Nephro Update Europe 2017

6-7 October, Vienna

Genetic Diseases

Olivier Devuyst, Switzerland

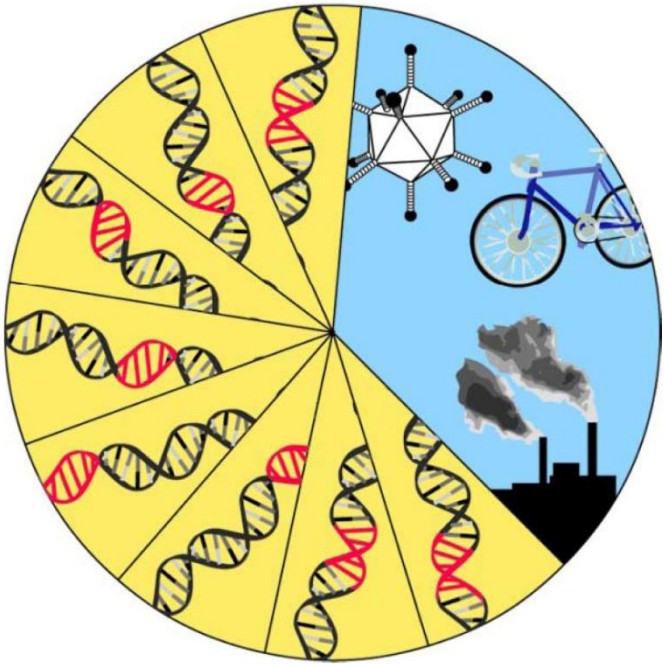
Are we born to get kidney disease ?

- Familial clustering and differing prevalence rates across ethnic groups
- Heritability of renal function (mGFR or eGFR): 50-60%
- Heritability of blood pressure: 40-50%
- Inbred strain effects in mouse & rat models

Robust genetic influence on renal function and risk of CKD or hypertension

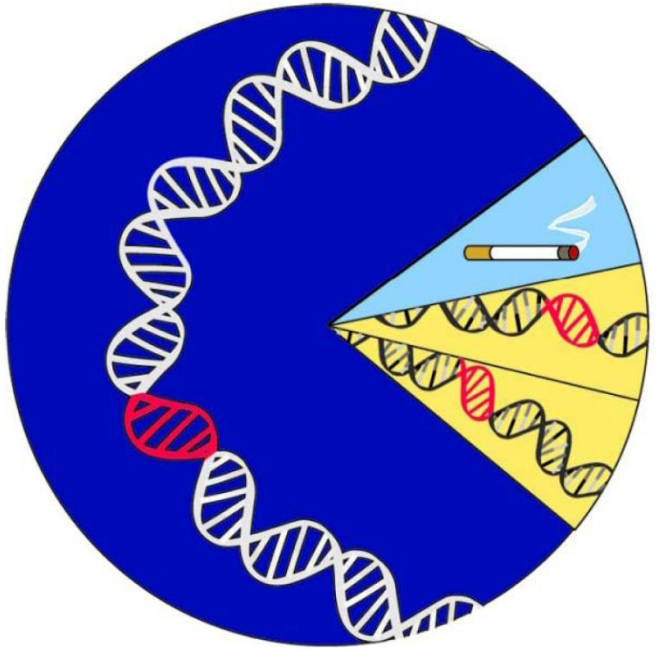
Genetic Influence on Disease

Complex disease



- Multiple variants - small effects

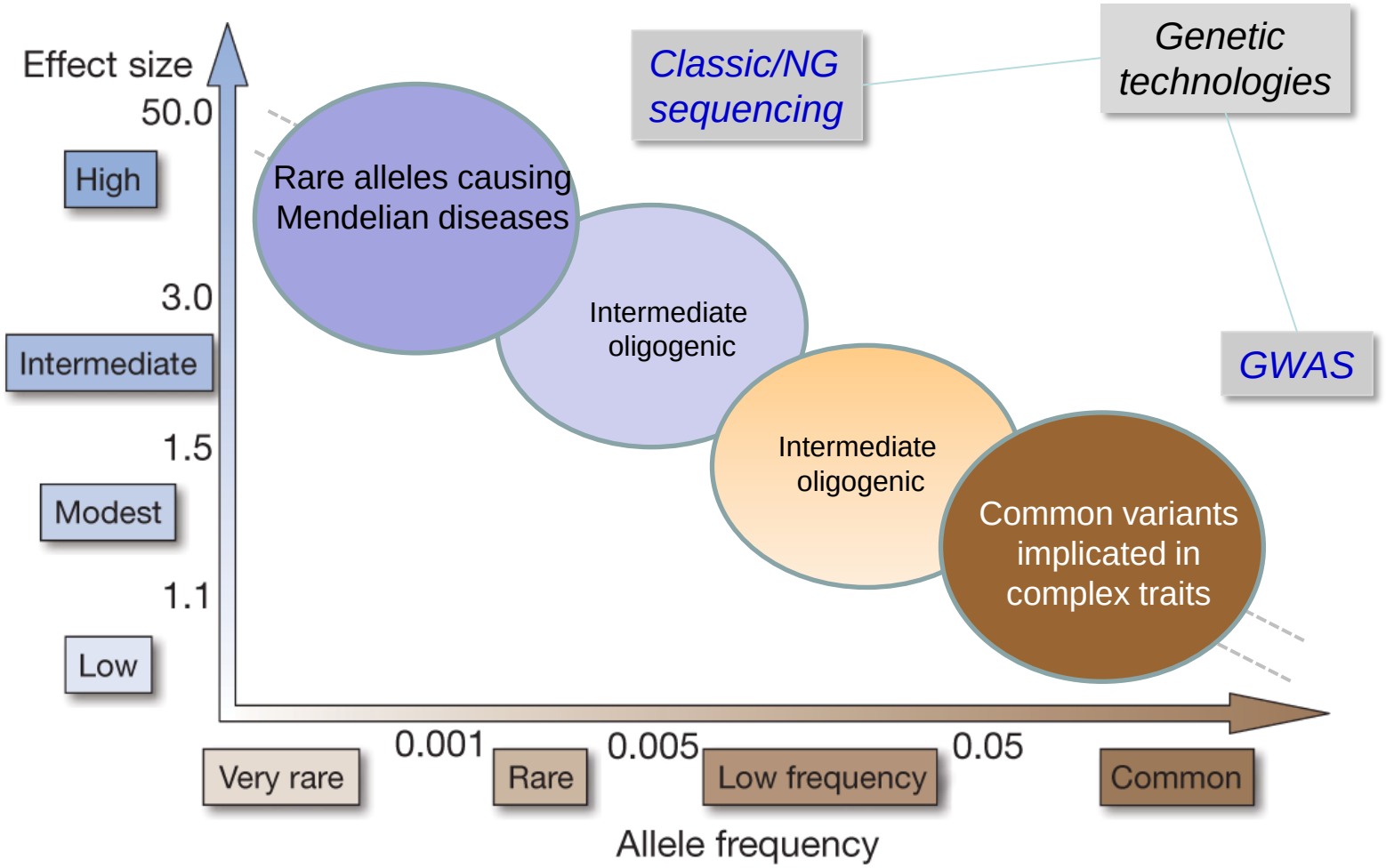
Monogenic disease



- Variant in a single gene – major effect

Manolio et al. J Clin Invest. 2008 May;118(5):1590-605.

Genomic Variation in the Spectrum of Disease

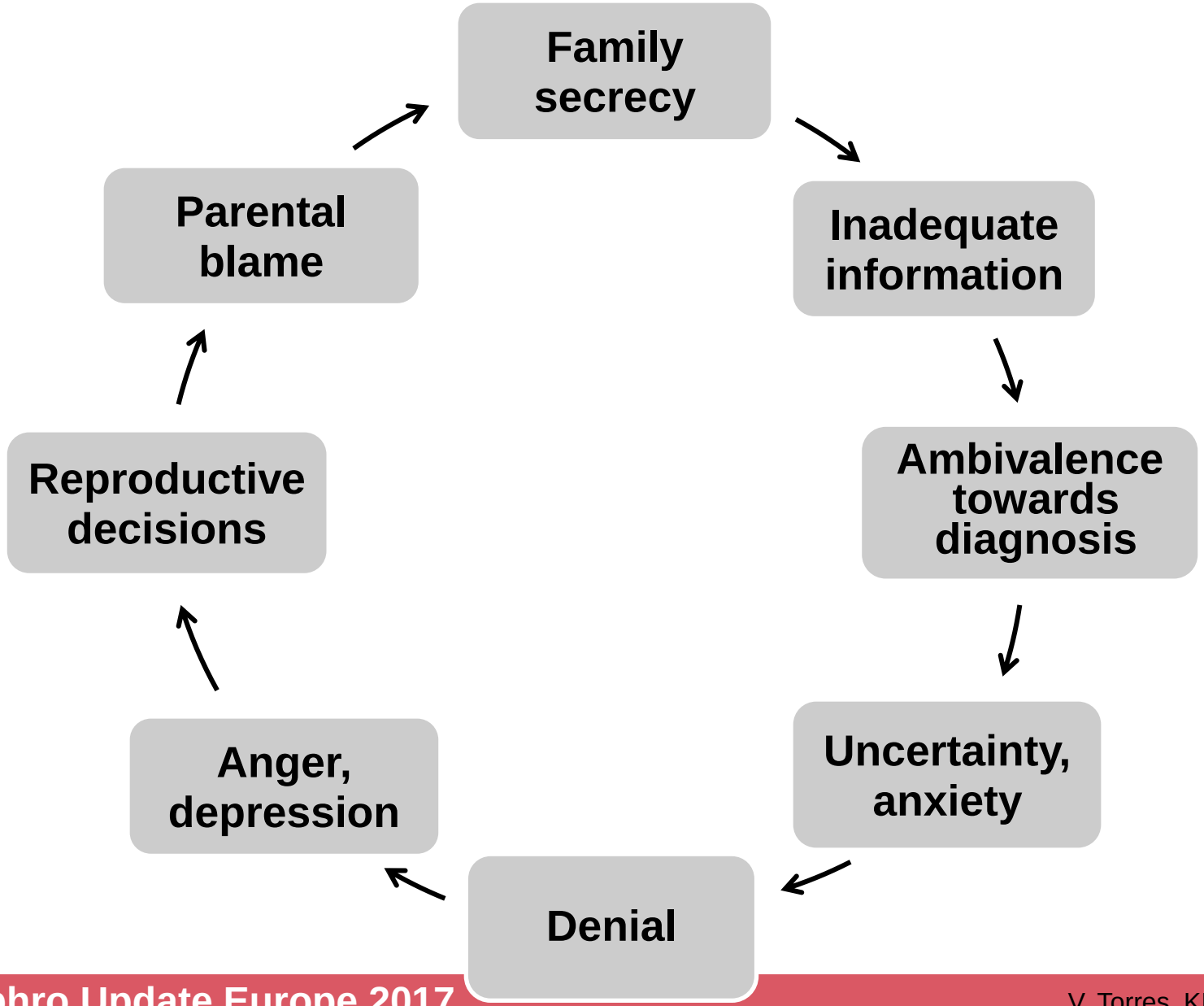


Manolio et al. Nature. 2009 Oct 8;461(7265):747-53.

Inherited (Rare) Kidney Diseases: Major Burden

- Severe, chronic, often degenerative or life-threatening
- Onset: 50% in childhood
- Disabling: quality of life compromised – loss of autonomy
- Psychological burden: patients, families, lack of hope, lack of support
- Incurable diseases, without effective treatment (sometimes symptomatic R/)
- Difficult to diagnose and manage; heterogeneity in terms of care

Emotional Burden of an Inherited Disease



Spectrum of (Rare) Inherited Kidney Disorders

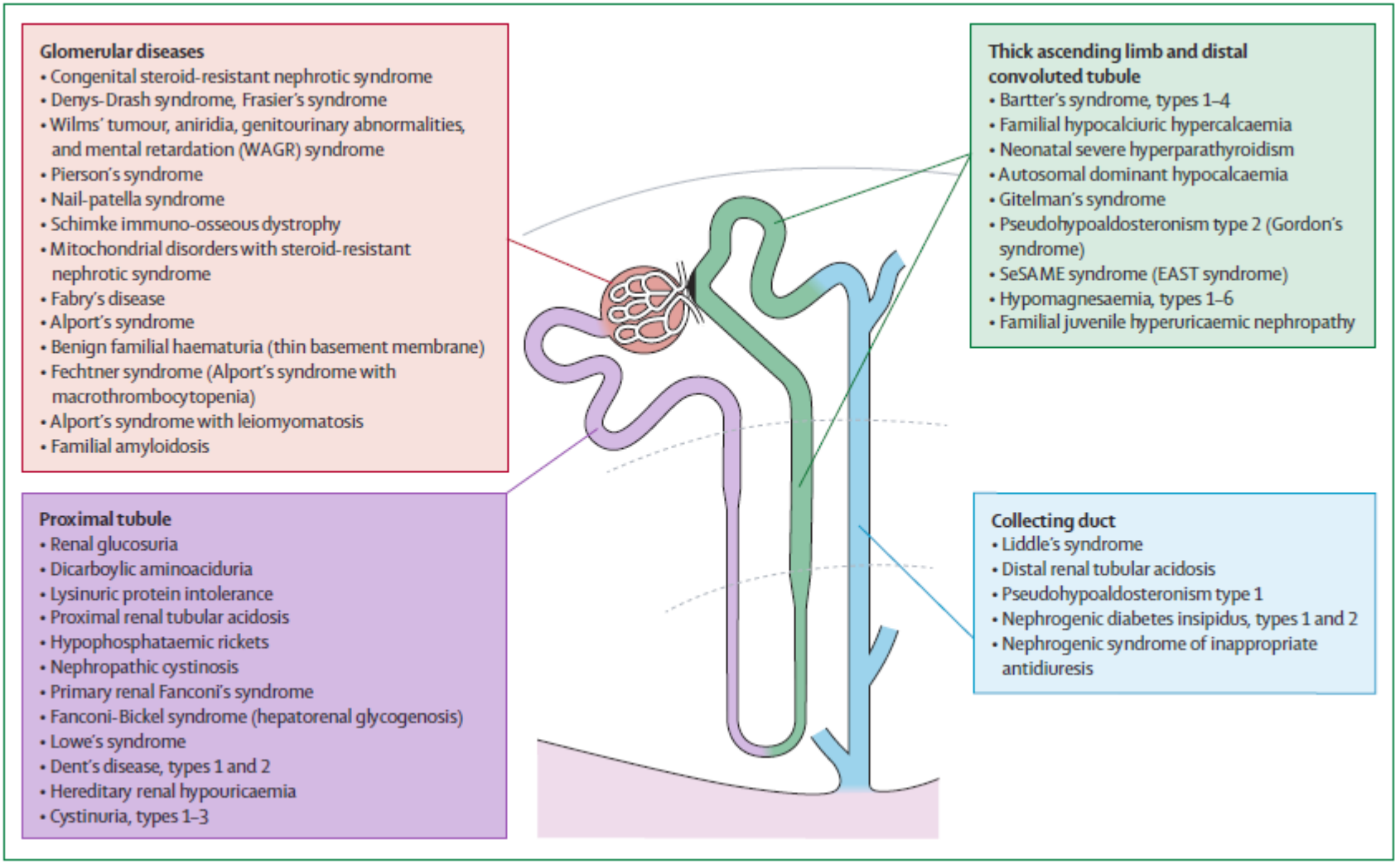
Rare Kidney Diseases

- Rare kidney diseases: > 200 disorders
- Overall prevalence: ~60-80 cases per 100,000
- At least 10% adults and virtually all children on RRT
- Fifth most common cause of ESRD (Diab > HT > GN > PyeloN)

- Patients with inherited kidney disorders rarely die (progresses in RRT)
- However: poor health, poor quality of life, multisystemic complications

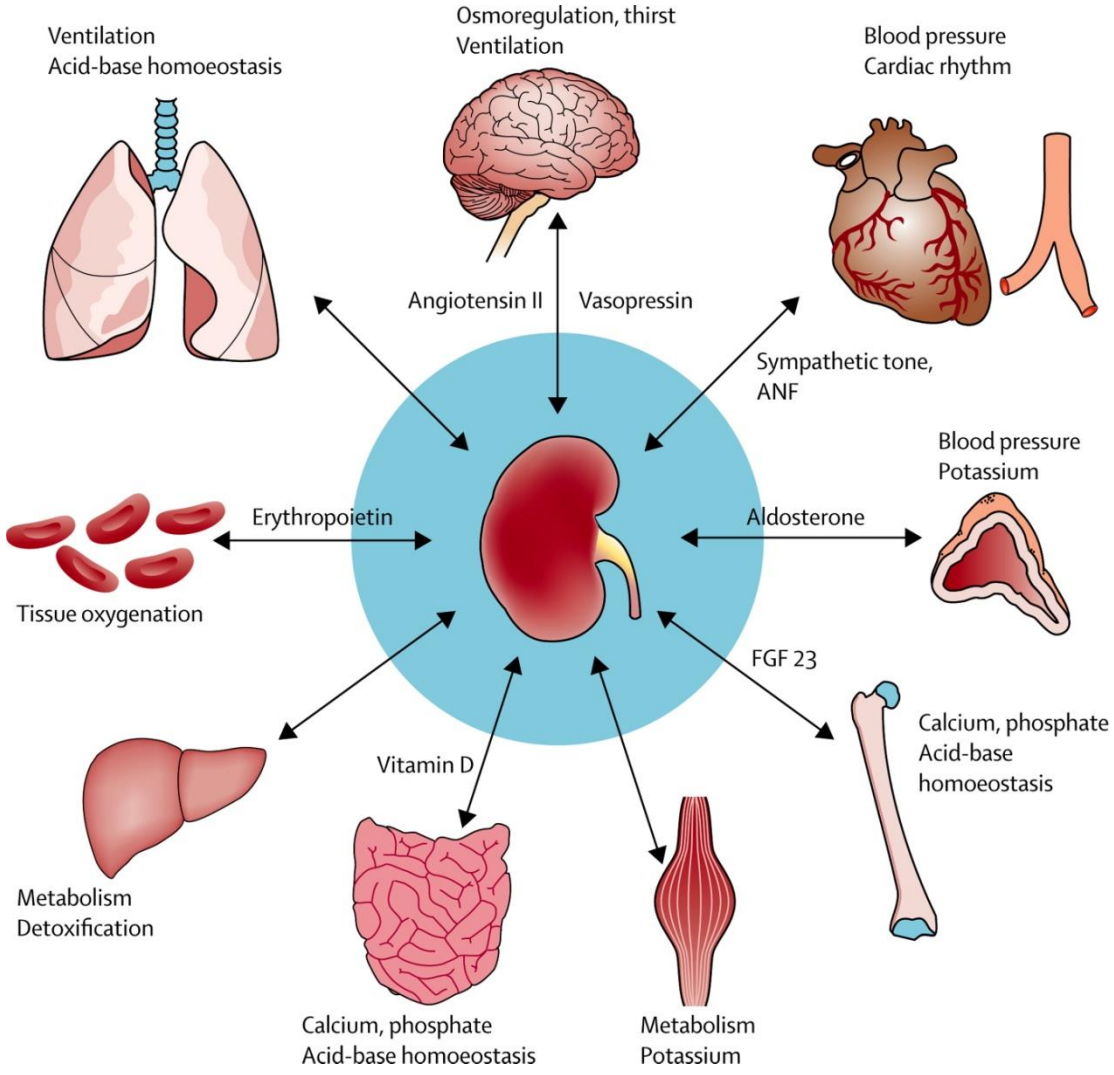
→ *children with severe congenital nephropathies can be dialysed from neonatal age onwards, but face many decades of life with ESRD and have a high likelihood of changes in physical, cognitive, and psychosocial development.*

Inherited Kidney Disorders: Segmental Distribution



Devuyst O et al. Lancet. 2014 May 24;383(9931):1844-59.

Kidney Function and Homeostasis



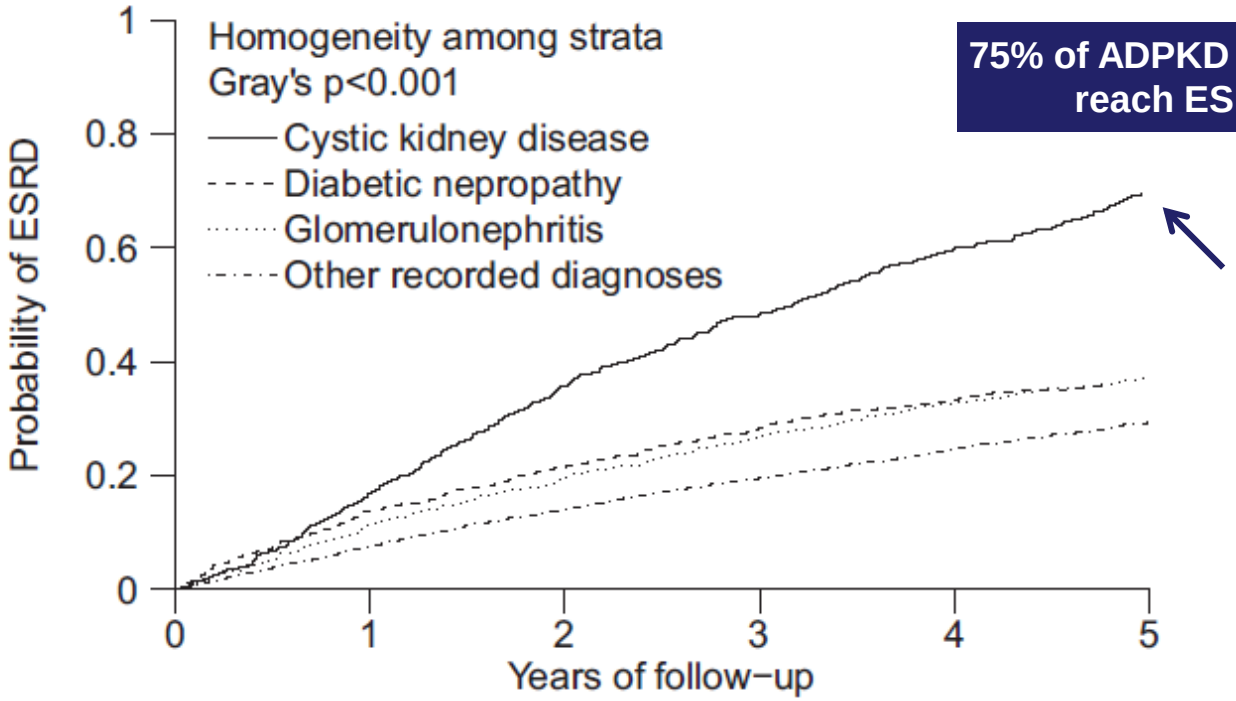
Eckardt KU et al Lancet. 2013 Jul 13;382(9887):158-69.

ADPKD

Autosomal Dominant Polycystic Kidney Disease

- Most frequent inherited nephropathy (1:400 - 1:1,000)
- Enlarged kidneys, multiple cysts < tubules
- Responsable for 4 - 10% of patients on dialysis - RRT

Evaluating the Contribution of the Cause of Kidney Disease to Prognosis in CKD: Results From the Study of Heart and Renal Protection (SHARP)



75% of ADPKD patients reach ESRD

Cumulative incidence curves for ESRD by cause of kidney disease. These cumulative incidence curves account for the competing risk of death.

Haynes et al. Am J Kidney Dis. 2014 Jul;64(1):40-8.

Autosomal Dominant Polycystic Kidney Disease : Time-points

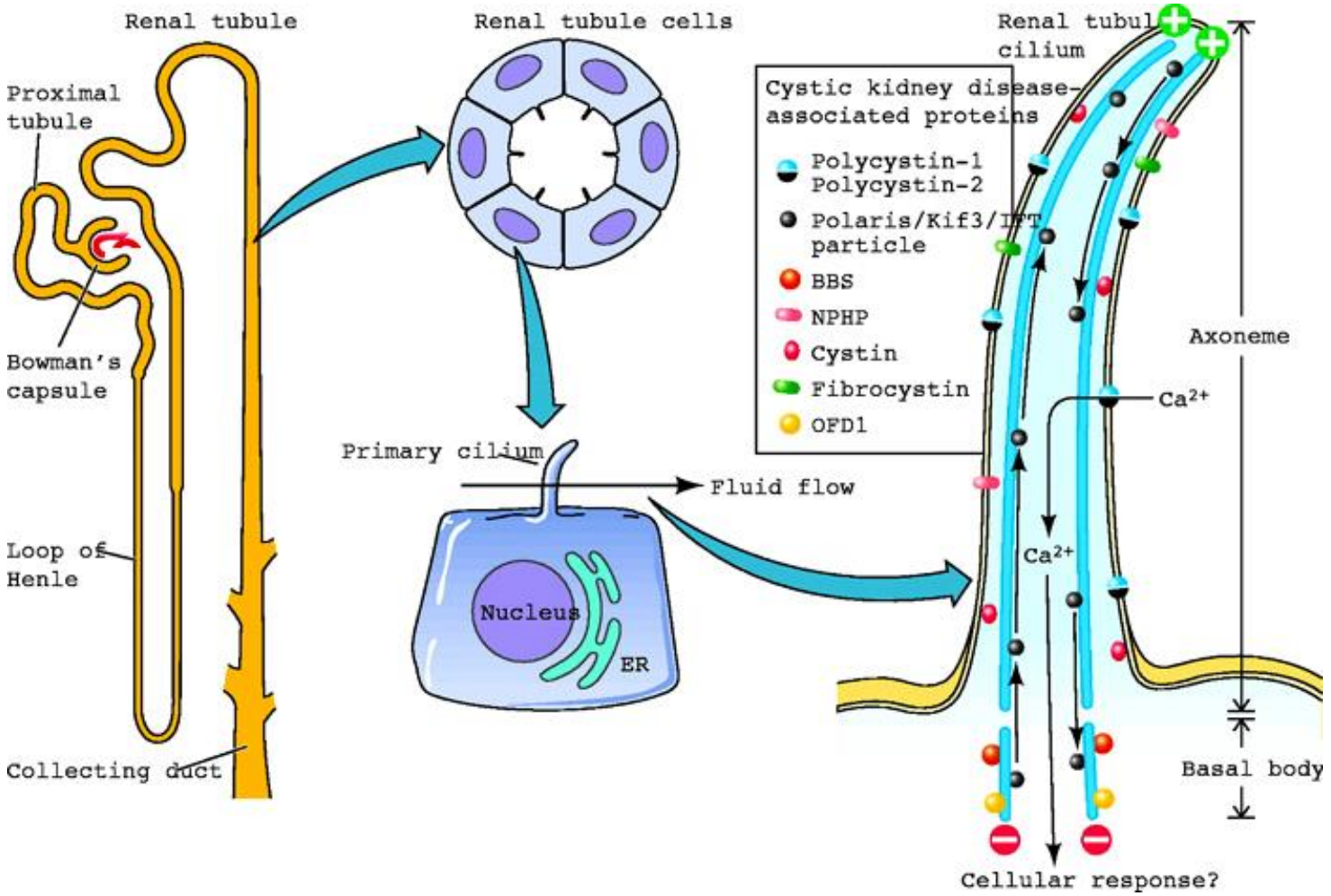
1985 : Localization of *PKD1* on Chr. 16

1995 : Identification of the *PKD1* gene

2006 : First targeted clinical trial

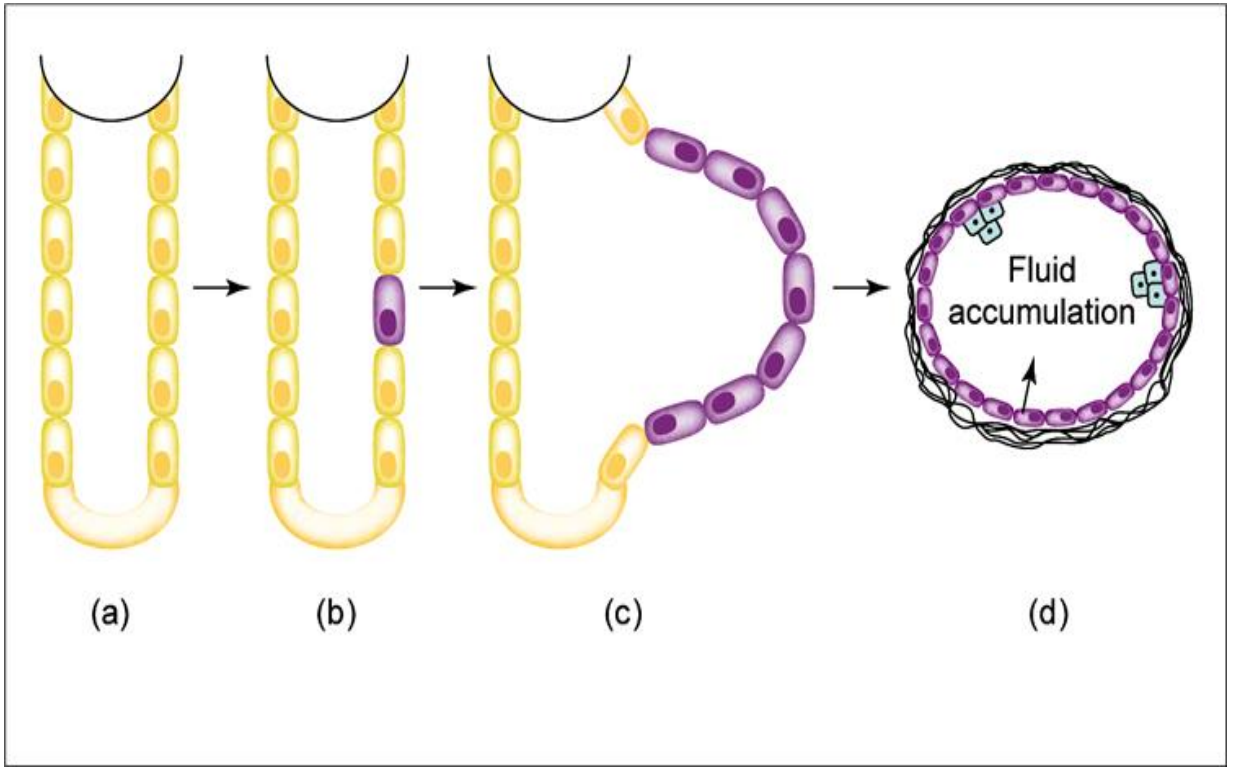
2012 : TEMPO trial results

ADPKD: Primary Cilium Disease



Zhang et al. Physiology 2004;19: 225-30

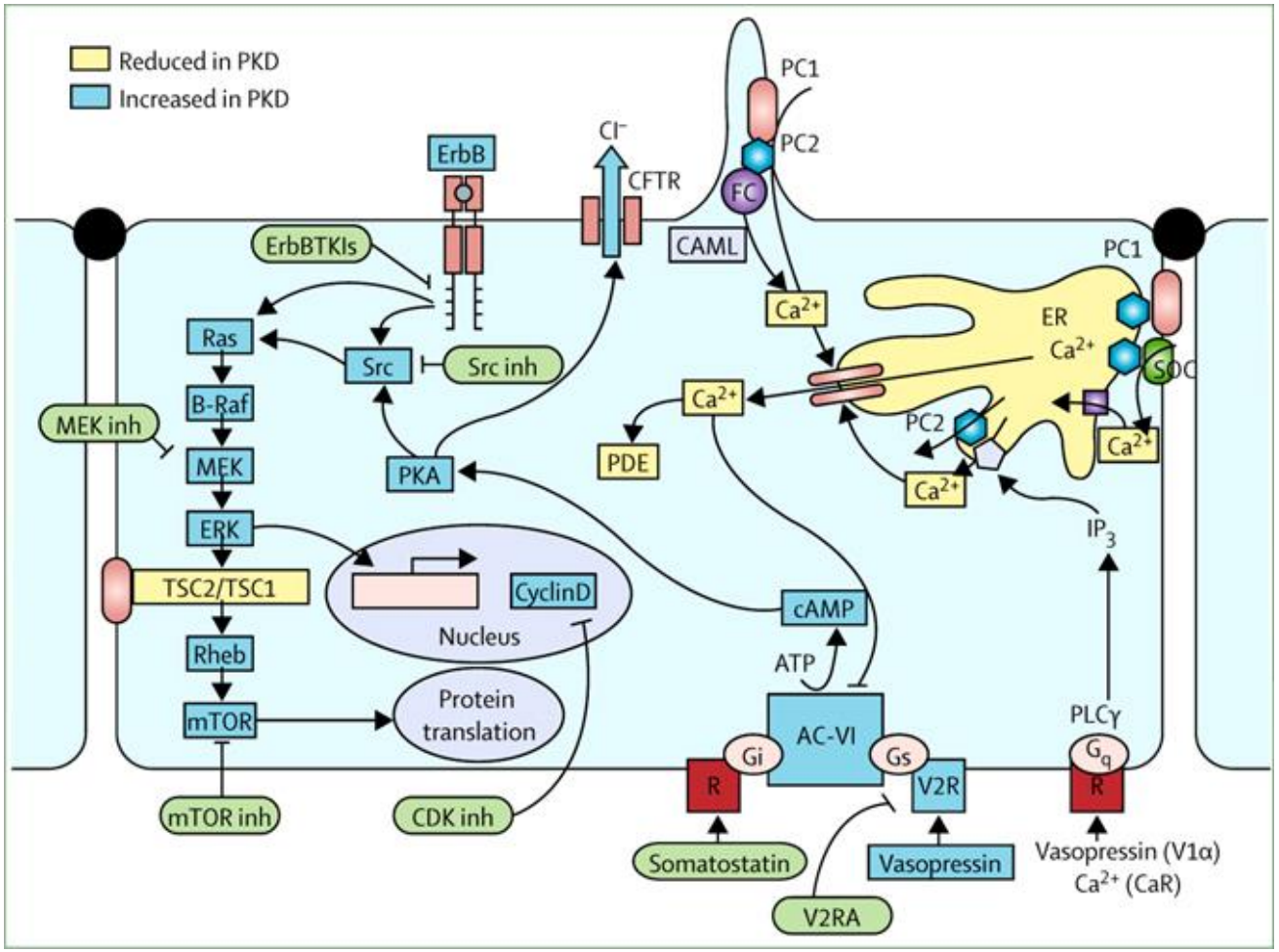
Mechanism of Cyst Formation in ADPKD



Proliferation – Dedifferentiation - Fluid secretion

Pei Y Trends Mol Med. 2001 Apr;7(4):151-6., Torres VE et al. Lancet. 2007 Apr 14;369(9569):1287-301.

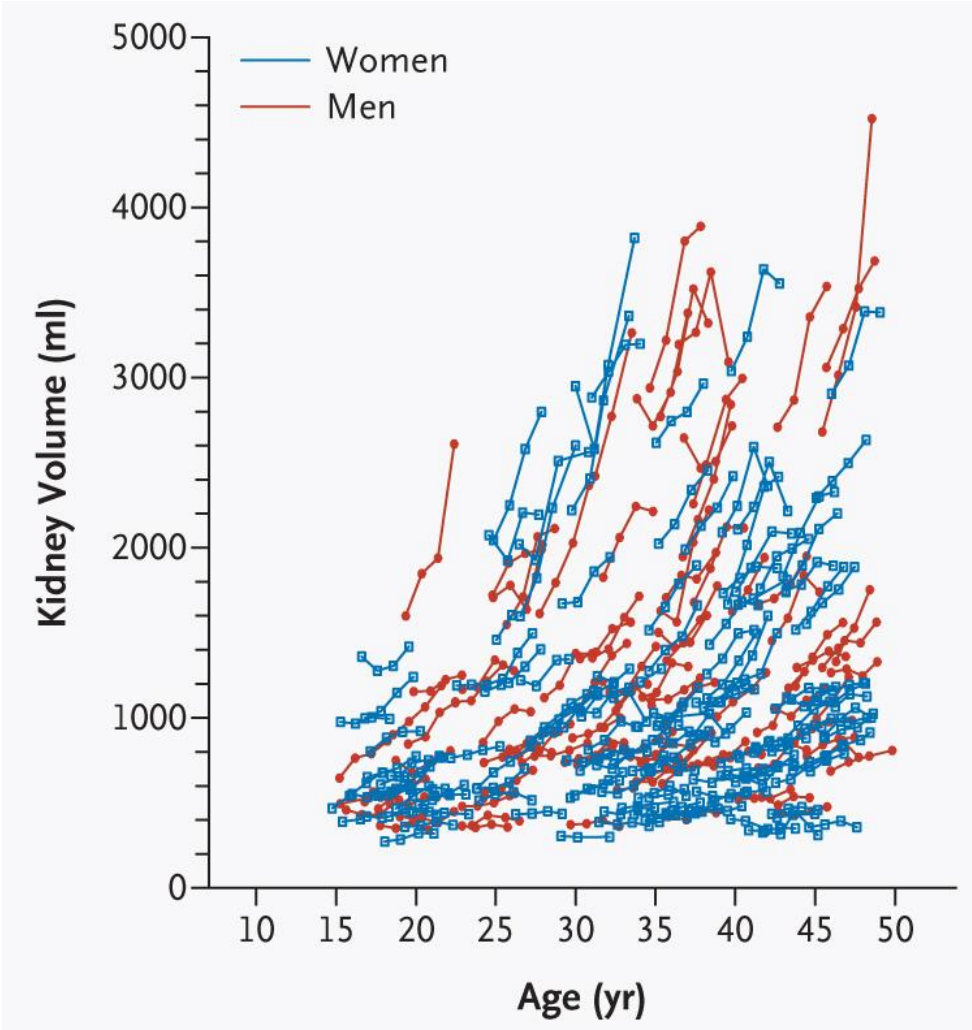
Mechanism of Cyst Formation in ADPKD



Proliferation – Dedifferentiation - Fluid secretion

Torres VE et al. Lancet. 2007 Apr 14;369(9569):1287-301.

Exponential Progression of Cysts in ADPKD: CRISP



Grantham et al, N Engl J Med. 2006 May 18;354(20):2122-30.

Autosomal Dominant Polycystic Kidney Disease

- Hypertension: early – almost always
- Bleeding: 50 % of cases
- Kidney stone: 20 % of cases
- Cyst infection: 10 % of cases
- Renal failure: 75% of cases

Treatment of ADPKD for last 20 Years

Multiple, small advances:

- Treatment of hypertension (e.g. ACEI/sartans)
- Antibiotics (e.g. fluoroquinolones)
- Endovascular treatment of intracranial aneurysms
- Surgery (cystic liver)
- Improved imaging techniques/volumetry (MRI)

….

Until recently, no treatment affecting renal cyst progression

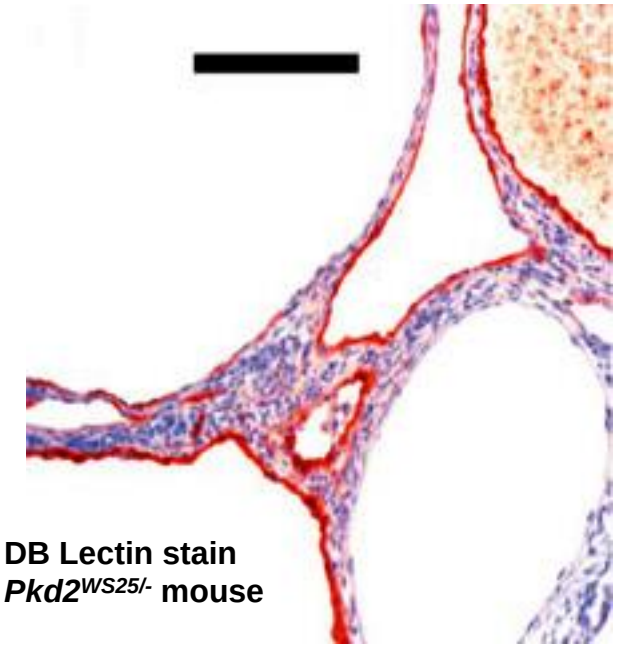
Targeting the vasopressin pathway in ADPKD?

cAMP at The Hub of Cystic Cycle

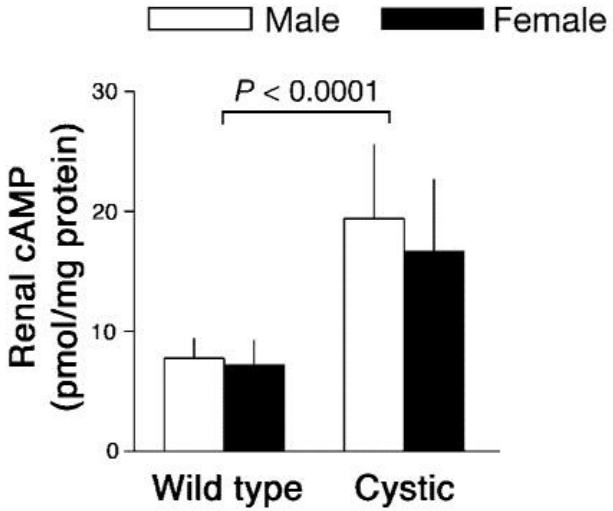
- Three rodent models with polycystic kidneys :
  - ARPKD (*PCK* rat)
  - Nephronophtisis (*pcy* mouse)
  - ADPKD (type 2) (*Pkd2WS25/-* mouse)

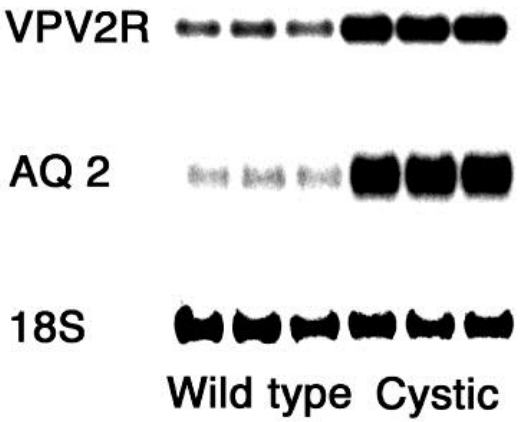
- Cysts predominantly from Collecting Duct

- Increased cAMP, AQP2 and V2R



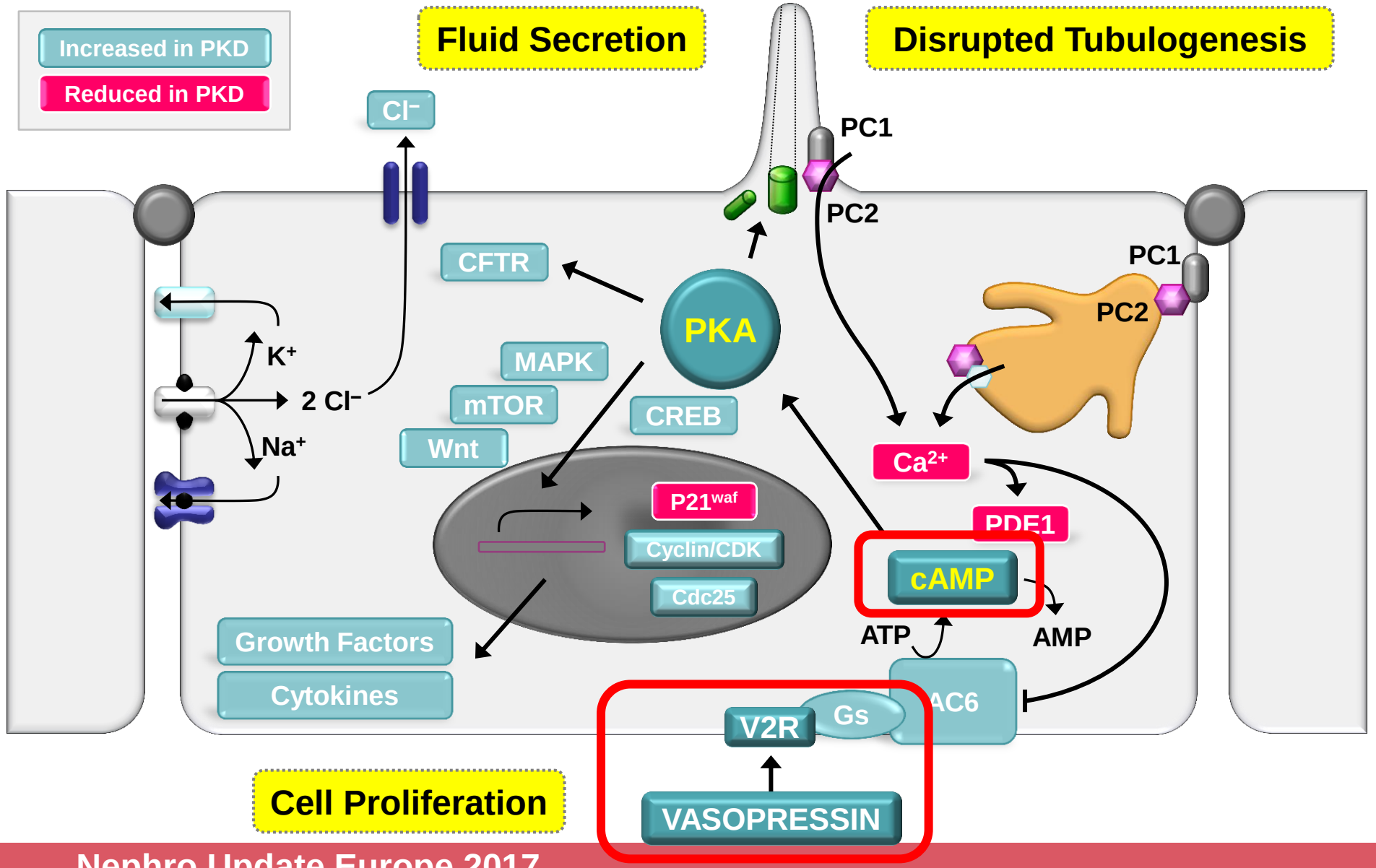
DB Lectin stain
***Pkd2*$^{WS25/-}$ mouse**





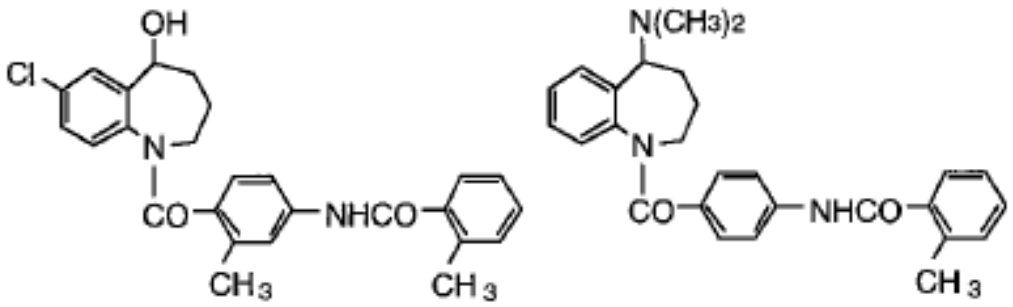
Torres V et al. Nat Med 2004;10:363-364

Rationale for V2R Antagonism in ADPKD



OPC-41061, a Highly Potent Human Vasopressin V_2-Receptor Antagonist: Pharmacological Profile and Aquaretic Effect by Single and Multiple Oral Dosing in Rats[1]

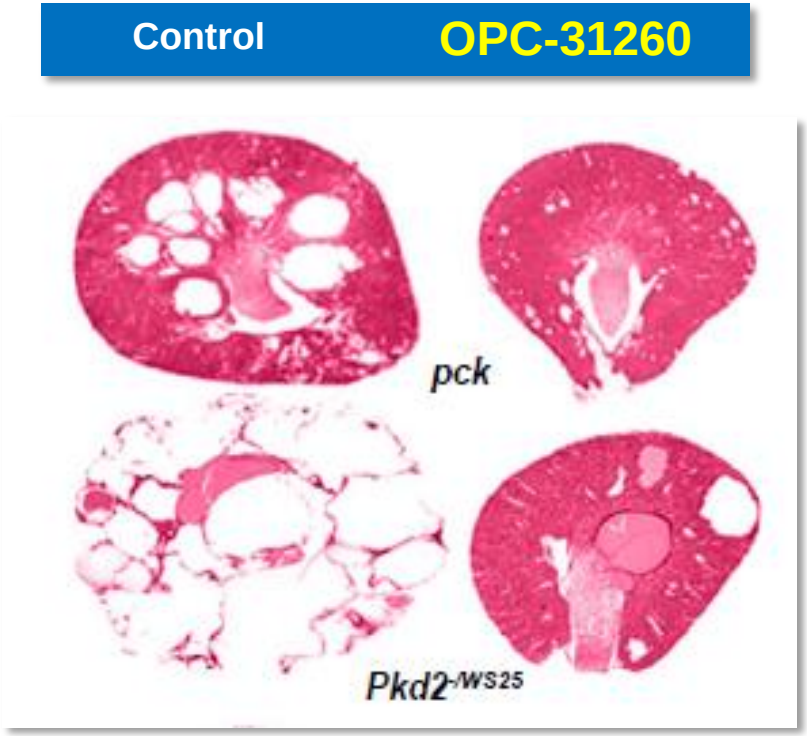
YOSHITAKA YAMAMURA, SHIGEKI NAKAMURA, SHUJI ITOH, TAKAHIRO HIRANO, TOSHIYUKI ONOGAWA, TATSUYA YAMASHITA, YOSHIHISA YAMADA, KENJI TSUJIMAE, MASASHI AOYAMA, KOUNORI KOTOSAI, HIDENORI OGAWA, HIROSHI YAMASHITA, KAZUMI KONDO, MICHIAKI TOMINAGA, GOZOH TSUJIMOTO and TOYOKI MORI

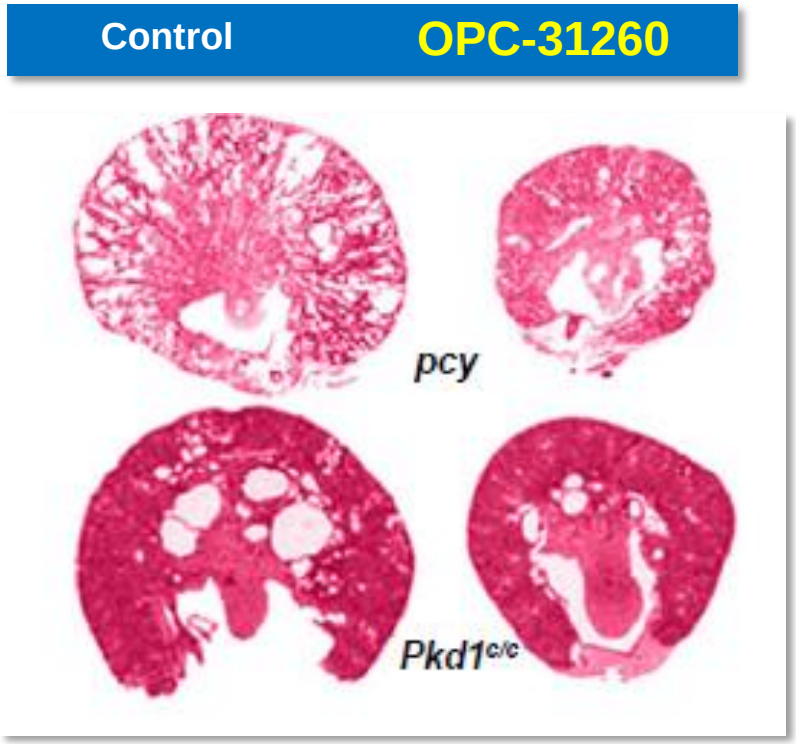


OPC-41061 **OPC-31260**

Yamamura et al, JPET 1998;287:860-867

Effect of V2R Antagonist in Animal Models of PKD





Gattone et al, Nat Med. 2003 Oct;9(10):1323-6.

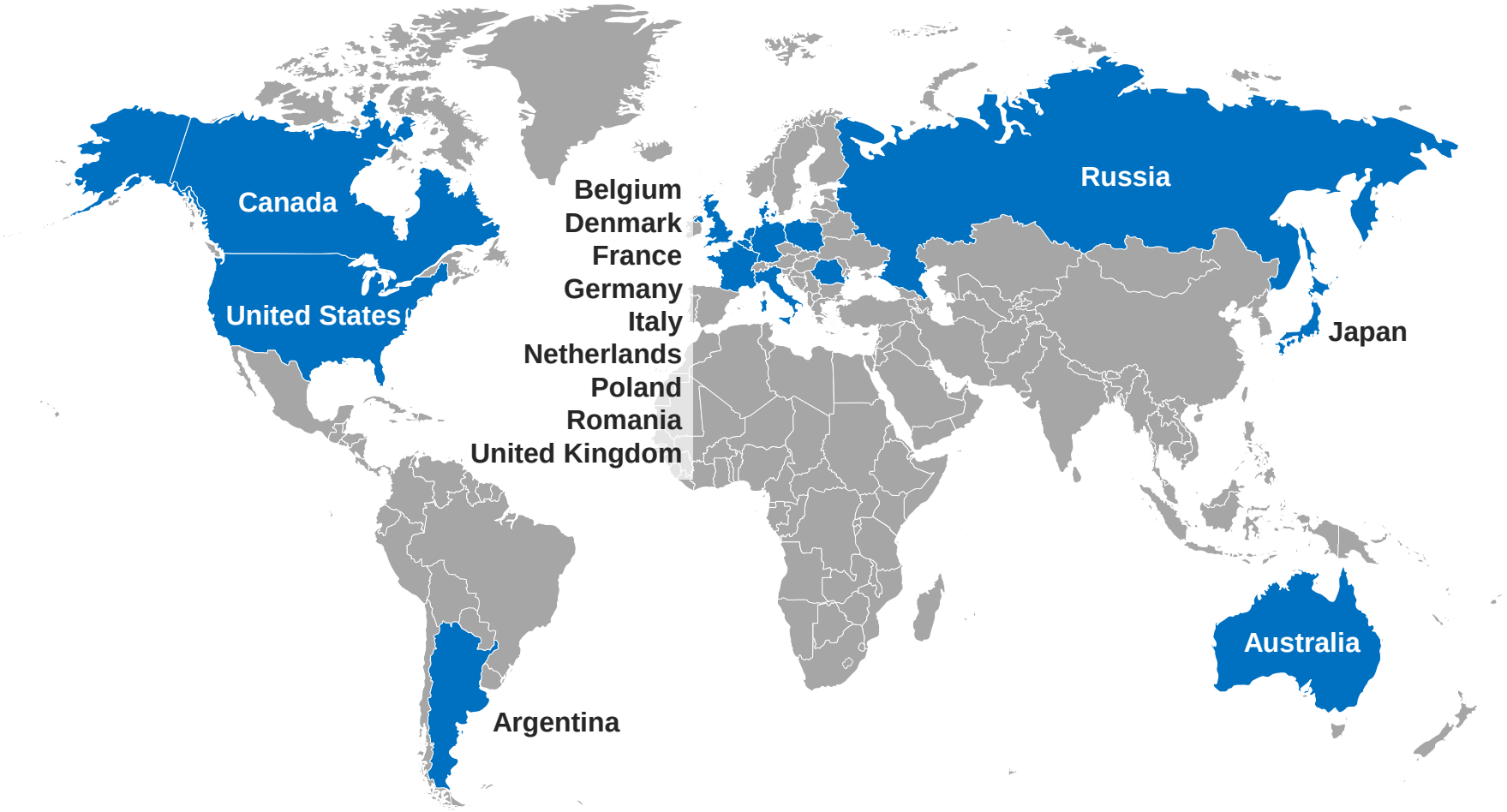
Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D.,
Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D.,
Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D.,
Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D.,
for the TEMPO 3:4 Trial Investigators*

Torres et al, N Engl J Med. 2012; 367: 2407-18

The TEMPO 3:4 Trial

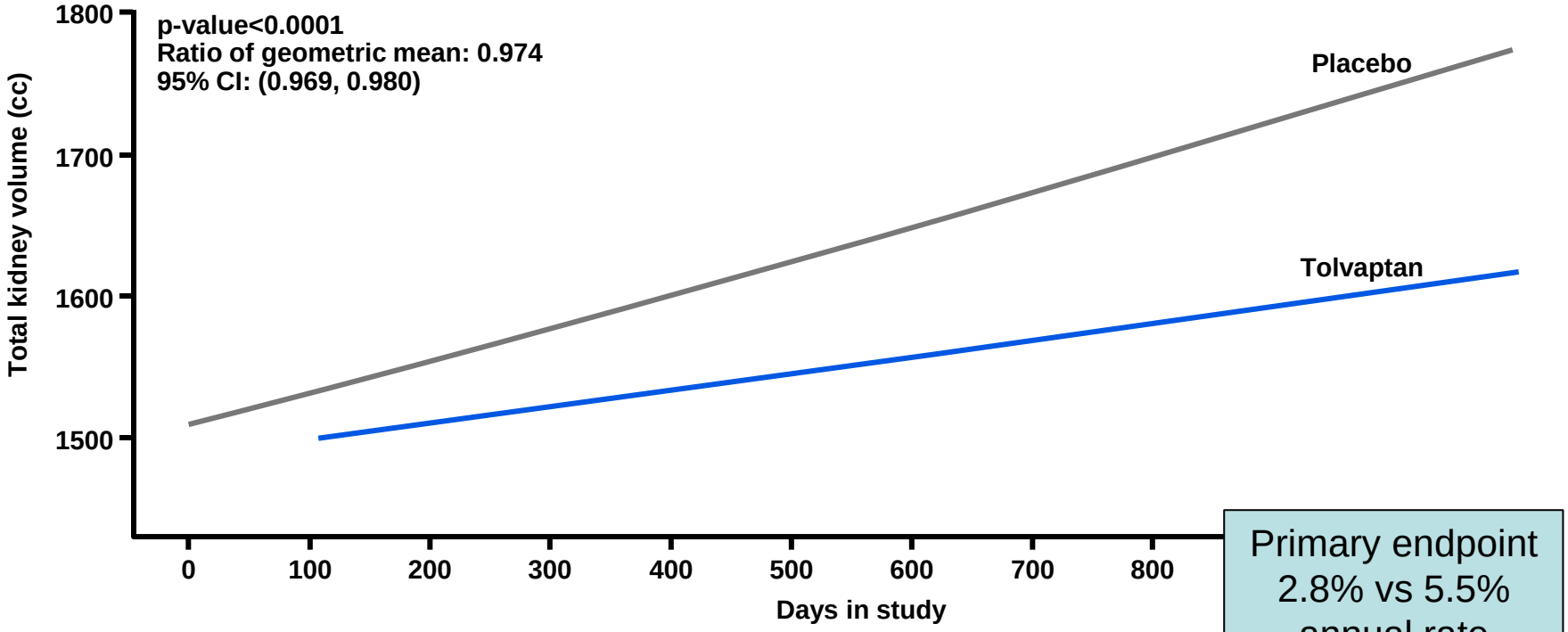
Phase 3, Randomized, Placebo-controlled, Parallel Arm, Three-year Trial of Tolvaptan in ADPKD



129 sites in 15 countries

Rate of percent growth in total renal volume (%/yr)

ITT within treatment period



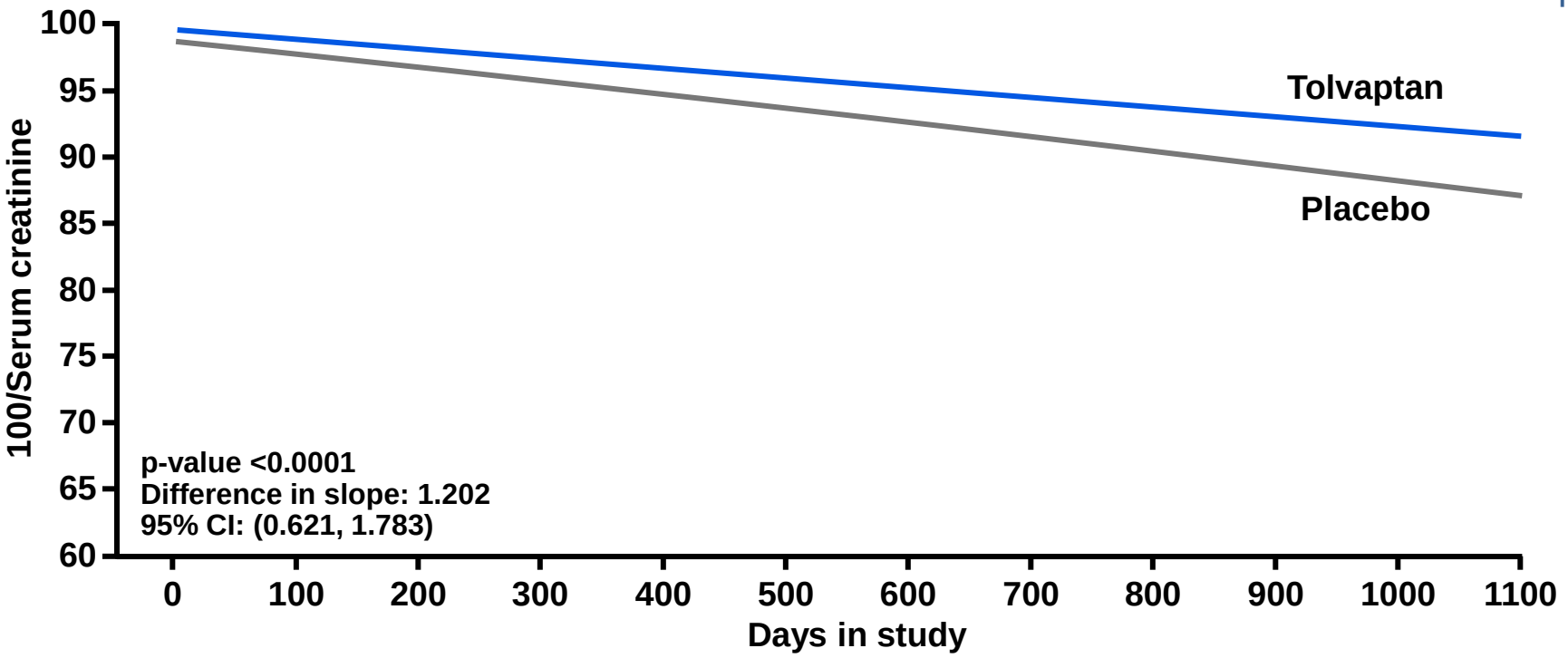
Primary endpoint
2.8% vs 5.5%
annual rate

		Rate of % growth/year				
Treatment group	N	Mean	Med	SD	Slope	p-value§
Tolvaptan	819	2.777	2.265	5.659	0.028	<0.0001
Placebo	458	5.608	5.585	5.330	0.055	

Torres V.E., et al. (2012). N Engl J Med. 367(25):2407-18.

Significant impact on rate of renal function decline

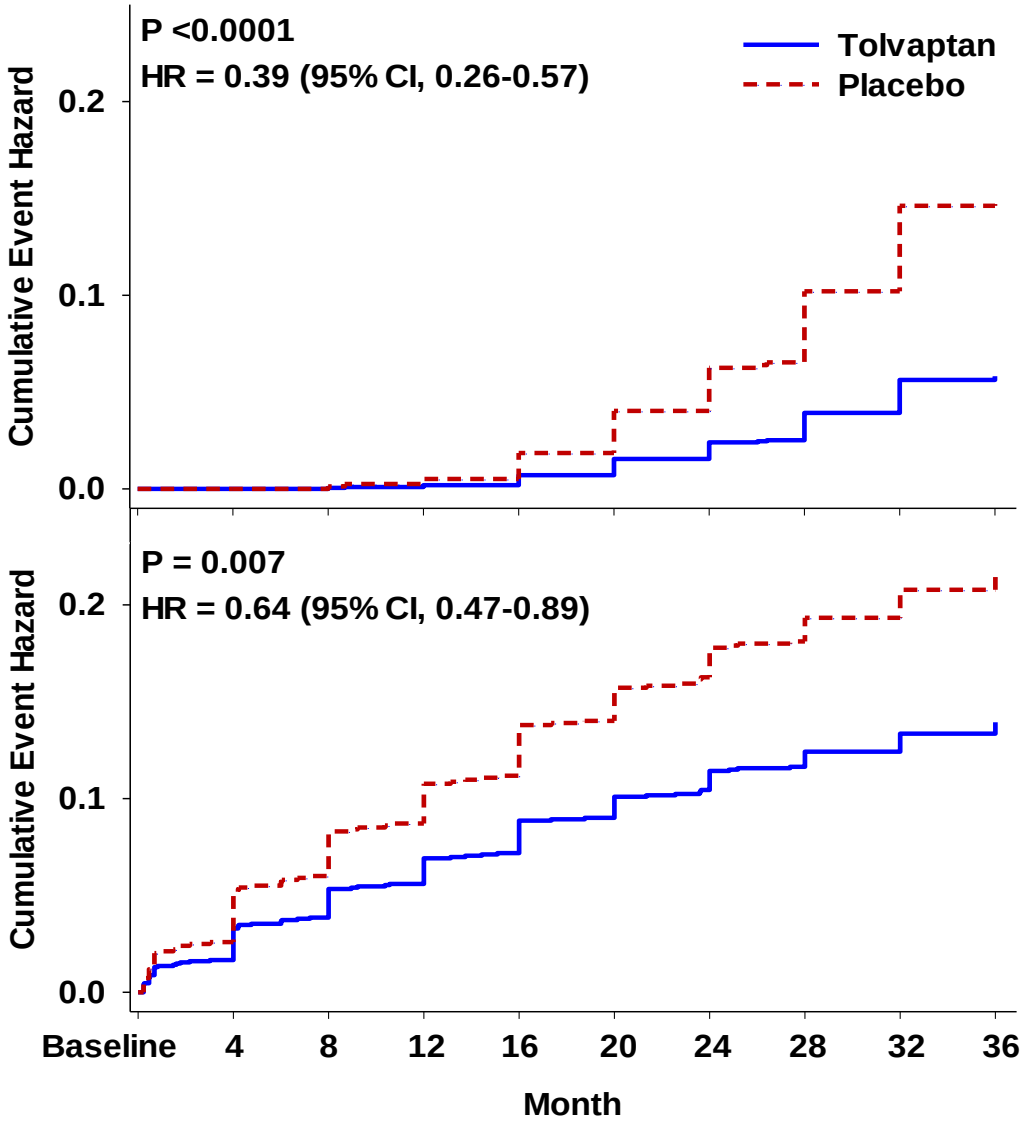
Reciprocal serum creatinine (100/(mg/dl))
ITT within treatment period



		Annual eGFR rate of change				
Treatment group	N	Mean	Med	SD	Slope	p-value
Tolvaptan	842	-2.555	-2.353	9.767	-2.610	<0.0001
Placebo	464	-3.682	-3.326	6.361	-3.812	

Torres V.E., et al. (2012). N Engl J Med. 367(25):2407-18.

Time to Worsening Kidney Function and Kidney Pain Events



Worsening Kidney Function

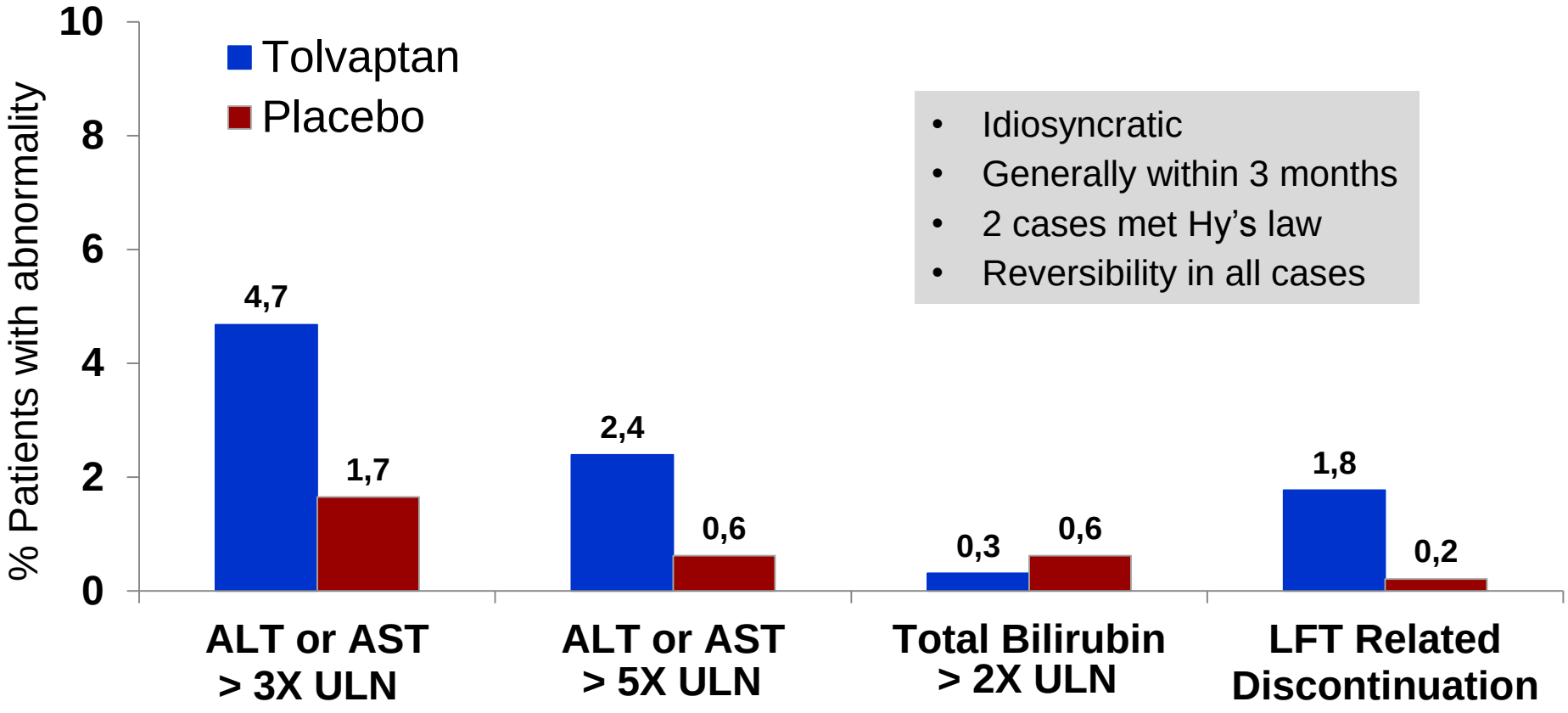
61% lower risk of 25% reduction in 1/SCr

Significant Kidney Pain

36% lower risk of kidney pain requiring intervention

Torres V.E., et al. (2012). N Engl J Med. 367(25):2407-18.

Tolvaptan Treated Patients had More Frequent Elevations in ALT or AST



At any time during the 3 year trial; ULN denotes Upper Limit of Normal

Torres V.E., et al. (2012). N Engl J Med. 367(25):2407-18.

27/02/2015

‘Tolvaptan’* recommended for approval in rare kidney disease

Medicine to slow down cyst formation

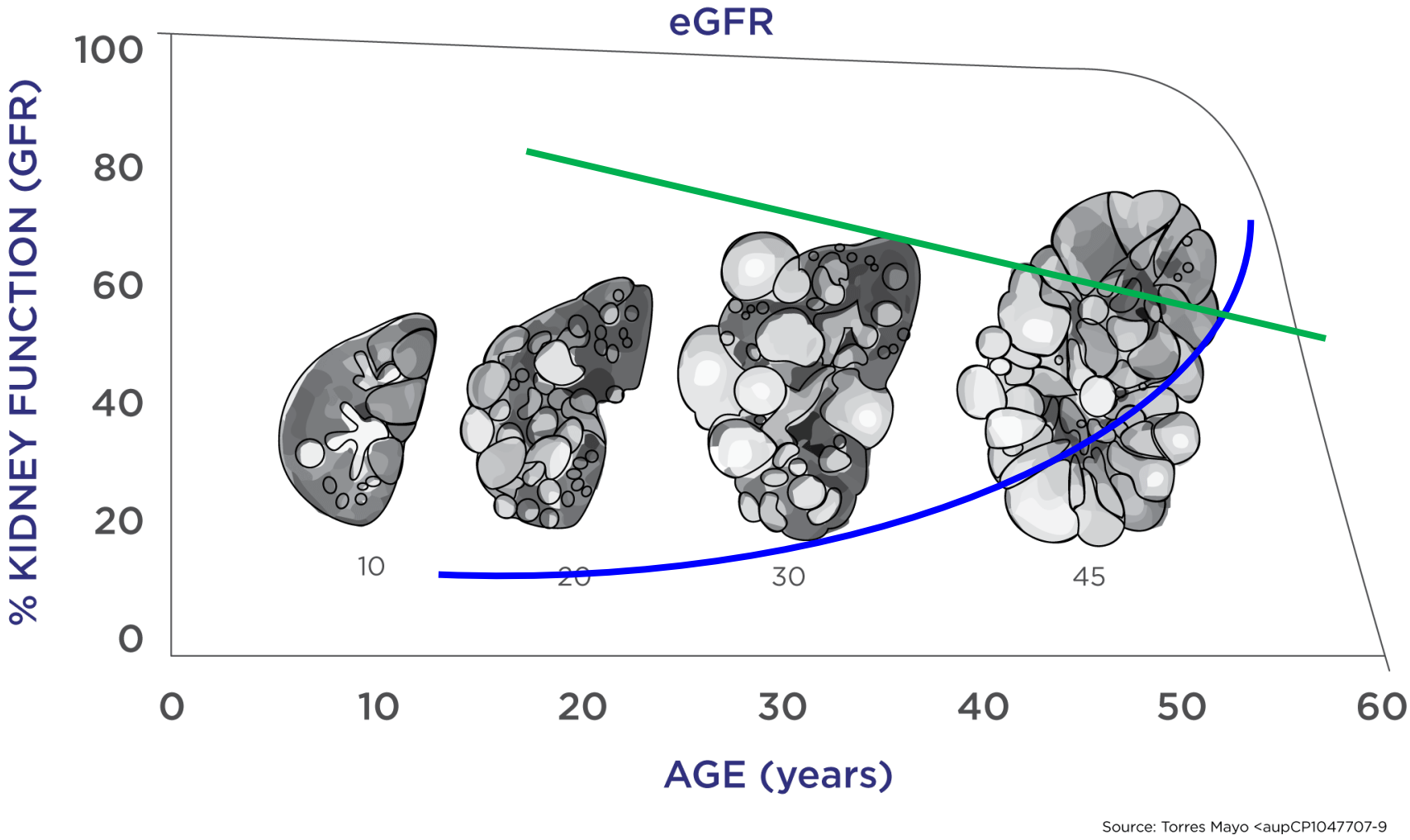
The European Medicines Agency (EMA) has recommended granting a marketing authorisation to ‘tolvaptan’*. ‘Tolvaptan’* is indicated to slow the progression of cyst development and failing kidney function in adult patients with autosomal dominant polycystic kidney disease (ADPKD). ‘Tolvaptan’* is for use in patients with normal to moderately reduced kidney function who have rapidly progressing ADPKD.

European Medicines Agency

*publisher has removed product name

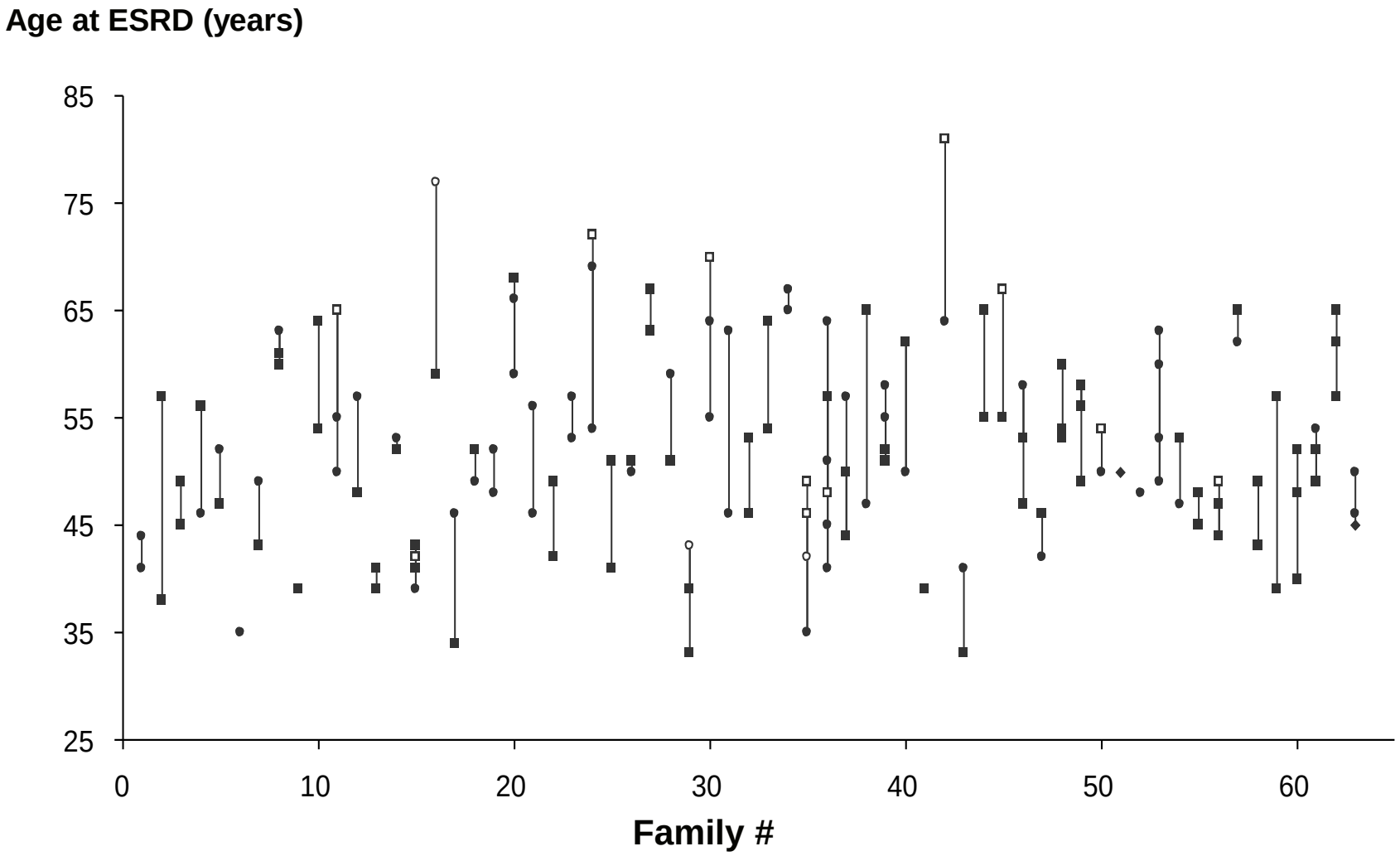
Prediction of ADPKD Progressors?

Slow Disease Progression in ADPKD: Renal Function vs. TKV



Source: Torres Mayo <aupCP1047707-9

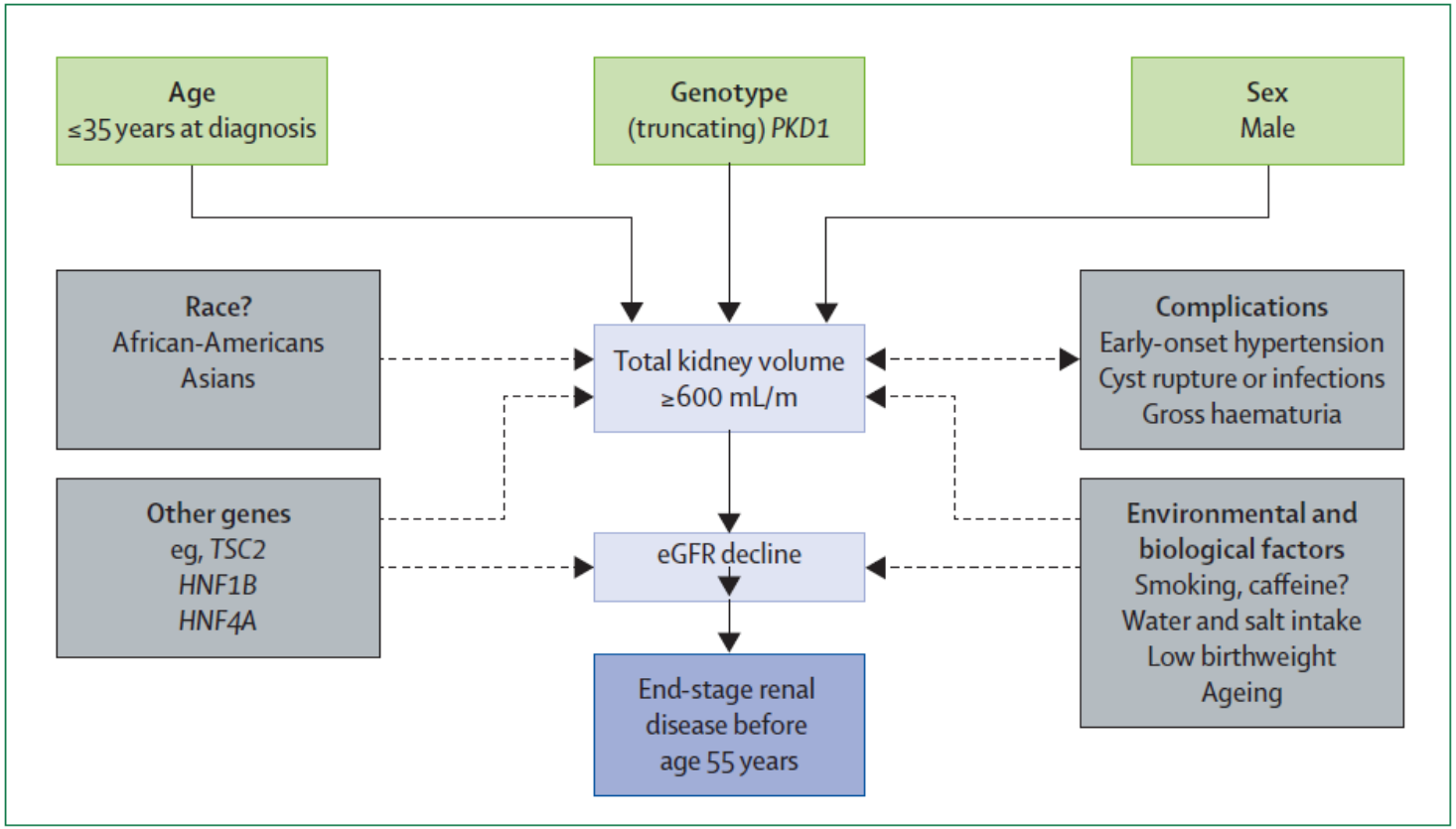
Inter- and Intra-familial Variability in ADPKD : A Multicentric Sib-pair Study



Persu et al. Kidney Int. 2004 Dec;66(6):2132-6.

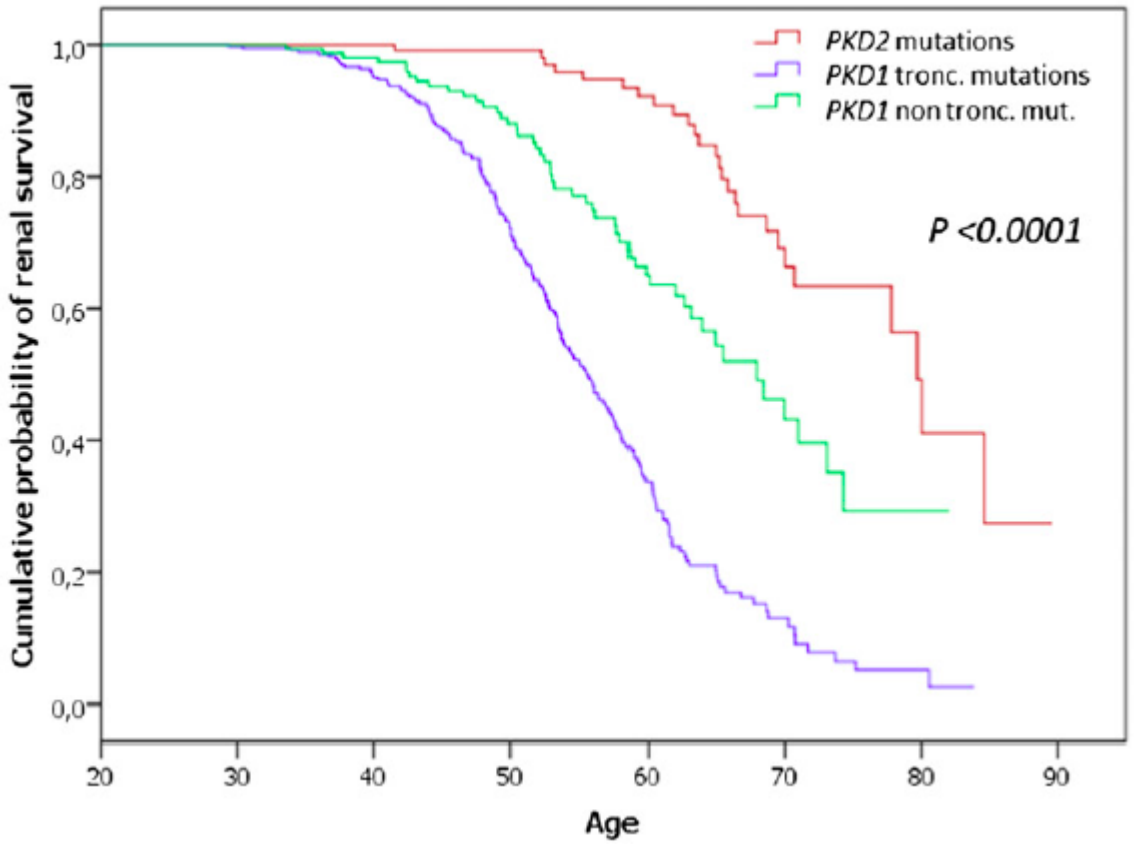
Autosomal dominant polycystic kidney disease: the changing face of clinical management

*Albert C M Ong, Olivier Devuyst, Bertrand Knebelmann, Gerd Walz, on behalf of the ERA-EDTA Working Group for Inherited Kidney Diseases**



Ong et al, Lancet 2015;385:1993-2002

Type of *PKD1* Mutation Influences Renal Outcome in ADPKD



Genkyst: 741 patients from 519 pedigrees

Cornec-Le Gall et al. J Am Soc Nephrol. 2013 May;24(6):1006-13.

The PROPKD Score: A New Algorithm to Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease

Variable	Patients (*n*)	HR (95% CI)	95% CI from Bootstrap Analysis	*P* Value	Points for PROPKD Score
Sex					
Female	541				0
Male	432	1.55 (1.29 to 1.88)	1.27 to 1.89	<0.001	1
Hypertension before age 35 yr					
No	679				0
Yes	294	2.11 (1.71 to 2.61)	1.71 to 2.62	<0.001	2
≥1 urologic event before age 35 yr					
No	734				0
Yes	239	1.73 (1.38 to 2.18)	1.35 to 2.24	<0.001	2
Mutation					
PKD2	186				0
PKD1 nontruncating	239	2.27 (1.57 to 3.28)	1.61 to 3.18	0.002	2
PKD1 truncating	548	4.75 (3.41 to 6.60)	3.63 to 6.60	<0.001	4

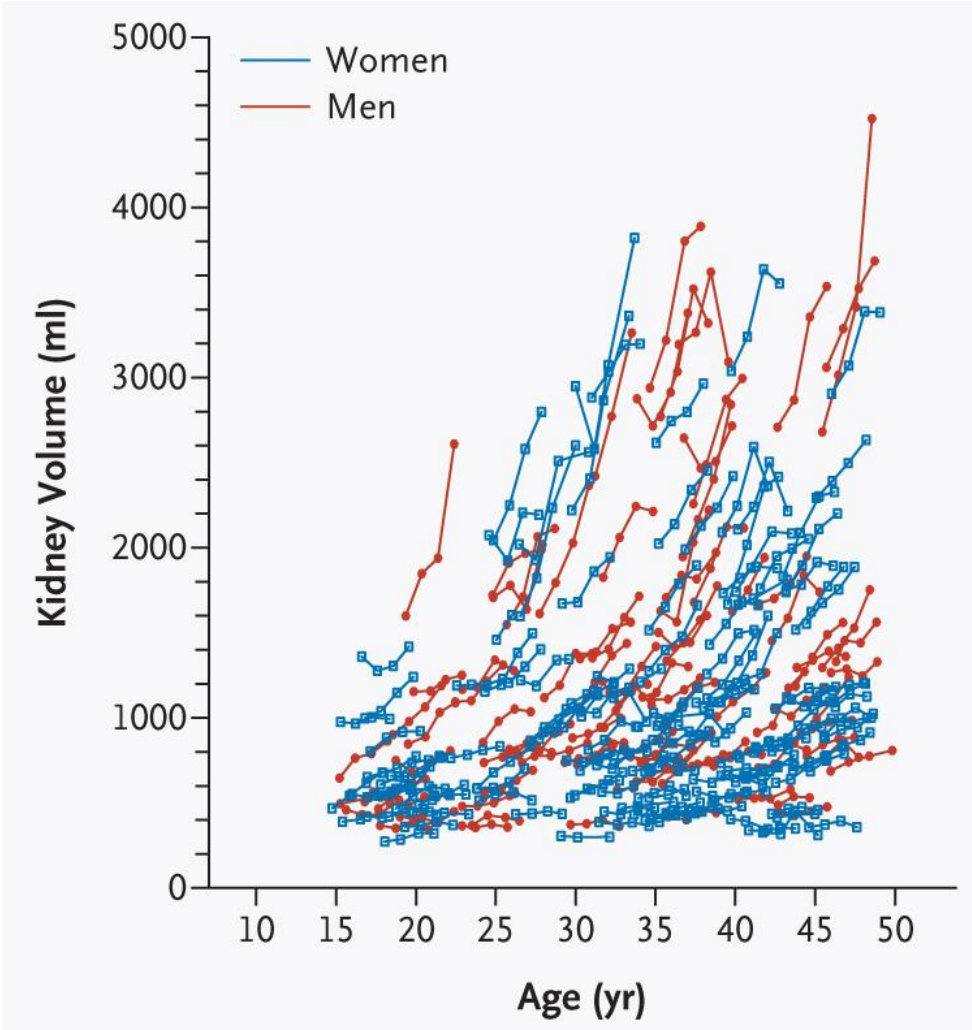
Urologic event: hemorrage, flank pain, infection

- Large GenKYST cohort from Brittany (N=1341)
- MV analysis: 4 risk factors → Score from 0 to 9
- Three risk categories

Cornec-Le Gall et al. J Am Soc Nephrol. 2016 Mar;27(3):942-51

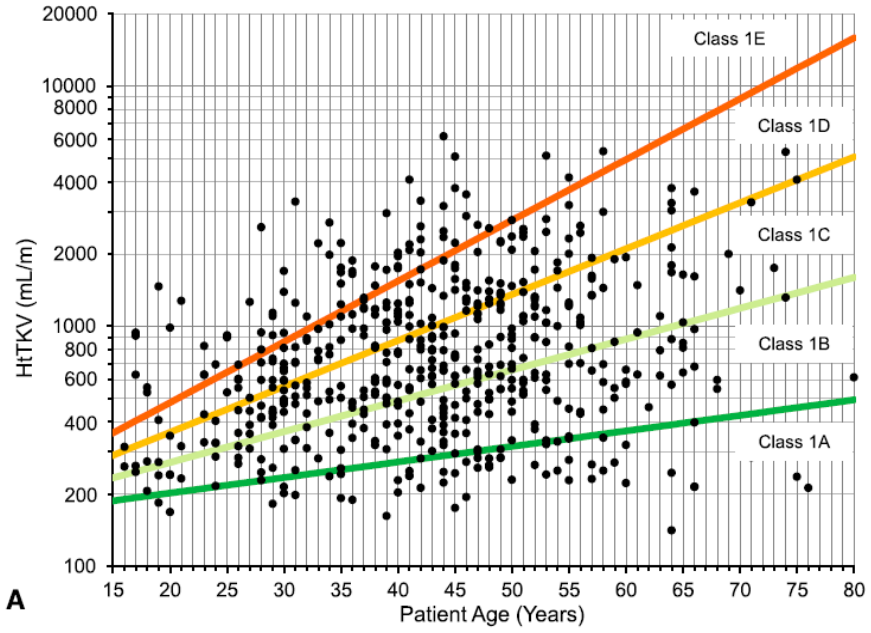
Exponential Progression of TKV in ADPKD: CRISP

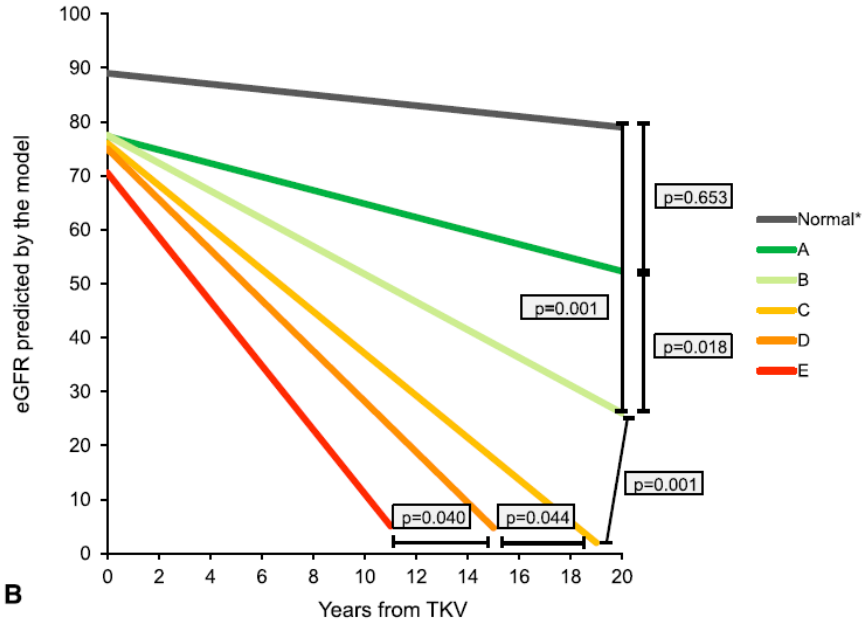
TKV measured by MRI



Grantham et al, N Engl J Med 2006; 354 : 2122-30

Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials





eGFR decline in 538 ADPKD patients from Mayo, with TKV imaging

Irazabal et al, J Am Soc Nephrol. 2015 Jan;26(1):160-72

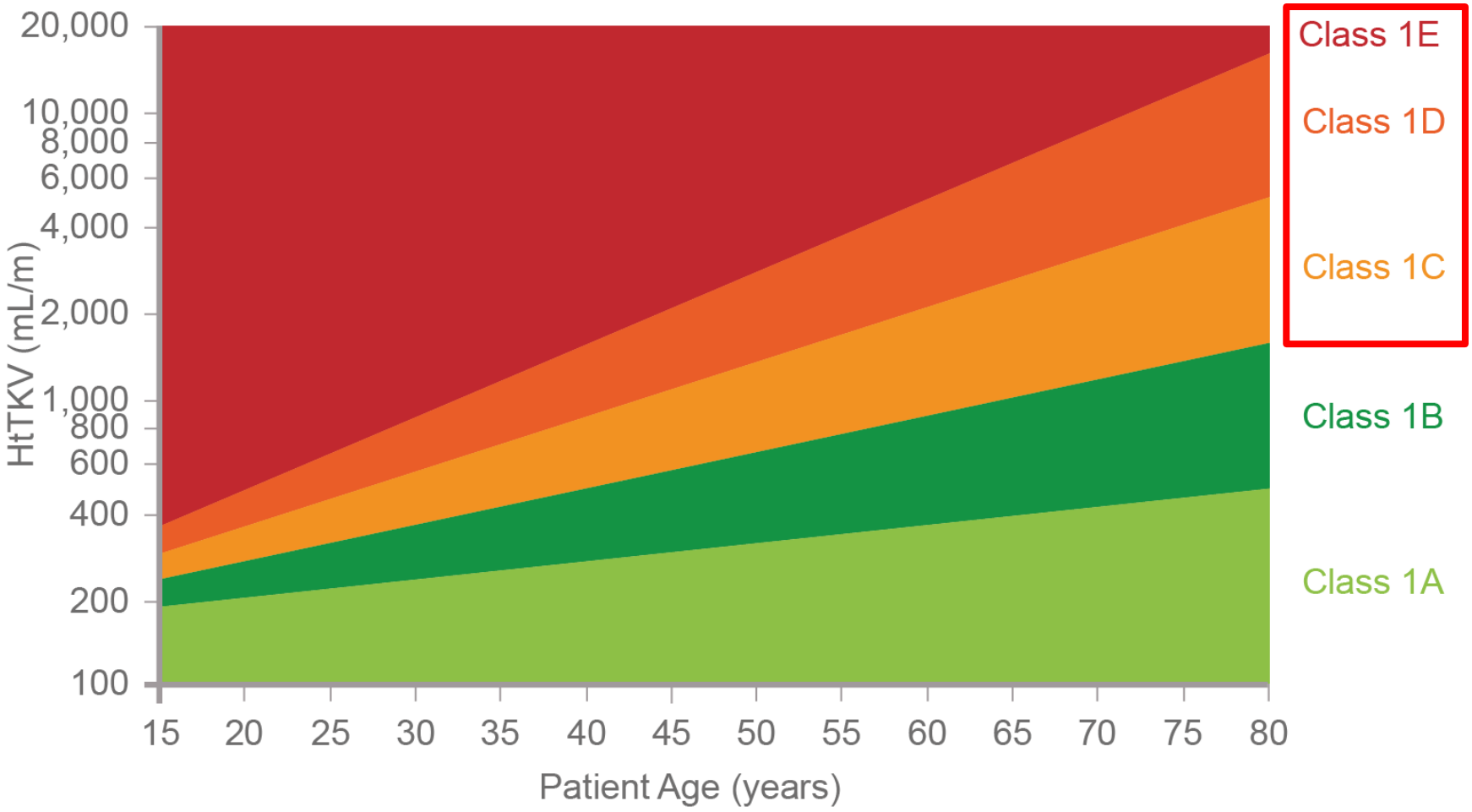
Mayo Classification Score

CLASSIFICATION OF TYPICAL ADPKD CALCULATOR

- Total kidney volume: mL
- Height: m
- Age: yrs

→ *Height-adjusted TKV*
→ *ADPKD classification*

The Mayo Clinic classification



Irazabal MV, et al. (2015) J Am Soc Nephrol. 26(1):160-72

Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice

Who should benefit from the treatment ?

Gansevoort et al, Nephrol Dial Transplant 2016;31:337-348

Recommendations for the use of tolvaptan in ADPKD

Tolvaptan can be prescribed to adult ADPKD patients aged <50 years with CKD stages 1 to 3a.

Rapid progressors:

- Historical renal function decline > 5 ml/min/1.73m^2/yr (or 2.5 ml/min / 5 yr)
- Historical TKV progression > 5% /yr

- Mayo class 1C-1E (HTKV, age)
- Truncating *PKD1* mutation and early clinical symptoms – Pro-PKD score >6

- Patients with a family history of ESRD before age 55 years

Available Drugs Currently Used in ADPKD

- V2 Receptor Antagonists “Aquaretics”
- Somatostatin Analogues

Lanreotide Reduces the Volume of Polycystic Liver: A Randomized, Double-Blind, Placebo-Controlled Trial

LOES VAN KEIMPEMA,* FREDERIK NEVENS,‡ RAGNA VANSLEMBROUCK,§ MARTIJN G. H. VAN OIJEN,* ASWIN L. HOFFMANN,‖ HELENA M. DEKKER,¶ ROBERT A. DE MAN,# and JOOST P. H. DRENTH*

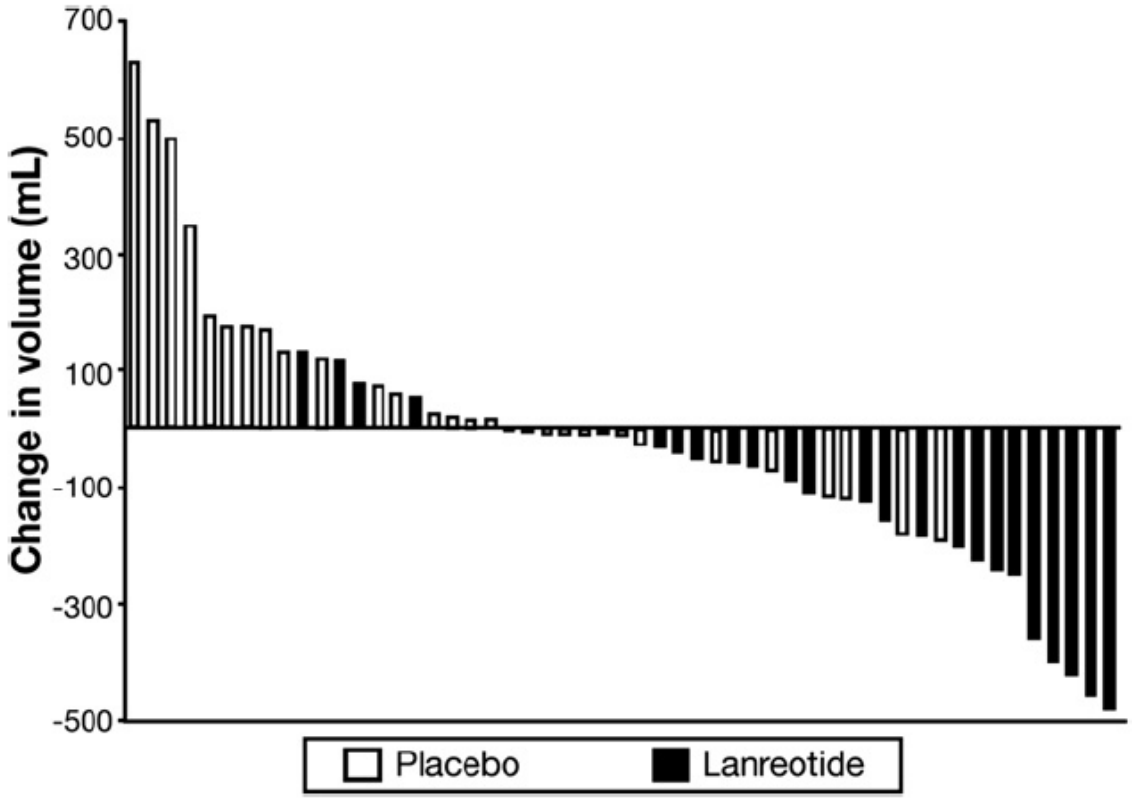


Figure 2. Absolute change in liver volume in all patients. Each *bar* represents 1 patient (n = 53).

Van Keimpema et al, Gastroenterology 2009;137:1661-1668

Somatostatin Analogues for Polycystic Liver Disease

Table 2 Outcomes of studies investigating the role of somatostatin analogues

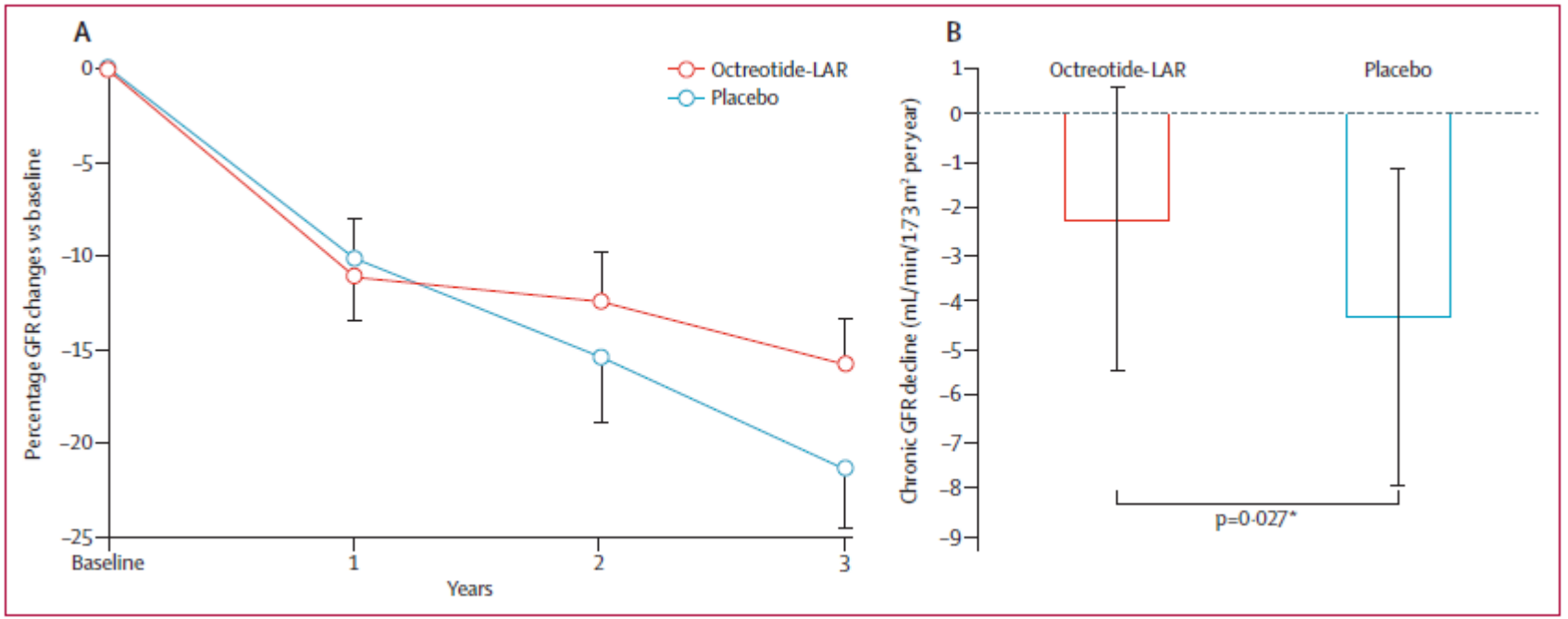
Study	Intervention	Primary outcome	Secondary outcomes	Method of assessment	Outcome		
					6 months	1 year	2 year
Van Keimpema *et al*[18]	Lanreotide	Liver volume	Kidney volume, QoL	CT volumetry	Mean reduction of 2.9% ($p<0.01$) in liver volume. Some improvement in QoL		
Caroli A. *et al*[19]	Octreotide	Kidney volume	Liver volume	CT volumetry	Liver volumes reduced from 1595+/- 478 ml to 1524+/- 453 ml ($p<0.005$)		
Hogan *et al*[3]	Octreotide	Liver volume	Kidney volume, QoL	MRI		Mean reduction of 4.95+/-6.77 % ($p=0.048$) in liver volume. Some improvement in QoL	
Chrispijn M. *et al*[21]	Lanreotide	Liver volume	Kidney volume, QoL	CT volumetry		Liver volume decreased by 4% (IQR 8% to 1%) after 12 months of treatment	
Hogan *et al*[20]	Octreotide	Liver volume	Kidney volume, QoL	MRI			0.77+/-6.82 % further reduction from first year ($p=0.57$)

QoL: quality of life, MRI, Magnetic resonance imaging, CT: computerised tomography

Khan et al, Ann R Coll Surg Engl 2016;98:18-23

Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial

Anna Caroli, Norberto Perico*, Annalisa Perna*, Luca Antiga, Paolo Brambilla, Antonio Pisani, Bianca Visciano, Massimo Imbriaco, Piergiorgio Messa, Roberta Cerutti, Mauro Dugo, Luca Cancian, Erasmo Buongiorno, Antonio De Pascalis, Flavio Gaspari, Fabiola Carrara, Nadia Rubis, Silvia Prandini, Andrea Remuzzi, Giuseppe Remuzzi*, Piero Ruggenenti*, for the ALADIN study group†*



Caroli et al, Lancet 2013;382:1485-95

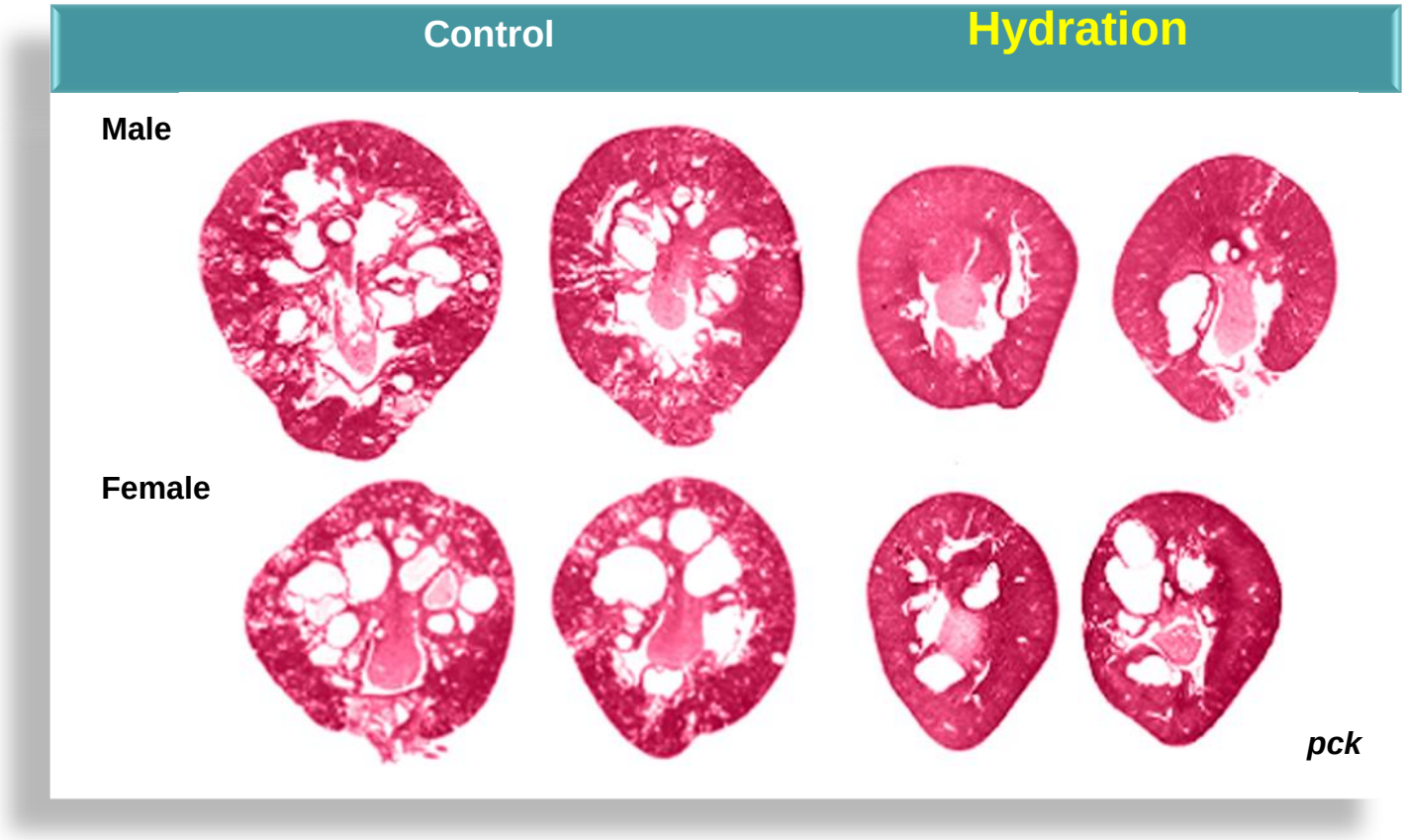
EDITORIALS www.jasn.org

Therapy for Polycystic Kidney Disease? It's Water, Stupid!

Jared J. Grantham

Grantham J Am Soc Nephrol. 2008 Jan;19(1):1-7.

Increased Water Intake Decreases Progression of Polycystic Kidney Disease in the PCK Rat



Nagao S. Et al. JASN 2006;17: 2220-7

High Water Intake in ADPKD: Practical

- Sustained increase in water intake: 3L/day
- Target: Uosmo < 300 mOsm/kg (gravimeter)
- Water: no sugar, no caffeine, tap vs. bottled ?
- Compliance : years
- Side-effects: urinary tract retention, social, nycturia

Water therapy: Which type of water ?

Chemiecocktail aus dem Wasserhahn

BERN. Fast in der ganzen Schweiz ist das Trinkwasser mit Chemikalien verseucht. Das kann zu Missbildungen führen.

Pestizide, Medikamente, Rostschutzmittel: Rückstände von Chemikalien, die wir benutzen, tropfen aus dem Hahn. Dies zeigt die «Kassensturz»-Analyse des Trinkwassers in 50 Städten (siehe Box). Die Resultate sind beunruhigend: In Zürich, Luzern, Bern und Basel wurden etwa Spuren des verbotenen Herbizids Atrazin gefunden. Dieses kann zu Missbildungen bei Fischen führen.

CHEMIE IM WASSER

Zahl gefundener Chemikalien im Trinkwasser QUELLE: «KASSENSTURZ»

Lausanne	14
Liestal	9
Zürich	8
Delémont	7
Frauenfeld	7
Luzern	3
Basel	3
Bern	2
Appenzell	0
St. Gallen	0

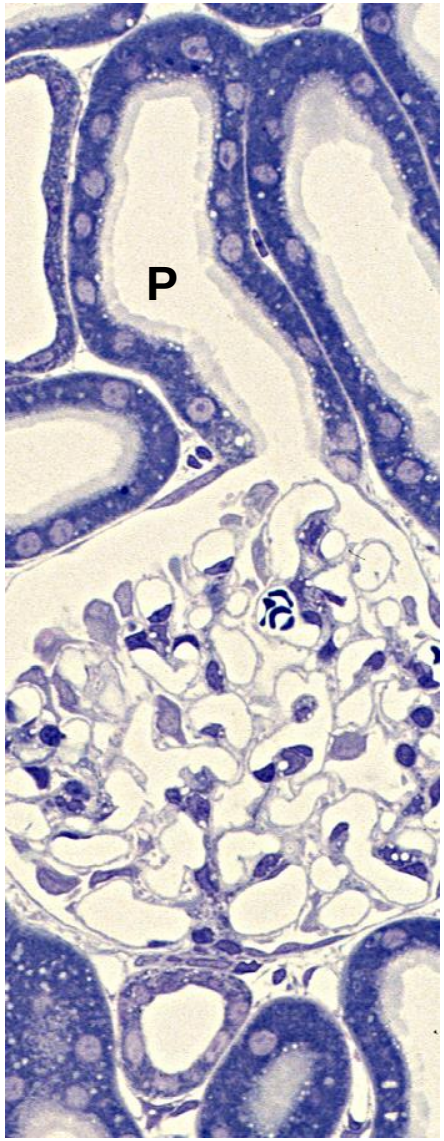
Dasselbe gilt für Rückstände der Antibabypille. Auch andere Tiere sind betroffen: Flusskrebse kommen wegen des Brustkrebsmittels Tamoxifen im Labor kleiner und mit unterentwickelten Fühlern zur Welt, wie eine laufende Analyse der Uni Lausanne zeigt.

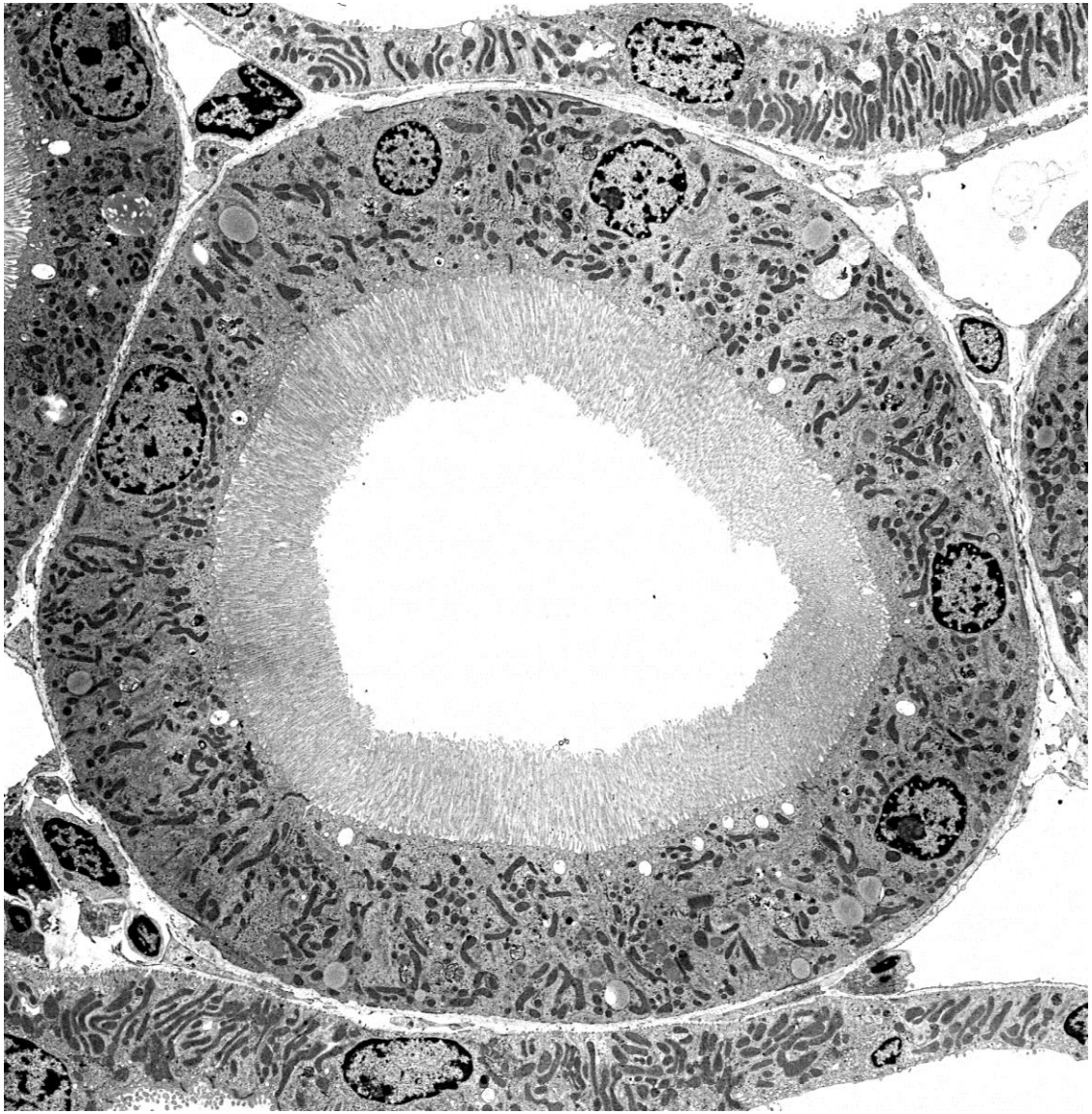
Ob dies langfristig Folgen hat, weiss niemand. «Es ist auch nicht ausgeschlossen, dass beim Menschen irgendwann Langzeiteffekte, zum Beispiel Abnormalitäten, auftreten», sagt Ökotoxikologin Nathalie Chèvre. Der Bund will in den nächsten 20 Jahren 100 der ungefähr 700 Abwasserreinigungsanlagen für 1,2 Mia. Franken mit weiteren Reinigungsstufen wie Aktivkohlefiltern oder Ozonierungsanlagen aufrüsten. «Ziel ist, dass so wenig Chemikalien wie möglich in die Gewässer gelangen», so Stephan Müller, Abteilungsleiter Wasser beim Bundesamt für Umwelt. Im Frühling will der Bundesrat eine Botschaft dazu ans Parlament verabschieden. LORENZ HANSELMANN

Ob der Schluck Hahnenwasser wohl bald zum Verhängnis wird? KEY

Tubulopathies

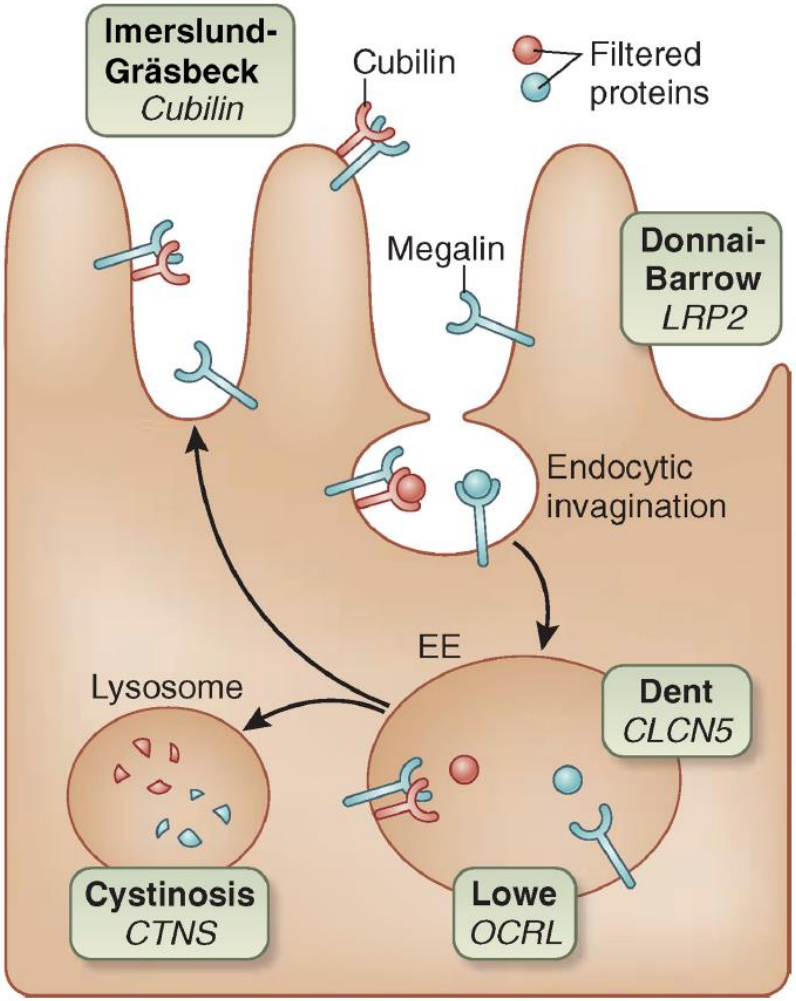
Proximal Tubule Segment





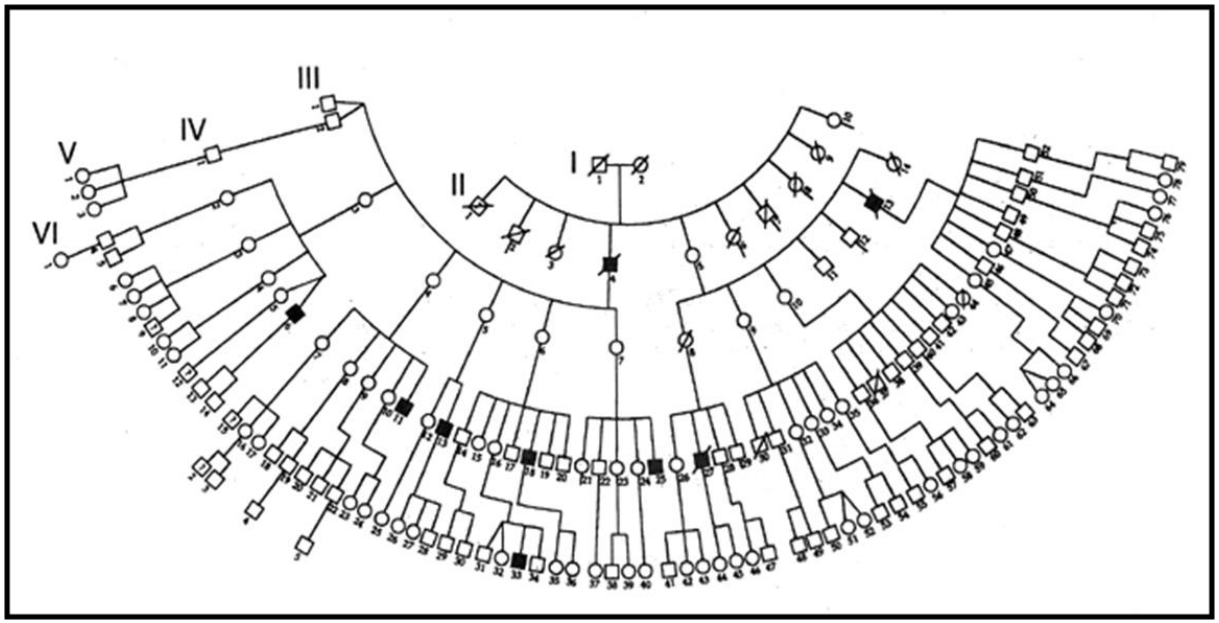
Courtesy: O. Devuyst

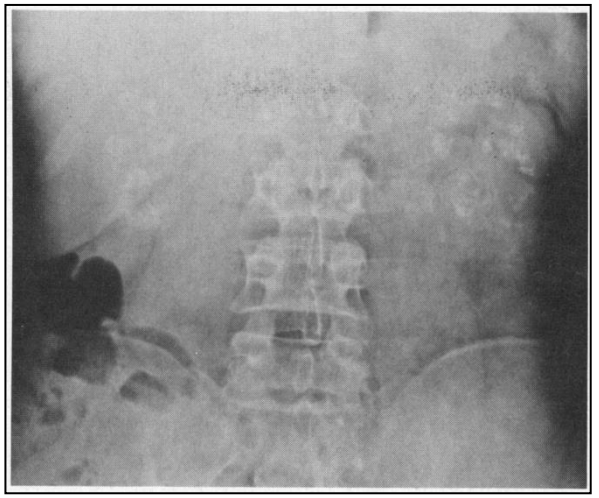
Renal Fanconi Syndrome:
Rare Disorders Targeting the Endolysosomal System



Willnow TE. Kidney Int 2017; 91:776-8

Dent's disease: *CLCN5* mutations
X-linked Inherited Hypophosphatemic Rickets and Kidney Stones





Frymoyer PA et al. N Engl J Med. 1991 Sep 5;325(10):681-6.

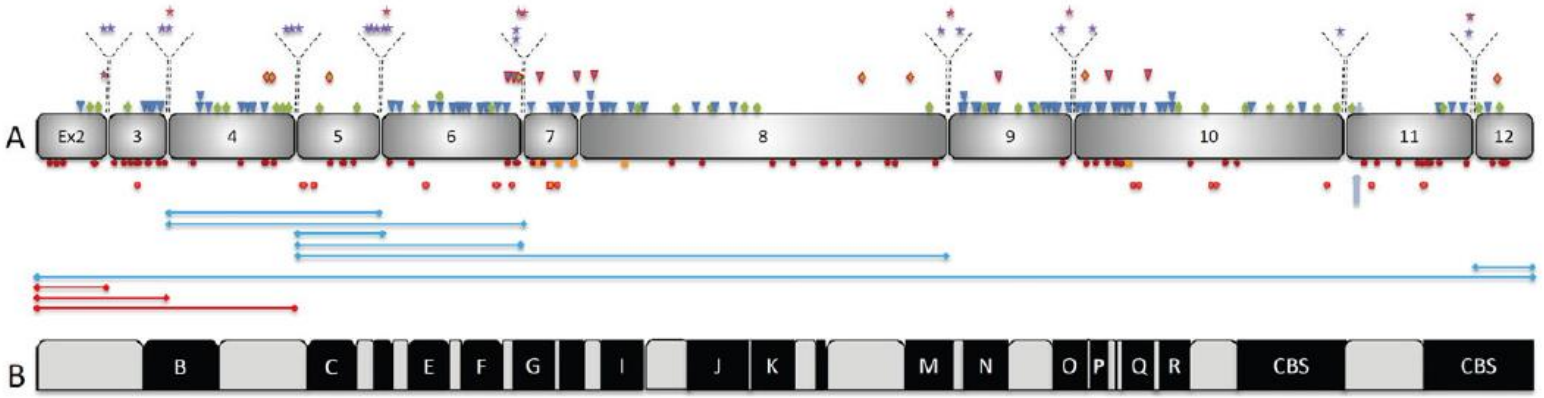
Features of Dent's Disease

• Low-molecular-weight proteinuria	100%
• Albuminuria	100%
• Aminoaciduria	100%
• Glucosuria	8/15
• Rickets	6/15
• Hypercalciuria	12/13
• Kidney stones	8/15
• Nephrocalcinosis	11/15
• Renal failure	11/15
• Impaired urinary concentration	9/9
• Acidification defect	7/14

Ludwig M et al. Nephrol Dial Transplant. 2006 Oct;21(10):2708-17.

Mutation Update of the *CLCN5* Gene Responsible for Dent Disease 1

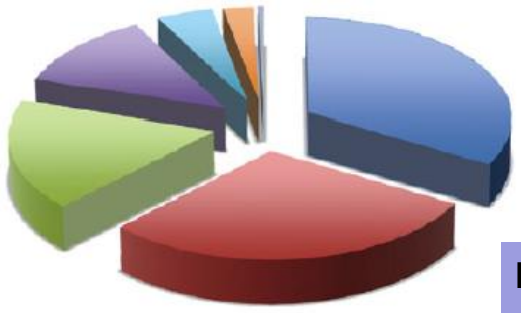
- 234 mutations
- 170 families



Type of mutation (n=234)

C

- Missense (33.33%)
- Frameshift (29.05%)
- Nonsense (17.52%)
- Splicing (12.39%)
- Large deletion (4.70%)
- Inframe (2.56%)
- Other (Alu insertion) (0.42%)
- Novel mutations



De novo mutation rate ~ 10%

Mansour-Hendili et al, Human Mutation 2015;36(8):743-752

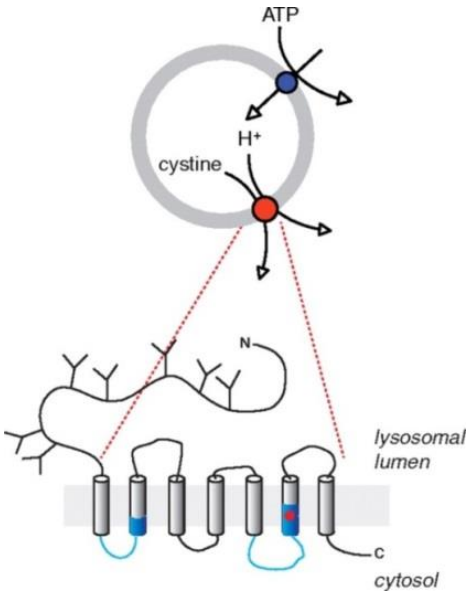
Dent Disease: Phenotype – Clinical Relevance

Clinical data from 377 male patients belonging to 334 families

- Micro or macrohaematuria (n = 71)
- Polyuria/polydipsia or urinary concentration defect (31/43)
- Proteinuria in the nephrotic range without hypoalbuminemia (n = 13)
- Proteinuria in 57 patients: median value 1.28 g/24 hr (0.27–4.50 g/24h)
- Enuresis (n = 5)
- Hypomagnesaemia (4/30)
- Secondary hyperaldosteronism with Bartter-like phenotype (n = 3)
- Night blindness responsive to vitamin A

Mansour-Hendili et al, Human Mutation 2015;36(8):743-752

Cystinosin: From Lysosome to Disease



→ *CTNS gene encodes the lysosomal transporter cystinosin*

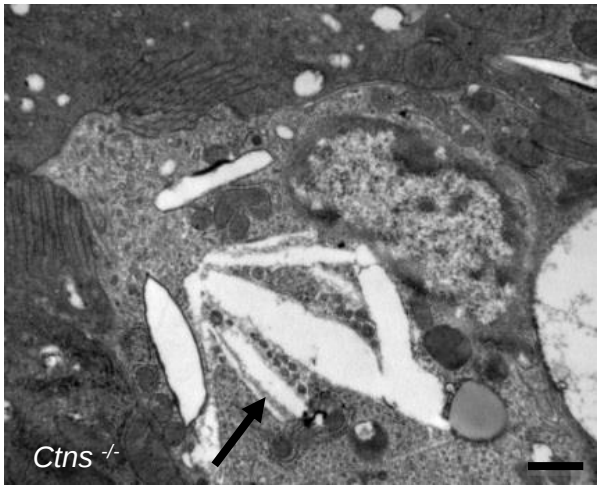
→ *Cystinosin mediates proton driven-exit of cystine from lysosomes*

Mutations or deletions in CTNS – loss of function

→ *Defective cystine efflux from lysosomes*

→ *Intralysosomal cystine accumulation: crystals*

→ *Multisystemic disorder - kidney*



Courtesy: O. Devuyst

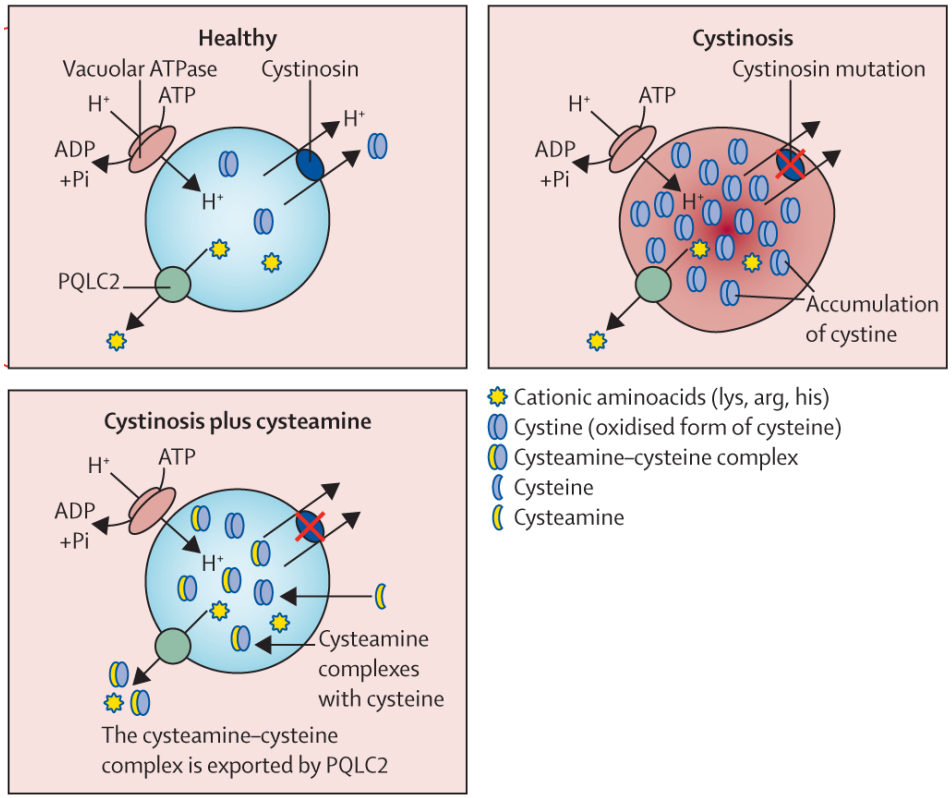
Time-course of Renal Phenotype in Nephropathic Cystinosis

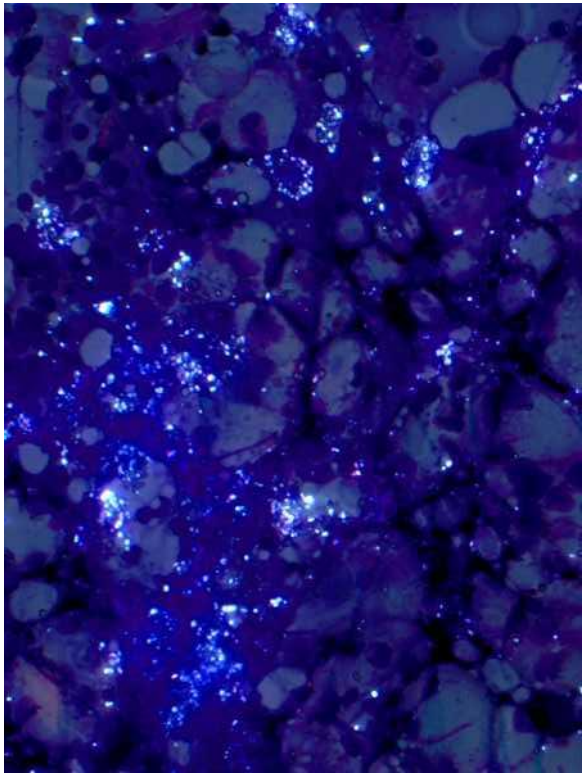
Age	Symptom or Sign	Prevalence in Affected Patients
		%
6–12 mo	Renal Fanconi's syndrome (polyuria, polydipsia, electrolyte imbalance, dehydration, rickets, growth failure)	95
5–10 yr	Hypothyroidism	50
8–12 yr	Photophobia	50
8–12 yr	Chronic renal failure	95
12–40 yr	Myopathy, difficulty swallowing	20
13–40 yr	Retinal blindness	10–15
18–40 yr	Diabetes mellitus	5
18–40 yr	Male hypogonadism	70
21–40 yr	Pulmonary dysfunction	100
21–40 yr	Central nervous system calcifications	15
21–40 yr	Central nervous system symptomatic deterioration	2

Early dysfunction of proximal tubule – before renal failure

Gahl WA et al. N Engl J Med. 2002 Jul 11;347(2):111-21.

Lysosomal Storage in Nephropathic Cystinosis





- Loss of function of cystinosin: lysosomal accumulation of cystine → lysosomal dysfunction
- Oral cysteamine : enters lysosomes and reacts with cystine to form a cysteamine-cysteine complex that can be exported, thus depleting cystine from lysosomes
- Difficult adherence to oral cysteamine; does not impact on renal Fanconi syndrome

Devuyst et al. Lancet 2014;383:1844-59

Hematopoietic Stem Cell Gene Therapy for the Multisystemic Lysosomal Storage Disorder Cystinosis

Frank Harrison[1], Brian A Yeagy[1], Celine J Rocca[1], Donald B Kohn[2,3], Daniel R Salomon[1] and Stephanie Cherqui[1]

Bone marrow transplantation improves proximal tubule dysfunction in a mouse model of Dent disease

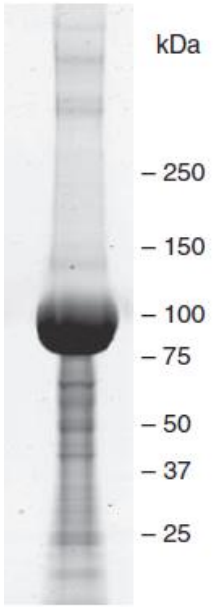
Sarah S. Gabriel[1,2,4], Hendrica Belge[1,4], Alkaly Gassama[1,4], Huguette Debaix[1], Alessandro Luciani[1], Thomas Fehr[1,2,3] and Olivier Devuyst[1]

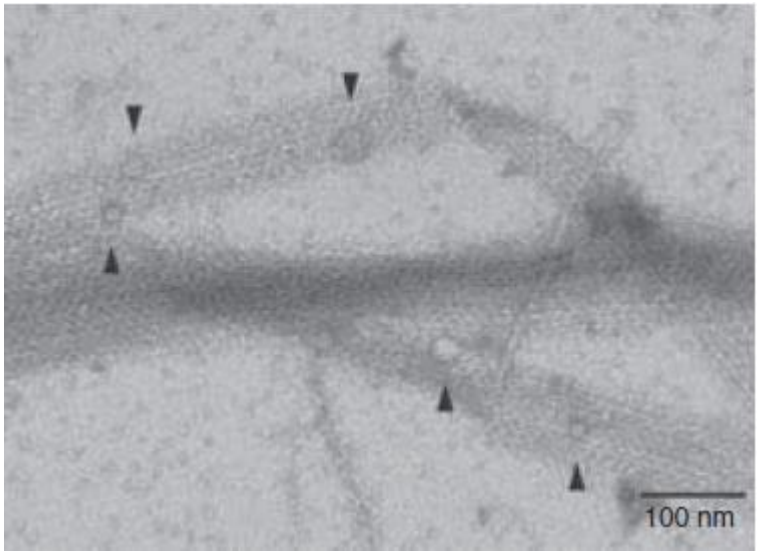
Harrison et al, Mol Ther. 2013 Feb;21(2):433-44.
Gabriel et al, Kidney Int. 2017 Apr;91(4):842-855.

From rare to common genetic disorders: Uromodulin

I. Tamm & F. Horsfall 1952 – D. Pennica 1987

Tamm-Horsfall protein - uromodulin:
the most abundant protein in nomal human urine (up to 100 mg/day)

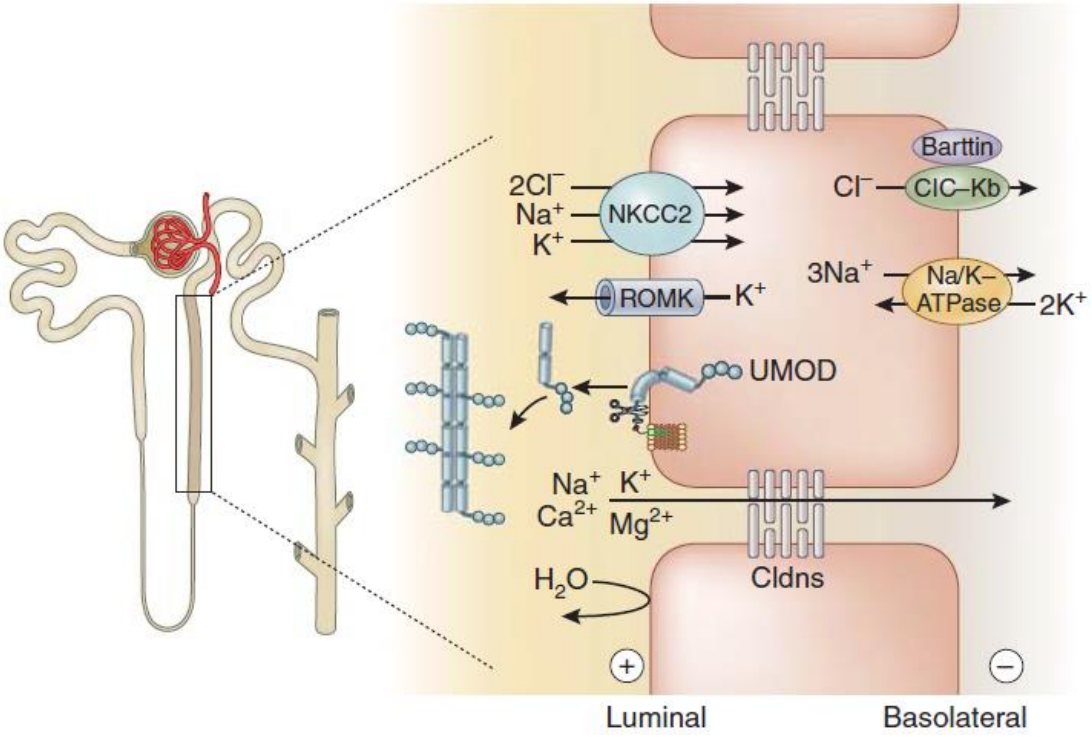




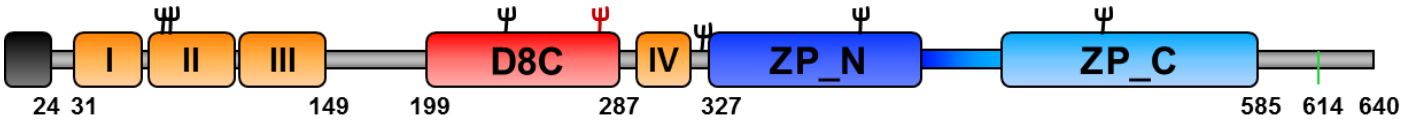
RNAs isolated from 150 different tissues and cell lines:
uromodulin mRNA detected only from human kidney.

Fernández-Llama P et al. Kidney Int. 2010; 77:736-42.

Uromodulin in TAL Segment

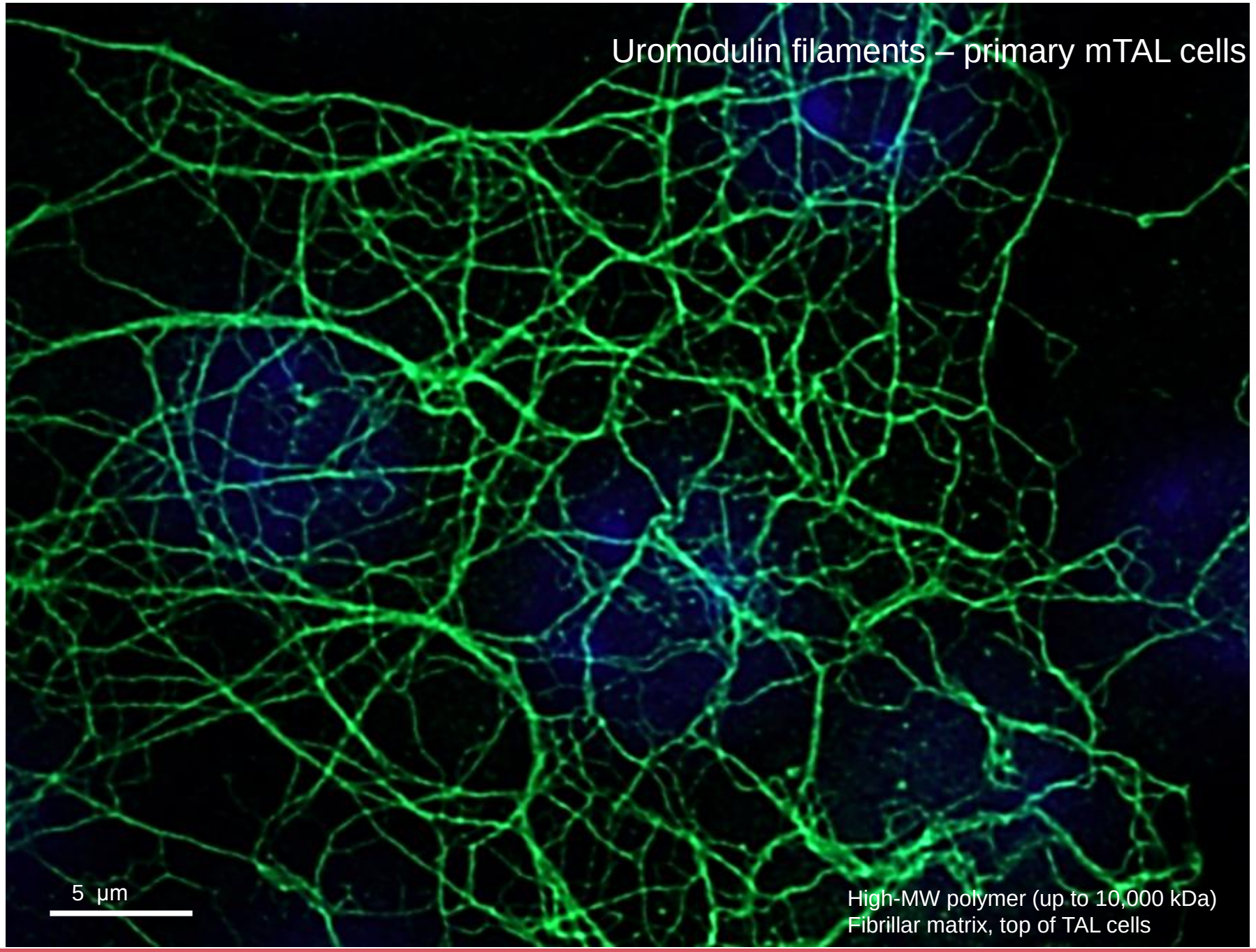


- Handling of NaCl:
  - Blood pressure
  - Urinary concentration
  - Loop diuretics
- Handling of Ca^{2+} & Mg^{2+}:
- Secretion of uromodulin
  - Local & downstream effects



- 640 AA, 48 cysteines (24 S-S), 7 N-glycosylation (25-30% carbohydrate content)
- GPI - Proteolytic cleavage → urine excretion & polymerisation → filaments

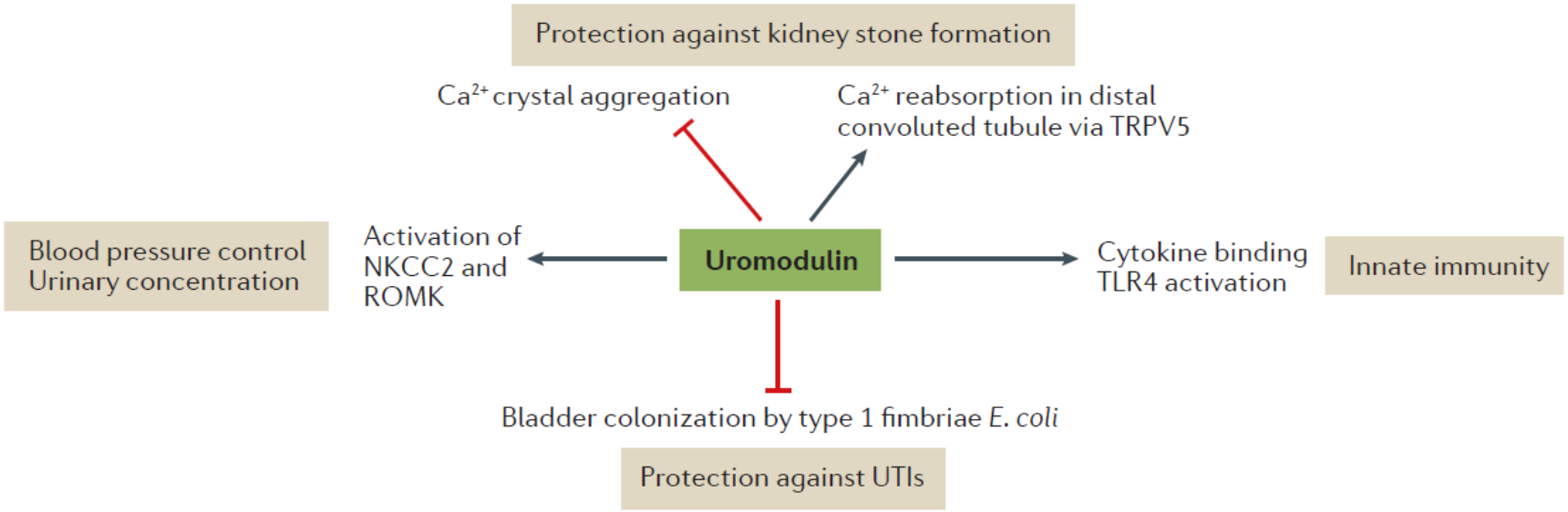
Devuyst O et al. Nat Rev Nephrol. 2017 Sep;13(9):525-544.



Courtesy: O. Devuyst

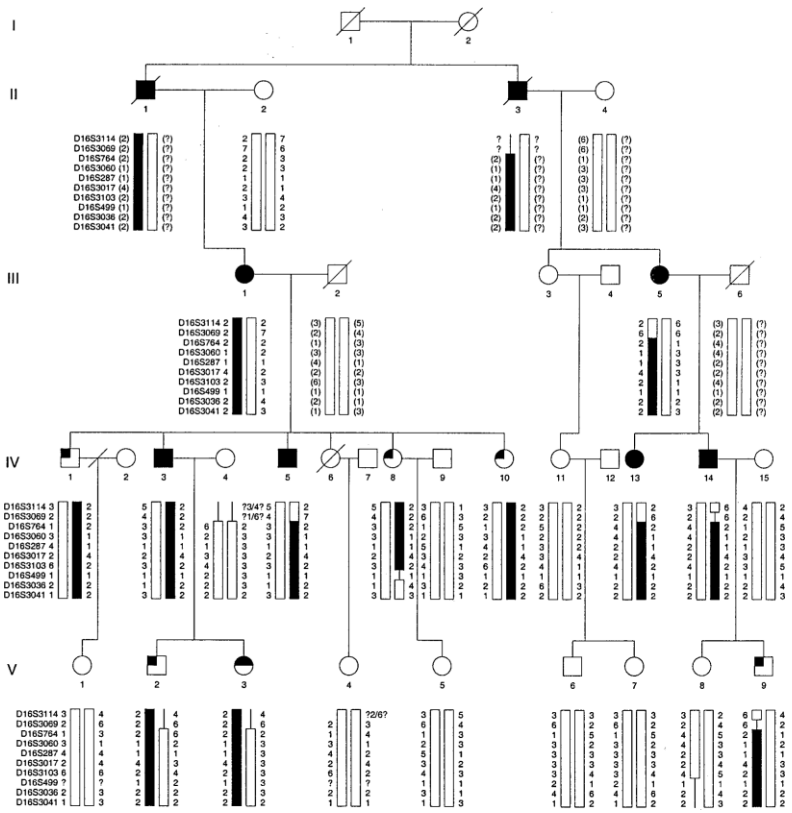
Uromodulin:

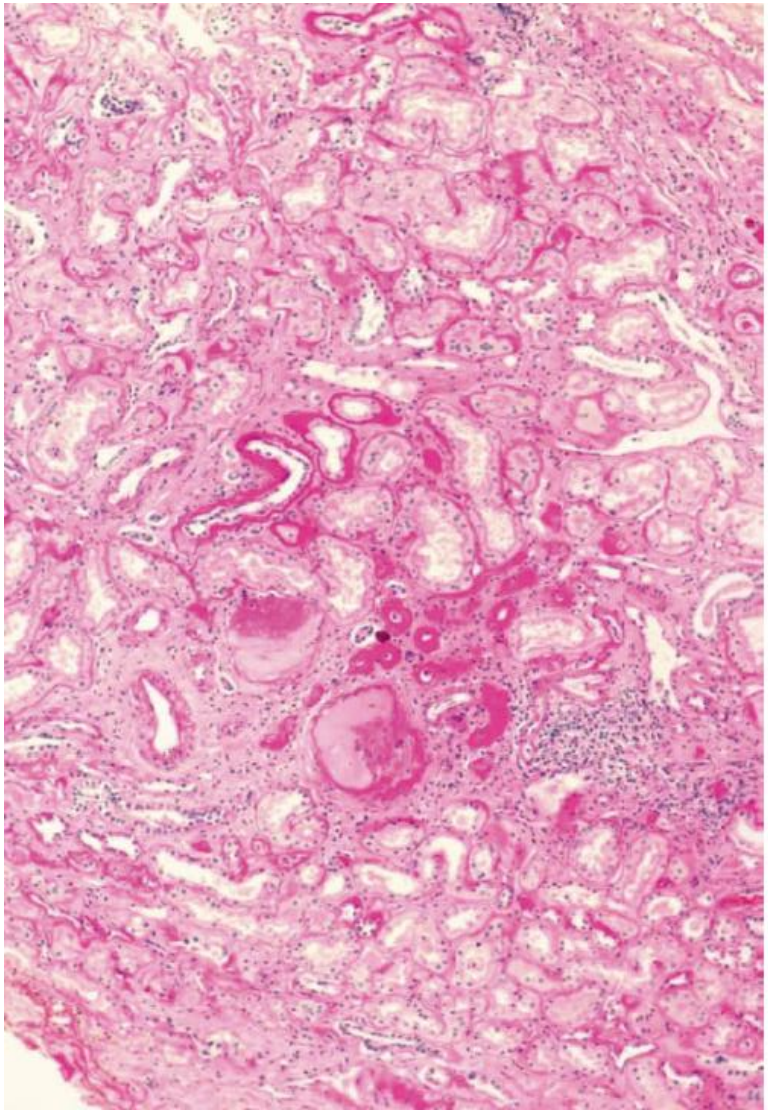
A multi-faceted protein in the urinary tract



Devuyst O et al. Nat Rev Nephrol. 2017 Sep;13(9):525-544.

Medullary Cystic Kidney Disease - Hyperuricemic Nephropathy

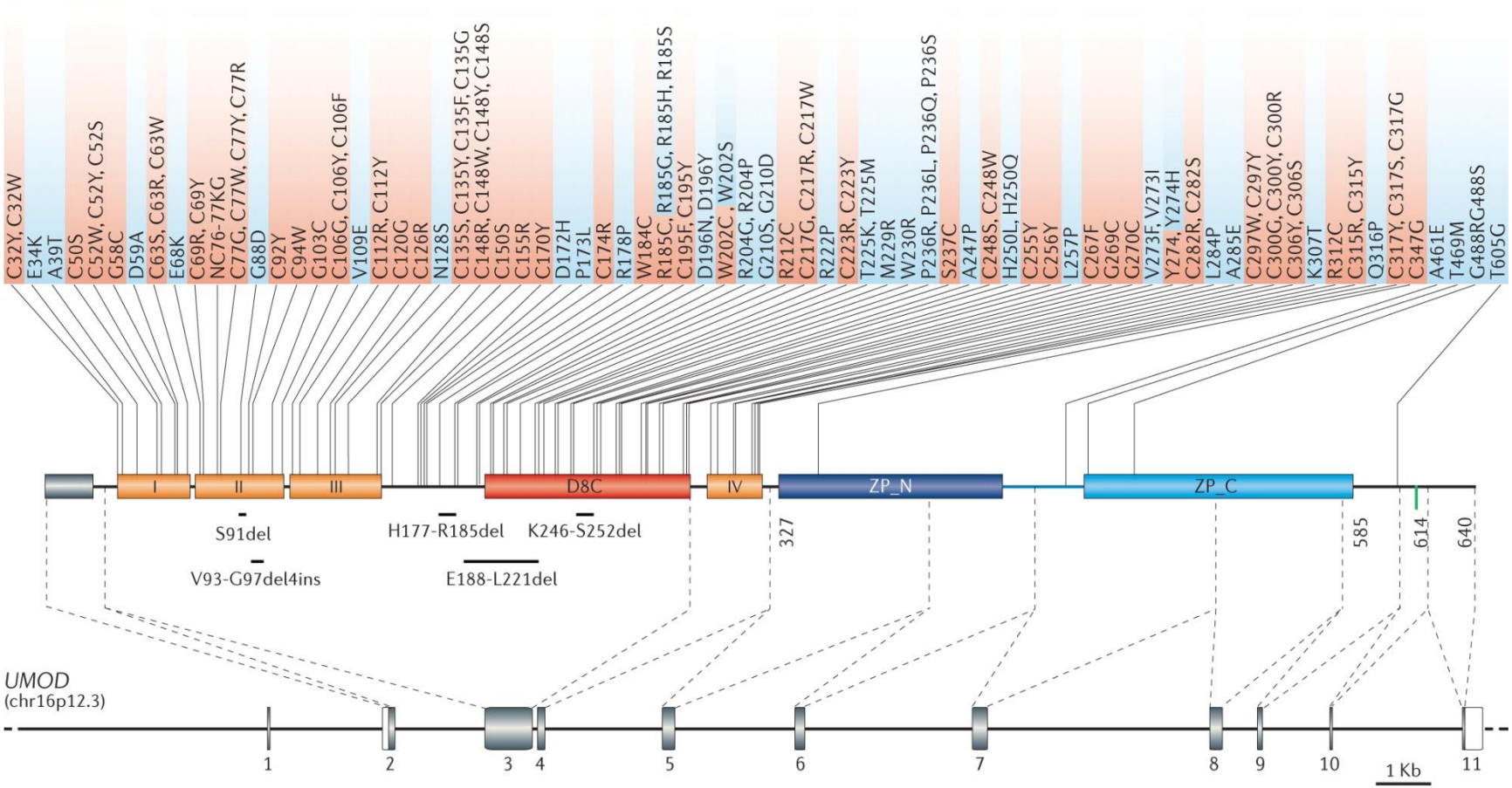




- Autosomal dominant
- Hyperuricemia (low FEurate) during childhood
- Tubulointersitital nephritis (thickening TBM)
- Progressive renal failure - adulthood

Dahan et al. JASN 2001;12: 2348-57

Uromodulin Mutations in ADTKD/FJHN

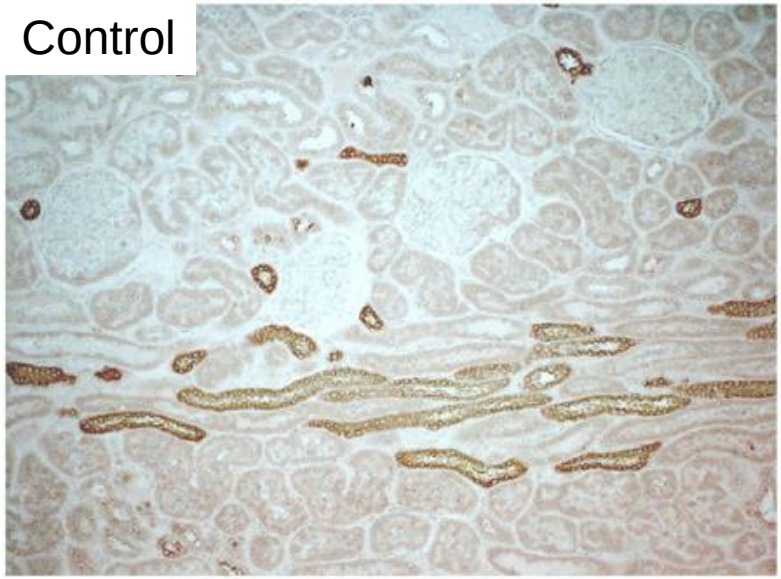


→ 125 mutations, 95% cluster in exons 3 and 4
→ 121/125 missense mutations, 4 in-frame deletions
→ Conserved sequence, cysteine residues (78/125)

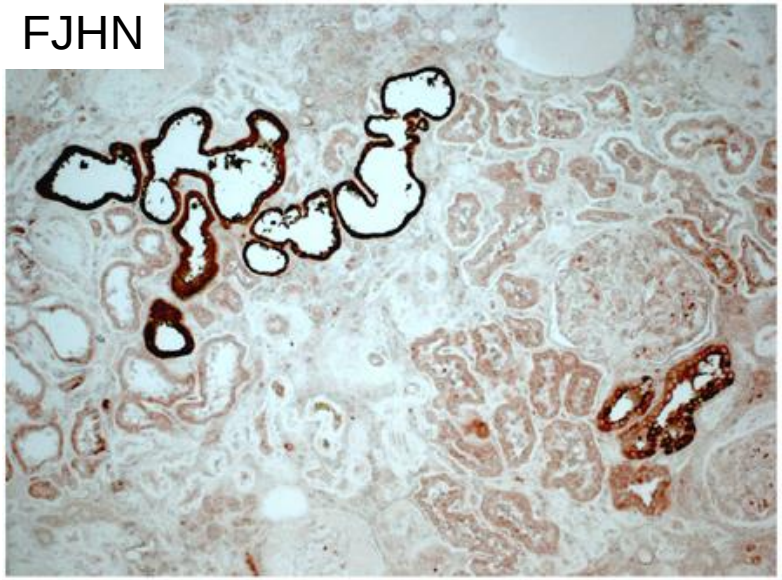
Devuyst O et al. Nat Rev Nephrol. 2017 Sep;13(9):525-544.

Accumulation of THP in FJHN patients with *UMOD* mutations

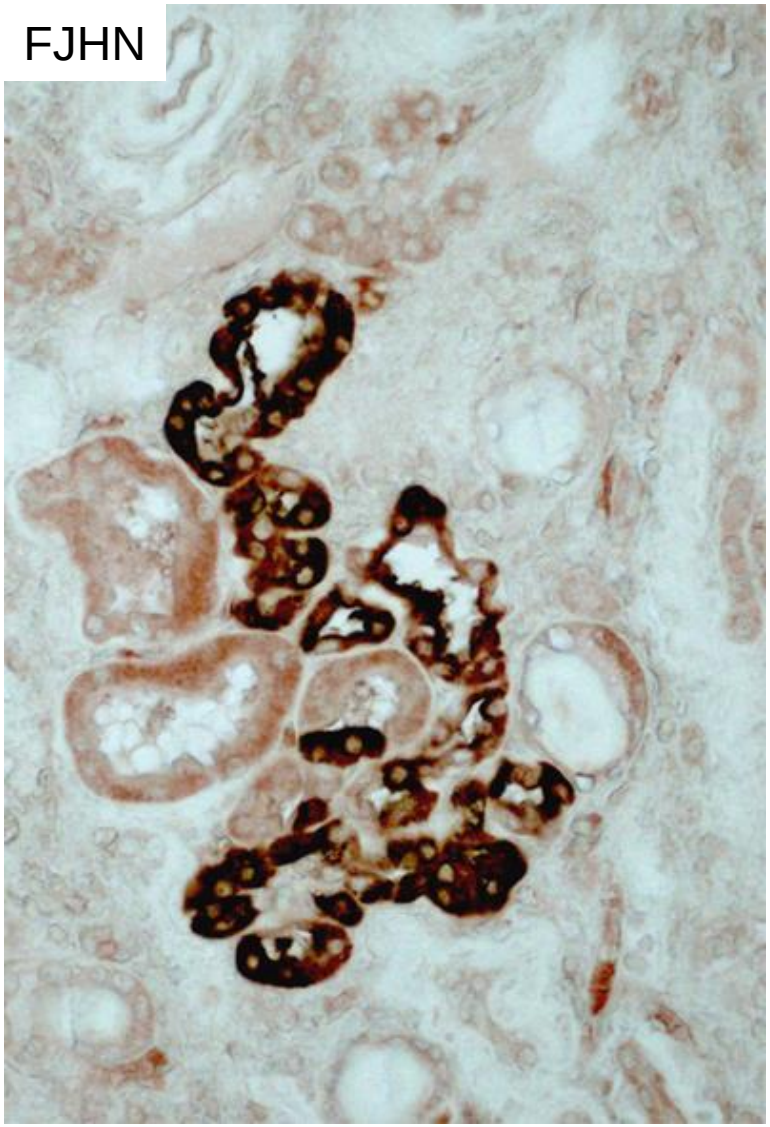
Control



FJHN

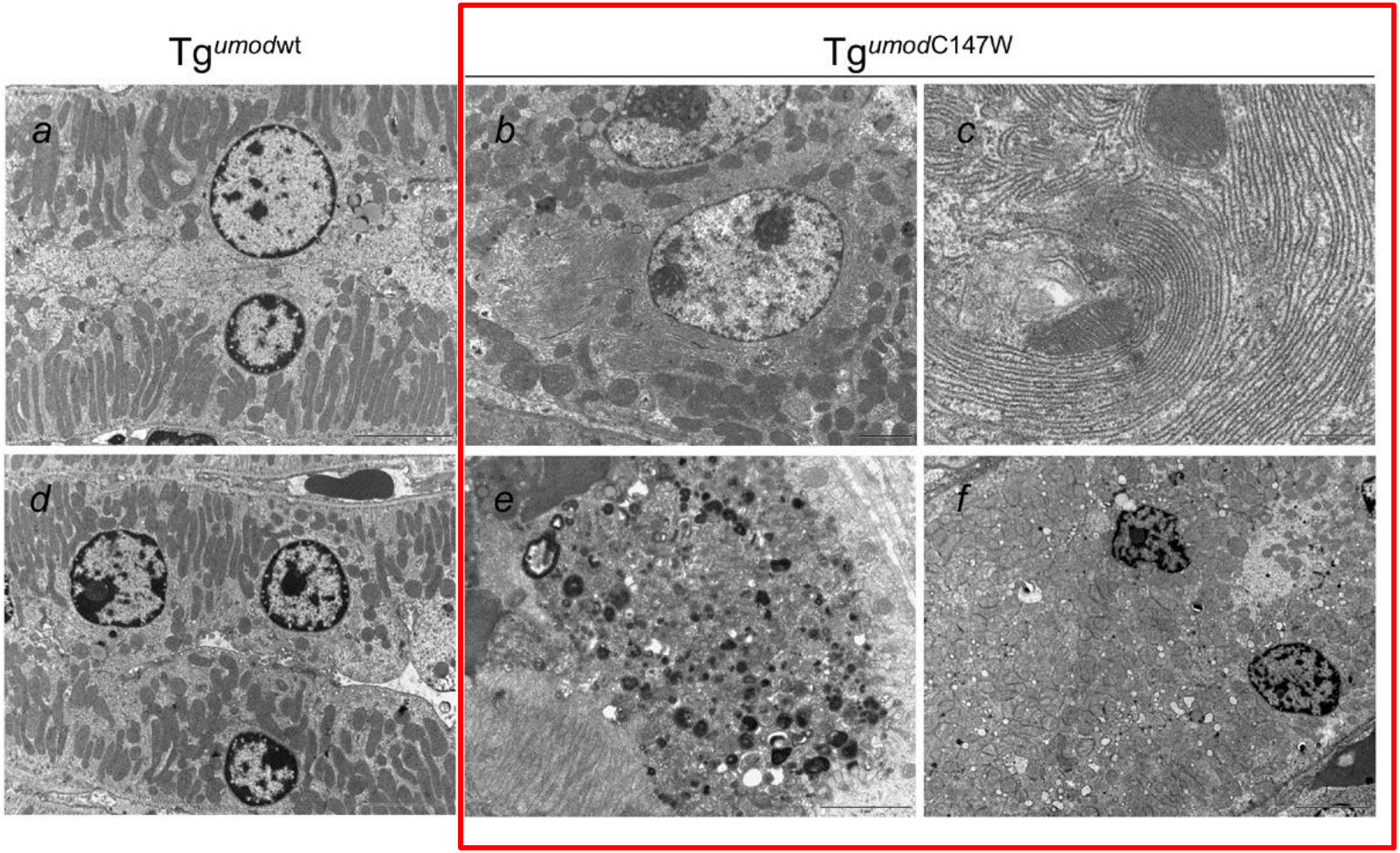


FJHN



Dahan K et al. JASN 2003;14: 2883-93

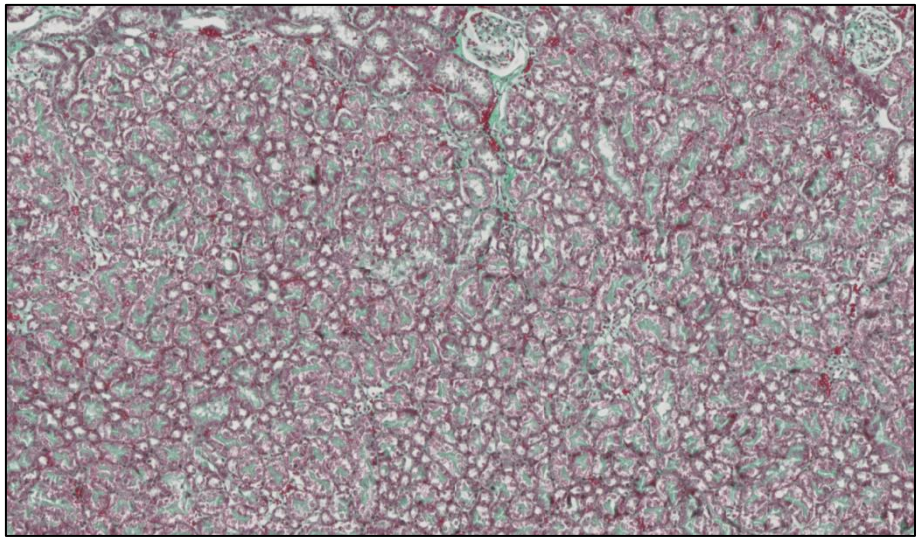
Expanded ER with folded membranes, cytosplasmic accumulation



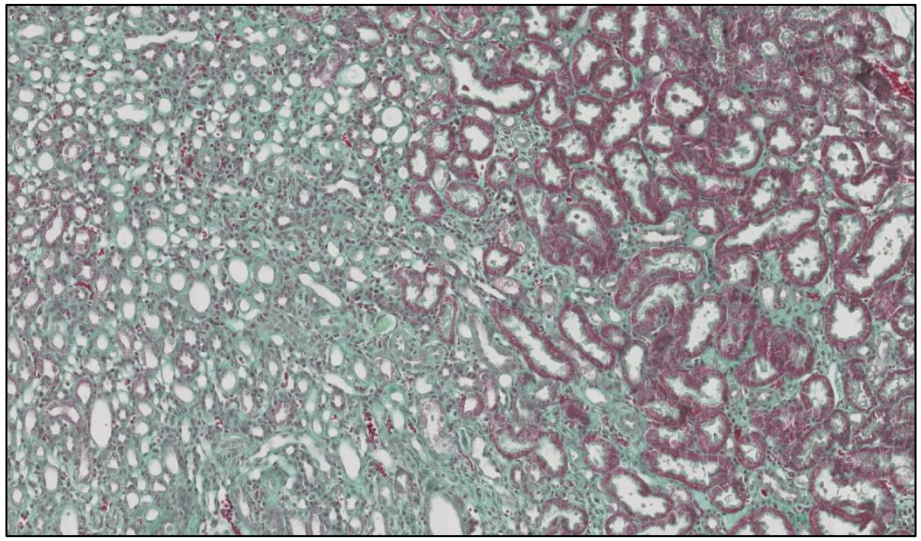
Bernascone et al. Hum Mol Genet. 2010 Aug 1;19(15):2998-3010.

Umod R185S mice develop severe interstitial fibrosis

Umod$^{+/+}$

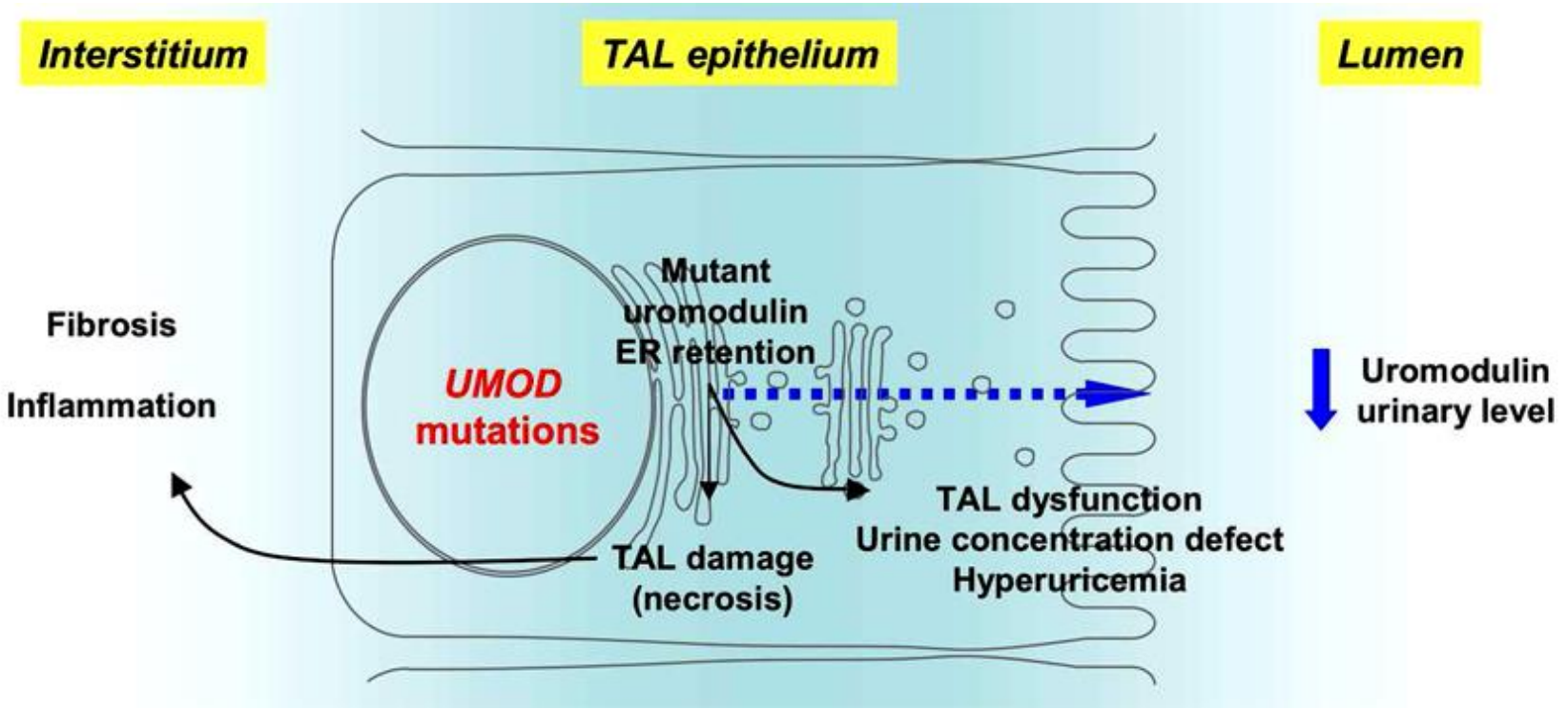


Umod$^{+/185S}$



Courtesy: O. Devuyst

Pathophysiology of ADTKD - UMOD



Mutant uromodulin: ER storage & UPR → Tubulointerstitial lesions

Rampoldi et al. Kidney Int. 2011;80:338-47

Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management—A KDIGO consensus report

Kai-Uwe Eckardt[1], Seth L. Alper[2], Corinne Antignac[3,4], Anthony J. Bleyer[5], Dominique Chauveau[6], Karin Dahan[7], Constantinos Deltas[8], Andrew Hosking[9], Stanislav Kmoch[10], Luca Rampoldi[11], Michael Wiesener[1], Matthias T. Wolf[12] and Olivier Devuyst[13]

Table 1 | New gene-based classification and terminology of different types of ADTKD

Causal Gene	Proposed terminology	Previously used terminology
UMOD	ADTKD–*UMOD*	UKD (Uromodulin Kidney Disease)[a] UAKD (Uromodulin-Associated Kidney Disease) FJHN (Familial Juvenile Hyperuricemic Nephropathy) MCKD2 (Medullary Cystic Kidney Disease type 2)
MUC1	ADTKD–*MUC1*	MKD (Mucin-1 Kidney Disease)[a] MCKD1 (Medullary Cystic Kidney Disease type 1)
REN	ADTKD–*REN*	FJHN2 (Familial Juvenile Hyperuricemic Nephropathy type 2)
HNF1B	ADTKD–*HNF1B*	MODY5 (Maturity-Onset Diabetes mellitus of the Young type 5) RCAD (Renal Cyst and Diabetes Syndrome)

Consensus for a single clinical entity: ADTKD - 4 genes

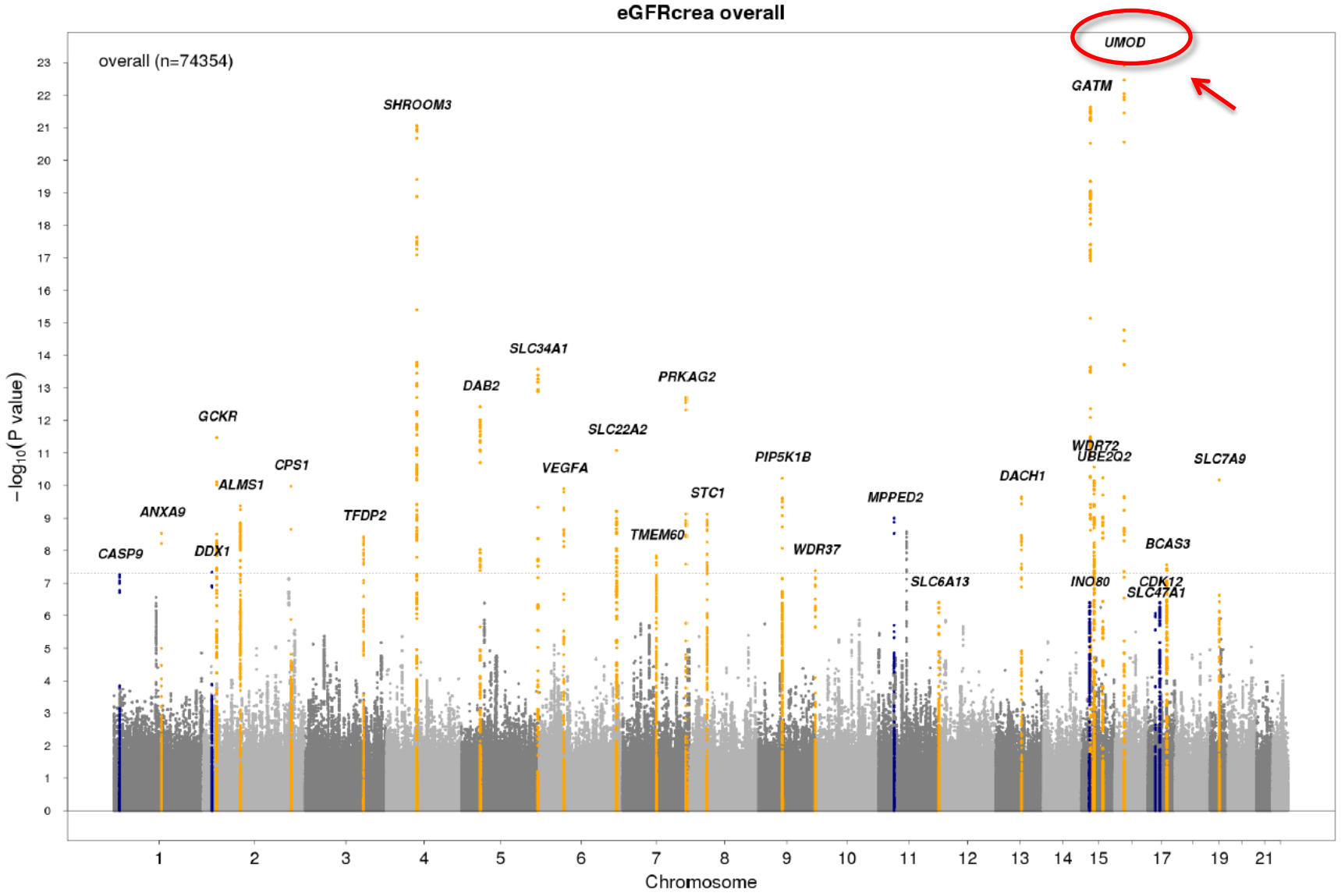
Eckardt et al, Kidney Int. 2015 Oct;88(4):676-83.

The Two Faces of *UMOD*

Monogenic diseases
ADTKD - FJHN

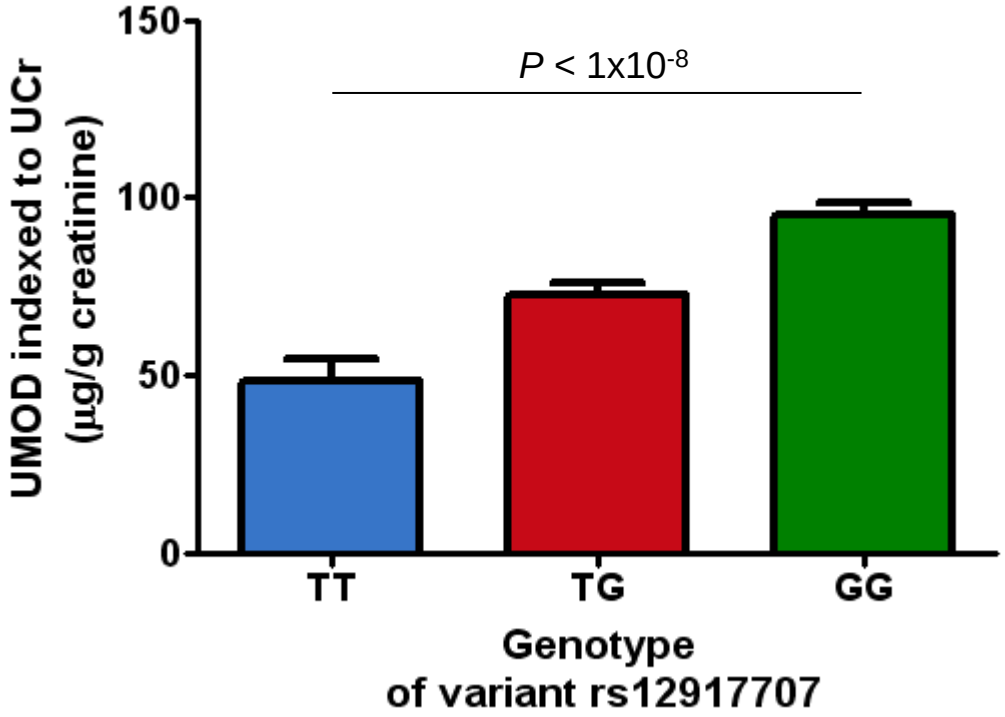
Complex diseases
CKD, hypertension

GWAS for the risk of CKD: *UMOD* is Lead SNP



Pattaro et al. PLoS Genet. 2012;8(3):e1002584. doi: 10.1371/journal.pgen.1002584. Epub 2012 Mar 29.

The *UMOD* Risk Allele Increases Urinary Uromodulin



Urinary uromodulin
N=10,884

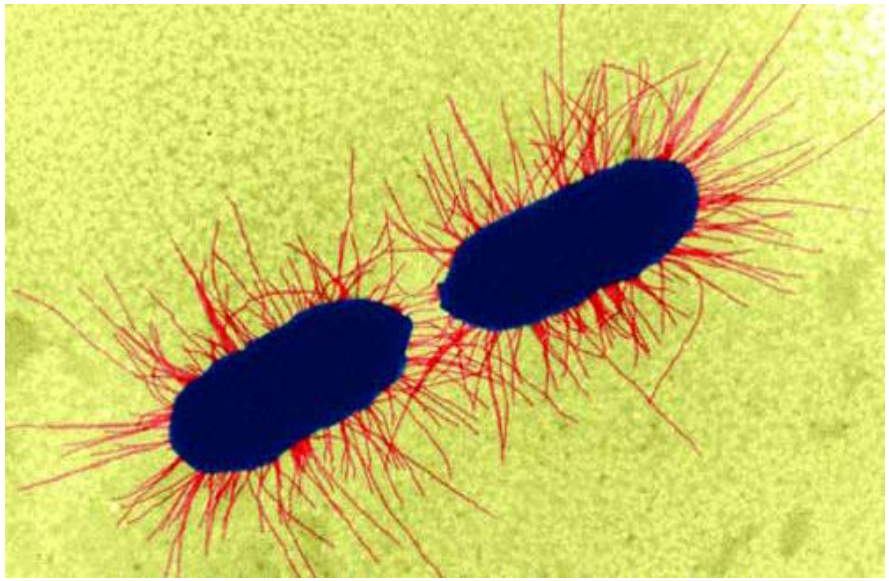
Each copy of the risk (G) allele of rs12917707 results in a significant *increase in urinary uromodulin* levels

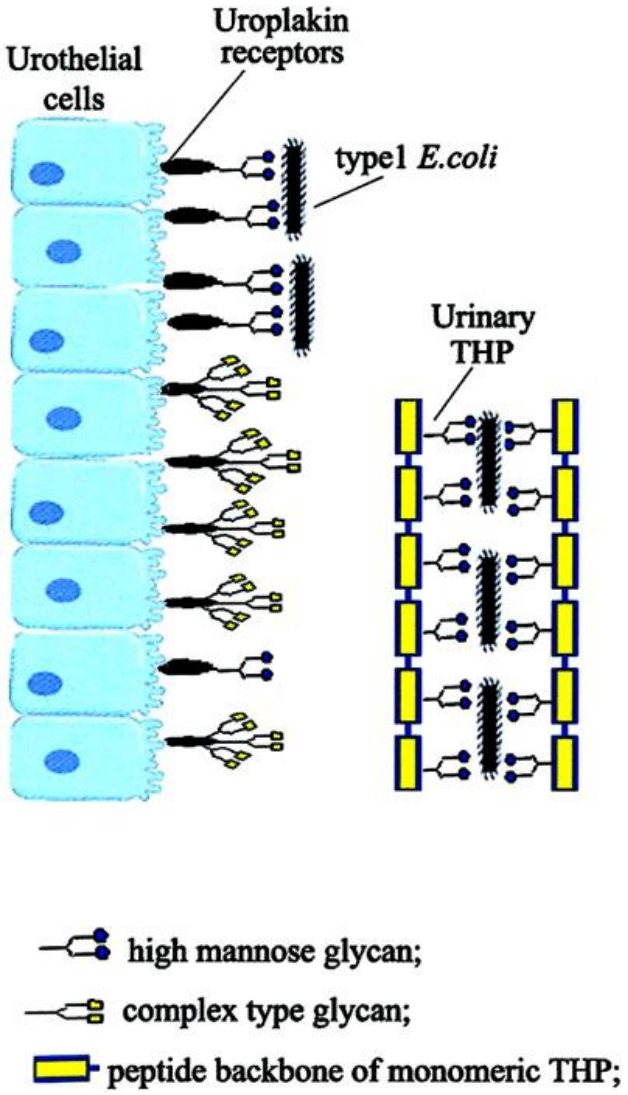
Olden M et al. JASN 2014;25:1869

In vitro binding of type 1-fimbriated *Escherichia coli* to uroplakins Ia and Ib: Relation to urinary tract infections

(epithelial differentiation/urothelium/bladder epithelium/receptor)

XUE-RU WU*†‡§, TUNG-TIEN SUN¶‖**, AND JUAN J. MEDINA*





Wu et al, Cell Biology 1996;93:9630-9635

COLAUS (N=2,497) – General Population Cohort:

Uromodulin Inversely Associated with Nitrites in Urine

Table 4. Multiple logistic regression for factors associated with the presence of urinary nitrites in the CoLaus study

Parameter (*N*=2497)	Odds Ratio	95% Confidence Interval	*P* Value
Age (yr)	1.04	1.02 to 1.08	0.001
Sex (1= women, 0= men)	4.01	2.02 to 7.98	<0.001
Square-root urinary creatinine (mg/dl)	1.19	1.08 to 1.30	<0.001
Square-root urinary uromodulin (μg/ml)	0.74	0.60 to 0.90	0.002

When accounting for urinary creatinine, age, and sex, urinary uromodulin was negatively associated with the presence of urinary nitrites.

www.colaus.ch

Ghirotto et al. J Am Soc Nephrol. 2016 Oct;27(10):2983-2996. Epub 2016 Mar 10.

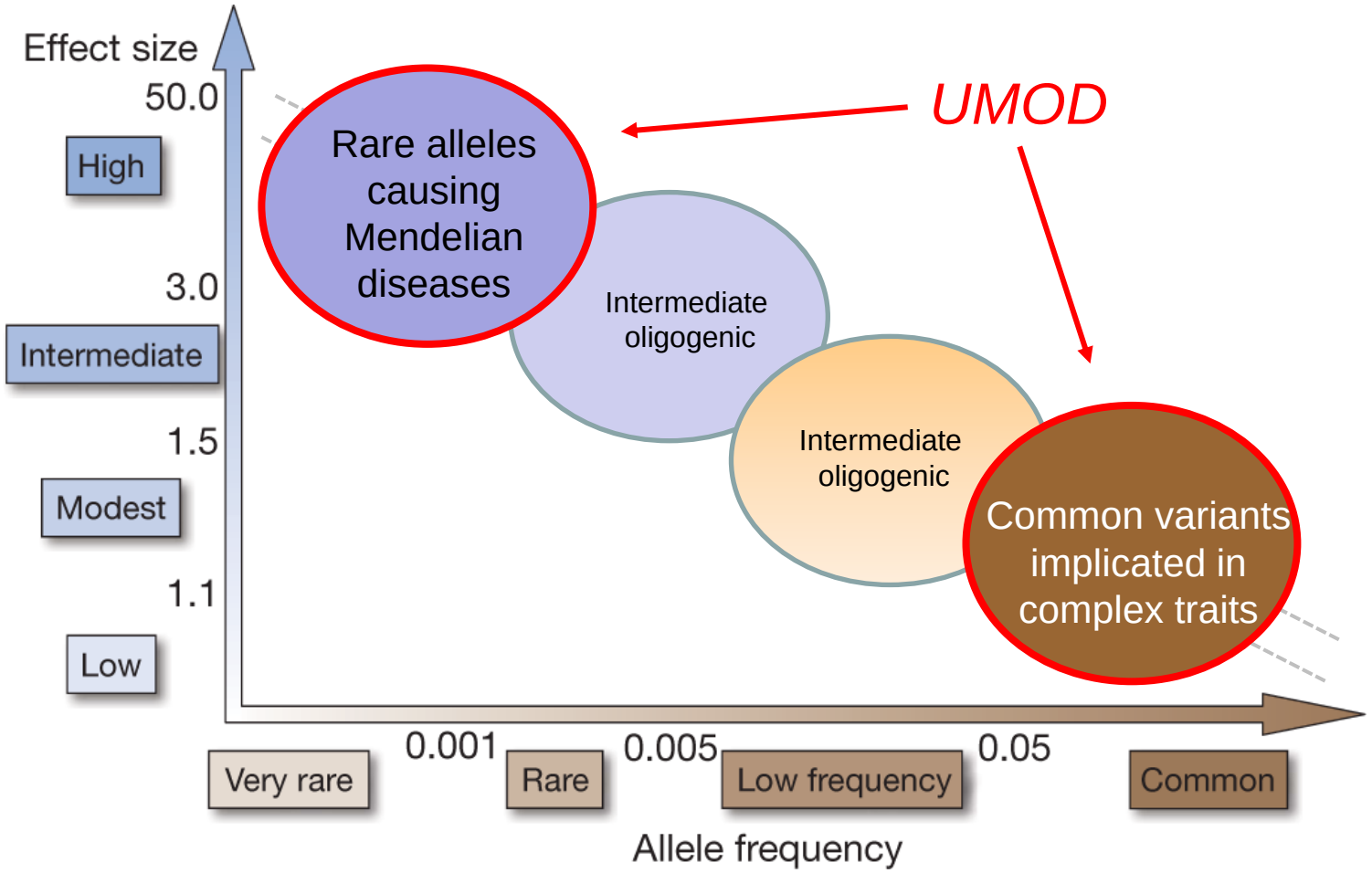
Urinary Uromodulin and Risk of Urinary Tract Infections: The Cardiovascular Health Study

Pranav S. Garimella, MD, MPH,[1] Traci M. Bartz, PhD,[2] Joachim H. Ix, MD, MAS,[3] Michel Chonchol, MD,[4] Michael G. Shlipak, MD, MPH,[5] Prasad Devarajan, MD,[6] Michael R. Bennett, PhD,[6] and Mark J. Sarnak, MD, MS[1]

- Prospective longitudinal cohort study in 953 participants enrolled in the Cardiovascular Health Study.
- Predictive value of urinary uromodulin on composite of outpatient UTI events adjusted for age, race, sex, body mass index, diabetes, eGFR, UAE.
- Results: Persons in the highest quartile of uromodulin concentration had a significantly lower risk for the composite outcome (incidence rate ratio [IRR], 0.47; 95% CI, 0.29-0.79) compared with those in the lowest quartile.
- Conclusions: High urinary uromodulin levels are associated with lower risk for UTI in older community-dwelling adults independent of traditional UTI risk factors. This finding supports prior laboratory data indicating a protective role of uromodulin against UTI.

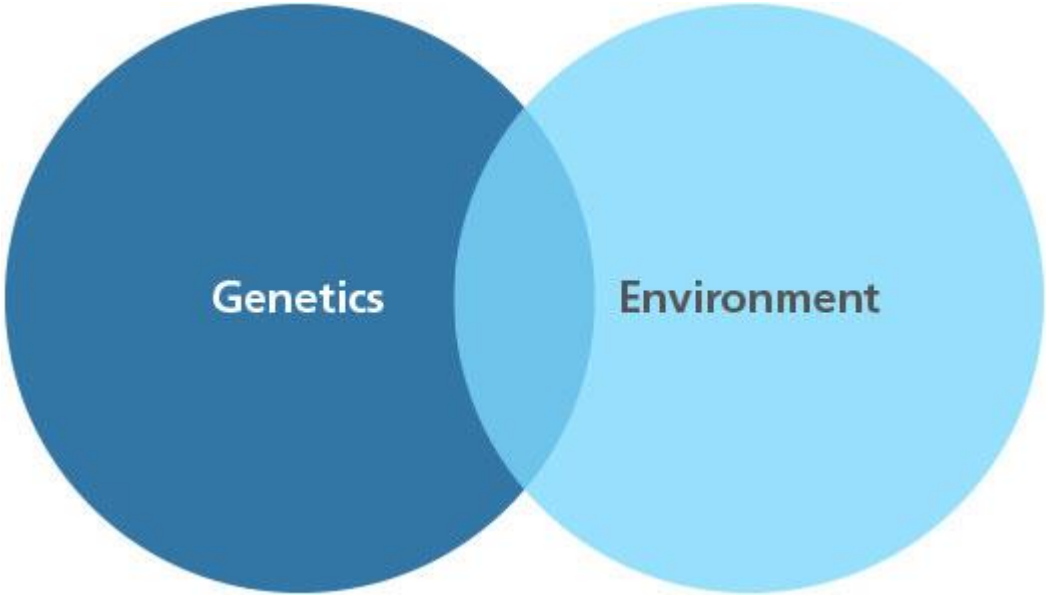
Garimella et al, Am J Kidney Dis. 2017 Jun;69(6):744-751.

Genomic Variation in the Spectrum of Disease



Manolio et al. Nature. 2009 Oct 8;461(7265):747-53.

Emerging Theme:
Gene, Environment, and Risk of Disease



Water

Salt

Temperature

Geography

Pathogens

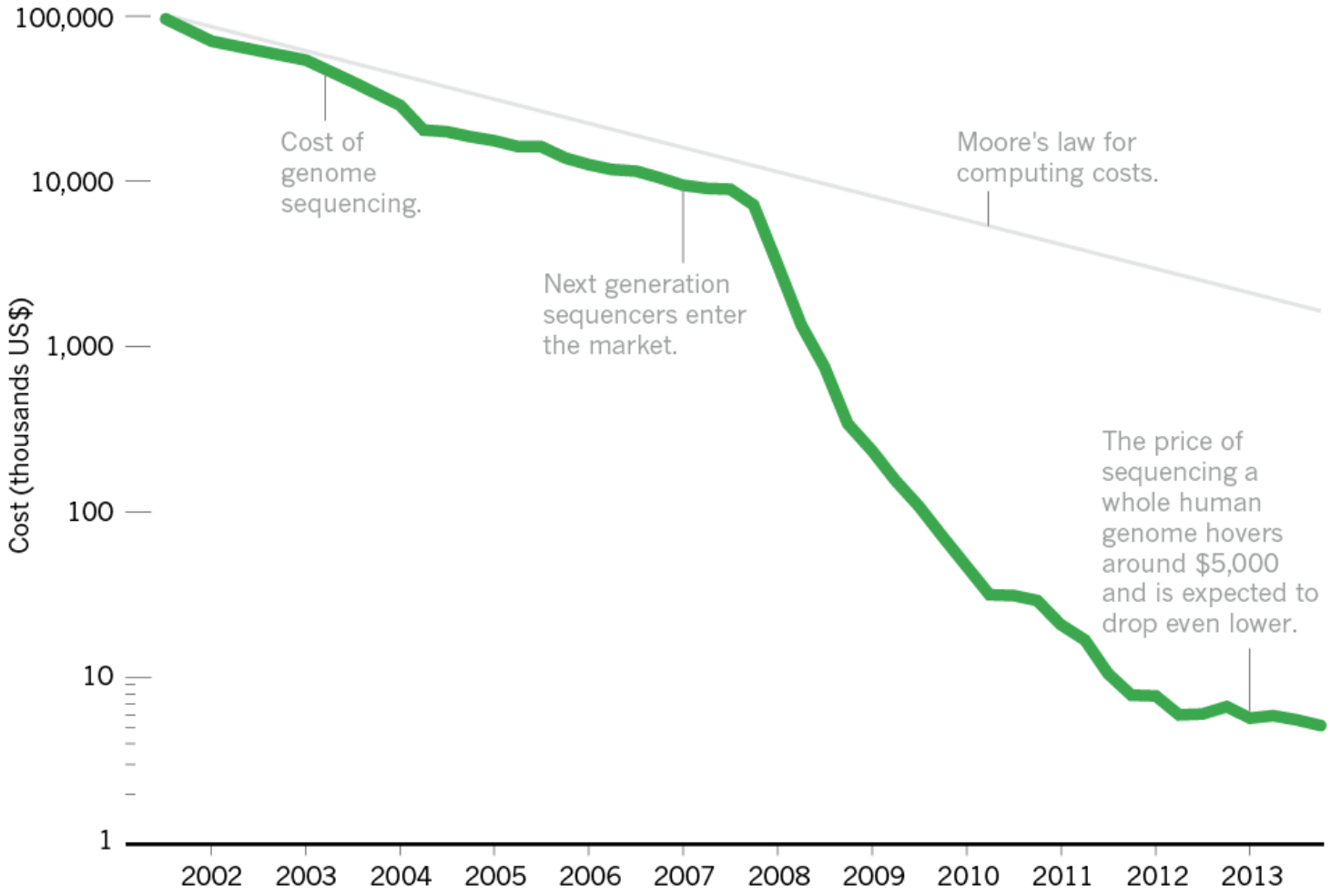
APOL1 – Trypanosome *IGAN – Schistosome* *UMOD – E. coli*

Inherited Kidney Diseases: Opportunities

Nature, 19 March 2014

Falling fast

In the first few years after the end of the Human Genome Project, the cost of genome sequencing roughly followed Moore's law, which predicts exponential declines in computing costs. After 2007, sequencing costs dropped precipitously.



Hayden Nature. 2014 Mar 20;507(7492):294-5

Inherited Kidney Disorders: Next-generation Sequencing

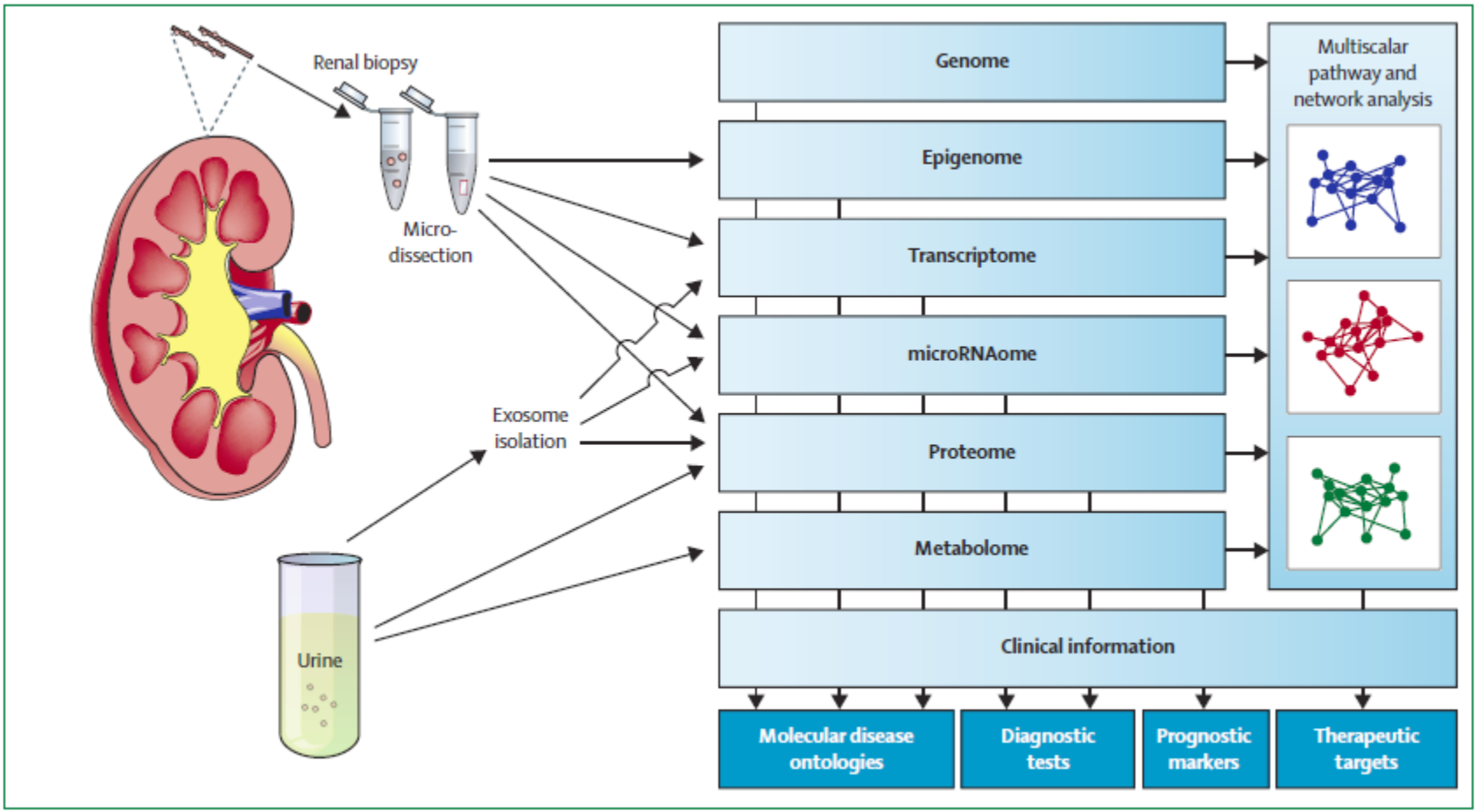
- Development and validation of multigene panels: *simultaneous investigation of all relevant genes for a given phenotype*

  → Reduced costs and turn-around times

- Successful application multigene panels/NGS for diagnostic:
  - Alport syndrome
  - Steroid-resistant nephrotic syndrome
  - Nephronophthisis - ciliopathies
  - Tubulopathies

- Whole exome and whole genome sequencing – new challenges

Inherited Kidney Disorders: Omics Technologies



Devuyst O, et al. Lancet 2014;383

Research Programmes, Cohorts, Biorepositories

Fragmentation of patient-related information represents a major obstacle for rare disease research.

- EPIRARE: European Platform for Rare Disease Registries (www.epirare.eu)
- PARENT: Patient Registries Initiative (www.patientregistries.eu)
- RD-CONNECT: A platform connecting databases, registries, biobanks
- IRDiRC: International Rare Diseases Research Consortium (www.irdic.org)
- EURenOmics: EU Consortium for High-Throughput Research in Rare Kidney Diseases
- ORPHANET: The portal for rare diseases and orphan drugs (www.orpha.net)
- EURORDIS: The European Organization for Rare Diseases (www.eurordis.org)
- Center for Mendelian Genomics (www.mendelian.org)
- …

Controversies Conferences examine what is known, what can be done with what is known and what needs to be known on topics of clinical relevance in nephrology.

- *Current practice recommendations*
- *Clinical questions and outstanding issues*
- *Research agenda*

- Gitelman Syndrome (Brussels, February 2016)
- Complement-Mediated Kidney Diseases (Barcelona, November 2015)
- Fabry Nephropathy (Dublin, October 2015)
- Nephropathic Cystinosis (Lisbon, December 2014)
- Autosomal Dominant Tubulointerstitial Kidney Disease (Boston, September 2014)
- Autosomal Dominant Polycystic Kidney Disease (ADPKD) (Edinburgh, January 2014)

KDIGO: Common Elements in Rare Kidney Diseases: Issues with Care in Patients with Genetic Defects

Aymé S et al. Kidney Int, in press

Patient Organizations and Research on Rare Diseases

Comment on: Efficacy and safety of sirolimus in lymphangioleiomyomatosis.

Ingelfinger et al N Engl J Med 2011;364:1670-1671

Common Elements in Nephrogenetics: Challenges and Topics

- Technological advances in diagnosis
- Consequences of improved genetic diagnosis
- Management of renal function, optimal pediatric transition care
- Challenges in trial design and conduct
- Development of novel biomarkers or surrogates
- Translation of new knowledge into clinical programs
- QOL issues
- Policy initiatives – various parts of the world

→ *Implementation of the resources in low-income countries ?*

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