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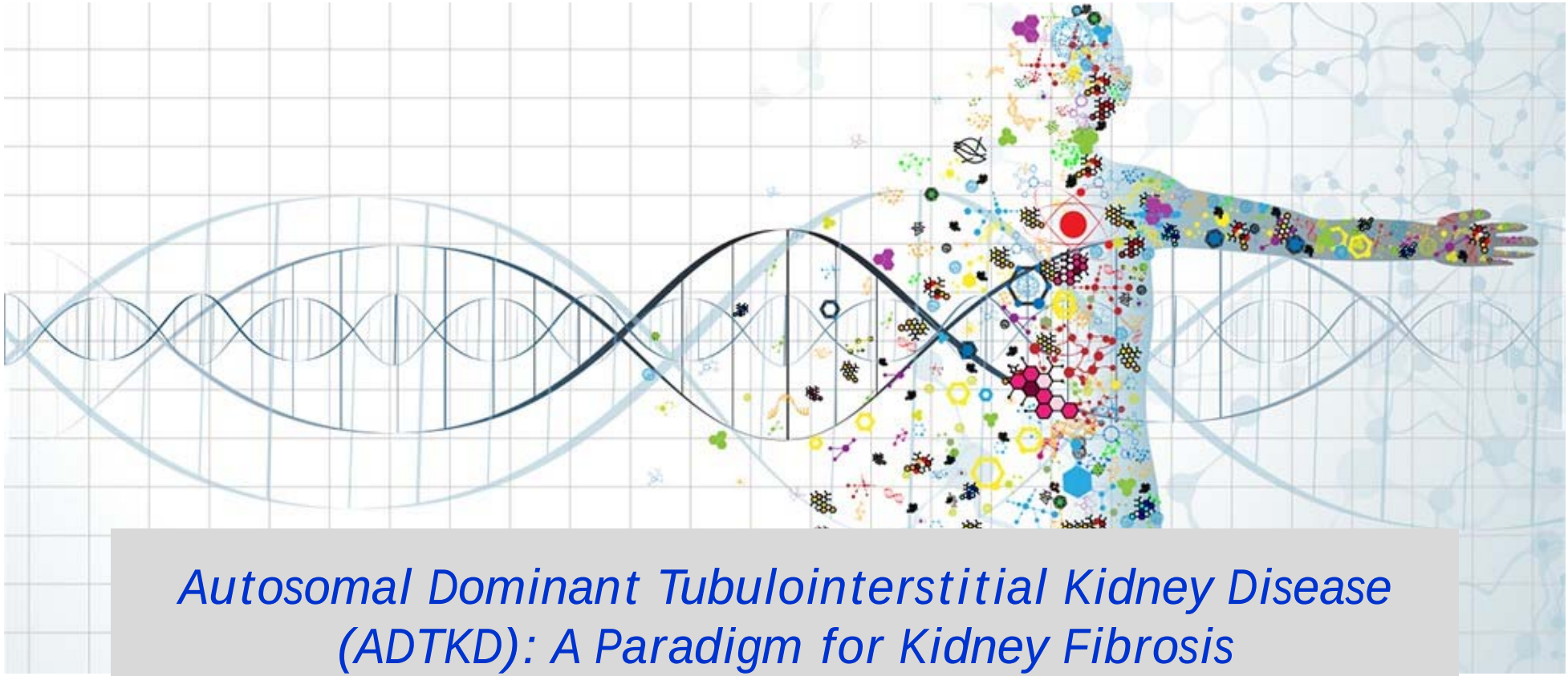
## ESPN/ERKNet
## Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: 06 October 2020

Topic: ADTKD

Speaker: Olivier Devuyst

Moderator: Elena Levtchenko



# *Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD): A Paradigm for Kidney Fibrosis*

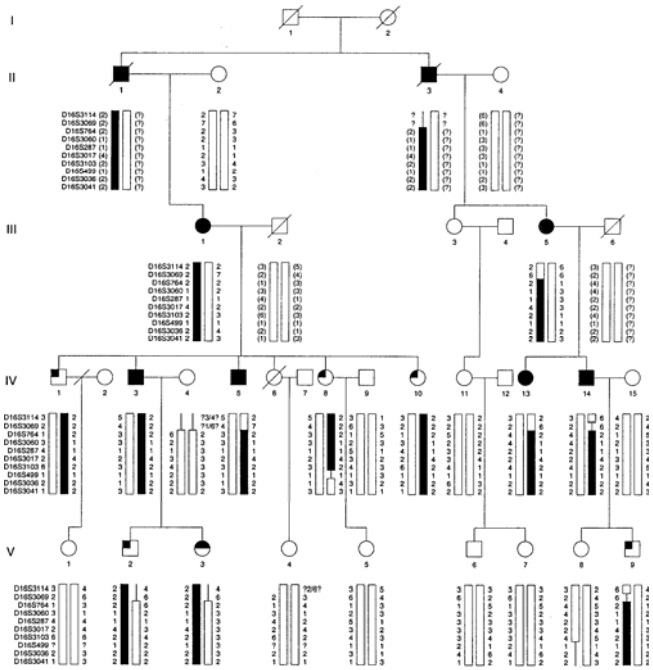
*Olivier Devuyst, MD, PhD*

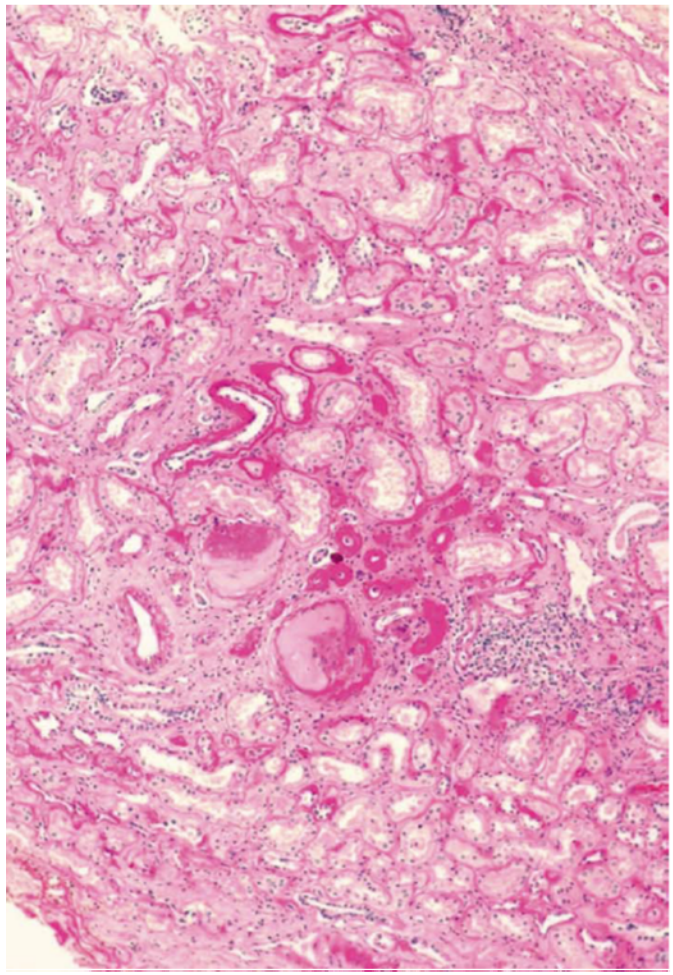
UCL

ERKNet
The European Rare Kidney Disease Reference Network

University of Zurich[UZH]

# A (rare) Familial Kidney Disease: Tubulointerstitial & Hyperuricemic Nephropathy





- Familial – dominant transmission
- Hyperuricemia (low FEurate) during childhood
- Tubulointersitital lesions – fibrosis (medullary cysts)
- Progressive kidney failure - adulthood

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

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


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

Clinical findings
- Autosomal dominant inheritance
- Progressive loss of kidney function
- Bland urine sediment
- No proteinuria (initially)
- Normal or small-sized kidneys
- Urinary concentrating defect
- (extrarenal features)

Kidney histology
- Interstitial fibrosis
- Tubular atrophy
- Thickening/lamellation of TBM
- Tubular dilatations

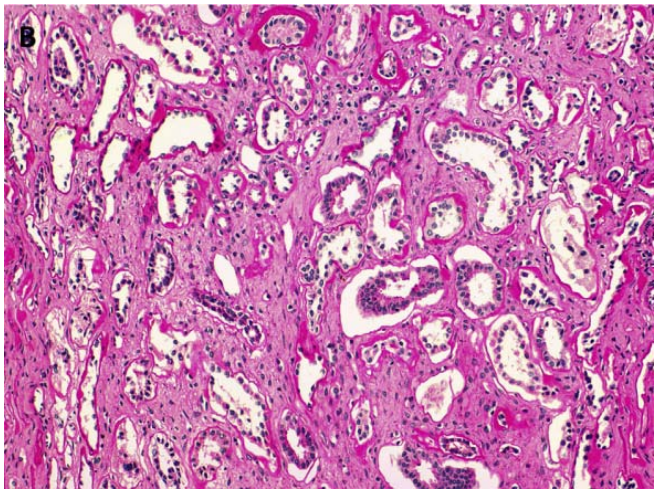



**Table 5 | Diagnostic criteria for ADTKD**

A. Criteria for suspecting a diagnosis of ADTKD
- Family history compatible with autosomal dominant inheritance of CKD fulfilling the clinical characteristics (Table 2).
- In absence of a positive family history of CKD fulfilling the clinical characteristics (Table 2), demonstration of compatible histology on kidney biopsy (Table 3) or extrarenal manifestations compatible with *HNF1B* mutations or history of early-onset hyperuricemia and/or gout.

B. Criteria for establishing the diagnosis of ADTKD
- Family history compatible with autosomal dominant inheritance of CKD fulfilling the clinical characteristics (Table 2) and compatible histology in at least one affected family member. (Note: it is not possible to make a definitive diagnosis by renal biopsy alone)

or

- Demonstration of a mutation in one of the four genes in an affected individual or at least one family member.

Eckardt KU et al. Kidney Int, 2015

# Autosomal dominant tubulointerstitial kidney disease

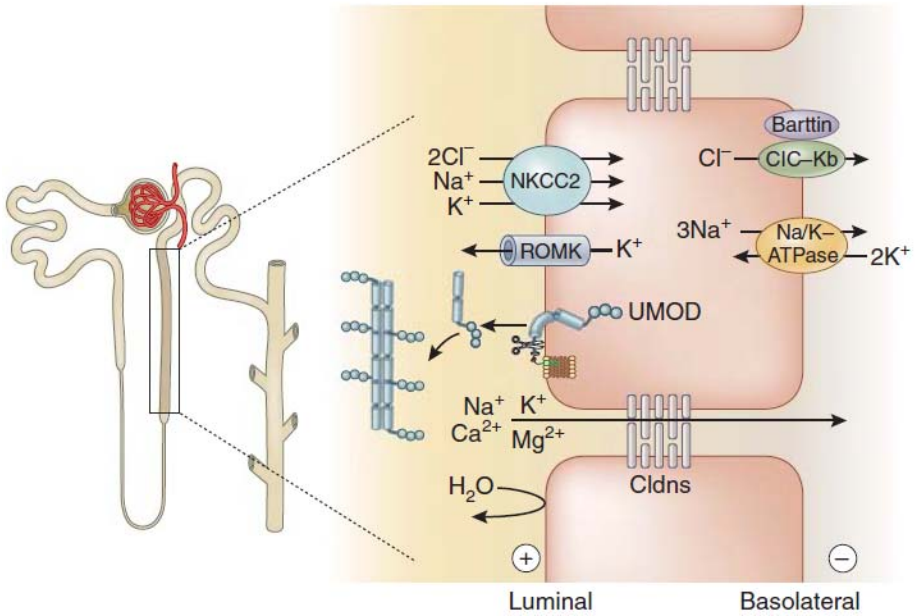
*Olivier Devuyst[1,2]*, Eric Olinger[1], Stefanie Weber[3], Kai-Uwe Eckardt[4], Stanislav Kmoch[5], Luca Rampoldi[6] and Anthony J. Bleyer[7]*

PRIMER

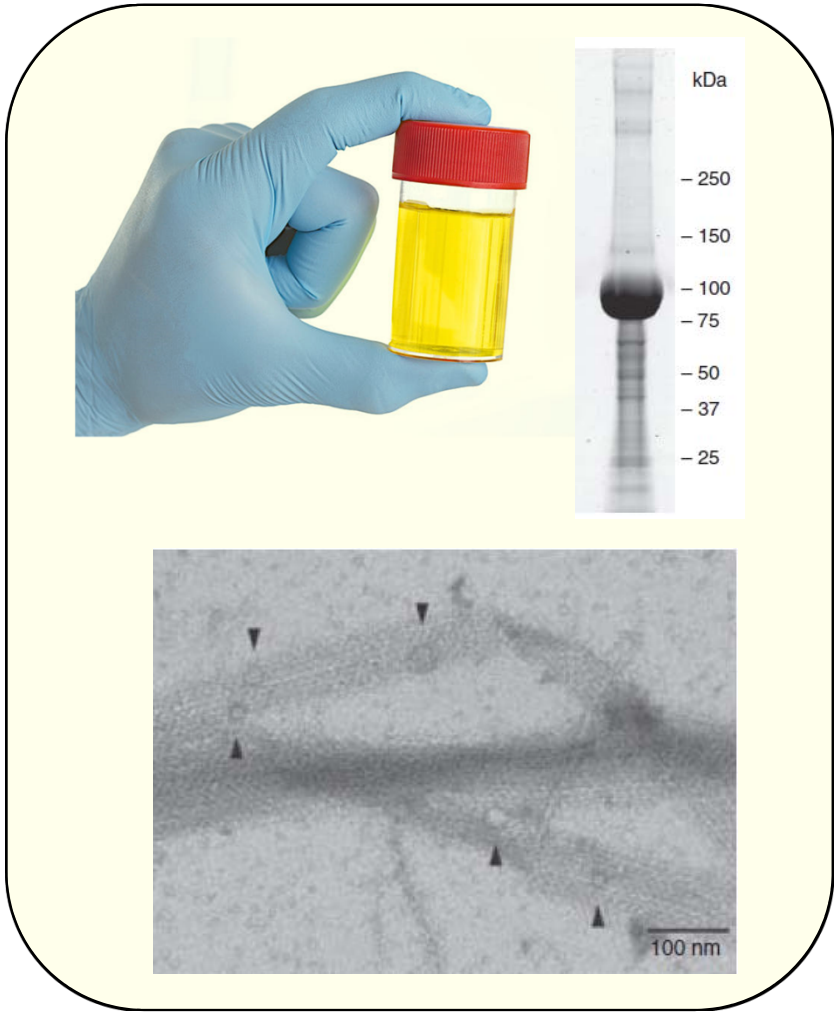
## ADTKD-*Gene:* Replacing FJHN, MCKD

| Affected Gene (OMIM ID; chromosome) | Terminology[a] | Protein | Expression (distribution) | Protein function(s) |
|---|---|---|---|---|
| *UMOD* (*191845; 16q12) | ADTKD-*UMOD* | Uromodulin | Kidney (TAL and DCT segments) | • Regulates transport, blood pressure and urinary concentration<br>• Protection against kidney stones<br>• Protection against urinary tract infections<br>• Regulation of innate immunity |
| *MUC1* (*158340; 1q22) | ADTKD-*MUC1* | Mucin 1 | Secretory epithelia (for example, lungs, stomach, intestine and kidney) | • Protection of epithelial mucus barrier<br>• Immunomodulatory properties<br>• Signal transduction |
| *HNF1B* (*189907; 17q12) | ADTKD-*HNF1B* | Hepatocyte nuclear factor 1β | Kidney, pancreas, liver, lung, intestine and urogenital tract | • Transcription factor involved in the (early) development of neural tube, pancreas, gut, liver, lung, kidney and genital tract |
| *REN* (*179820; 1q32) | ADTKD-*REN* | Preprorenin | Kidney (juxtaglomerular apparatus) | • Protease, cleavage of angiotensinogen (renin–angiotensin–aldosterone axis)<br>• Role in nephrogenesis |
| *SEC61A1* (*609213; 3q21.3) | ADTKD-*SEC61A1* | α1 subunit of SEC61 | Ubiquitous | • Component of SEC61 channel-forming translocon complex that mediates transport of signal peptide-containing precursor polypeptides across the ER |

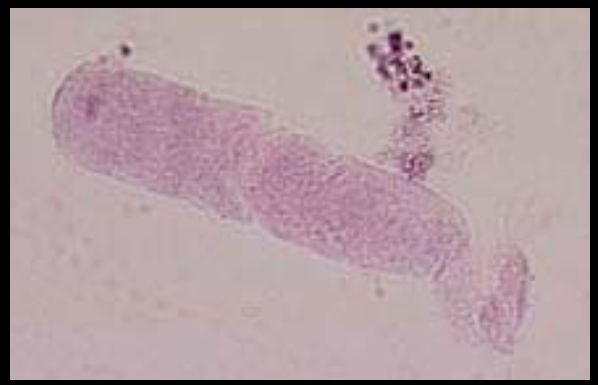
# *UMOD* → Uromodulin: Produced by the kidney and excreted in urine

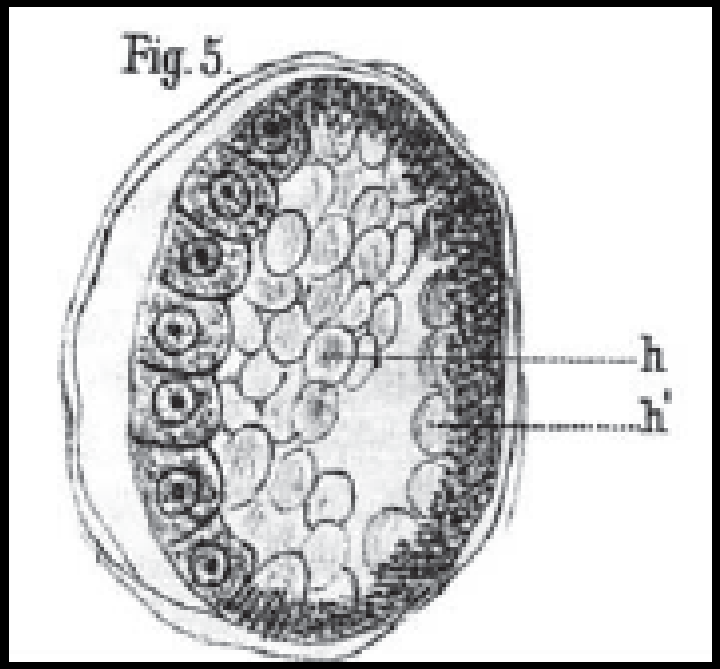



*Tamm-Horsfall protein – uromodulin:*
*the most abundant protein in nomal human urine*
*(up to 150 mg/day)*



Carlo R. Rovida (Univ. Turin) first described a wax-like substance, **cilindrina**, produced by kidney tubular cells and forming hyaline casts.

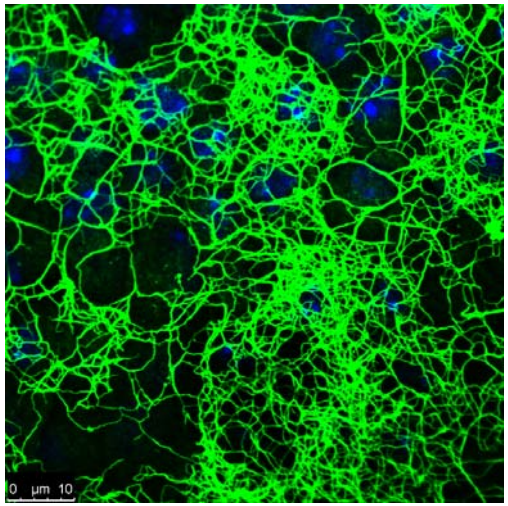


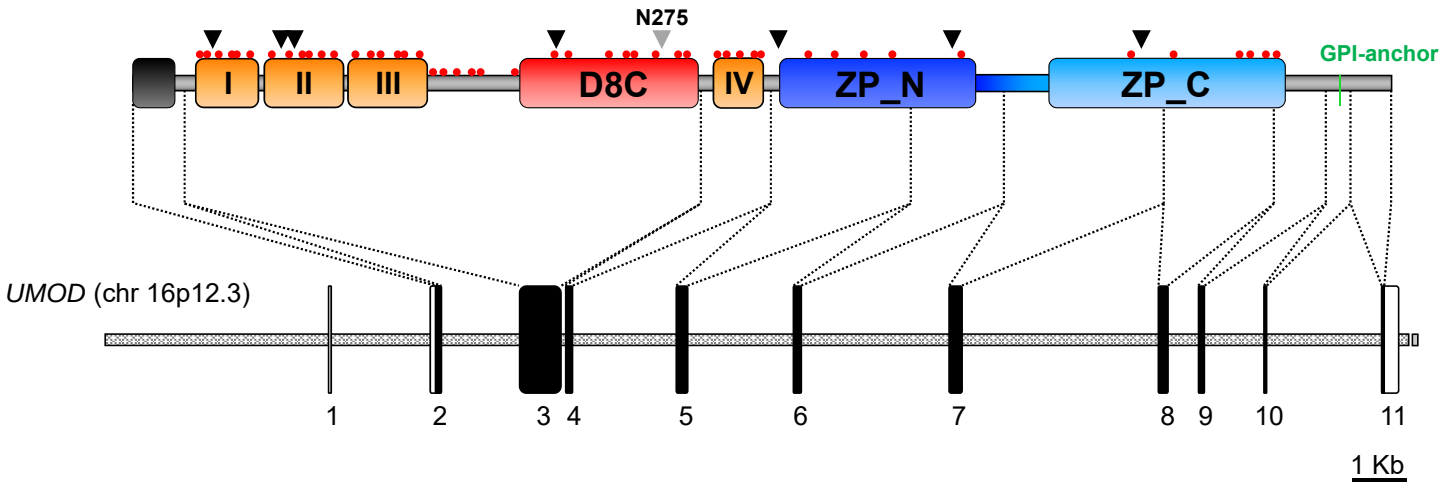


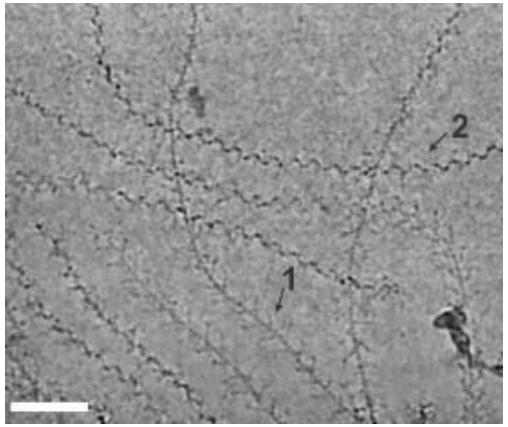

***Rovida CL**: Conclusione degli studi intorno all'origine istologica dei cilindri dell'urina. Riv Clin Bologna 1873; 2a: 303–306.*

# Uromodulin: biochemical characteristics

- *UMOD* gene on chromosome 16: 11 exons (10 coding)
- Most abundant urinary protein (50-150mg/24h)
- Mature protein of 616aa, 48 cysteines (7.8%)
- Heavy glycosylation (~30% of MW), mostly sialic acid (pH(I) 3.5)
- High molecular weight polymers in urine



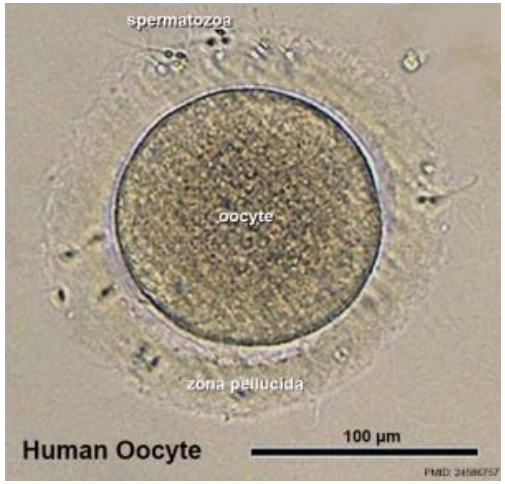



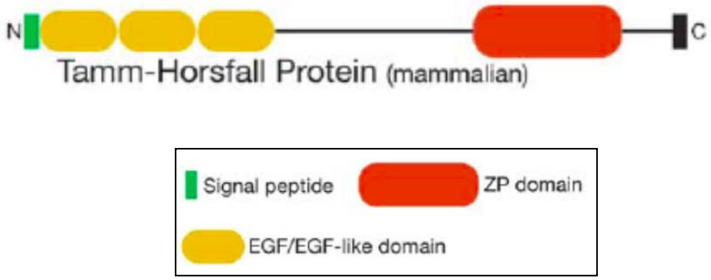




Devuyst O, Olinger E, Rampoldi L. Nat Rev Nephrol., 2017
Stanisich JJ et al. eLife, 2020

# Zona Pellucida (ZP) Domain Proteins

| ZP domain proteins | Primary source | Other domains |
|---|---|---|
| Mammalian | | |
| ZP1–3 | Ovary | P/trefoil |
| Tectorins | Inner ear | G1, D |
| Tamm-Horsfall protein | Kidney | EGF |
| TGF-$\beta$ type III receptor | Heart | |
| LZP | Liver | EGF |
| GP-2 | Pancreas, kidney | |
| Muclins | Intestine, pancreas | SRCR, CUB |
| Ebnerin | Tongue | SRCR, CUB |
| Vomeroglandin | Nose | SRCR, CUB |
| DMBT1 | Brain, lung | SRCR, CUB |
| Hensin | Brain, epithelia | SRCR, CUB |
| Itmap-1 | Pancreas | CUB |
| UTCZP | Uterus | CUB |
| ERG-1 | Uterus, oviduct | CUB |
| UO-44 | Ovary | CUB |
| PLAC1 | Placenta | |
| Oosp1 | Ovary, spleen | |

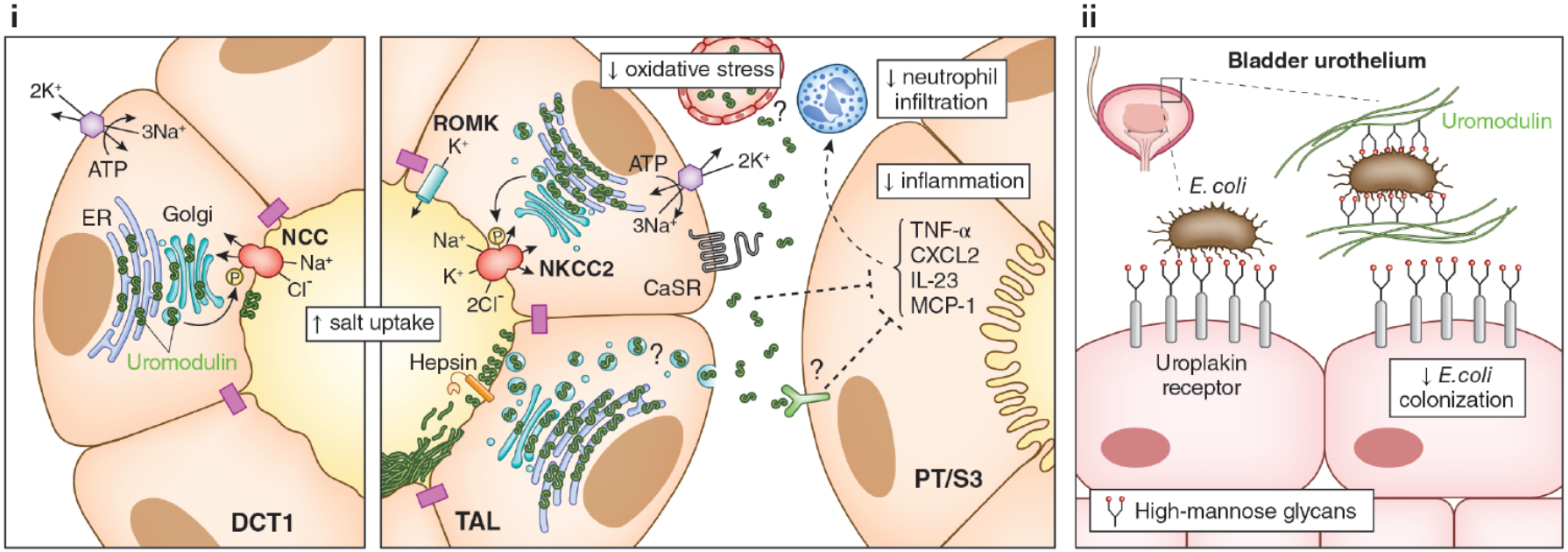



- ZP domain: present in extracellular proteins from nematodes to mammals
- ~260 amino acids with eight conserved cysteine (Cys) residues
- ZP domain proteins are often glycosylated, trend to polymerize and form filaments/matrix
- Functions: structural components of egg coats, mucous houses, mecanotransducers

Jovine L et al. Annu. Rev. Biochem. 2005, 74

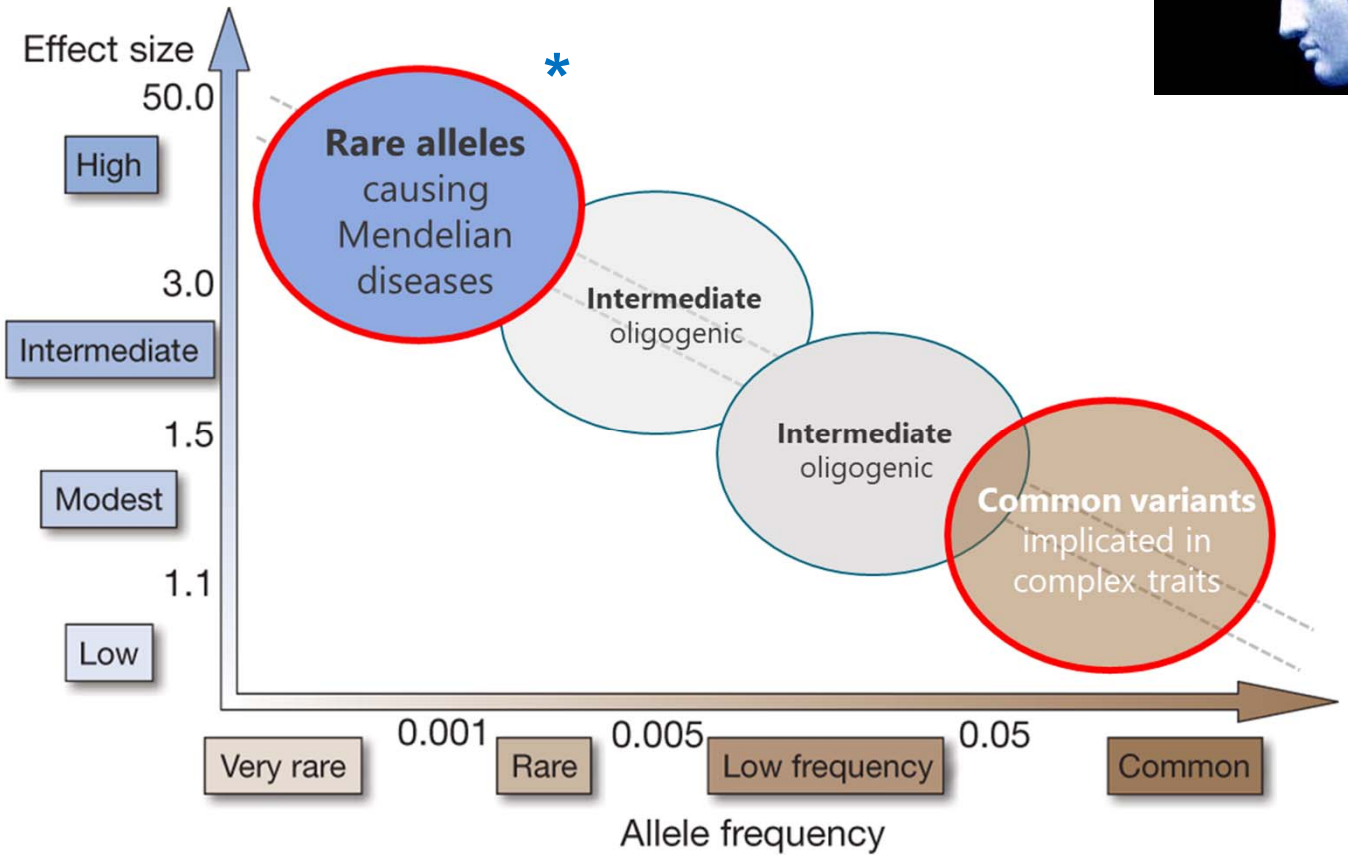
# What does uromodulin do?




- Increasing salt transport in the TAL + DCT segments
- Modulating inflammatory responses
- Protection from urinary tract infection
- Protection against $Ca^{2+}$ kidney stones

Kipp A & Olinger E, CJASN, 2020

# *UMOD* in rare and common kidney diseases




Manolio et al. Nature 461, 2009

# Mutations in *UMOD* cause Autosomal Dominant Tubulointerstitial Kidney Disease

ORIGINAL ARTICLE

Mutations of the *UMOD* gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy

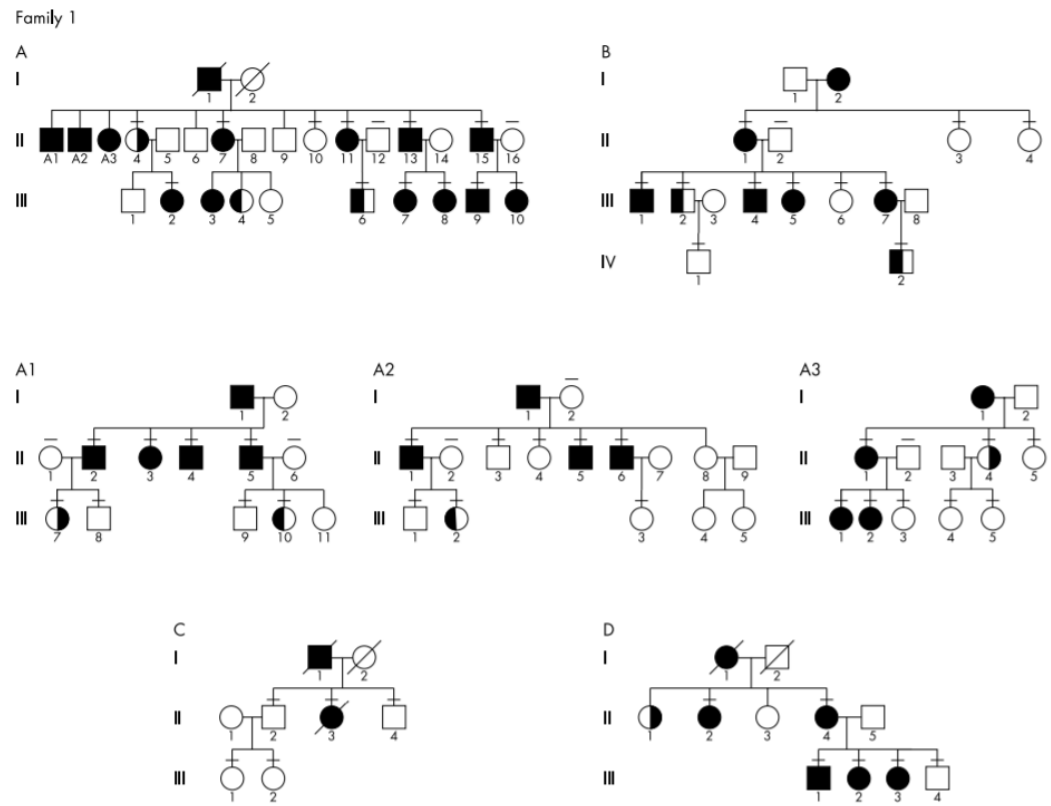
T C Hart, M C Gorry, P S Hart, A S Woodard, Z Shihabi, J Sandhu, B Shirts, L Xu, H Zhu, M M Barmada, A J Bleyer

*J Med Genet* 2002;**39**:882–892

J Am Soc Nephrol 14: 2883–2893, 2003

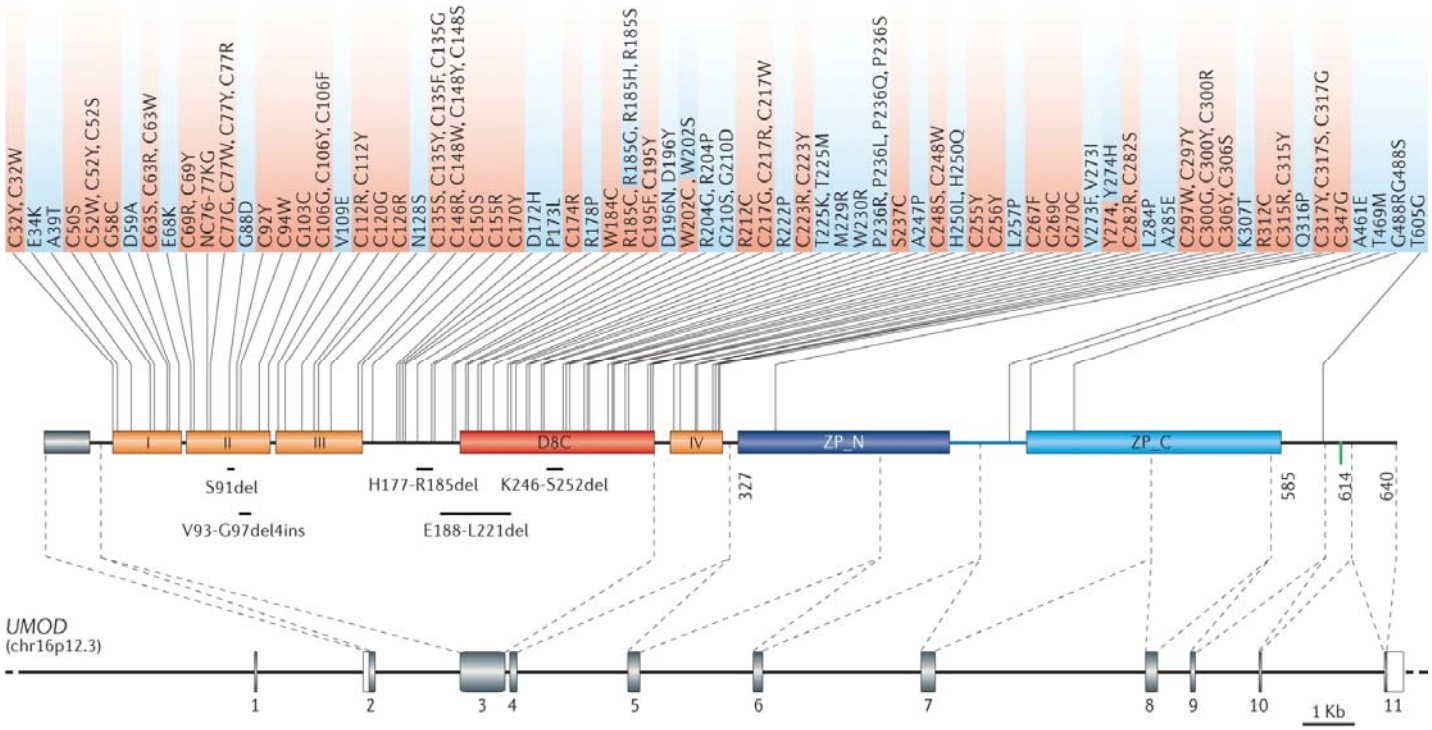
A Cluster of Mutations in the UMOD Gene Causes Familial Juvenile Hyperuricemic Nephropathy with Abnormal Expression of Uromodulin

KARIN DAHAN,* OLIVIER DEVUYST,† MICHÈLE SMAERS,* DIDIER VERTOMMEN,† GUY LOUTE,§ JEAN-MICHEL POUX,‖ BÉATRICE VIRON,¶ CHRISTIAN JACQUOT,# MARIE-FRANCE GAGNADOUX,** DOMINIQUE CHAUVEAU,†† MATHIAS BÜCHLER,‡‡ PIERRE COCHAT,§§ JEAN-PIERRE COSYNS,‖‖ BÉATRICE MOUGENOT,¶¶ MARK H. RIDER,‡ CORINNE ANTIGNAC,## CHRISTINE VERELLEN-DUMOULIN*, and YVES PIRSON†




Hart TC et al. J Med Genet., 2002
Dahan K et al. J Am Soc Nephrol., 2003

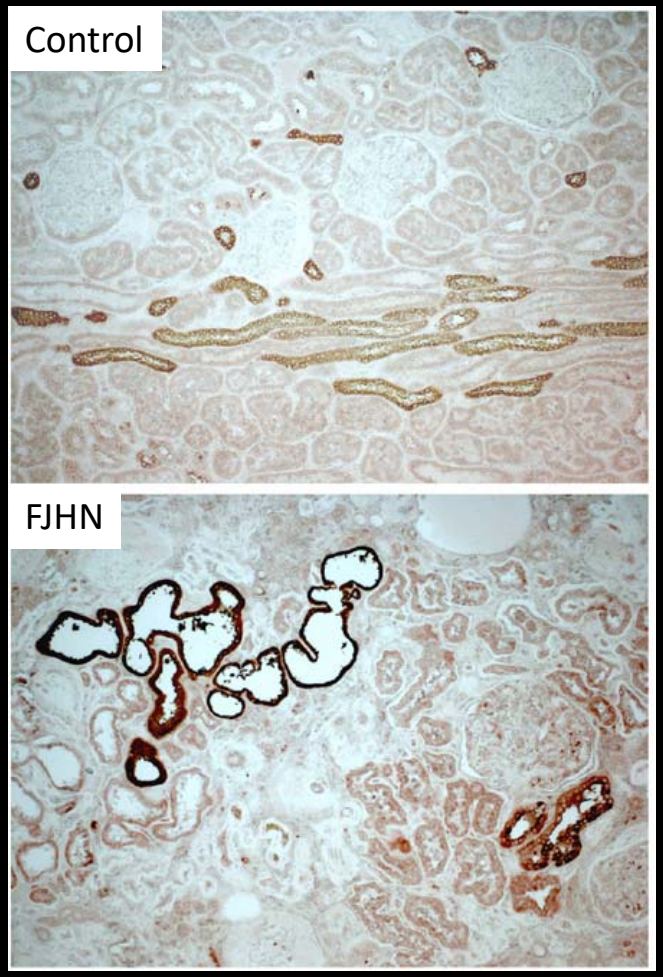
# Landscape of *UMOD* Mutations in ADTKD

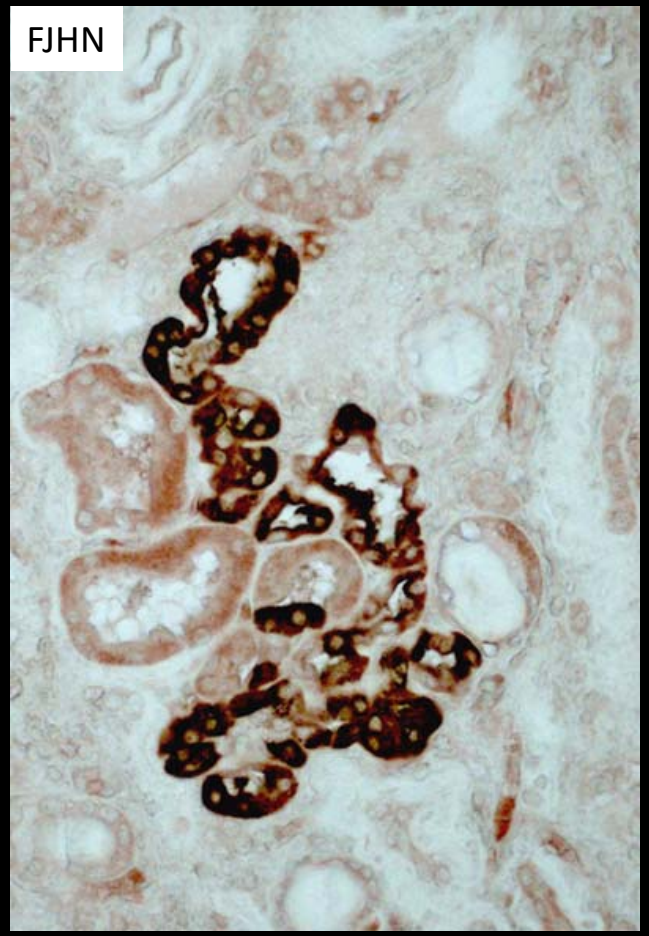



→ 125 mutations, 95% cluster in exons 3 and 4
→ 121/125 missense mutations, 4 in-frame deletions
→ Conserved sequence, cysteine residues (78/125)

Devuyst O et al. *Nat Rev Nephrol* 2017

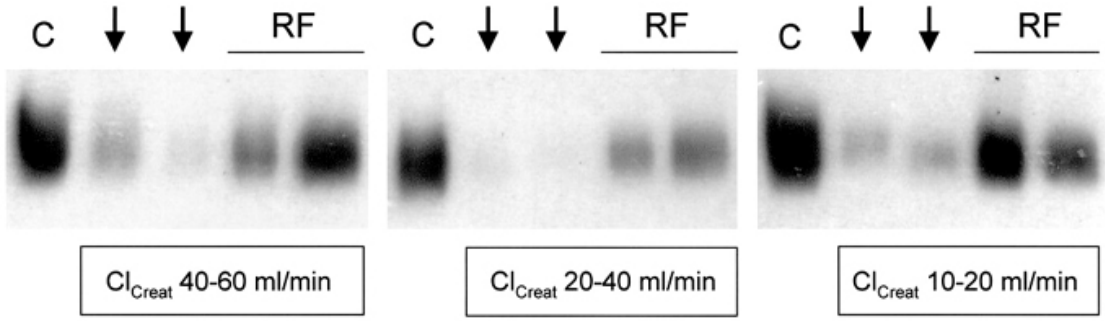
## Accumulation of Mutant Uromodulin in Kidney Tubules: Storage Disease

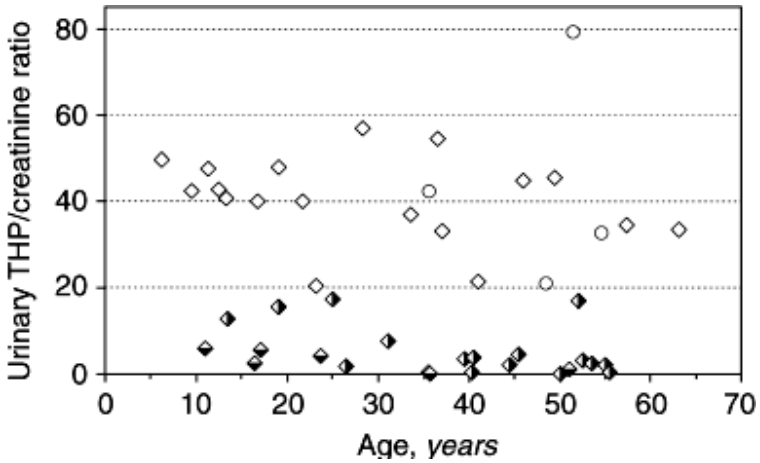



Dahan K et al. JASN 14: 2883-93, 2003

# Mutations in *UMOD* Decrease Uromodulin Excretion in Urine



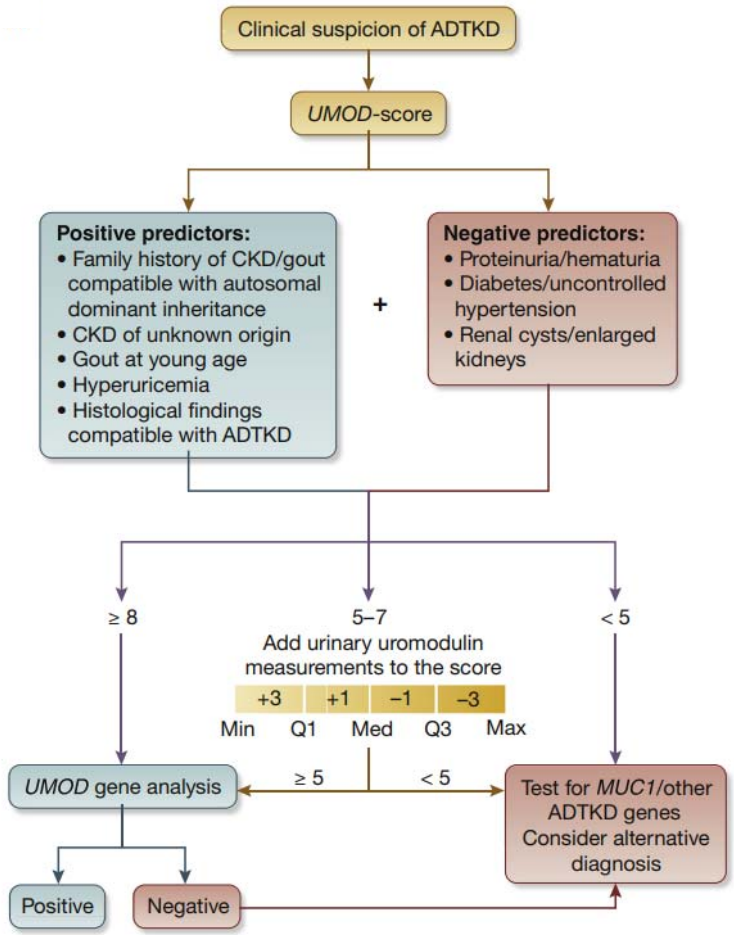



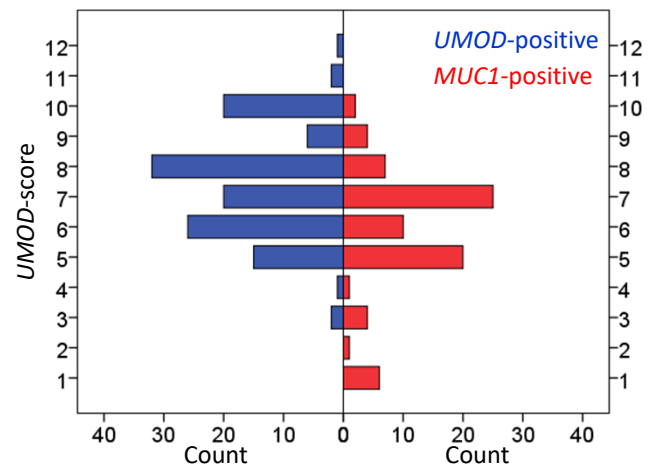

ELISA for uromodulin
Families +/- *UMOD* mutations

- Reduced excretion
- Irrespective of gender, age, GFR, mutation type

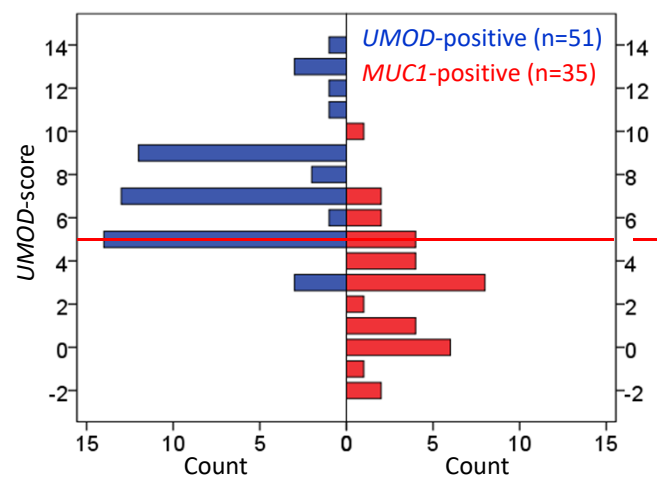
Dahan K et al. JASN 14: 2883-93, 2003
Bleyer et al. Kidney Int 66: 974-7, 2004

# Diagnostic algorithm: integration of clinical factors and urine uromodulin



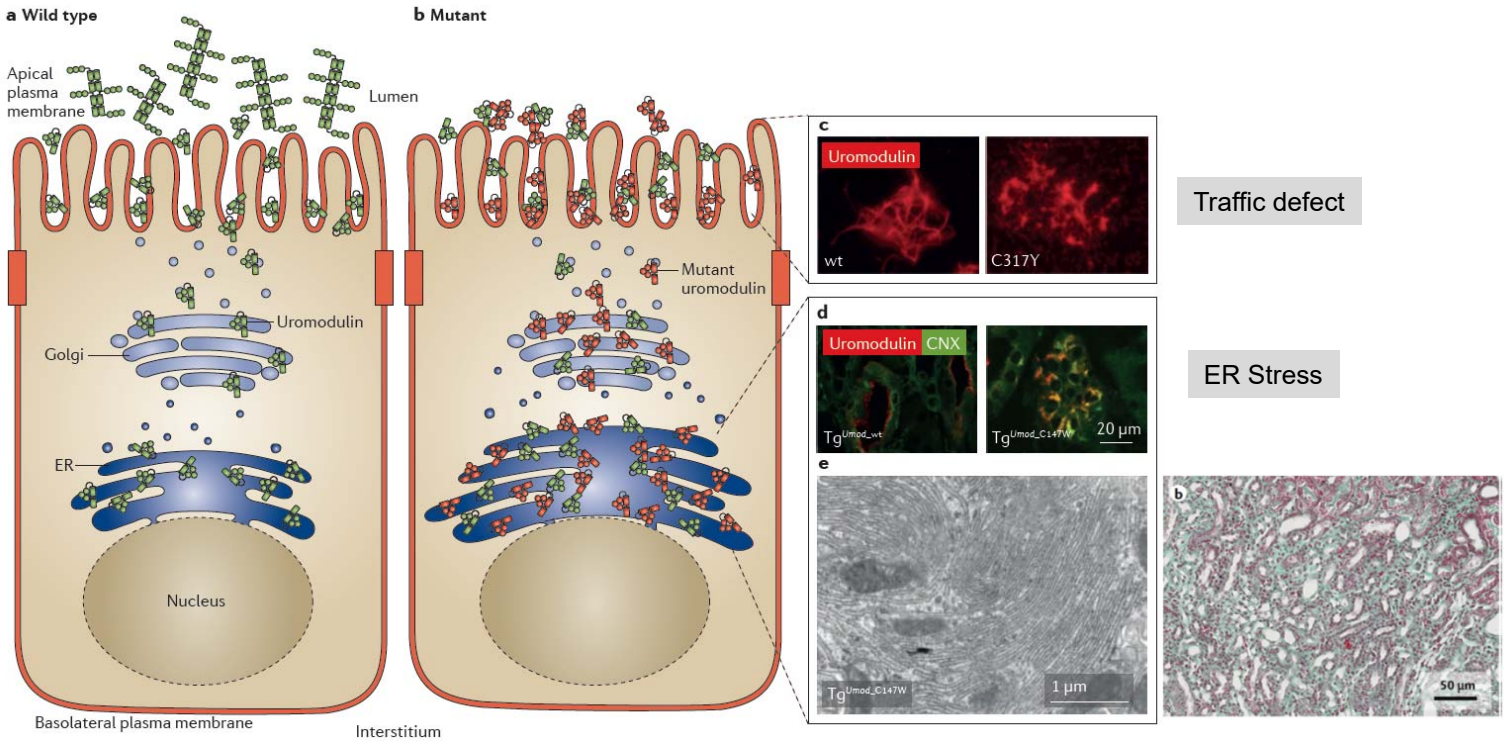

+urine UMOD




NPV of 89.7%
PPV of 84.2%
for *UMOD*

Olinger E et al. *Kidney Int* 98, 2020

# ADTKD – *UMOD*: Mechanism of Disease

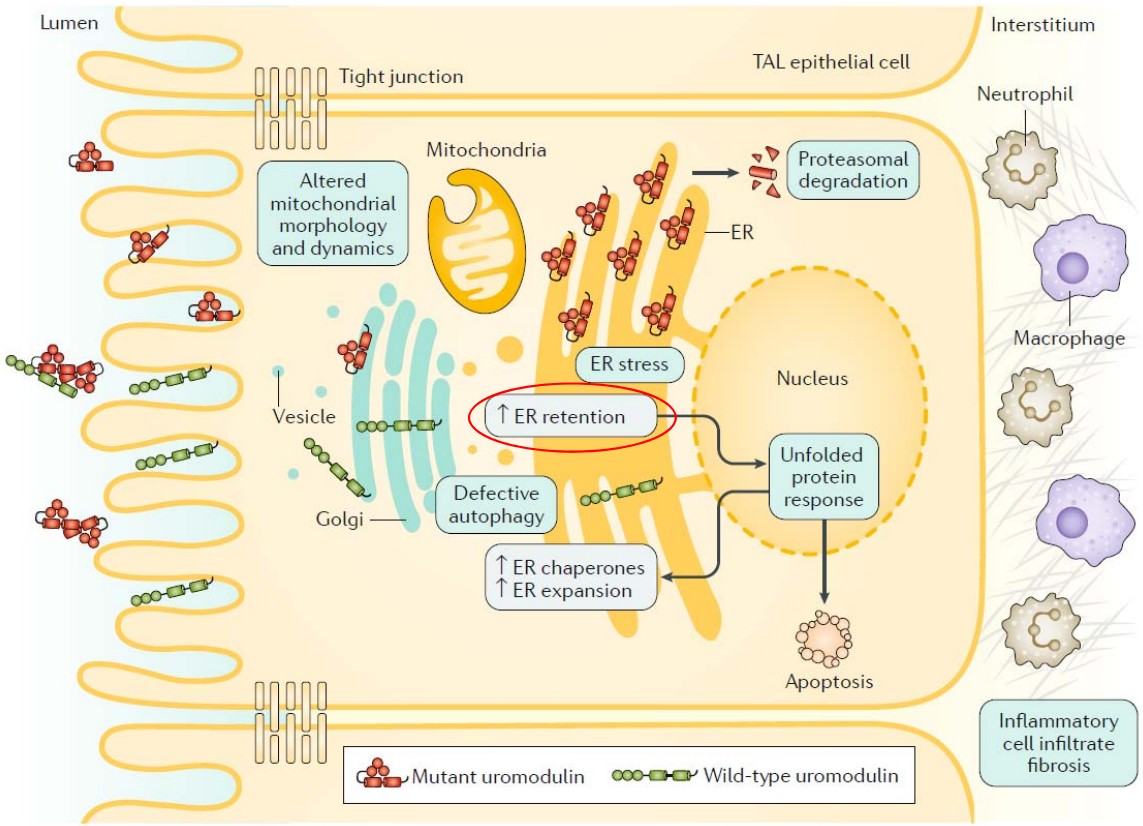


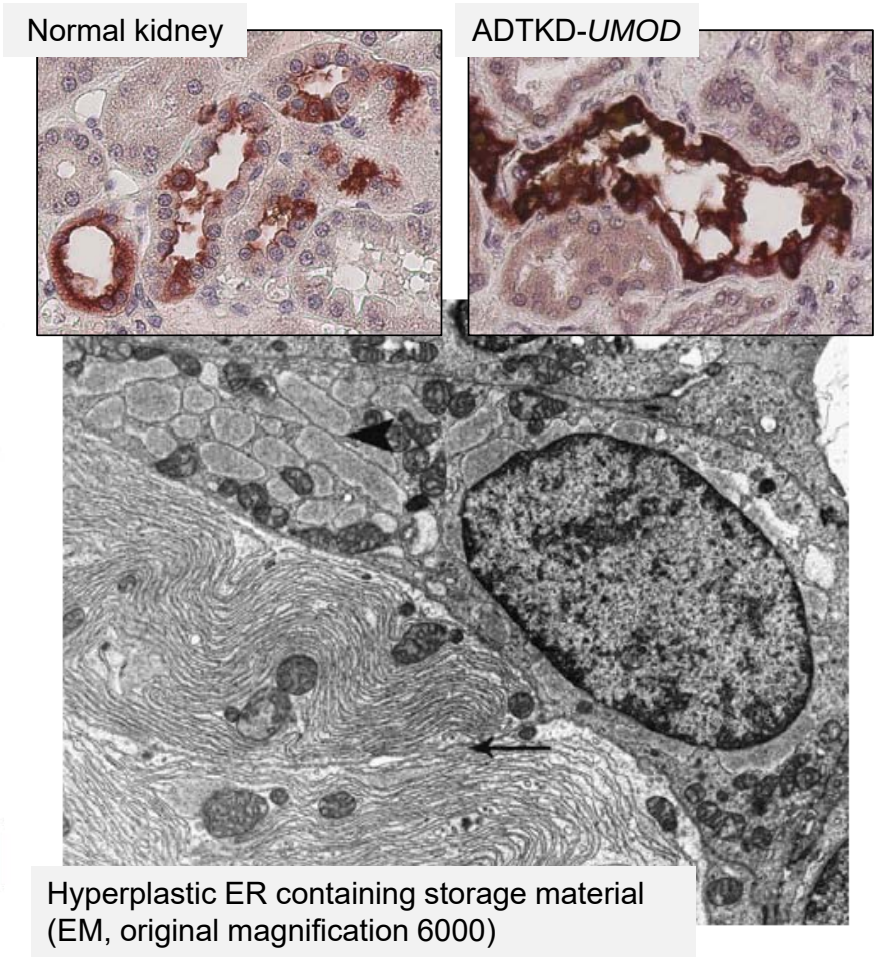

Traffic defect

ER Stress

- Gain of toxic function: Formation & accumulation of aggregates in ER → UPR
- Storage disease in the TAL → tubulointerstitial damage

Devuyst O et al. *Nat Rev Nephrol* 2017




Hyperplastic ER containing storage material (EM, original magnification 6000)

Devuyst O et al. Nat Rev Dis Primers, 2019
Nasr et al. Kidney Int, 2008

# Epidemiology of ADTKD

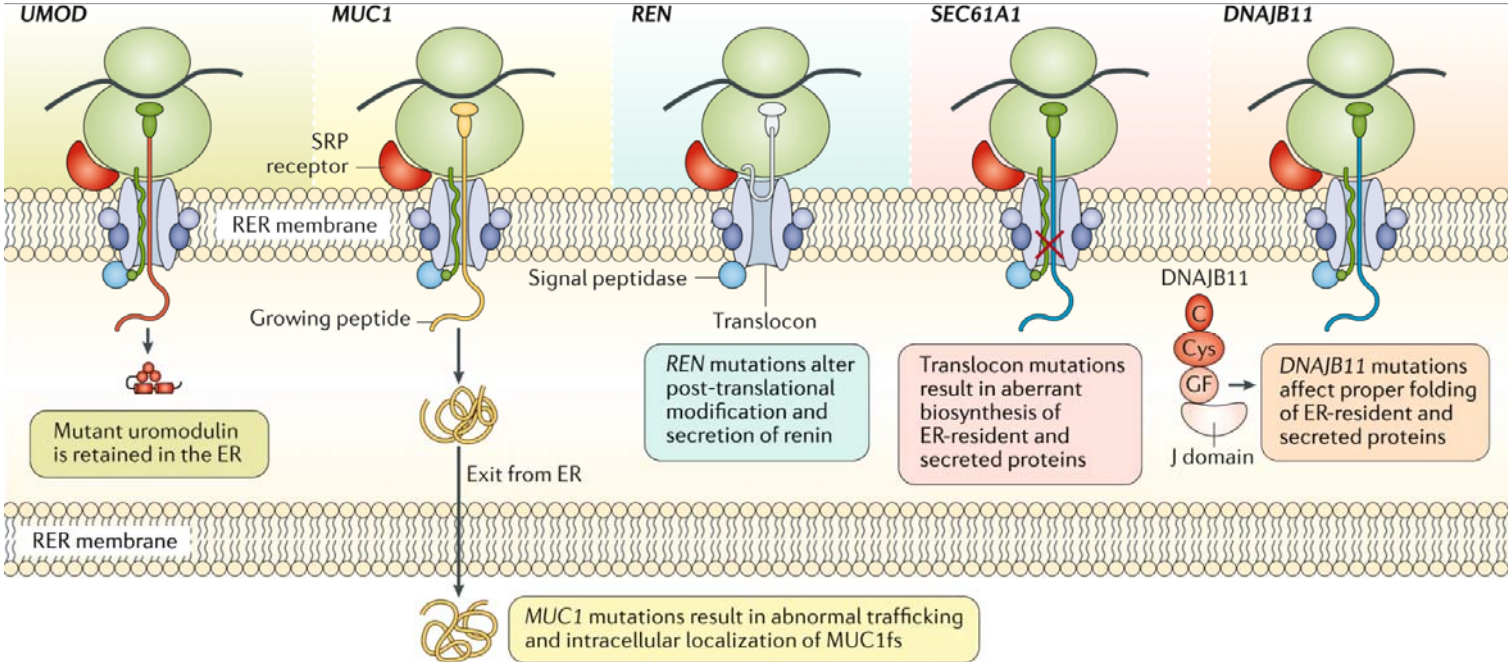
Rare – recent clinical characterization – underdiagnosed

- Handful of cases reported before 2000
- Austria (single center): Prevalence of ADTKD 1,67 cases per million (Lhotta et al. Nephron Extra 2012)
- Ireland: Prevalence of ADTKD-*UMOD*: 3 cases per million (Cormican at al. JASN Abstract 2017)
- England (single center): 16 per million (Gast et al. BMC Nephrol 2018)
- USA: *UMOD* mutations account for 3% of monogenic disorders causing CKD (Groopman et al. NEJM 2019)
- Ireland: *UMOD* mutations 2,6% of genetic causes of CKD (Connaughton et al. Kidney Int 2019)

*1% of patients with CKD stages 3–5 and 2% of patients with ESRD had ADTKD- UMOD*

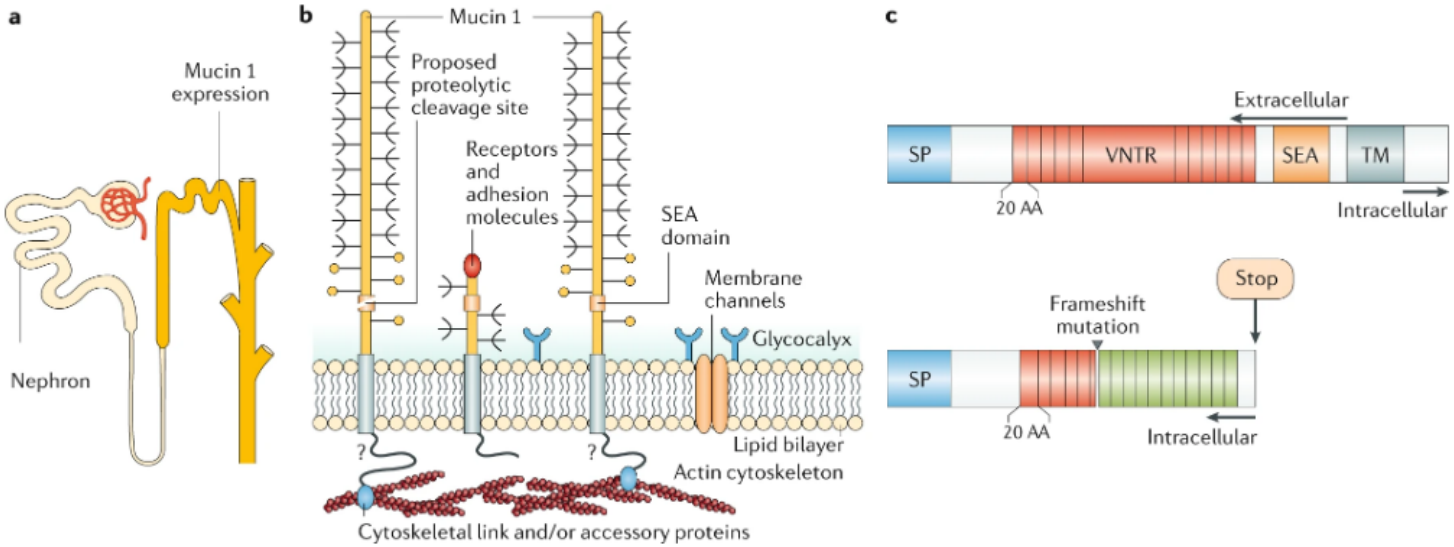
*→ most common monogenic kidney disease after collagen IV mutations and ADPKD*

# Genetic heterogeneity, ER stress and Unfolded Protein Response in ADTKD



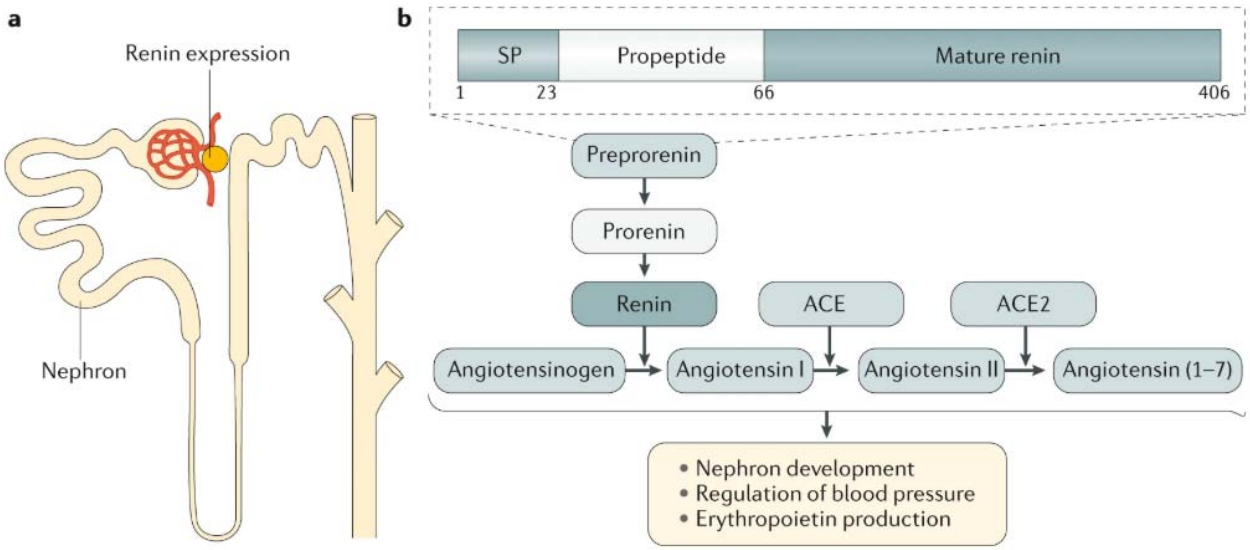

Devuyst, O. et al. (2019) Autosomal dominant tubulointerstitial kidney disease
*Nat. Rev. Dis. Primers* doi.org/10.1038/ s41572-019-0109-9

# Pathophysiology of ADTKD-*MUC1*



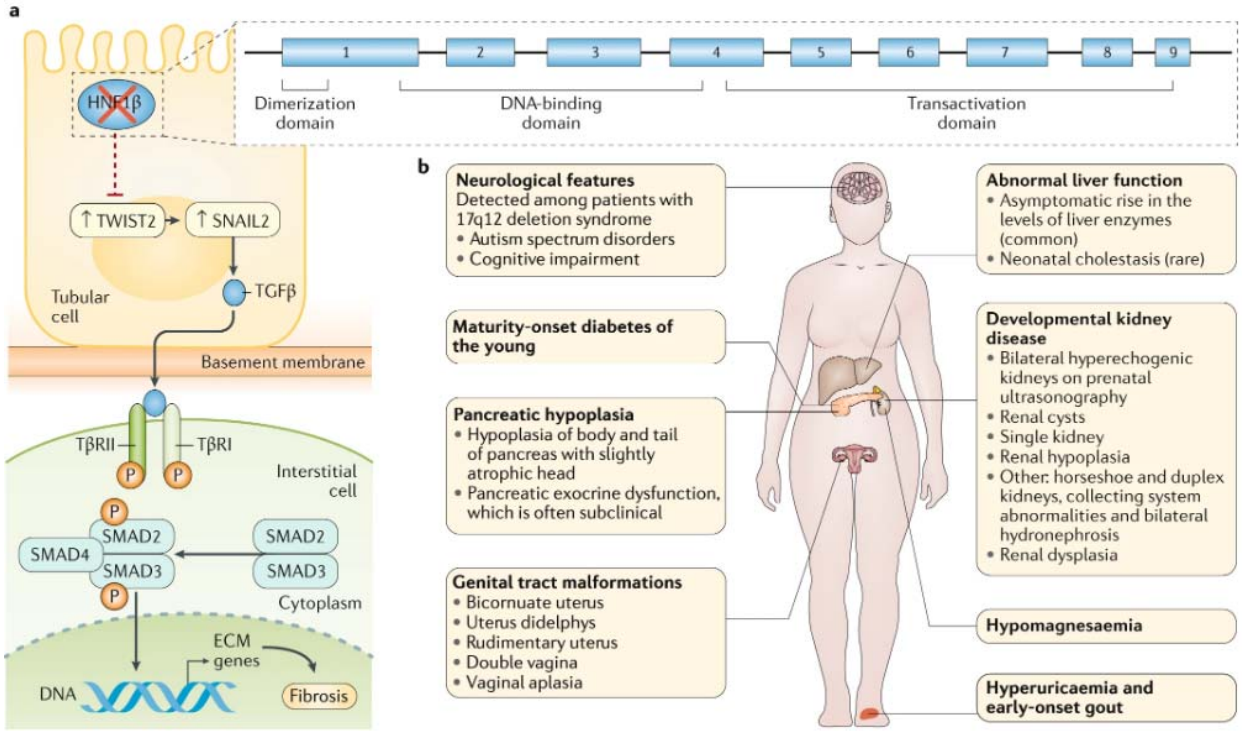

Devuyst, O. et al. (2019) Autosomal dominant tubulointerstitial kidney disease
*Nat. Rev. Dis. Primers* doi.org/10.1038/ s41572-019-0109-9

# Pathophysiology of ADTKD-*REN*




Devuyst, O. et al. (2019) Autosomal dominant tubulointerstitial kidney disease
*Nat. Rev. Dis. Primers* doi.org/10.1038/ s41572-019-0109-9

# The transcription factor HNF1β and ADTKD-*HNF1B*




Devuyst, O. et al. (2019) Autosomal dominant tubulointerstitial kidney disease
*Nat. Rev. Dis. Primers* doi.org/10.1038/ s41572-019-0109-9

www.kidney-international.org clinical investigation

# Clinical and genetic spectra of autosomal dominant tubulointerstitial kidney disease due to mutations in *UMOD* and *MUC1*

Check for updates

see commentary on page 549

OPEN

*Kidney International* (2020) **98,** 717–731

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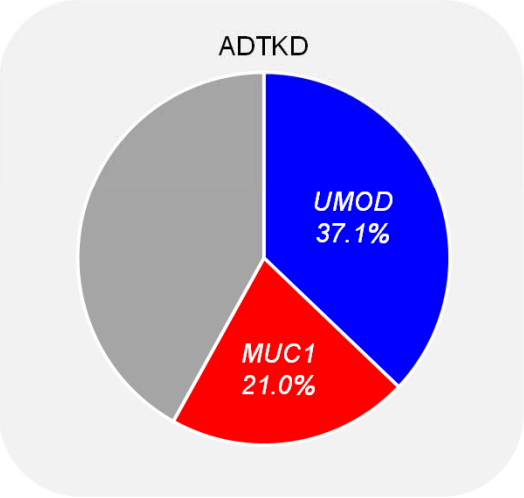
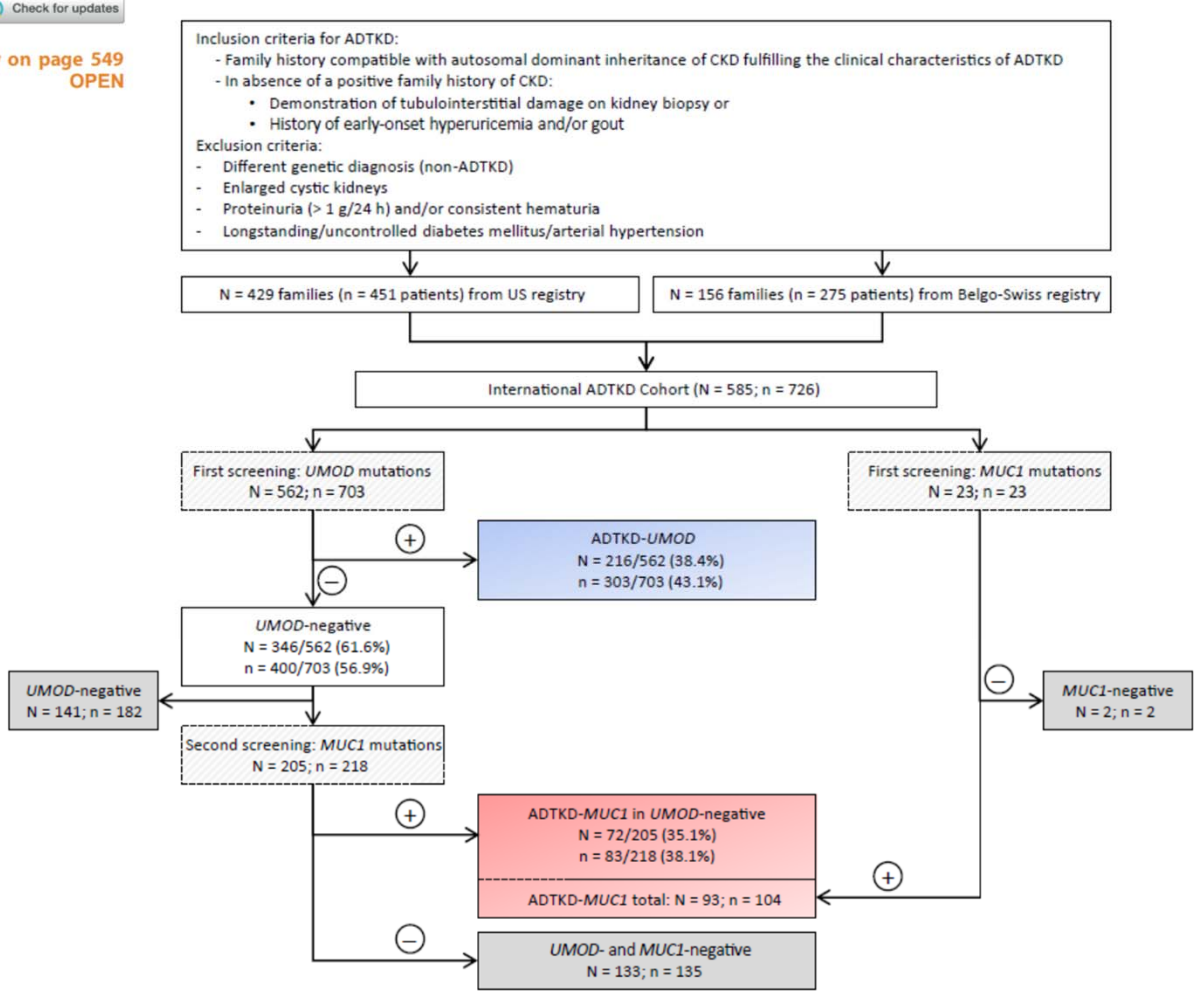
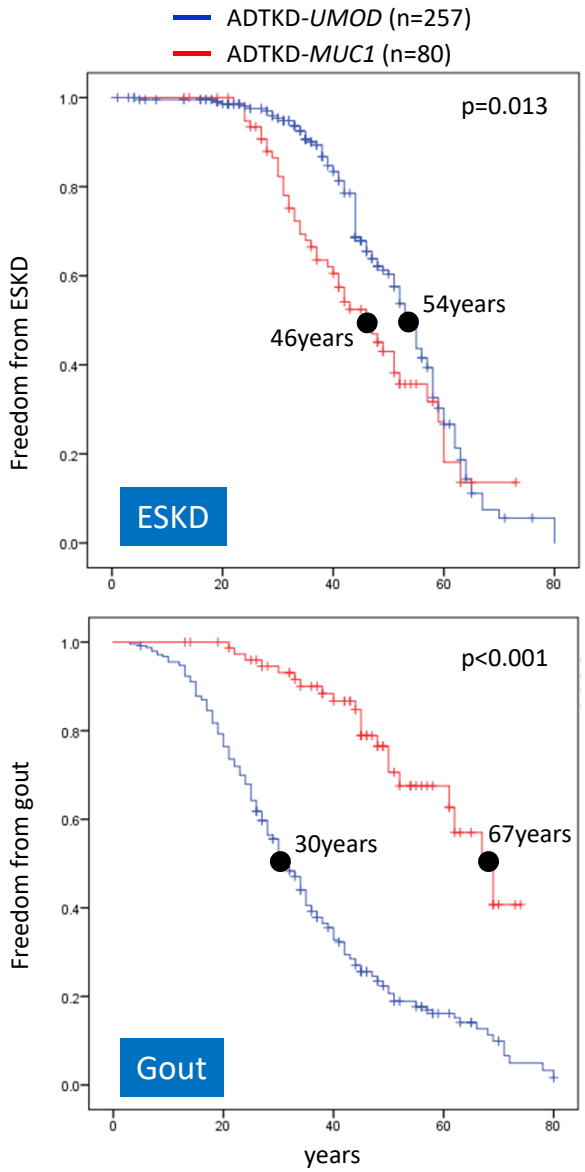


# Clinical Characteristics: ADTKD-*UMOD* vs ADTKD-*MUC1*

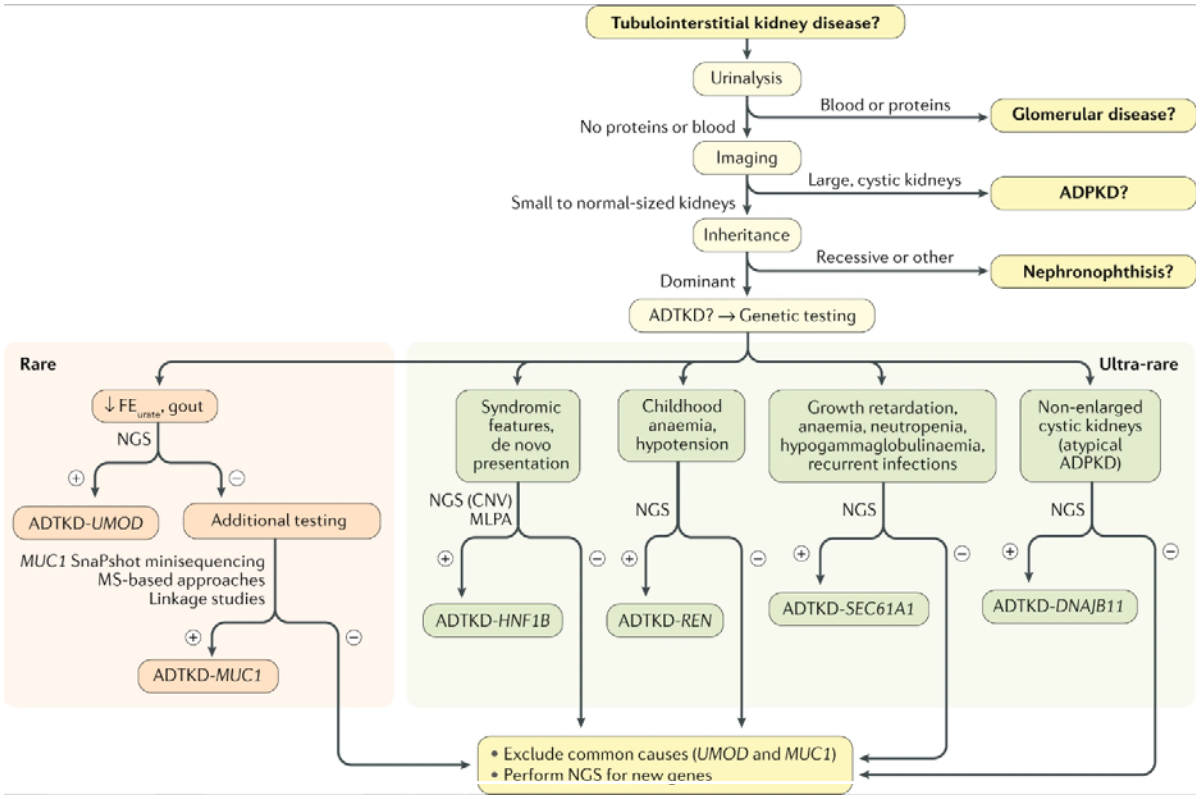
| | ADTKD-*UMOD* (n=303) | ADTKD-*MUC1* (n=104) | n (*UMOD*/*MUC1*) | p-value |
|---|---|---|---|---|
| Number of families | N=216 | N=93 | | |
| Sex (%) | | | 257/80 | 1.0 |
| - Female | 130 (51) | 40 (50) | | |
| - Male | 127 (49) | 40 (50) | | |
| Age at presentation (y) | 42 (27;53) | 47 (37; 57) | 218/78 | **0.005** |
| Positive family history (Gout/CKD) (%) | 243/257 (95) | 69/80 (86) | | **0.007** |
| eGFR at presentation (mL/min) | 39.2 ± 20.3 | 50 ± 51.9 | 136/52 | 0.157 |
| CKD (%) | 231/257 (90) | 53/80 (66) | | **<0.001** |
| ESKD (%) | 112/257 (44) | 46/80 (58) | | **0.04** |
| - Age at ESKD (y) | 46 (39; 57) | 36 (30; 46) | 224/80 | **<0.0001** |
| Serum uric acid (µmol/L) | 497.9 ± 136.6 | 443.6 ± 121.7 | 110/14 | 0.159 |
| - Female | 478.7 ± 133.2 | 418.7 ± 136.1 | 53/5 | 0.341 |
| - Male | 515.7 ± 138.5 | 457.4 ± 119.2 | 57/9 | 0.237 |
| Gout (%) | 202/257 (79) | 21/80 (26) | | **<0.001** |
| - Female | 96/130 (74) | 4/40 (10) | | **<0.001** |
| - Male | 106/127 (83) | 17/40 (43) | | **<0.001** |
| Age at gout onset (y) | 27 (19; 37) | 45 (29; 51) | 199/18 | **0.001** |
| - Female | 30 (21; 43) | 28 (21; 41) | 93/4 | 0.828 |
| - Male | 26 (18; 34) | 45 (33; 54) | 106/14 | **<0.001** |

- Generally more severe kidney disease in ADTKD-*MUC1*
- Earlier and more prevalent gout in ADTKD-*UMOD*




Olinger E et al. *Kidney Int* 98, 2020

# Diagnosis of ADTKD: Clinical and genetic features




Devuyst, O. et al. (2019) Autosomal dominant tubulointerstitial kidney disease
*Nat. Rev. Dis. Primers* doi.org/10.1038/ s41572-019-0109-9

# Therapeutic Options for ADTKD

- Follow established CKD guidelines
- No data in ADTKD patients concerning possible benefits of ACEIs and ARBs on CKD progression
- Hyperuricemia: losartan - lowers serum urate levels (increased FEurate)
- Patients with ADTKD-UMOD and gout: Allopurinol
- Diuretics should be used with caution: aggravate hyperuricemia and volume depletion
- Low-salt diet is NOT recommended for ADTKD-UMOD and ADTKD-REN patients (it may aggravate hyperuricemia & volume depletion)
- Liberal water intake to compensate for possible urinary concentration defects

http://www.kidney-international.org


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

Eckardt KU et al. Kidney Int 88, 676-83, 2015

Received: 15 September 2019 | Revised: 30 December 2019 | Accepted: 7 January 2020
DOI: 10.1111/ctr.13783

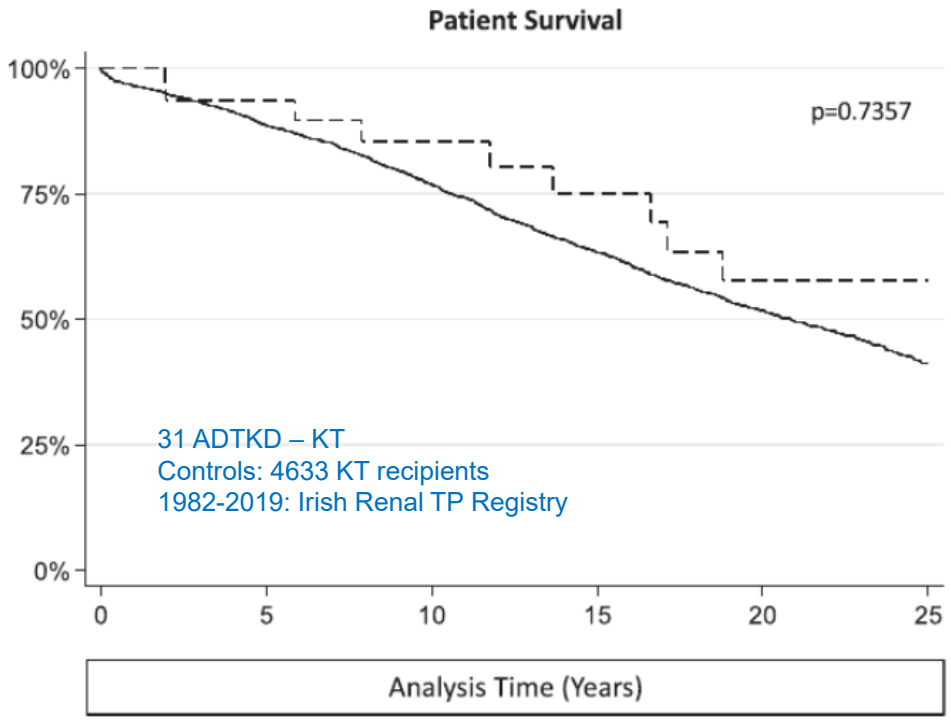
ORIGINAL ARTICLE

Clinical TRANSPLANTATION WILEY

# Renal transplant outcomes in patients with autosomal dominant tubulointerstitial kidney disease

Sarah Cormican[1] | Claire Kennedy[1,2] | Dervla M. Connaughton[1,3,4] | Patrick O'Kelly[1] | Susan Murray[1,2] | Martina Živná[5] | Stanislav Kmoch[5] | Neil K. Fennelly[6] | Katherine A. Benson[1,2] | Eoin T. Conlon[1] | Gianpiero L. Cavalleri[2] | Claire Foley[4,7] | Brendan Doyle[6] | Anthony Dorman[2,6] | Mark A. Little[4,8] | Peter Lavin[8] | Kendrah Kidd[5,9] | Anthony J. Bleyer[9] | Peter J. Conlon[1,2]

| | Category | Status of diagnosis | Criteria met | No. of individuals per family with renal transplant |
|---|---|---|---|---|
| 1 | ADTKD-MUC1 | C | Bx, GT, Rel | 7 |
| 2 | ADTKD-MUC1 | C | Bx, GT, Rel | 1 |
| 3 | ADTKD-MUC1 | C | Bx, GT, Rel | 1 |
| 4 | ADTKD-MUC1 | C | Bx, GT, Rel | 1 |
| 5 | ADTKD-UMOD | C | Bx, GT, Rel | 4 |
| 6 | ADTKD-UMOD | C | Bx, GT, Rel | 1 |
| 7 | ADTKD-UMOD | C | Bx, GT, Rel | 2 |
| 8 | ADTKD-UMOD | C | Bx, GT, Rel | 2 |
| 9 | ADTKD-HNF1B | C | Bx, GT, Rel | 3 |
| 10 | ADTKD-HNF1B | C | Bx, GT, Rel | 1 |
| 11 | ADTKD-NOS | C | Bx, Rel | 1 |
| 12 | ADTKD-NOS | C | Bx, Rel | 2 |
| 13 | ADTKD-NOS | C | Bx, Rel | 2 |
| 14 | ADTKD-NOS | S | Bx | 1 |
| 15 | ADTKD-NOS | S | Rel | 1 |
| 16 | ADTKD-NOS | S | Rel | 1 |
| Total number | | | | 31 |

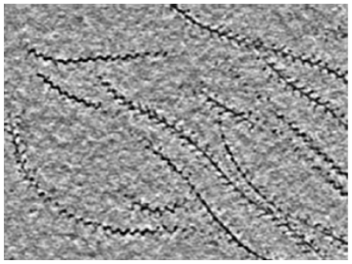


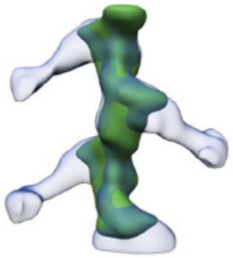

No differences in graft or patient survival

- Supportive management of CKD complications, cardiovascular risk factors & nephrotoxins
- Treatment of extrarenal complications (gout)

## Take home messages

- Aspecific presentation of ADTKD -> probably underdiagnosed | genetic testing required
- Mutations in *UMOD* are the most common form of ADTKD
- A positive family history and early gout are associated with ADTKD-*UMOD*
- Variability in disease progression: gender, mutation score + genetic modifiers ?
- Clinical features & urine uromodulin levels can help to discriminate between ADTKD-*UMOD*, ADTKD-*MUC1* or other diagnoses (non-ADTKD)
- No specific therapy available to date – Gain of toxic function mechanism





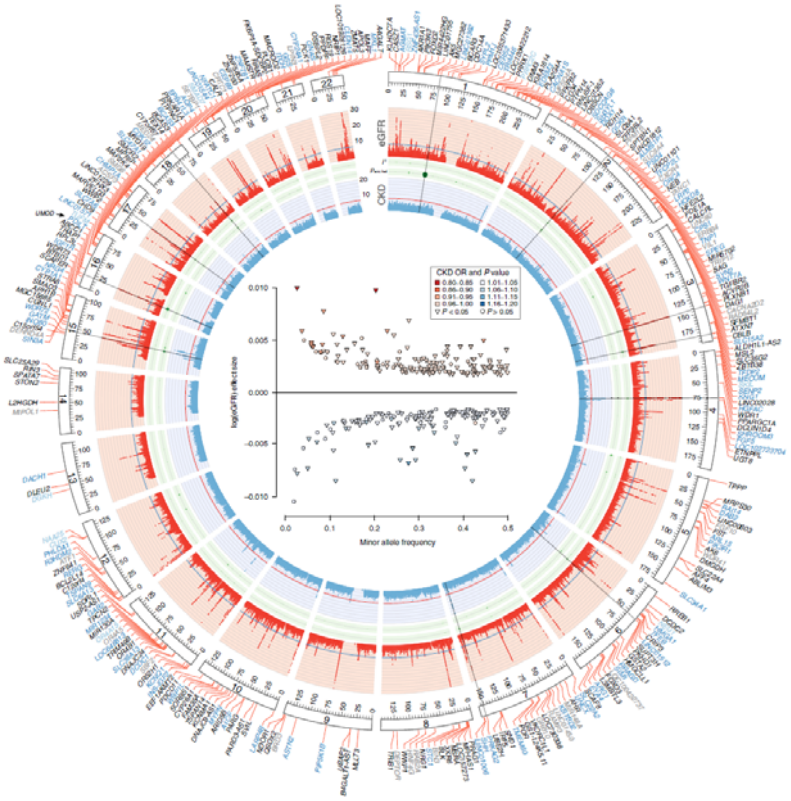
nature genetics

ARTICLES

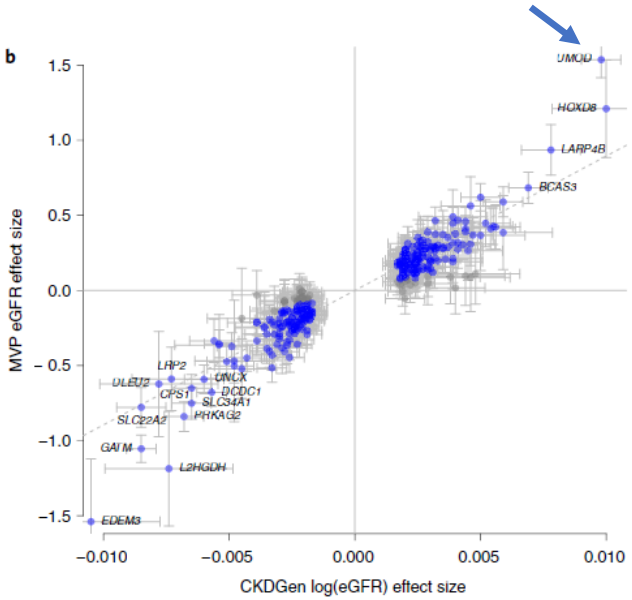
https://doi.org/10.1038/s41588-019-0407-x

# A catalog of genetic loci associated with kidney function from analyses of a million individuals

NATURE GENETICS | VOL 51 | JUNE 2019 | 957–972 |



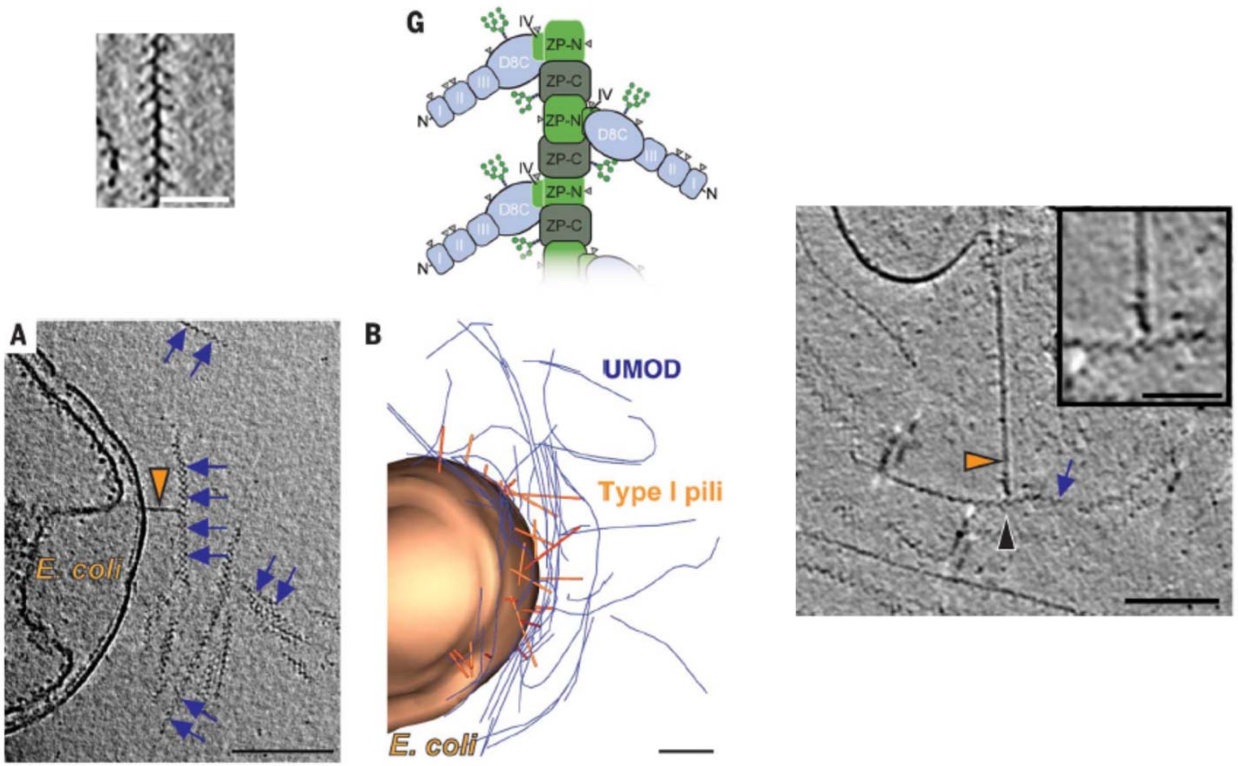

308 loci associated with eGFR
Largest effect on risk of CKD: *UMOD* locus



MICROBIOLOGY

# Architecture and function of human uromodulin filaments in urinary tract infections

Gregor L. Weiss[1]*, Jessica J. Stanisich[1]*, Maximilian M. Sauer[1]*†, Chia-Wei Lin[2]‡, Jonathan Eras[1], Dawid S. Zyla[1], Johannes Trück[3], Olivier Devuyst[4,5], Markus Aebi[2], Martin Pilhofer[1]§, Rudi Glockshuber[1]

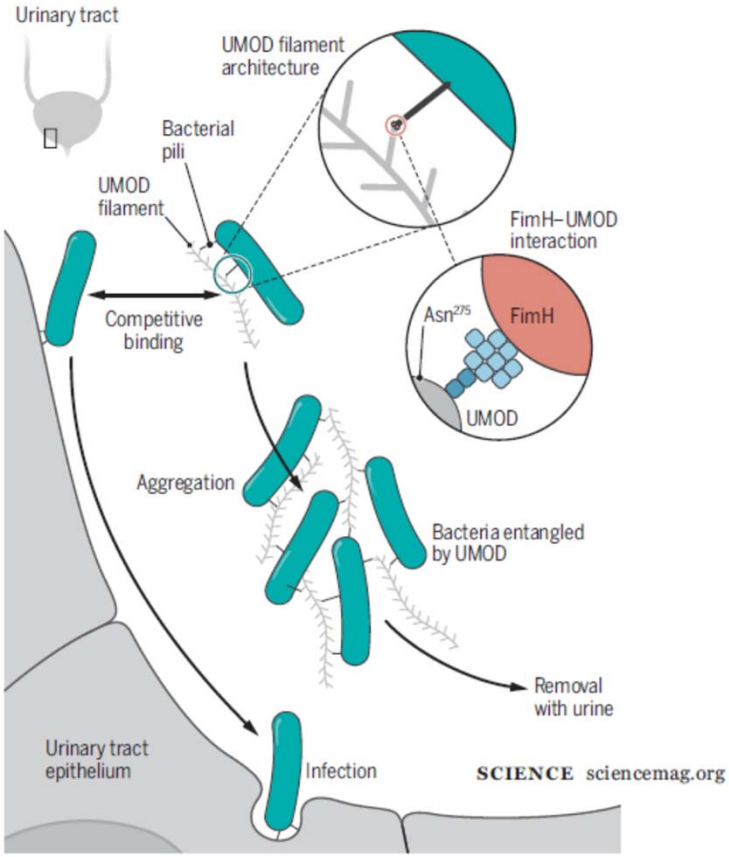



Weiss *et al.*, *Science* **369**, 1005–1010 (2020) 21 August 2020

BIOMEDICINE

# A glycoprotein in urine binds bacteria and blocks infections

Direct imaging of a human fluid illuminates the molecular basis of urinary tract protection from disease



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The European Rare Kidney Disease Reference Network

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SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

*Thank you very much for your attention!*

# Next Webinars





## ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders

Date: **27 Oct 2020**

Speaker: **Rezan Topaloglu**

Topic: **Classification and Physiopathology of Vasculitis**

## ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **03 Nov 2020**

Speaker: **Marina Vivarelli**

Topic: **Steroid Resistant Nephrotic Syndrome**

## IPNA Clinical Practice Webinars

Date: **12 Nov 2020**

Speaker: **Agnes Trautmannn**

Topic**: IPNA Clinical Practice Recommendations for the Diagnosis and Management of Children with Steroid-resistant Nephrotic Syndrome**

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