Cystic kidney disease

The clinician's perspective

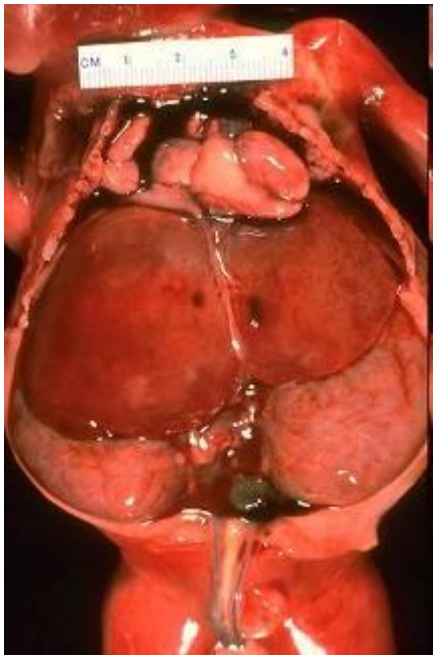
George Reusz

First Department of Pediatrics

Semmelweis University

Polycystic kidney diseases

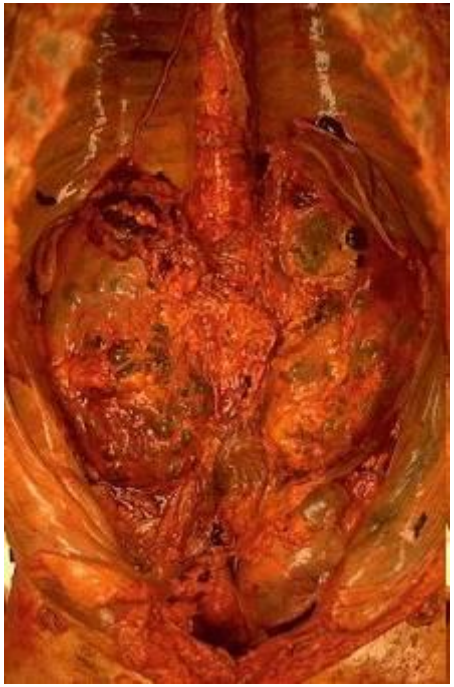
ARPKD



PKHD1

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

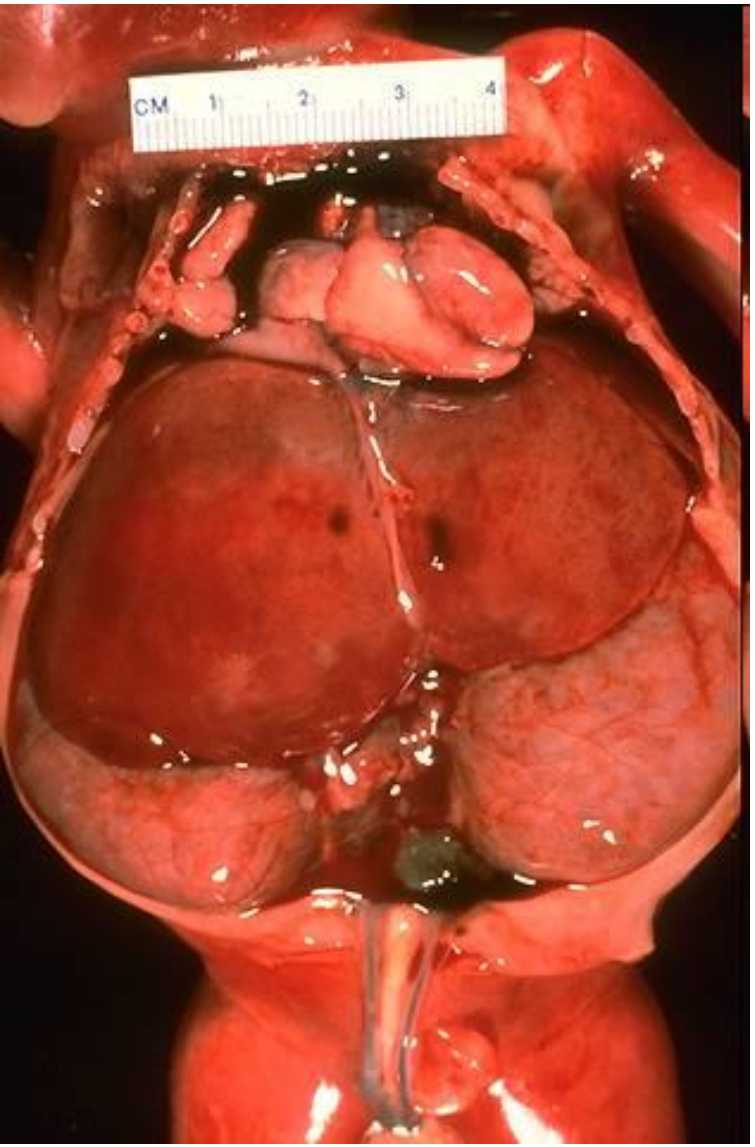
ADPKD



PKD1>PKD2

Incidence 1:500-1.000 (5% sporadic)
Fourth cause of ESRD
ESRD at 54 (PKD1)-74 (PKD2) yrs
Collecting duct, distal nephron
Liver and pancreatic cists

ARPKD

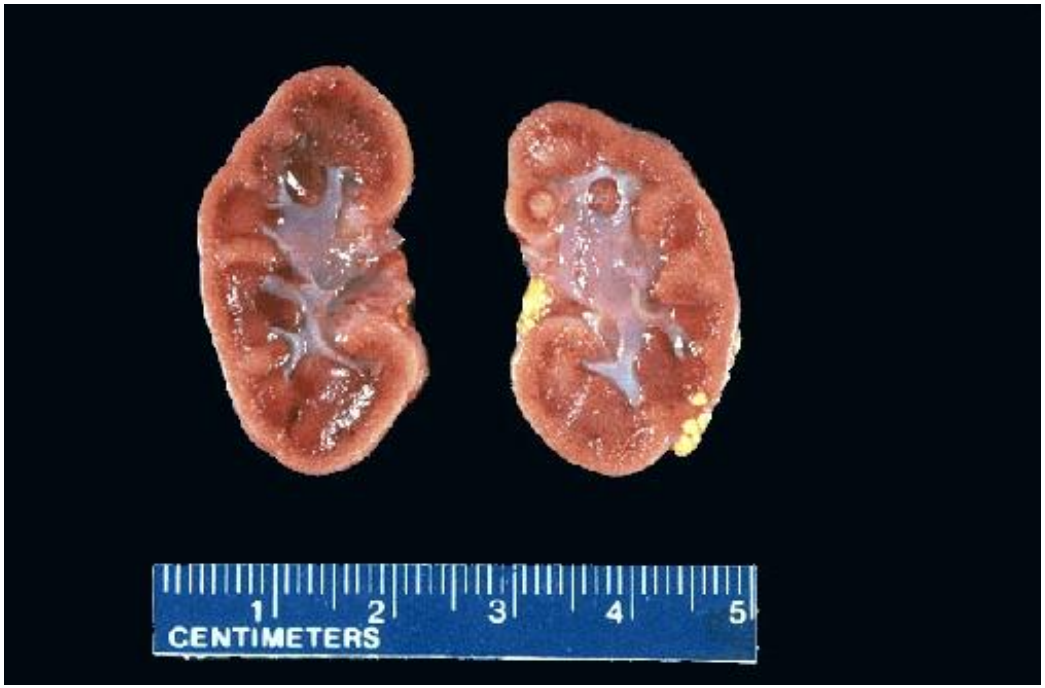


The enlarged kidneys are filling
the abdominal cavity.

The child was delivered at the 23 gestational week
and died soon after ue to respiratory failure

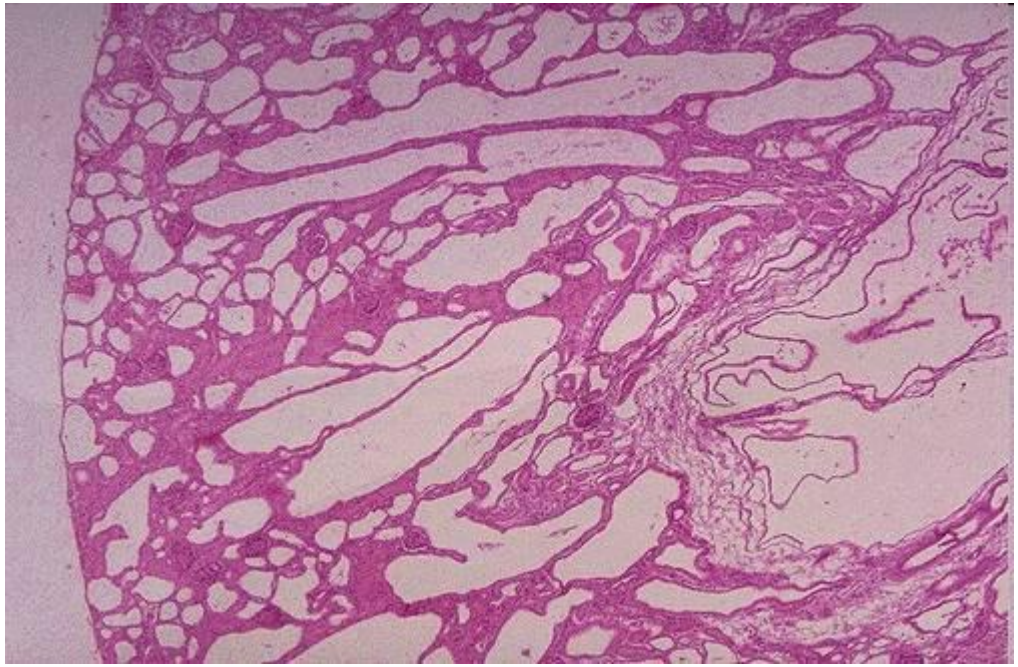
ARPKD

Cross section of a normal kidney



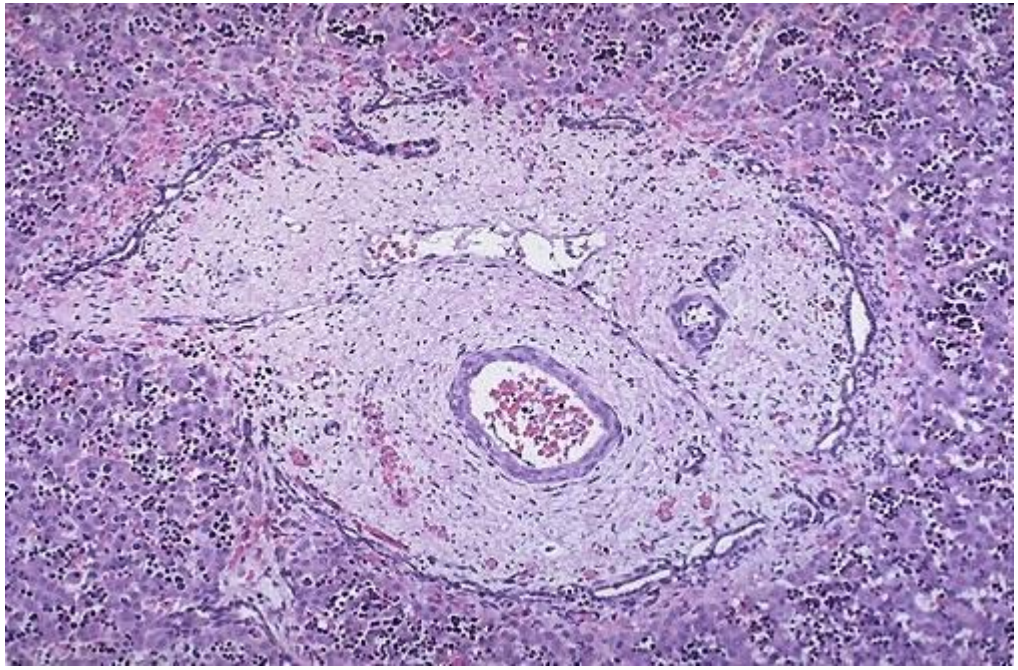
Cross section of a kidney with ARPKD

The kidney is enlarged, the cortico-medullary boundary is blurred



ARPKD

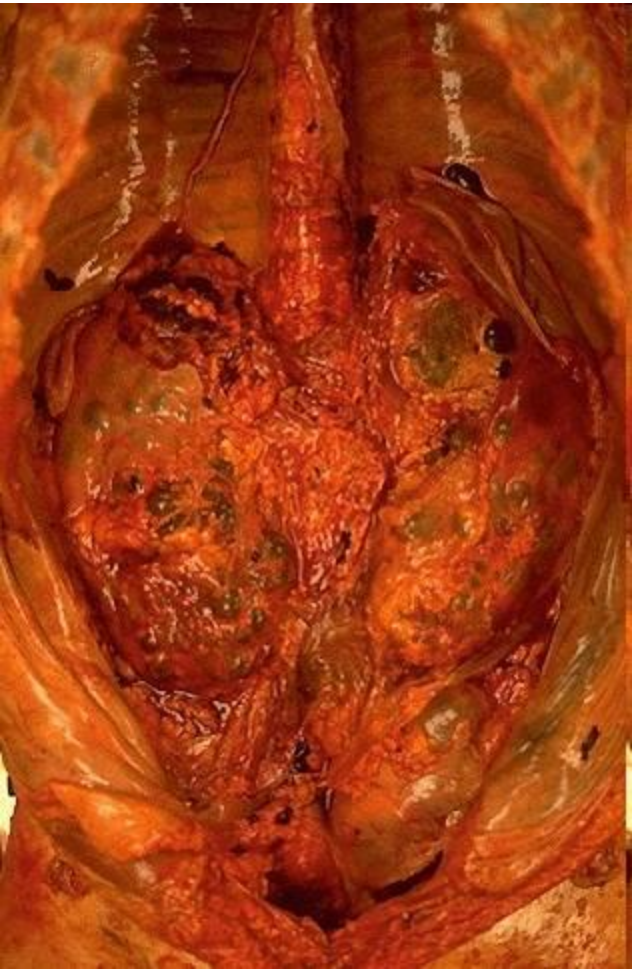
the kidney parenchyma is replaced by cists

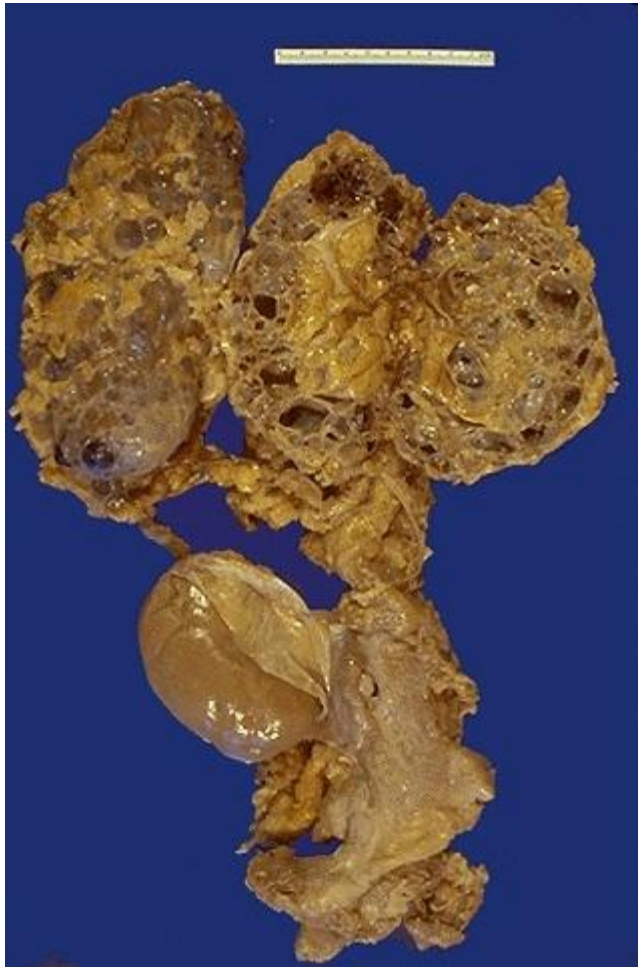


ARPKD: congenital liver fibrosis

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

ADPKD





Enlarged kidneys filling the retroperitoneum and the abdominal cavity

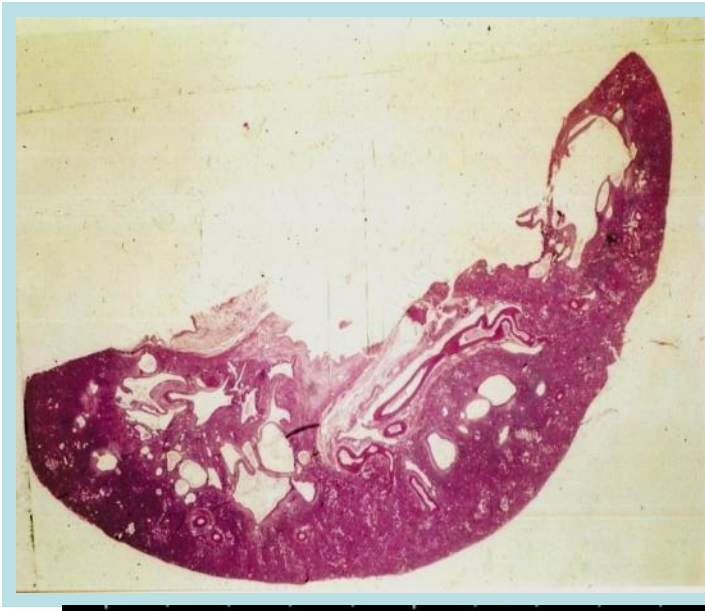
The parenchyma is replaced by cysts

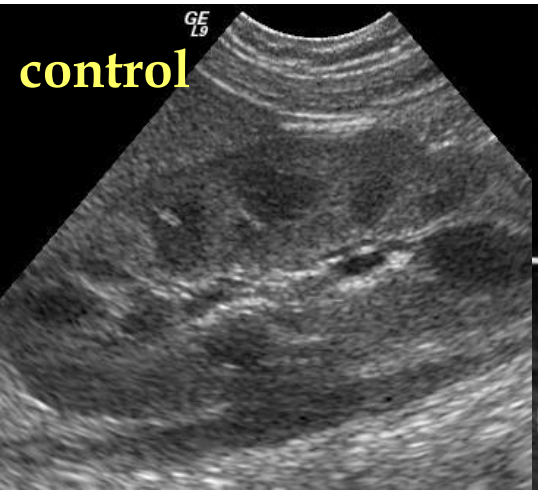
Nephronophthisis – macroscopic morology

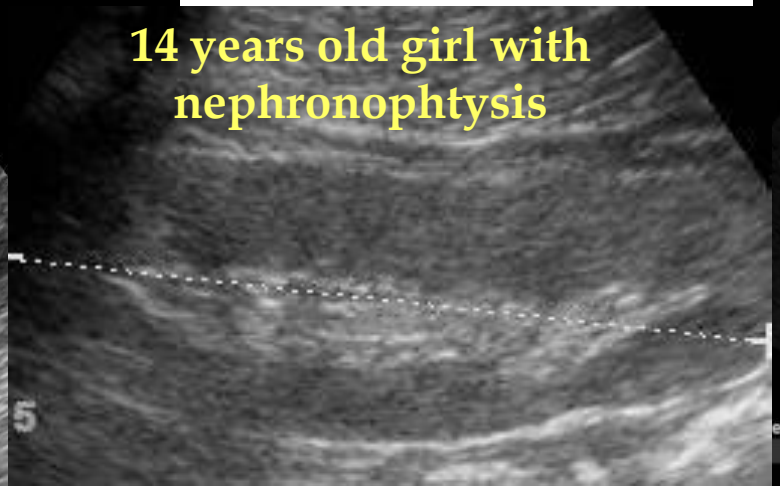
1. Dimension: in juvenile NPH the kindey is usually small, in the infantile type it may be enlarged (+2-3 SD)

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

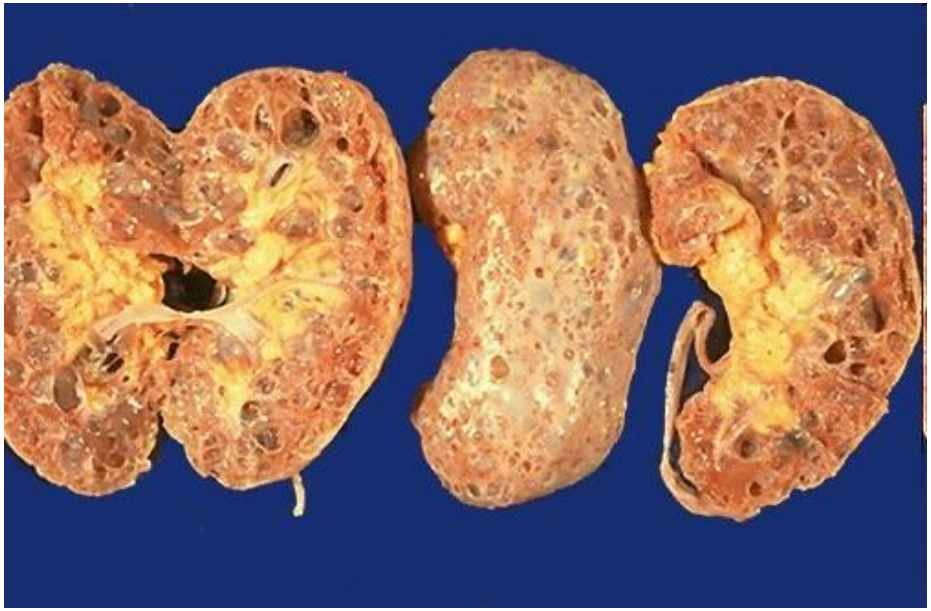
3. **Hyperechogenic**, the cortico-medullary boundary is blurred



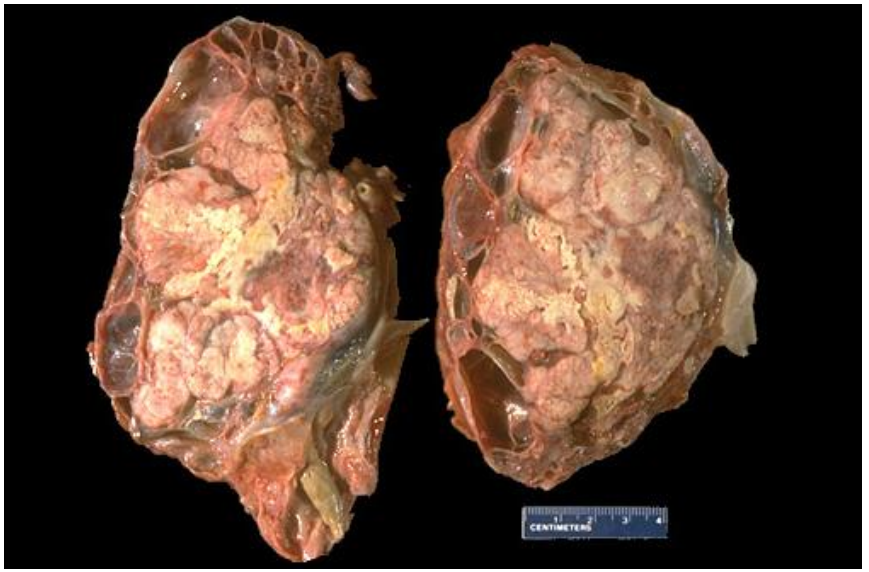




Degenerative cysts in ESRD



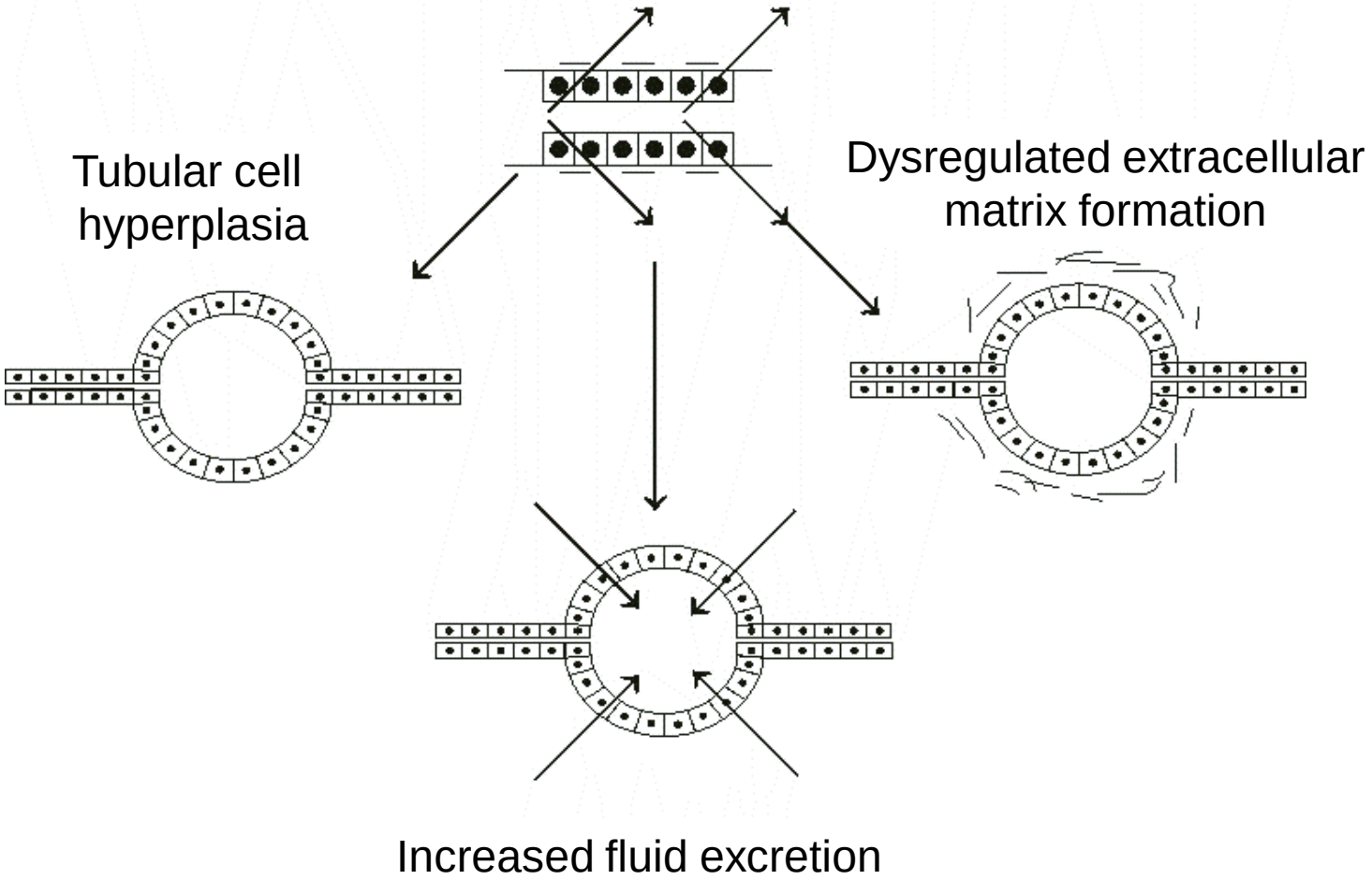
In ESRD cysts are developing in the fibrotic kidneys



Renal carcinoma in ESRD

Hereditary cystic diseases

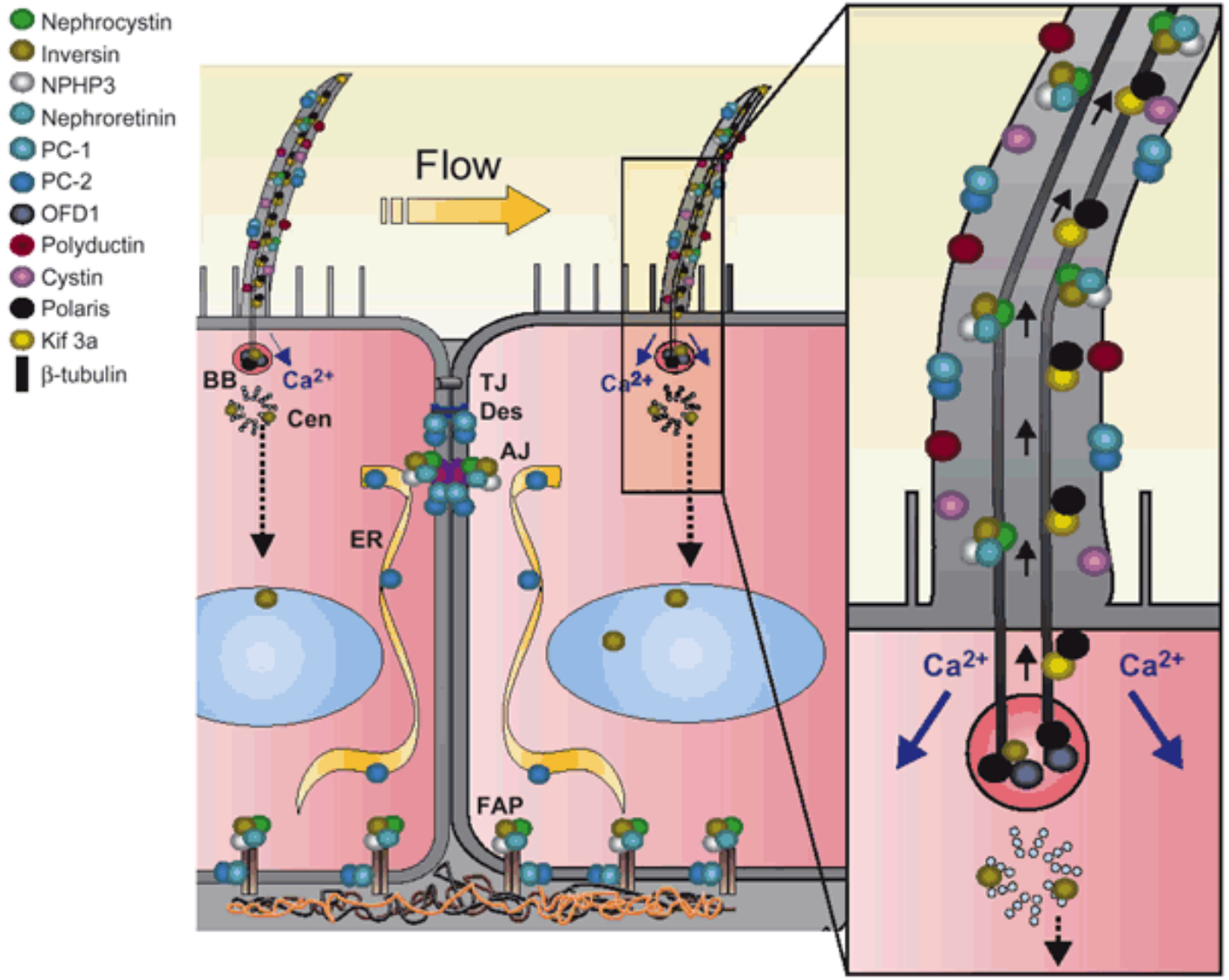
Common pathomechanisms?



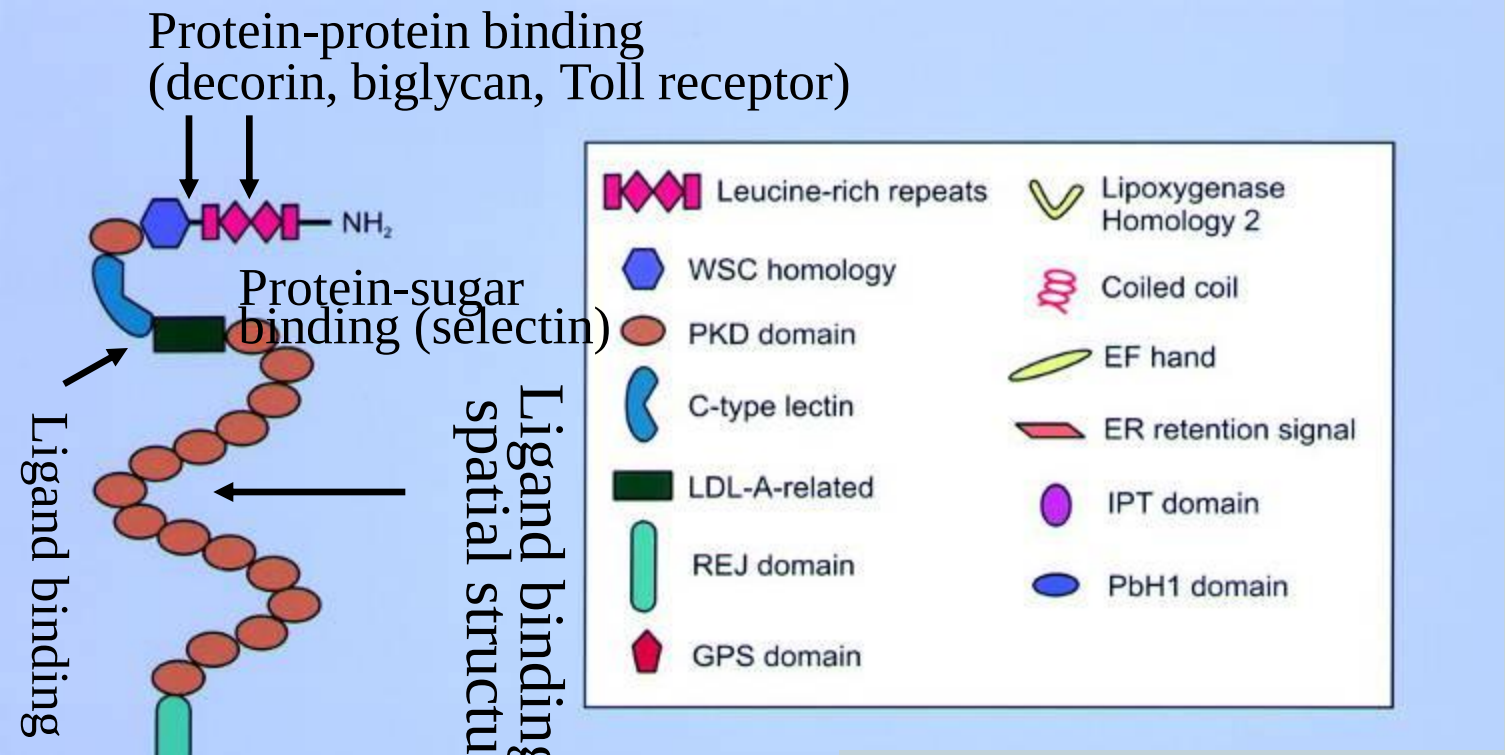
The Cilia Saga

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



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
COOH
Tyrosin (SH 1-4)
PKA-C target
G protein act.
Coiled coil region
Polycystin-1

Polycystin-1

- function:
  - Mechanosensor/chemosensor
    - Function conserved for 1.5 billion years
      - PKD1 and PKD2 present in the sensorneural ciliae of Caenorhabditis elegans
  - Acrosomal reaction - Ca influx
  - Modulation of G protein signal transduction
  - Regulation of cell proliferration

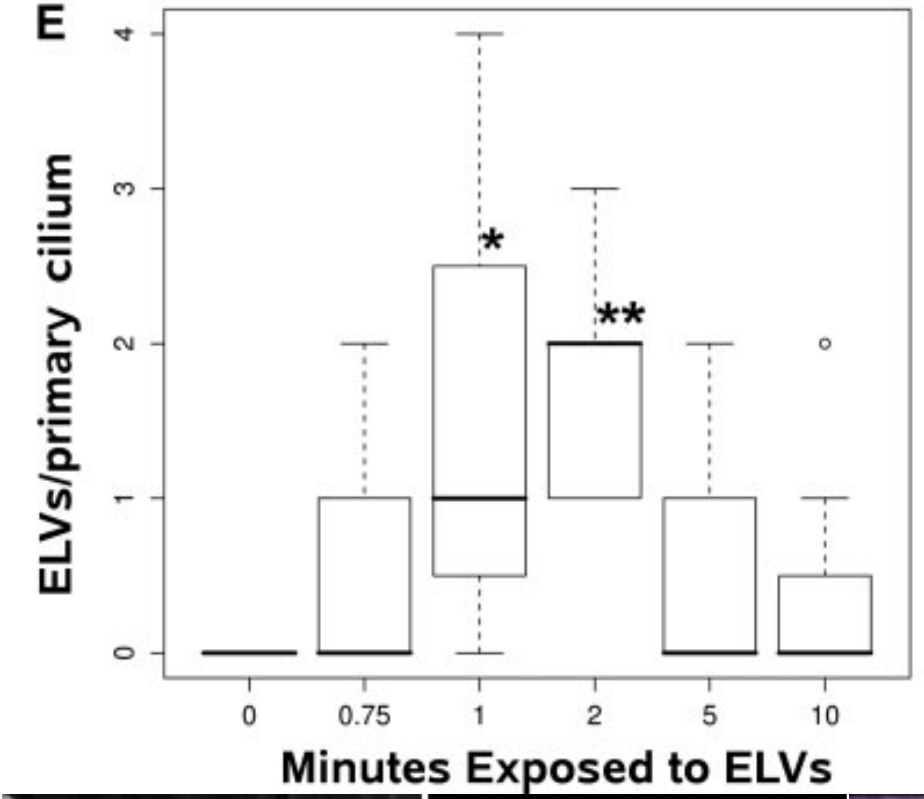
Polycystin-2

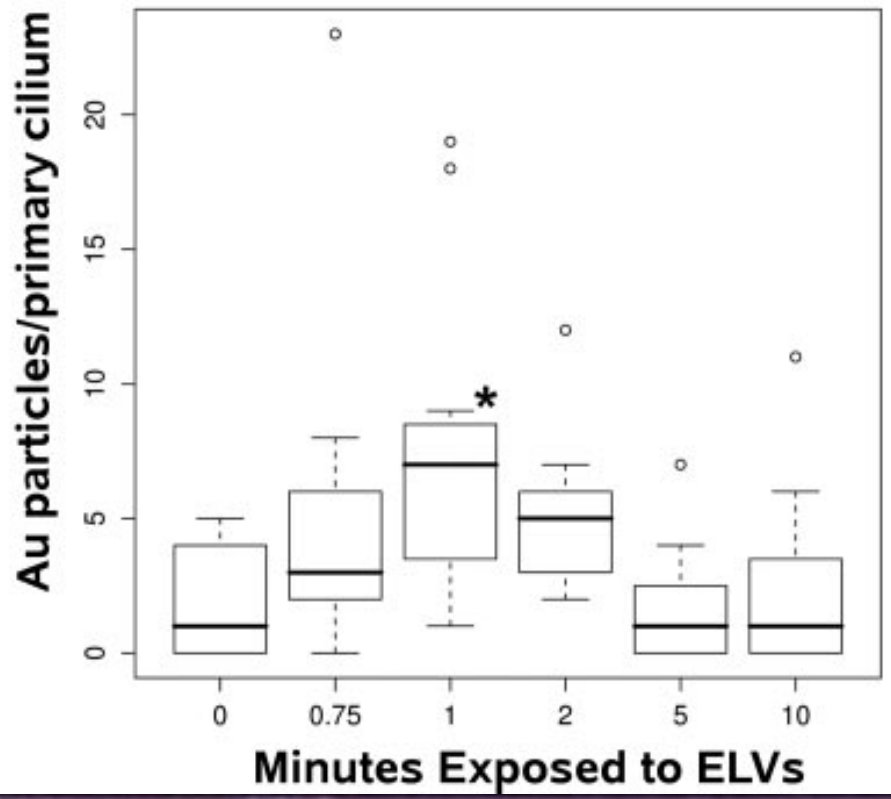
- 50% homology with polycystin-1
- Voltage activated Ca channel
- Couples with polycystin 1 via the COOH-terminal region
- Localizes to the ER and the cell surface

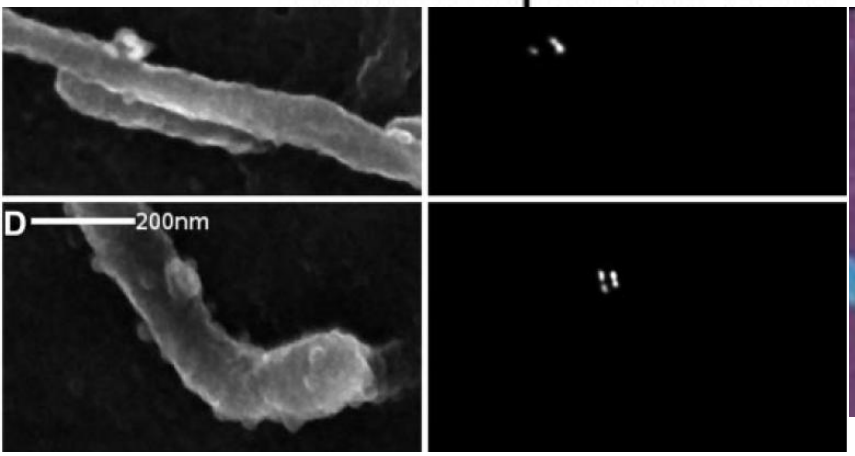
ARPKD

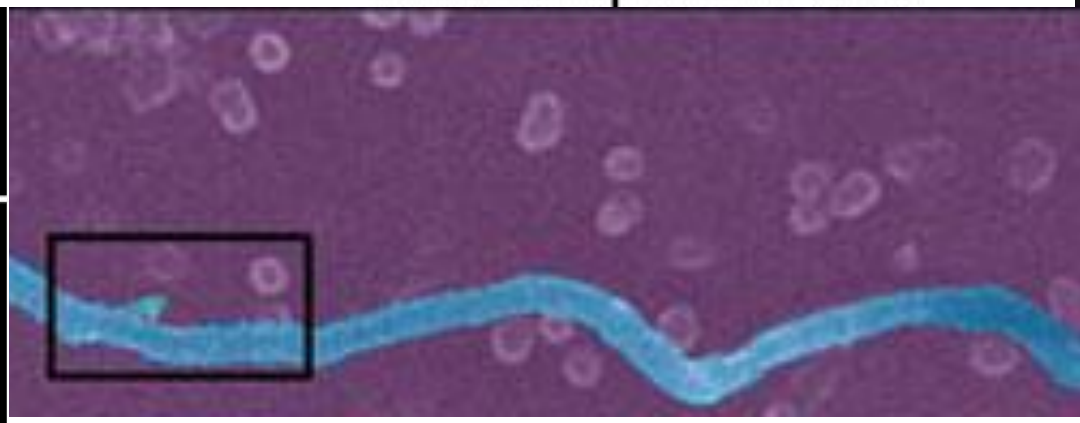
- 6p21.1-p12 region
- 86 exons
- Gene product: Polyductin/Fibrocystin
- Cell surface receptor and/or secreted protein
  - The intracellular fibrocystin is transported out of the cell
  - fibrocystin-containing exosome like vesicles (ELV) rapidly associate with primary cilia
  - ELVs may be the means by which cells communicate with each other.
- A novel function ascribed to fibrocystin is maintenance of planar cell polarity (PCP) in the kidney

- Mouse model: absence of left/right assymetry









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

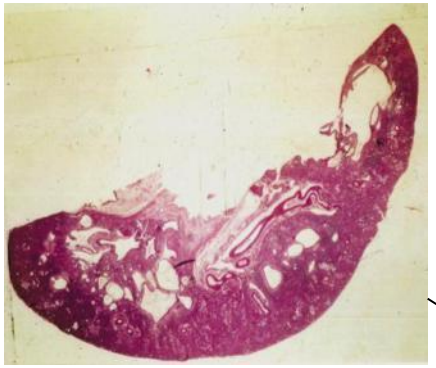
- diversity

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

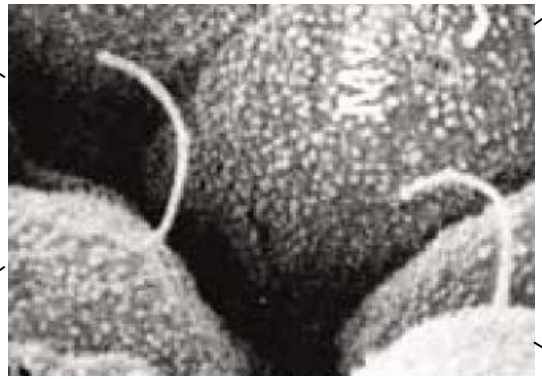
- … and ciliae

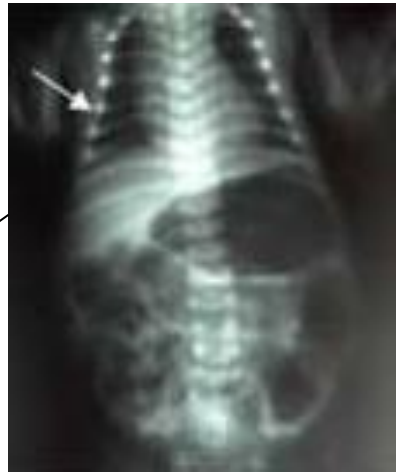
Ciliary proteins – the nephrocystins

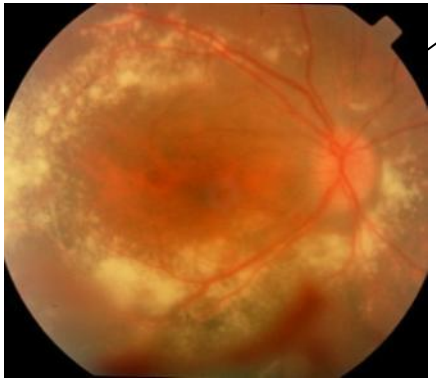


Nephrocystin 1-10

IFT-80



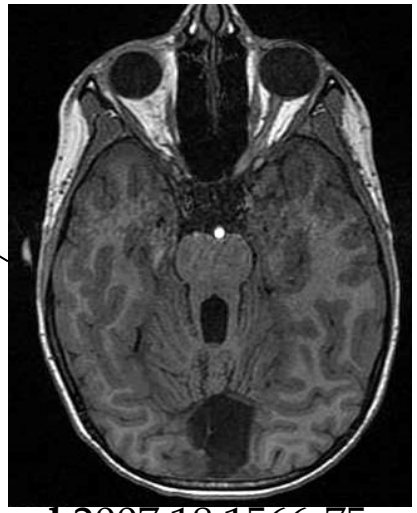




Nephrocystin 1,3,4,5,6,

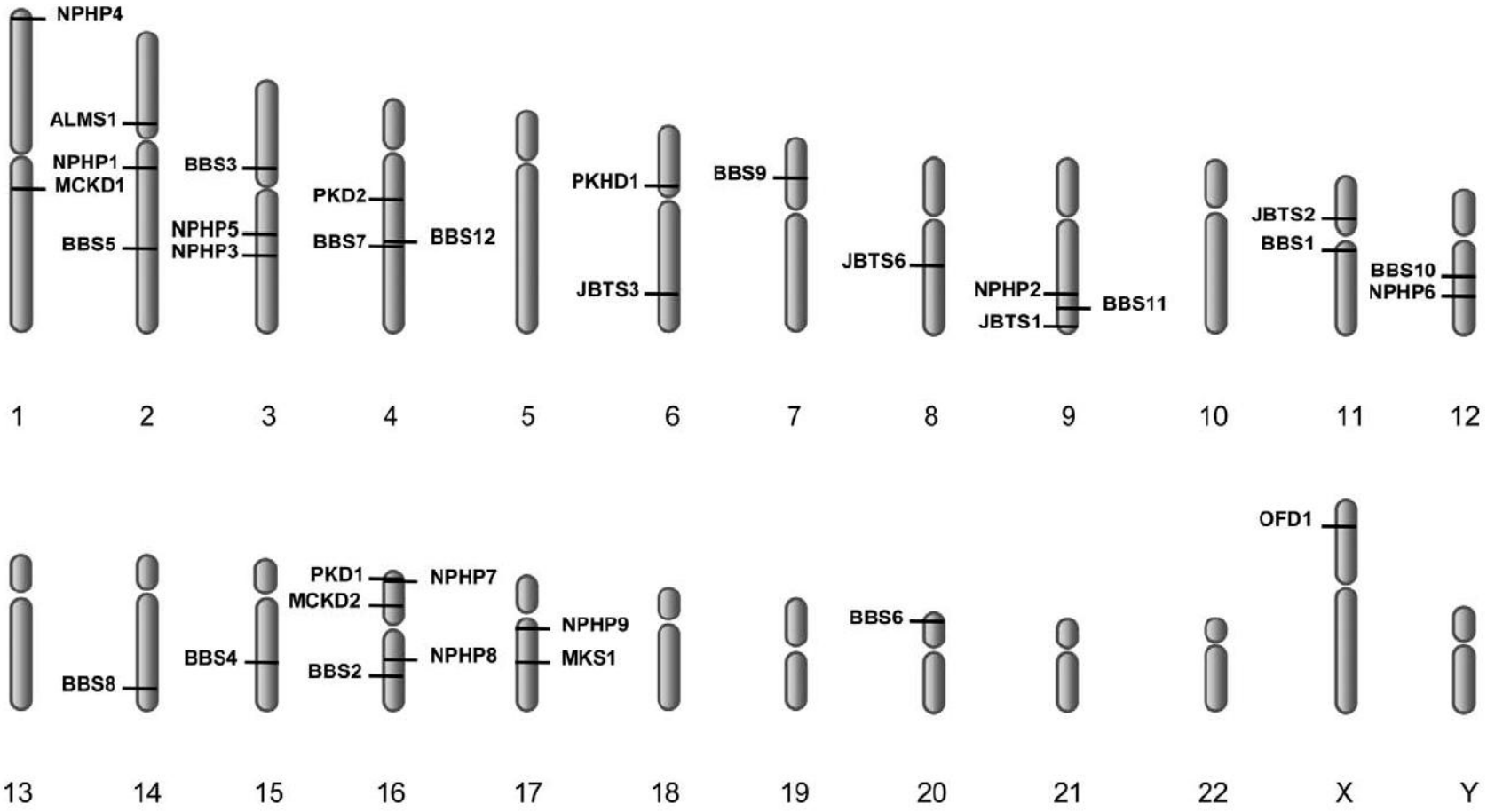
RPGR, RPGRIP1

Nephrocystin 1,6,8, meckelin

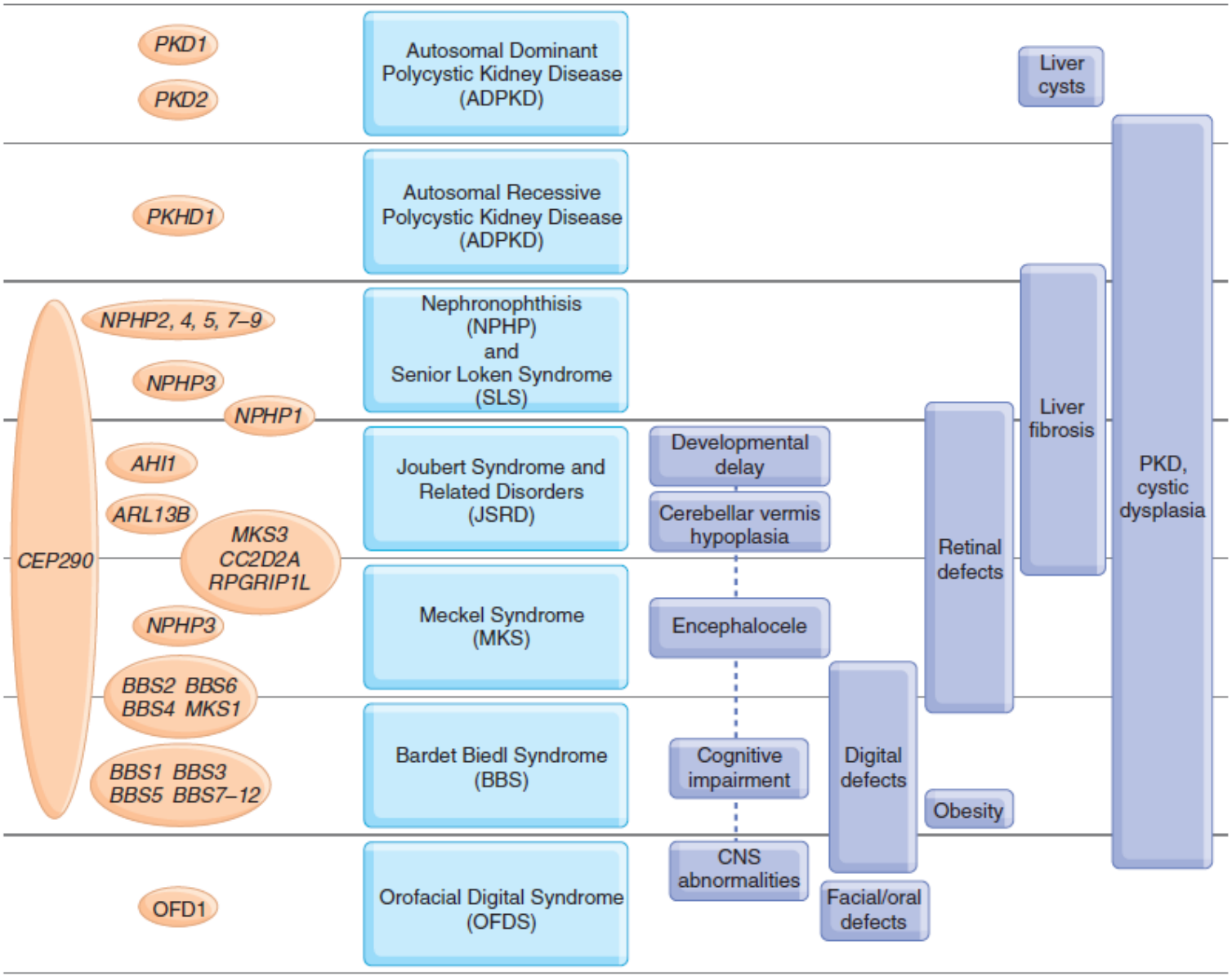


Tory K et al. **J Am Soc Nephrol** 2007;18:1566-75.

Cystic Diseases of the Kidney
Molecular Biology and Genetics

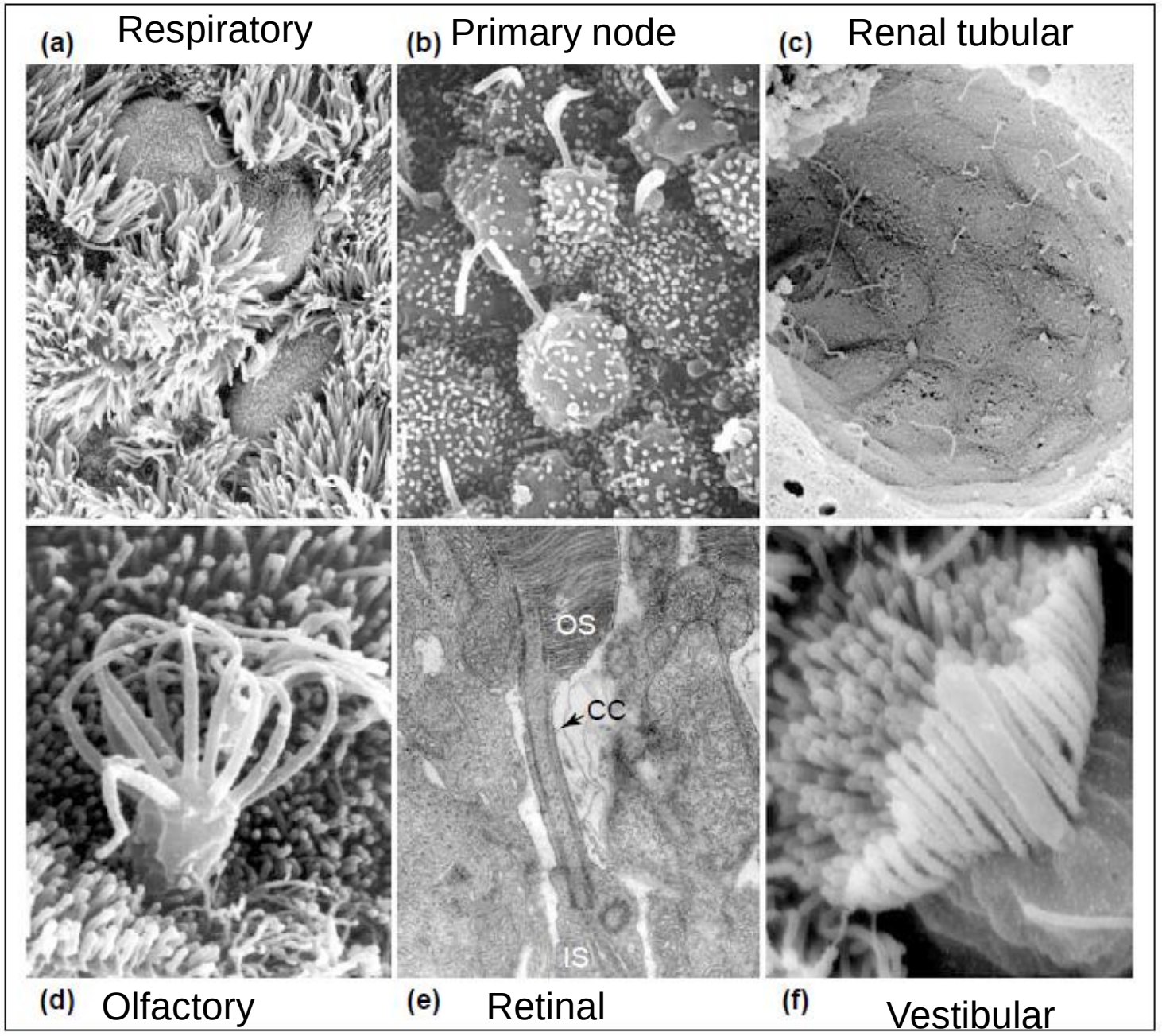


Constantinos Deltas, PhD; Gregory Papagregoriou, MRes
***Arch Pathol Lab Med.* 2010;134:569–582)**

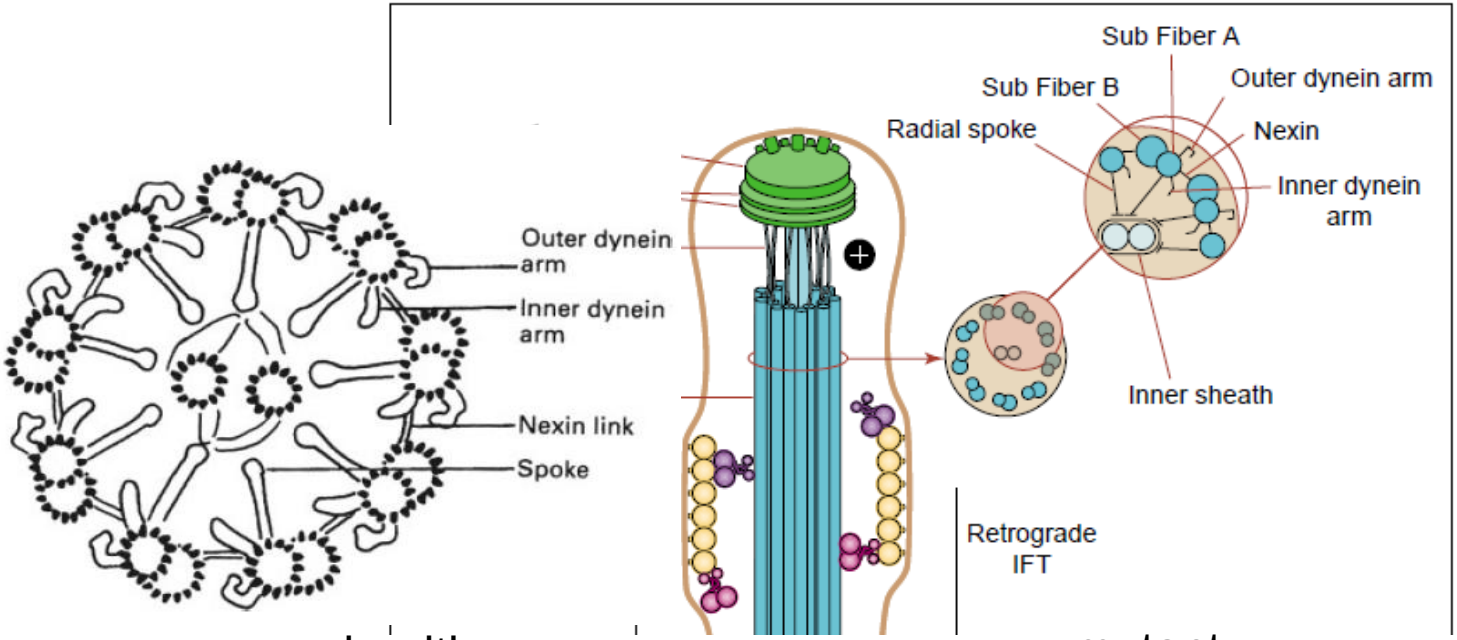

PKD1
PKD2
Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Liver cysts
PKHD1
Autosomal Recessive Polycystic Kidney Disease (ADPKD)
NPHP2, 4, 5, 7–9
NPHP3
NPHP1
Nephronophthisis (NPHP) and Senior Loken Syndrome (SLS)
Liver fibrosis
PKD, cystic dysplasia
AHI1
ARL13B
CEP290
MKS3
CC2D2A
RPGRIP1L
Joubert Syndrome and Related Disorders (JSRD)
Developmental delay
Cerebellar vermis hypoplasia
Retinal defects
NPHP3
Meckel Syndrome (MKS)
Encephalocele
BBS2 BBS6
BBS4 MKS1
Bardet Biedl Syndrome (BBS)
Cognitive impairment
Digital defects
Obesity
BBS1 BBS3
BBS5 BBS7–12
CNS abnormalities
OFD1
Orofacial Digital Syndrome (OFDS)
Facial/oral defects

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

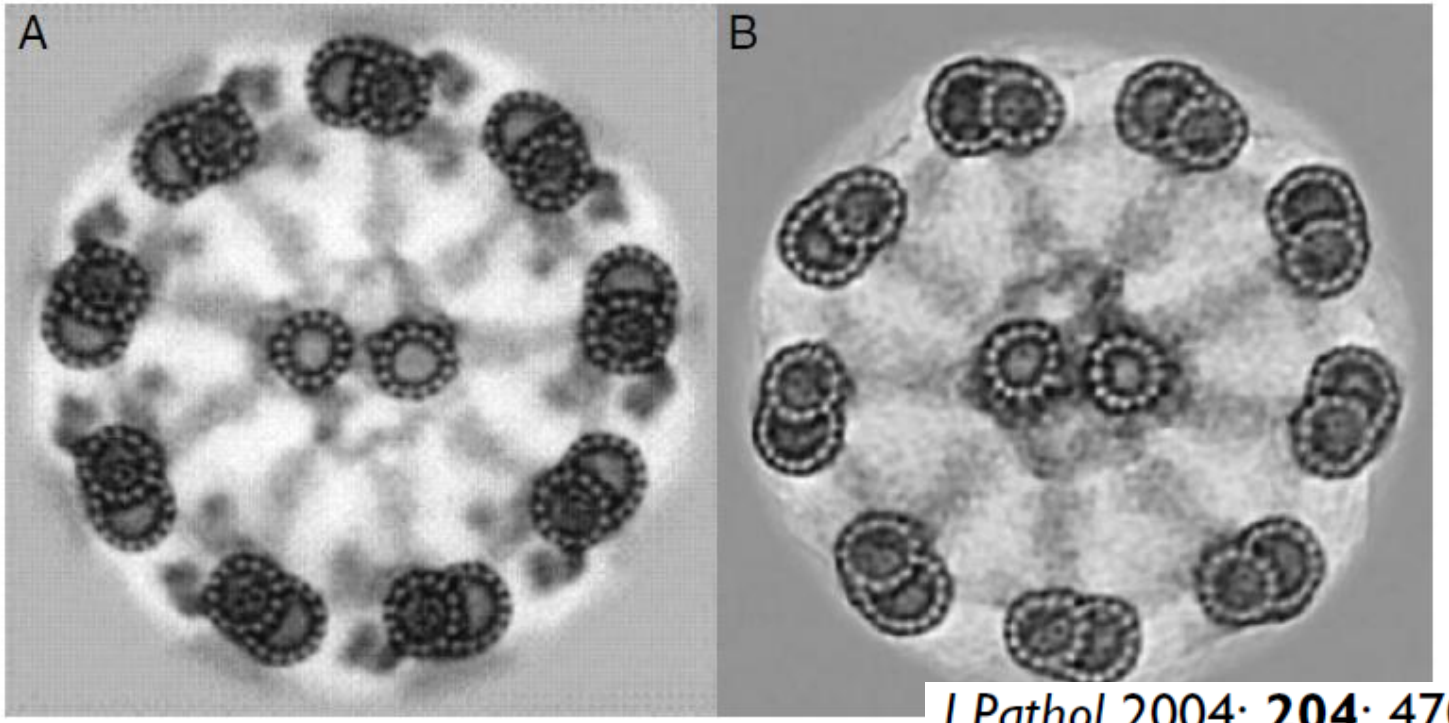


Current Opinion in Genetics & Development 2005, 15:308–314



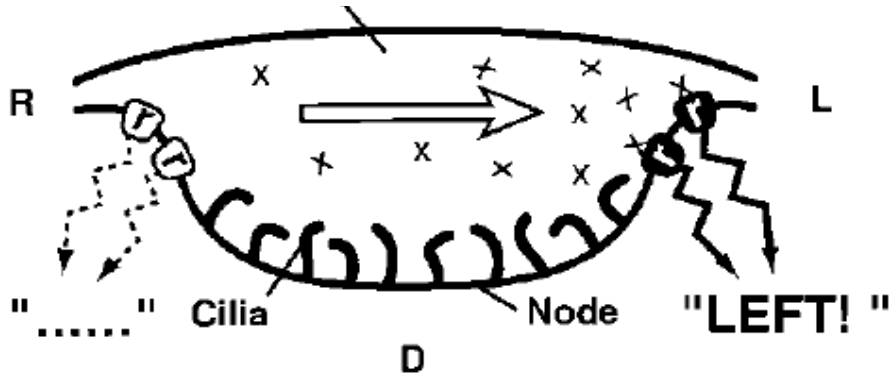
healthy

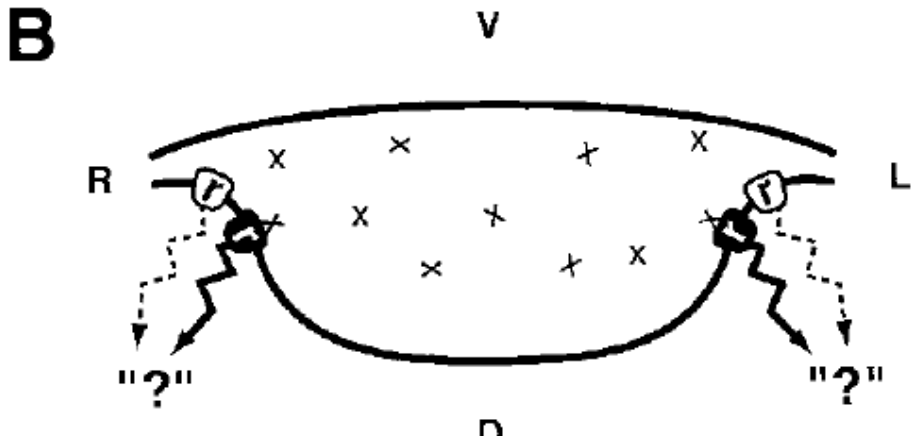
mutant



J Pathol 2004; **204**: 470–477

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

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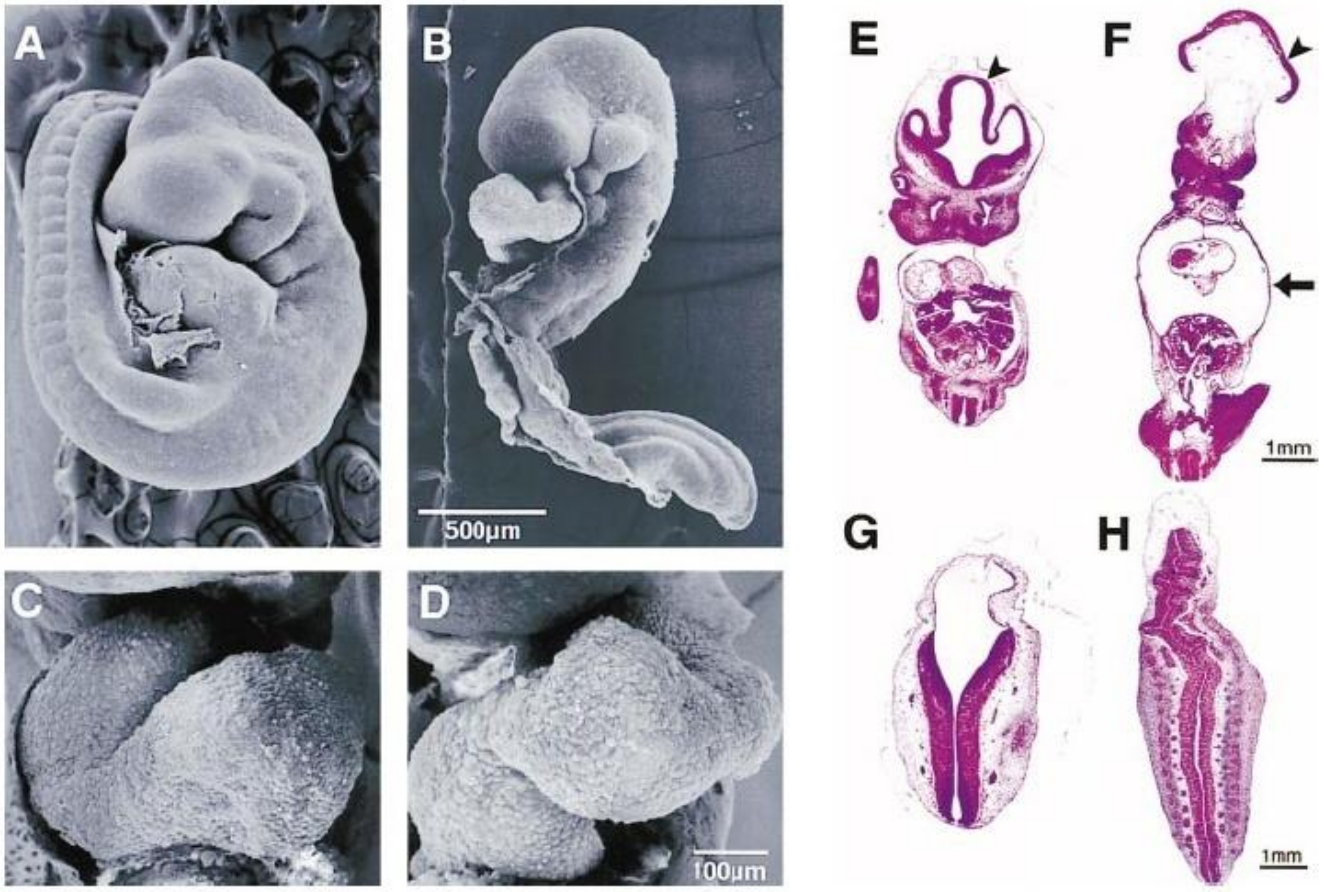
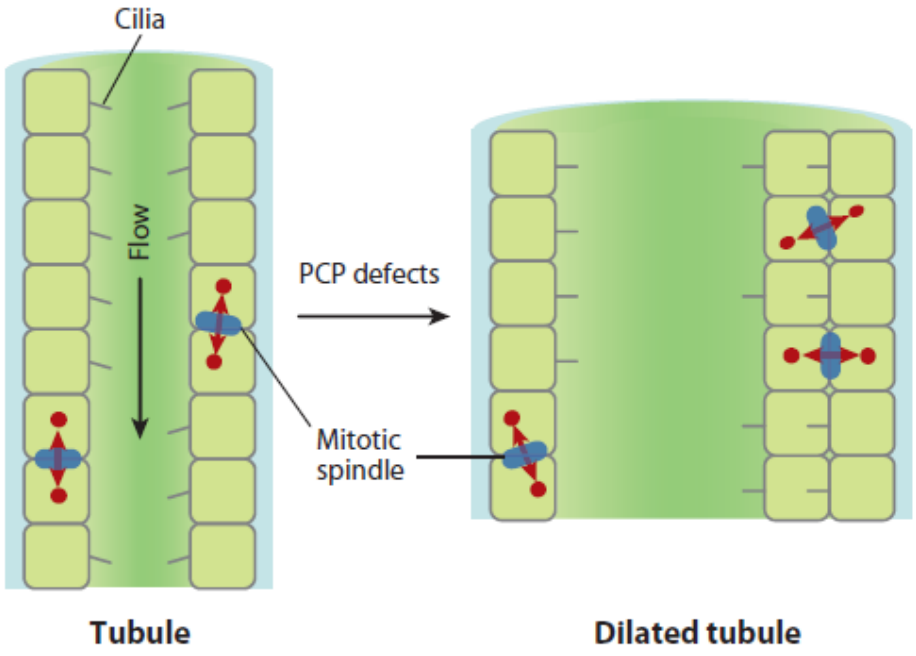


Cell, Vol. 95, 829–837, December 11, 1998, Copyright ©1998 by Cell Press

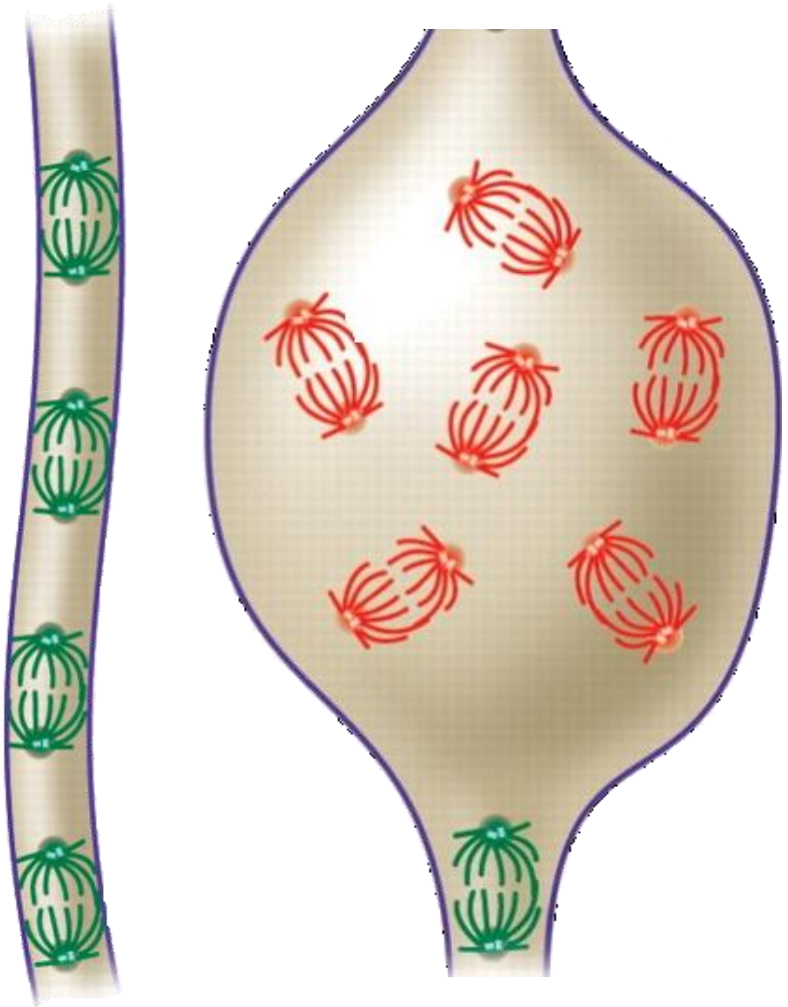
Ciliary disease and the kidney: „loss of orientation”



Annu. Rev. Physiol. 2009. 71:83–113

Loss of Planar Polarity: Cyst Initiation

Normal



PKD

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

CRITICAL THRESHOLD

ARPKD

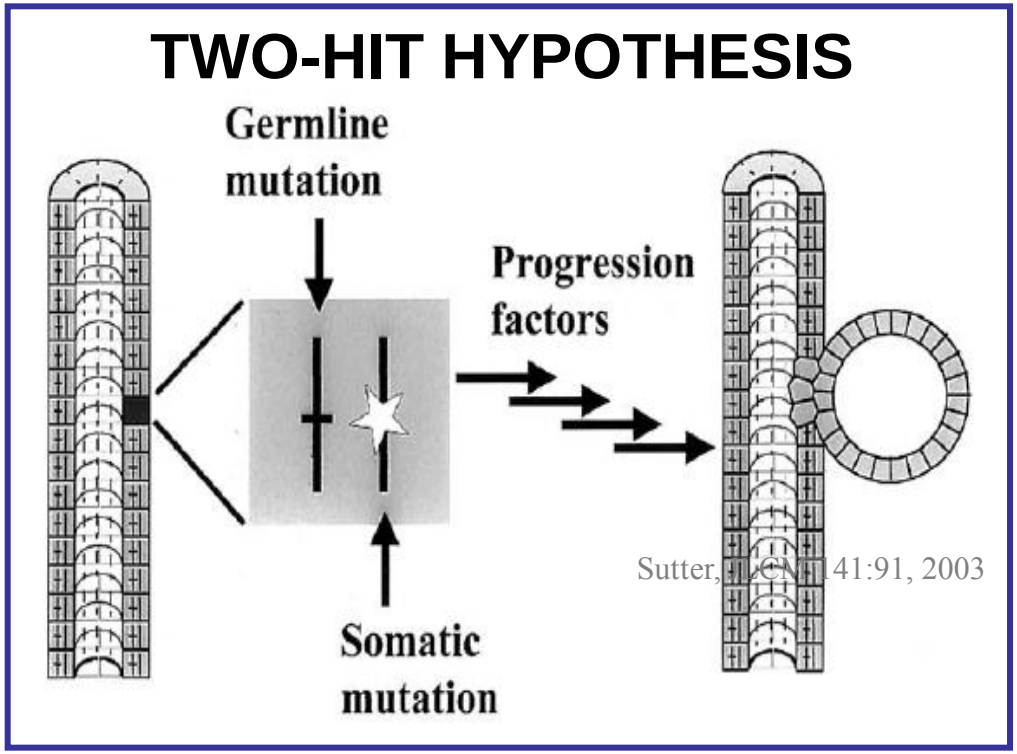
TWO INACTIVATING MUTATIONS

PERINATAL DEATH

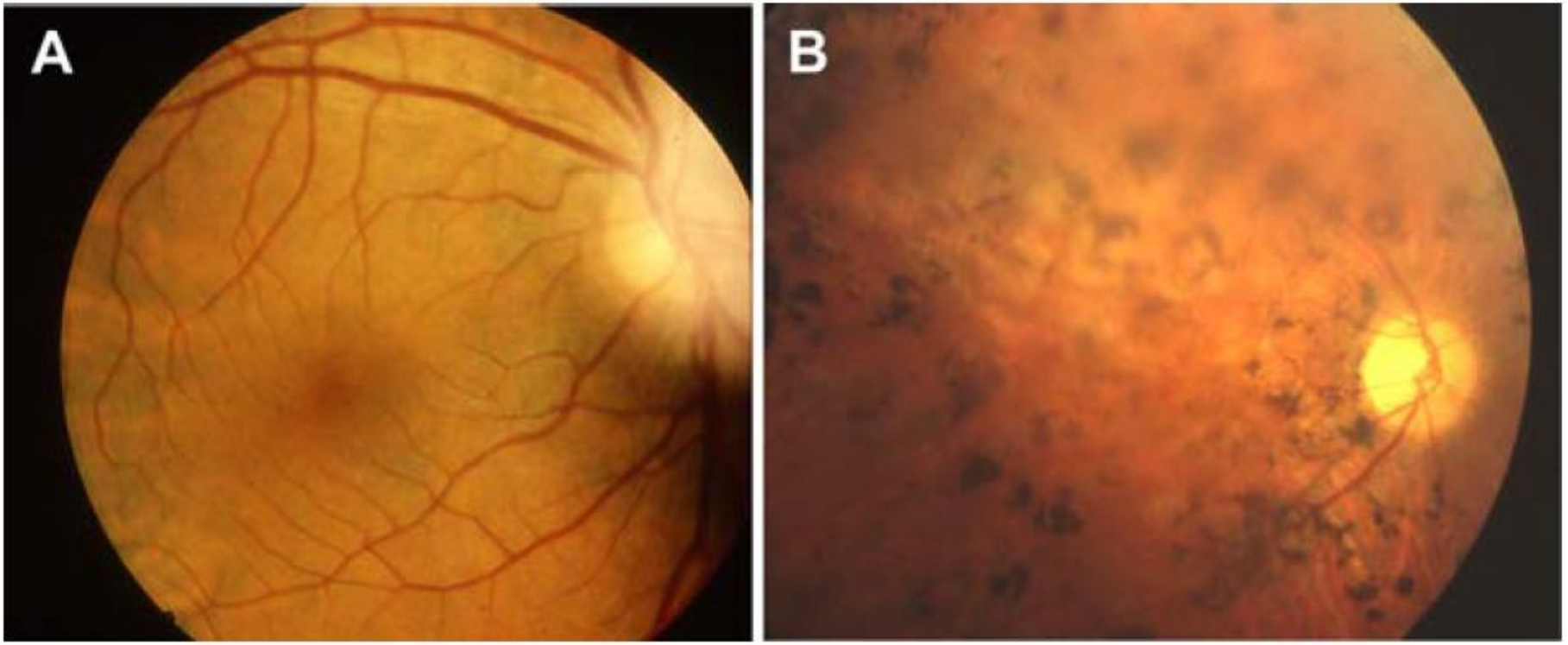
AT LEAST ONE MISSENSE MUTATION

LESS SEVERE PHENOTYPE

ADPKD



Ciliary disease and the retina: transport defect



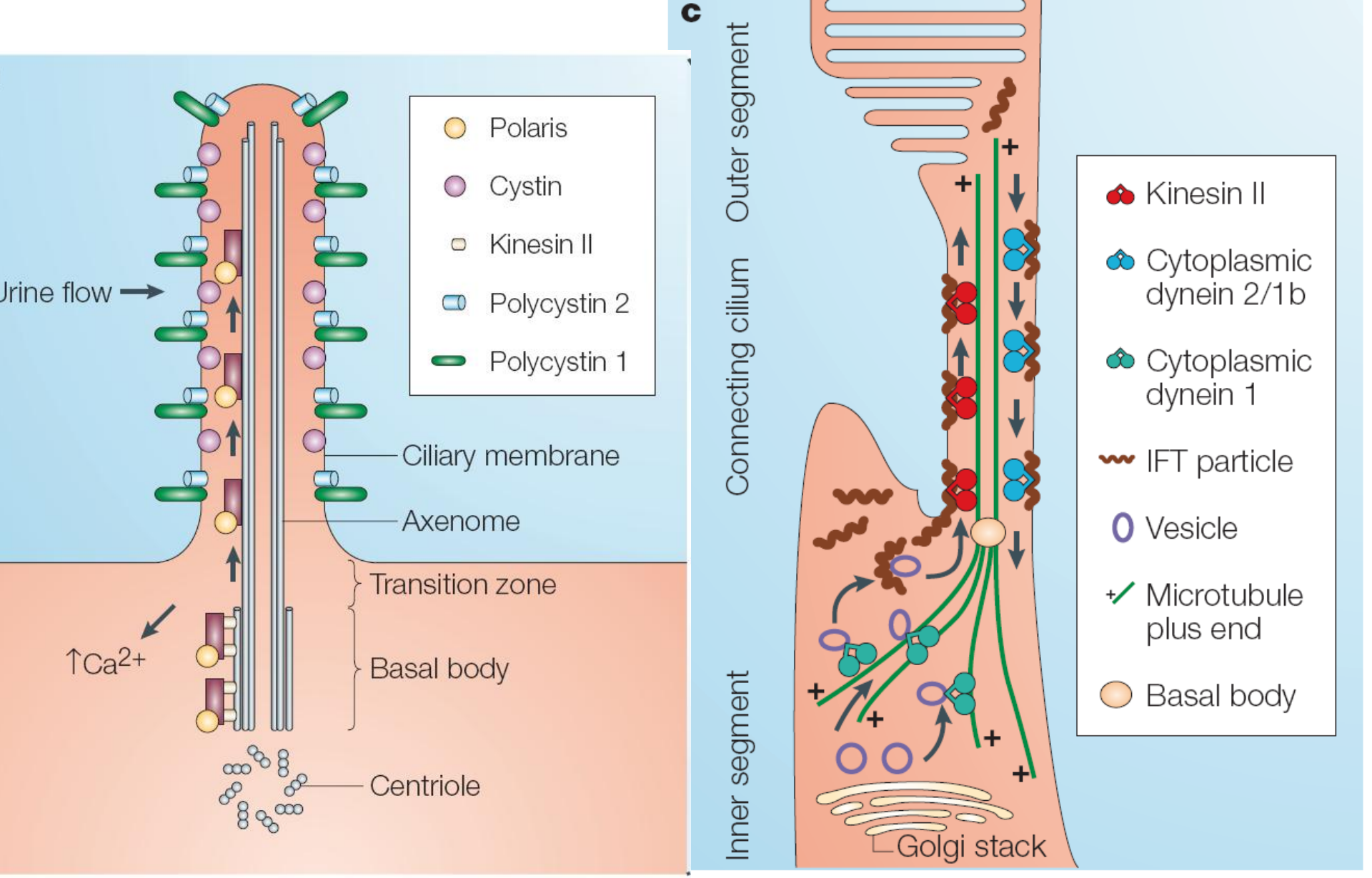
Nephronophthisis

Rémi Salomon · Sophie Saunier · Patrick Niaudet

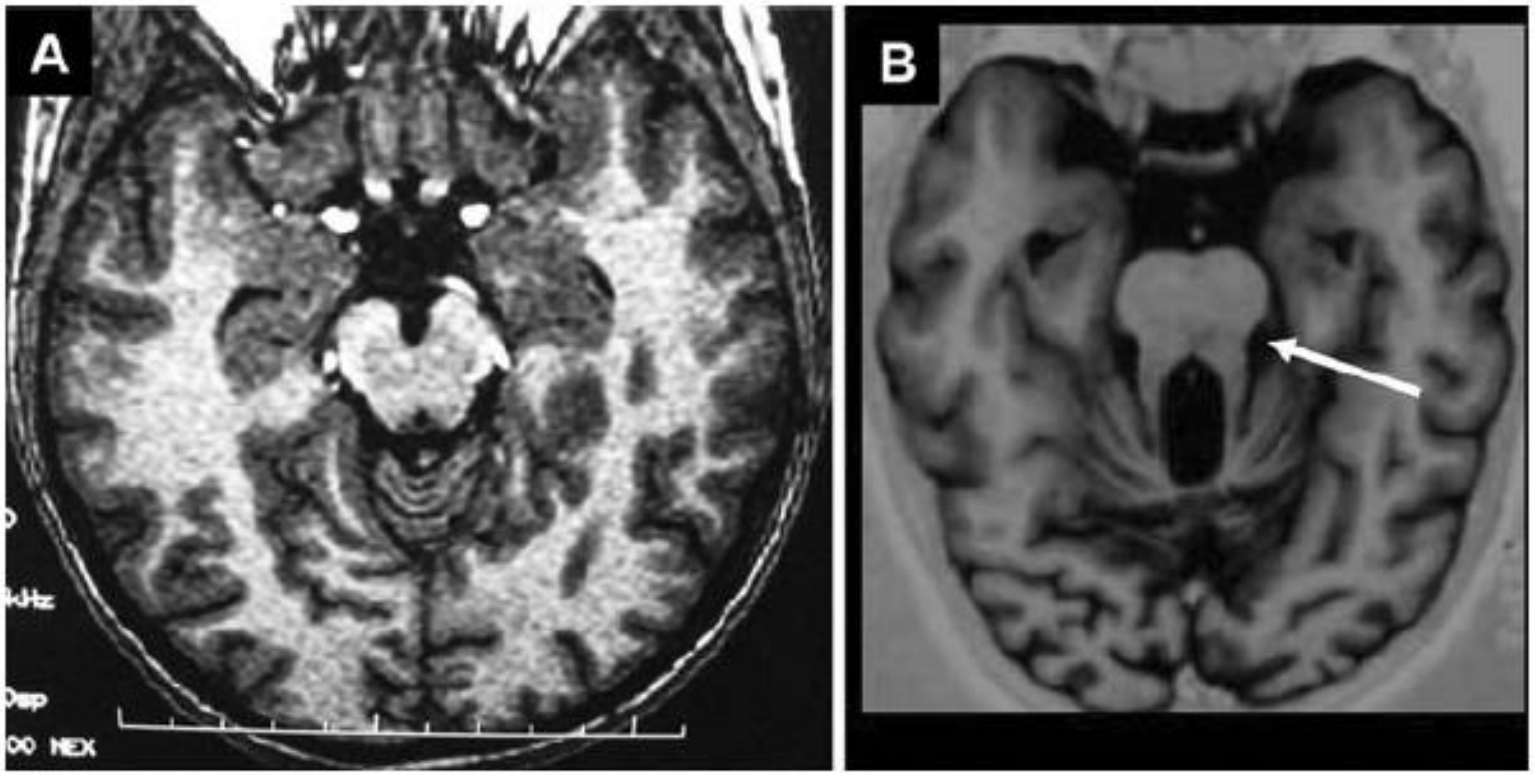
Pediatr Nephrol (2009) 24:2333–2344

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
↑Ca2+
Basal body
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



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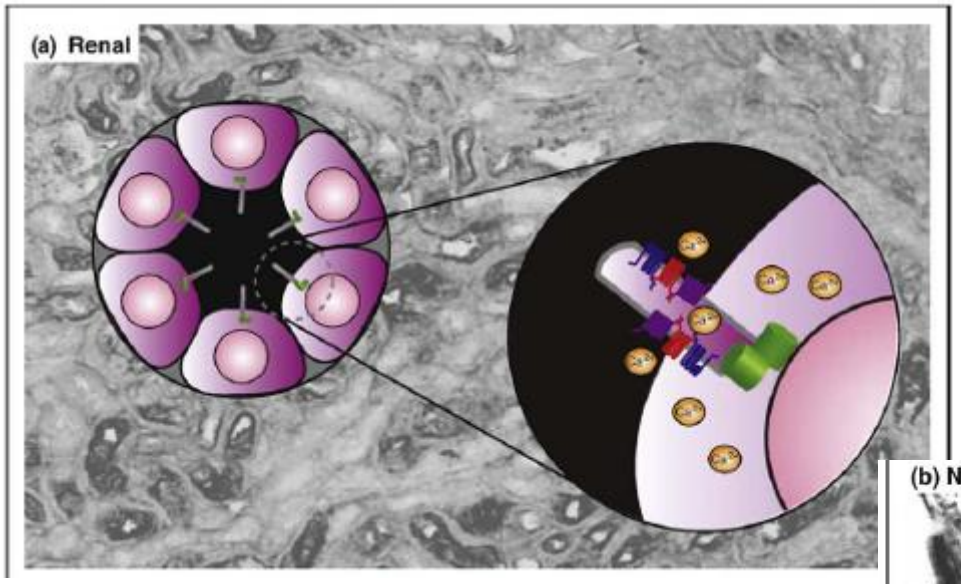
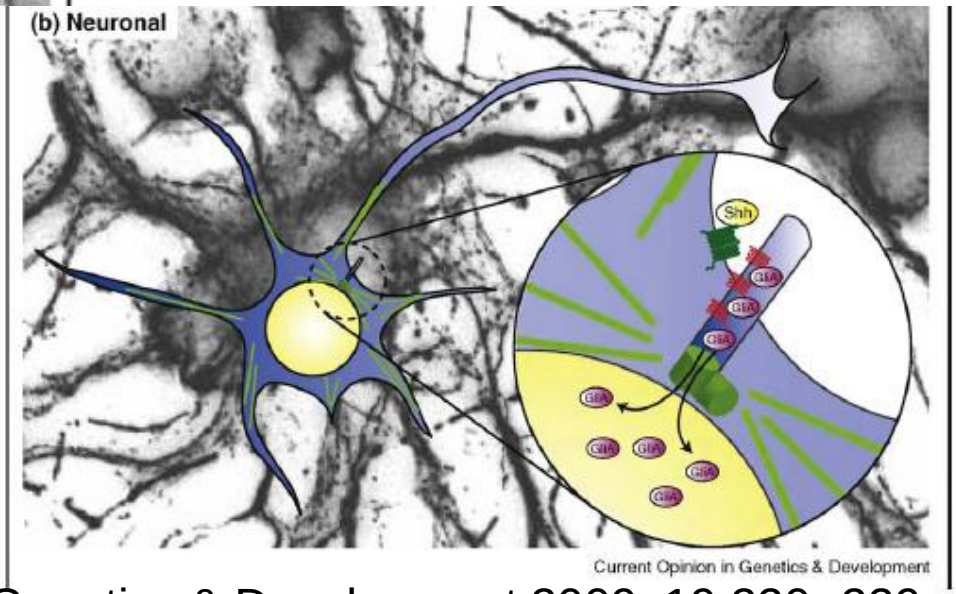
Ciliary disease and the central nervous system: defect of migration & orientation

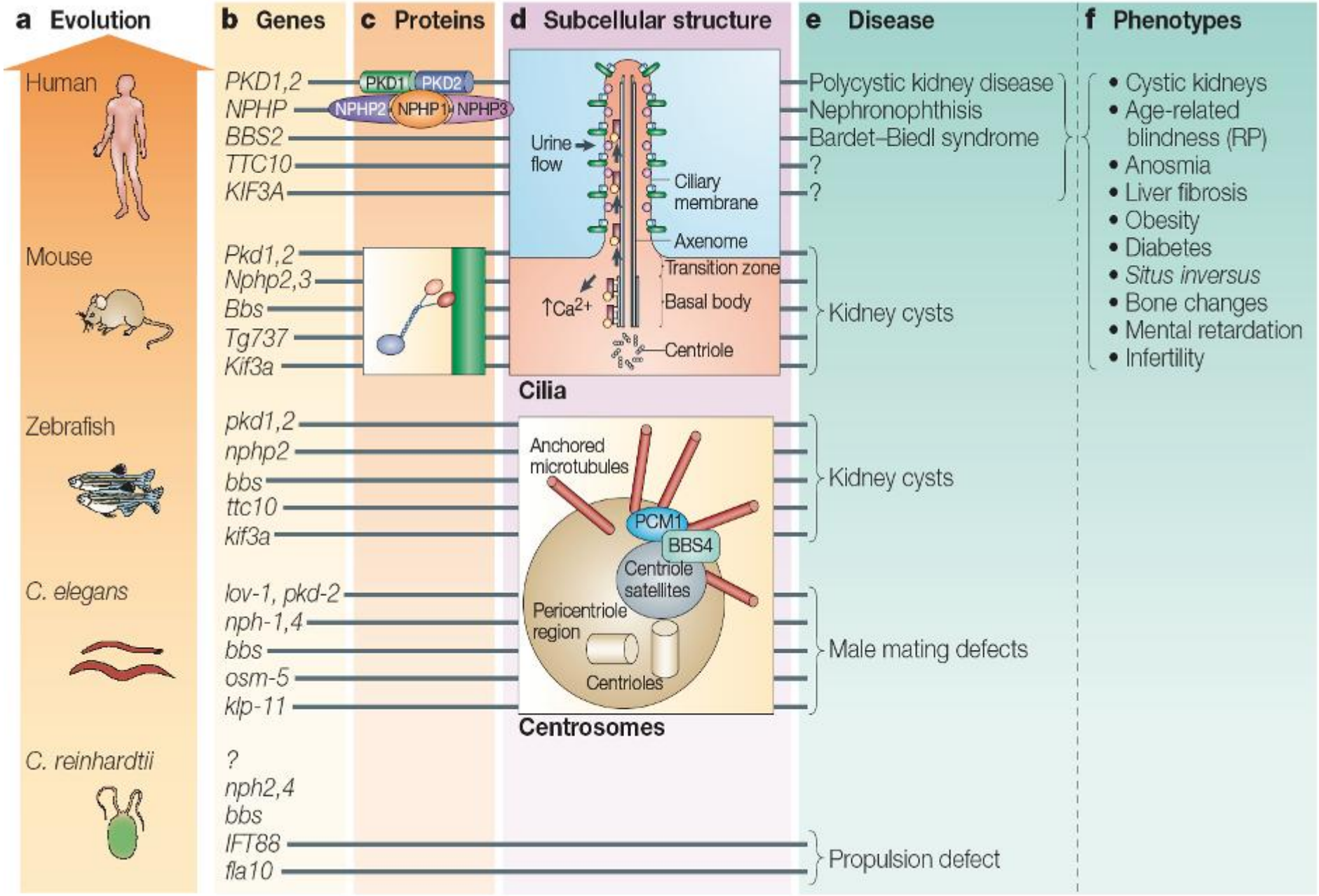


Tubular cell

Hyppocampic neurons in cell culture



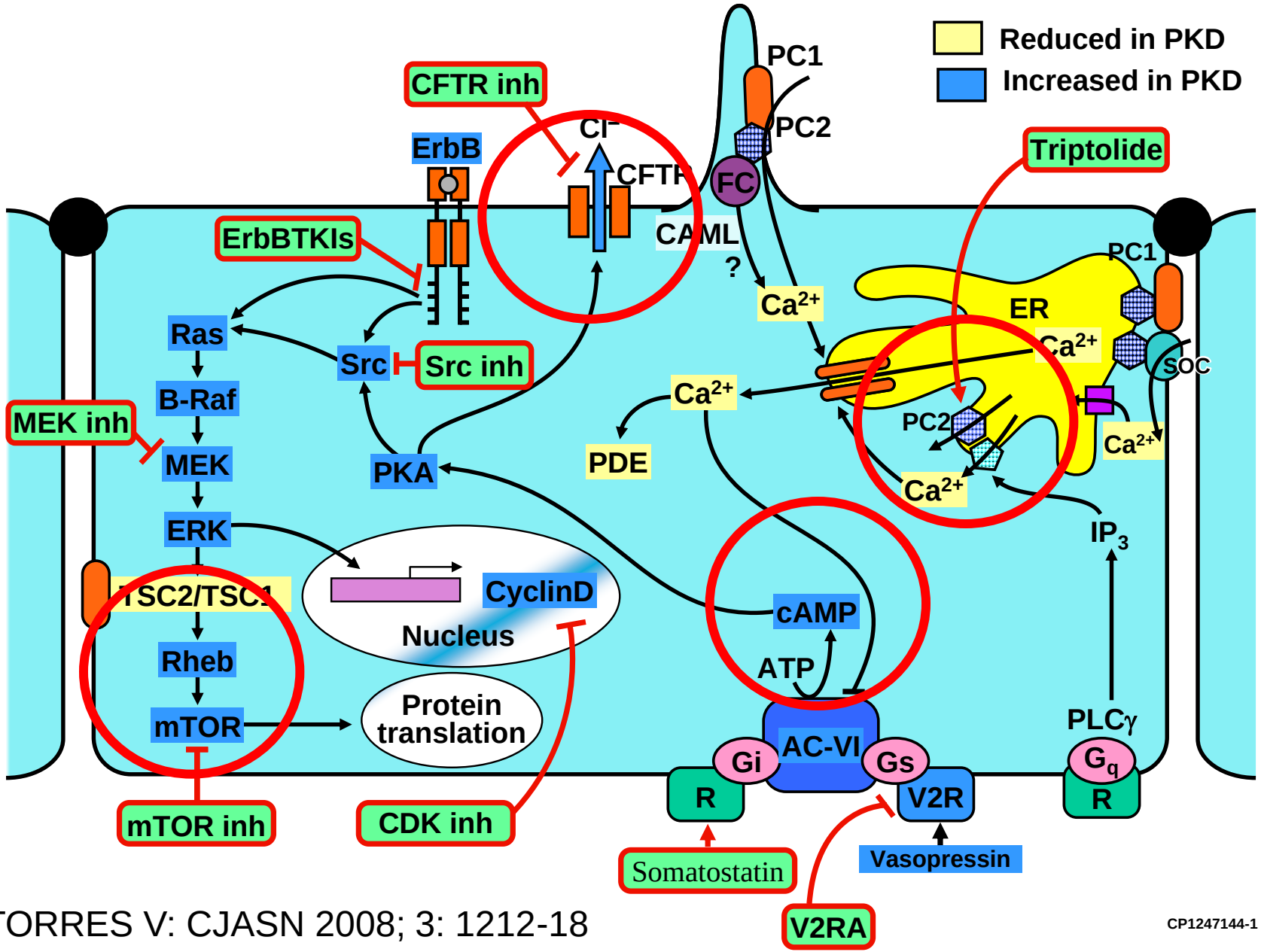
Madeline A Lancaster: Current Opinion in Genetics & Development 2009, 19:220–229


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
Axoneme
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

Therapeutic perspective

Signalling pathways

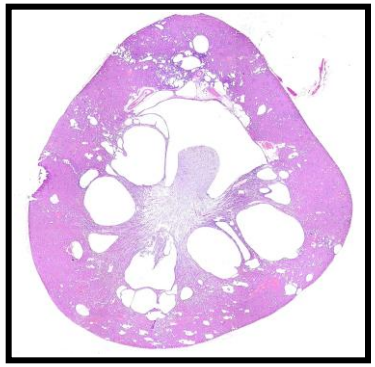
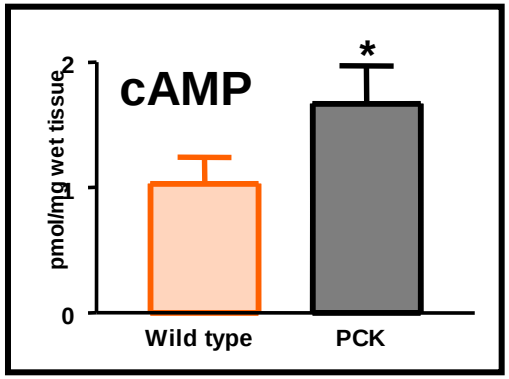
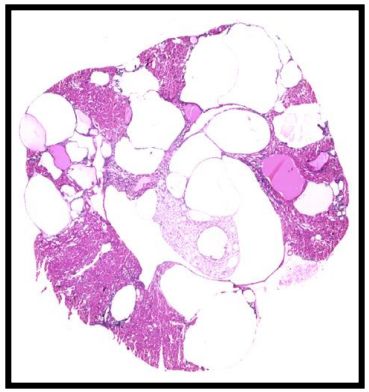
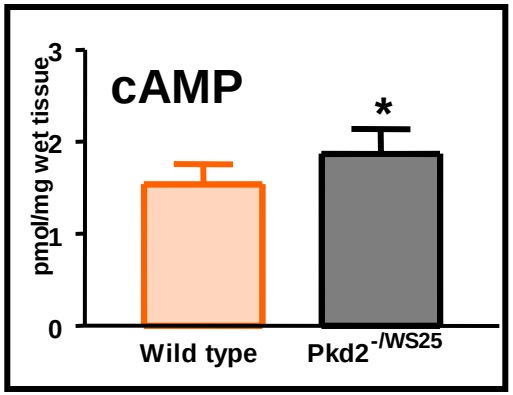
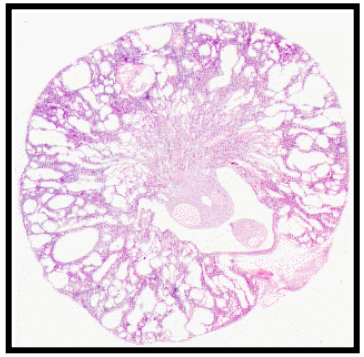
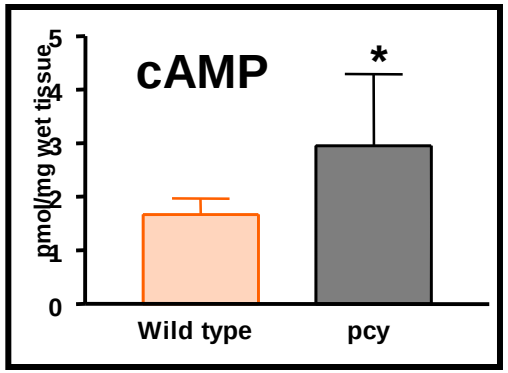
Targets for intervention



TORRES V: CJASN 2008; 3: 1212-18

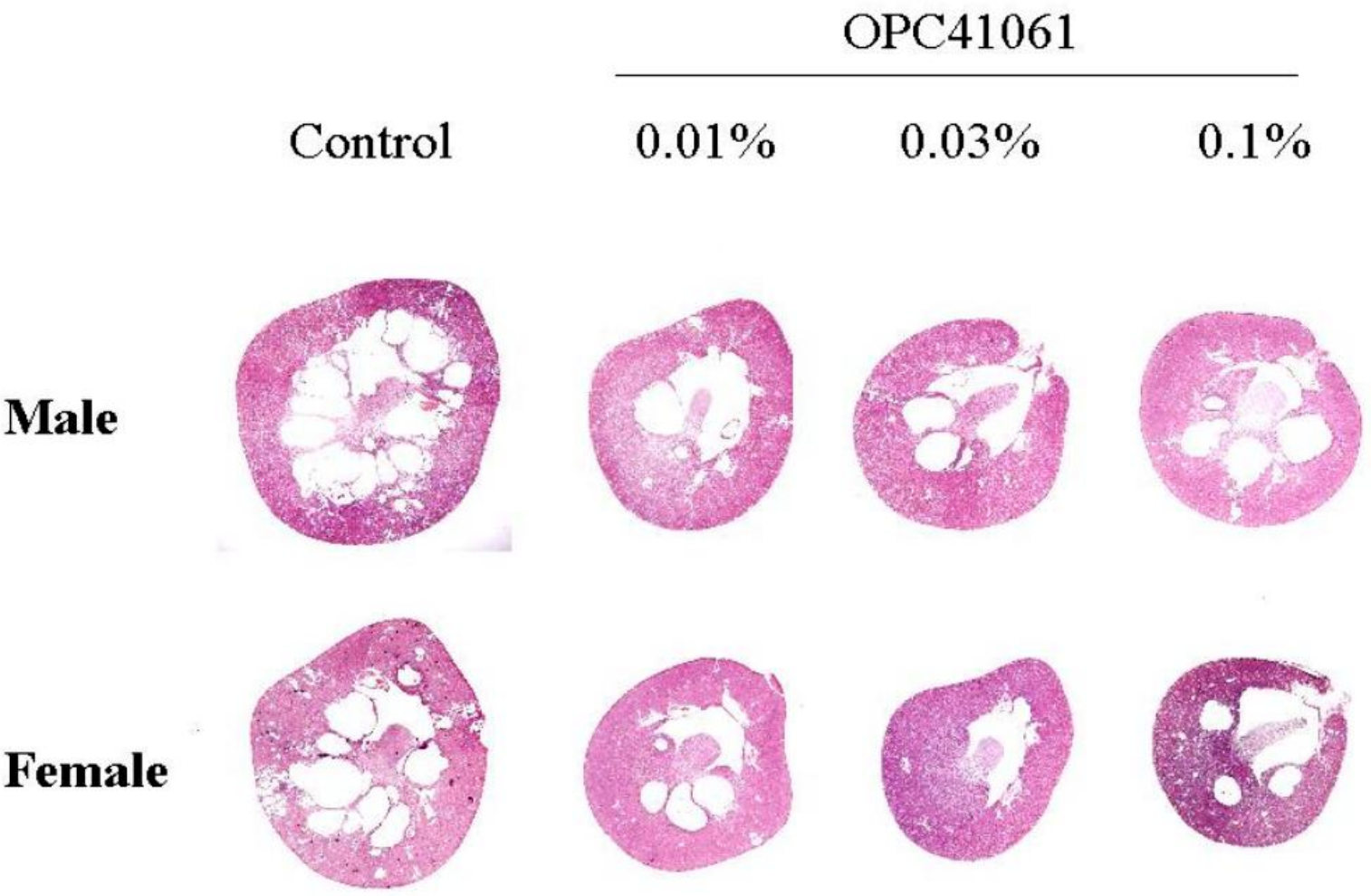
CP1247144-1

Human disease and animal homologues

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

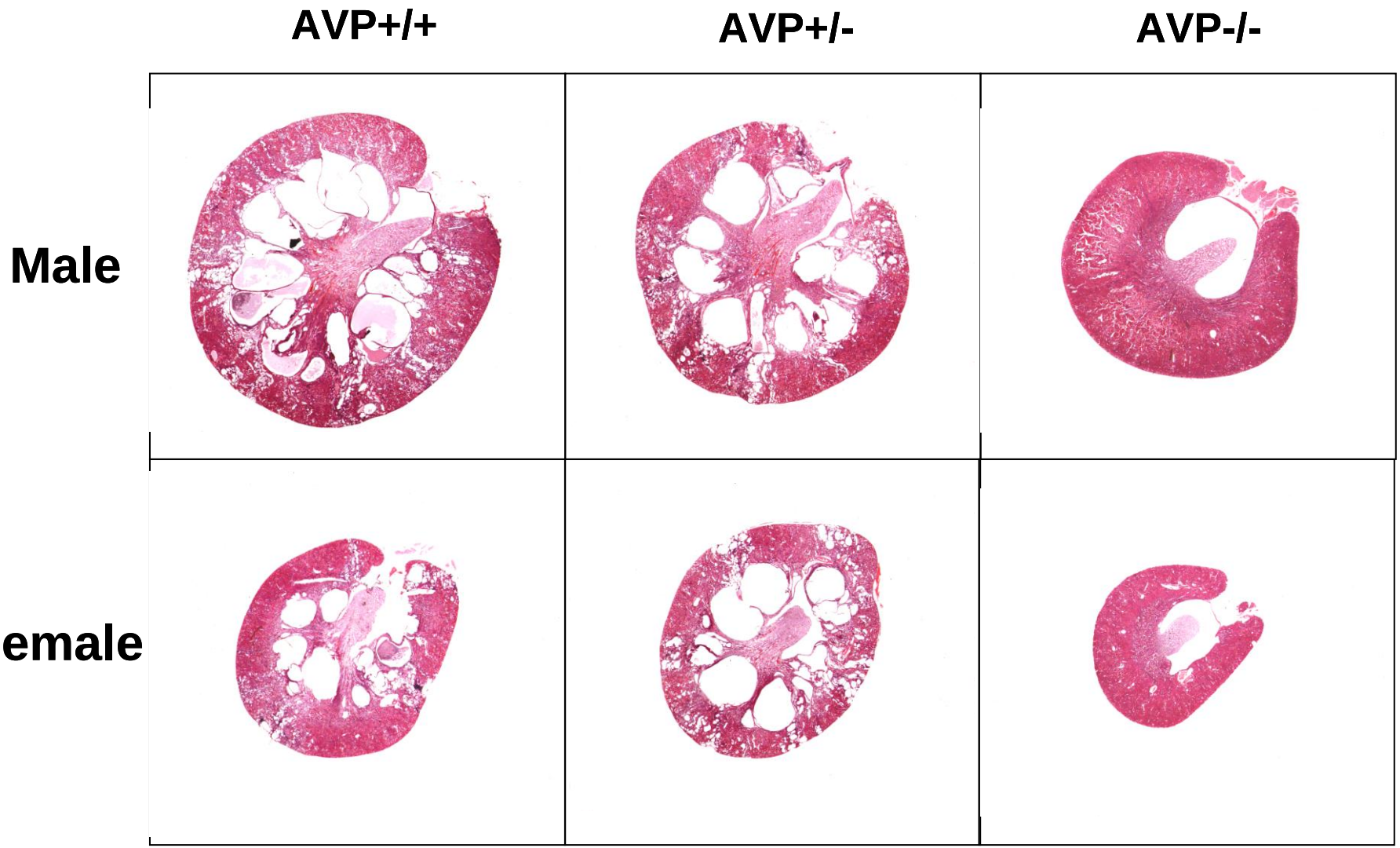
Torres V: 2007

Vasopressin antagonists



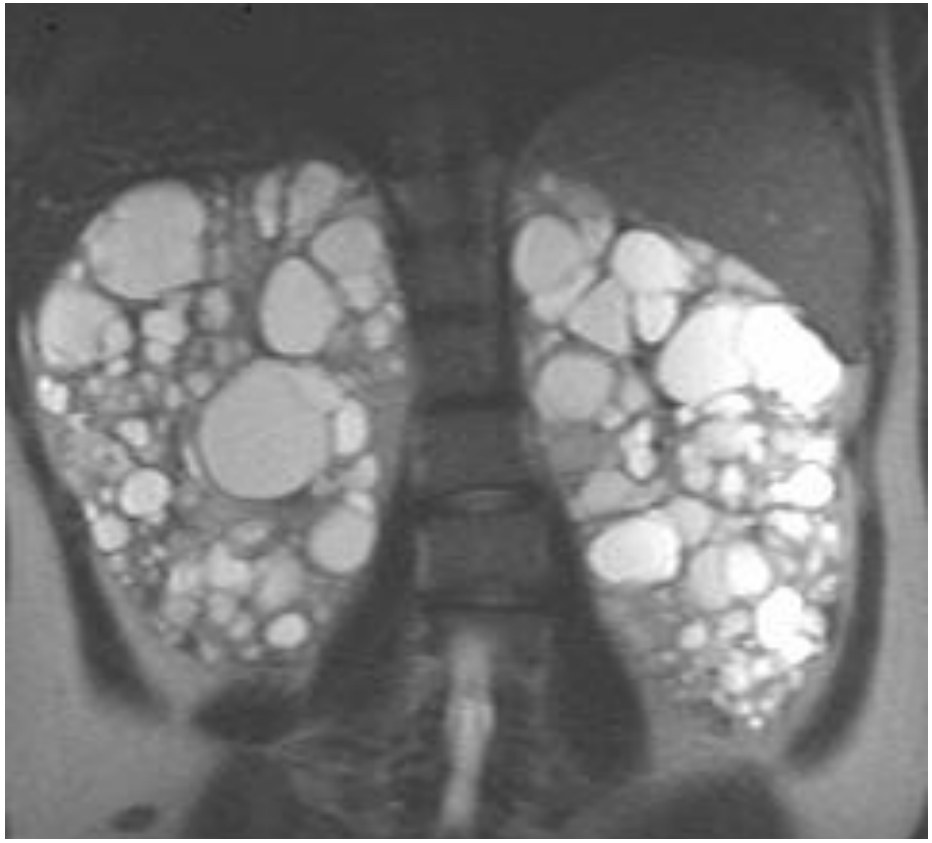
Wang JASN 16:846, 2005

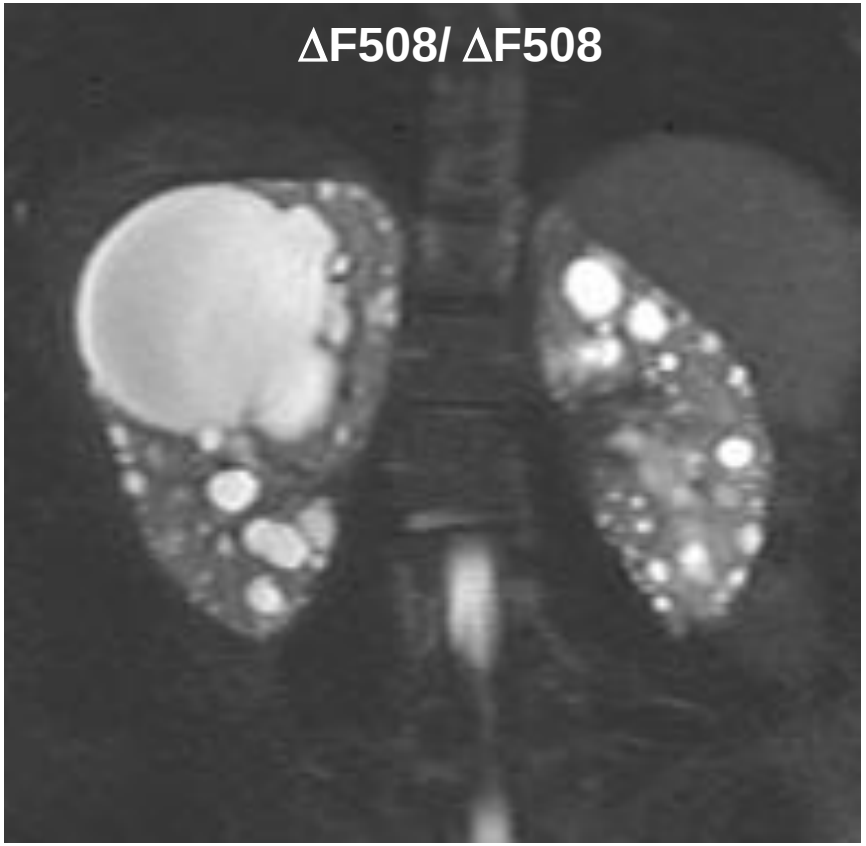
The effect of PKD and combined vasopressin receptor deficiency



Wang X et al: J Am Soc Nephrol 2007, 19: 102–108, 2008

CFTR INHIBITION:
ADPKD COEXISTING WITH CYSTIC FIBROSIS
MILDER PHENOTYPE





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

Summary

- Cystic diseases are due to the defective function of ciliary proteins
- Insight into structure and function offers new therapeutic targets

ADPKD: Clinical studies

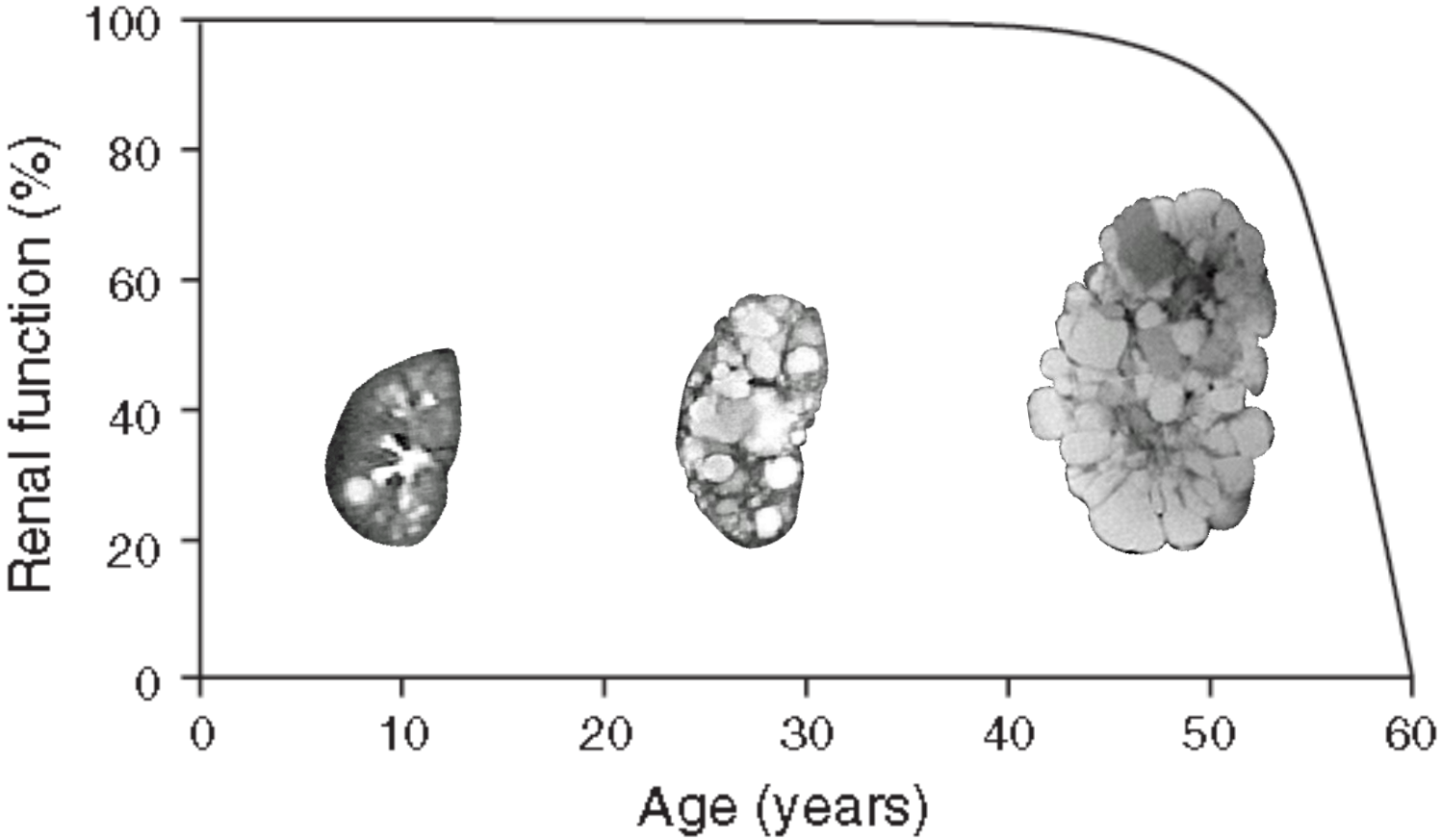
- CRISP – morphology and function
- V2 receptor antagonists: tolvaptan
- Somatostatin analogues: octreotide, lanreotide
- mTOR inhibitors: sirolimus, everolimus
- ACEI & ACEI+ARB: lisinopril - telmisartan

CRISP

Consortium for Radiological Imaging in Studies of Polycystic Kidney Disease

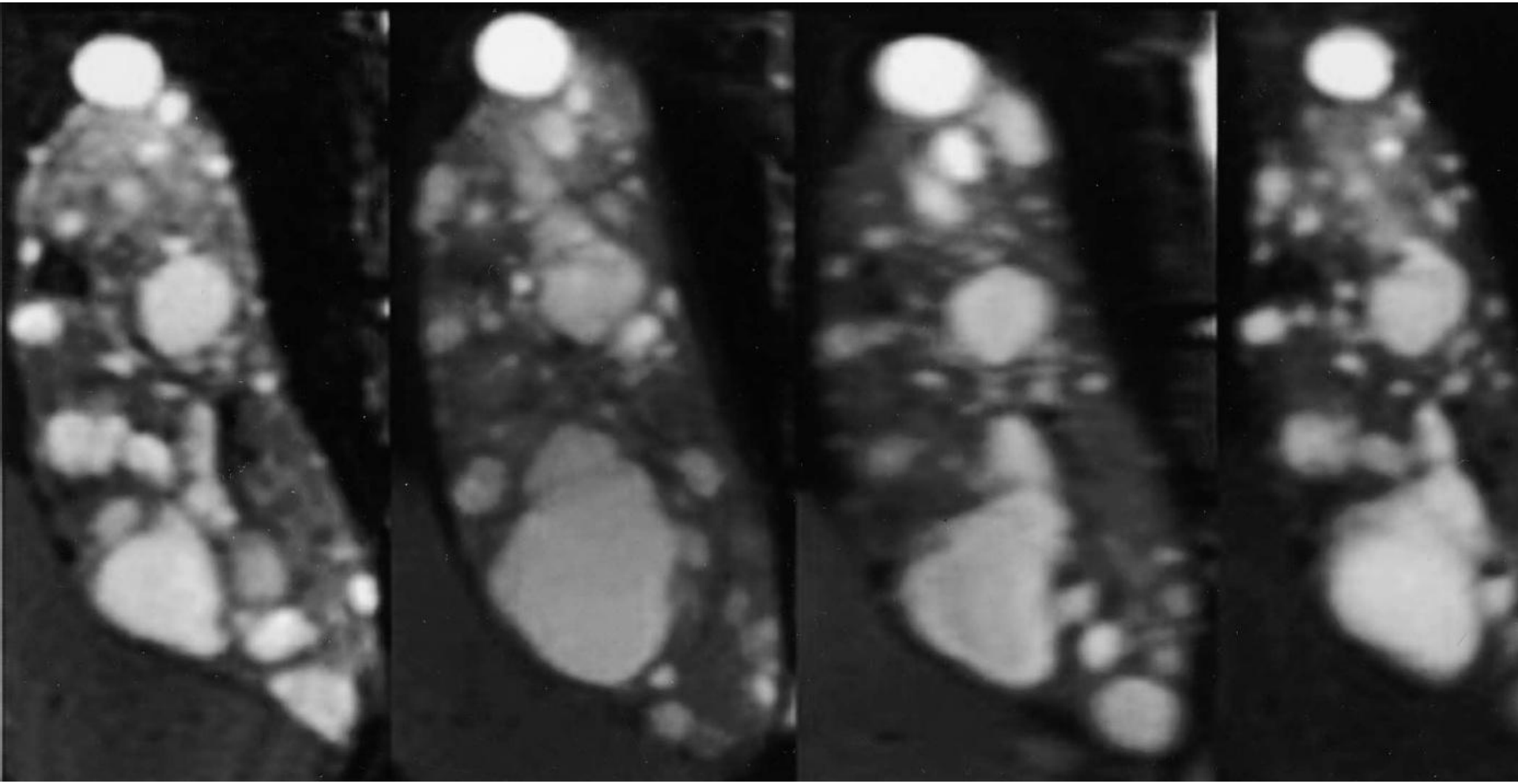
- Offers a tool to evaluate the results of different studies
- Prospective observational study
- Patients with eGFR >70 ml/min
- Whether kidney/cyst volume changes
  – can be detected over a short period of time
  – and are associated with loss of renal function

Renal survival curve in autosomal dominant polycystic kidney disease



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.

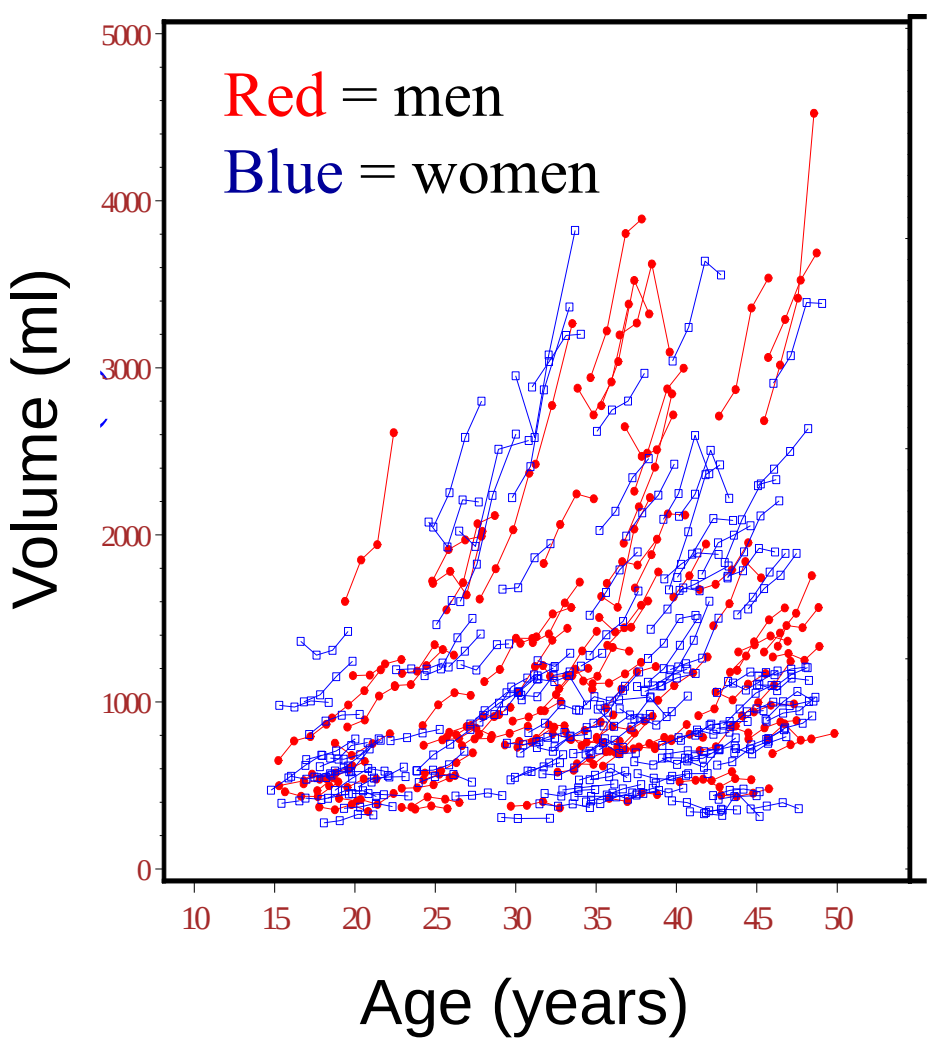


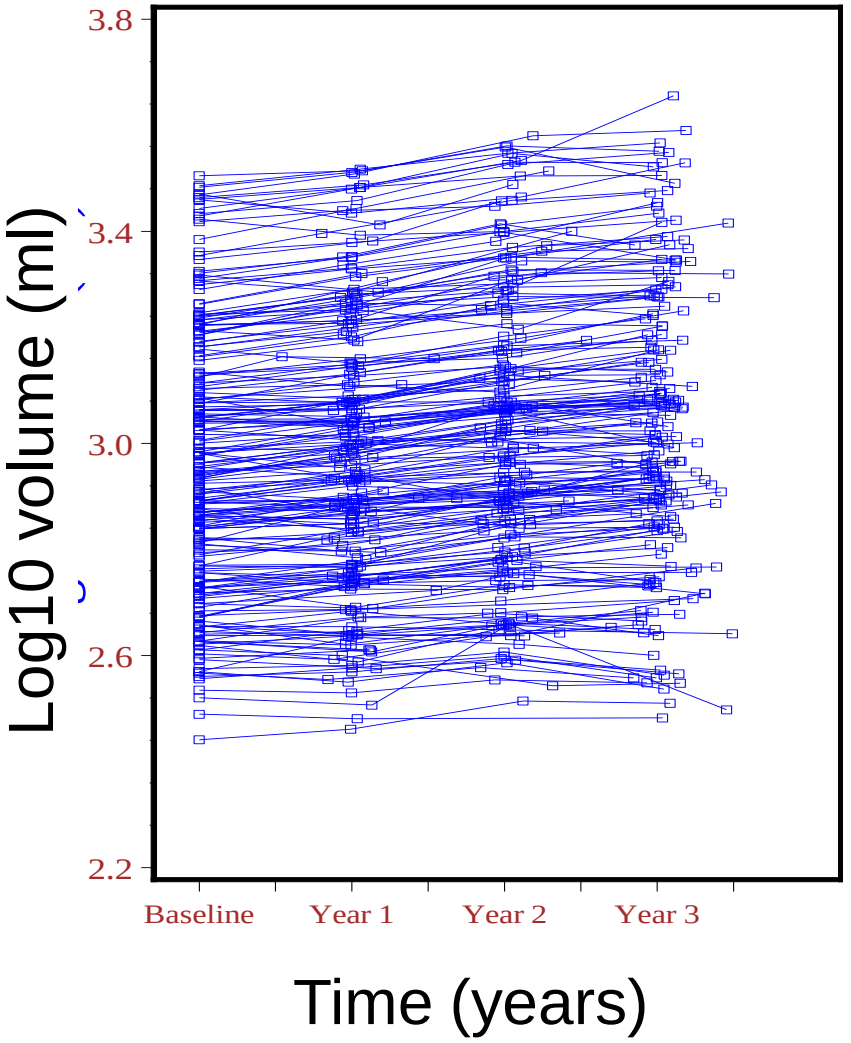
the standardization study in the same subject at each participating clinical center

Chapman AB; Kidney International, Vol. 64 (2003), pp. 1035–1045

MRI

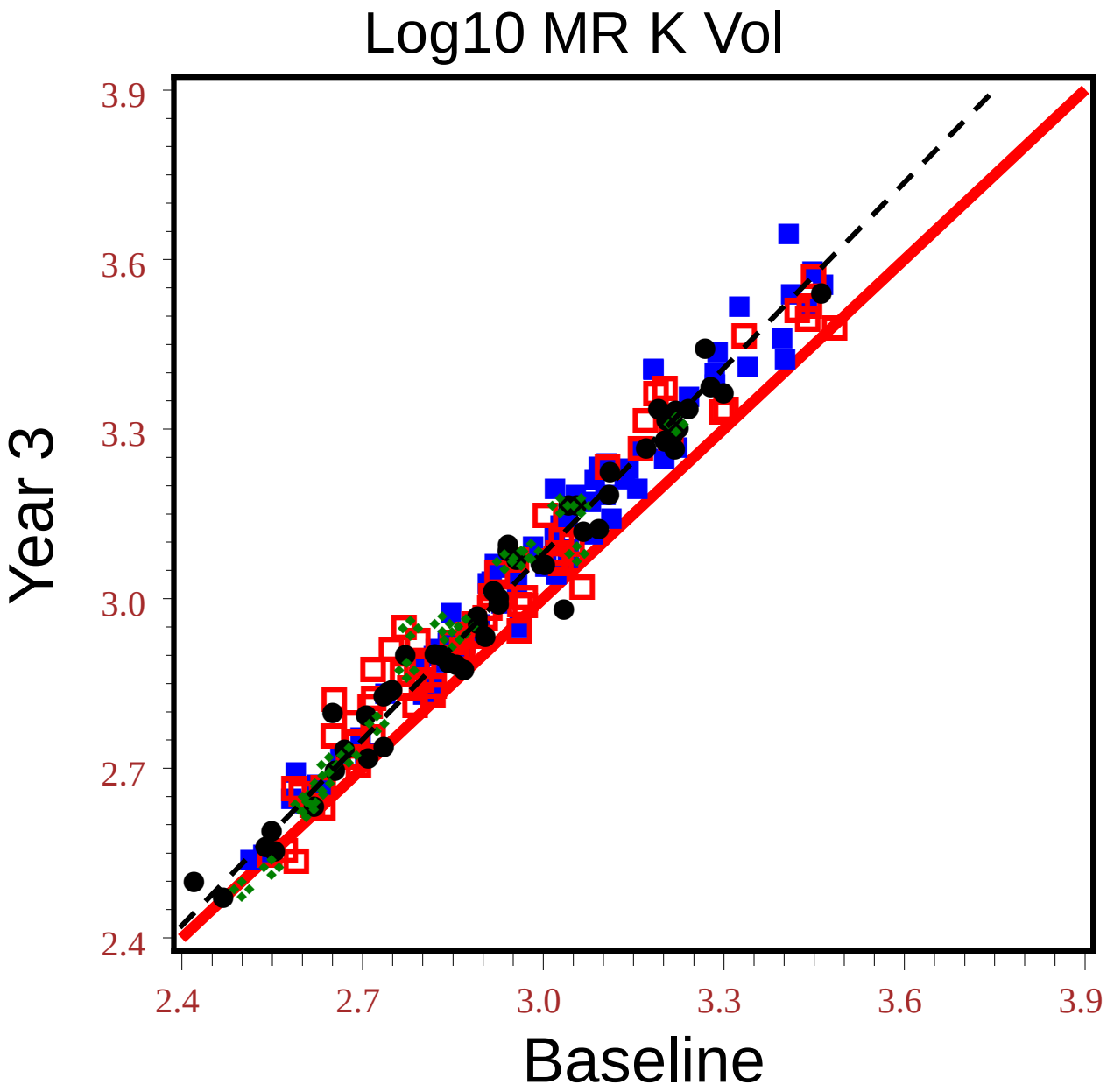
Kidney enlargement is detectable over a short period of time, it is continuous and relatively constant





Grantham NEJM 354:2122-2130, 2006

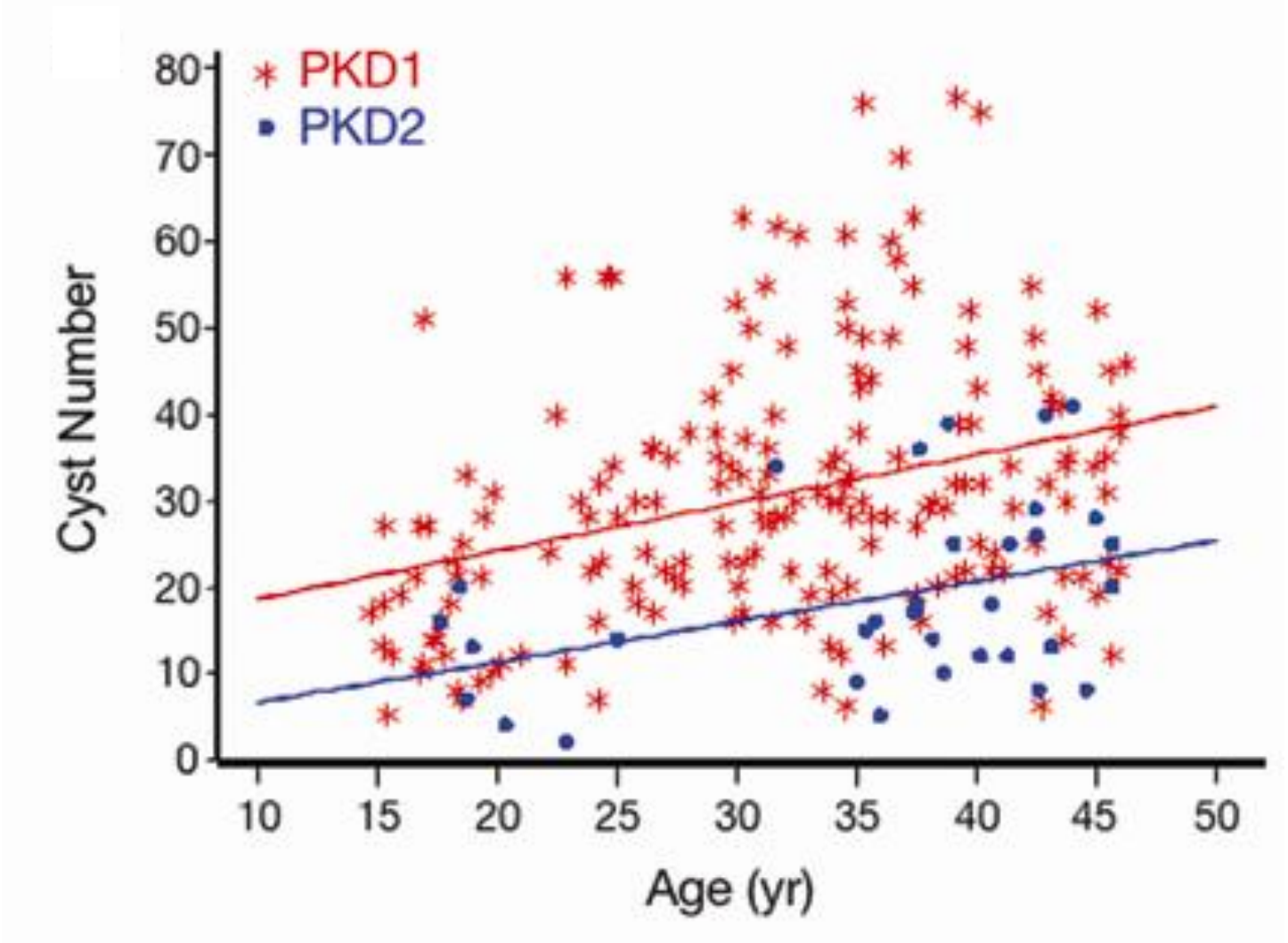
Renal volume predicts rate of enlargement



5.3 % average yearly increase in renal size

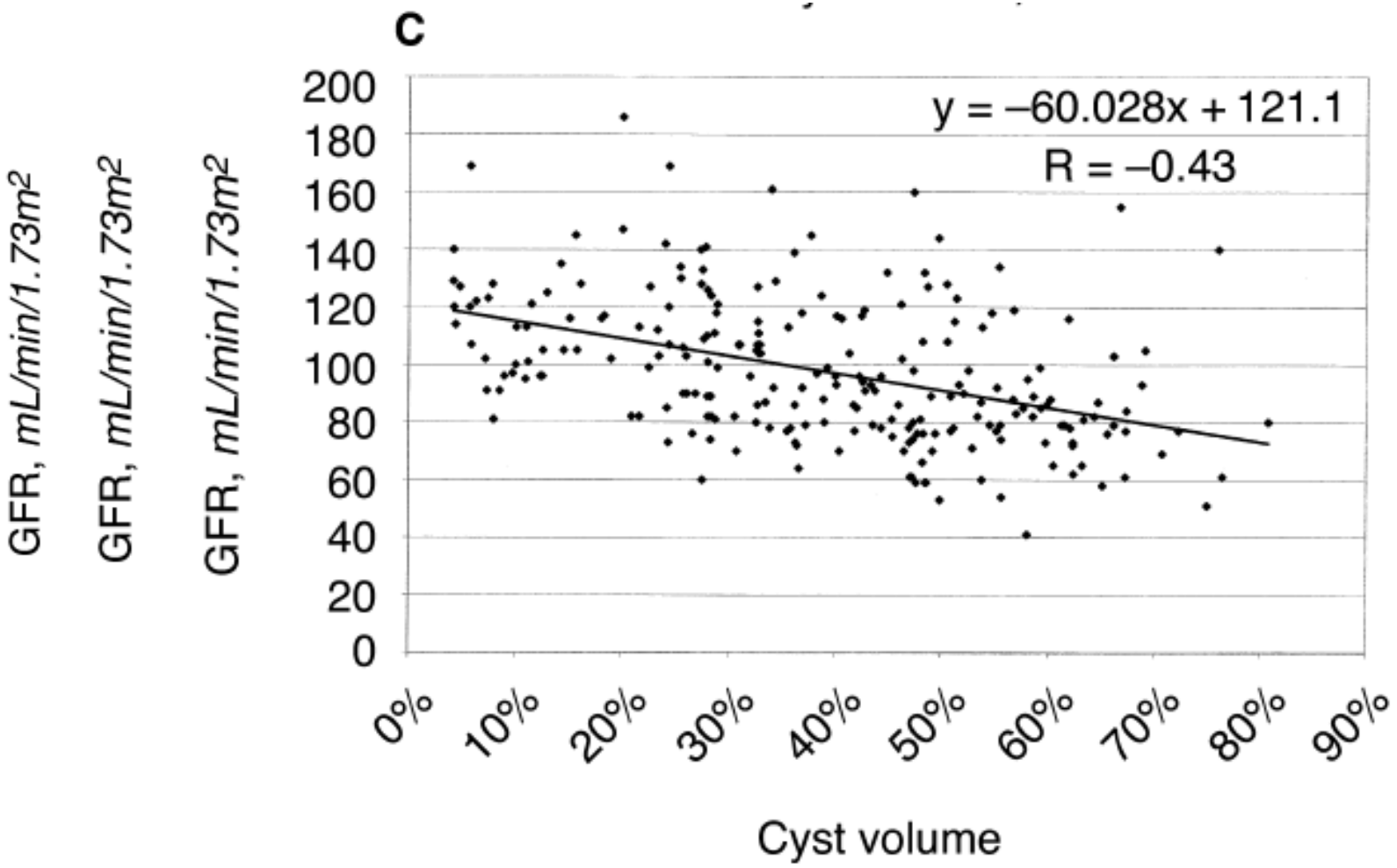
Grantham NEJM 354:2122-2130, 2006

Genotype affects cyst initiation and number, but not rate of progression



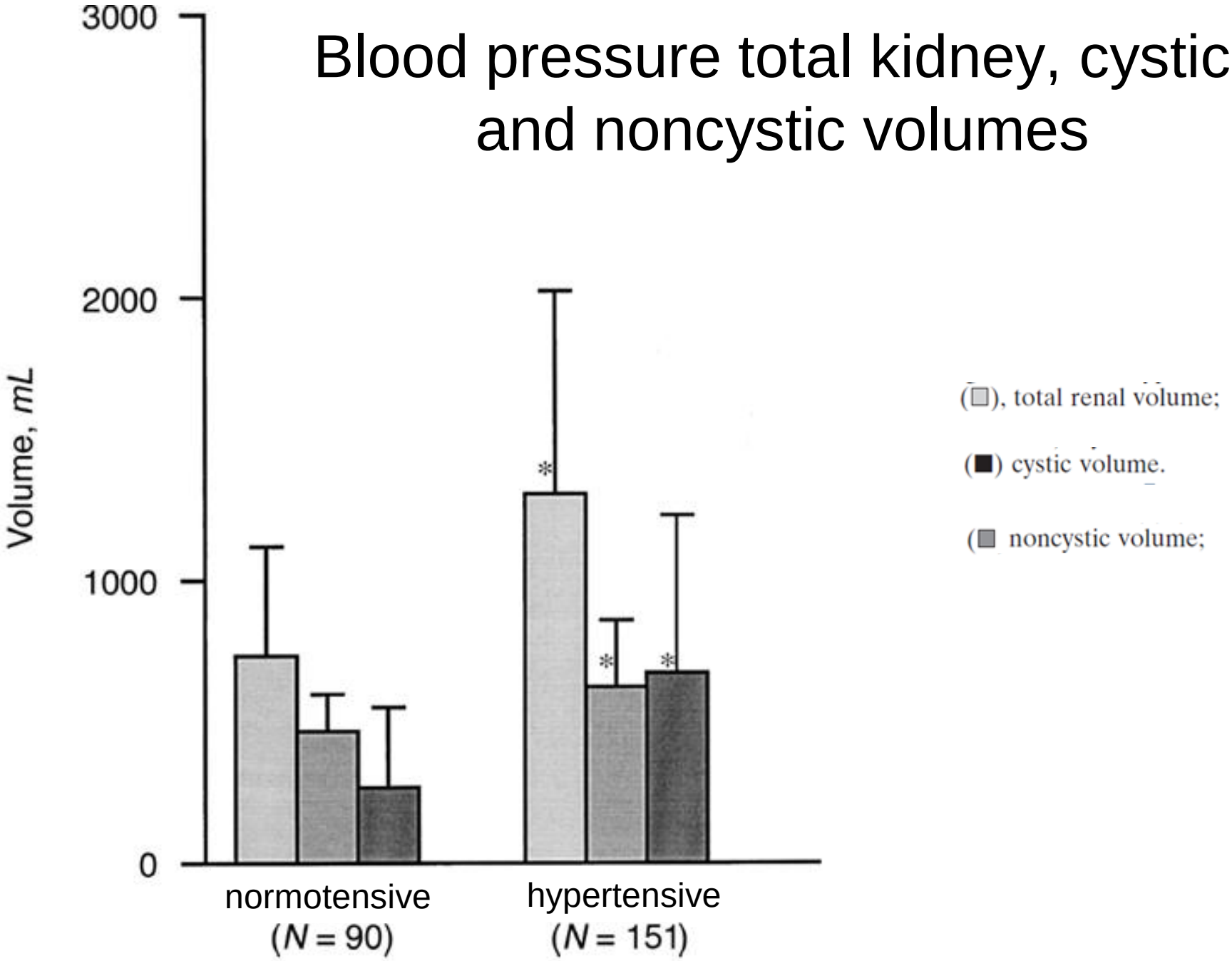
Harris, JASN 17:3013, 2006

Relationship between GFR and age adjusted renal volumes



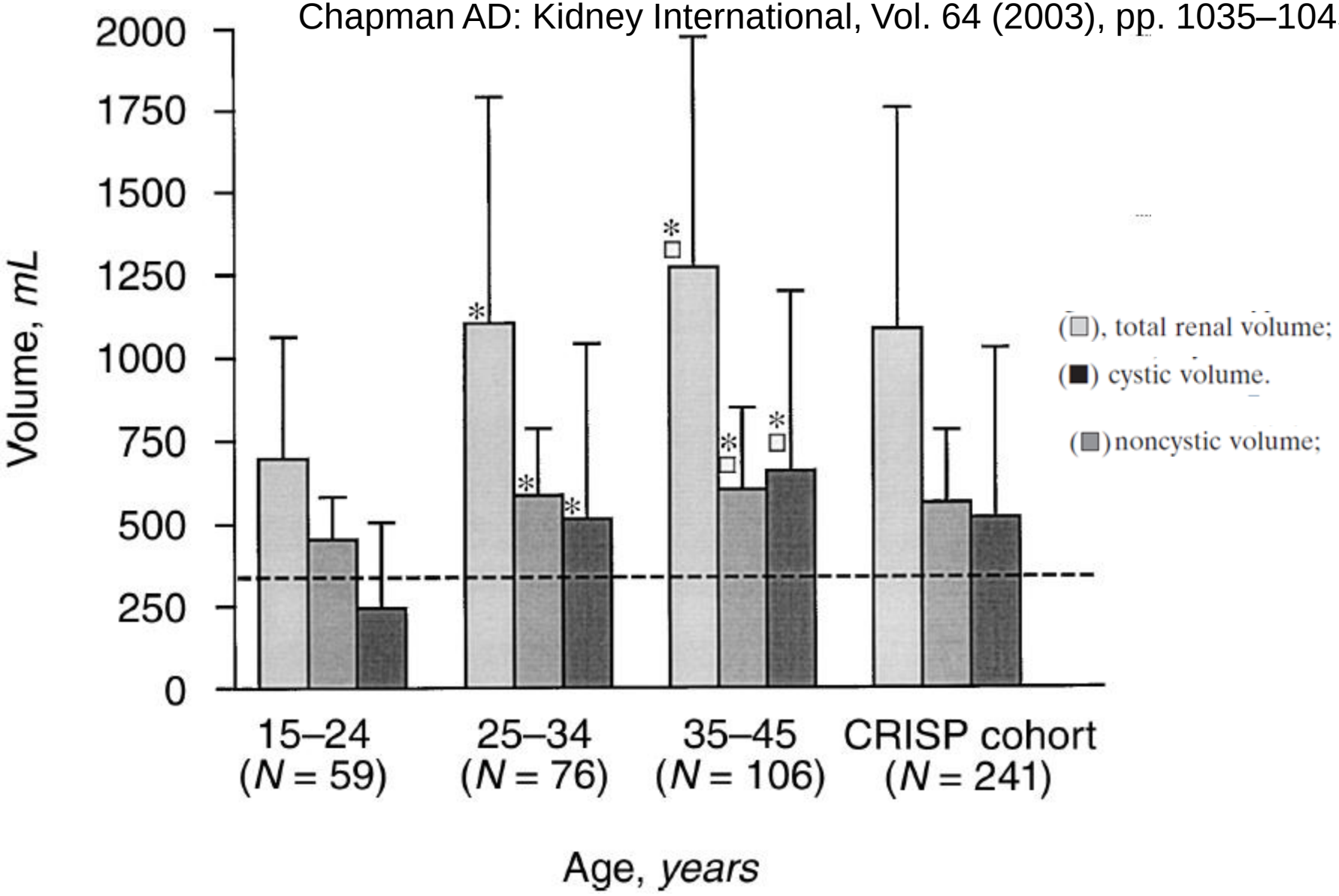
Chapman AD: Kidney International, Vol. 64 (2003), pp. 1035–1045

Blood pressure total kidney, cystic- and noncystic volumes

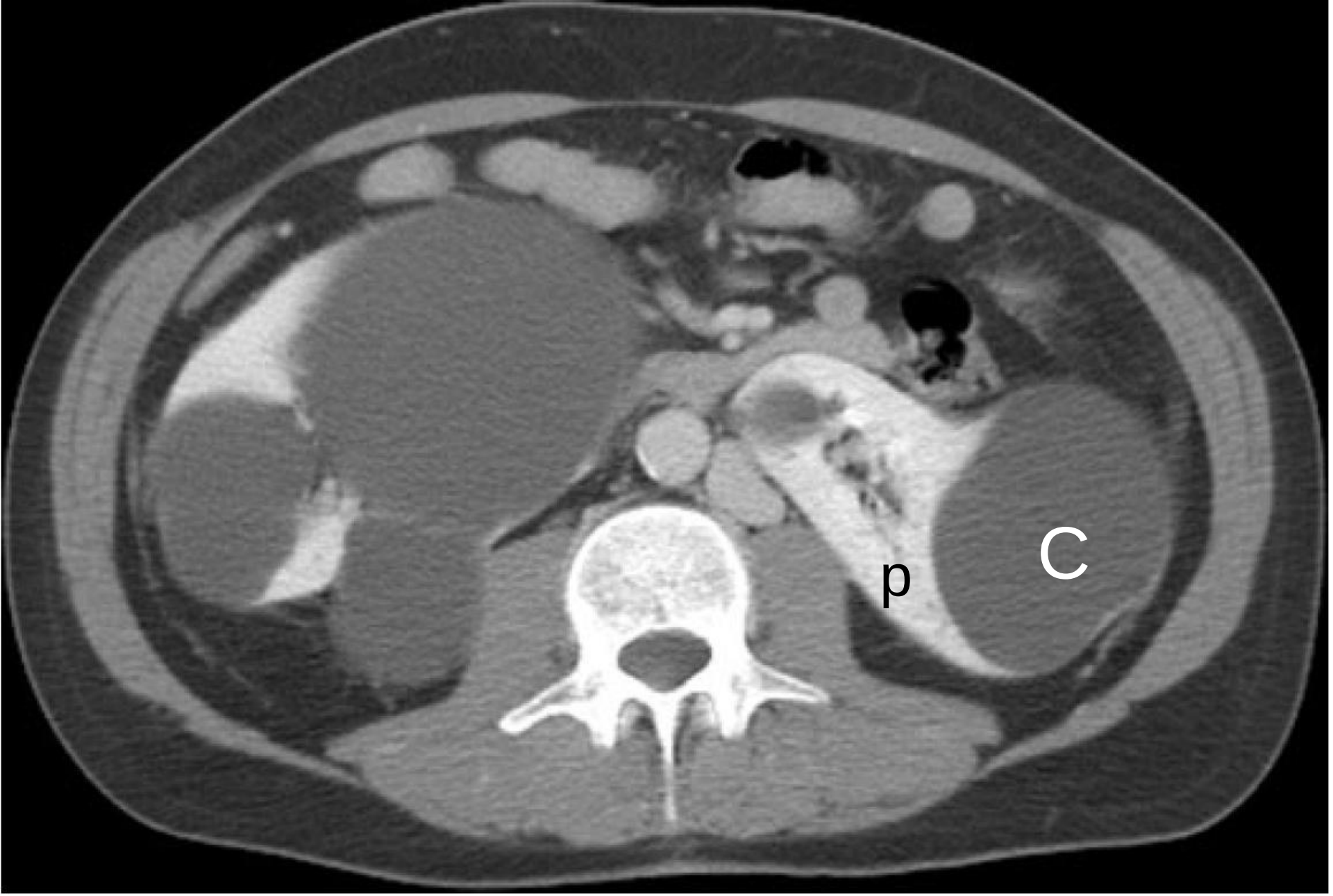


Chapman AD: Kidney International, Vol. 64 (2003), pp. 1035–1045

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



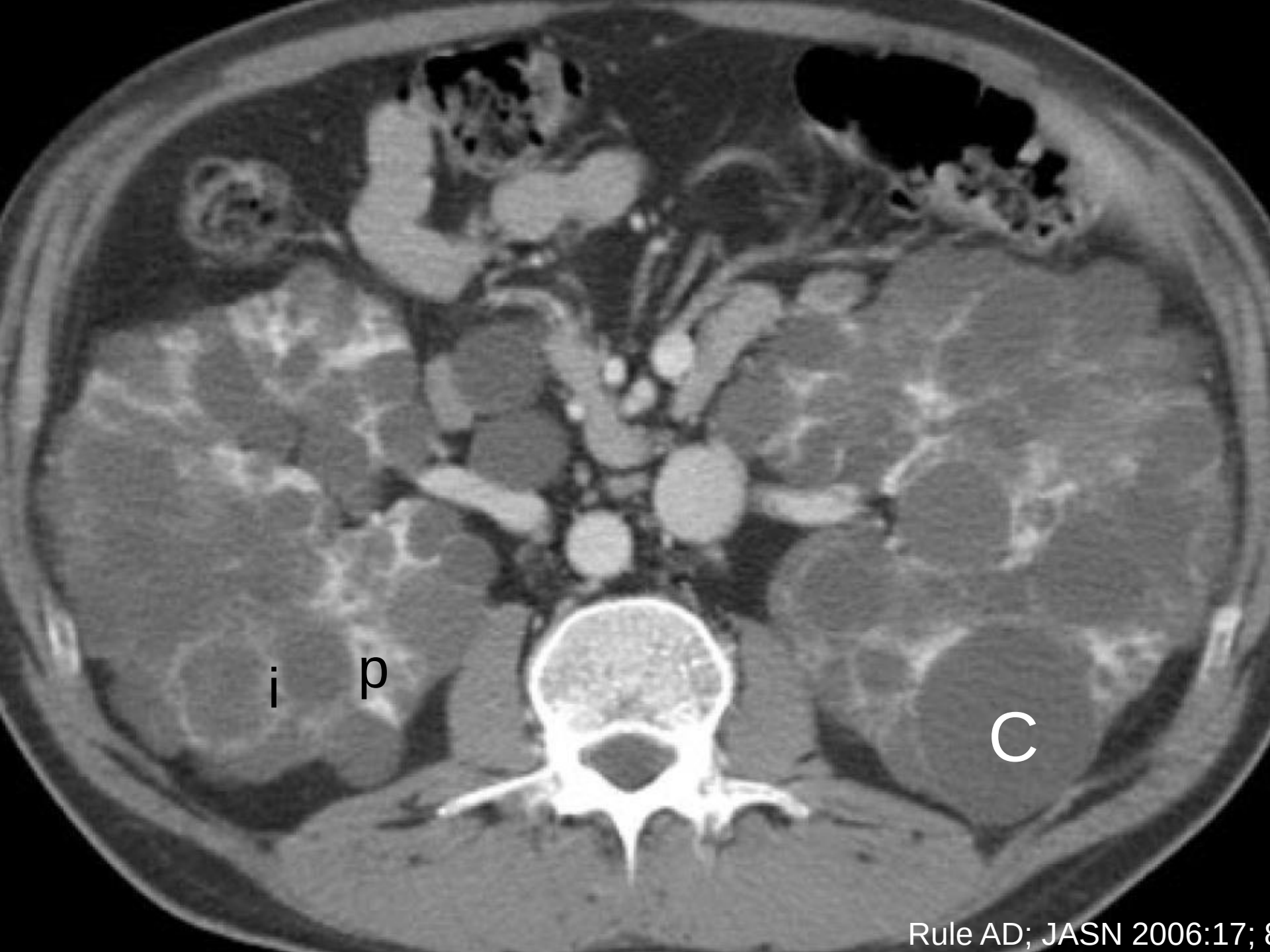
Mean total renal, cystic, and noncystic volumes in the entire Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort, in those between 15 to 24, 25 to 34, and 35 to 45



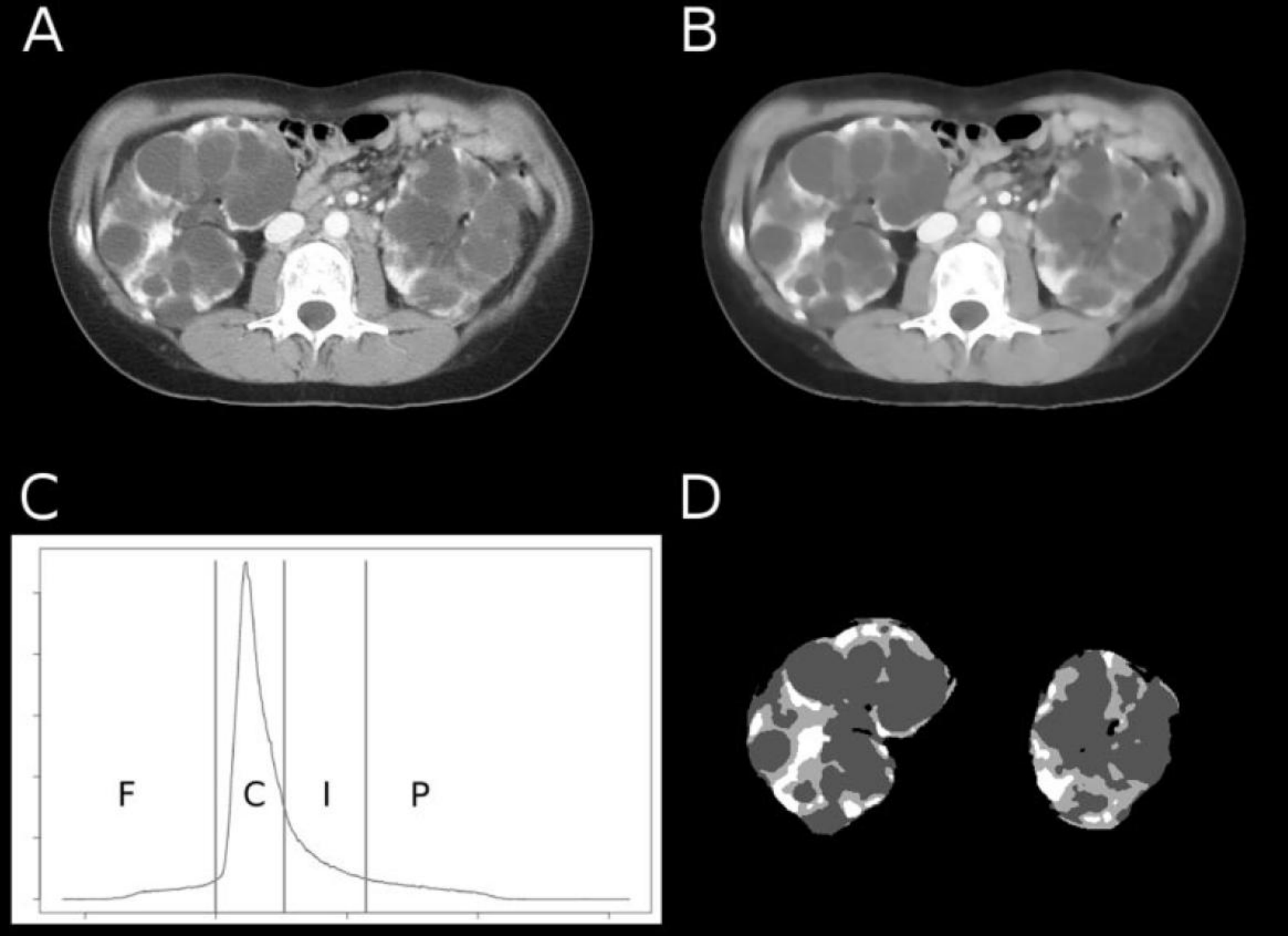
C=cyst P=parenchyma

CT

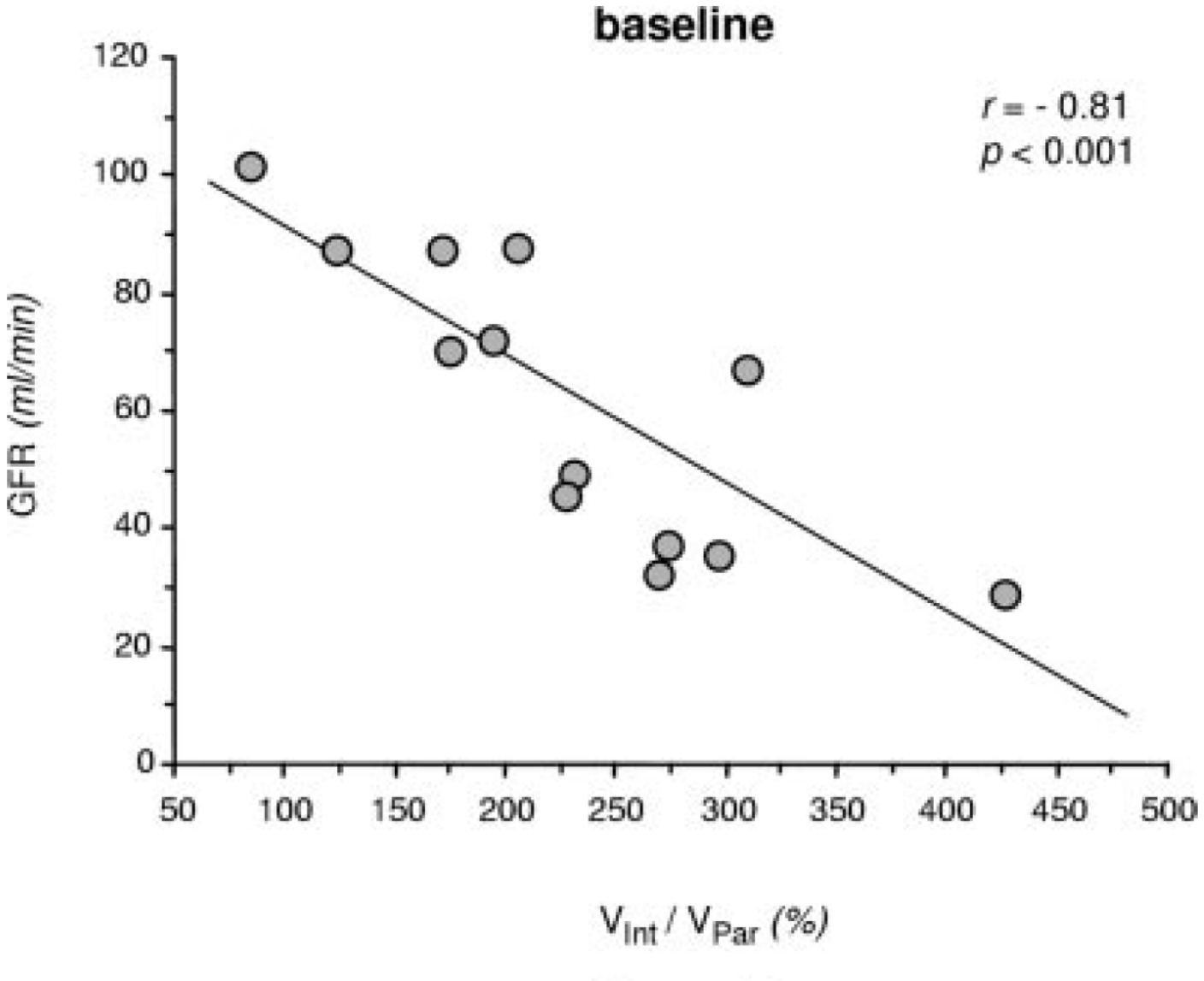
Rule AD; JASN 2006:17; 854-862



Rule AD; JASN 2006:17; 8


A
B
C
F
C
I
P
D

Intermediate volume: parenchyme in destruction?



Antiga L: Clin J Am Soc Nephrol 1: 754–760, 2006.

CRISP results

- 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

CRISP Conclusions

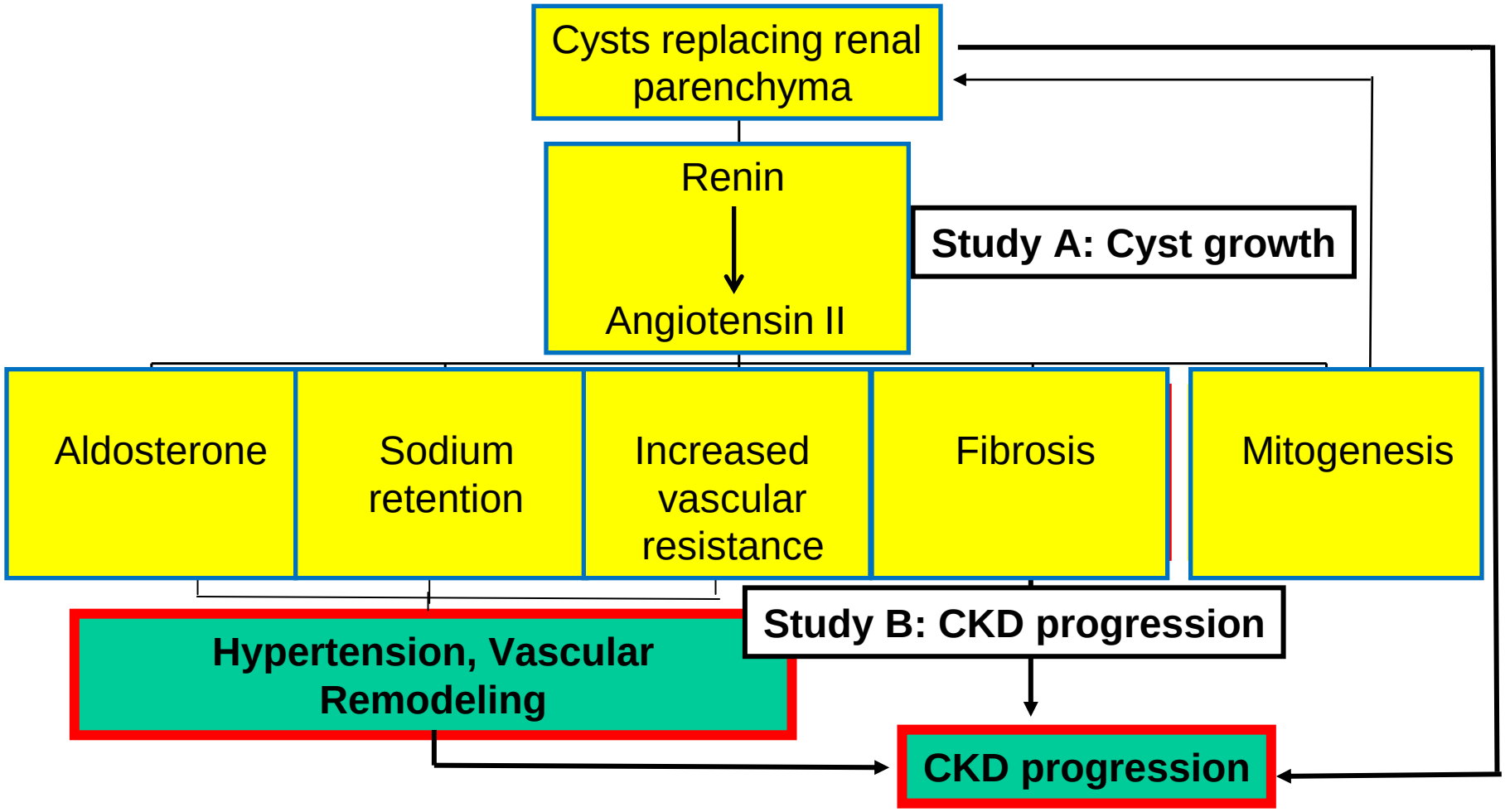
Kidney enlargement is

- 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

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)

Analysis of baseline parameters in the HALT polycystic kidney disease trials

	Intervention	SBP Target (mmHg)	Primary Outcome
Study A (CKD 1-2)	**1. ACE+ARB** **2. ACE** **3. ACE+ARB** **4. ACE**	**120-130** **120-130** **95-110** **95-110**	**Change in Renal Volume by MRI**
Study B (CKD 3)	**1. ACE +ARB** **2. ACE**	**110-130** **110-130**	**Doubling Serum Creatinine/ ESRD/Death**

A: n=558 B: n=486

Secondary outcomes: Changes in GFR, RBF, LV mass, albuminuria Hospitalizations, QOL

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

Interventional studies

V2 receptor antagonist

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

- Phase 2 (completed)

Ascending-dose and split-dose studies

Polyuria well tolerated, safe

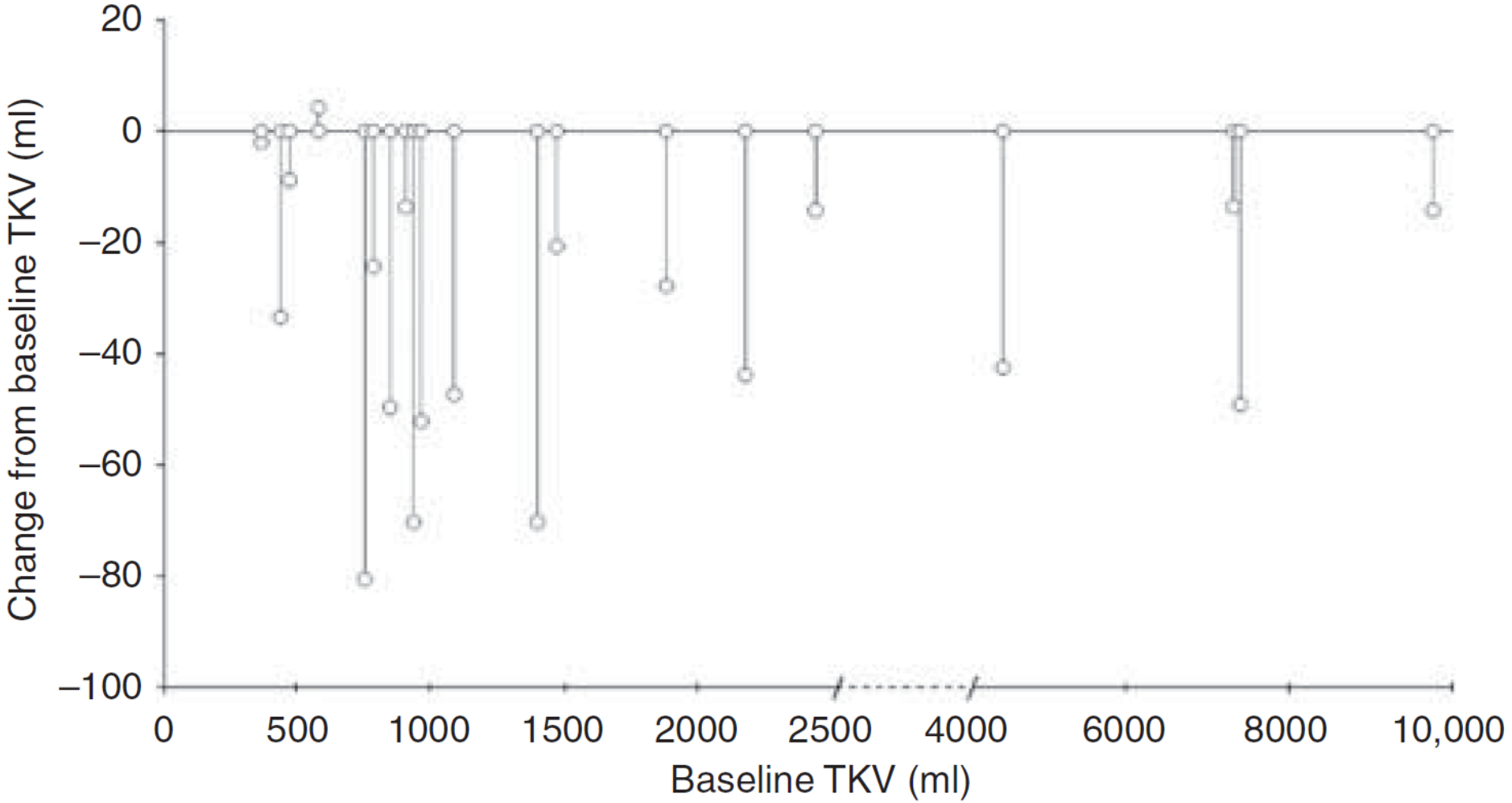
Twice daily administration necessary

- Phase 3 (to be published)

Well tolerated and safe

Able to achieve sustained urine hypotonicity

Short-term (1 week) effects of tolvaptan on renal function and volume in patients with ADPKD



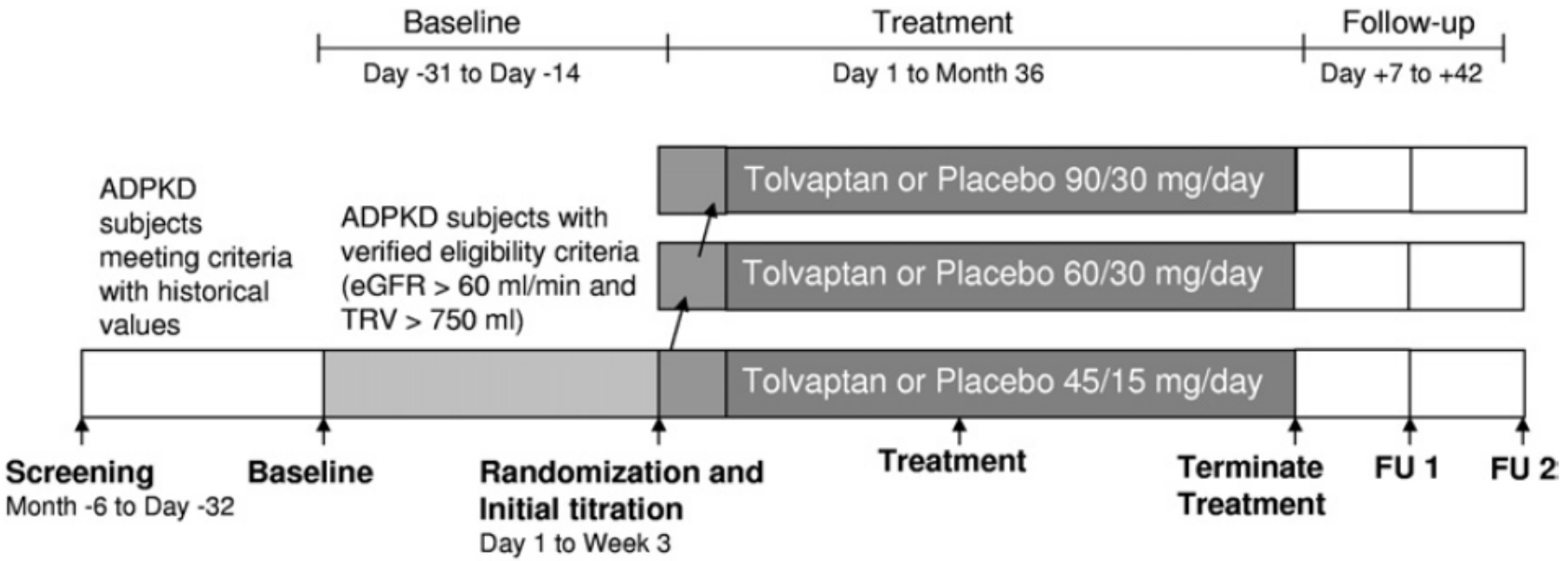
Irazabal et al: Kidney International (2011) 80, 295–301;

TEMPO (Tolvaptan Efficacy and Safety in Management of PKD and Outcomes)

- Phase 3
- Placebo controlled (2:1), double blind
  - 1445 ADPKD patients in ~100 centers
  - Inclusion criteria: Age 18-50 years
  - Total kidney volume >750 mL
    - baseline median total kidney volume was 1.46 L,.
  - eGFR >60 mL/min/1.73 sq.m
    - estimated creatinine clearance was 105 mL/min.

- Primary outcome: Renal volume change by MRI
- Duration: 3 years treatment, 5 years total

TEMPO study design

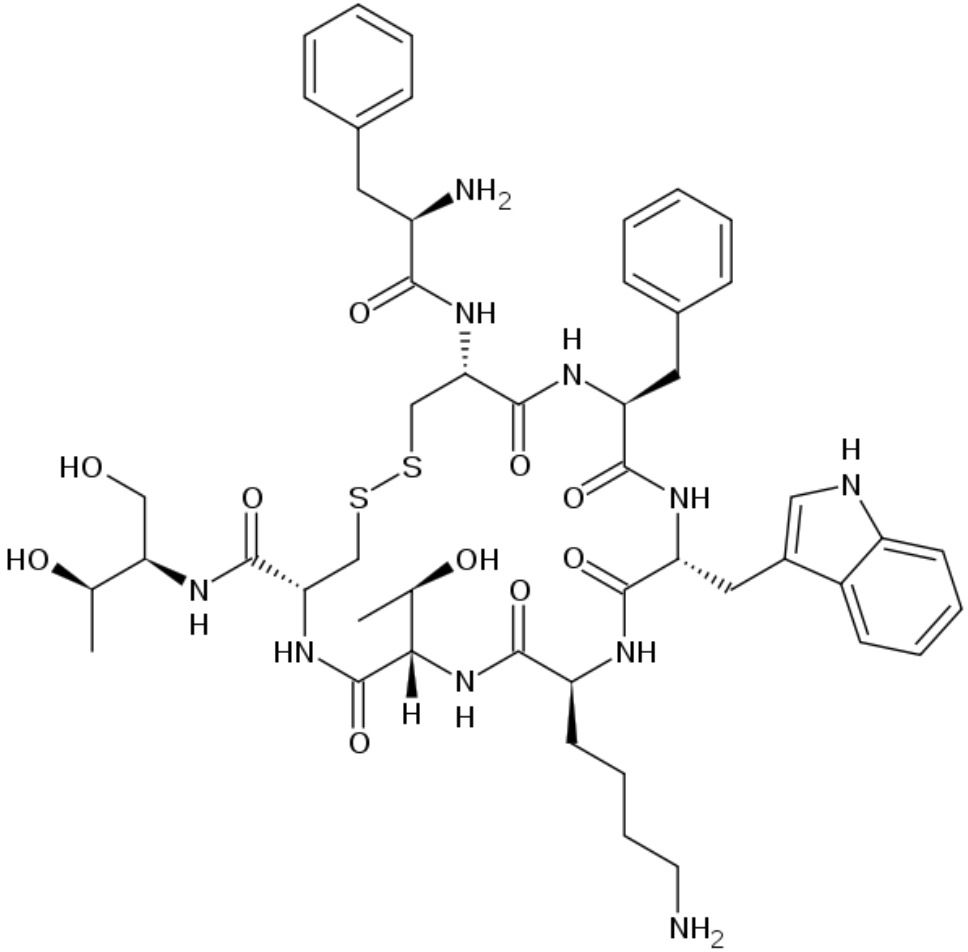


Interventional studies

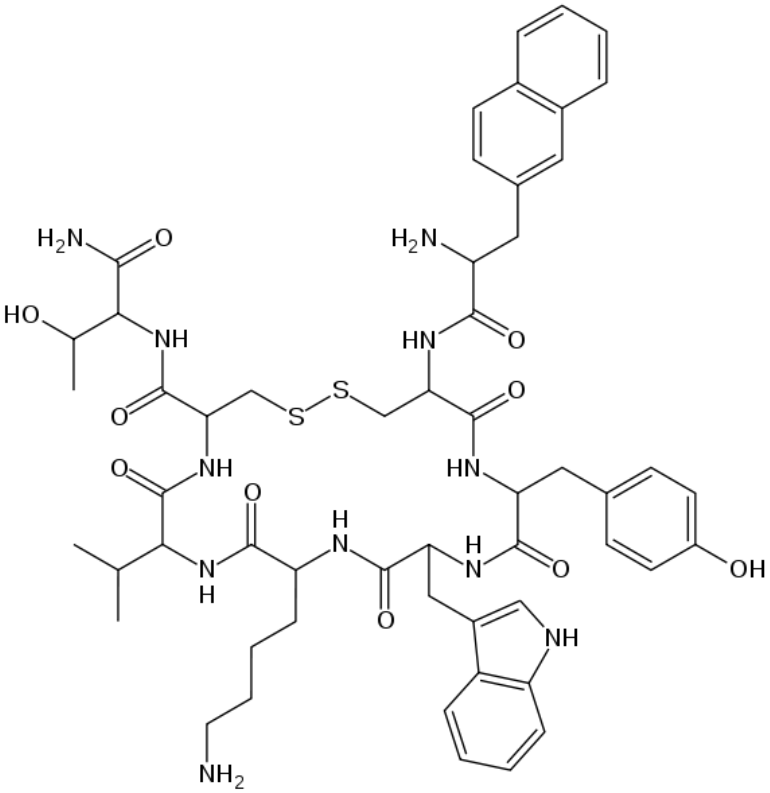
Somatostatin analogues

Somatostatin analogues

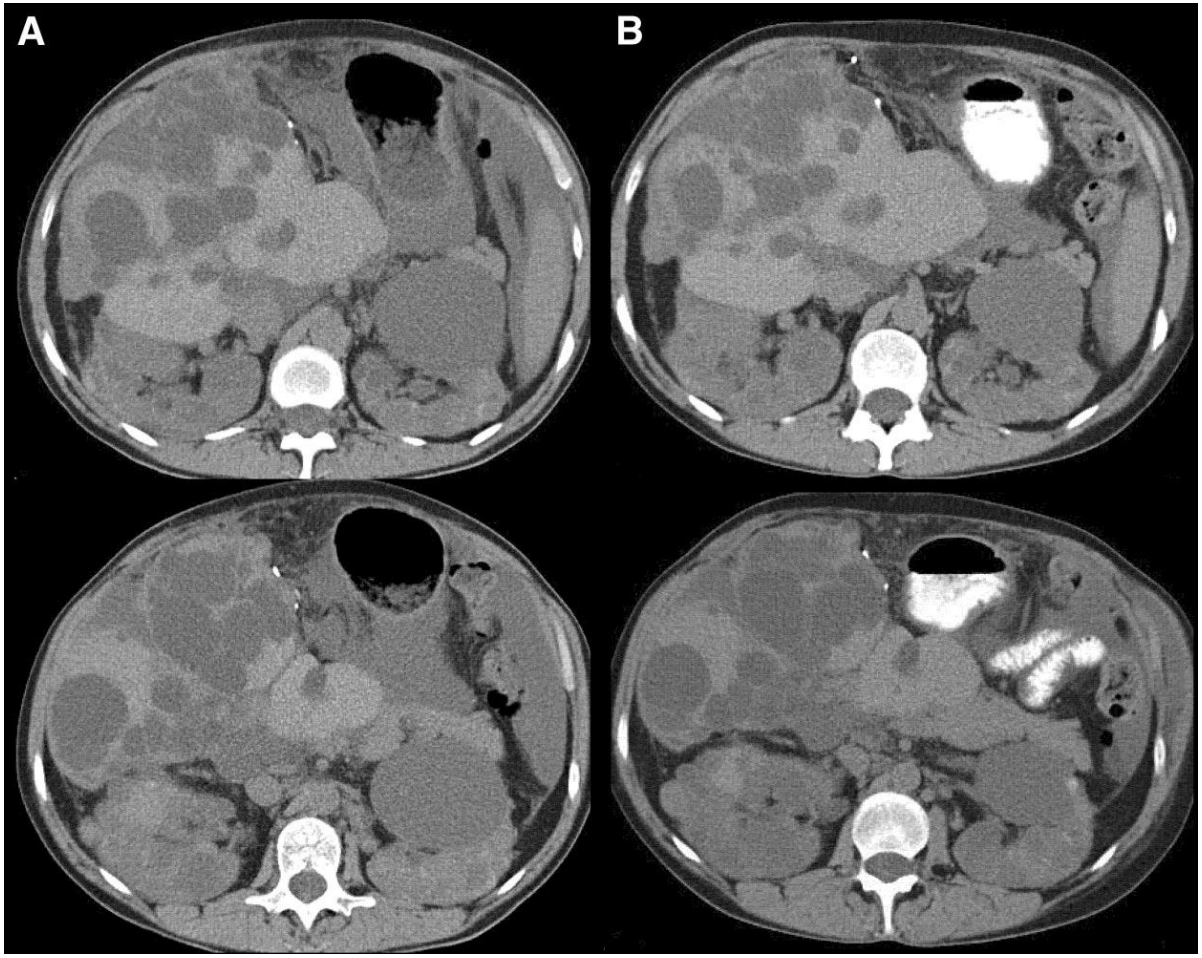
Octreotide (Sandostatin)



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.

LONG-ACTING OCTREOTIDE TRIAL

Double blind, placebo controlled (2:1), 42 patients

Octreotide LAR 40 mg IM every 4 weeks

Inclusion criteria:

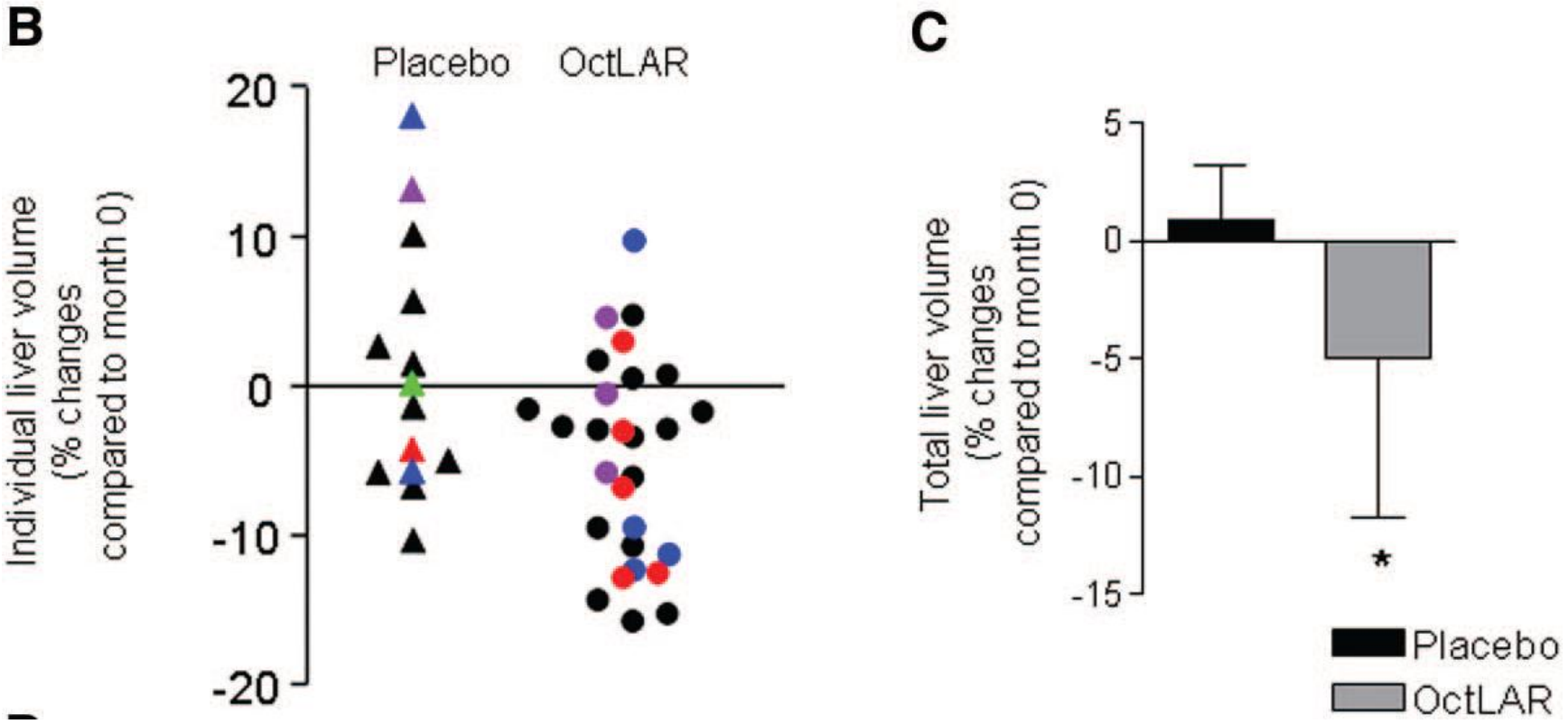
- Age ≥ 18 years
- Liver volume >4000 mL or symptomatic
- Not a candidate for or declining surgery
- Serum creatinine <3 mg/dL

Primary outcome: Liver volume change by MRI

Duration: 2 years (1 year open label)

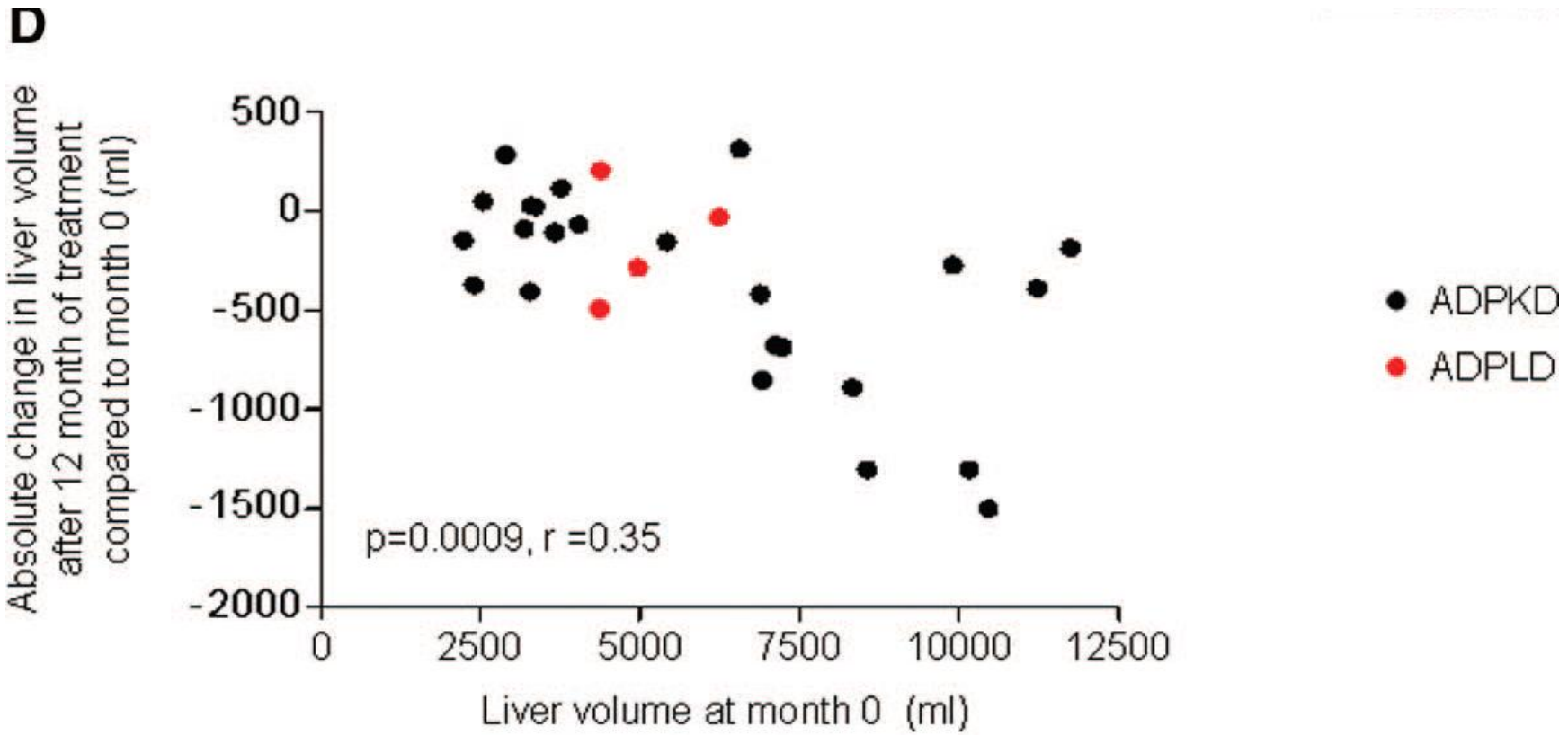
J Am Soc Nephrol 21: 1052–1061, 2010.

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



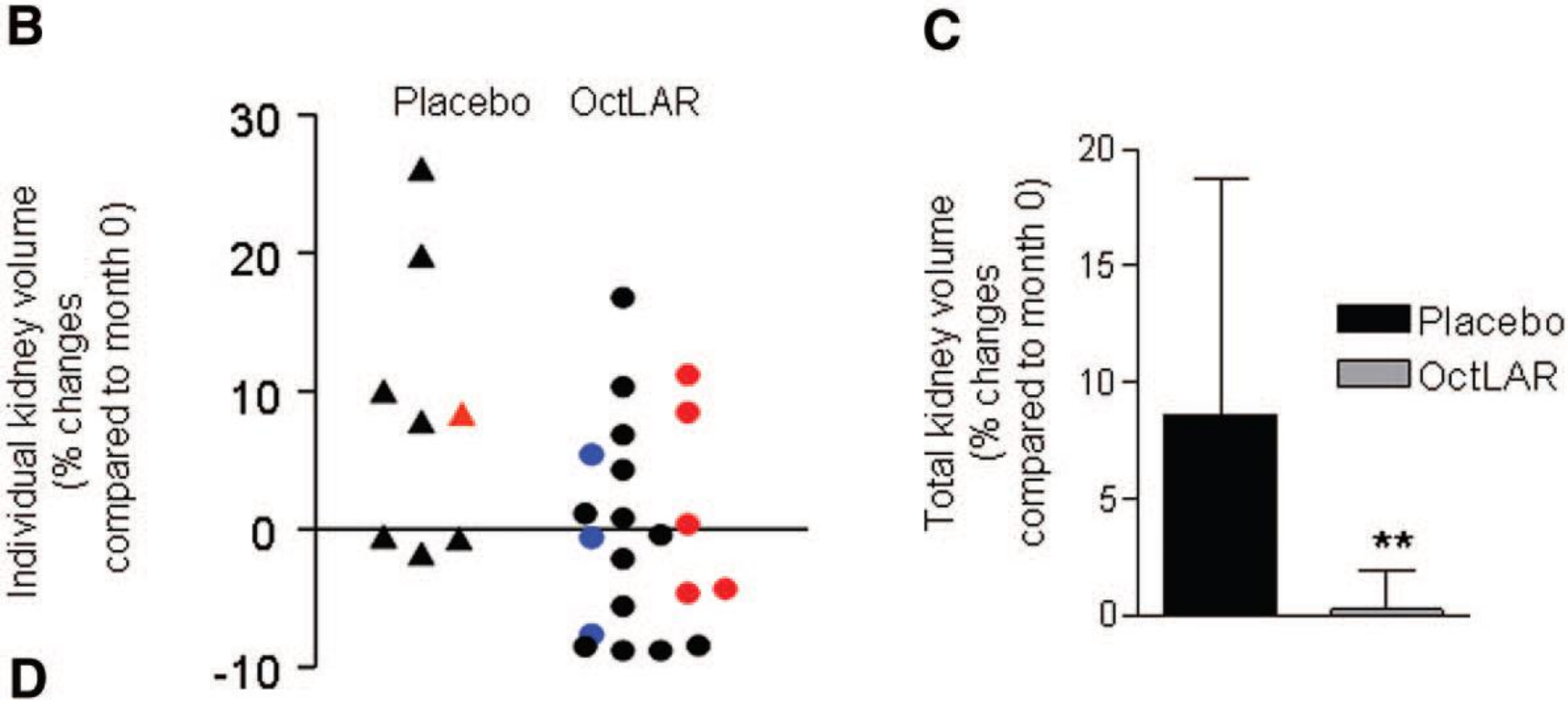
J Am Soc Nephrol 21: 1052–1061, 2010.

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



J Am Soc Nephrol 21: 1052–1061, 2010.

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



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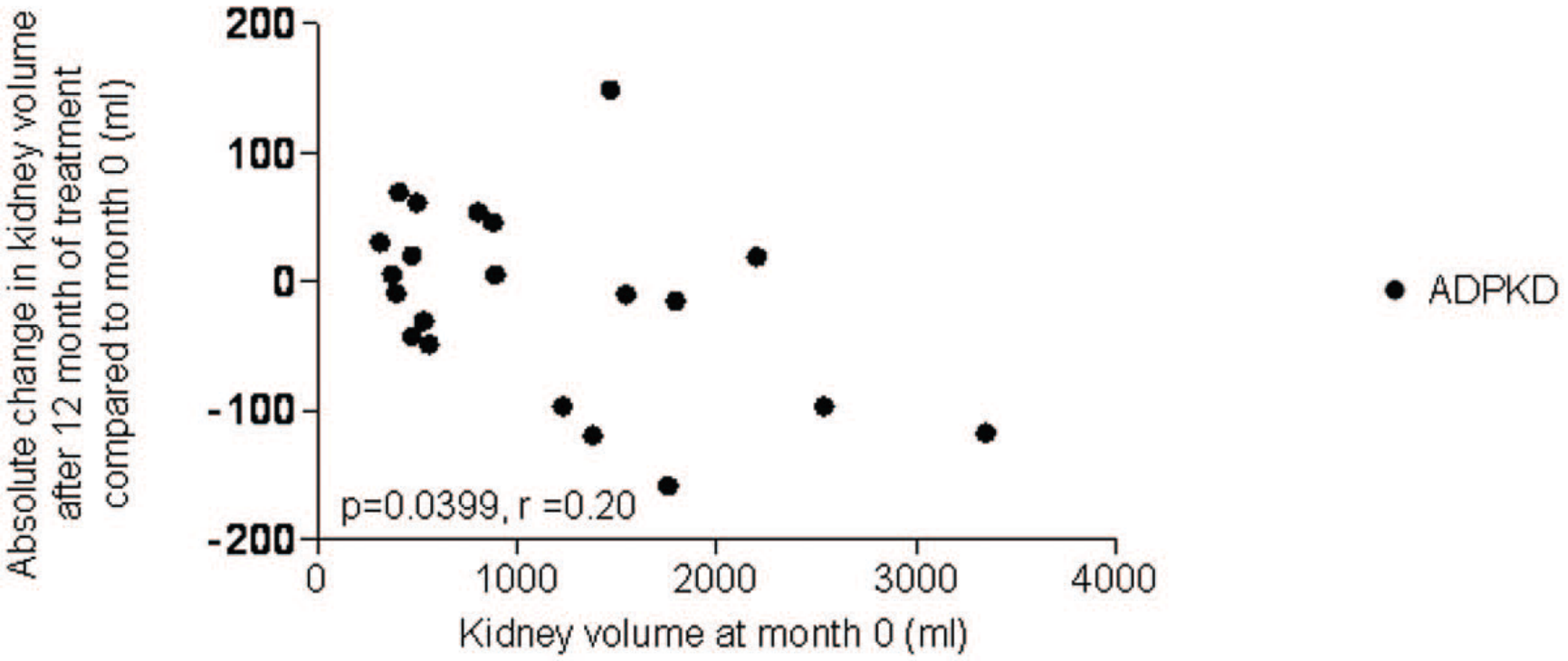
Randomized Clinical Trial of Long-Acting Somatostatin for Autosomal Dominant Polycystic Kidney and Liver Disease



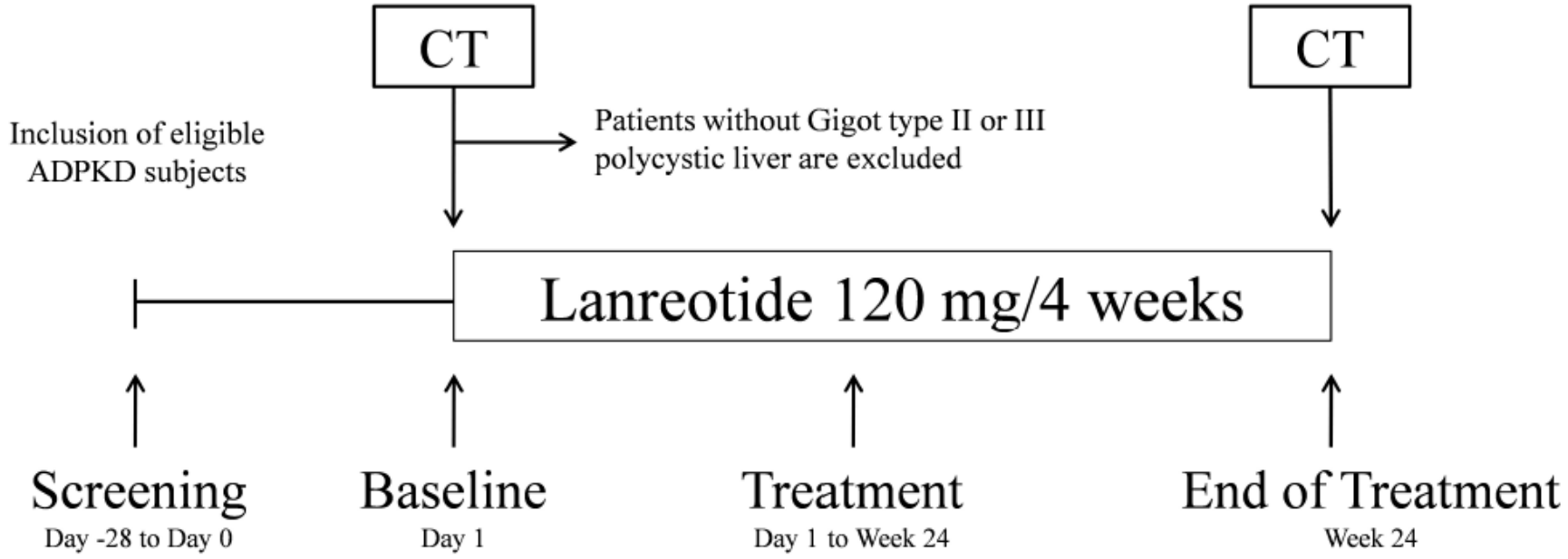
J Am Soc Nephrol 21: 1052–1061, 2010. doi: 10.1681/ASN.2009121291

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

Rationale and design of the RESOLVE trial: lanreotide as a volume reducing treatment for polycystic livers in patients with autosomal dominant polycystic kidney disease



BMC Nephrology 2012, 13:17 doi:10.1186/1471-2369-13-17

Interventional studies

mTOR inhibitors

Sirolimus

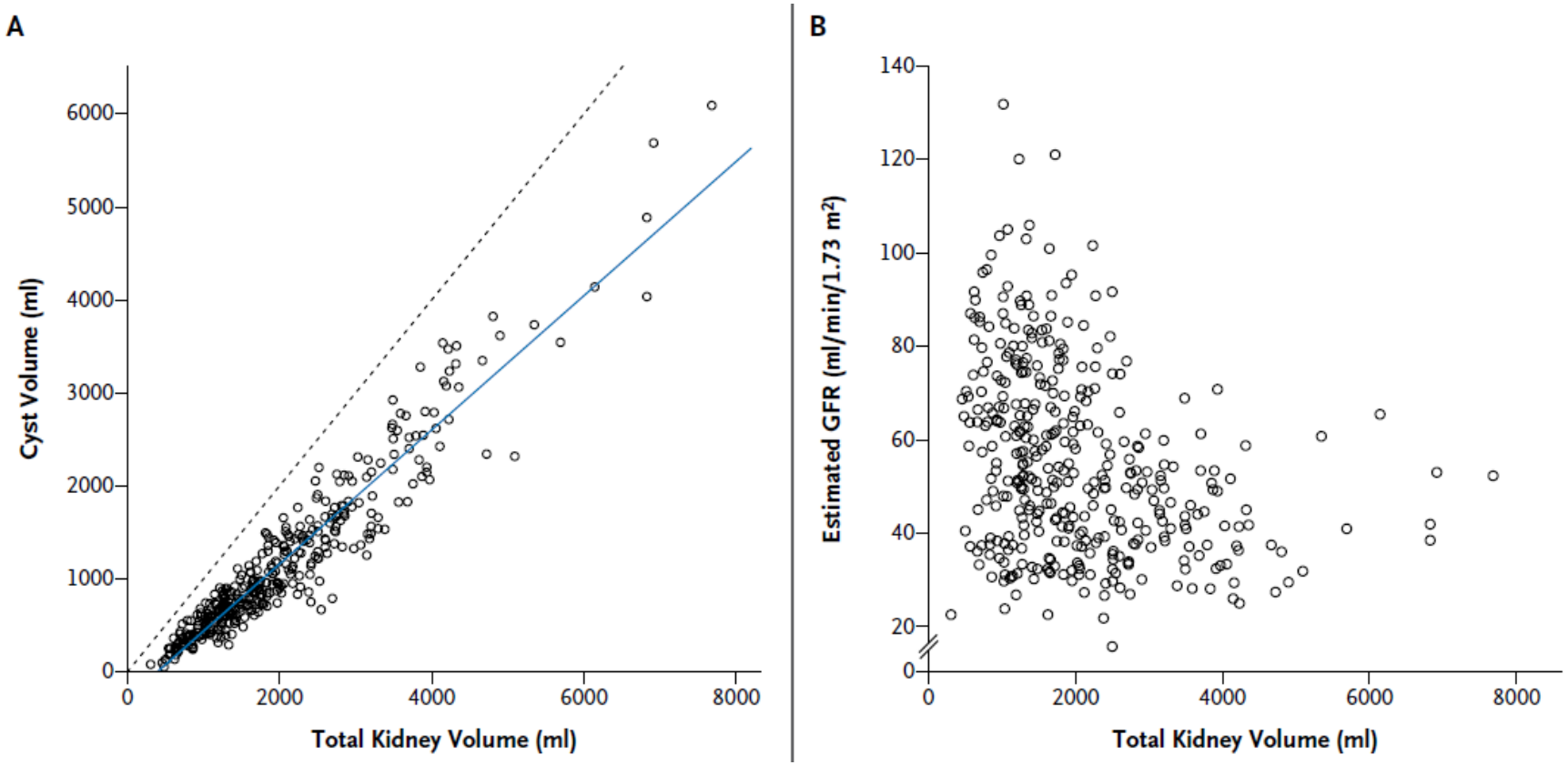
Everolimus

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 ***

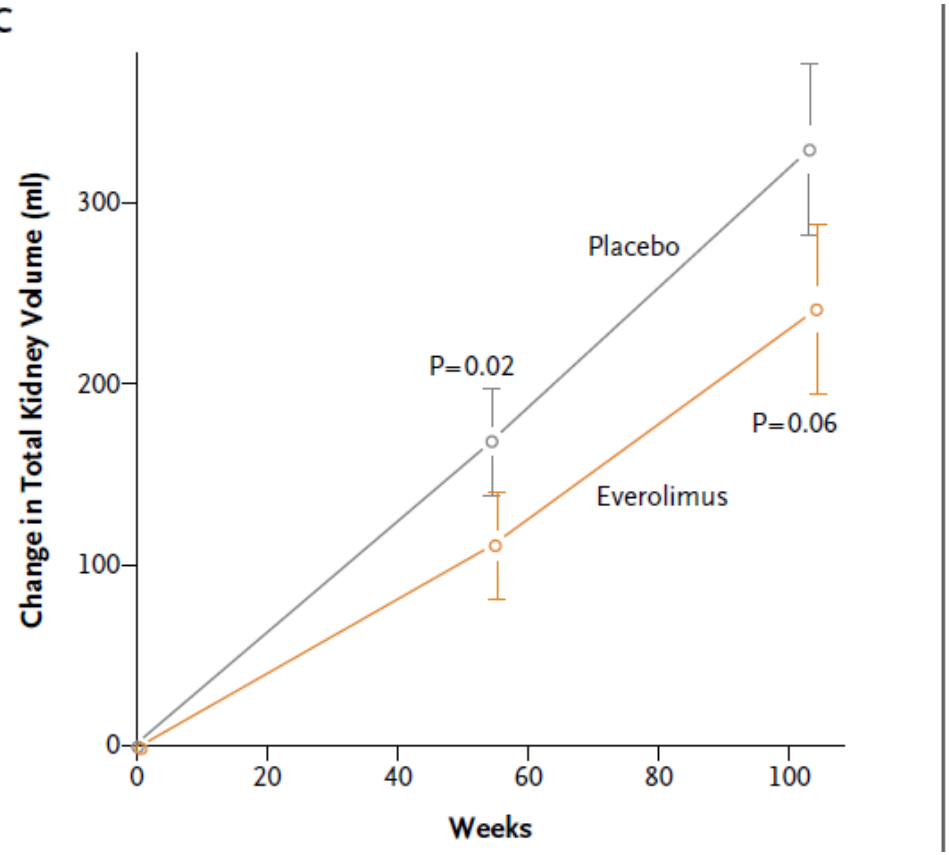
Current Opinion in Gastroenterology 2011, 27:294–300

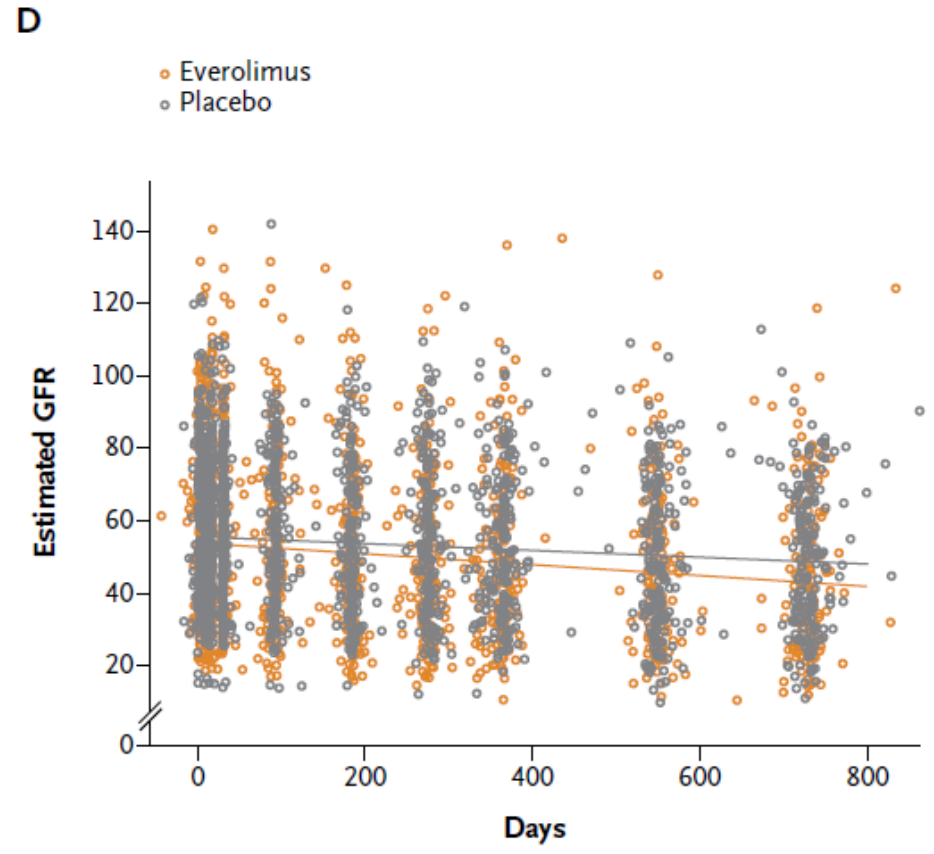
Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease



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

Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease





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

Serious Aderse Events in the Safety Population, According to Study Group*

Serious Adverse Event	Everolimus (N =214)	Placebo (N = 217)	P Value**
	no.of patients (%)		
Any	**80 (37.4)**	**51 (23.5)**	**0.002**
Death	**2 (0.9)**	**1 (0.5)**	**0.62**
Hematopoietic system			
Anemia	**37 (17.3)**	**11 (5.1)**	**<0.001**
Leukopenia	**38 (17.8)**	**6 (2.8)**	**<0.001**
Thrombocytopenia	**30 (14.0)**	**2 (0.9)**	**<0.001**
Gastrointestinal			
Stomatitis or oral ulcer	**91 (42.5)**	**13 (6.0)**	**<0.001**
Diarrhea	**51 (23.8)**	**35 (16.1)**	**0.05**
Gastritis	**11 (5.1)**	**4 (1.8)**	**0.07**
Nausea	**20 (9.3)**	**12 (5.5)**	**0.15**
Vomiting	**12 (5.6)**	**14 (6.5)**	**0.84**

Serious Aderse Events in the Safety Population, According to Study Group*

Serious Adverse Event	Everolimus (N =214) no.of patients (%)	Placebo (N = 217)	P Value**
Infection	**156 (72.9)**	**140 (64.5)**	**0.06**
Nasopharyngitis	**83 (38.8)**	**83 (38.2)**	**0.92**
Bronchitis	**22 (10.3)**	**23 (10.6)**	**1.0**
Sinusitis	**15 (7.0)**	**13 (6.0)**	**0.70**
Pneumonia	**7 (3.3)**	**2 (0.9)**	**0.10**
Folliculitis	**8 (3.7)**	**0**	**0.004**
Herpes zoster	**7 (3.3)**	**3 (1.4)**	**0.22**
Tuberculosison lymph-node examination	**1 (0.5)**	**0**	**0.497**
Urinary tract infection	**31 (14.5)**	**25 (11.5)**	**0.39**

Serious Aderse Events in the Safety Population, According to Study Group*

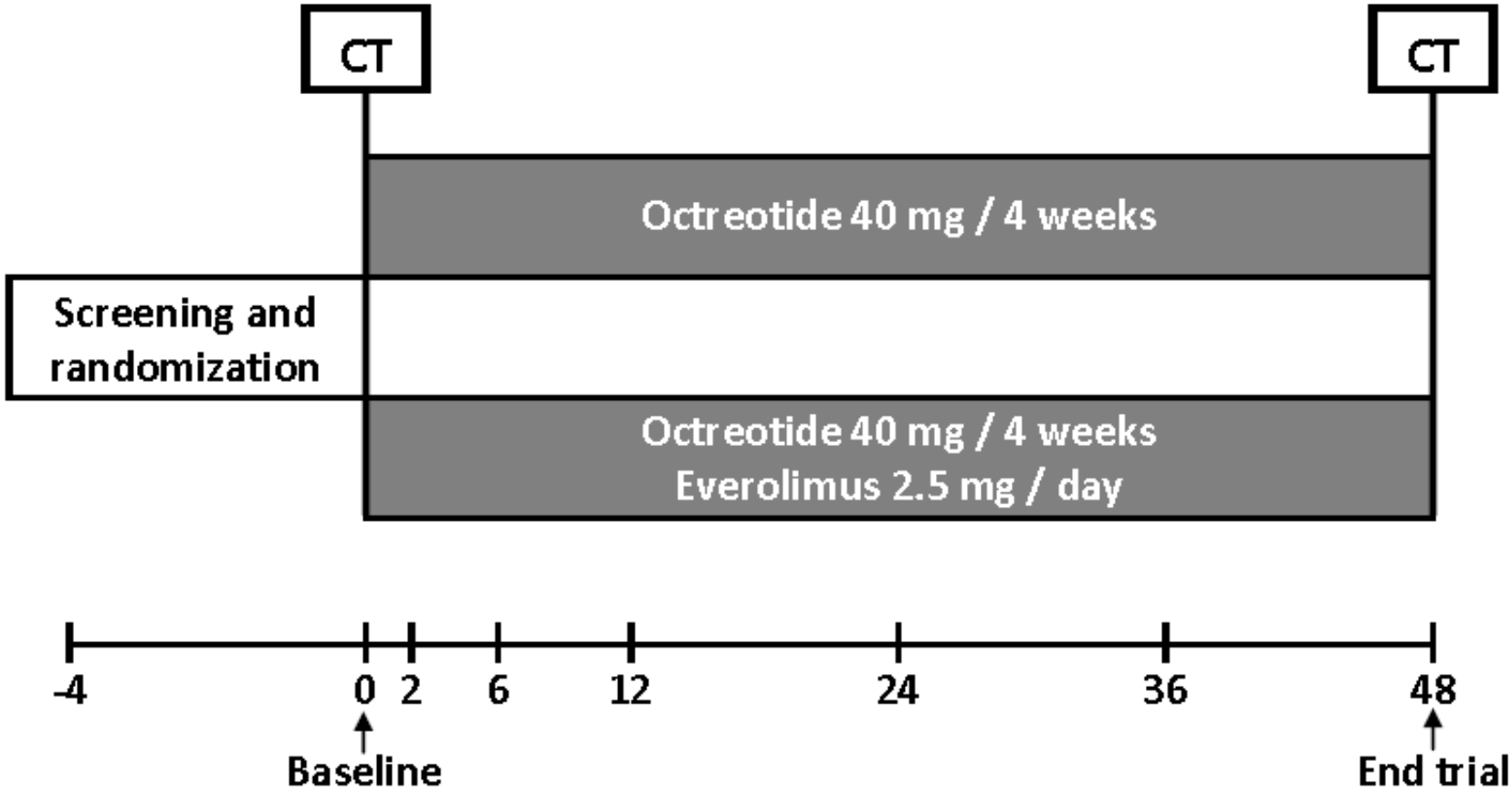
Serious Adverse Event	Everolimus (N =214)	Placebo (N = 217)	P Value**
	no.of patients (%)		
Metabolism			
Hyperlipidemia	**28 (13.1)**	**5 (2.3)**	**<0.001**
Hypercholesterolemia	**46 (21.5)**	**8 (3.7)**	**<0.001**
Hypertrigliceridemia	**15 (7.0)**	**8 (3.7)**	**0.14**
New-onset diabetes	**7 (3.3)**	**2 (0.9)**	**0.10**
Skin			
Acne	**30 (14.0)**	**6 (2.8)**	**<0.001**
Angioedema	**12 (5.6)**	**0**	**<0.001**

Serious Adverse Event	Everolimus (N =214)	Placebo (N = 217)	P Value**
	no. of patients (%)		
Other			
Arthralgia	14 (6,5)	5 (2.3)	0.04
Myalgia	17 (7.9)	4 (1.8)	0.003
Myositis	1 (0.5)	0	0.497
Ovarian cyst	12 (5.6)	0	<0.001
Pneumonitis	2 (0.9)	0	0.25
Epistaxis	10 (4.7)	2 (0.9)	0.02
Neoplasm			
Benign	6 (2.8)	5 (2.3)	0.77
Malignant	3 (1.4)	4 (1.8)	1.00
Flank or abdominal pain	53 (24.8)	50 (23.0)	0.74
Peripheral edema	44 (20.6)	20 (9.2)	0.001
Weight			
Decreased	14 (6.5)	3 (1.4)	0.006
Increased	3 (1.4)	7 (3.2)	0.34

*The safety population consisted of all patients who received at least one dose of the study medication

** P values were calculated with the use of Fisher's exact test.

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

Potential therapeutic modalities

- Lonidamine:
  - inhibits the cystic fibrosis transmembrane conductance regulator (CFTR) cchannel activity
- Curcumin
  - C. analog 2a inhibits proliferative pathways activated in cancer – smaller doses
- Src inhibiton

- Metformin
  - Inhibits both CFTR and mTOR pathways by activating AMP-activated protein kinase

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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