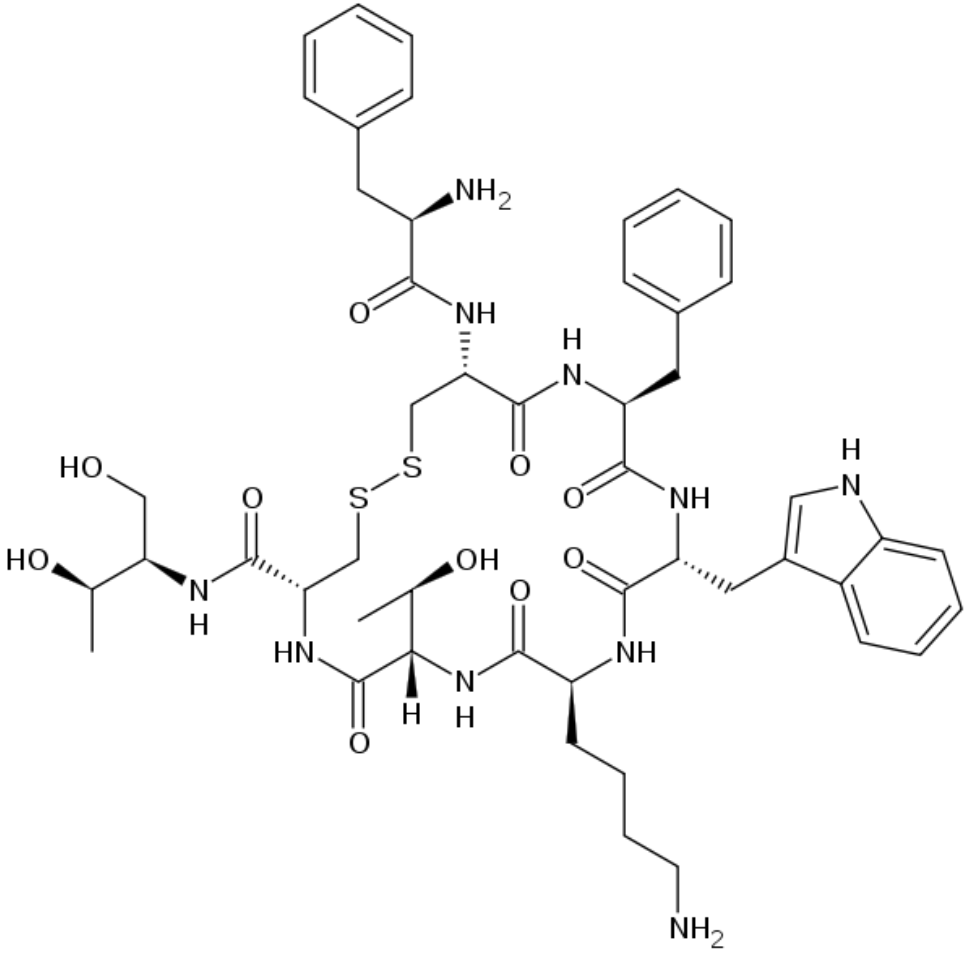
Higashihara E et al: Nephrol Dial Transplant (2014) 0: 1–10

Interventional studies

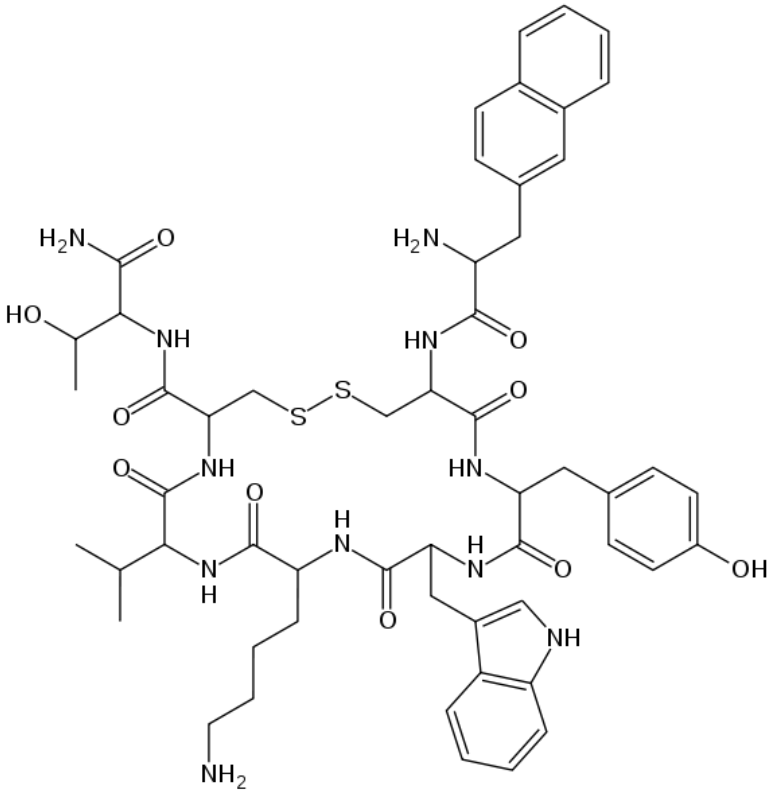
Somatostatin analogues

Somatostatin analogues

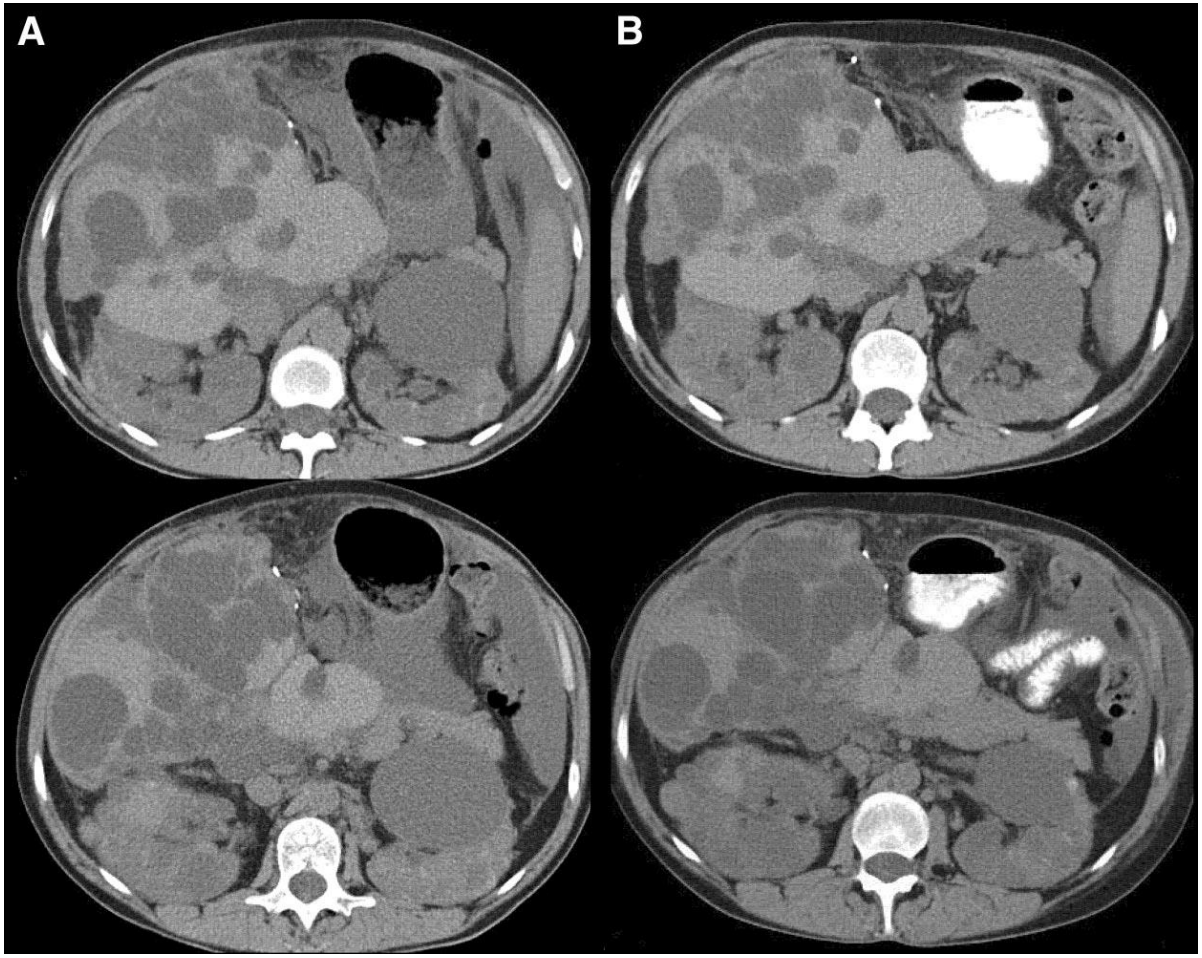
Octreotide (Sandostatin)



Lanreotide (Somatuline LA and Depot)



Administration of octreotide LAR to a patient with severe PLD



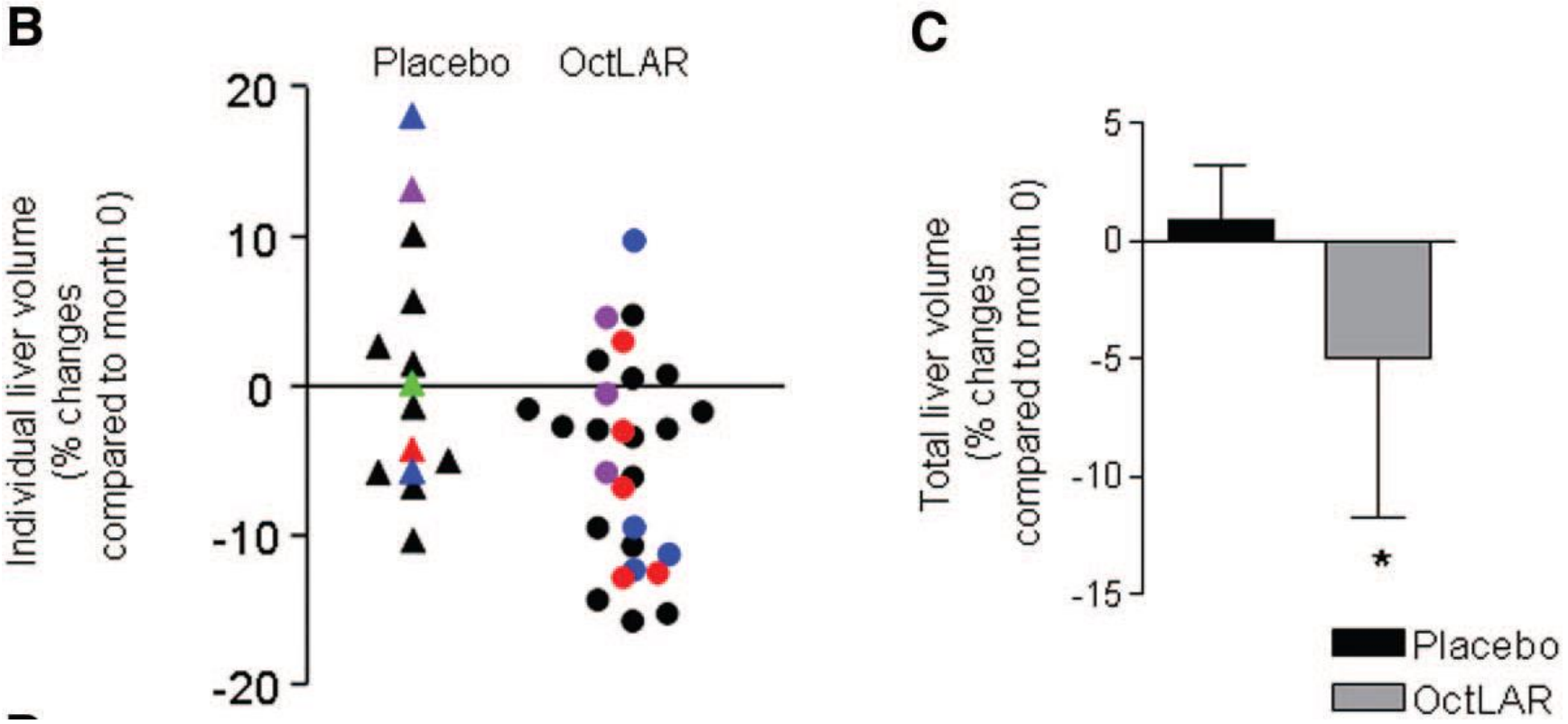
Administration of octreotide LAR to a patient with severe PLD Total liver volume decreased by 18% , total kidney volume decreased by 12%.

J Am Soc Nephrol 21: 1052–1061, 2010.

Randomized Clinical Trial of Long-Acting Somatostatin for Autosomal Dominant Polycystic Kidney and Liver Disease

LAR 40 mg IM every 4 weeks for 2 years

LIVER



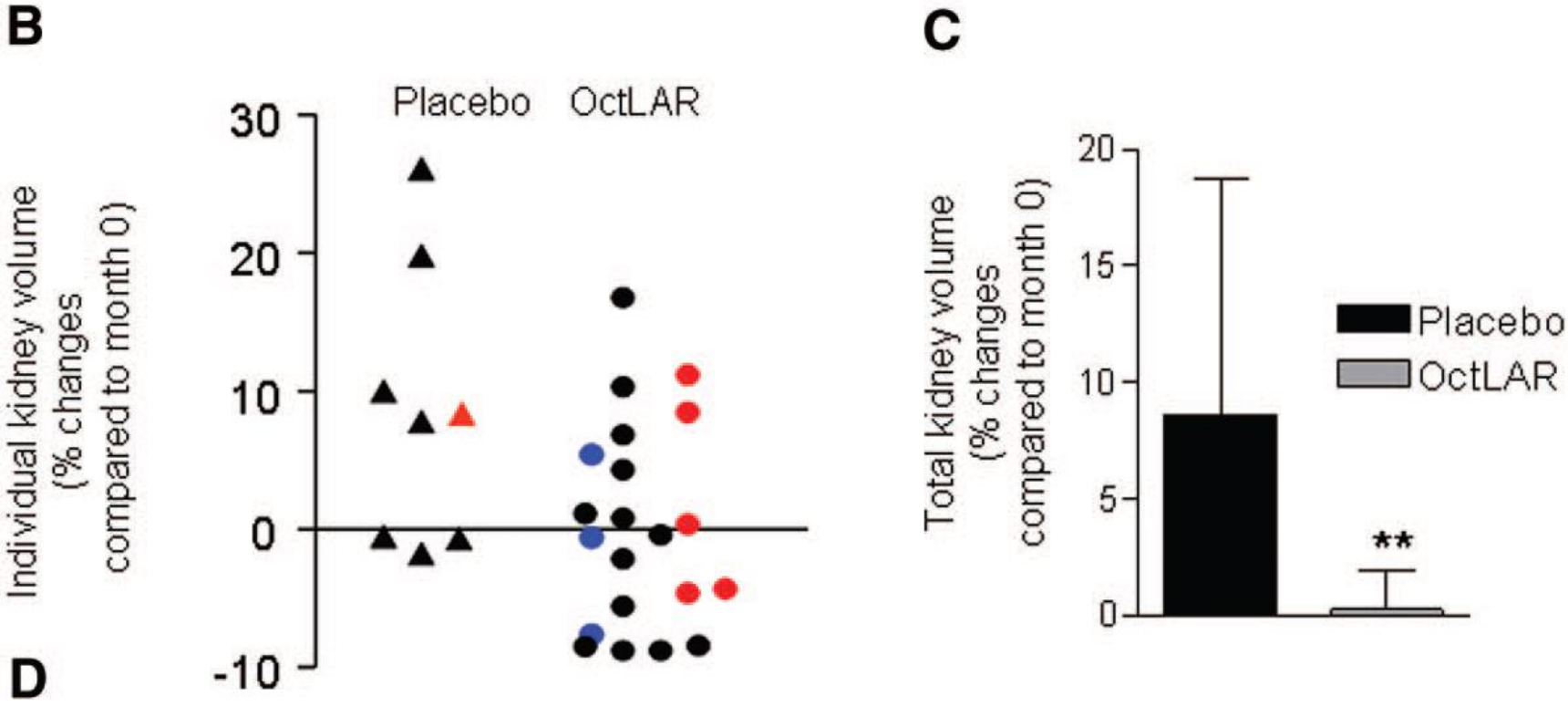
N=42
Liver volume >4000 mL

J Am Soc Nephrol 21: 1052–1061, 2010.

Randomized Clinical Trial of Long-Acting Somatostatin for Autosomal Dominant Polycystic Kidney and Liver Disease

LAR 40 mg IM every 4 weeks for 2 years

KIDNEY



N=42
Liver volume >4000 mL

J Am Soc Nephrol 21: 1052–1061, 2010.

Most important trials involving somatostatin analogues

Study	Study drug	Patients (n)	Treatment duration (months)	Treatment regimen	Change in baseline volume in treatment group (5)	Change in baseline volumen in placebo group (%)
Van Keimpema et al (5*)	Lanreotide	54	6	120 mg monthly	Liver: -2.9 Kidney: -1.5	Liver: +1.6* Kidney: +3.4*
Hogan et al. (6**)	Octreotide	42	12	40 mg monthly	Liver: -5.0 Kidney: +0.3	Liver: +0.9* Kidney: +8.6*
Caroli et al. (7**)	Octreotide	12	6	40 mg monthly	Liver: -4.5 Kidney: +2.2	Liver: +0.9* Kidney: +5.9 *

Current Opinion in Gastroenterology 2011, 27:294–300

Interventional studies

mTOR inhibitors

Sirolimus

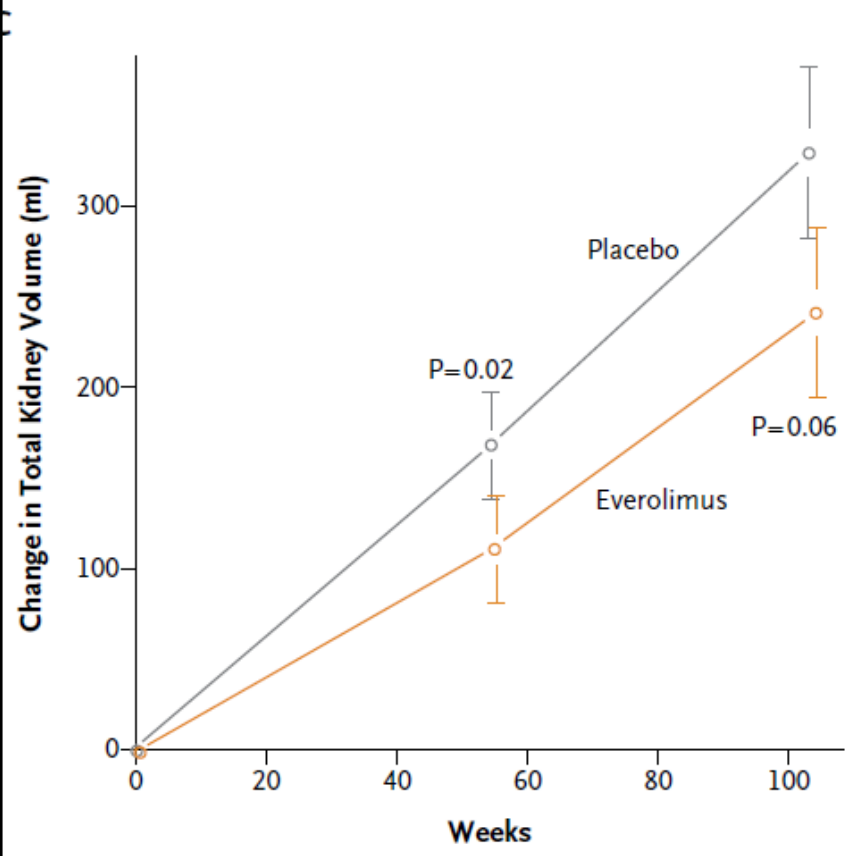
Everolimus

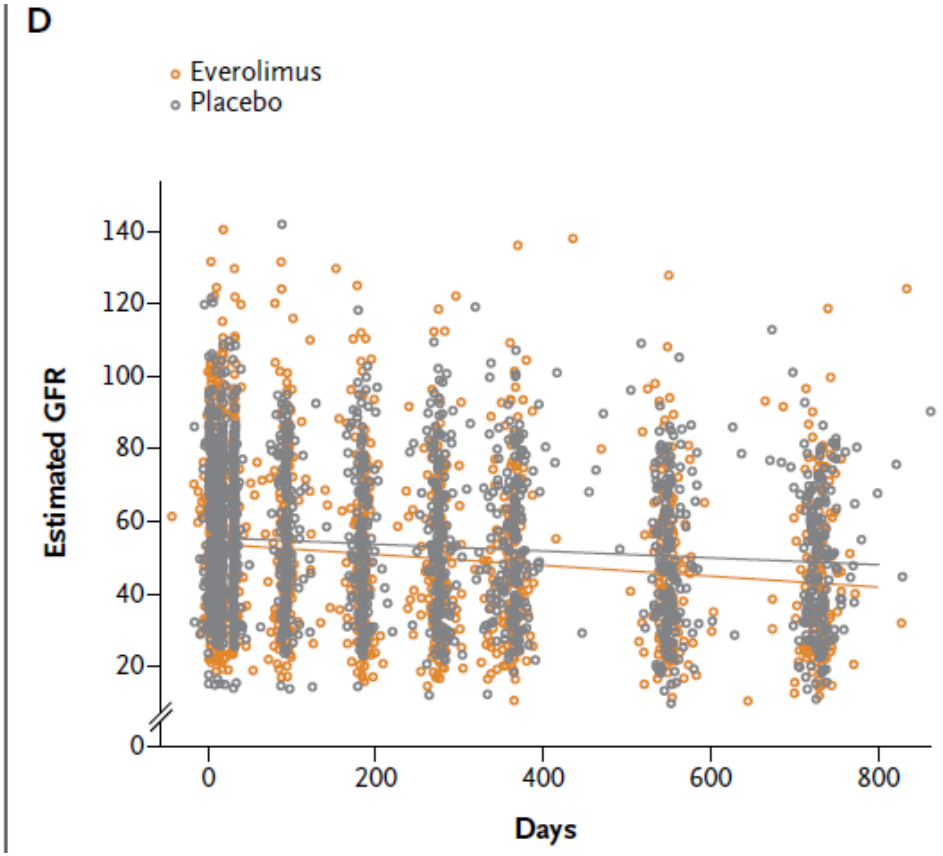
Most important trials involving mTOR inhibitors

Study	Study drug	Patients (n)	Treatment duration (months)	Treatment regimen	Change in baseline volume in treatment group (5)	Change in baseline volumen in placebo group (%)
Perico et al. (23*)	**Sirolimus**	**15**	**6**	**3 mg daily**	**Kidney: +2.2**	**Kidney: +3.7**
Serra et al. (24)**	**Sirolimus**	**100**	**18**	**2 mg daily**	**Kidney: +10.9**	**Kidney: +9.7**
Walz et al. (25)**	**Everolimus**	**433**	**24**	**5 mg daily**	**Kidney: +11.3**	**Kidneyx: +15.8 ***

Current Opinion in Gastroenterology 2011, 27:294–300

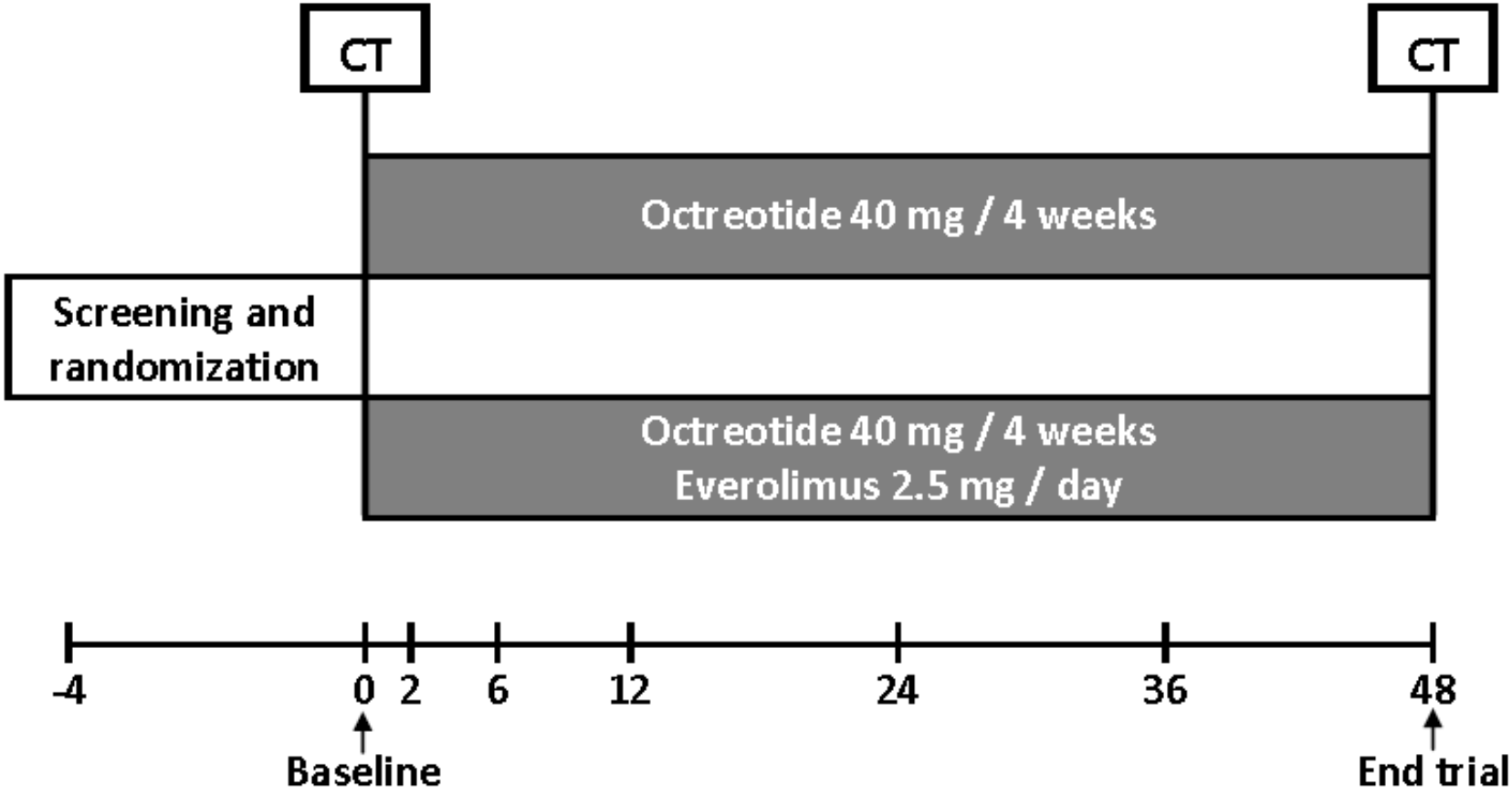
Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease





N Engl J Med 2010;363:830-40.

Everolimus and long acting octreotide as a volume reducing treatment of polycystic livers (ELATE): study protocol for a randomized controlled trial



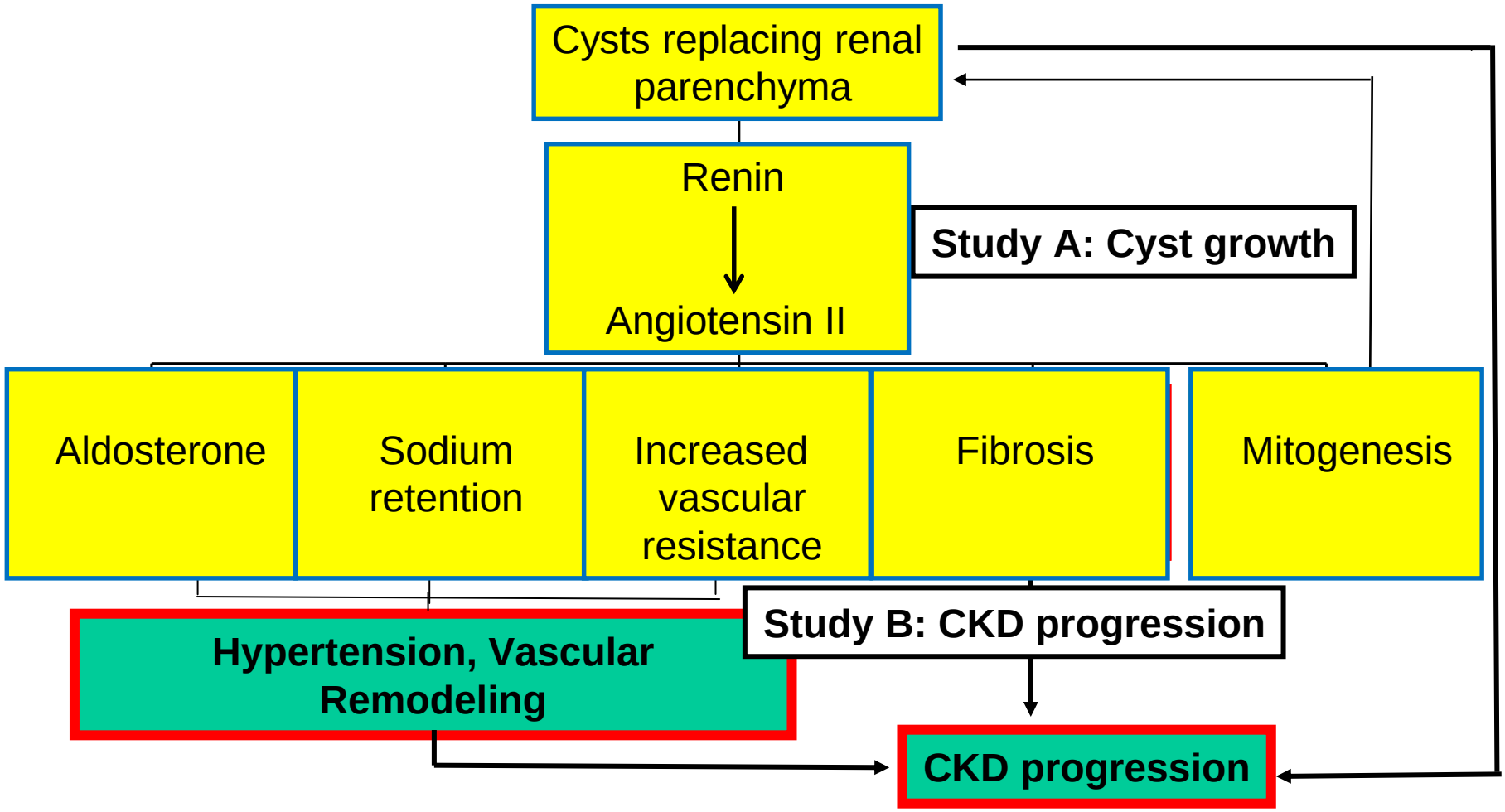
ClinicalTrials.gov: NCT01157858

Chrispijn and Drenth Trials 2011, 12:246

Interventional studies

ACEI - ARB

RATIONALE for HALT-PKD:



HALT-PKD Goals

Determine the effects on progression of:

1) ACEI + ARB > ACEI alone (Studies A and B)

2) Low > standard BP target (Study A)

A: n=558 B: n=486

Primary outcome
Change in Renal Volume by MRI
Doubling Serum Creatinine/ ESRD/Death
Secondary Outcomes
Changes in GFR, RBF, LV mass, albuminuria Hospitalizations, QOL

Kidney International (2012) 81, 577-585; doi: 10.1038/ki.2011.411;

Conclusions

- Promising results of interventional studies
- Still to be answered:
  - When should we intervene?
  - Potential side effects of life-long treatment
    - Mutagenic, cancerogenic immunosuppressive
- Known complications
  - Hypertension, LVH, nephrolithiasis, bleeding, UTI, cerebral aneurisms
  - should be monitored closely