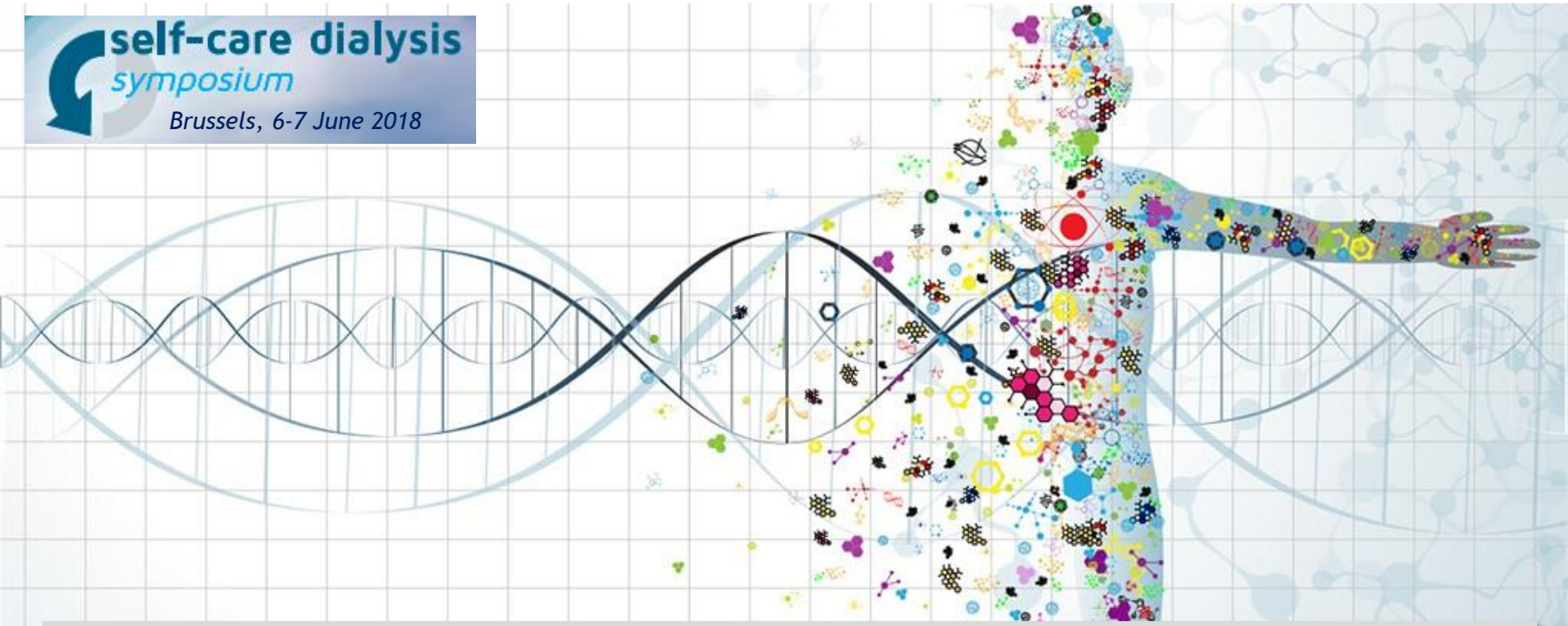
self-care dialysis symposium

Brussels, 6-7 June 2018



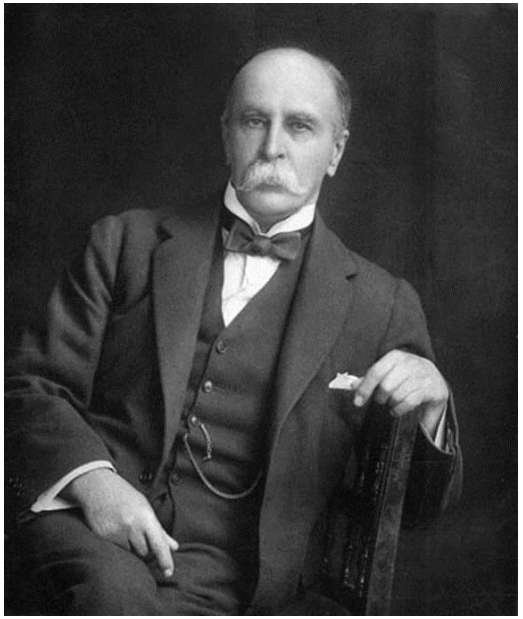
Precision Medicine in Nephrology: Perspectives

Olivier Devuyst, MD, PhD

UCL Université catholique de Louvain

EURenOmics

University of Zurich[UZH]



“The good physician treats the disease; the great physician treats the patient who has the disease”.

Sir William Osler, 1903

2018: Era of precision (stratified) medicine

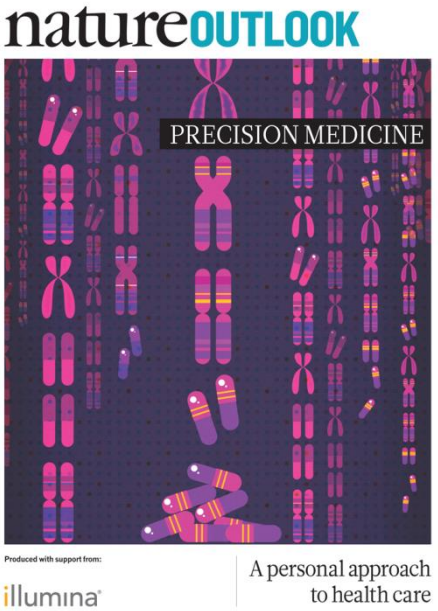
* Using genetics and other “omics” as predictive tools to evaluate health risks
* Identifying patients with distinct mechanisms of disease and particular responses to treatments
* Define treatments that are effective for subgroups of patients

Precision Medicine: Where are we ?

- Promise: to treat with a given drug only responders and patients not predisposed to toxicity.
- Very well developed in cancer medicine: successful precision medicine applications in breast, prostate, ovarian, colon and pancreatic cancer.
- Cardiovascular medicine, nephrology and hypertension lag behind oncology.

Rare monogenic syndromes: a single mutation explains the disease & dictates pharmacogenetics-led prescription:

- Liddle syndrome: R/ Amiloride
- Pseudohypoaldosteronism type II (Gordon syndrome): R/ Thiazide diuretics



Dominiczak et al. Hypertension 69, 2017

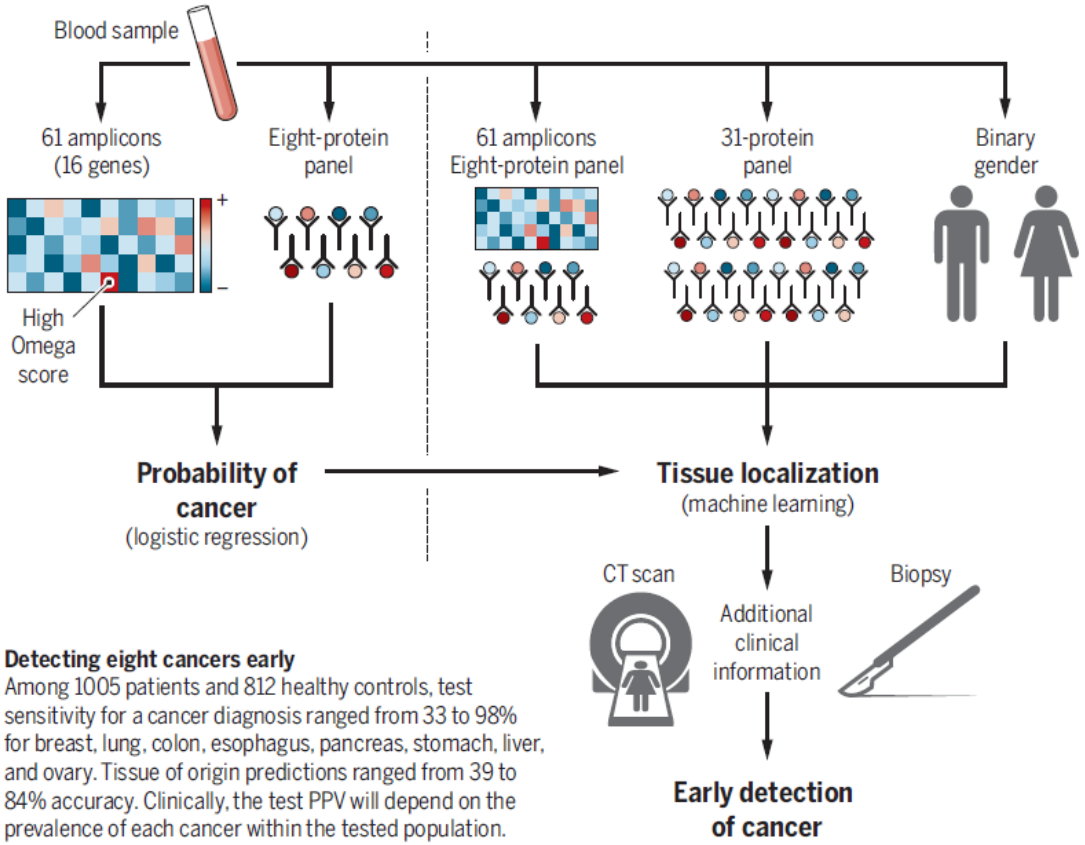
SCIENCE 23 FEBRUARY 2018 • VOL 359 ISSUE 6378

Cancer detection: Seeking signals in blood

Combining gene mutations and protein biomarkers for earlier detection and localization

How the CancerSEEK algorithm works

Plasma-based sequencing of 16 cancer genes generates an Omega score that is combined with eight cancer-associated serum proteins to derive a probability for having any of eight different types of cancer. A machine learning algorithm then integrates these data with 31 additional serum proteins and patient gender to predict the tissue of origin.



Detecting eight cancers early

Among 1005 patients and 812 healthy controls, test sensitivity for a cancer diagnosis ranged from 33 to 98% for breast, lung, colon, esophagus, pancreas, stomach, liver, and ovary. Tissue of origin predictions ranged from 39 to 84% accuracy. Clinically, the test PPV will depend on the prevalence of each cancer within the tested population.

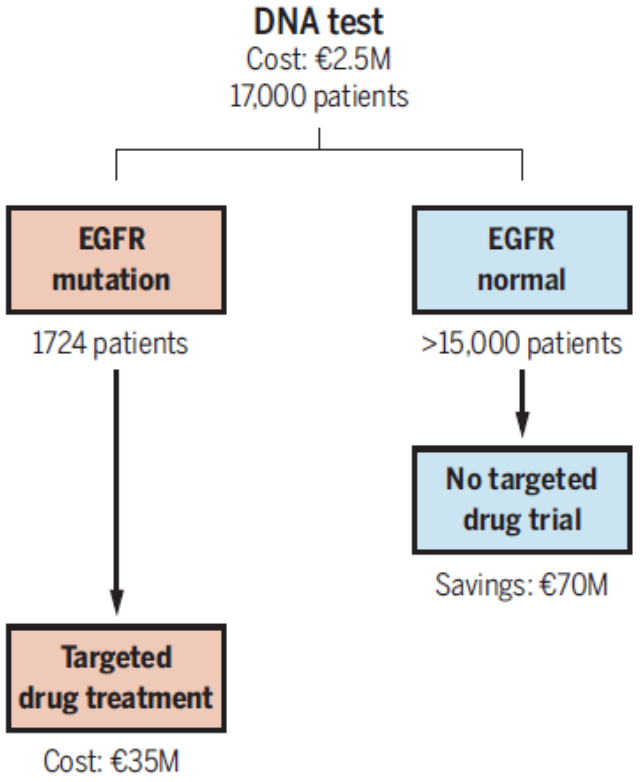
Insurance for broad genomic tests in oncology

Insurance coverage should precede rather than follow clinical validation of broad genomic testing in oncology

"The line between clinical care and clinical investigation is shifting."

The economic benefit of testing for somatic mutations in cancers

Without testing for mutation in the gene encoding the epidermal growth factor receptor (EGFR), all patients with lung adenocarcinoma would receive an 8-week trial of a drug targeting the EGFR and continue with treatment only if they showed an image-validated response. Patients in this 2010 study (*19*) whose tumors were found to have a mutation in the EGFR-encoding gene were treated with the targeted drug; the other patients were spared the costs and delay of an 8-week trial for a drug that would not work for them.



MEDICINE'S FUTURE?

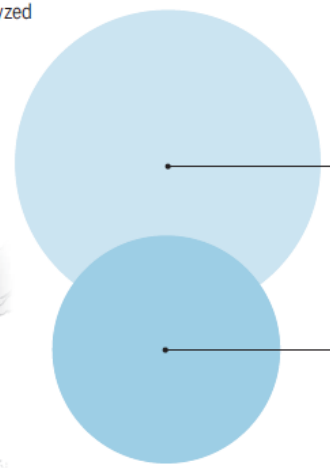
In an ambitious experiment, a rural U.S. health system is trying to integrate genomic screening into routine care

> ***"This is the future of health care."***
>
> **Michael Snyder**,
> Stanford Medicine's Center for Genomics and Personalized Medicine

Pennsylvania's pioneering genomic medicine program

A half-million of Geisinger Health System's patients may have their DNA analyzed for disease mutations.

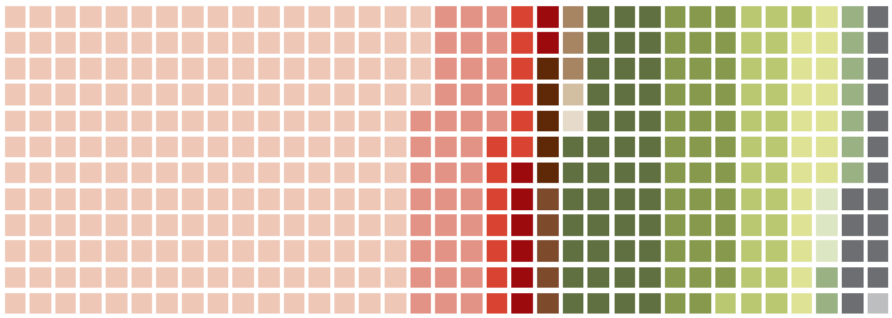
Geisinger informs patients of mutations in 76 genes solidly connected to various diseases.



166,772
People who have agreed to have their DNA screened (all data as of 1 October).

92,456
People whose protein-coding DNA, or exome, has been sequenced.

417
People who were found to have 420 mutations spanning 36 genes.



Cancer risk genes

Grouped by types of cancer or syndrome

- *BRCA2, BRCA1*
- *PMS2, MSH6, MSH2, MLH1*
- *RET*
- *SDHB, SDHC, SDHD*
- *MEN1*
- *TP53*
- *PTEN*
- *TSC2*
- *APC*

Cardiovascular risk genes

Grouped by condition or symptoms

- *APOB, LDLR*
- *MYH7, MYBPC3, TPM1, TNNI3, TNNT2, MYL3*
- *SCN5A, KCNQ1, KCNE1, KCNH2*
- *DSP, PKP2, DSG2*
- *FBN1*
- *ACTA2*

Other

- *RYR1*
- *GLA*

SCIENCE

27 OCTOBER 2017 • VOL 358 ISSUE 6362

Precision Medicine: Challenges and Opportunities

Outline

- Insights from genetics – rare (kidney) diseases
- Use of genetic information – targeted treatments
- Insights from GWAS – risk of CKD, hypertension
- Perspectives for peritoneal dialysis

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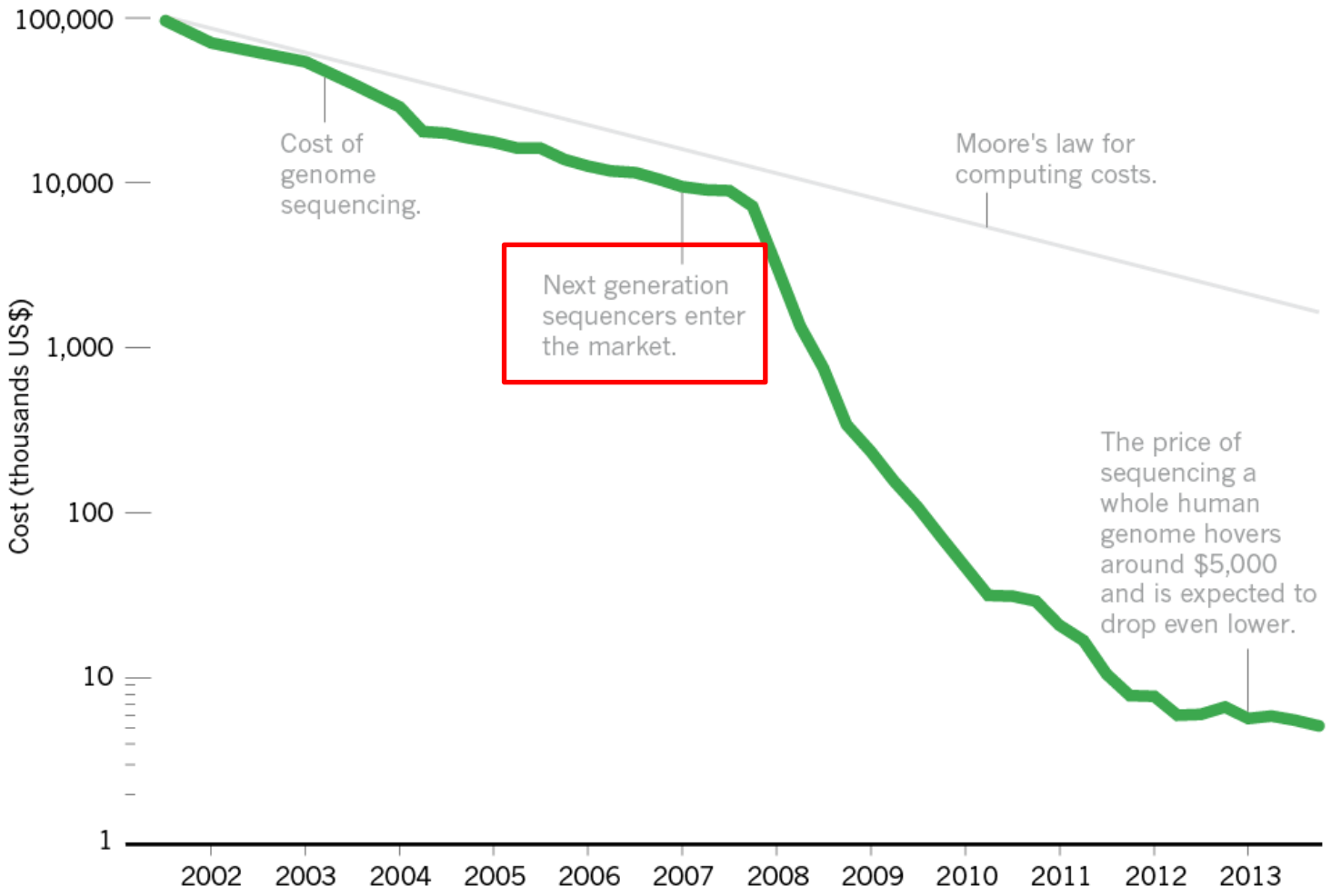
Nature, 19 March 2014

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.



Next-generation Sequencing: Impact for Rare Diseases

- 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

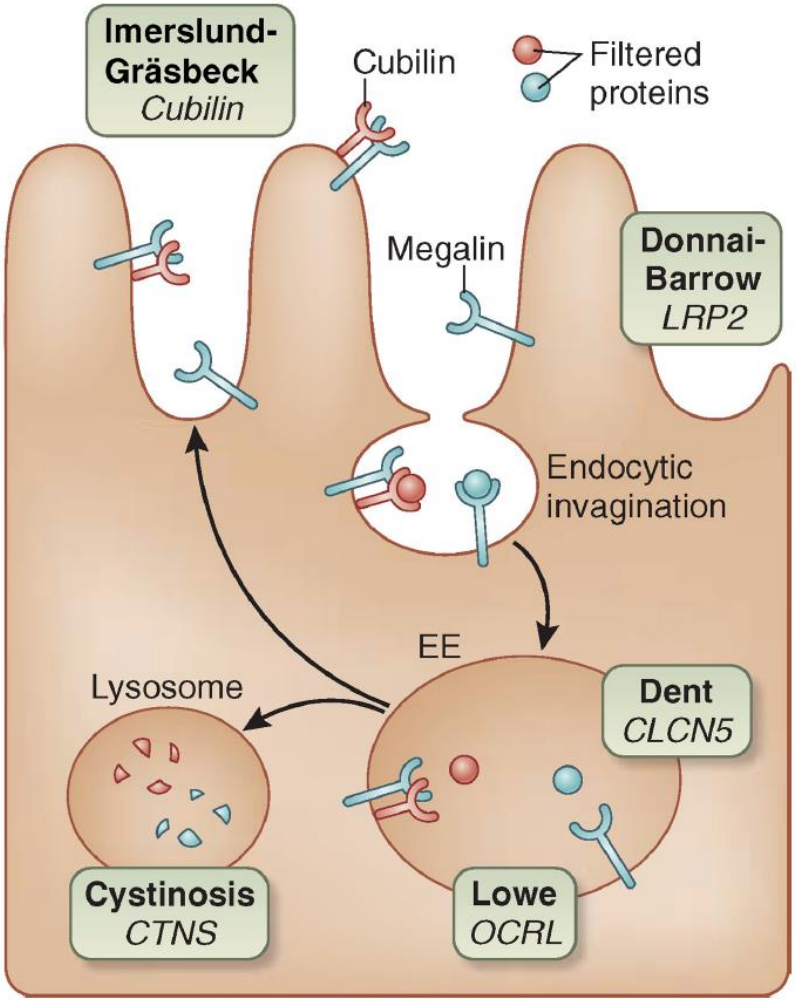
EUReno Omics

Simultaneous sequencing of 37 genes identified causative mutations in the majority of children with renal tubulopathies

- *These results demonstrate a high diagnostic yield of genetic testing in children with a clinical diagnosis of renal tubulopathy.*
- *Genetic testing established a definitive diagnosis in almost two-thirds of patients - informing prognosis, management and genetic counseling.*

Kidney International (2018)

Renal Fanconi Syndrome:
Rare Disorders Targeting the Endolysosomal System



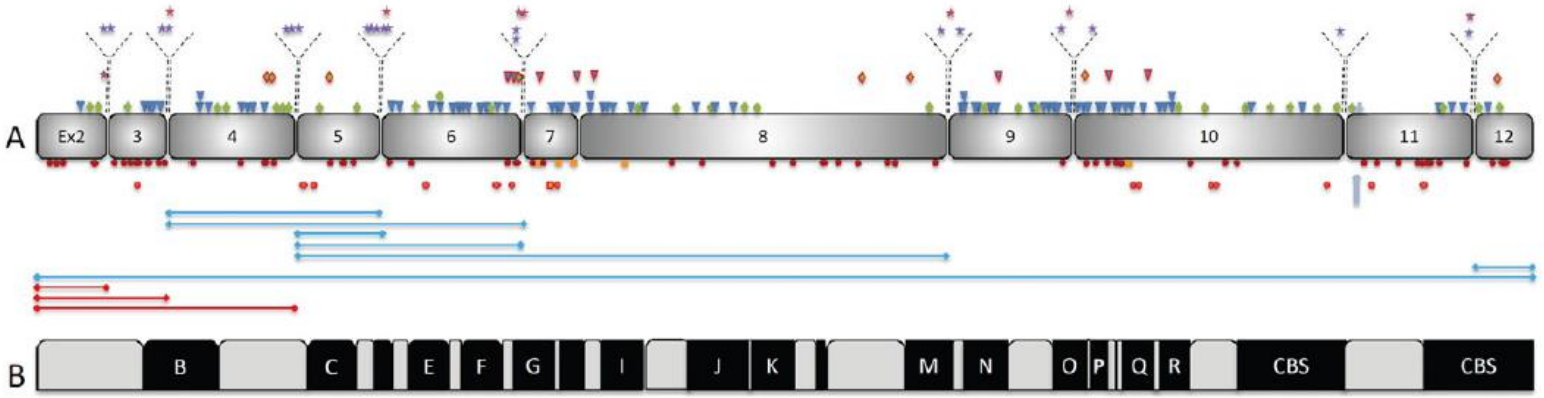
Willnow TE. Kidney Int 2017; 91:776-8

Human Mutation

OFFICIAL JOURNAL
HGVS
HUMAN GENOME VARIATION SOCIETY

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

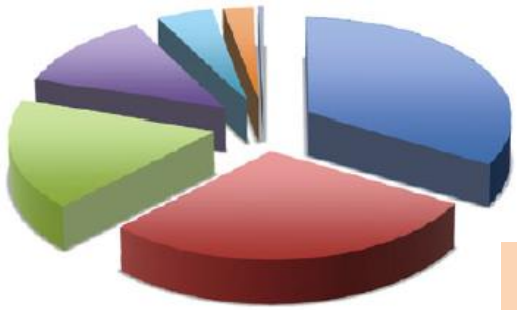
- 234 mutations
- 170 families



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%

Dent Disease: Renal Fanconi Syndrome & Kidney Stones

• 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. NDT 21, 2006

Dent Disease: Phenotype Heterogeneity

Clinical data from 377 male patients belonging to 334 families

- Micro or macrohaematuria (n = 71)
- Polyuria/polydipsia (31/43)
- Proteinuria (n = 57): median value 1.28 g/24 hr
- Proteinuria in the nephrotic range (n = 13)
- Enuresis (n = 5)
- Hypomagnesaemia (4/30)
- Night blindness responsive to vitamin A

→ *New phenotypes: specific management and treatment*

EUReni Omics

Mansour-Hendili L et al. Hum Mutat 36, 2015
Blanchard A et al. Kidney Int 90, 2016

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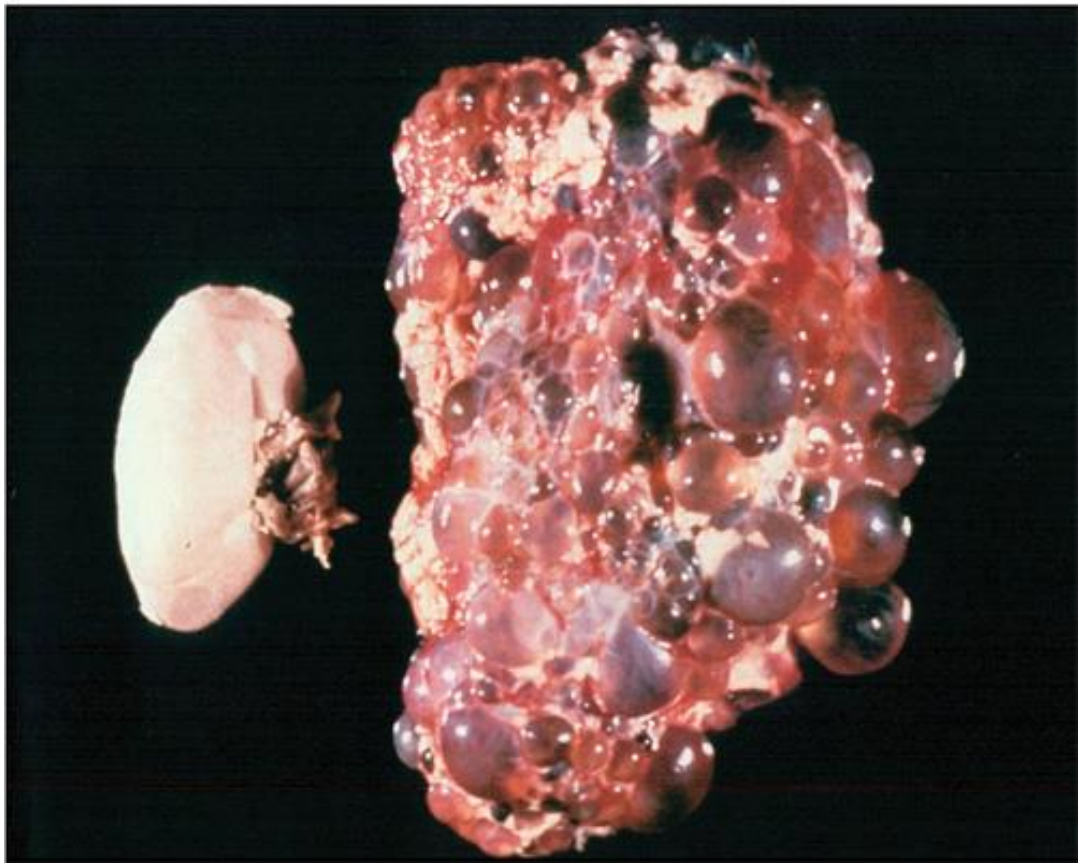
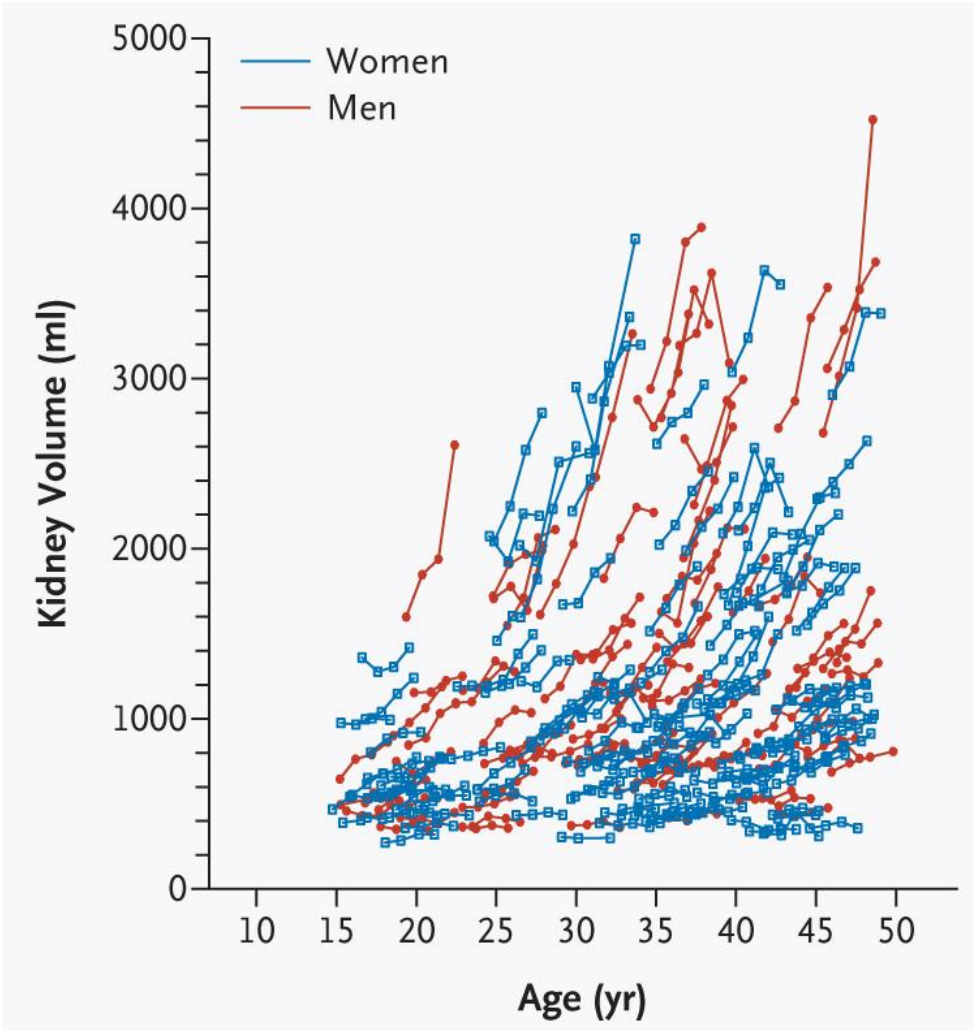
Autosomal Dominant Polycystic Kidney Disease

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

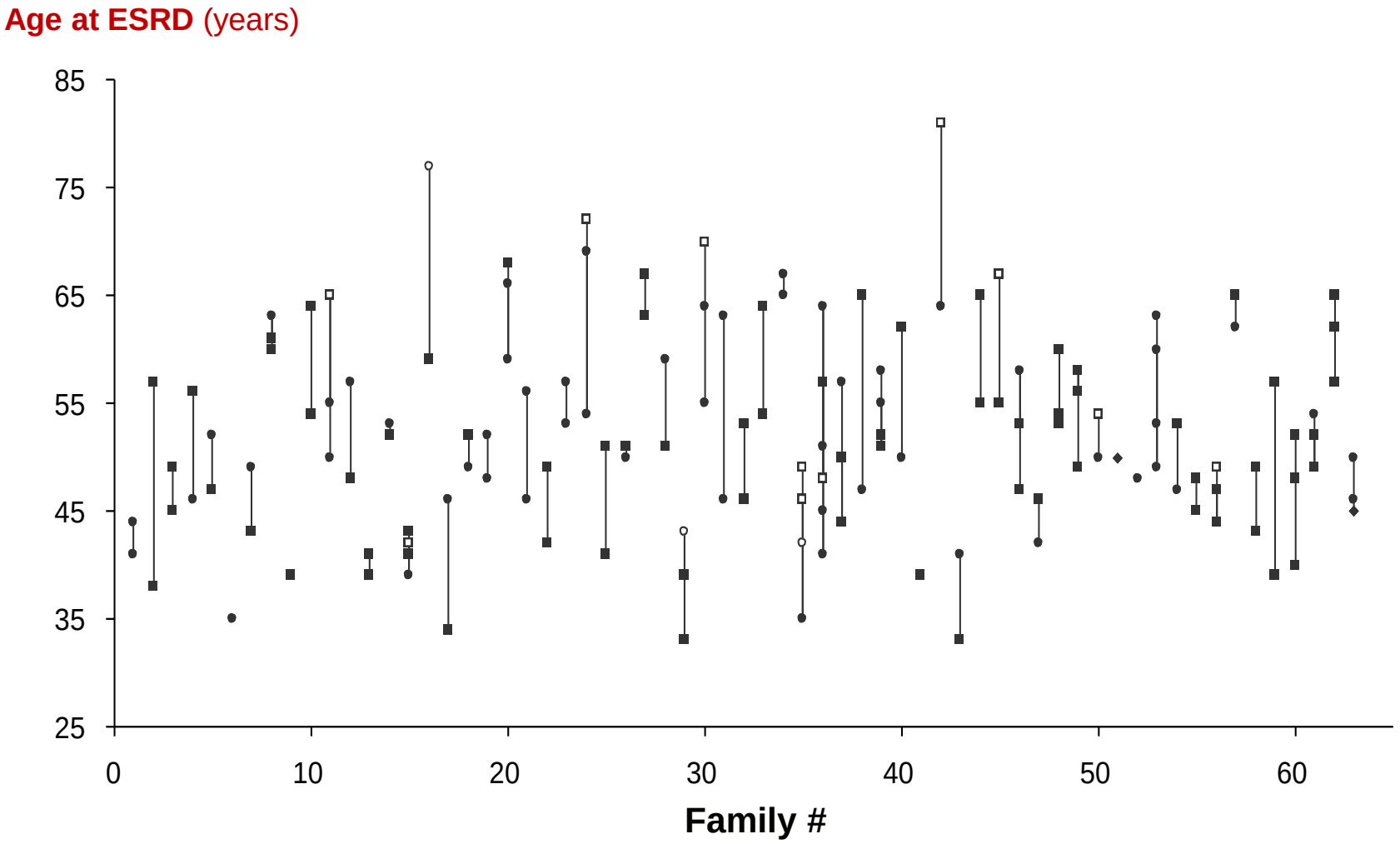


Exponential Progression of Cysts –Kidney Volume in ADPKD



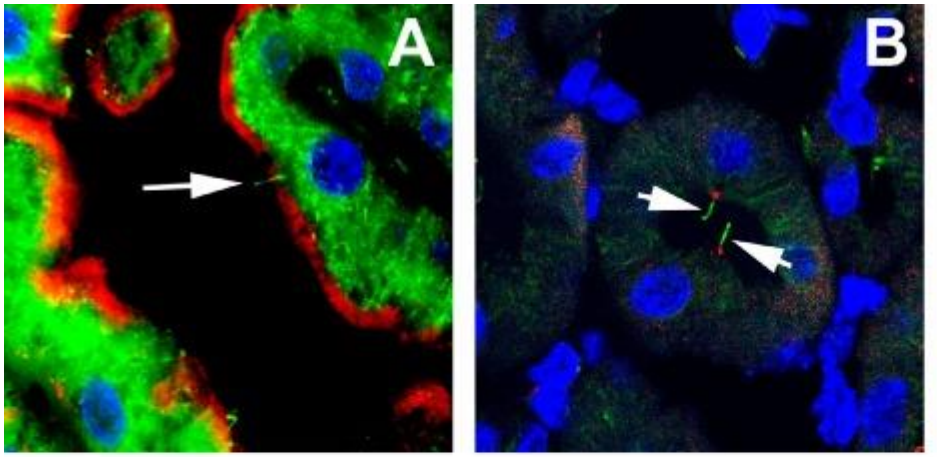
N Engl J Med 2006; 354 : 2122-30

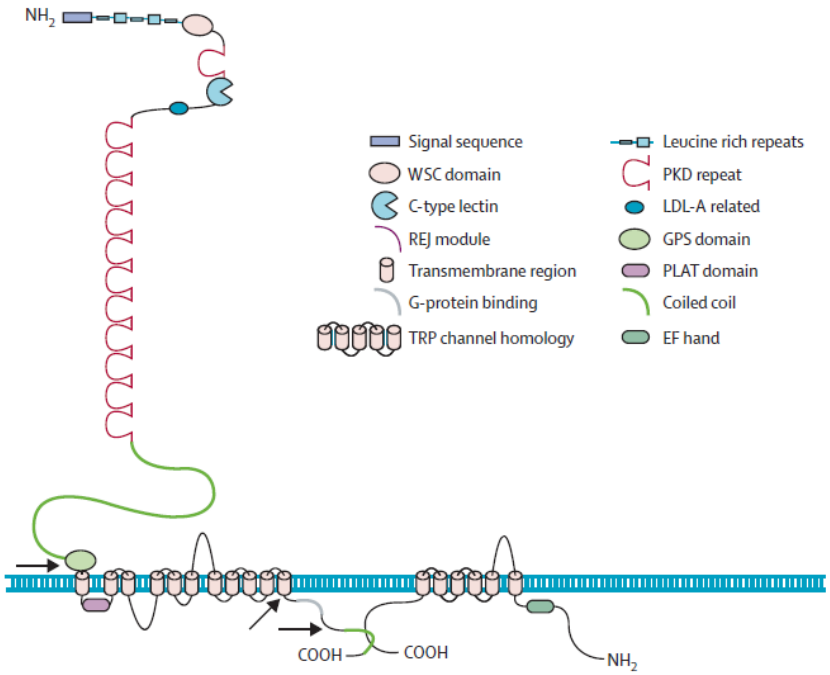
Inter- and Intra-familial Variability in ADPKD:
A Multicentric Sib-pair Study

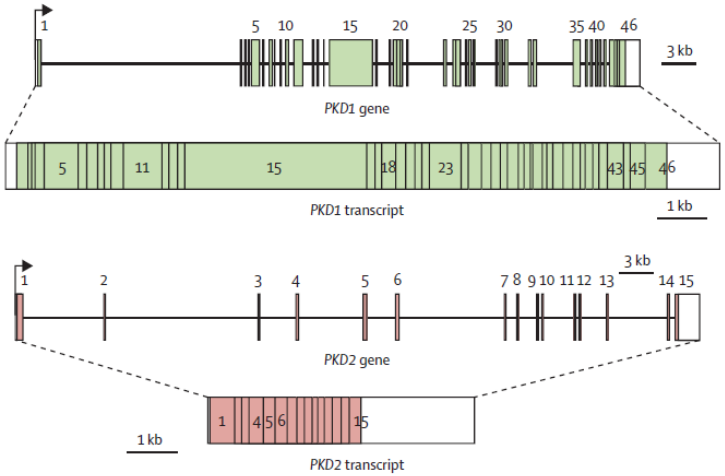


Persu et al. Kidney Int 66, 2004

Molecular Basis of ADPKD: Mutations in *PKD1* and *PKD2*



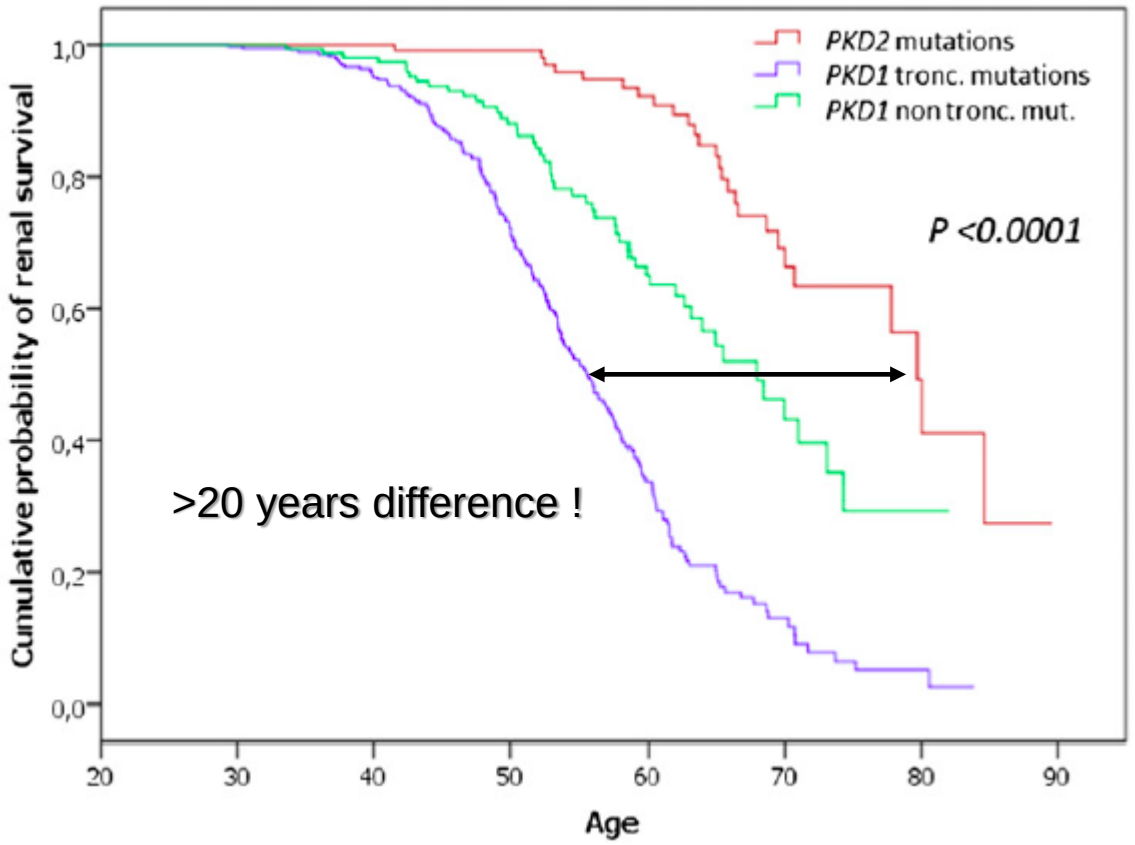




Lancet 2007; 369: 1287–301

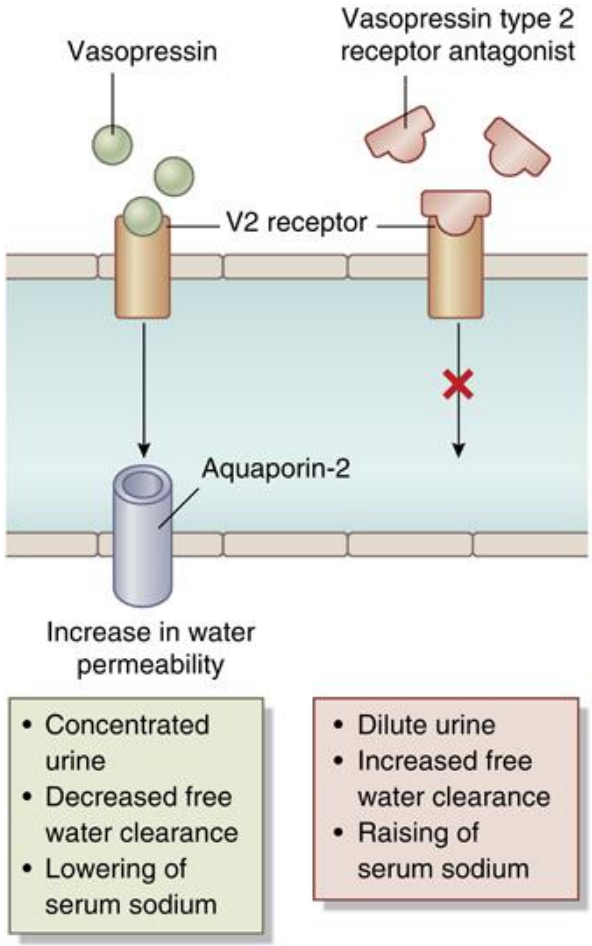
Cornec-Le Gall et al. JASN 24, 2013

Type of *PKD1* Mutation Influences Renal Outcome in ADPKD



Genkyst: 741 patients from 519 pedigrees

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

N Engl J Med. 2012; 367: 2407-18

27/02/2015

Jinarc recommended for approval in ADPKD

The EMA has recommended granting a marketing authorisation to Jinarc (tolvaptan). Jinarc is indicated to slow the progression of cyst development and failing kidney function in adult patients with ADPKD.
Jinarc is for use in patients with normal to moderately reduced kidney function who have rapidly progressing ADPKD.

Nephrol Dial Transplant (2016) 31: 337–348
doi: 10.1093/ndt/gfv456
Advance Access publication 29 January 2016

ndt
Nephrology Dialysis Transplantation

NDT Perspectives

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 ?

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

WGiKD

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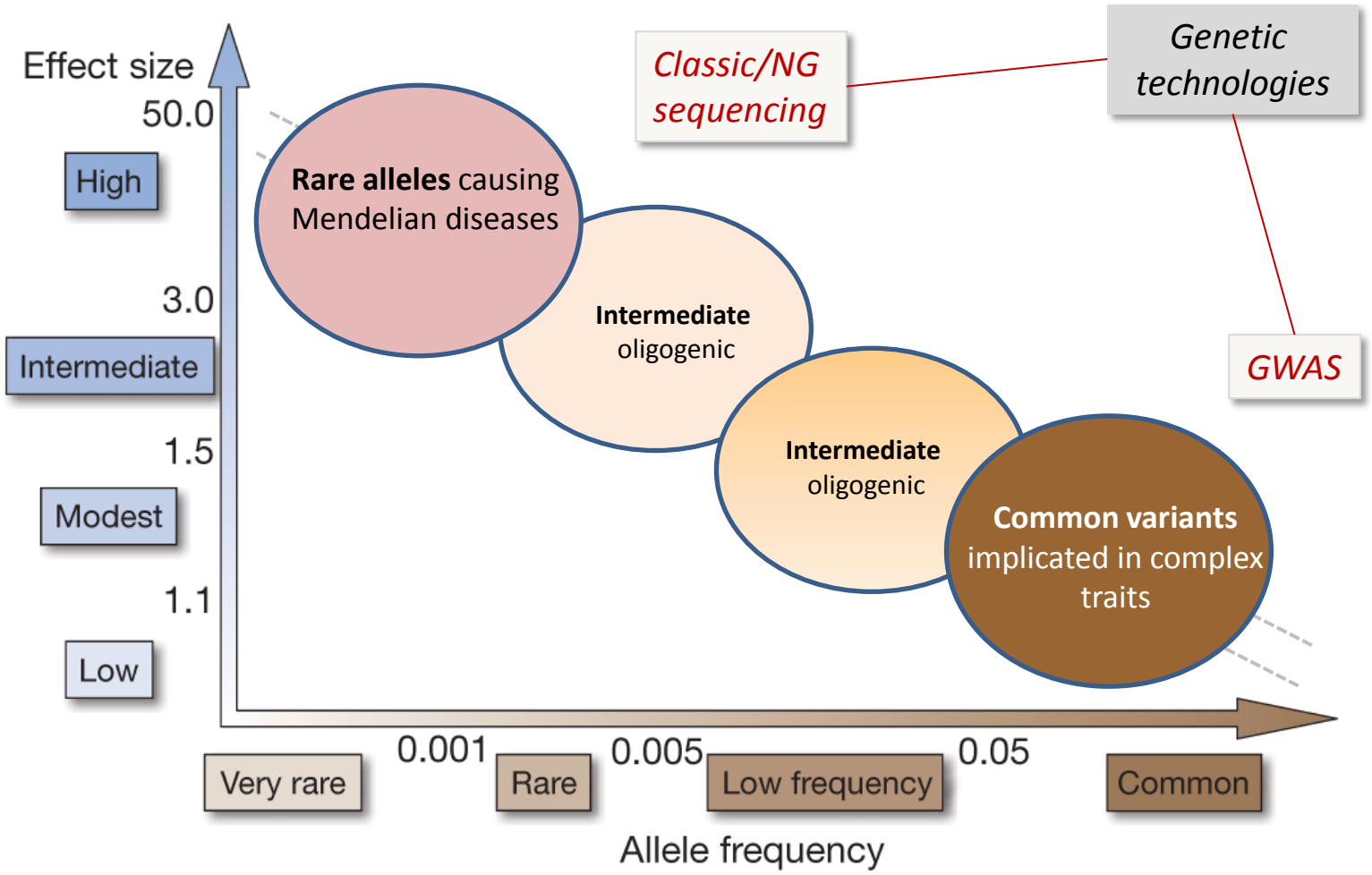
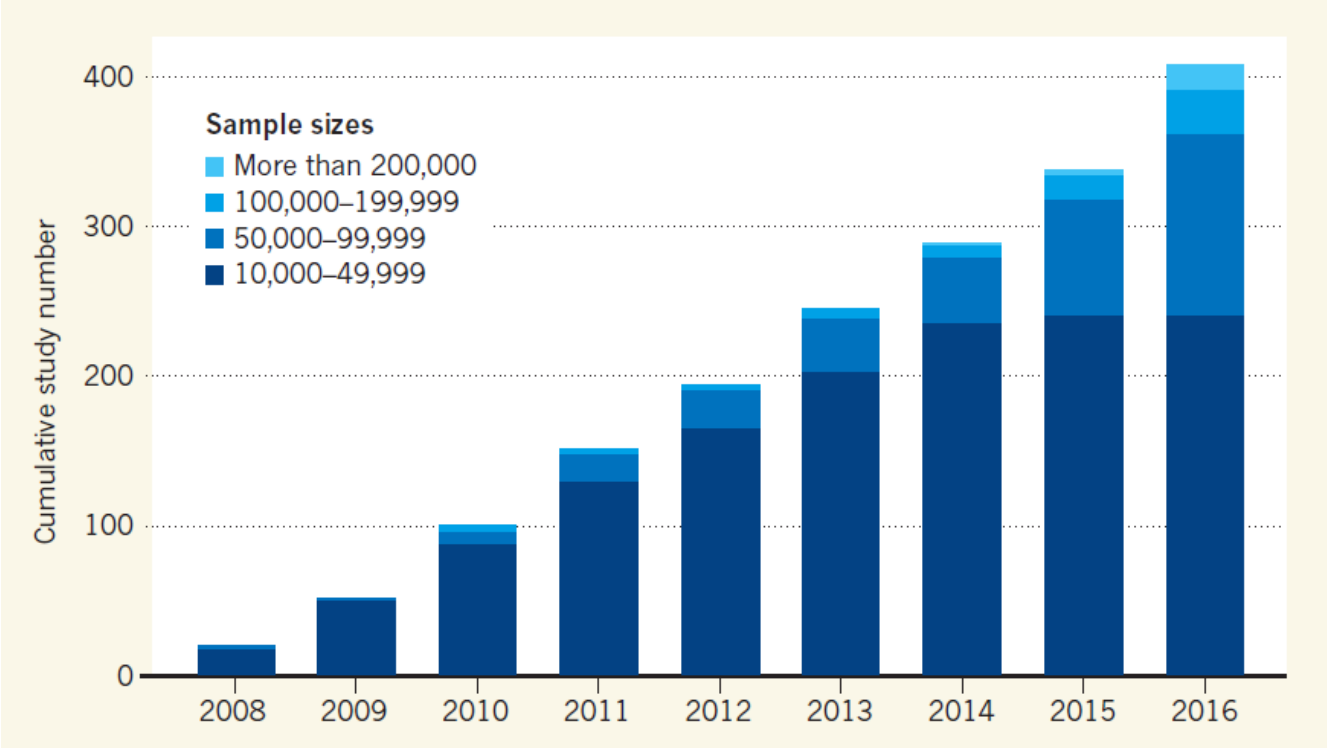
Genetic Architecture of Disease



Manolio et al. Nature 461, 2009

A decade of shared genomic associations

Big data !



- Surprising associations: e.g. Completment Factor H gene and blindness (*Science* 2005)
- Less than 10% of associations lie in protein-coding regions of the genome
- Specific regions associated with multiple, seemingly separate diseases

MEDICAL RESEARCH

Genome studies attract criticism

Geneticists question ability of genome-wide association studies to find useful disease links.

In a paper published in *Cell* on 15 June, Pritchard and two other geneticists suggest that **many GWAS hits have no specific biological relevance to disease** (Boyle EA et al. *Cell* **169,** 2017). Rather, these 'peripheral' variants probably act through complex biochemical regulatory networks to influence the activity of a few 'core' genes that are more directly connected to an illness.

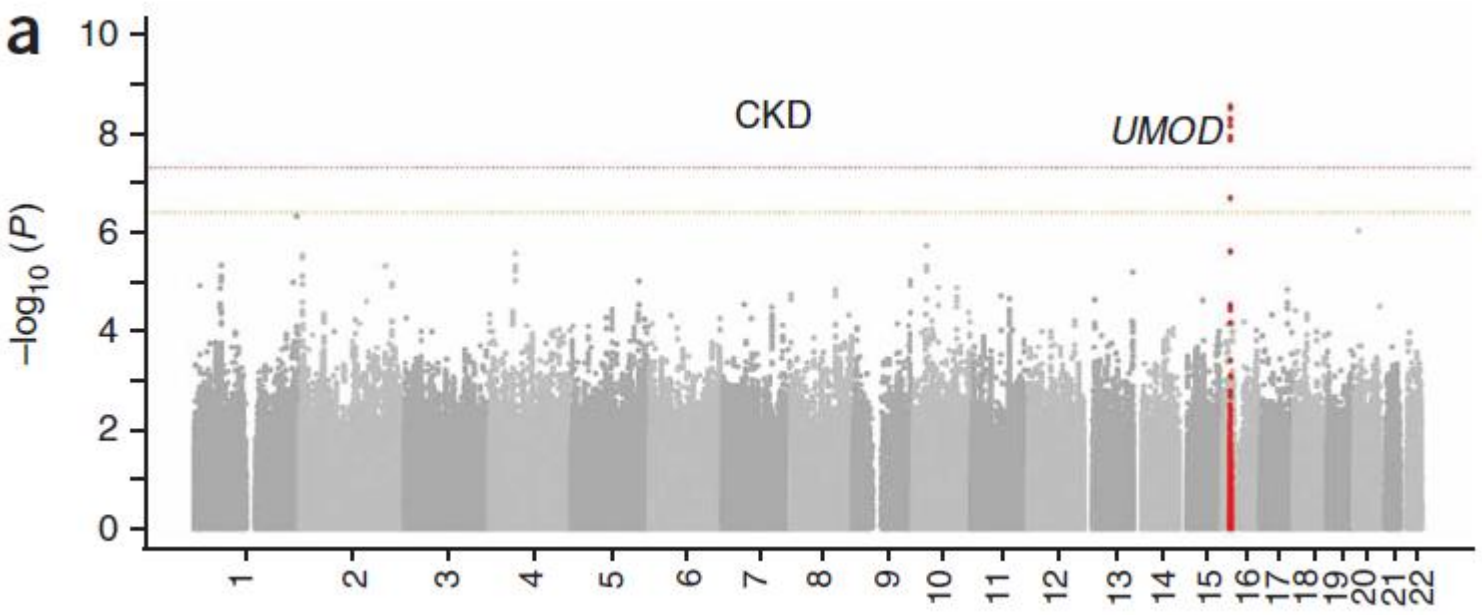
Challenge in genomics: collecting ever more genetic associations over understanding the biology behind them.

Multiple loci associated with indices of renal function and chronic kidney disease

Anna Köttgen[1,25], Nicole L Glazer[2,25], Abbas Dehghan[3,24,25], Shih-Jen Hwang[4,25], Ronit Katz[5], Man Li[1], Qiong Yang[6], Vilmundur Gudnason[7,8], Lenore J Launer[9], Tamara B Harris[9], Albert V Smith[7], Dan E Arking[10], Brad C Astor[1], Eric Boerwinkle[11], Georg B Ehret[10,12], Ingo Ruczinski[13], Robert B Scharpf[13], Yii-Der Ida Chen[14], Ian H de Boer[15], Talin Haritunians[14], Thomas Lumley[5], Mark Sarnak[16], David Siscovick[17], Emelia J Benjamin[18], Daniel Levy[4], Ashish Upadhyay[19], Yurii S Aulchenko[3], Albert Hofman[3], Fernando Rivadeneira[20], André G Uitterlinden[20], Cornelia M van Duijn[3], Daniel I Chasman[21], Guillaume Paré[21], Paul M Ridker[21], W H Linda Kao[1], Jacqueline C Witteman[3,24,26], Josef Coresh[1,13,26], Michael G Shlipak[22,26] & Caroline S Fox[4,23,26]

nature genetics

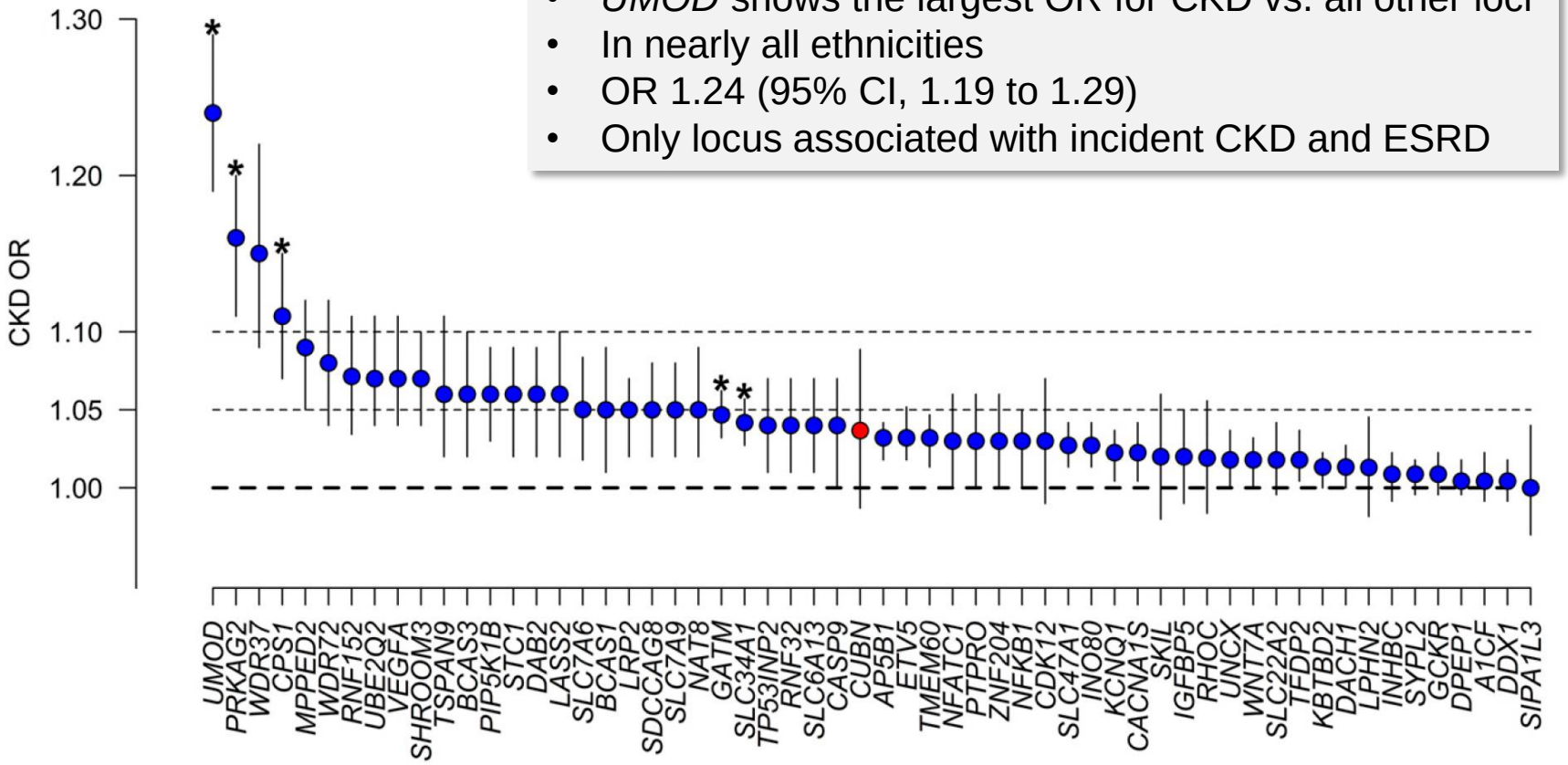
VOLUME 41 | NUMBER 6 | JUNE 2009 NATURE GENETICS



UMOD locus: First discovered in association with eGFRcrea in EU ancestry, associated with CKD at genome-wide significant level

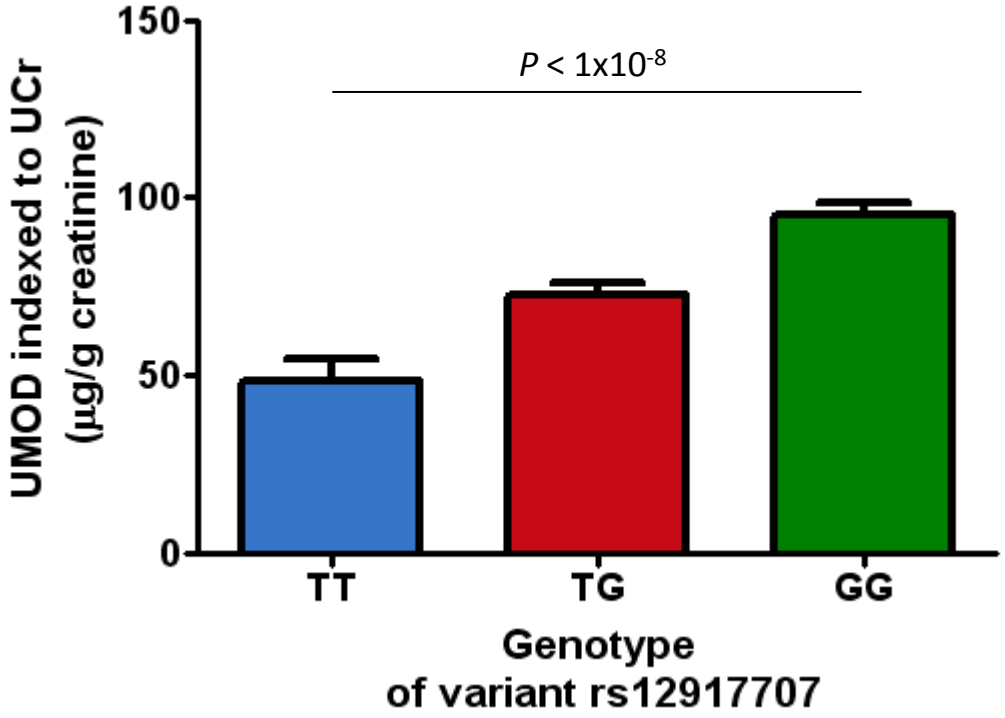
UMOD is Standing among Genetic Loci for CKD

- *UMOD* shows the largest OR for CKD vs. all other loci
- In nearly all ethnicities
- OR 1.24 (95% CI, 1.19 to 1.29)
- Only locus associated with incident CKD and ESRD



Devuyst & Pattaro, JASN 2017, in press

The *UMOD* Risk Allele: Increased Urinary Uromodulin



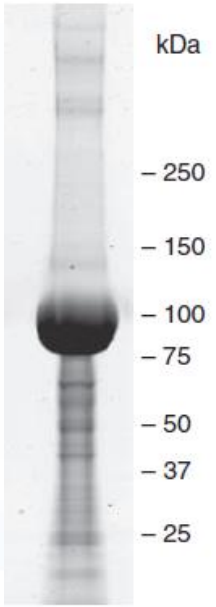
Urinary uromodulin
N=10,884

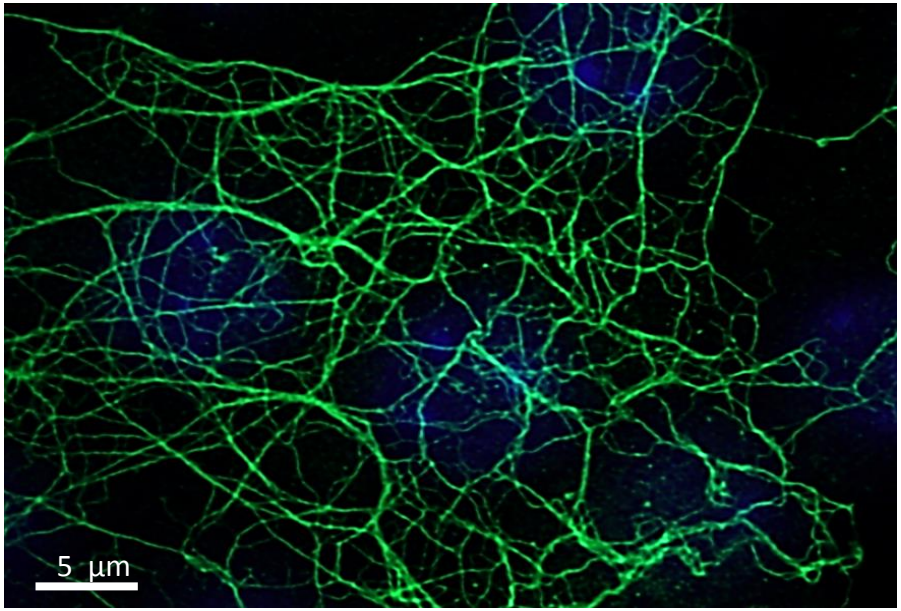
Each copy of the **risk (G) allele** of rs12917707 is associated with a significant ***increase in urinary uromodulin*** levels

Olden M et al. *J Am Soc Nephrol* 25, 2014

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

Tamm-Horsfall protein - uromodulin:
the most abundant protein in nomal human urine (50-100 mg/day)





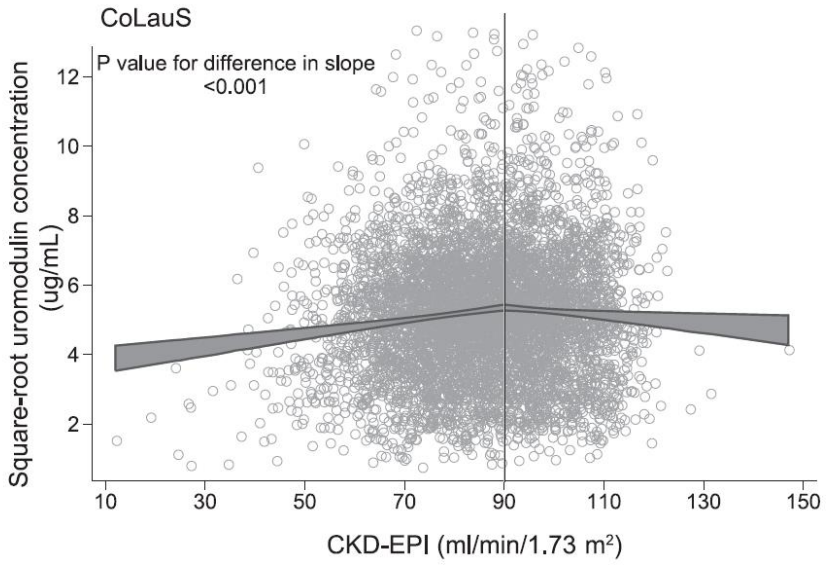
RNAs isolated from 150 different tissues and cell lines:
uromodulin mRNA detected only from the kidney.

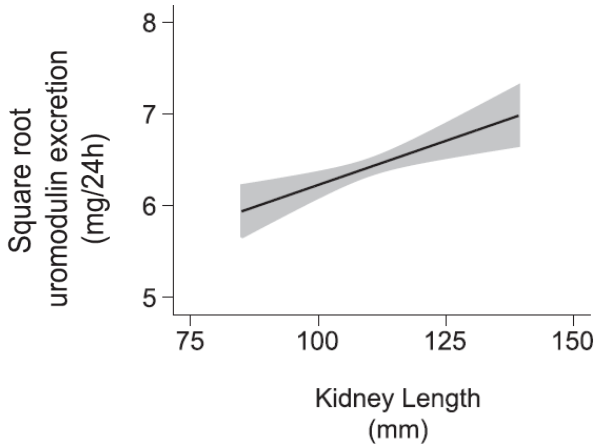
Biomarker value of uromodulin ?

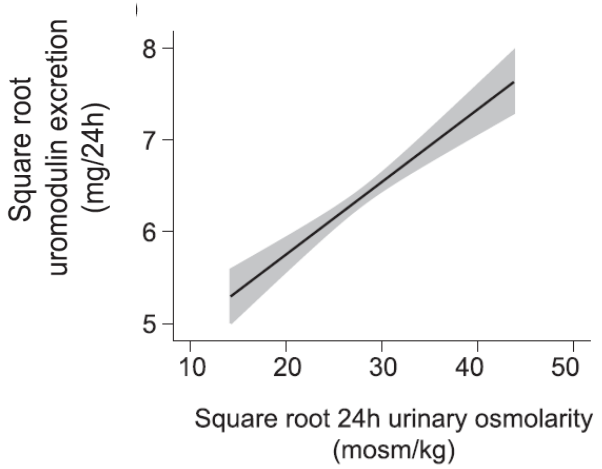
Associations of Urinary Uromodulin with Clinical Characteristics and Markers of Tubular Function in the General Population

Clin J Am Soc Nephrol. 11, 2016

Menno Pruijm, Belen Ponte, Daniel Ackermann, Fred Paccaud, Idris Guessous, Georg Ehret, Antoinette Pechère-Bertschi, Bruno Vogt, Markus G. Mohaupt, Pierre-Yves Martin, Sonia C. Youhanna, Nadine Nägele, Peter Vollenweider, Gérard Waeber, Michel Burnier, Olivier Devuyst, and Murielle Bochud







Uromodulin levels correlate with eGFR, kidney length/mass and tubular activity

clinical investigation http://www.kidney-international.org

see commentary on page 944

Urinary uromodulin, kidney function, and cardiovascular disease in elderly adults

Pranav S. Garimella[1], Mary L. Biggs[2], Ronit Katz[3], Joachim H. Ix[4], Michael R. Bennett[5], Prasad Devarajan[5], Bryan R. Kestenbaum[6], David S. Siscovick[7], Majken K. Jensen[8], Michael G. Shlipak[9], Paulo H.M. Chaves[10] and Mark J. Sarnak[1]

- uUMOD in 192 participants of the Cardiovascular Health Study with over a 30% decline in estimated glomerular filtration rate (eGFR) over 9 years, 54 with incident end-stage renal disease (ESRD), and in a random subcohort of 958 participants.

- In a case–control study evaluating eGFR decline, each 1-s.d. higher uUMOD was associated with a 23% lower odds of eGFR decline (odds ratio 0.77 (95% CI 0.62–0.96)) and a 10% lower risk of mortality (hazard ratio 0.90 (95% CI 0.83–0.98)) after adjusting for demographics, eGFR, albumin/creatinine ratio, and other risk factors.

Low uUMOD levels identify persons at risk of progressive kidney disease and mortality.
Higher levels of uromodulin – protective !

Association of Preoperative Urinary Uromodulin with AKI after Cardiac Surgery

Pranav S. Garimella, Bertrand L. Jaber,† Hocine Tighiouart,‡§ Orfeas Liangos,‖ Michael R. Bennett,¶ Prasad Devarajan,¶ Tarek M. El-Achkar,** and Mark J. Sarnak**

Clin J Am Soc Nephrol 12: 10–18, 2017.

- A post hoc analysis of a prospective cohort study of 218 adults undergoing on–pump cardiac surgery to evaluate the associations of preoperative urinary uromodulin with postoperative AKI

- Lower urinary uromodulin associated with higher odds for AKI (OR, 1.49 per 1-SD lower uromodulin; 95% CI, 1.04 to 2.13), marginally attenuated after adjustment.

- The lowest uromodulin-to-creatinine ratio quartile was also associated with higher odds for AKI relative to the highest quartile (odds ratio, 2.94; 95% CI, 1.19 to 7.26).

Lower uromodulin-to-creatinine ratio is associated with higher odds of AKI
Higher levels of uromodulin – protective !

AJKD
Original Investigation

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.
- Persons in the highest quartile of uromodulin concentration had a significantly lower risk for UTIs (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 a protective role of uromodulin against UTI.*

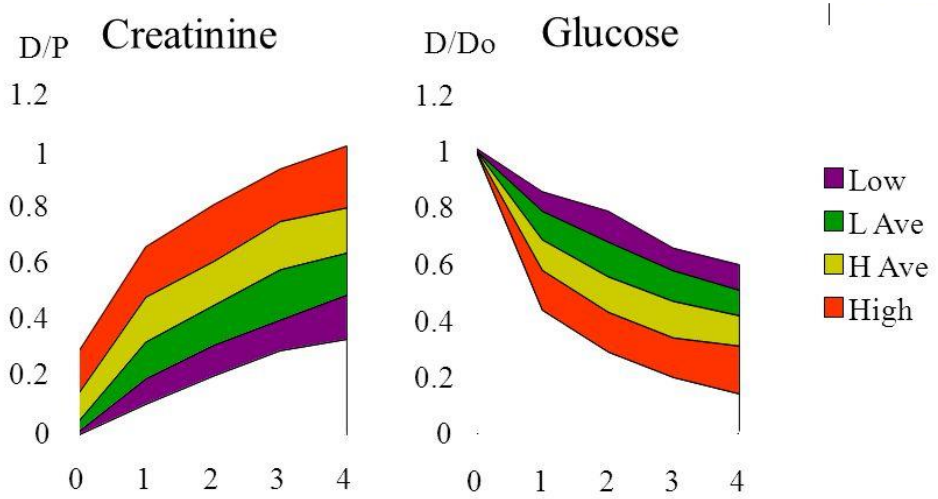
Am J Kidney Dis. 2016 Oct 28.

Precision Medicine: Challenges and Opportunities

Outline

- Insights from genetics – rare (kidney) diseases
- Use of genetic information – targeted treatments
- Insights from GWAS – risk of CKD, hypertension
- Perspectives for peritoneal dialysis

Precision Medicine in PD: Peritoneal Equilibration Test

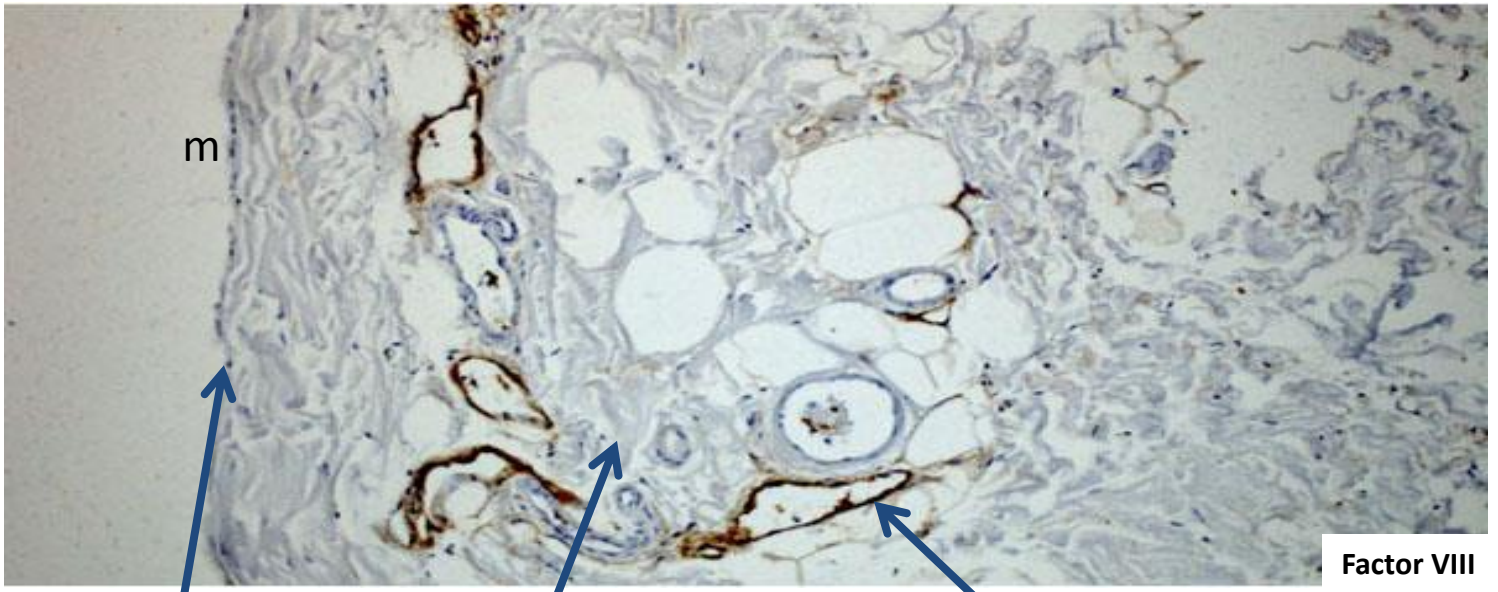


Biological parameter influencing dialysate prescription

Peritoneal solute transport	Drain volume	Predicted long-term response to standard-dose CAPD or CCPD[a] after loss of residual renal function		Preferred dialysis prescription after loss of residual renal function
		ultrafiltration	dialysis	
High	low	poor	adequate	NIPD, DAPD[b]
High average	low average	adequate	adequate	standard-dose PD[a]
Low average	high average	good	adequate or inadequate[c]	standard-dose PD[a] high-dose PD[d]
Low	high	excellent	inadequate	high-dose PD[d] or hemodialysis[e]

Twardowski et al. Perti Dial Bull 1987; 7: 138-47

The Peritoneal Membrane as Model for Transport

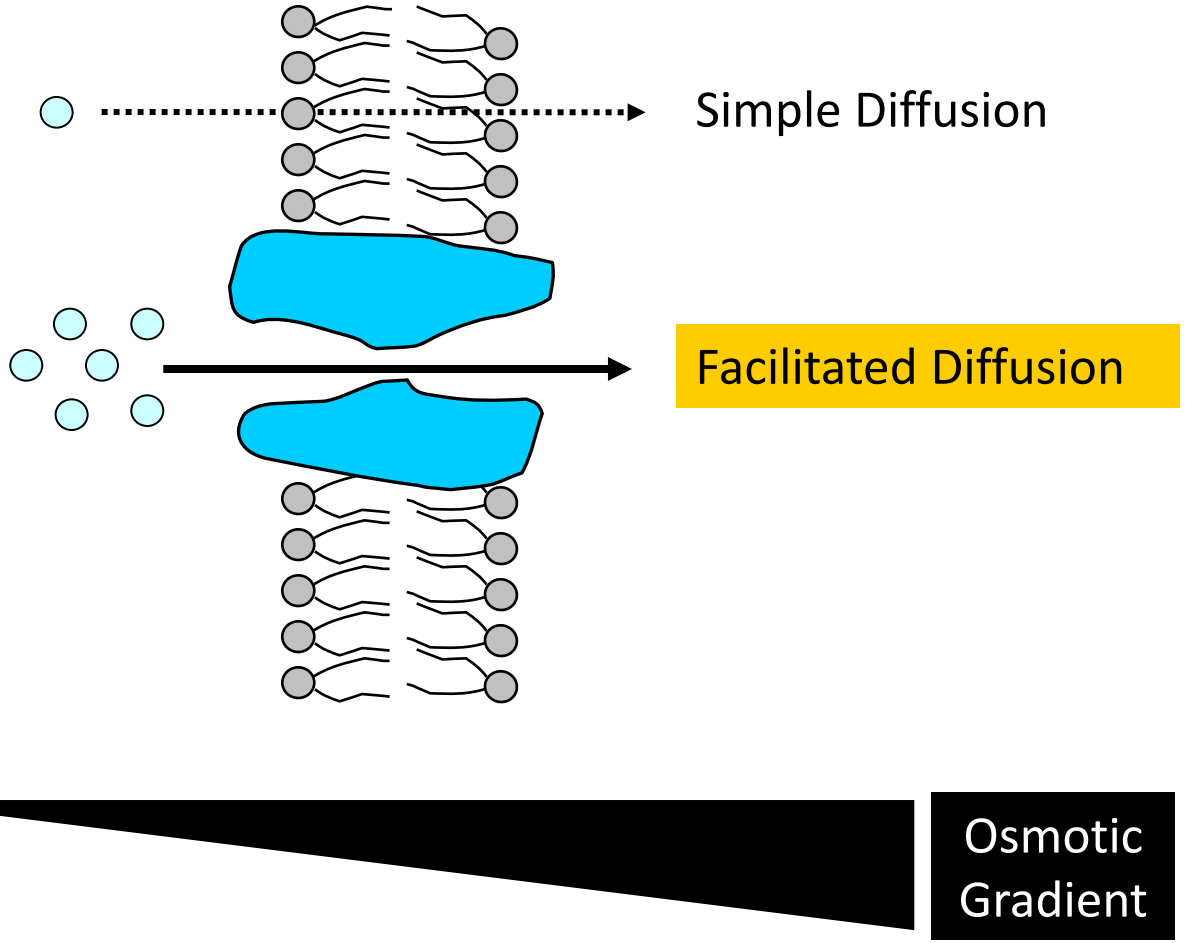


Mesothelium

Interstitium

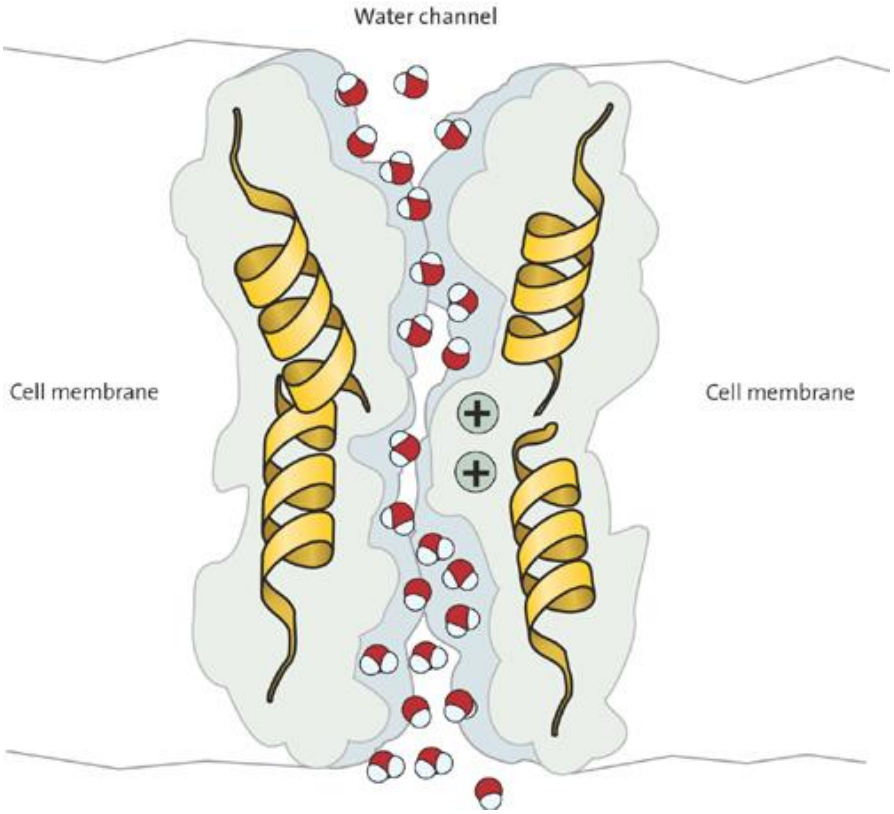
Capillary endothelium
Main functional barrier to solute & fluid transport

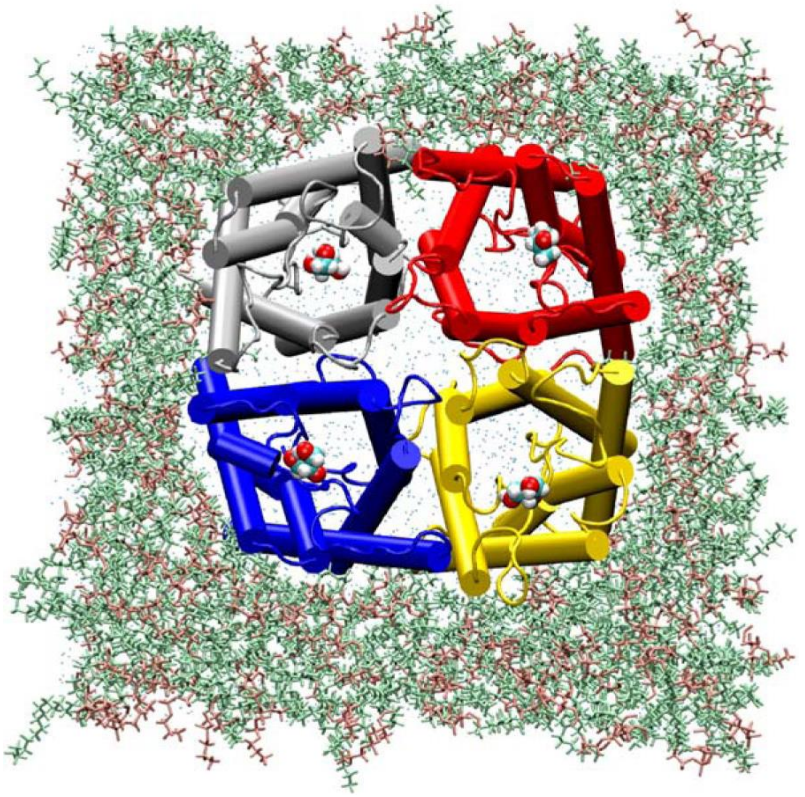
Overton : Water Pores in Cell Membranes



Macey et al. *Am J Physiol* 1984

Structure of Aquaporins

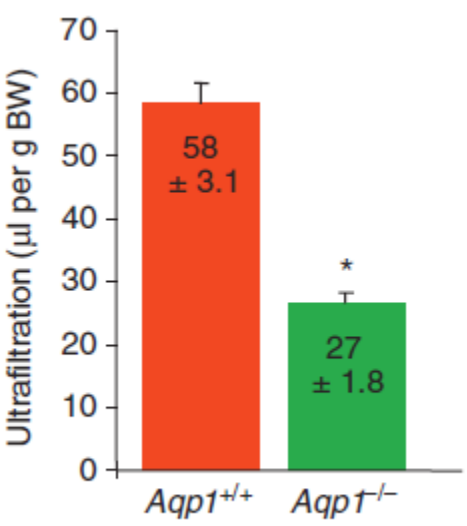


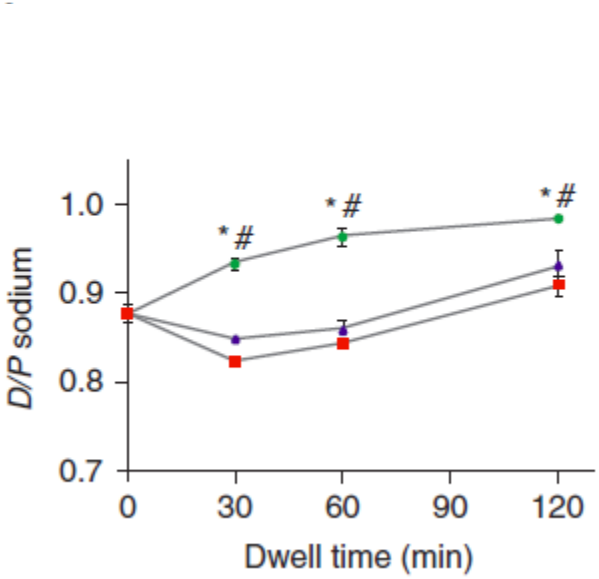


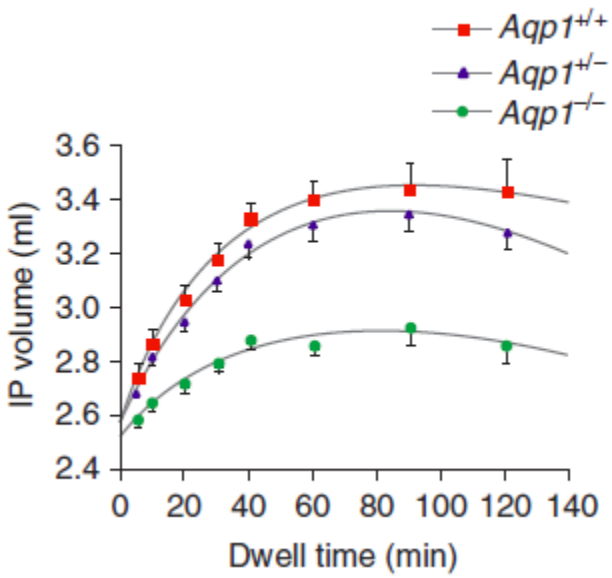
AQP1 tetramers: 3 billions of water molecules per second

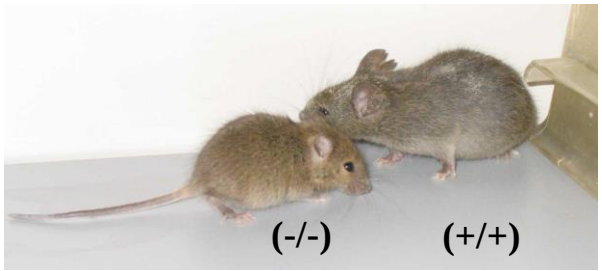
Walz T et al. Nature 387, 1997
Wang et al. Structure 13, 2005

Peritoneal Dialysis in *Aqp1* Knockout Mice







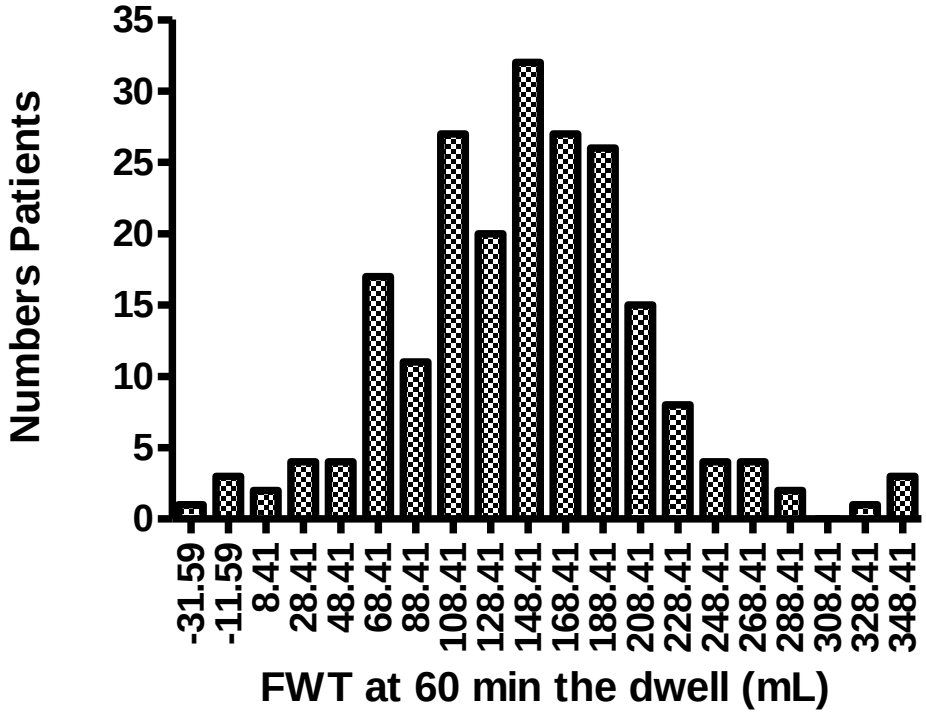


- *AQP1 pores mediate 50% of UF*
- *AQP1 pores mediate sodium sieving*
- *Dose-effect: Heterozygous mice*

Ni J et al. *Kidney Int* 2006; 69: 1518-25

Genetics – Useful for Peritoneal Dialysis ?

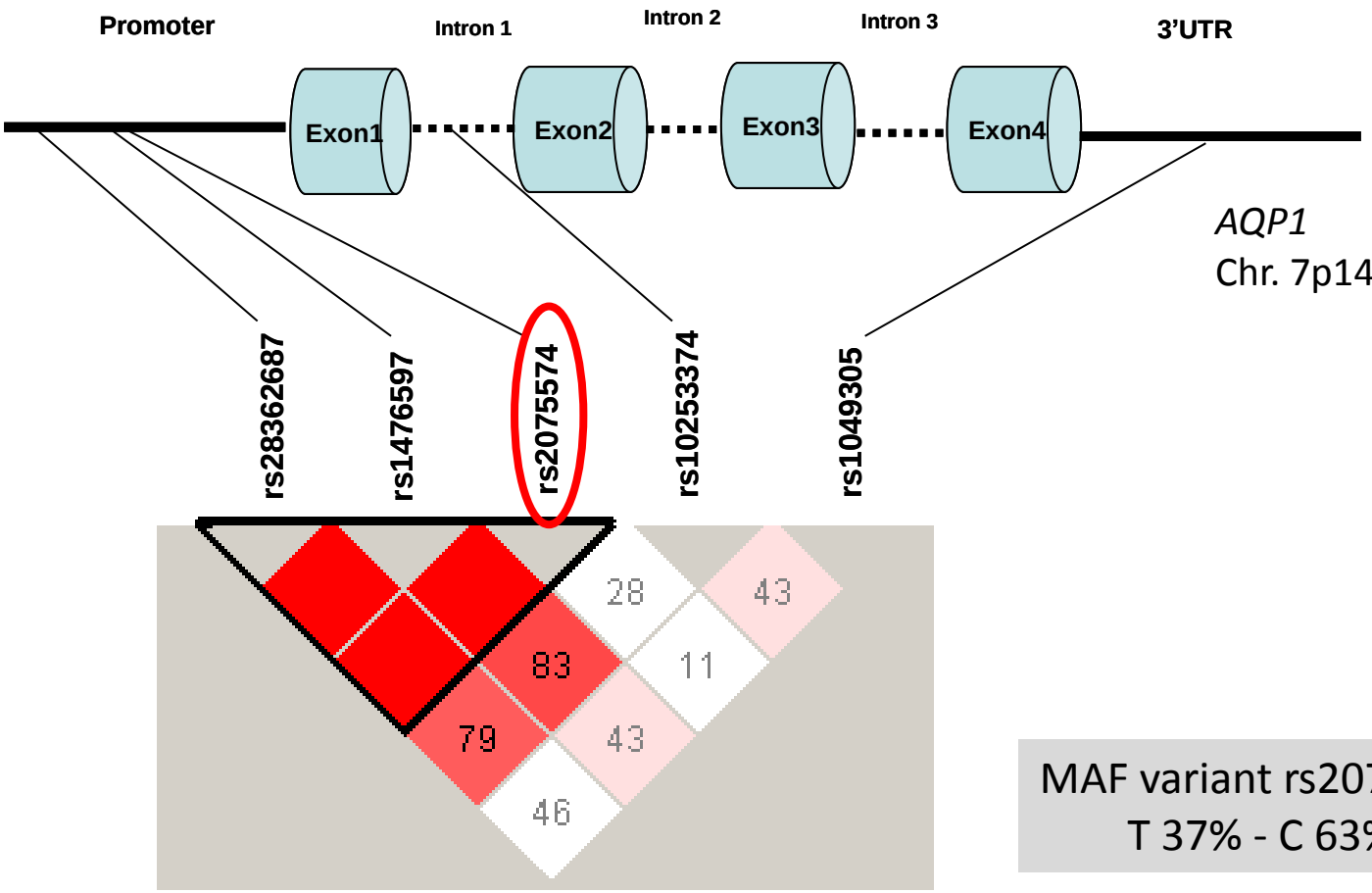
Distribution of Water Transport in PD Patients



Amsterdam data – SPA test
60 min – hypertonic dwell
Incident PD patients, n=211

Clinical variables account for only ~ 20% of the variability:
→ Genetic Influence ?

AQP1 Haplotype: Frequent Promoter Variants

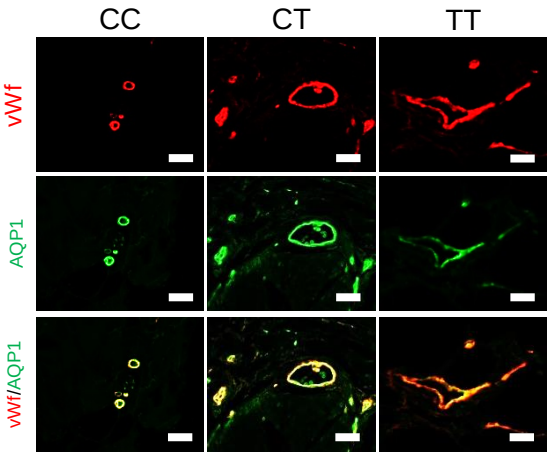


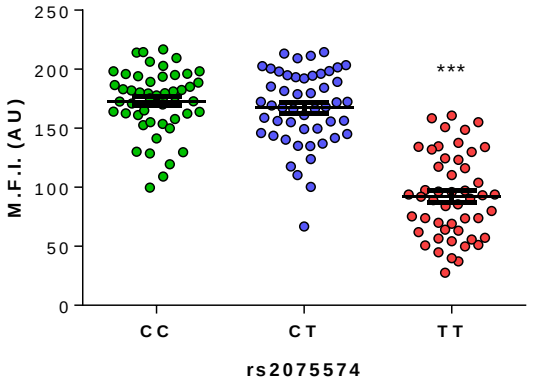
AQP1
Chr. 7p14.3

MAF variant rs2075574
T 37% - C 63%

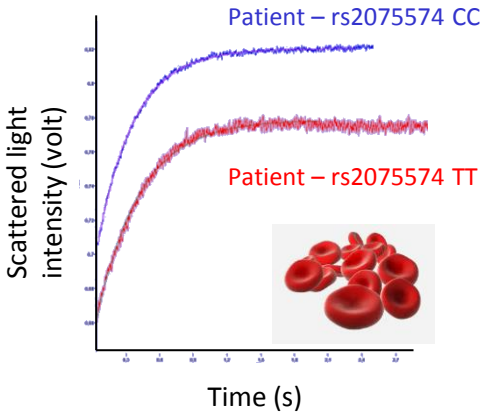
The *AQP1* Promoter Variant: Influences Water Transport and Outcome during PD

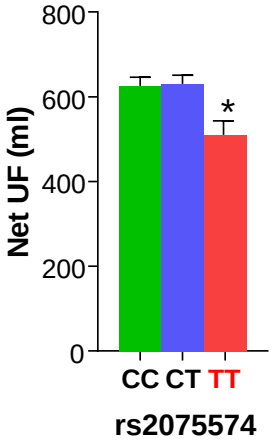
The TT variant of rs2075574 - decreased *AQP1* gene expression in peritoneal microvasculature





Water transport in human erythrocytes and across the peritoneal membrane



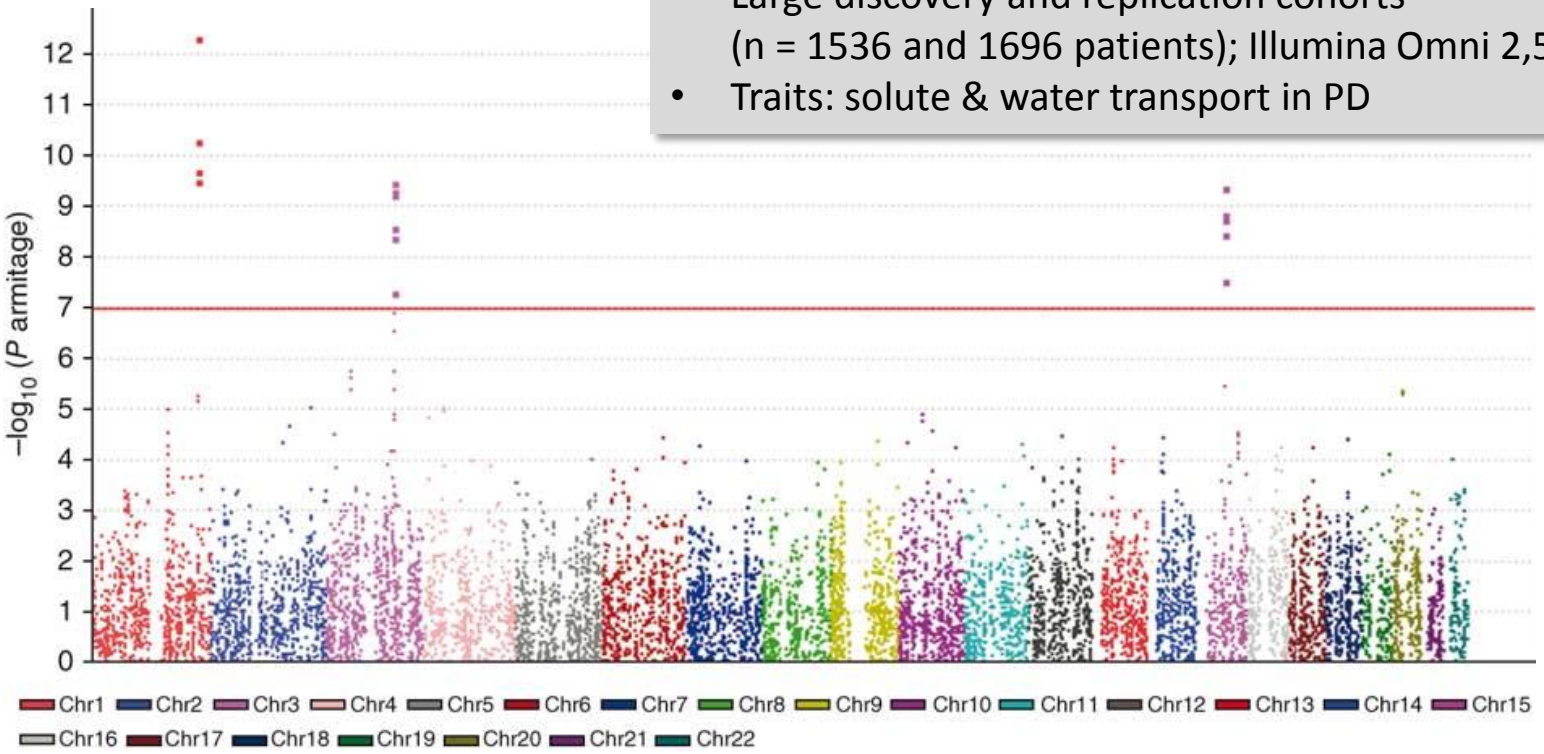


Outcome:
Patient & technique survival

Coll. S. Davies, R. Selgas, R. Krediet

Unbiased Approach: Bio-PD Study
GWAS to Identify Loci Influencing Peritoneal Transport

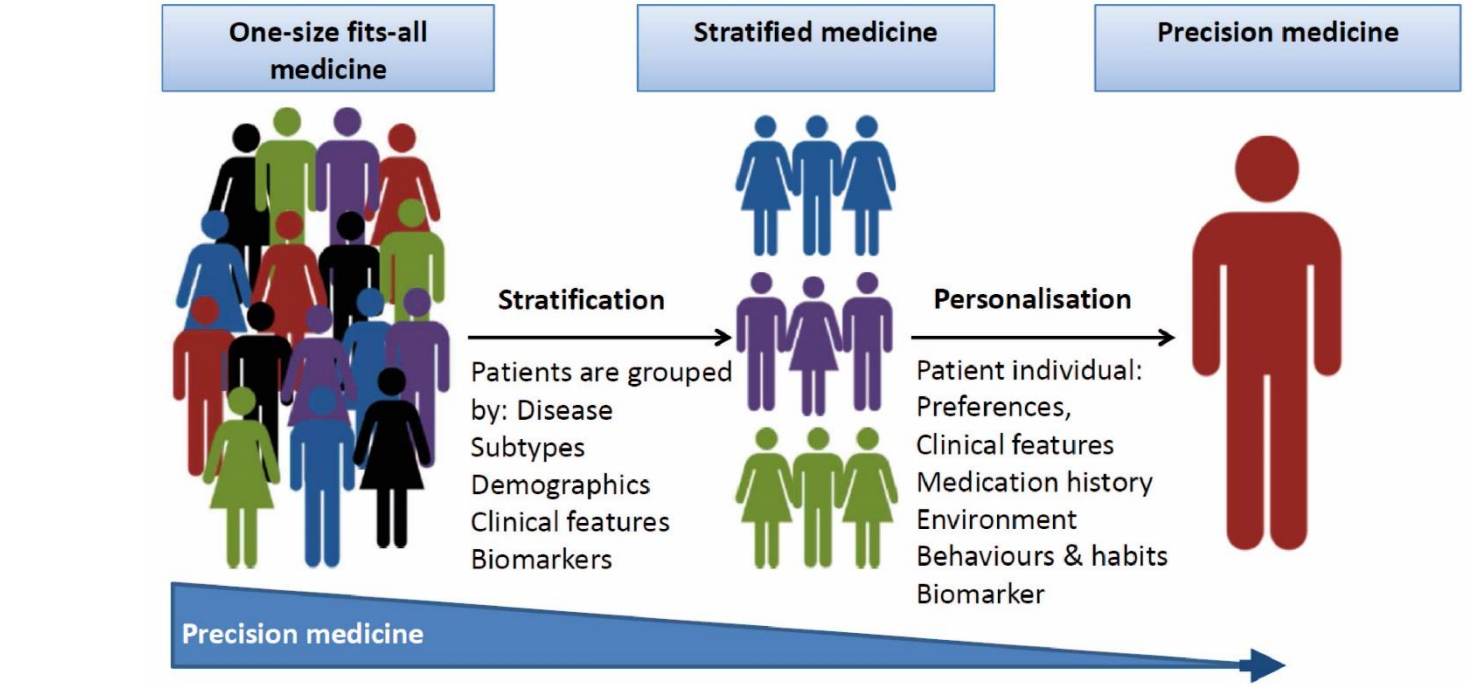
- Multicentric: USA & Europe
- Large discovery and replication cohorts
  (n = 1536 and 1696 patients); Illumina Omni 2,5M
- Traits: solute & water transport in PD

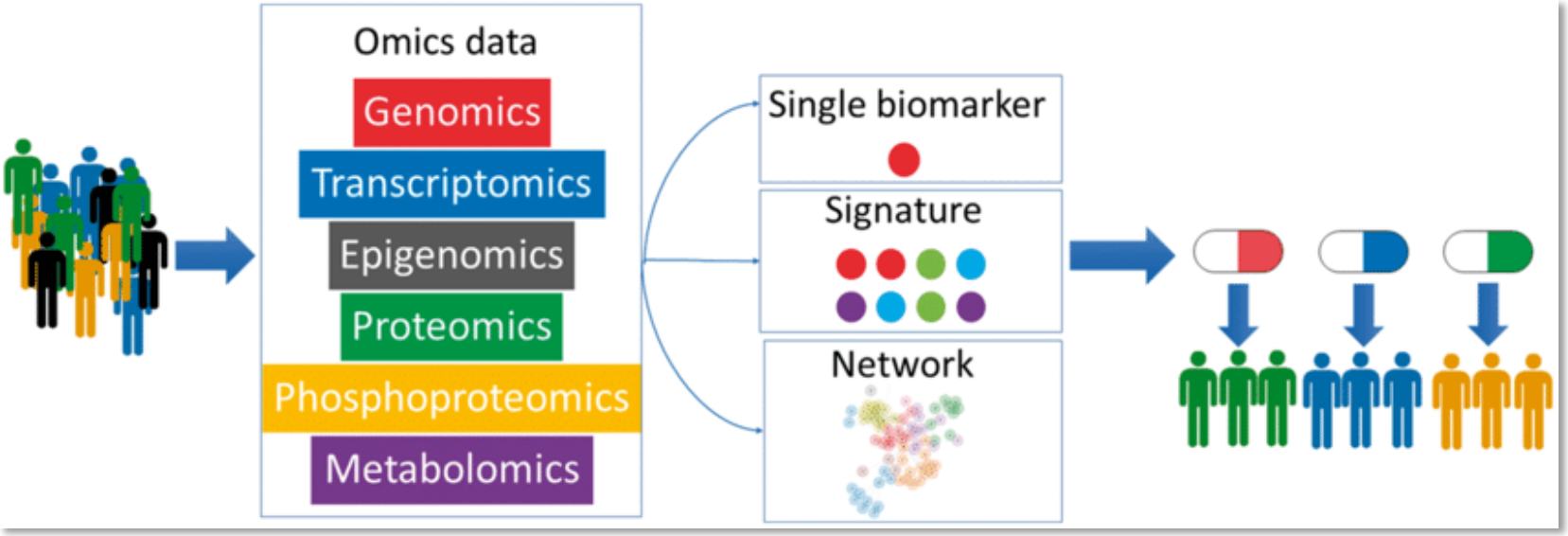


Coordinator: Raj Mehrotra

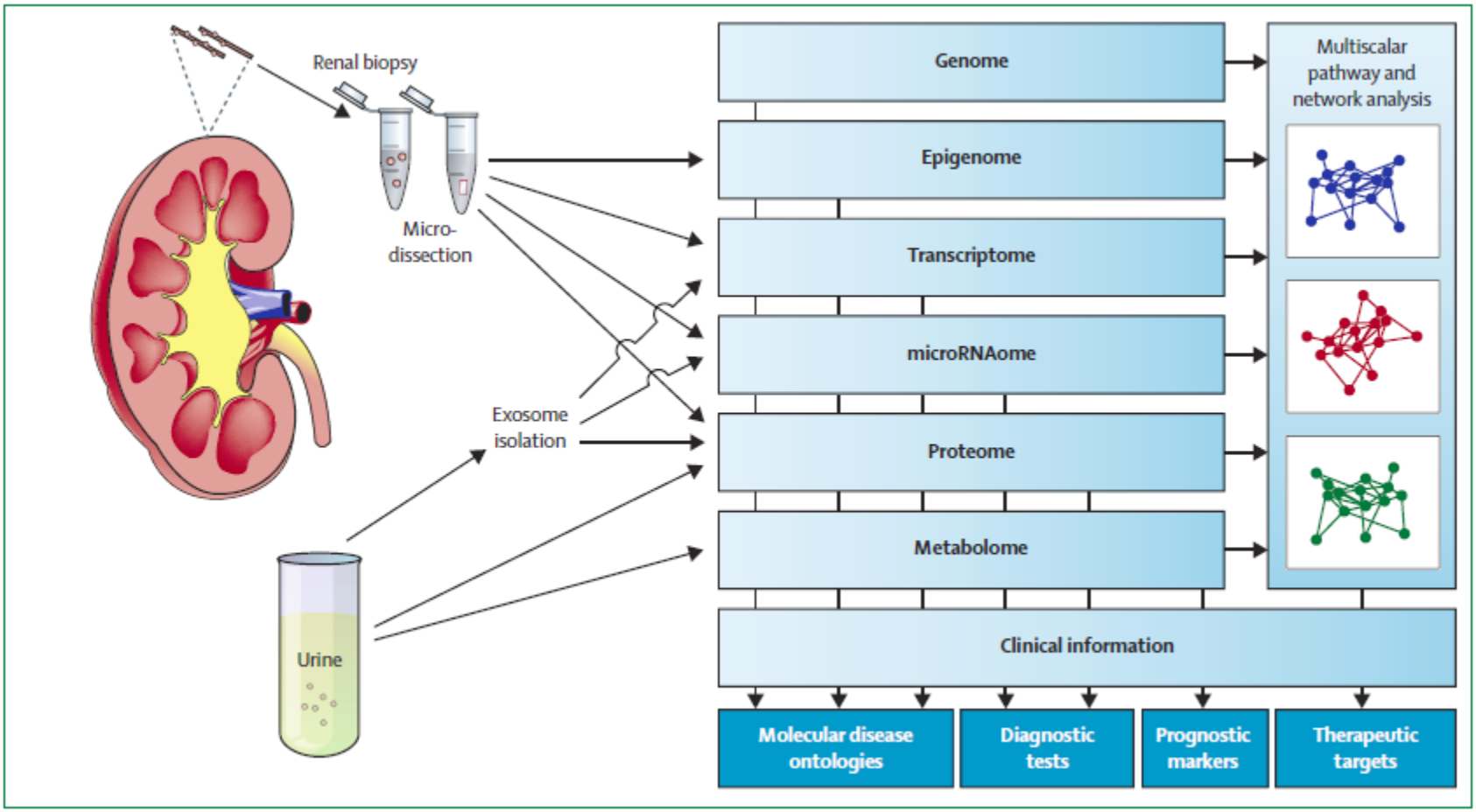
NIH

Conclusions – Take Home Messages


One-size fits-all medicine
Stratified medicine
Precision medicine
Stratification
Patients are grouped by: Disease Subtypes Demographics Clinical features Biomarkers
Personalisation
Patient individual: Preferences, Clinical features Medication history Environment Behaviours & habits Biomarker
Precision medicine

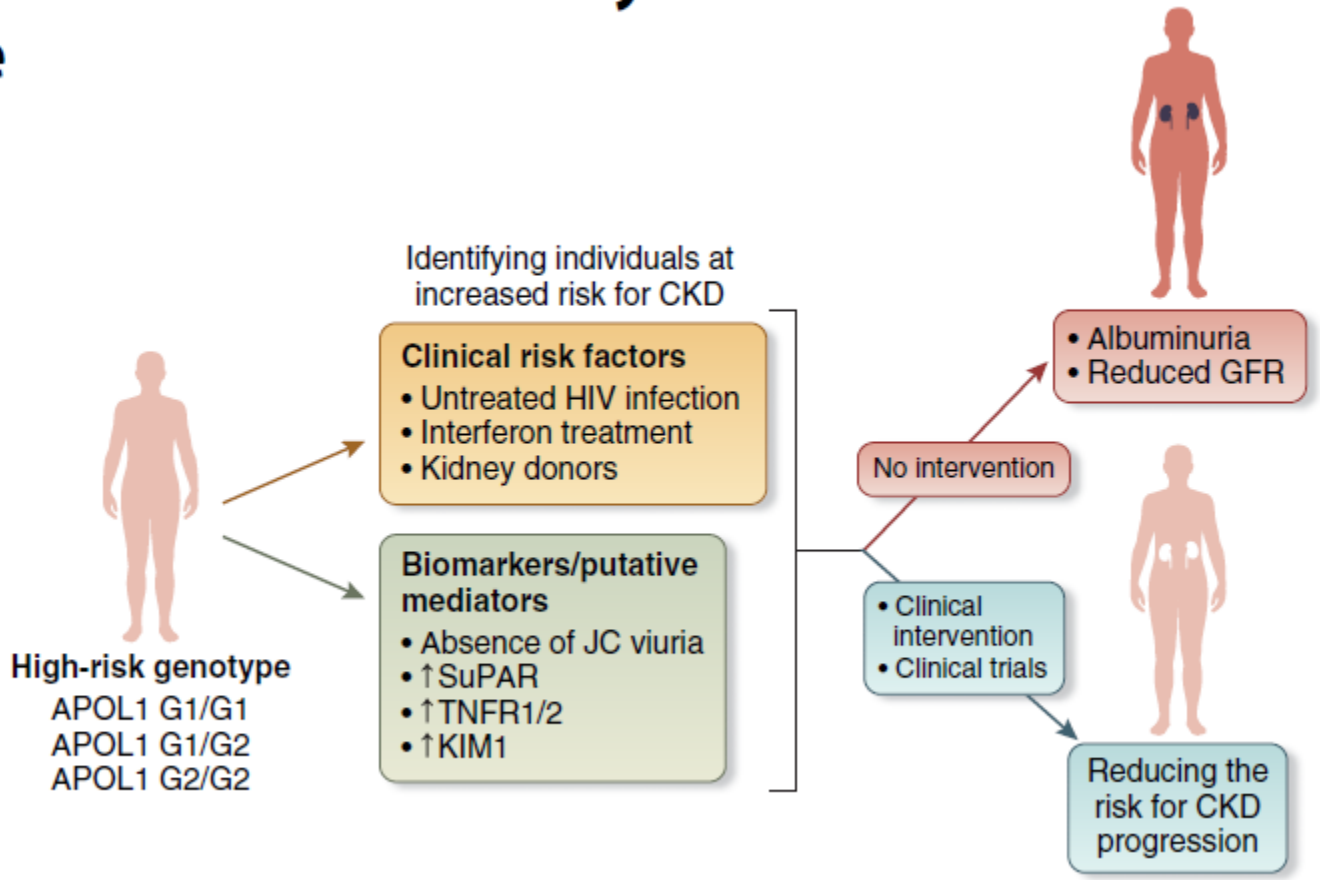

Omics data
Genomics
Transcriptomics
Epigenomics
Proteomics
Phosphoproteomics
Metabolomics
Single biomarker
Signature
Network

Kidney Disorders: Multi-omics Technologies



Devuyst O, et al. Lancet 383, 2014

"Biomarking" the transition from genetic risk to kidney disease



Identifying individuals with high-risk APOL1 genotype, at increased risk for CKD. Only some individuals harboring APOL1 high-risk genotype (pink figure, left column) will go on to develop CKD. Clinical risk factors as well as biomarkers would help in identifying the individuals who are more prone to develop CKD (red figure, right column). Clinical intervention to reduce these risk factors (e.g., HIV treatment, avoiding interferon treatment, and consultation regarding the risk of kidney donation) would reduce the risk for CKD progression (pink figure, right column). Adding biomarkers, such as soluble urokinase plasminogen activating receptor (SuPAR), tumor necrosis factor receptor ½ (TNFR1/2), and kidney injury molecule-1 (KIM1) to the risk stratification should improve clinical trial design and hopefully translate to reduced renal events.

Kruzel-Davilla & Skorecki, Kidney International (2018) 93, 1265–1280

Merci pour votre attention

NEWS

SCIENCE sciencemag.org

4 MAY 2018 • VOL 360 ISSUE 6388

Precision medicine study launches

BIOMEDICINE | The U.S. National Institutes of Health detailed its plans to open national enrollment for a massive study of personalized medicine on 6 May, with a goal of enlisting 1 million people.

The All of Us project will explore links between genes, lifestyle, and disease by following participants' health for 10 years.

Participants will be asked to share their electronic medical records, and some will be invited to give blood and urine samples and wear a Fitbit-like device that gathers health data.

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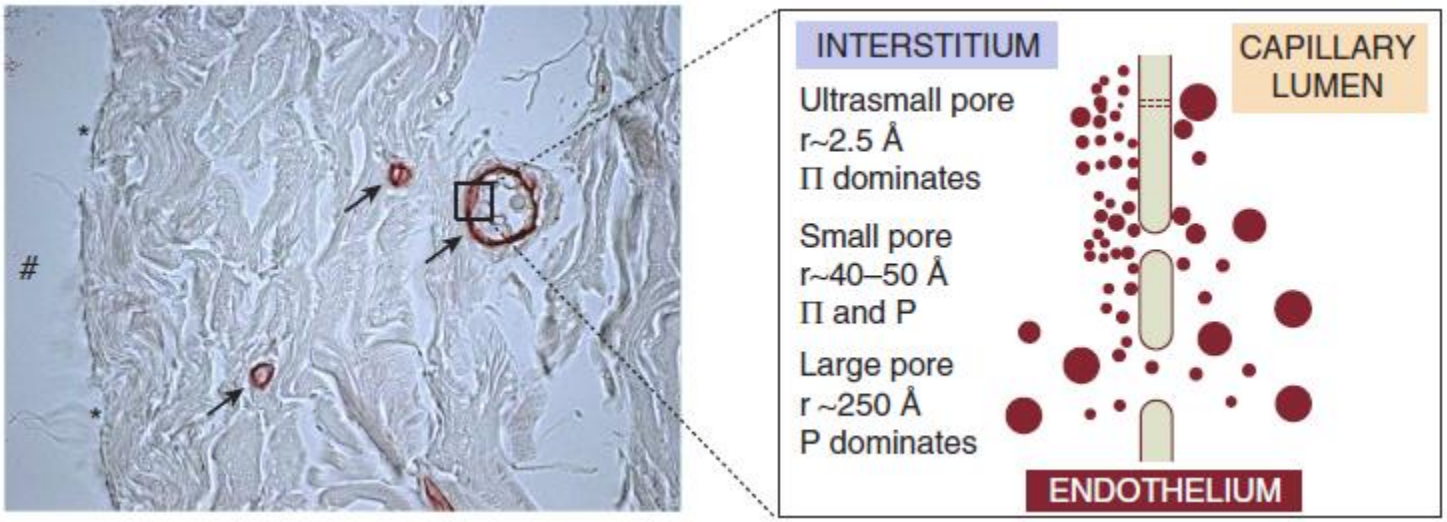
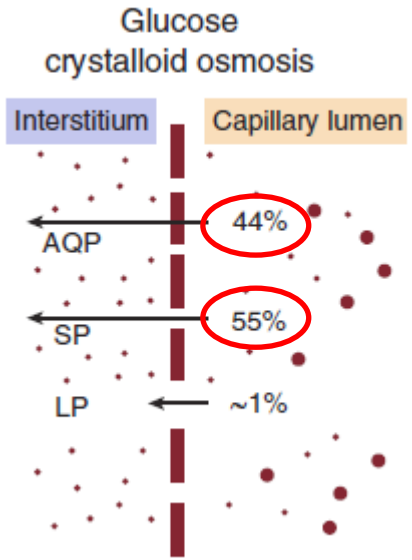
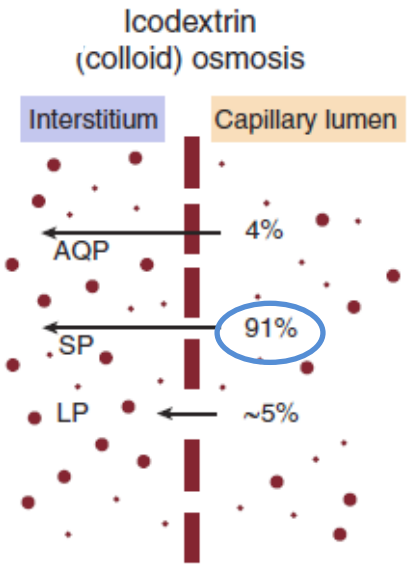
The 3-Pore Model: Endothelium as a Functional Barrier in PD







Devuyst & Rippe, Kidney Int 85, 2014

Accumulating evidence has suggested that many causal GWAS variants might be common regulatory variants. Efforts to re-sequence disease-associated genes identified in GWAS, such as UMOD for eGFR27, and PLA2R1 in MN48, have failed to identify common or rare missense variants that could explain the observed GWAS signals either individually or in combination.

Instead, the latest GWAS meta-analysis from the CKDGen Consortium reported that eGFR-associated variants and/or their proxies map into regions with regulatory potential more often in kidney tissues than in a set of control tissues19. This observation is further supported by a study linking eGFR-associated SNPs to transcript expression in different renal tissues28.

More generally, a large 2015 study by the Genotype- Tissue Expression Project linked genetic variation to gene expression across a variety of human tissues and found that SNPs that are associated with transcript levels (also called expression quantitative trait loci (eQTL)) are enriched for GWAS SNPs, with the tissue often matching the pathophysiology of the disease under study70.

This report, which does not include data from kidney tissue, also presents selected examples of GWAS signals that can be explained by eQTLs. In the field of kidney disease, variants in the UMOD gene region, identified in GWAS of eGFR, modulate CKD risk by altering the expression of the UMOD transcript.

An exception is APOL1, for which the causal variants are coding and directly affect protein sequence.

Hypertension. 2014 Nov;64(5):918-23.

Uromodulin, an emerging novel pathway for blood pressure regulation and hypertension.

Padmanabhan S[1], Graham L[2], Ferreri NR[2], Graham D[2], McBride M[2], Dominiczak AF[2].

Future Perspectives

GWAS discovery followed by functional validation has resulted in renewed interest in *UMOD* and its role in BP regulation. These early functional data while promising highlights the importance of further work that needs to be prioritized to elucidate the underpinning molecular mechanisms. Some of the crucial questions that need to be investigated include the role of uromodulin in maintaining water impermeability in TAL; the effect of uromodulin on NKCC2, macula densa, tubuloglomerular feedback, distal sodium transporters, renin–angiotensin–aldosterone system; and whether immune mechanisms play a role in BP regulation by uromodulin. More importantly, further research in these areas will enable development of a therapeutic application (either novel drug or repurposing an existing drug or a screening diagnostic) for targeted treatment. This is crucial because despite major advances in cardiovascular health, hypertension remains the risk factor contributing most to the overall burden of disease globally and there is a paucity of novel antihypertensive drugs in clinical trials or pharmaceutical development pipeline. More fundamentally, the uromodulin story highlights the power of GWAS in identifying novel pathways of disease.

Precision medicine – blended model see Circulation figure

OUTLOOK
Climate change

nature

THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

BEING HUMAN

Cataloguing the effects of genetic variation on gene expression in healthy tissues PAGES 190, 204, 239, 244 & 249

BUSINESS

PERSONAL GENETICS

The turbulent story of 23andMe

PAGE 174

POLITICS

STAR LAWS

Time to update the Outer Space Treaty

PAGE 182

ENGINEERING

MOLTEN-METAL MACHINE

Ceramic pump handles liquid metals at record temperatures

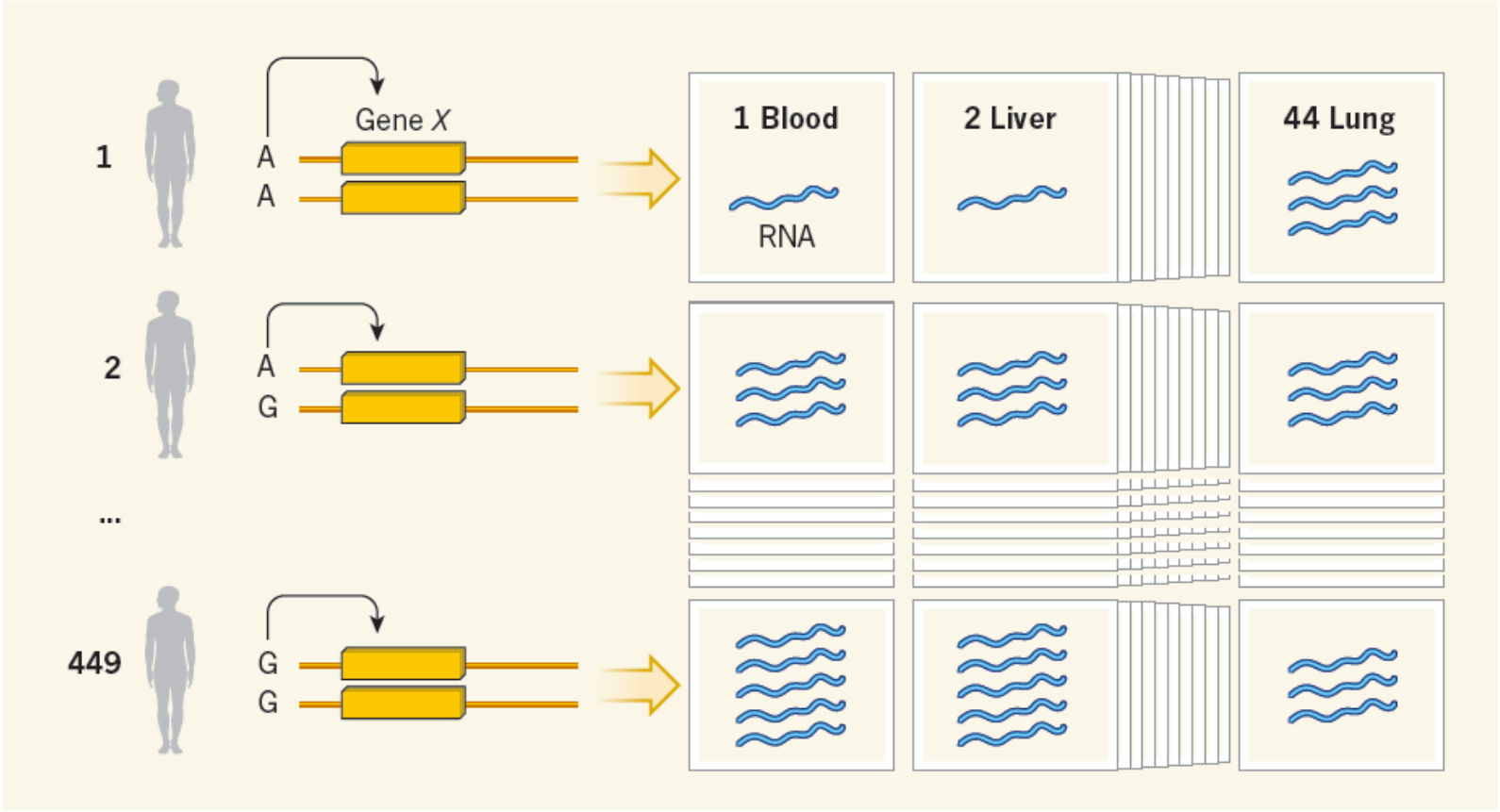
PAGES 194 & 199

NATURE.COM/NATURE
12 October 2017
Vol. 550, No. 7675

HUMAN GENOMICS

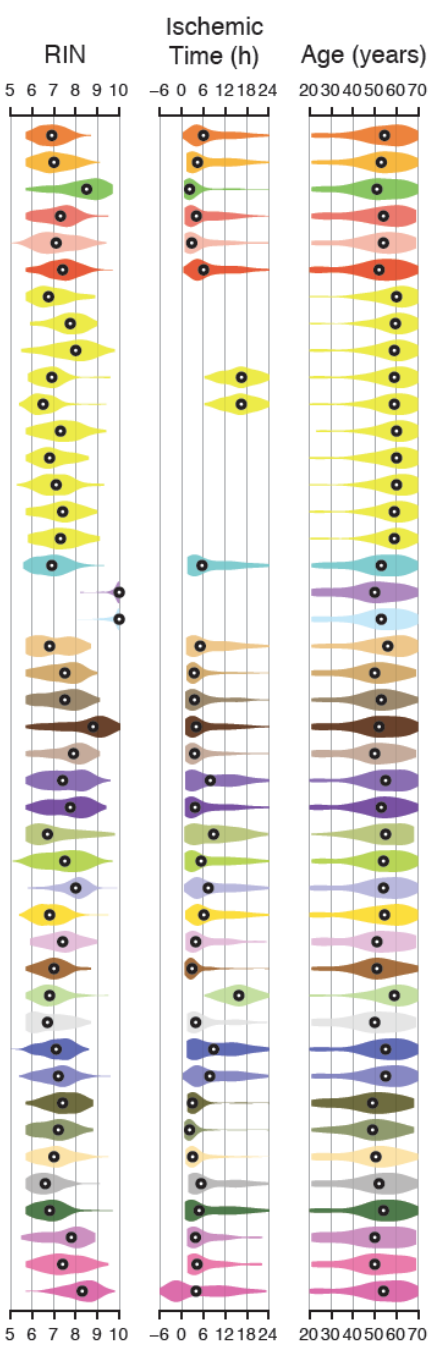
Cracking the regulatory code

A collection of papers catalogues the associations between genetic variation and gene expression in healthy tissues — the largest analysis of this kind so far. SEE ARTICLE P.204 & LETTERS P.239, P.244 & P.249



Data collection by the Genotype-Tissue Expression (GTEx) Consortium. The consortium1–4 collected tissue samples from 44 tissues in 449 human individuals. The researchers analysed these samples to look for genetic differences between individuals — in this example, one individual harbours two adenosine bases (As) at a particular point on two sister chromosomes, another harbours one A and one guanine (G), and a third harbours two Gs. The authors measured RNA levels to determine whether such genetic variation was associated with differences in gene expression (here, in the levels of RNA transcribed from gene *X). Different genetic variants were associated with different expression in different tissues.*

Tissue Site Detail	Abbreviation	Color	Samples from genotyped donors
Adipose - Subcutaneous	ADPSBQ	#FF6600	298
Adipose - Visceral (Omentum)	ADPVSC	#FFAA00	185
Adrenal Gland	ADRNLG	#33DD33	126
Artery - Aorta	ARTAORT	#FF5555	197
Artery - Coronary	ARTCRN	#FFAA99	118
Artery - Tibial	ARTTBL	#FF0000	285
Brain - Anterior cingulate cortex (BA24)	BRNACC	#EEEE00	72
Brain - Caudate (basal ganglia)	BRNCDT	#EEEE00	100
Brain - Cerebellar Hemisphere [Frozen]	BRNCHB	#EEEE00	89
Brain - Cerebellum [PAXgene]	BRNCHA	#EEEE00	103
Brain - Cortex [PAXgene]	BRNCTXA	#EEEE00	96
Brain - Frontal Cortex (BA9) [Frozen]	BRNCTXB	#EEEE00	92
Brain - Hippocampus	BRNHPP	#EEEE00	81
Brain - Hypothalamus	BRNHPT	#EEEE00	81
Brain - Nucleus accumbens (basal ganglia)	BRNNCC	#EEEE00	93
Brain - Putamen (basal ganglia)	BRNPTM	#EEEE00	82
Breast - Mammary Tissue	BREAST	#33CCCC	183
Cells - EBV-transformed lymphocytes	LCL	#CC66FF	114
Cells - Transformed fibroblasts	FIBRBLS	#AAEEFF	272
Colon - Sigmoid	CLNSGM	#EEBB77	124
Colon - Transverse	CLNTRN	#CC9955	169
Esophagus - Gastroesophageal Junction	ESPGEJ	#8B7355	127
Esophagus - Mucosa	ESPMCS	#552200	241
Esophagus - Muscularis	ESPMSL	#BB9988	218
Heart - Atrial Appendage	HRTAA	#9900FF	159
Heart - Left Ventricle	HRTLV	#660099	190
Liver	LIVER	#AABB66	97
Lung	LUNG	#99FF00	278
Muscle - Skeletal	MSCLSK	#AAAAFF	361
Nerve - Tibial	NERVET	#FFD700	256
Ovary	OVARY	#FFAAFF	85
Pancreas	PNCREAS	#995522	149
Pituitary	PTTARY	#AAFF99	87
Prostate	PRSTTE	#DDDDDD	87
Skin - Not Sun Exposed (Suprapubic)	SKINNS	#0000FF	196
Skin - Sun Exposed (Lower leg)	SKINS	#7777FF	302
Small Intestine - Terminal Ileum	SNTTRM	#555522	77
Spleen	SPLEEN	#778855	89
Stomach	STMACH	#FFDD99	170
Testis	TESTIS	#AAAAAA	157
Thyroid	THYROID	#006600	278
Uterus	UTERUS	#FF66FF	70
Vagina	VAGINA	#FF5599	79
Whole Blood	WHLBLD	#FF00BB	338



Summary of the 44 tissues and 7,051 samples used for eQTL analyses from the GTEx v6p release.

doi:10.1038/nature24277

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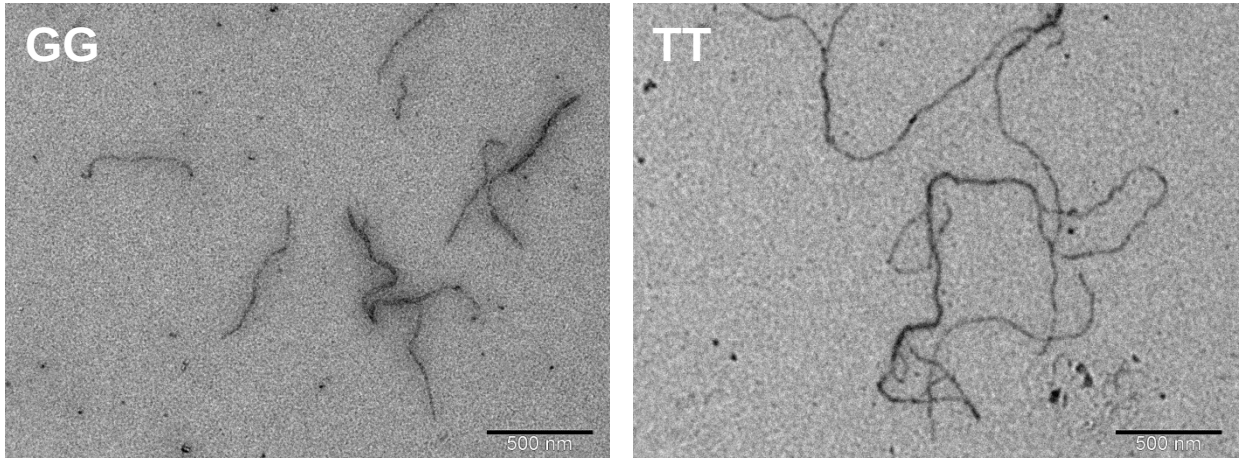
Uromodulin – FimH dynamic Interaction:

- Purification of uromodulin, *UMOD* genotypes
- FimH/uromodulin complex (SEC, SDS-PAGE): N of FimH binding per monomer
- Binding stoichiometry, Rate of dissociation from FimH
- Influence of glycosylation patterns, modulation by NaCl, urea, …



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 19, 2014 VOL. 370 NO. 25

Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux

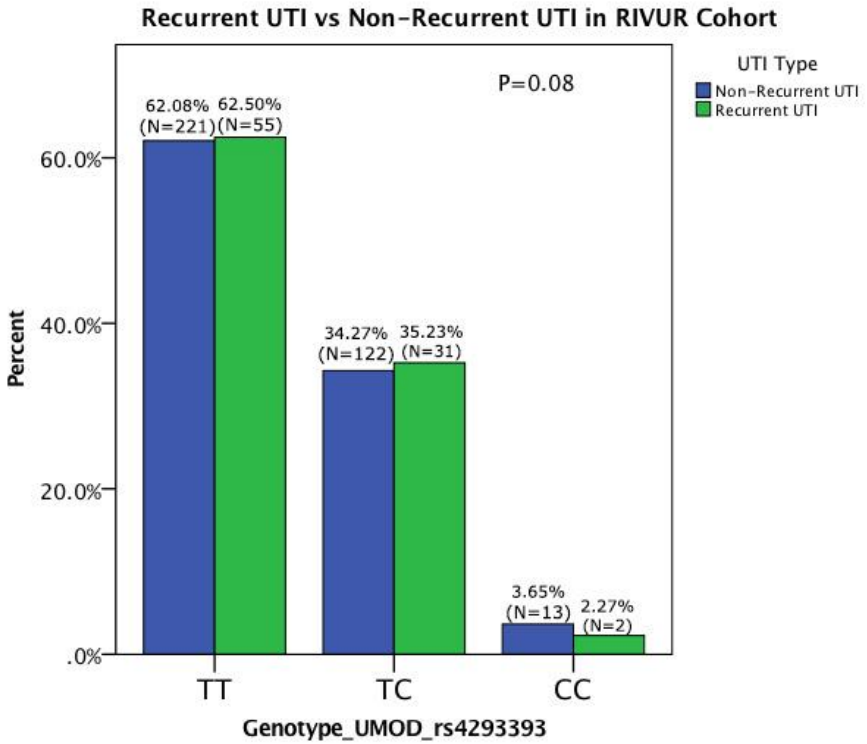
The RIVUR Trial Investigators*

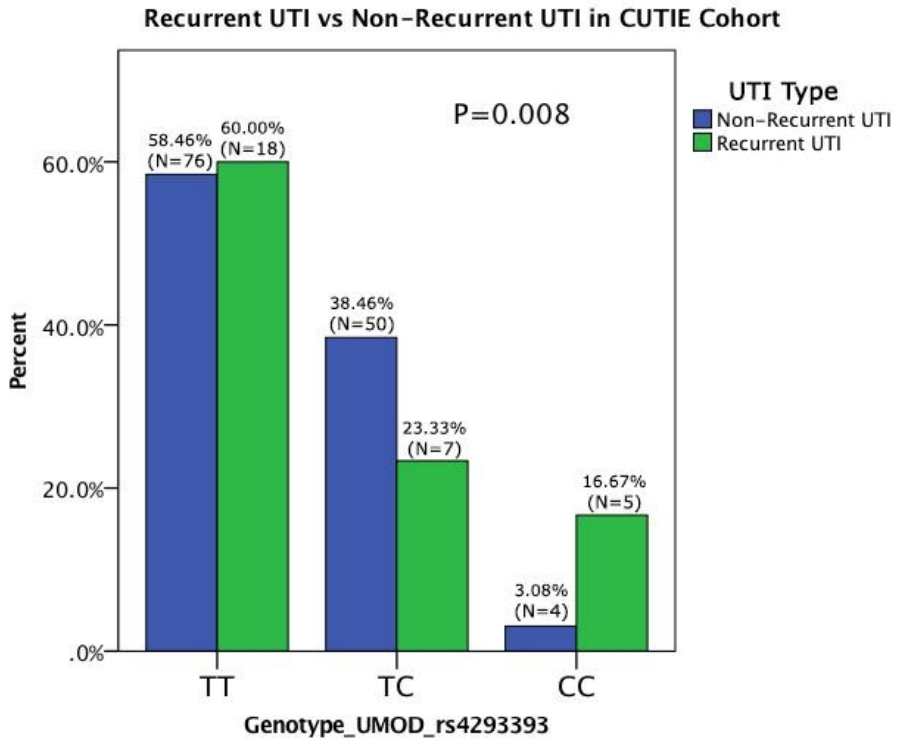
2-yr, multisite prospective cohort to identify risk factors for recurrent UTIs in children aged 2- 70 months

- RIVUR: randomized intervention for VUR, N=305
- CUTIE: careful UTI evaluation - without VUR, N=195
- Female, 90%; Caucasians, 75%; *E. coli*, 90%; febrile & symptomatic UTIs, 50%

Coll. D.S. Hains, Univ. Tennessee

Effect of *UMOD* Genotype on Recurrence of UTI in Children

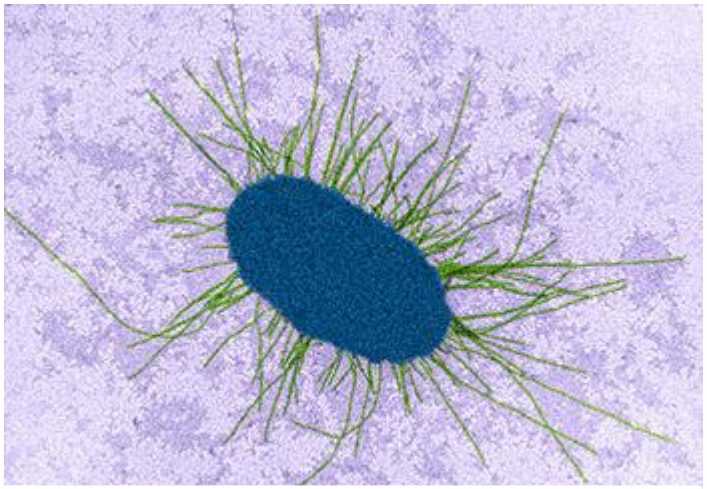


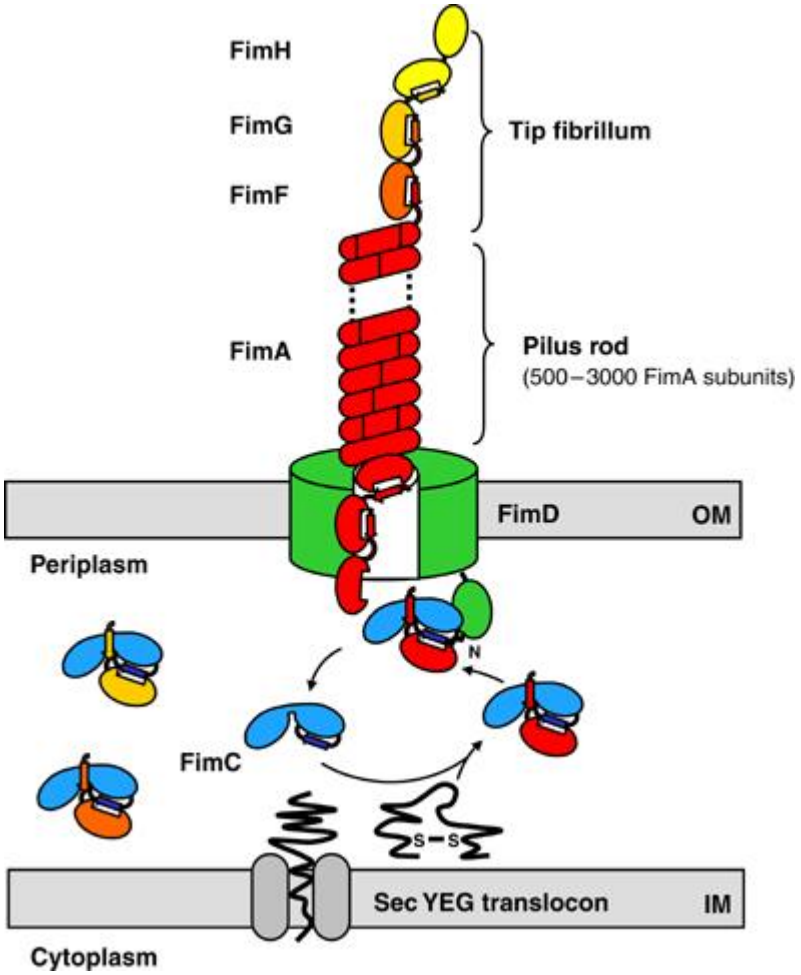


Excess of CC allele (low uromodulin) in children with recurrent UTIs without VUR

Coll. D.S. Hains, Univ. Tennessee

Uropathogenic E. coli : Type-1 Fimbriae

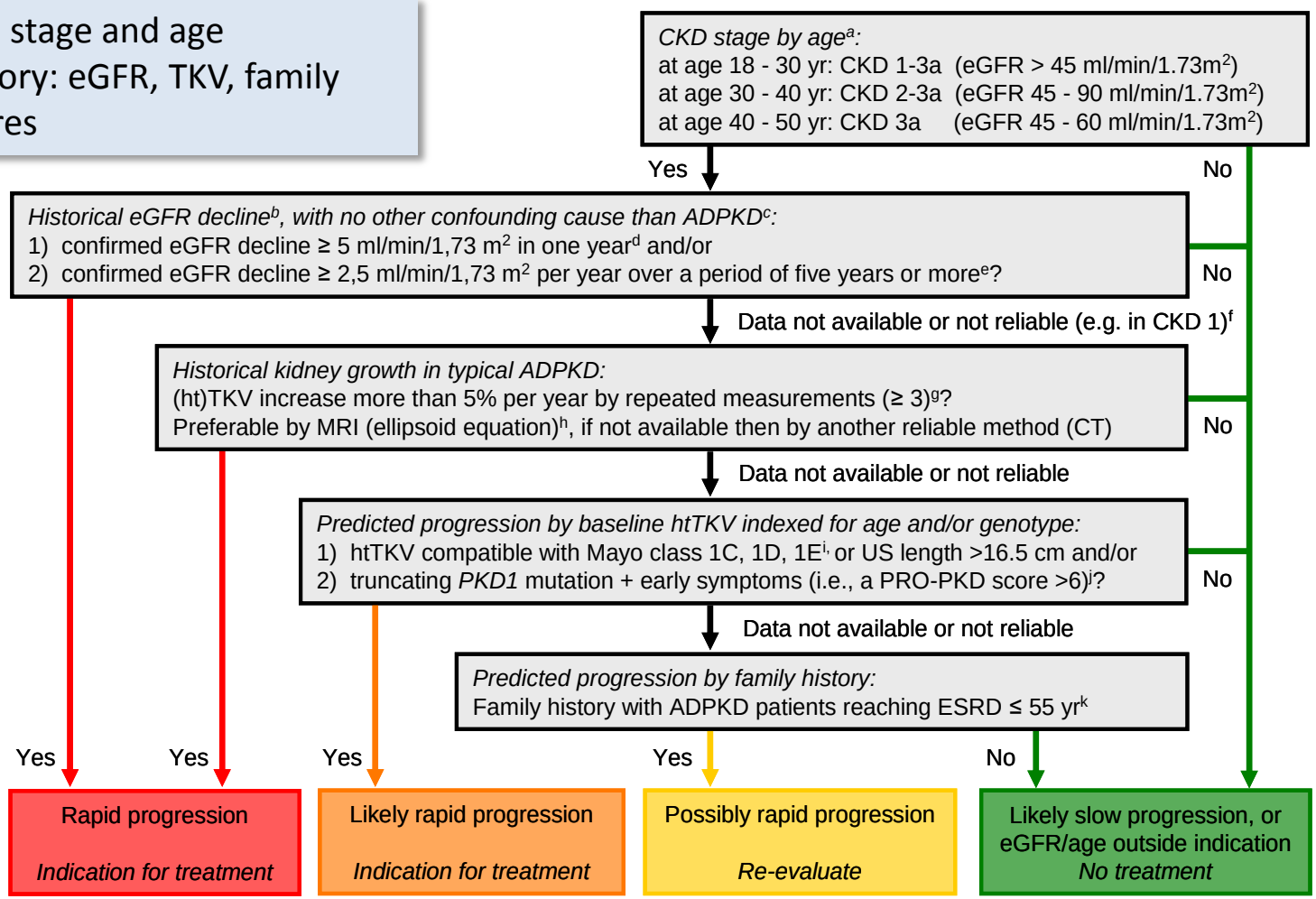




- Highly stable, multi-protein complexes
- Required for bacterial attachment to glycoprotein receptor uroplakin – urothelial cells
- Virulence factor

Algorithm to assess indications for treatment in ADPKD

- CKD stage and age
- History: eGFR, TKV, family
- Scores



WGiKD

Other associations of the UMOD locus:

Risk of hypertension and incident CVD in extreme case-control study

Global BPGen consortium

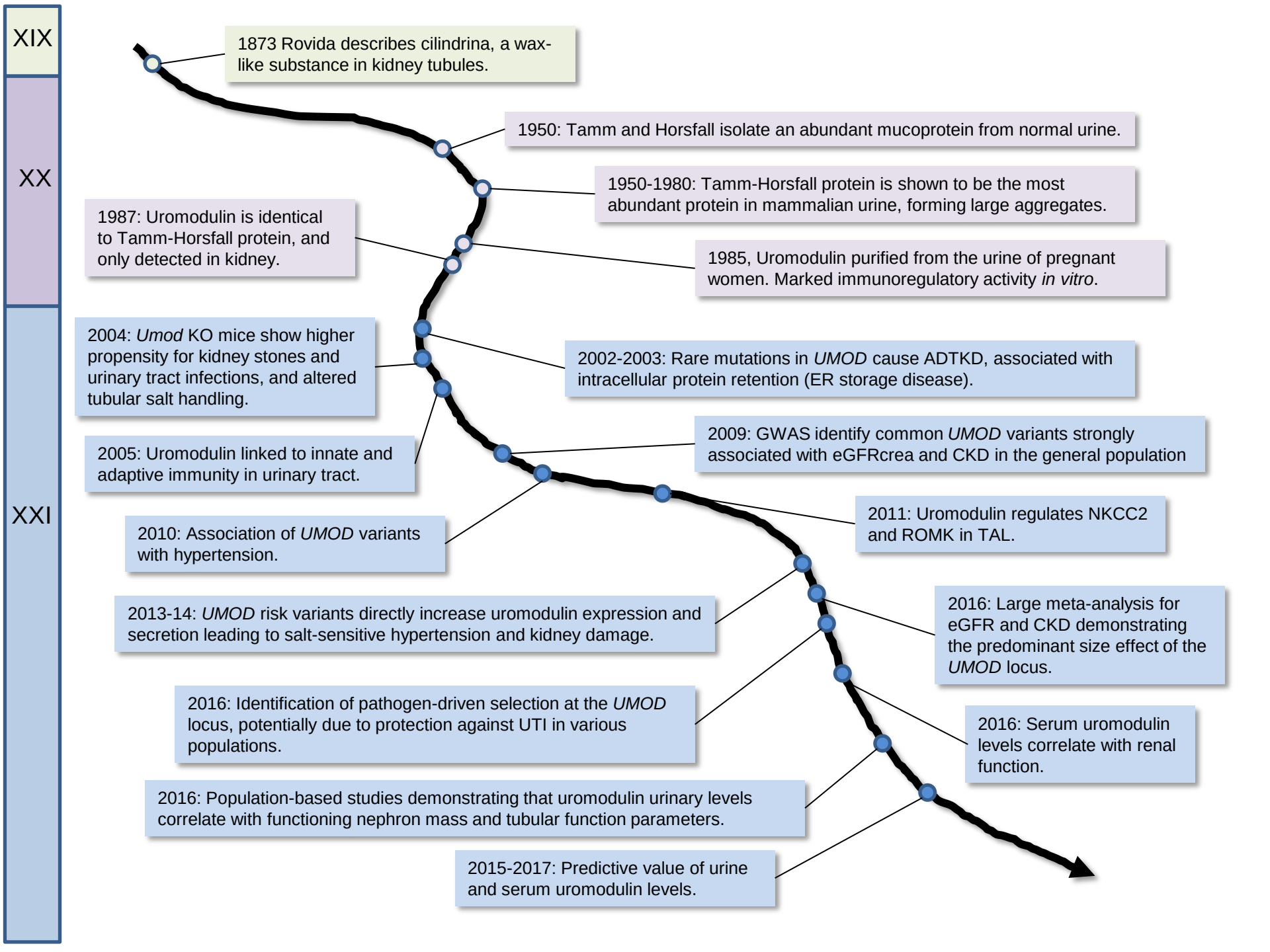
Reduced risk of kidney stones

combined Dutch and Icelandic sample

Urinary levels of uromodulin

Meta-analysis – 10,884 individuals EU descent

GWAS of blood pressure extremes, which identified variants in the uromodulin gene (UMOD) associated with hypertension. The special feature of this study was the selection of 2000 so called hypercontrols, subjects who had BP below 120/80 mmHg and were free from cardiovascular events during 10 year follow-up


XIX
XX
XXI
1873 Rovida describes cilindrina, a wax-like substance in kidney tubules.
1950: Tamm and Horsfall isolate an abundant mucoprotein from normal urine.
1950-1980: Tamm-Horsfall protein is shown to be the most abundant protein in mammalian urine, forming large aggregates.
1987: Uromodulin is identical to Tamm-Horsfall protein, and only detected in kidney.
1985, Uromodulin purified from the urine of pregnant women. Marked immunoregulatory activity *in vitro*.
2004: *Umod* KO mice show higher propensity for kidney stones and urinary tract infections, and altered tubular salt handling.
2002-2003: Rare mutations in *UMOD* cause ADTKD, associated with intracellular protein retention (ER storage disease).
2009: GWAS identify common *UMOD* variants strongly associated with eGFRcrea and CKD in the general population
2005: Uromodulin linked to innate and adaptive immunity in urinary tract.
2011: Uromodulin regulates NKCC2 and ROMK in TAL.
2010: Association of *UMOD* variants with hypertension.
2013-14: *UMOD* risk variants directly increase uromodulin expression and secretion leading to salt-sensitive hypertension and kidney damage.
2016: Large meta-analysis for eGFR and CKD demonstrating the predominant size effect of the *UMOD* locus.
2016: Identification of pathogen-driven selection at the *UMOD* locus, potentially due to protection against UTI in various populations.
2016: Serum uromodulin levels correlate with renal function.
2016: Population-based studies demonstrating that uromodulin urinary levels correlate with functioning nephron mass and tubular function parameters.
2015-2017: Predictive value of urine and serum uromodulin levels.

Clinical, Genetic, and Urinary Factors Associated with Uromodulin Excretion

Stéphan Troyanov, Catherine Delmas-Frenette,* Guillaume Bollée,† Sonia Youhanna,‡ Vanessa Bruat,§‖ Philip Awadalla,§‖ Olivier Devuyst,‡ and François Madore**

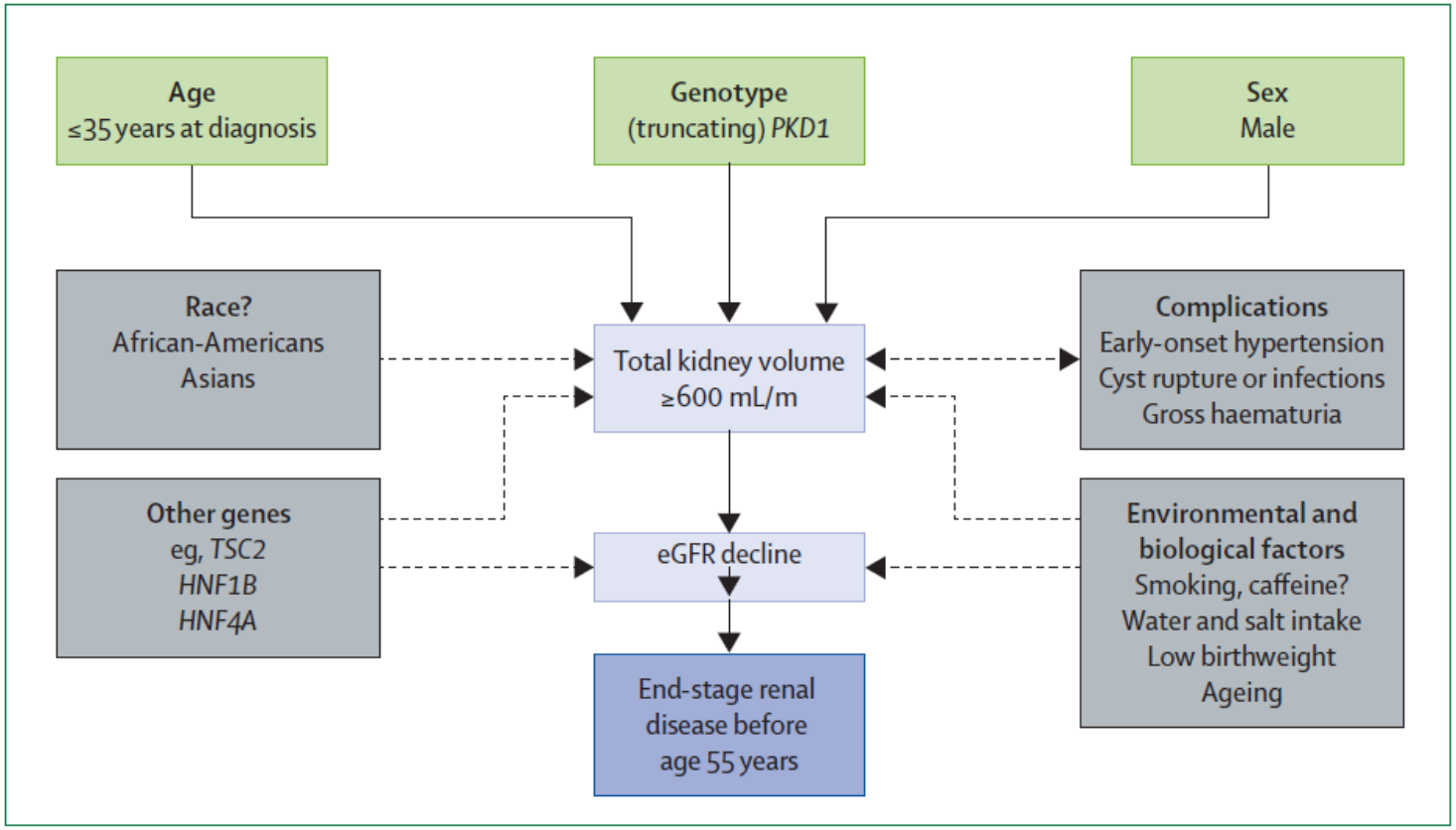
Table 3. Multivariate predictors of uromodulin

Variables	Standardized-β	*P* Value
GFR (CKD-EPI; ml/min per 1.73 m^2)	0.11	0.001
rs4293393 (TT compared with CC with CT)	0.07	0.04
rs12446492 (TT compared with AA with AT)	0.09	<0.01
FE-Na	0.10	<0.01
Presence of glycosuria	−0.07	0.02
FE-Ua	0.29	<0.001
Use of uricosuric drugs	−0.07	0.02

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

Lancet 2015; 385: 1993–2002

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



The Two Faces of *UMOD*

Complex diseases; GWAS
CKD, hypertension

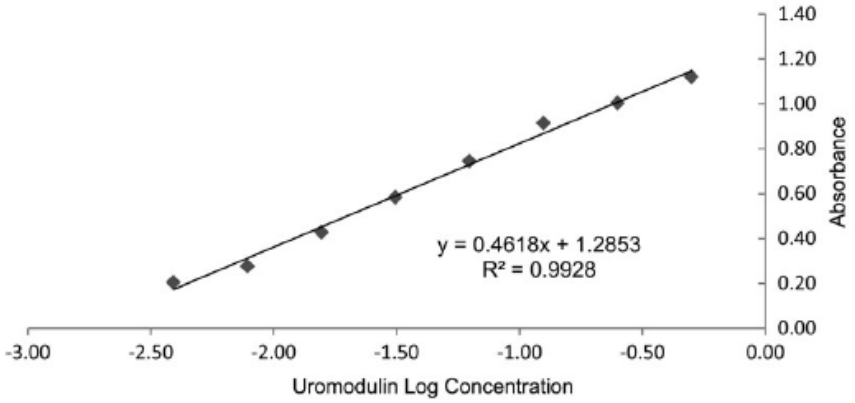
Monogenic, rare diseases
ADTKD-*UMOD*

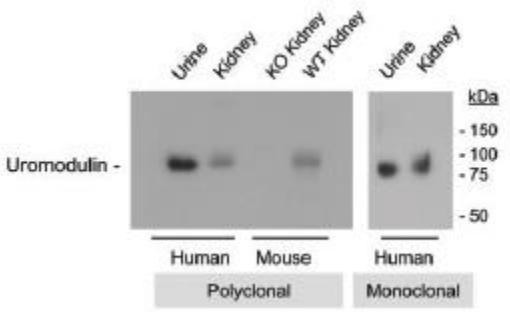
Nephrol Dial Transplant (2013) 0: 1–10
doi: 10.1093/ndt/gft345

S. Youhanna et al. NDT 2013

Original Article

Determination of uromodulin in human urine: influence of storage and processing





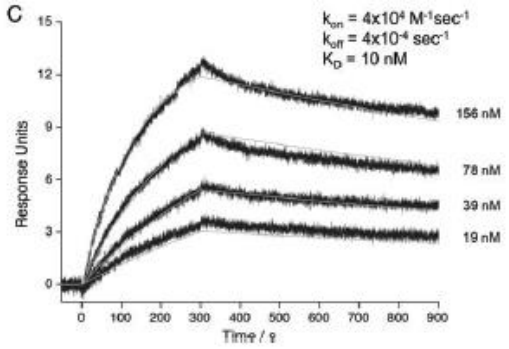
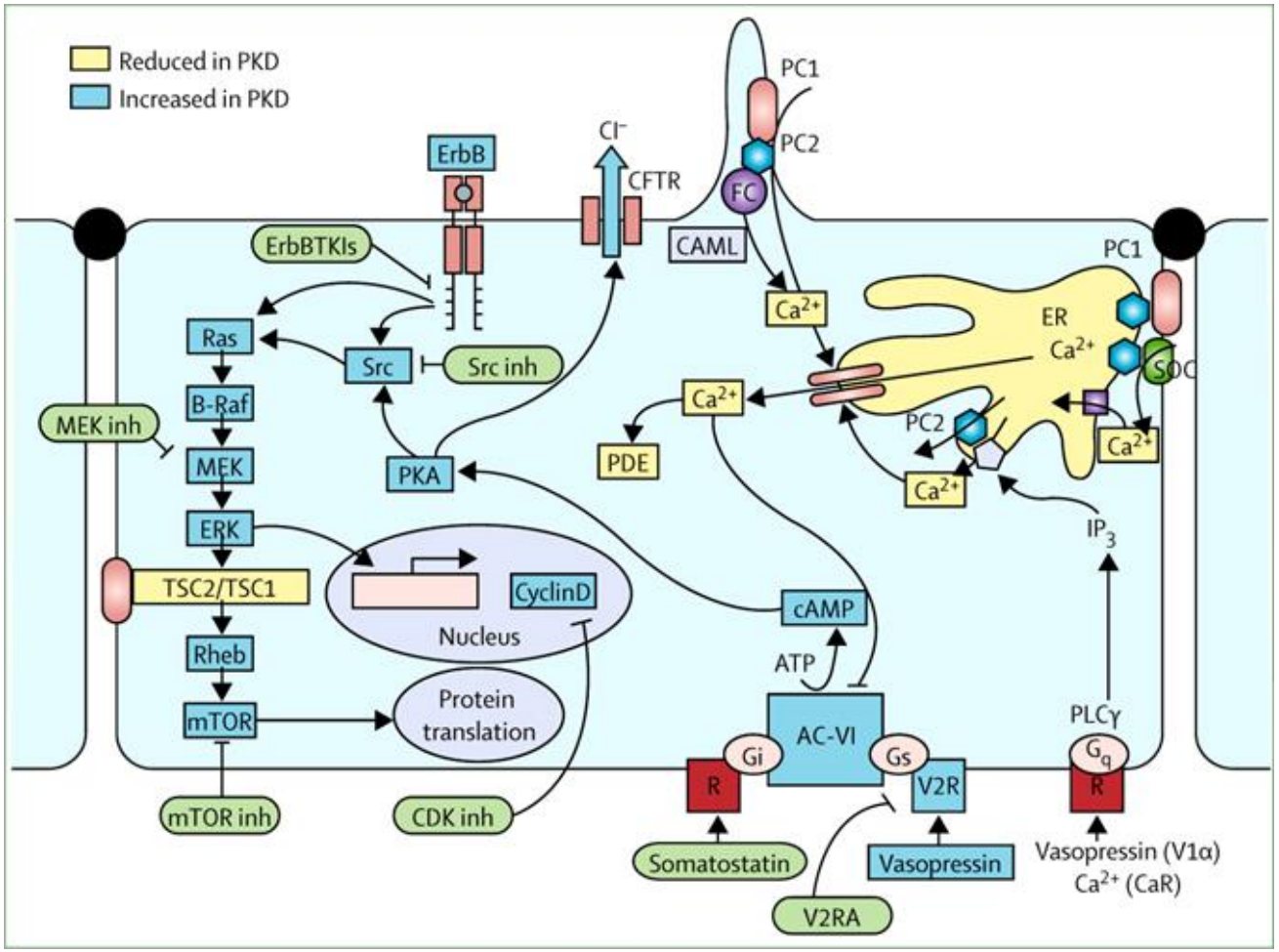


Table 1. Comparison of the characteristics of the in-house ELISA for uromodulin and the commercially available ELISA kits

Kit	Detection range (standard curve) (ng/mL)	Inter-assay variability (%)	Intra-assay variability (%)
In-house	3.9–500	3.28	5.46
MD Bioproduct (Cat. M036020)	2.34–150	11.63	8.36
BioVendor (Cat. RD191163200R)	0.5–32	6.4	2
USCN Life Science, Inc. (Cat. E96918 Hu)	3.13–200	<12	<10

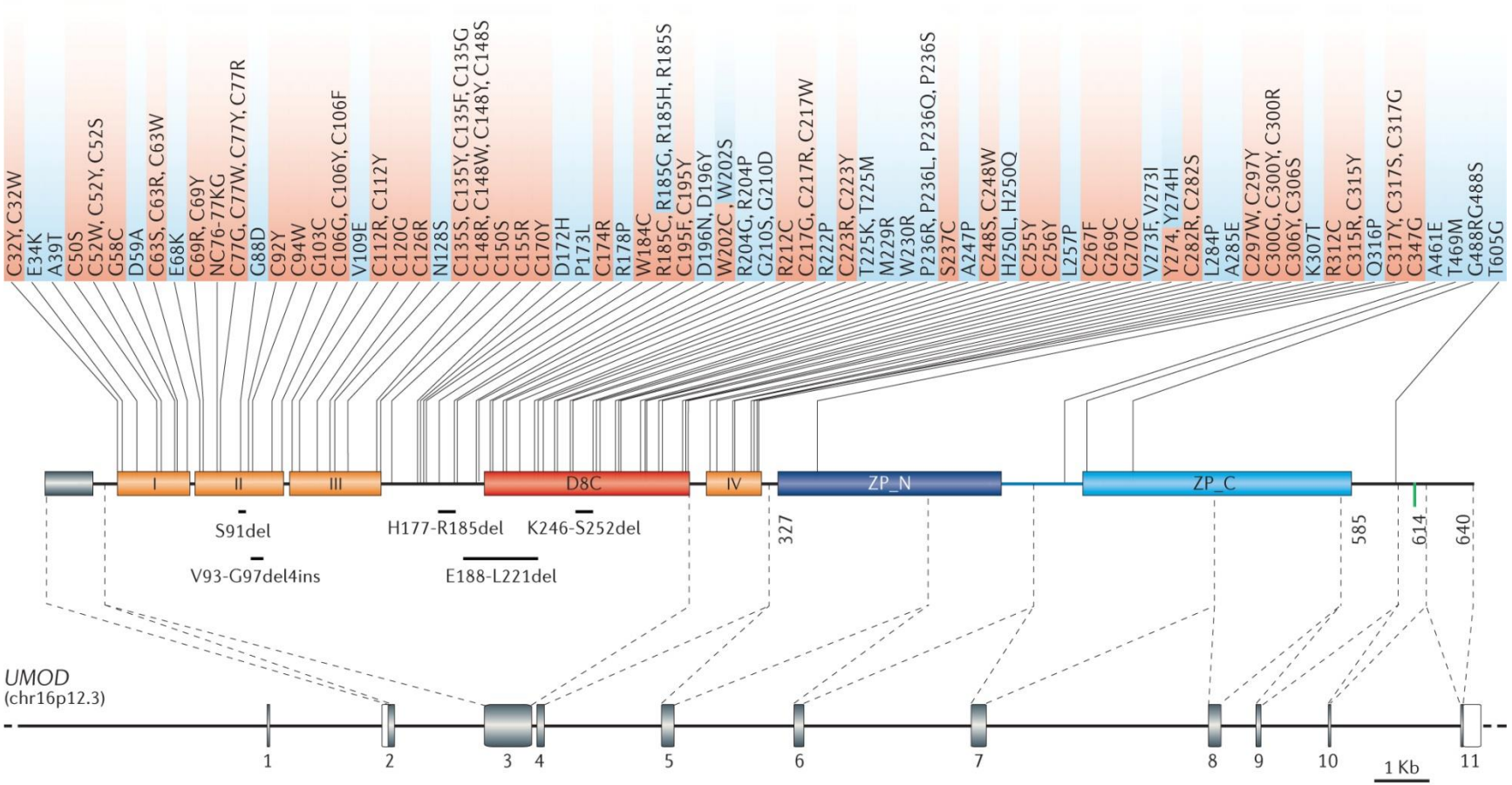
Mechanism of Cyst Formation in ADPKD



Proliferation – Dedifferentiation - Fluid secretion

Torres VE et al. *Lancet* 369:1287, 2007

Uromodulin Mutations in ADTKD/FJHN

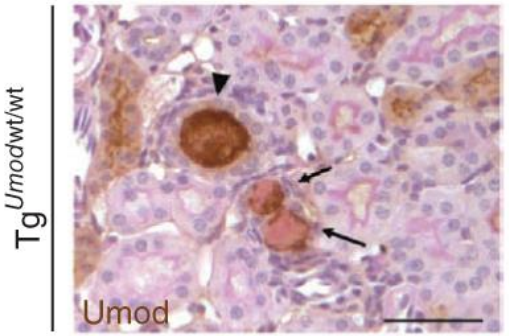


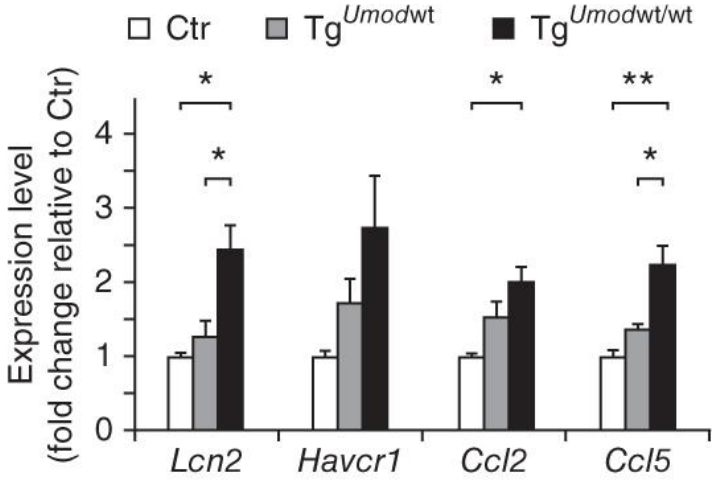
→ 125 mutations, 95% cluster in exons 3 and 4
→ 121/125 missense mutations, 4 in-frame deletions
→ Conserved sequence, cysteine residues (78/125)

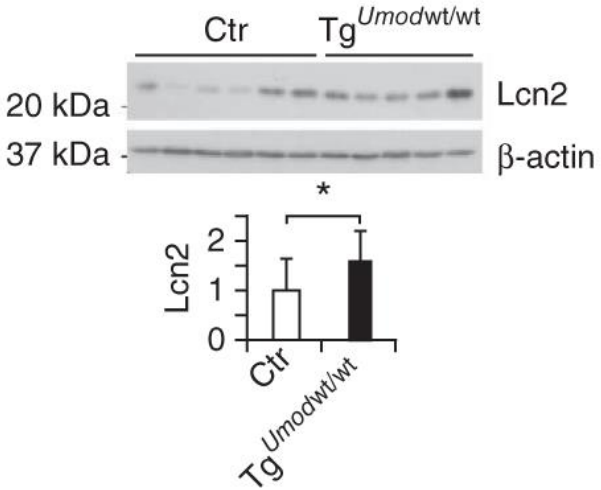
Devuyst O et al. *Nat Rev Nephrol* 13, 2017

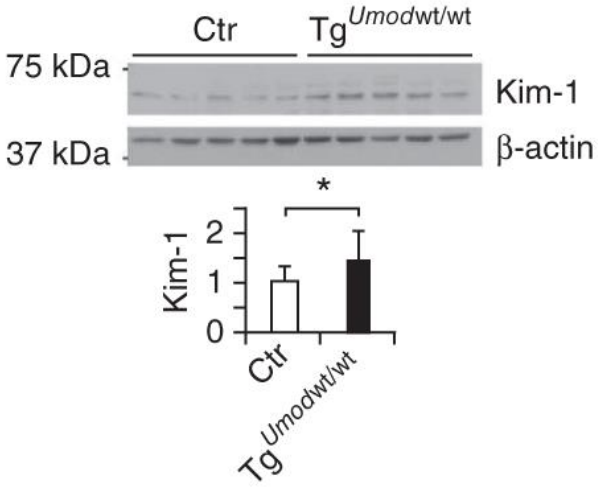
Uromodulin Overexpression: Kidney Damage

Tg *Umod* Mice









Trudu M. et al. Nat Med 19, 2013

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)
- …

The *UMOD* locus stands out among all loci

* First discovered in association with eGFRcrea & CKD in EU ancestry

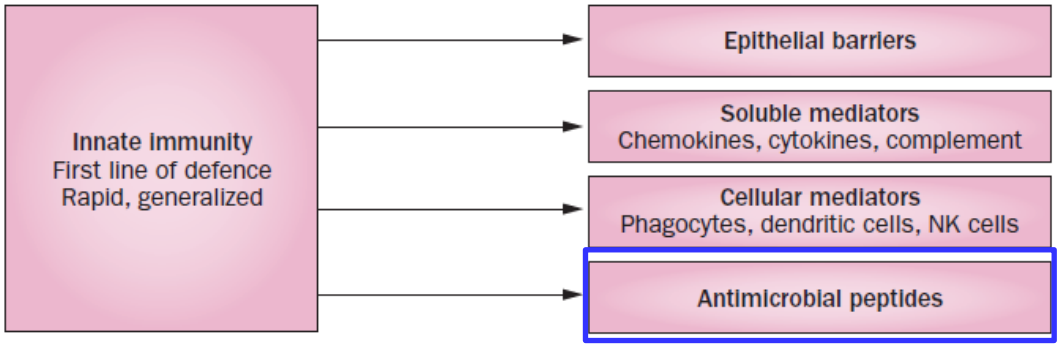
(Köttgen 2009)

* Largest effect size on both eGFR and CKD risk
* Consistency of effect among different ethnic groups
* Relationship with age: effect very significant after age 60 years
* Only locus associated with incident CKD (OR 1.3 with each copy of risk allele)

All eGFRcrea loci account for 4% of variance: *UMOD* >1%
i.e. 25% of eGFRcrea variability explained by genetic factors

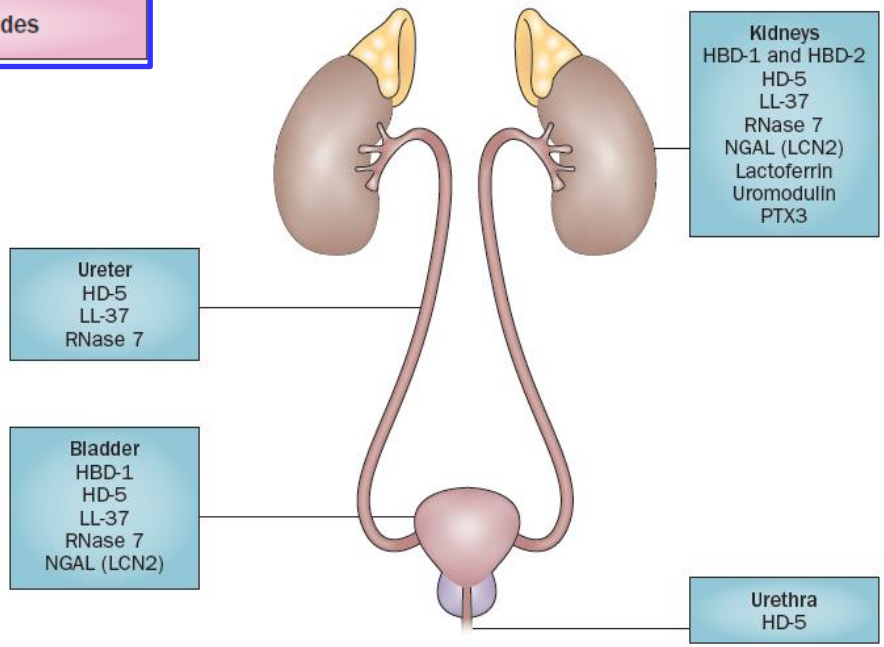
Devuyst & Pattaro, JASN 2017, in press

Innate Immune Response: Principal Mechanism of Defense against UTI



Uromodulin defense against UPEC:

- Limits attachment to uroplakin receptors
- Promotes dendritic cell maturation via TLR4
- Activates innate & adaptative immunity
- Danger signal - dendritic cells – inflammasome



Becknell et al. NRN 11, 2015

Pediatr Nephrol
https://doi.org/10.1007/s00467-017-3823-0

ORIGINAL ARTICLE

Preoperative levels of urinary uromodulin predict acute kidney injury after pediatric cardiopulmonary bypass surgery

Michael R. Bennett[1] · Olivia Pyles[1] · Qing Ma[1] · Prasad Devarajan[1]

One hundred and one children undergoing CPB were enrolled. Urine was collected prior to CPB, and AKI was defined as ≧50% increase in serum creatinine from preoperative baseline within 48 h of surgery.

Forty-seven patients (47%) developed AKI, and 92% of participants in the lowest quartile of preoperative uUMOD concentrations developed AKI compared with 8% in the highest quartile.

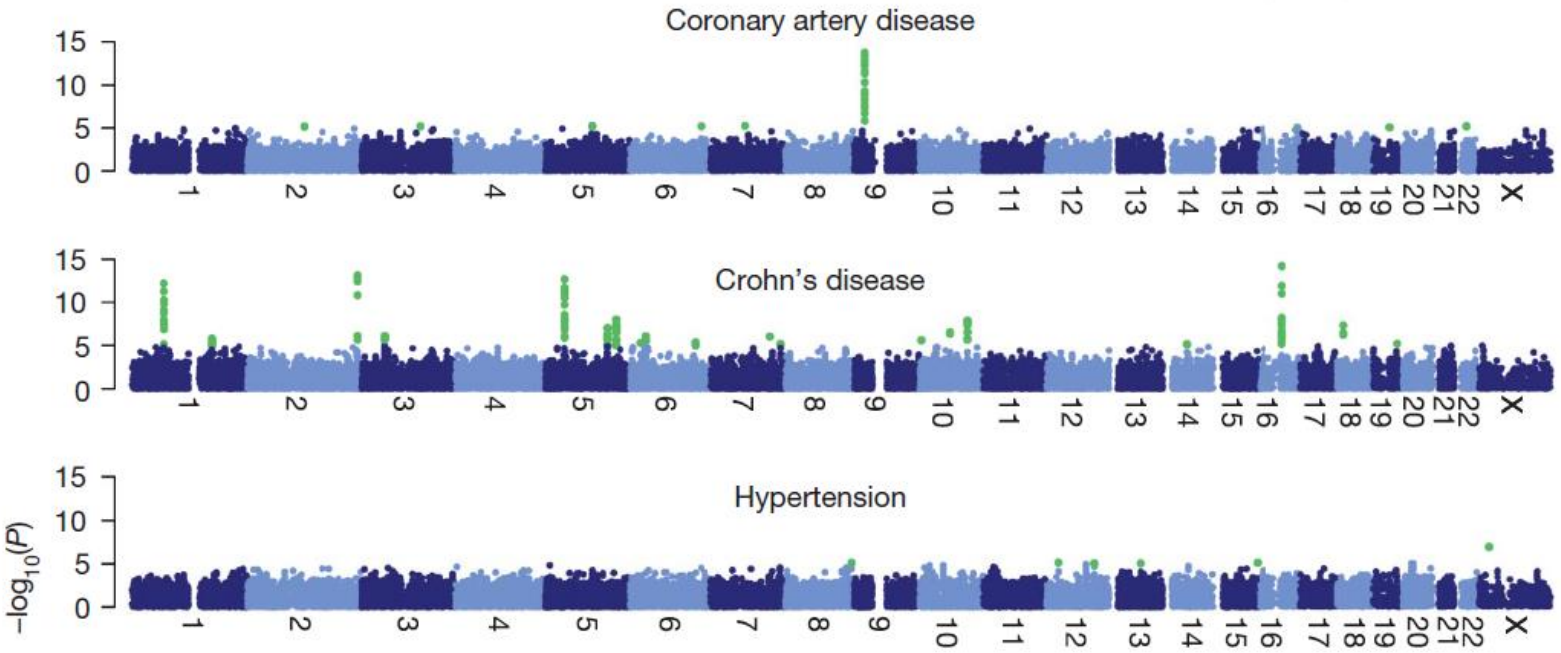
Children with lowest preoperative levels of uUMOD have greatly increased risk of AKI post-CPB. If uUMOD were used to risk-stratify patients undergoing CPB, clinical measures could be taken to minimize AKI development.

Vol 447|7 June 2007|doi:10.1038/nature05911 nature

ARTICLES

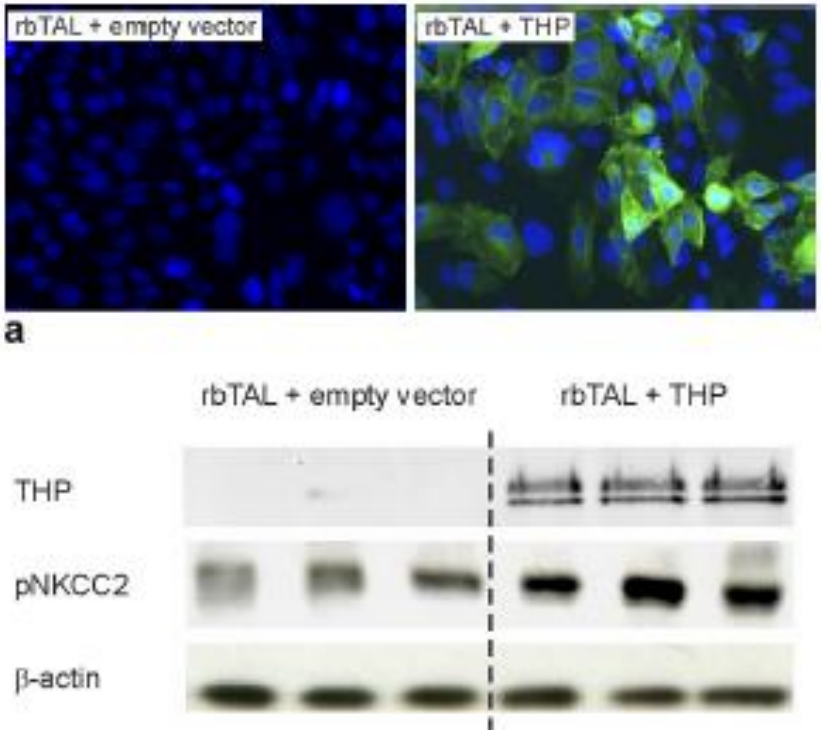
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

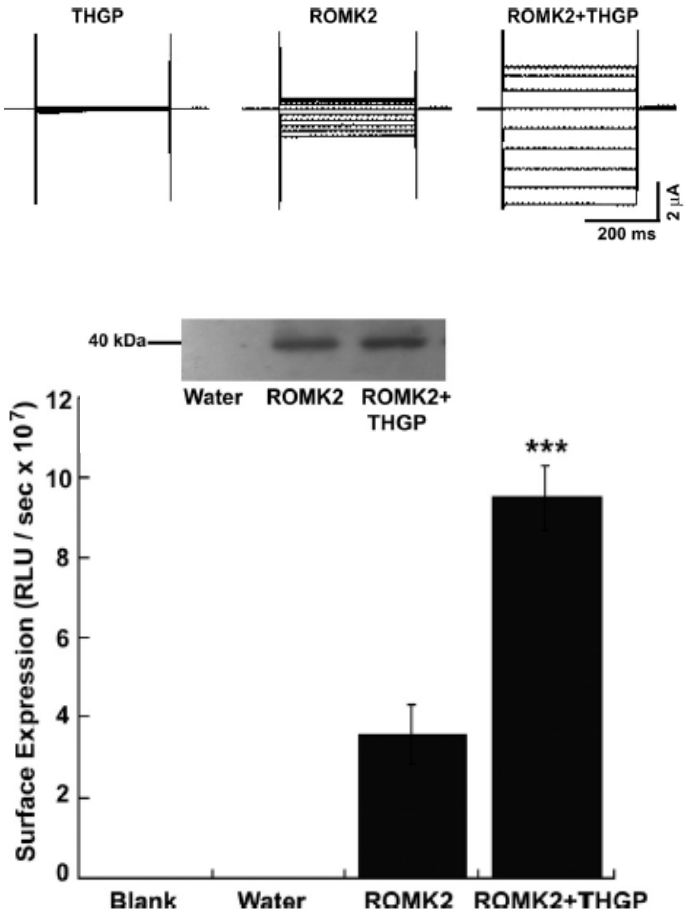


- Welcome Trust Case Control Consortium, 50 groups in UK
- Seven diseases (2'000 cases each) compared to 3'000 controls
- 24 loci in 6 traits – none for hypertension

TAL: Uromodulin Regulates NKCC2 and ROMK



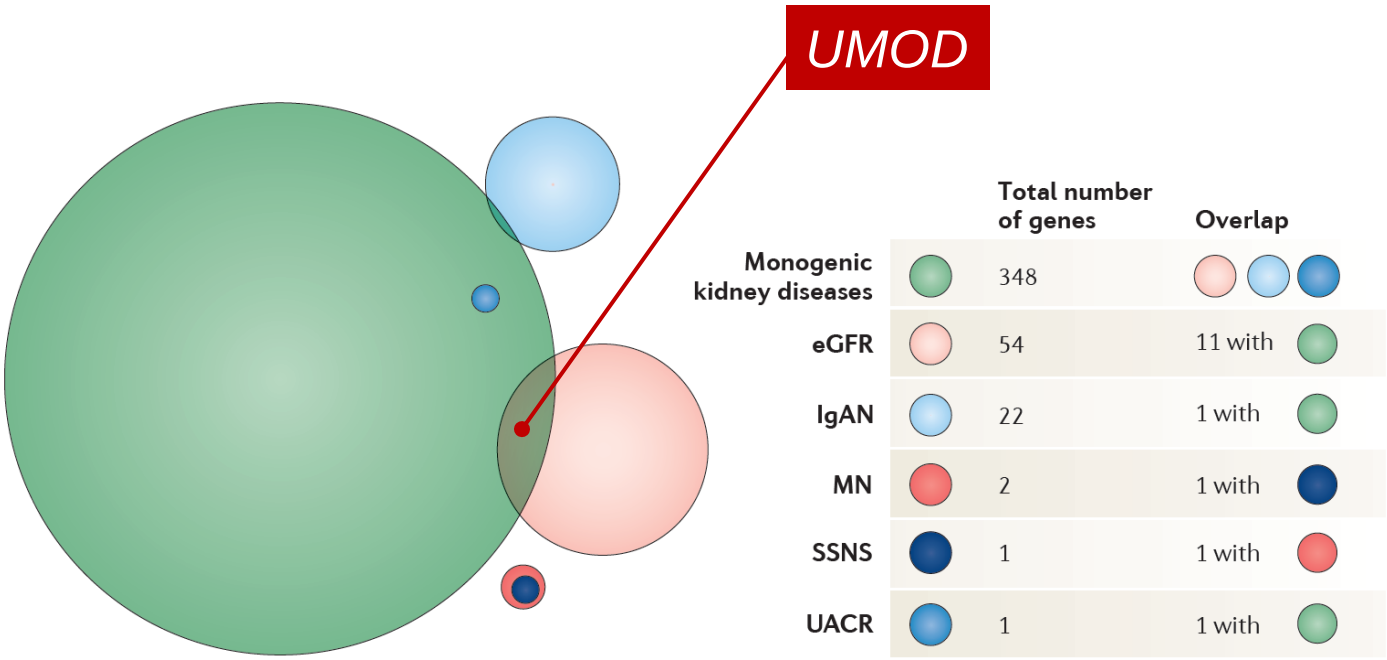
rbTAL cells: effect of THP on pNKCC2



Xenopus oocytes: ROMK currents/surface

Mutig et al. JBC 286, 2011
Renigunta et al. JBC 286, 2011

Monogenic kidney disease genes map into GWAS loci



→ Indicates a continuum between rare disruptive mutations and common regulatory variants in genes that are important for kidney development and function.

Wuttke & Köttgen, Nat Rev Nephrol 2016

http://www.kidney-international.org meeting report

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

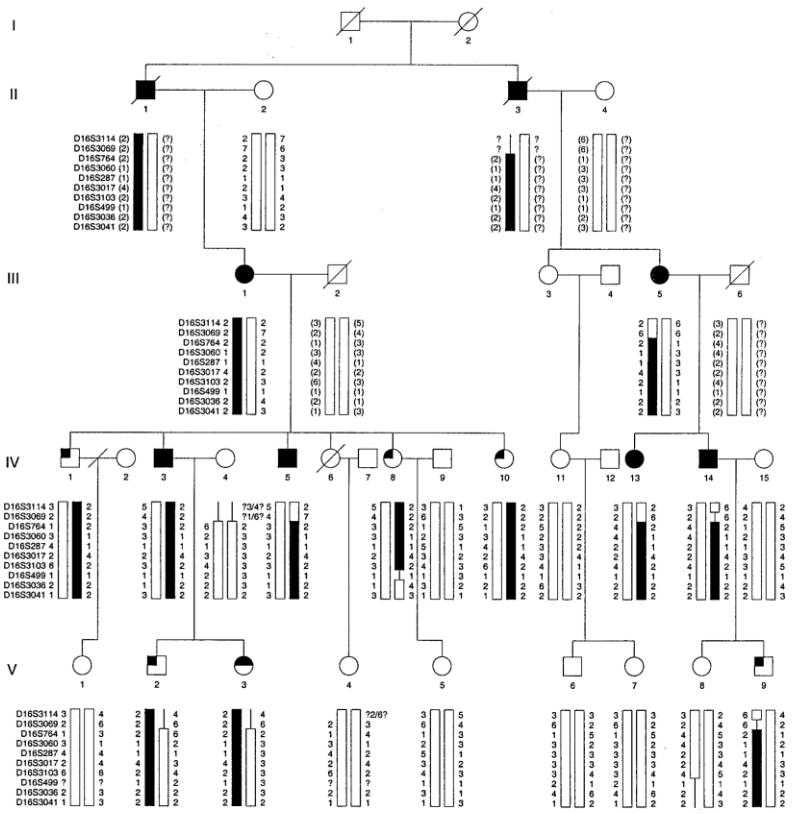
Kai-Uwe Eckardt[1], Seth L. Alper[2], Corinne Antignac[3,4], Anthony J. Bleyer[5], Dominique Chauveau[6], Karin Dahan[7], Constantinos Deltas[8], Andrew Hosking[9], Stanislav Kmoch[10], Luca Rampoldi[11], Michael Wiesener[1], Matthias T. Wolf[12] and Olivier Devuyst[13]

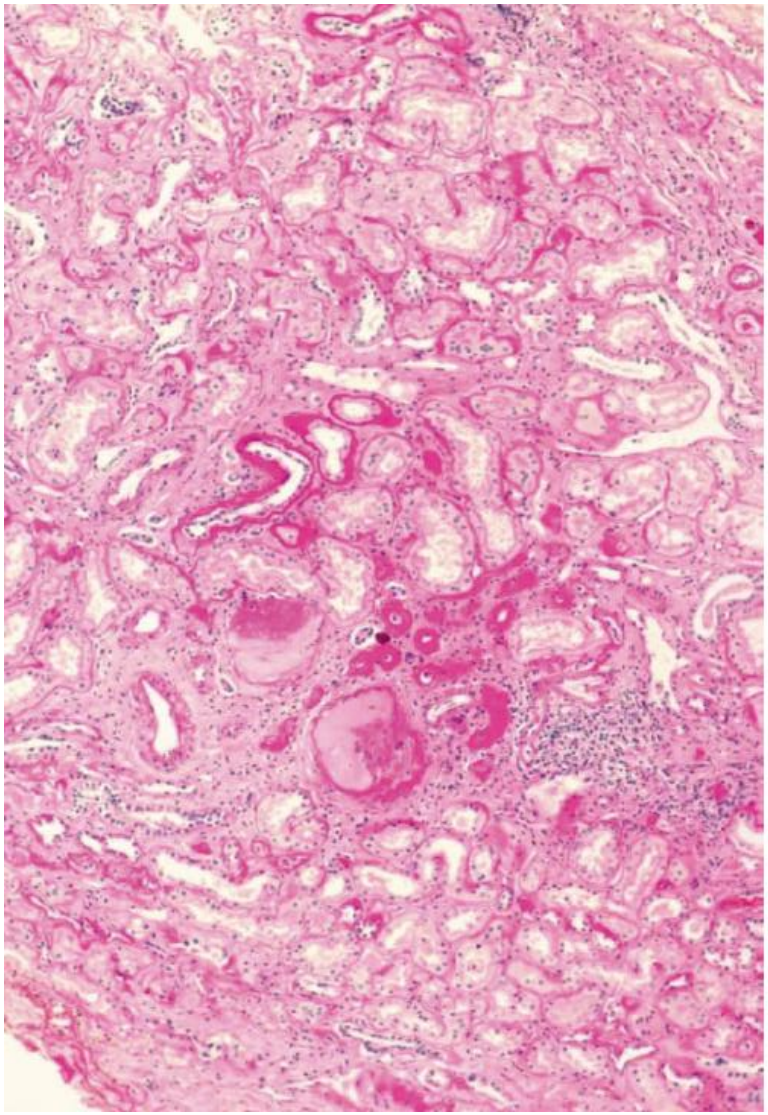
Table 1 | New gene-based classification and terminology of different types of ADTKD

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

Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)



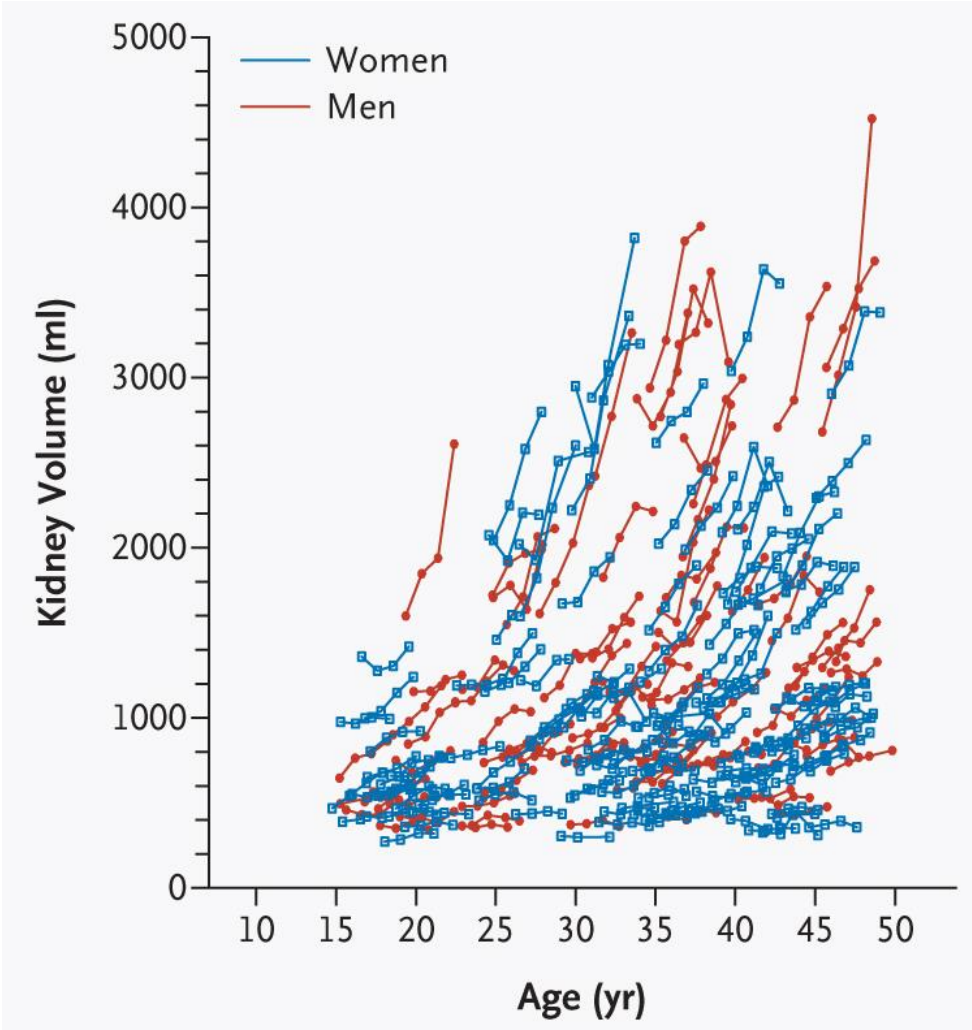


- Hyperuricemia (low FEurate) during childhood
- Tubulointersititial nephritis (thickening TBM)
- Progressive renal failure - adulthood

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

Exponential Progression of TKV in ADPKD: CRISP

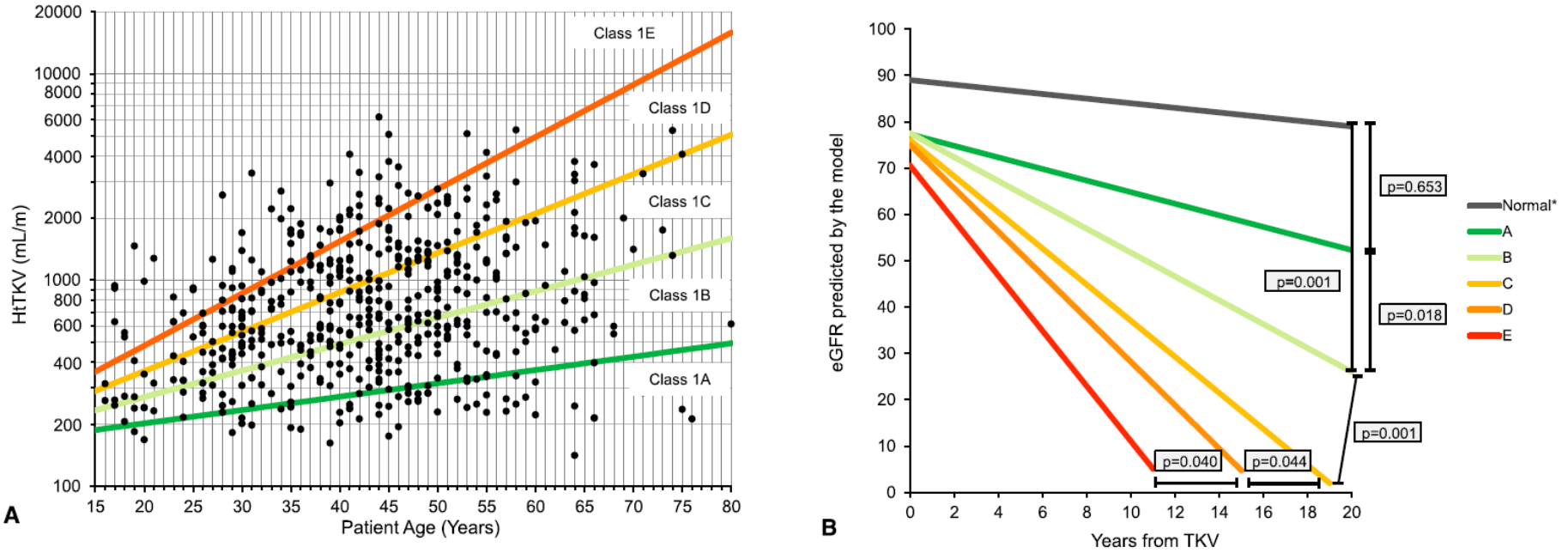
TKV measured by MRI



N Engl J Med 2006; 354 : 2122-30

J Am Soc Nephrol 26: 160–172, 2015.

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

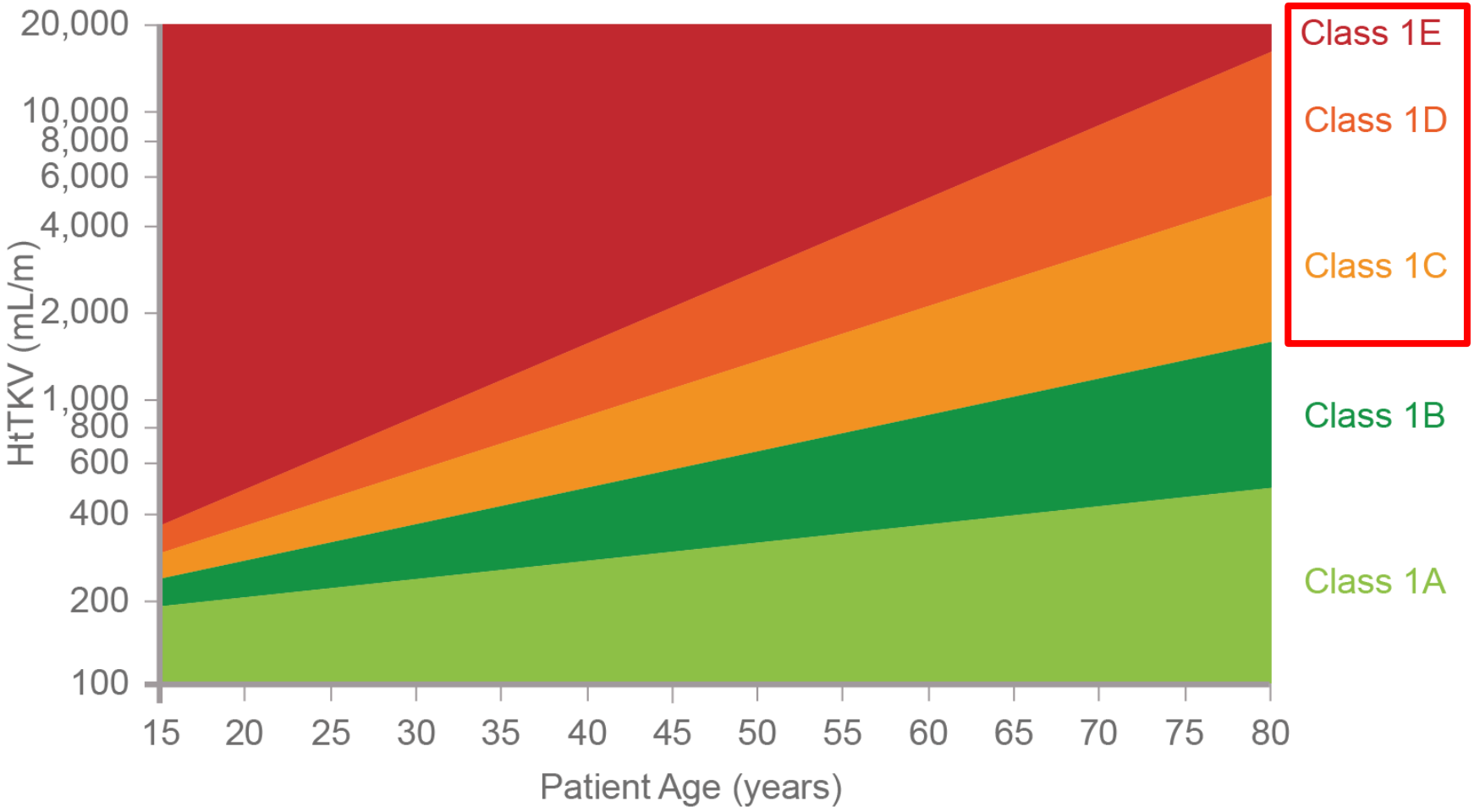
Mayo Classification Score

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

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

Nephrol Dial Transplant (2016) 31: 337–348
doi: 10.1093/ndt/gfv456
Advance Access publication 29 January 2016

ndt
Nephrology Dialysis Transplantation

NDT Perspectives

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 ?

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:

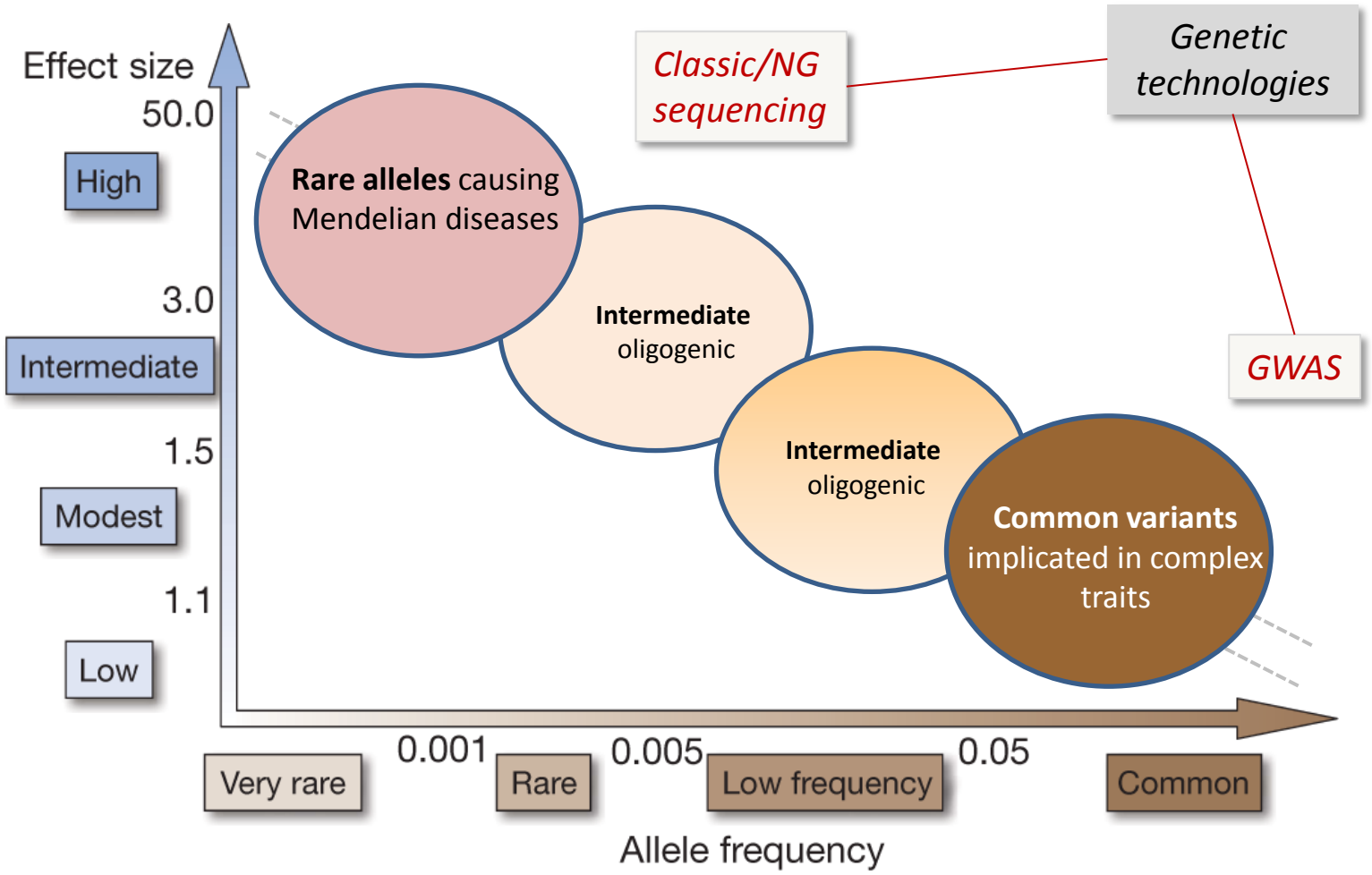
- Historical renal function decline > 5 ml/min/1.73m^2/yr (or 2.5 ml/min / 5 yr)
- Historical TKV progression > 5% /yr

- 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

WGiKD

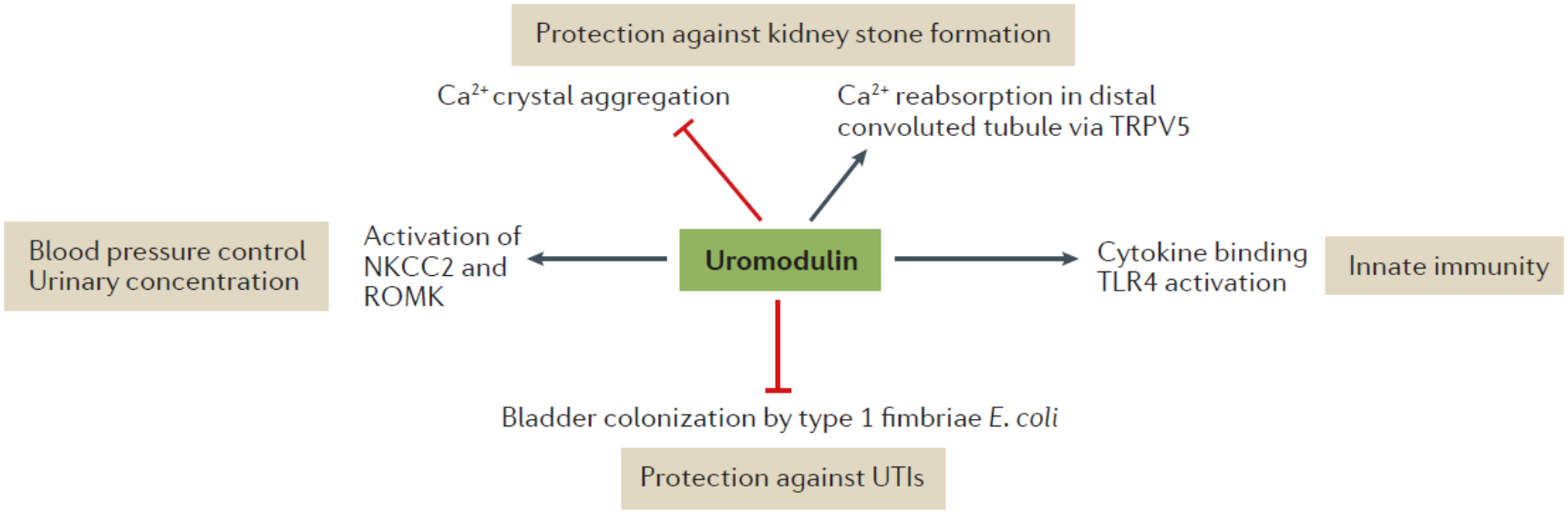
Genetic Architecture of Kidney Disease



Manolio et al. Nature 461, 2009

Uromodulin:

A multi-faceted protein in the urinary tract



Devuyst O et al. *Nat Rev Nephrol* 13, 2017

OPEN ACCESS Freely available online

PLoS GENETICS

Association of eGFR-Related Loci Identified by GWAS with Incident CKD and ESRD

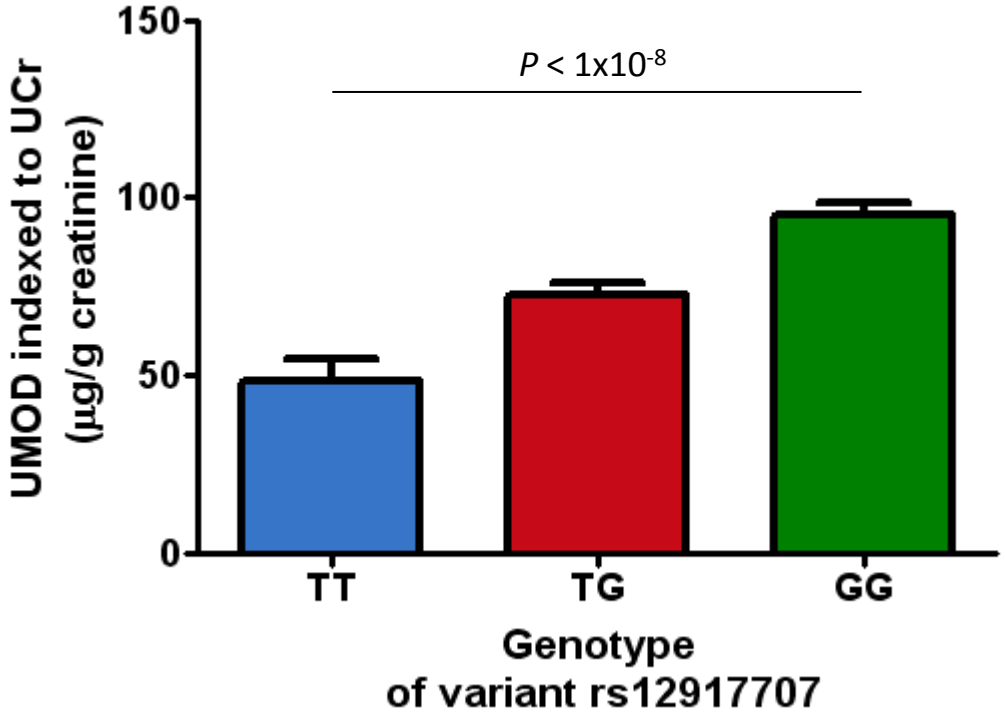
Böger CA, Gorski M, Li M, Hoffmann MM, Huang C, et al.

September 2011 | Volume 7 | Issue 9 | e1002292

- *UMOD* is associated with incident CKD at a genome-wide significant level
  → OR of 1.3 per copy of risk allele

- *UMOD* is also associated with incident ESRD

The *UMOD* Risk Allele Increases Urinary Uromodulin

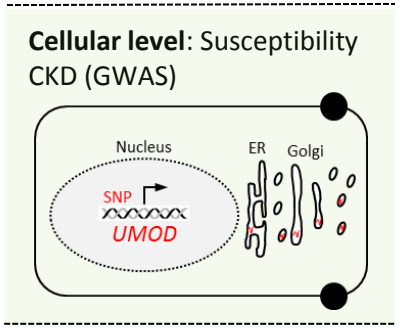


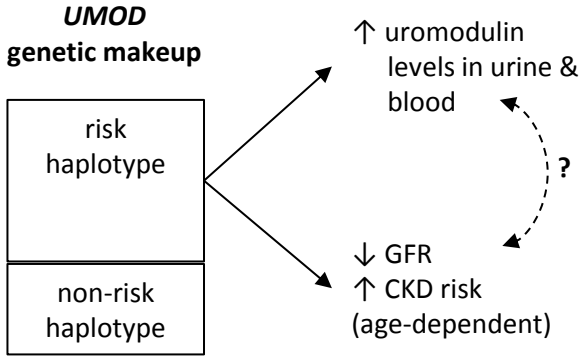
Urinary uromodulin
N=10,884

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

Olden M et al. *J Am Soc Nephrol* 25, 2014

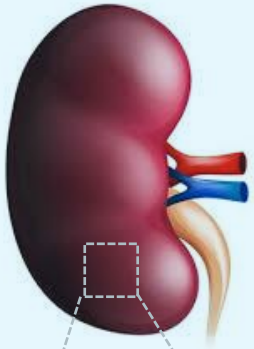
Genetic studies: healthy individuals



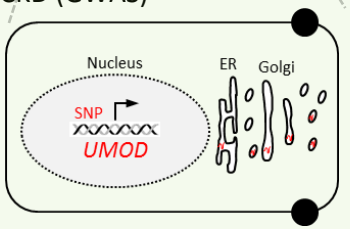


Observational epidemiological studies

Organ level: Biomarker for kidney health



Cellular level: Susceptibility CKD (GWAS)



Cross-sectional studies healthy subjects

↑ uromodulin levels ⟷ **associated with** ↑ GFR, ↑ kidney length & volume, ↑ tubular activity

Uromodulin levels ← Kidney Mass

Causality

Genetic studies: healthy individuals

***UMOD* genetic makeup**

risk haplotype

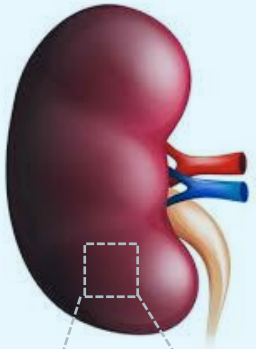
non-risk haplotype

↑ uromodulin levels in urine & blood

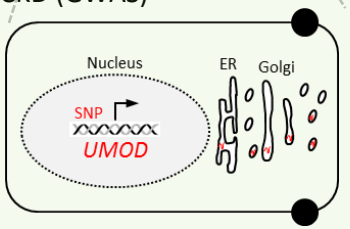
?

↓ GFR
↑ CKD risk (age-dependent)

Organ level: Biomarker for kidney health



Cellular level: Susceptibility CKD (GWAS)



Observational epidemiological studies

Cross-sectional studies
healthy subjects

↑ uromodulin levels ↔ **associated with** ↑ GFR, ↑ kidney length & volume, ↑ tubular activity

Uromodulin levels ← Kidney Mass

Causality

Prospective studies
risk subjects (aged, early CKD)

↑ uromodulin levels ↔ **associated with** ↓ GFR decline odds, ↓ AKI risk odds, ↓ mortality risk

Uromodulin levels ?⇄ Kidney Disease

Reverse causality

Genetic studies: healthy individuals

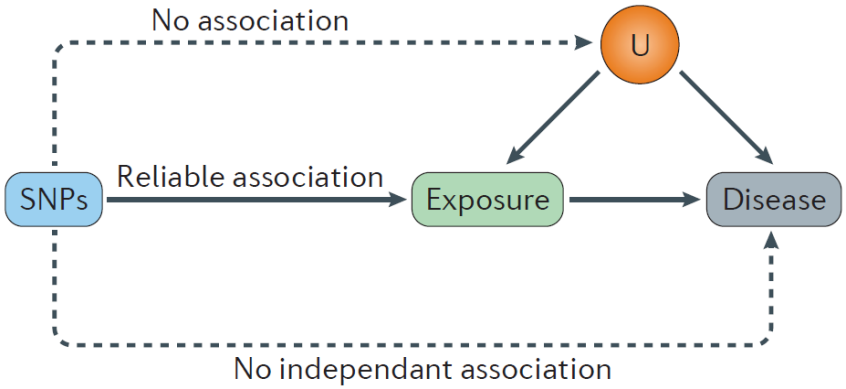
UMOD **genetic makeup**

risk haplotype → ↑ uromodulin levels in urine & blood

non-risk haplotype → ↓ GFR, ↑ CKD risk (age-dependent)

↑ uromodulin levels in urine & blood ? ↓ GFR, ↑ CKD risk (age-dependent)

Causality of Uromodulin levels? Mendelian Randomization

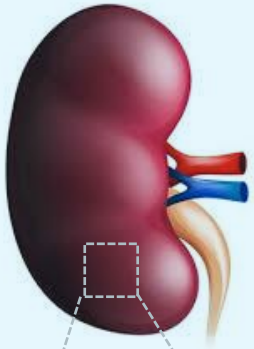


The three principles of instrumental variable analysis are:

1. the instrumental variable (a genetic variant here) must associate with the exposure
2. the instrumental variable must not associate with confounders that are either known or unknown (U)
3. there is no pathway from the SNP to disease that does not include the exposure of interest.

Holmes MV et al. Nat Rev Cardiol 2017
Sekula P et al. JASN 27, 2016

Organ level: Biomarker for kidney health



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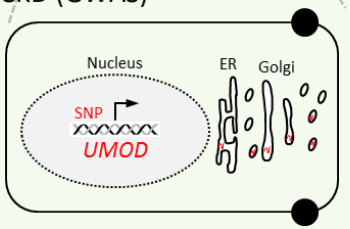

Observational epidemiological studies

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Reverse causality

Genetic studies: healthy individuals

***UMOD* genetic makeup**

risk haplotype

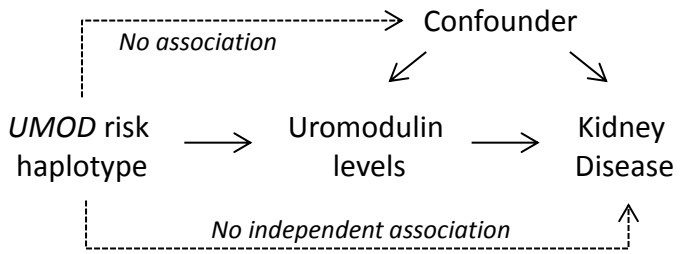
non-risk haplotype

↑ uromodulin levels in urine & blood

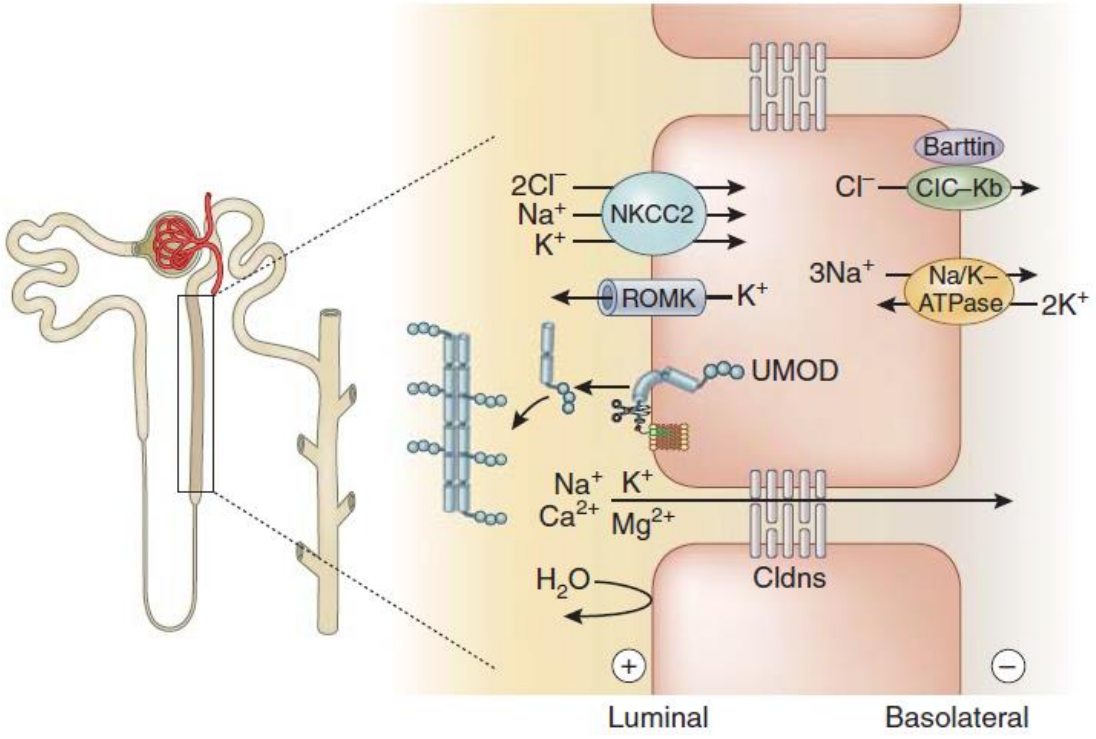
?

↓ GFR
↑ CKD risk (age-dependent)

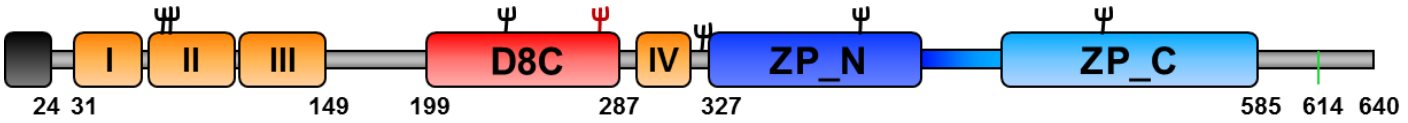
A proposed Mendelian randomization study



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

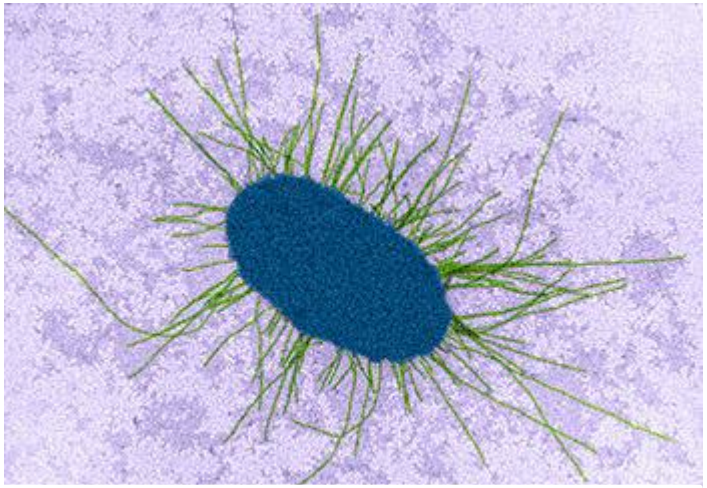
Devuyst O et al. *Nat Rev Nephrol* 13, 2017

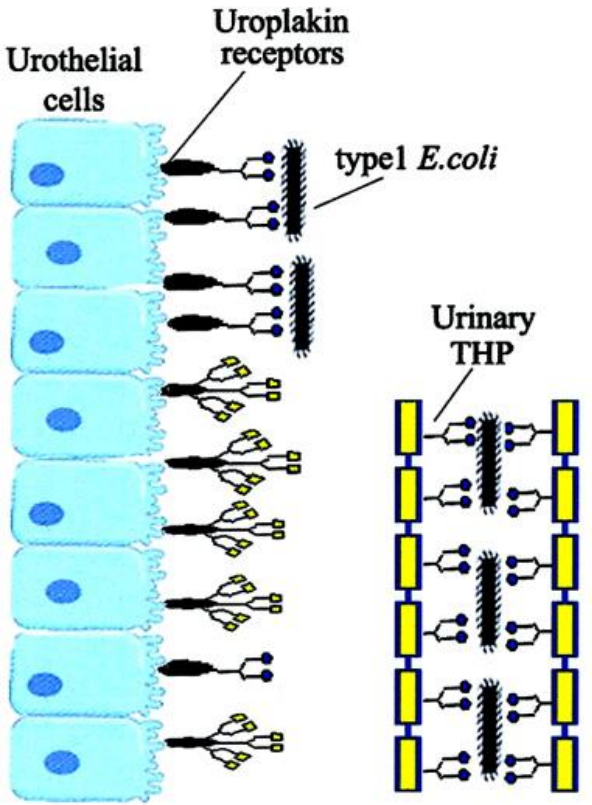
Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 9630–9635, September 1996
Cell Biology

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*





- Highly stable, multi-protein complexes
- Required for bacterial attachment to glycoprotein receptor uroplakin – urothelial cells
- Virulence factor

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.

Ghirotto et al. JASN 27, 2016

AJKD
Original Investigation

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

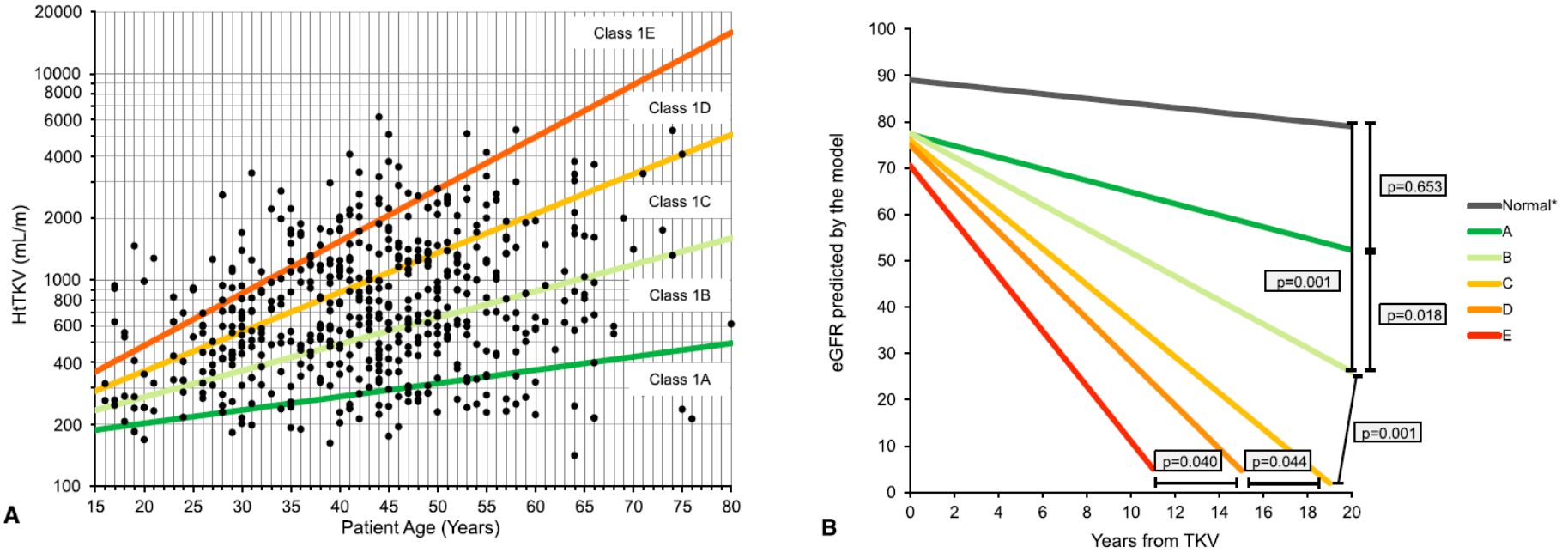
Pranav S. Garimella, MD, MPH,[1] Traci M. Bartz, PhD,[2] Joachim H. Ix, MD, MAS,[3] Michel Chonchol, MD,[4] Michael G. Shlipak, MD, MPH,[5] Prasad Devarajan, MD,[6] Michael R. Bennett, PhD,[6] and Mark J. Sarnak, MD, MS[1]

- 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.

Am J Kidney Dis. 2017; 69:744-751

J Am Soc Nephrol 26: 160–172, 2015.

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

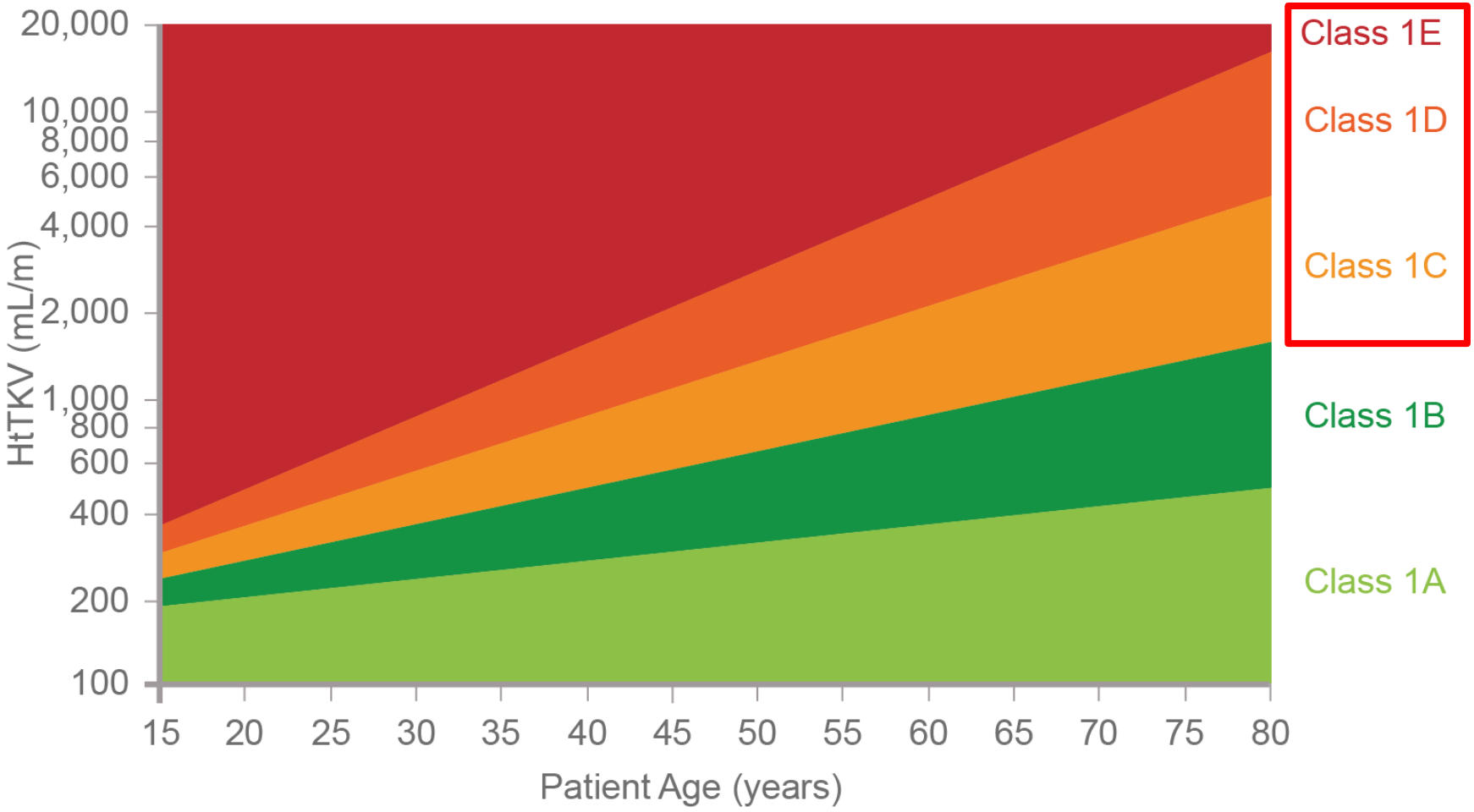
Mayo Classification Score

CLASSIFICATION OF TYPICAL ADPKD CALCULATOR

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

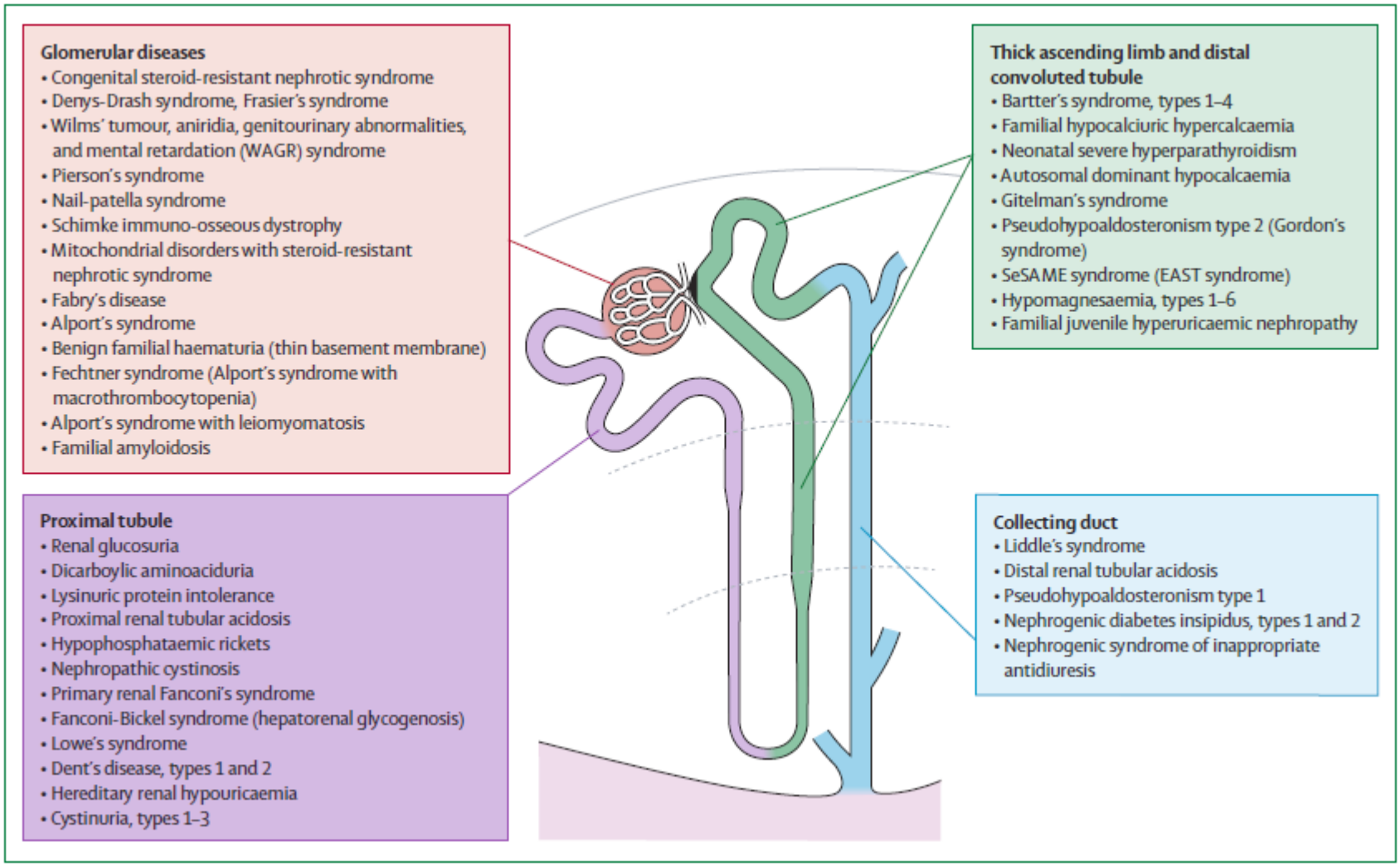
→ *Height-adjusted TKV*
→ *ADPKD classification*

The Mayo Clinic classification



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

- Rare kidney diseases: > 200 disorders (very rare to ADPKD)
- Overall prevalence: ~60-80 cases per 100,000
- At least 10% adults and virtually all children on RRT



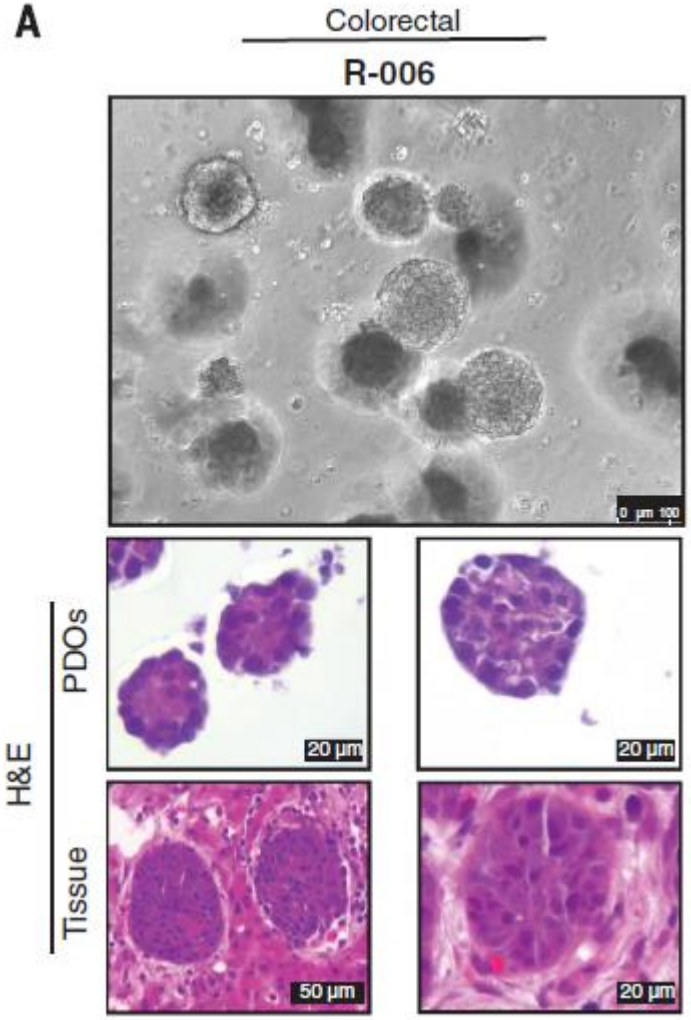
Devuyst O, et al. Lancet 383, 2014

ORGANOIDS

Patient-derived organoids model treatment response of metastatic gastrointestinal cancers

- Patient-derived organoids (PDOs) emerged as robust preclinical models.
- Biobank of PDOs from metastatic colorectal and gastroesophageal cancer patients in phase 1/2 clinical trials.
- Phenotypic and genotypic profiling of PDOs showed a high degree of similarity to the original patient tumors.
- Molecular profiling of tumor organoids was matched to drug-screening results, suggesting that PDOs could complement existing approaches in defining cancer vulnerabilities and improving treatment responses.

Our data suggest that PDOs can recapitulate patient responses in the clinic and could be implemented in personalized medicine programs.



Vlachogiannis *et al.*, *Science* **359**, 920–926 (2018)

GWAS: CKD-defining Traits

- >20 GWAS on CKD-defining traits (eGFRcrea, UACR)

  incl. 2 on renal function decline
- >60 loci associated with CKD-defining traits (eGFRcre – European ancestry)
- Most recent GWAS of kidney function: 11 million SNPs (imputed)

But: * *Modest effect size*

* *Very small fraction of variance explained*

* *Biological relevance ?*

GWAS: Concept

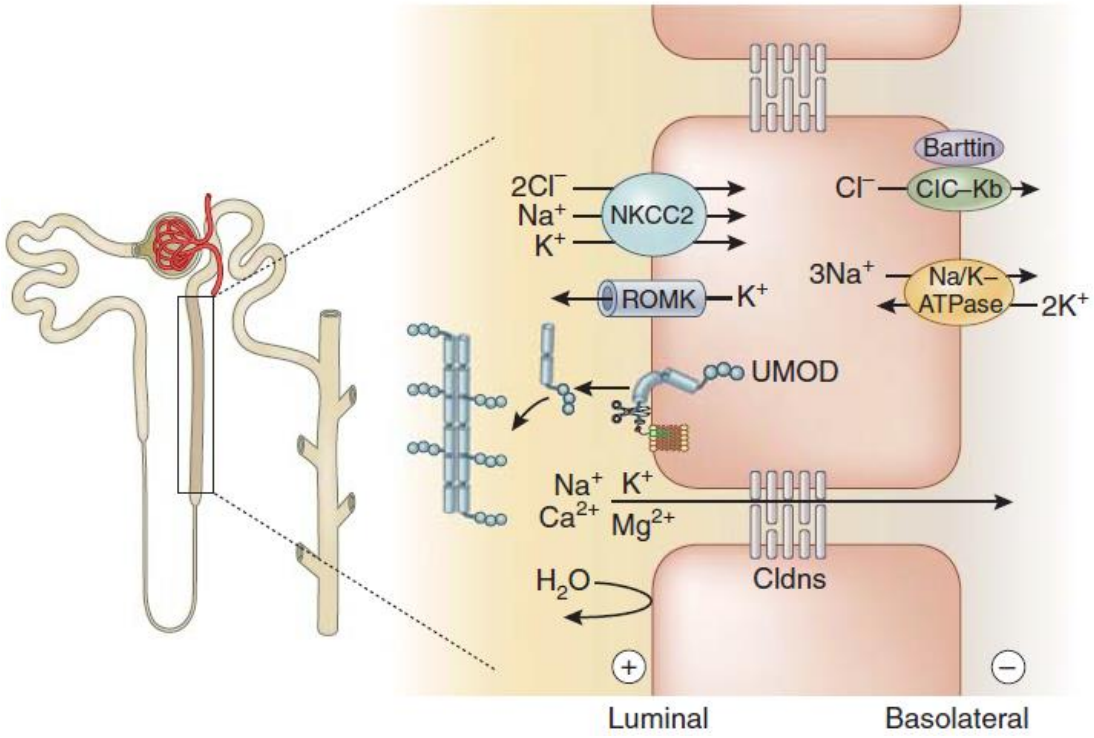
Complex diseases (CKD, hypertension, diabetes, …) are underlined by a number of common genetic variants, present in >1% of the population

- Conceptual simplicity of GWAS:
  - 10 millions SNPs over the 3 billions bp – not random distribution
  - Linkage disequilibrium blocks – tag SNPs
  - Association tests between SNPs and given trait in large populations
  - Expansion of the coverage using genetic imputation (e.g. 1000 Genomes)

Thousands of loci associated with complex disorders and biomarkers

Hypothesis-free, unbiased approach

Prognostic Value of Uromodulin ?



Production in TAL

- Handling of NaCl:
  - Blood pressure
  - Loop diuretics
- Handling of Ca^{2+} & Mg^{2+}:

Devuyst O et al. *Nat Rev Nephrol* 13, 2017

Transgenic Mouse Models to Mimic Human Situation

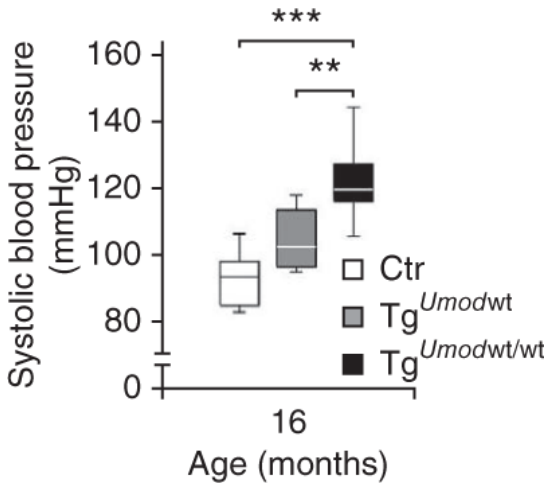
Wild-type *Umod*
«protective» variant

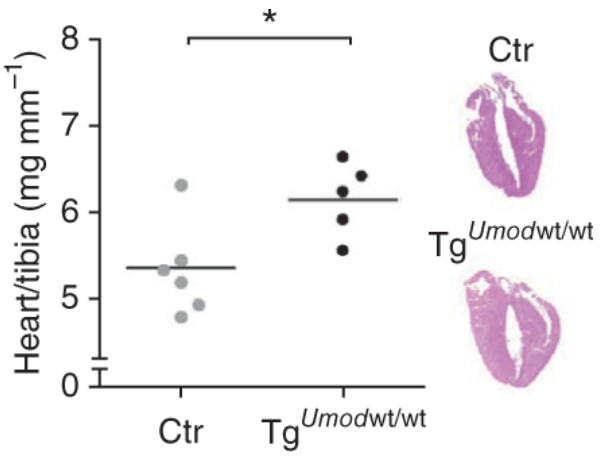
Transgenic *Umod*
«deleterious» variant

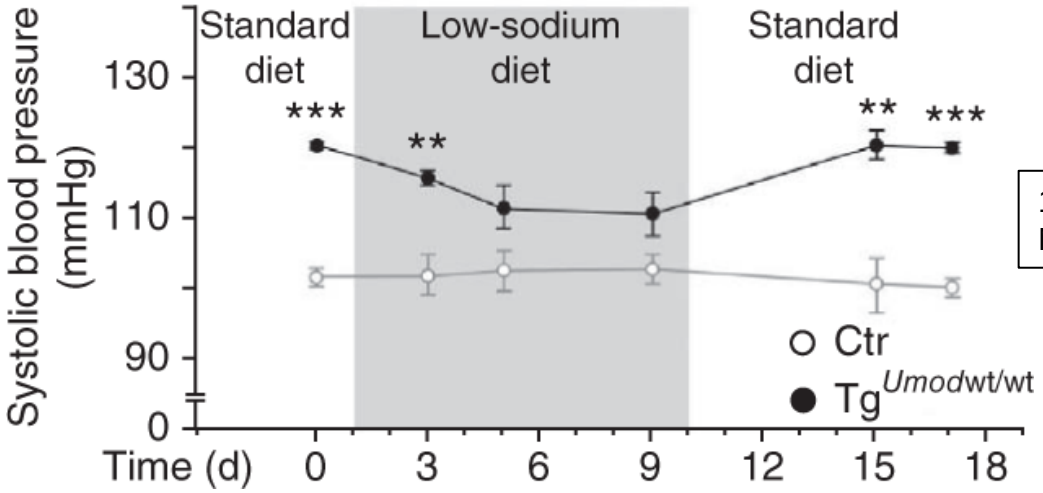
Clinical studies in human cohorts – known UMOD genotype

Uromodulin Overexpression: NaCl-sensitive Hypertension

Tg *Umod* Mice







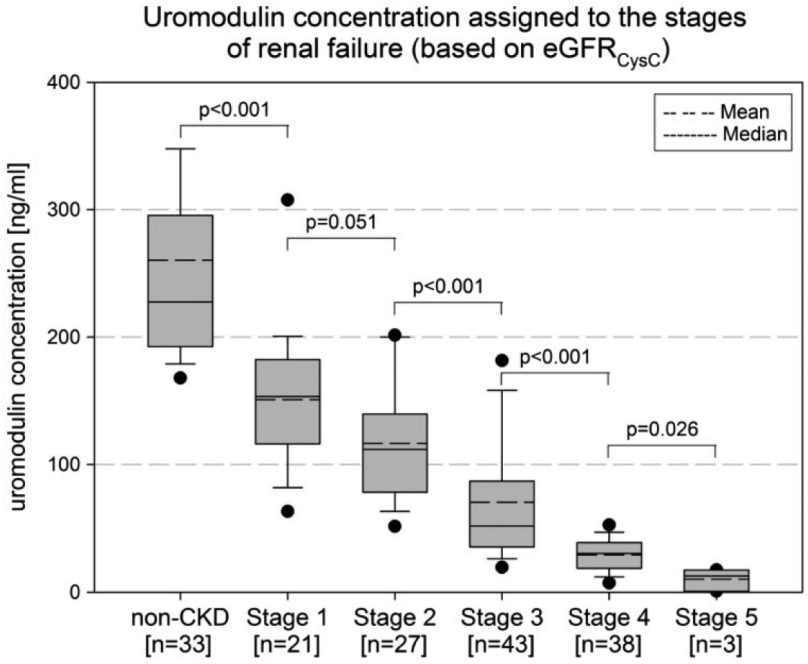
1% vs. 0.01% Nacl
N=7 per group

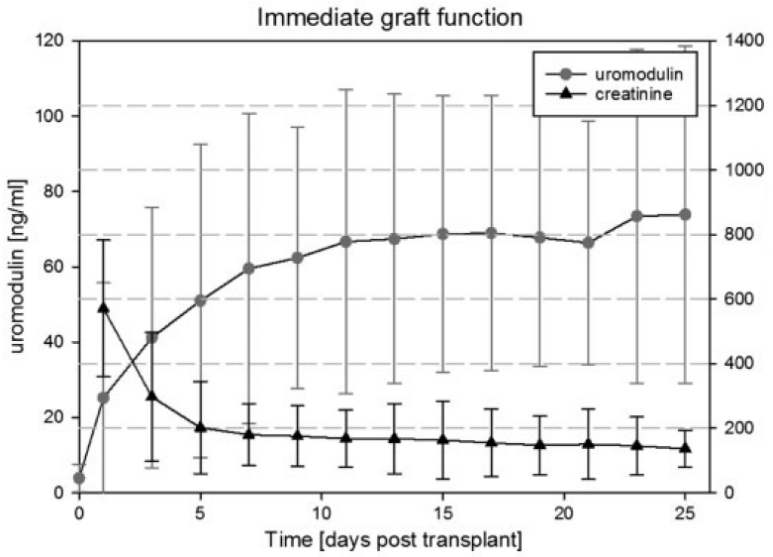
Trudu M. et al. Nat Med 2013

Serum uromodulin—a marker of kidney function and renal parenchymal integrity

Nephrol Dial Transplant (2017) 1–12
doi: 10.1093/ndt/gfw422

Jürgen E. Scherberich[1], Rudolf Gruber[2], Wolfgang Andreas Nockher[3], Erik Ilsø Christensen[4], Hans Schmitt[5], Victor Herbst[6], Matthias Block[6], Jürgen Kaden[7] and Wolfgang Schlumberger[6]

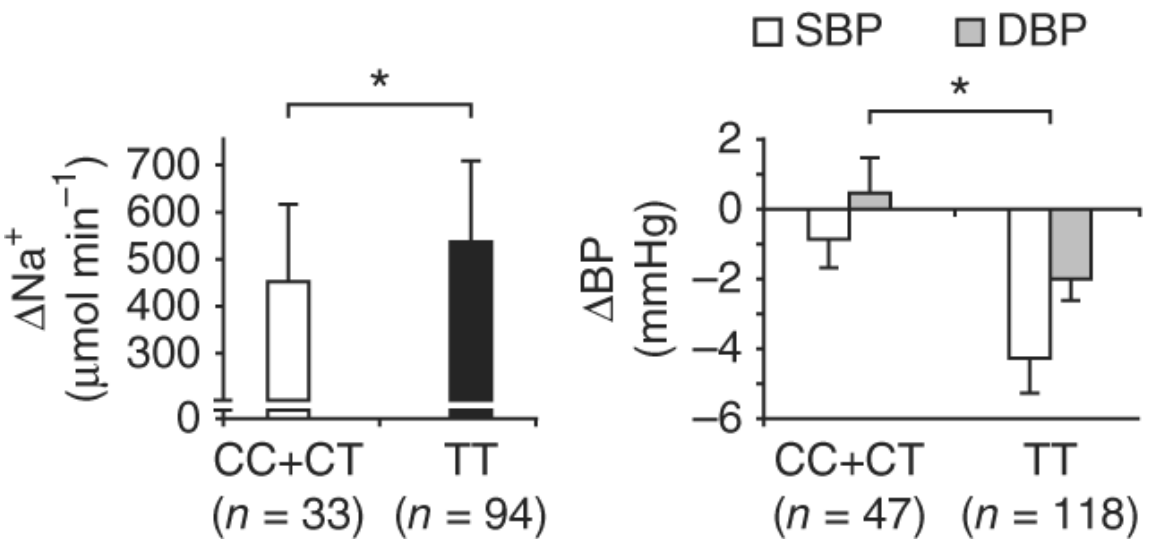




Uromodulin levels correlate with eGFR, and parallel renal function after transplantation

Uromodulin Overexpression: Increased NKCC2 Activity

Furosemide test
Cohort of subjects with hypertension – stratified for UMOD genotype



Differential response to diuretics – depending on UMOD genotype

Trudu M. et al. Nat Med 2013

Dominiczak, A. , Delles, C. and Padmanabhan, S.

University of Glasgow

Volume overload is a cause for uncontrolled hypertension and yet loop diuretics are rarely used in hypertension without edema, heart failure or chronic kidney disease.

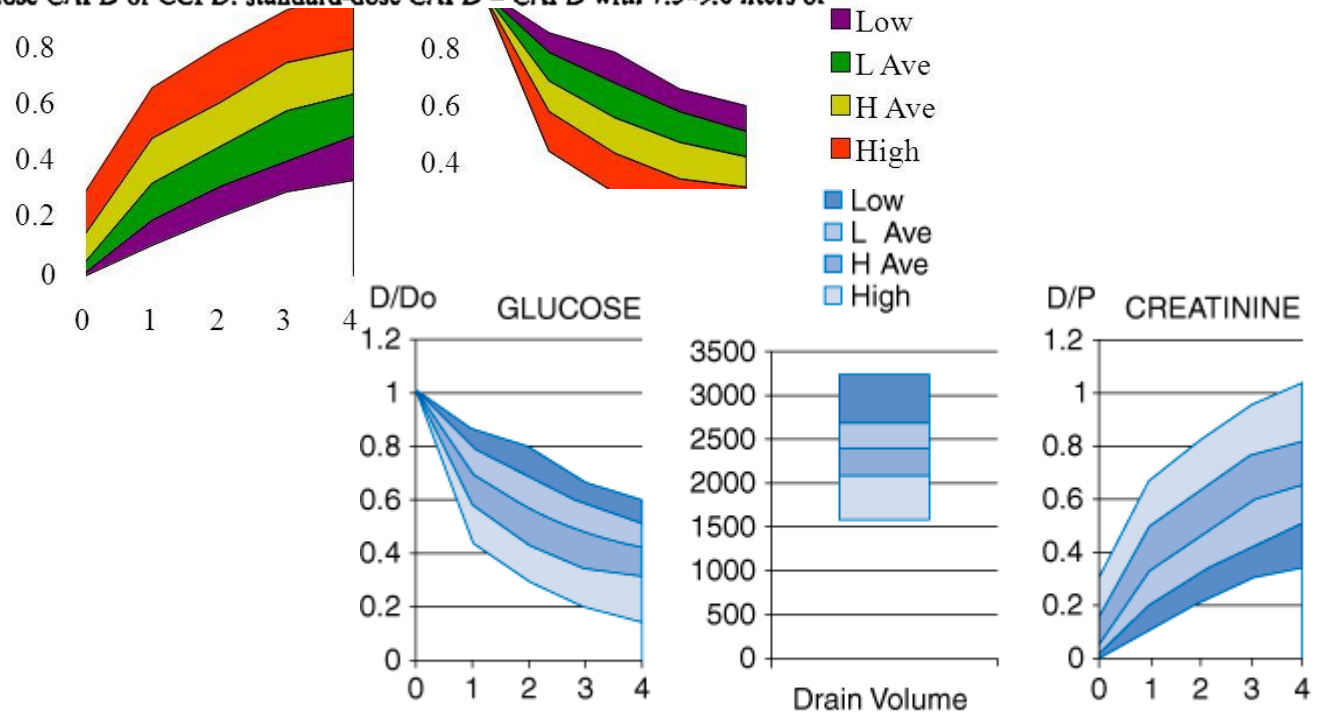
A prospective genotype directed trial of a long-acting loop diuretic, torasemide in uncontrolled hypertensive patients to test the hypothesis that the high *UMOD* genotype patients are good responders to loop diuretics.

Precision medicine trial funded by the British Heart Foundation (CS.16/1/31878).

British Heart Foundation

Peritoneal solute transport	Drain volume	Predicted long-term response to standard-dose CAPD or CCPD[a] after loss of residual renal function		Preferred dialysis prescription after loss of residual renal function
		ultrafiltration	dialysis	
High	low	poor	adequate	NIPD, DAPD[b]
High average	low average	adequate	adequate	standard-dose PD[a]
Low average	high average	good	adequate or inadequate[c]	standard-dose PD[a] high-dose PD[d]
Low	high	excellent	inadequate	high-dose PD[d] or hemodialysis[c]

[a] Standard-dose PD = Standard-dose CAPD or CCPD: standard-dose CAPD = CAPD with 7.5–9.0 liters of



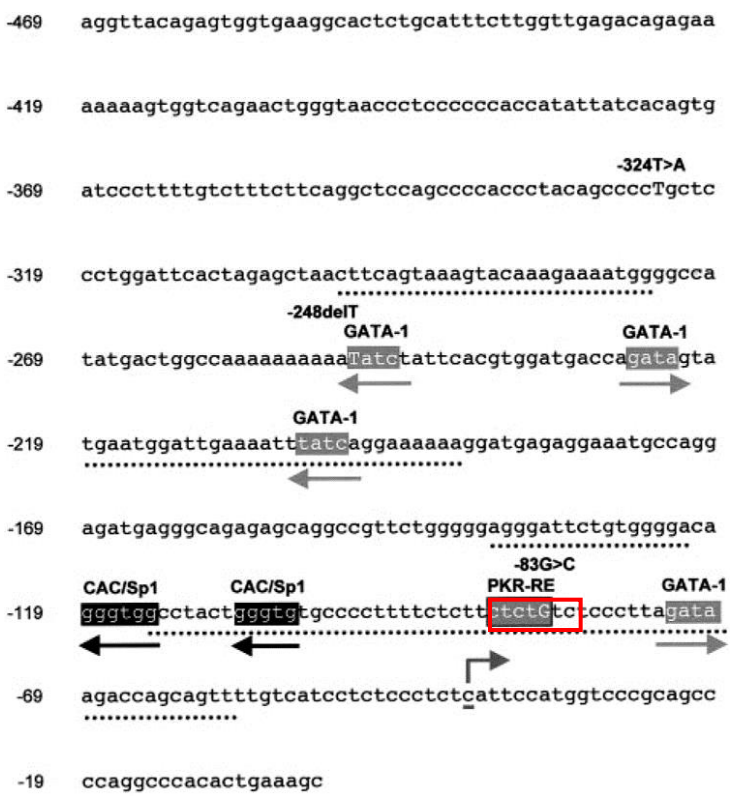
PET (peritoneal equilibration test) 2

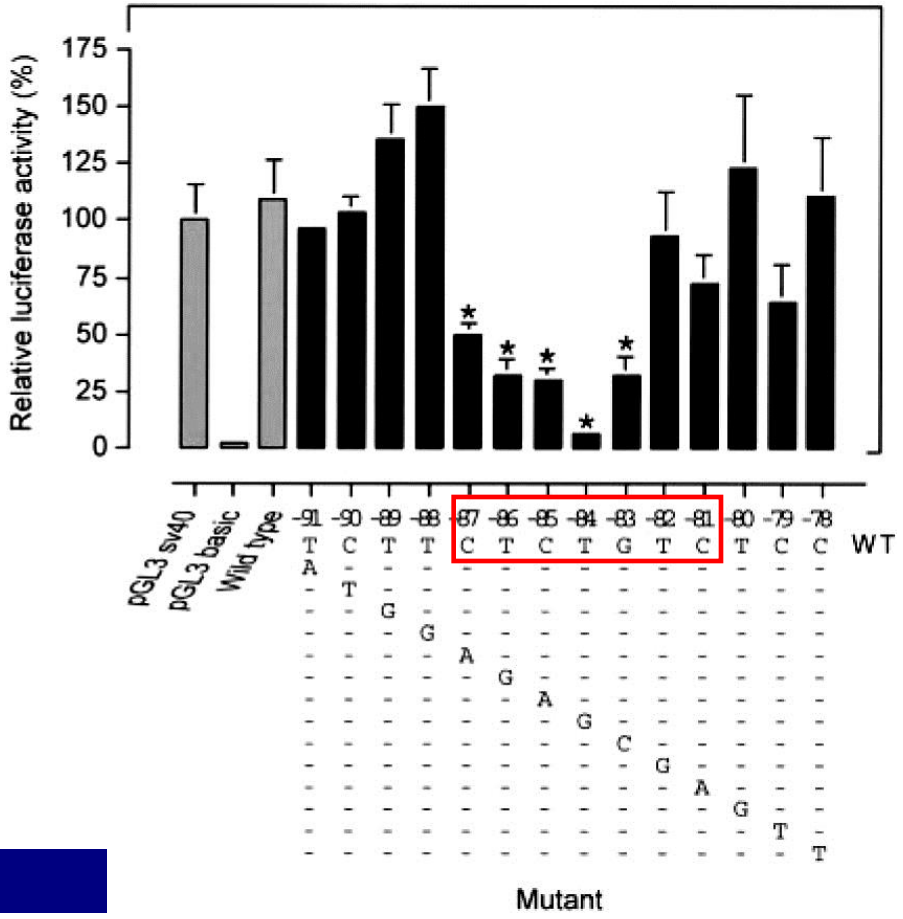
Transporter	Waste removal	Water removal	Best type of PD
High	Fast	Poor	Frequent exchanges, short dwells – APD
Average	OK	OK	CAPD or APD
Slow	Slow	Good	CAPD, 5 exchanges daily + 1 exchange at night

Disruption of a novel regulatory element in the erythroid-specific promoter of the human *PKLR* gene causes severe pyruvate kinase deficiency

Richard van Wijk, Wouter W. van Solinge, Claus Nerlov, Ernest Beutler, Terri Gelbart, Gert Rijksen, and Finn C. Nielsen

Blood 2003; 101: 1596-1602





CTCTG, core binding motif of a regulatory element for PKLR