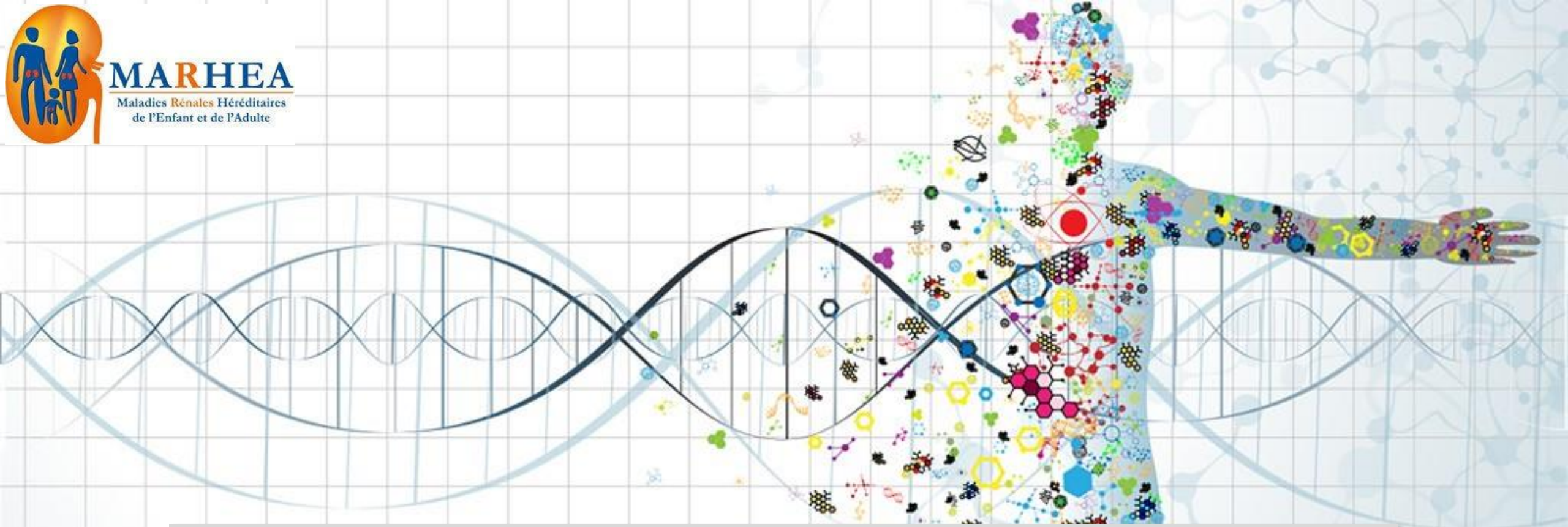
MARHEA
Maladies Rénales Héréditaires de l'Enfant et de l'Adulte



ADTKD-*UMOD*: What's new ?

Prof. Dr. med. Olivier Devuyst

Train CKDis · UCL · FNSNF · EURenOmics · ITINERARE · University of Zurich[UZH]

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

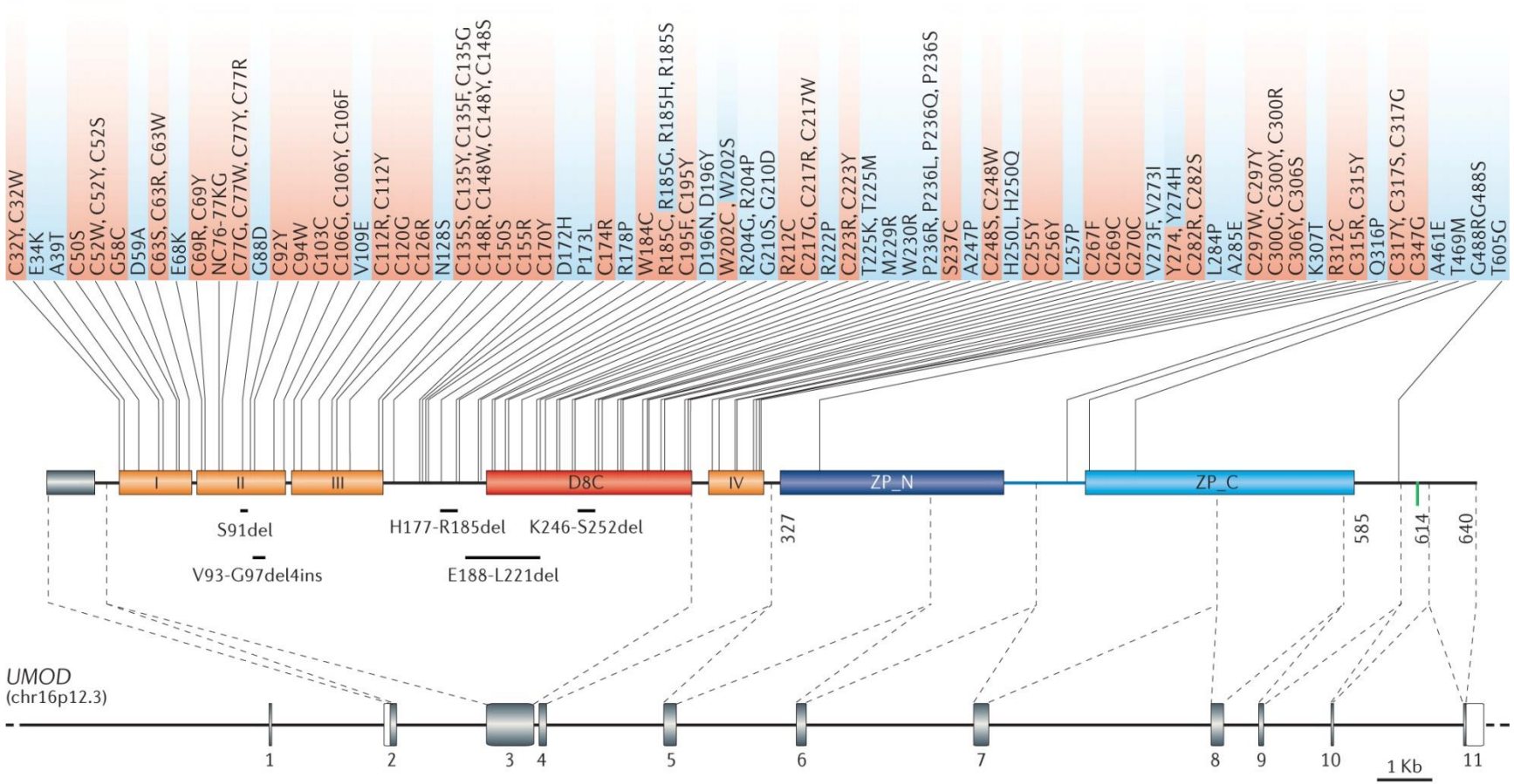
ADTKD-*Gene:* Replacing FJHN, MCKD

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 • Protection against kidney stones • Protection against urinary tract infections • 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 • Immunomodulatory properties • 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
[illegible] (*609213; 3q21.3)	[illegible]	α1 subunit of SEC61	Ubiquitous	• Component of SEC61 channel-forming translocon complex that mediates transport of signal peptide-containing precursor polypeptides across the ER

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*

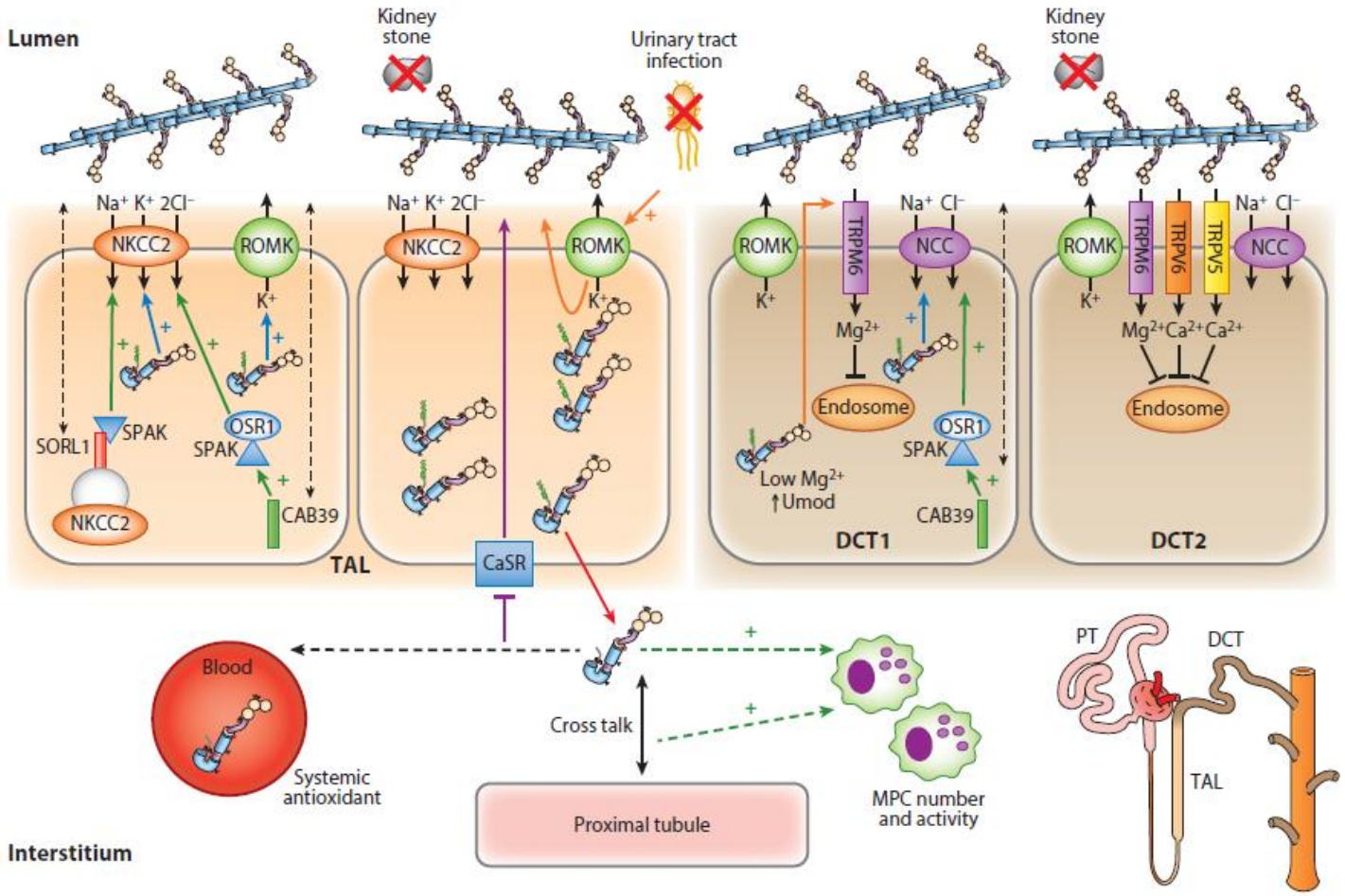
Landscape of *UMOD* Mutations in ADTKD

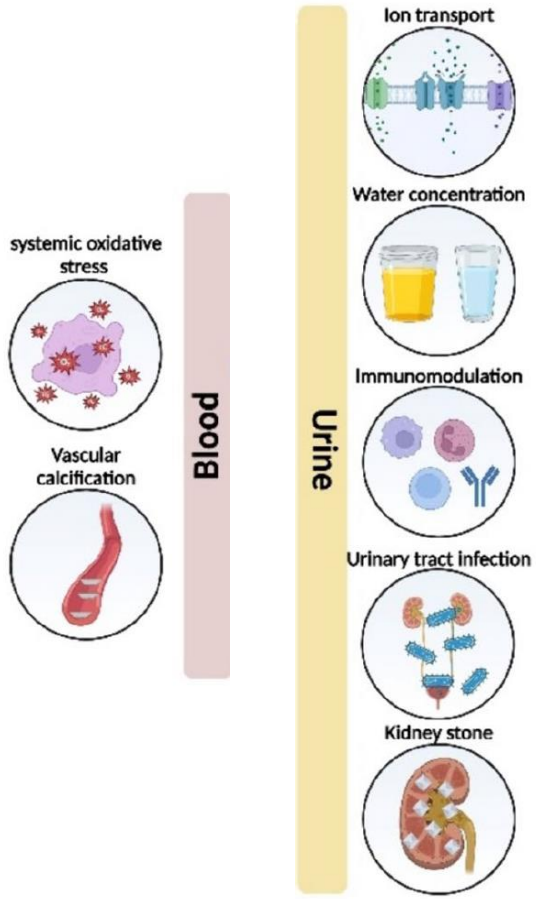


→ >130 mutations, 95% cluster in exons 3 and 4
→ 96% missense mutations, 4 in-frame deletions
→ Cysteine residues (~60%)

Devuyst O et al. *Nat Rev Nephrol* 2017

What does uromodulin do?



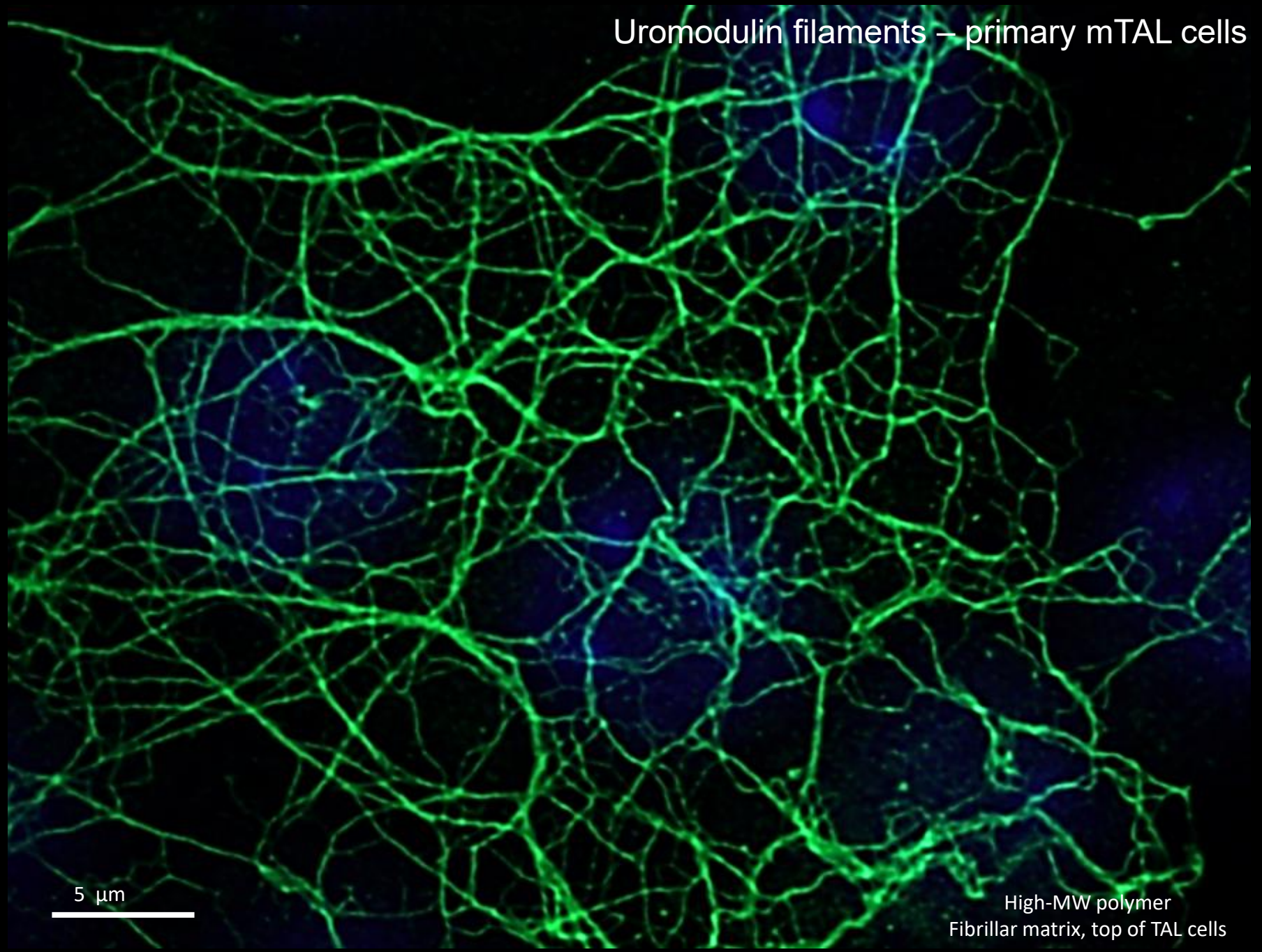


Devuyst O et al. *Nat Rev Nephrol* 13, 2017

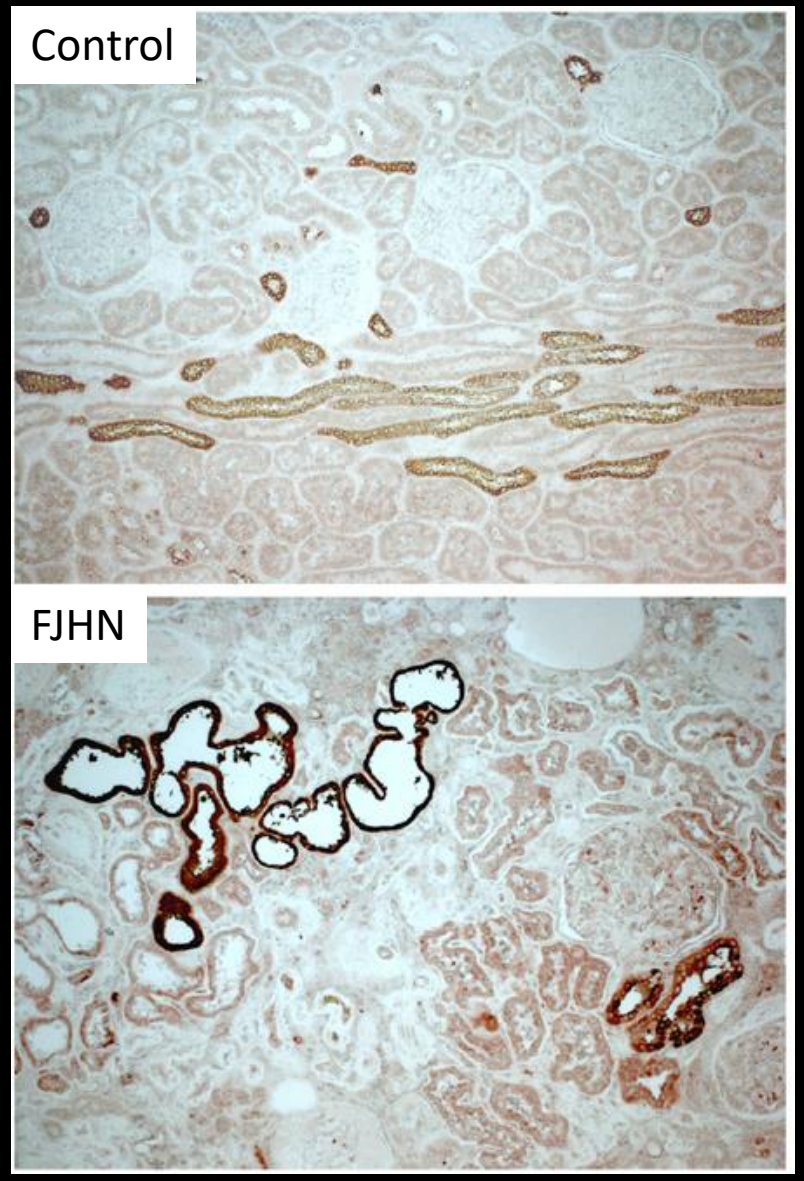
Schaffer, Devuyst & Rampoldi. *Annu Rev Physiol* 83, 2021

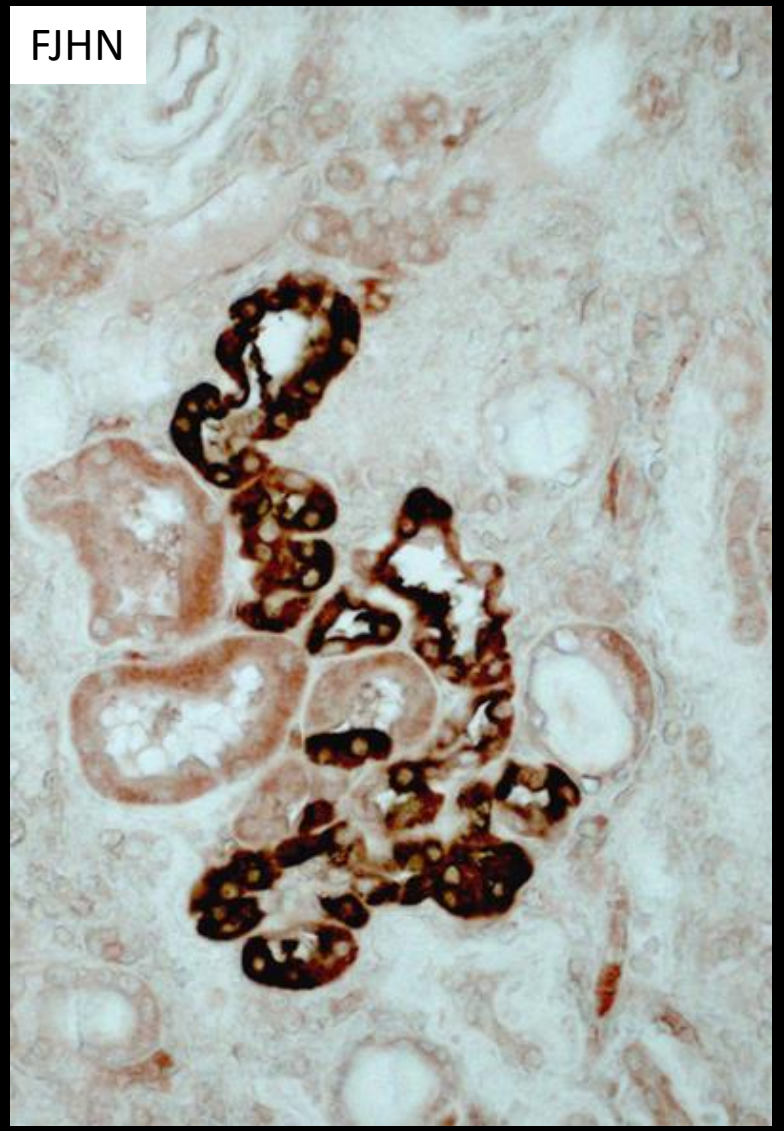
Zhou M et al. *Curr Hypertension Rep*, 2024

Uromodulin filaments – primary mTAL cells



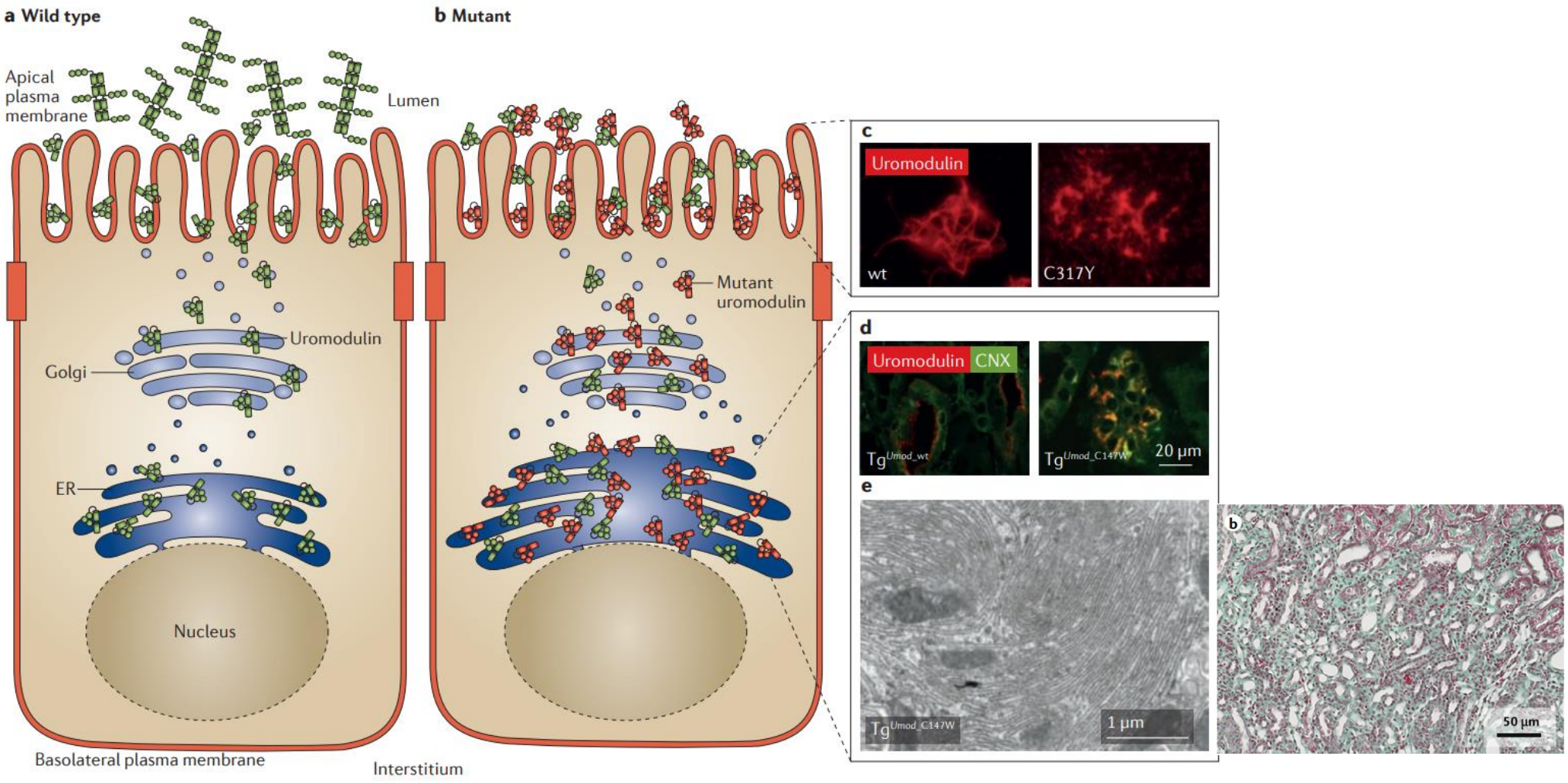
Accumulation of Mutant Uromodulin in Kidney Tubules: Storage Disease





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

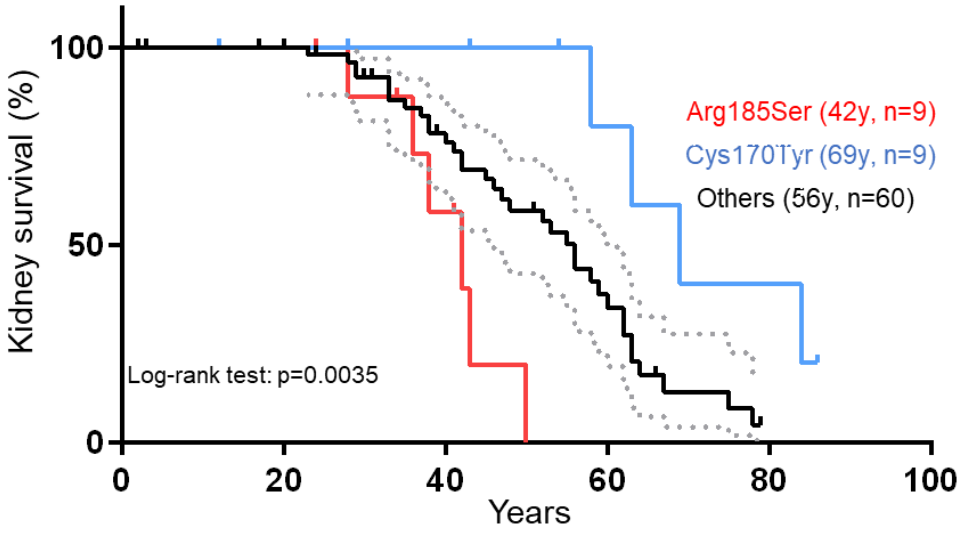
Pathophysiology of ADTKD-*UMOD*

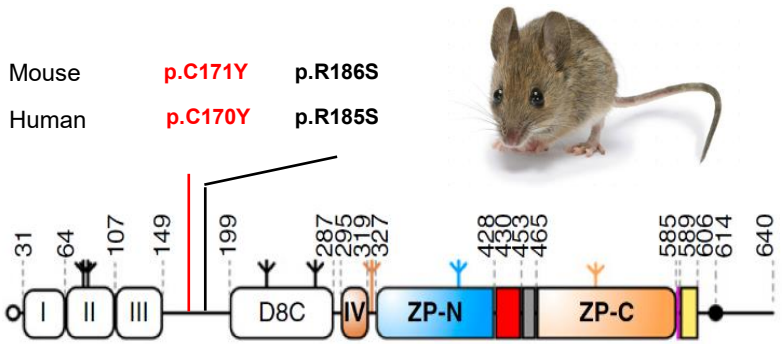


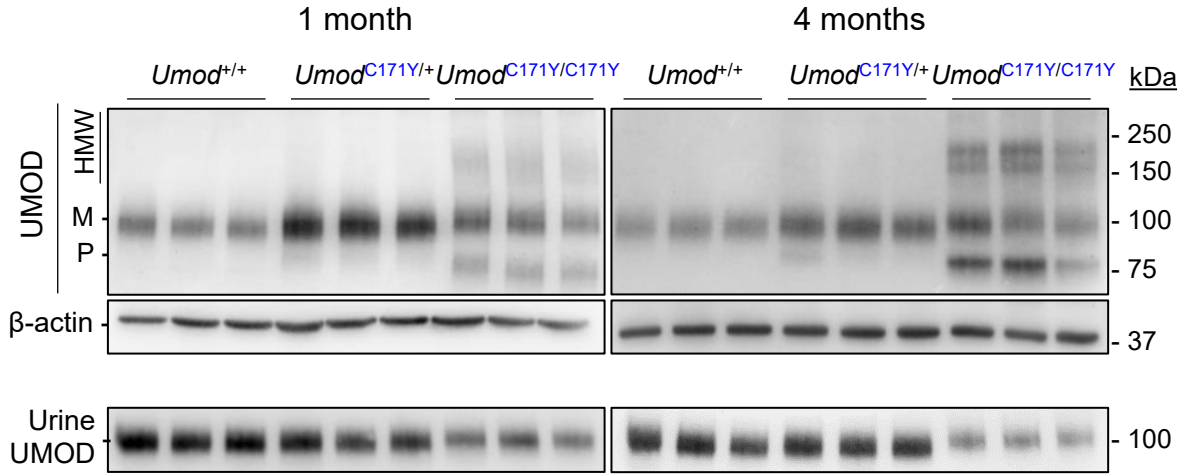
- Mutant uromodulin is misfolded and accumulates in the ER – ER stress and UPR pathways
- Dominant, gain of toxic function mechanism

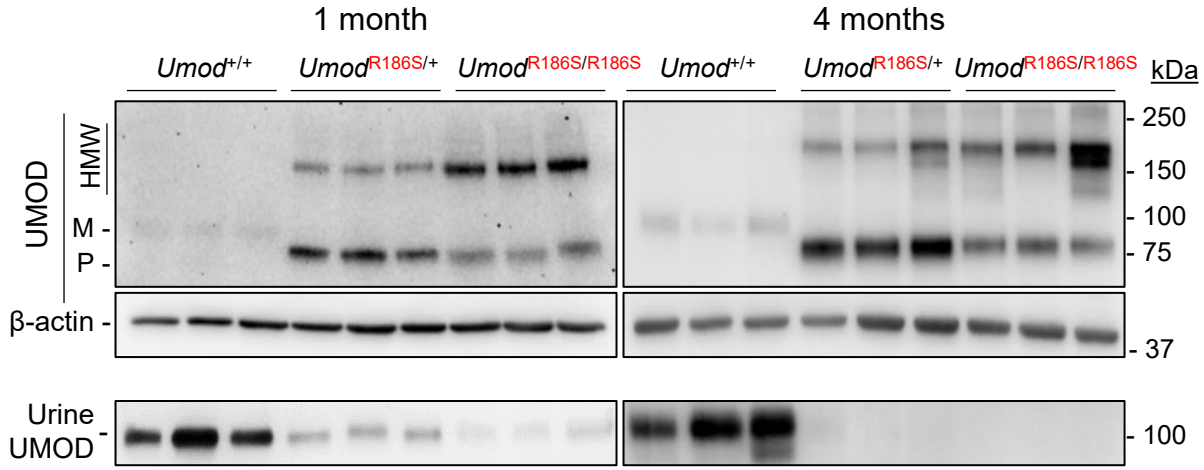
Devuyst Olinger & Rampoldi, *Nat Rev Nephrol*, 2017

ADTKD-*UMOD*: Allelic and Gene Dosage Effects





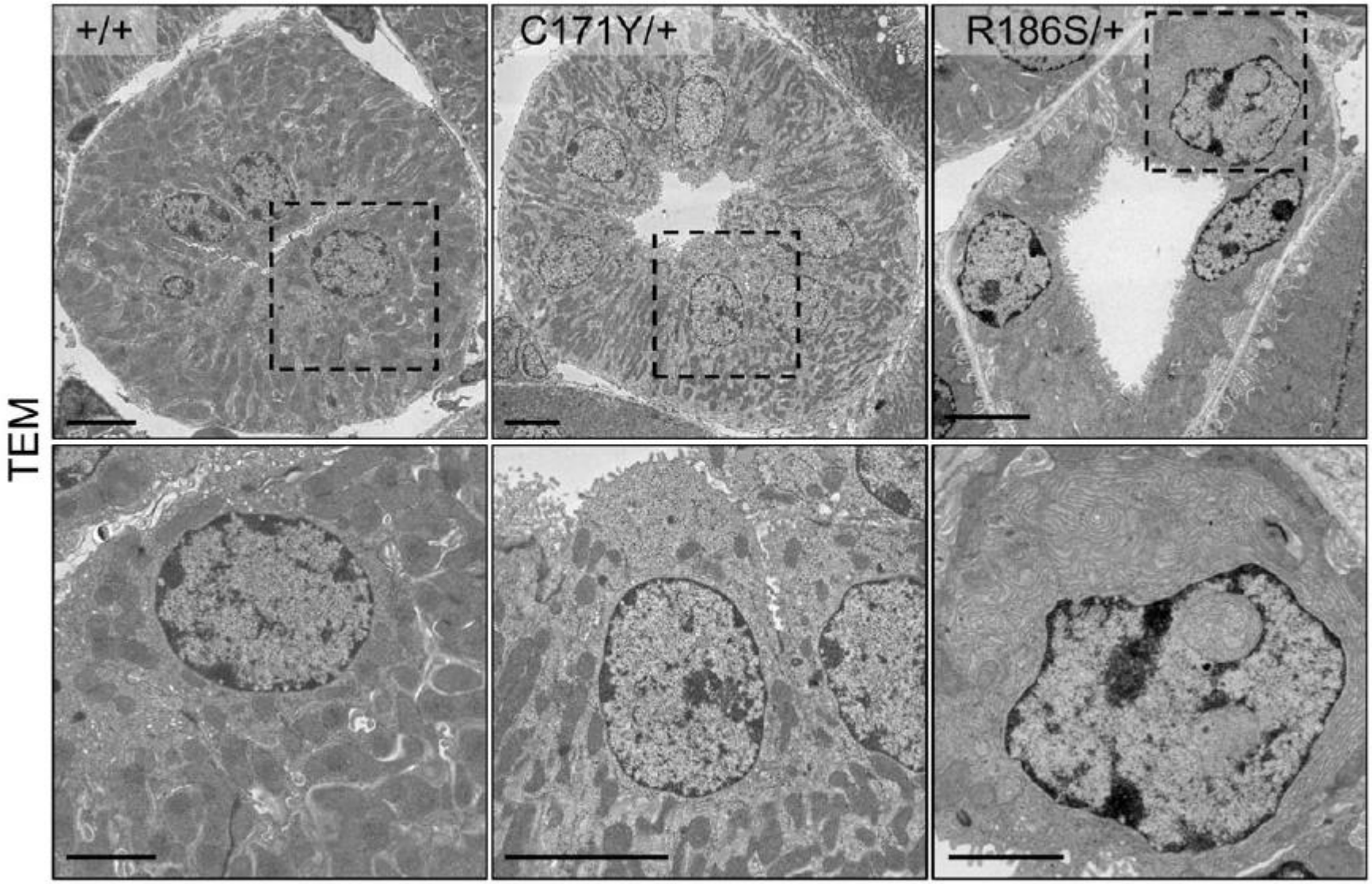




- *Umod* KI mice show an age-dependent increase of uromodulin in the kidney and reduced levels in the urine
- Each model: defective maturation - precursor and high MW aggregates isoforms

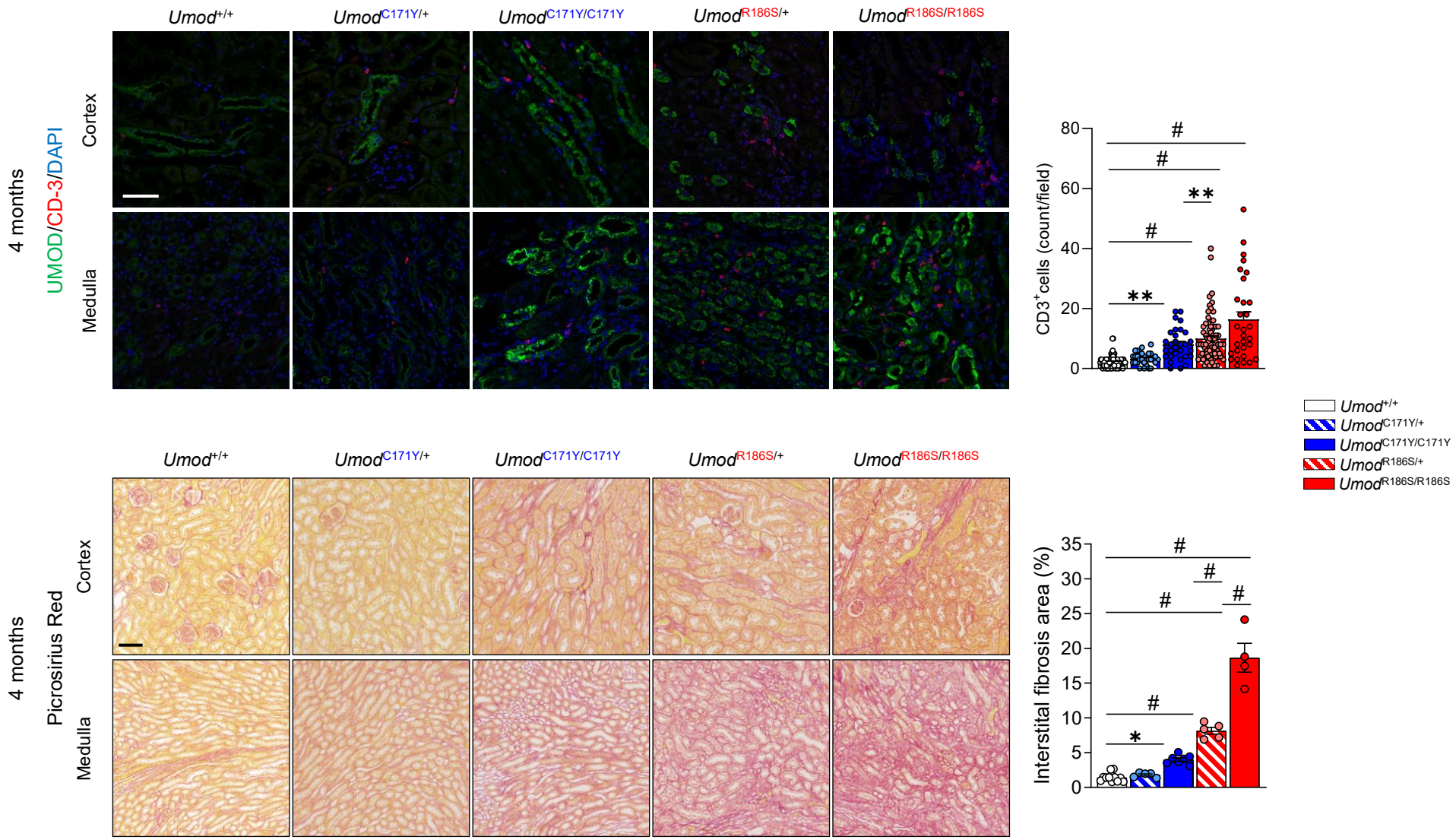
Schiano, et al. *EMBO Mol Med* 2023

ER Expansion in Kidneys from *Umod* KI Mice



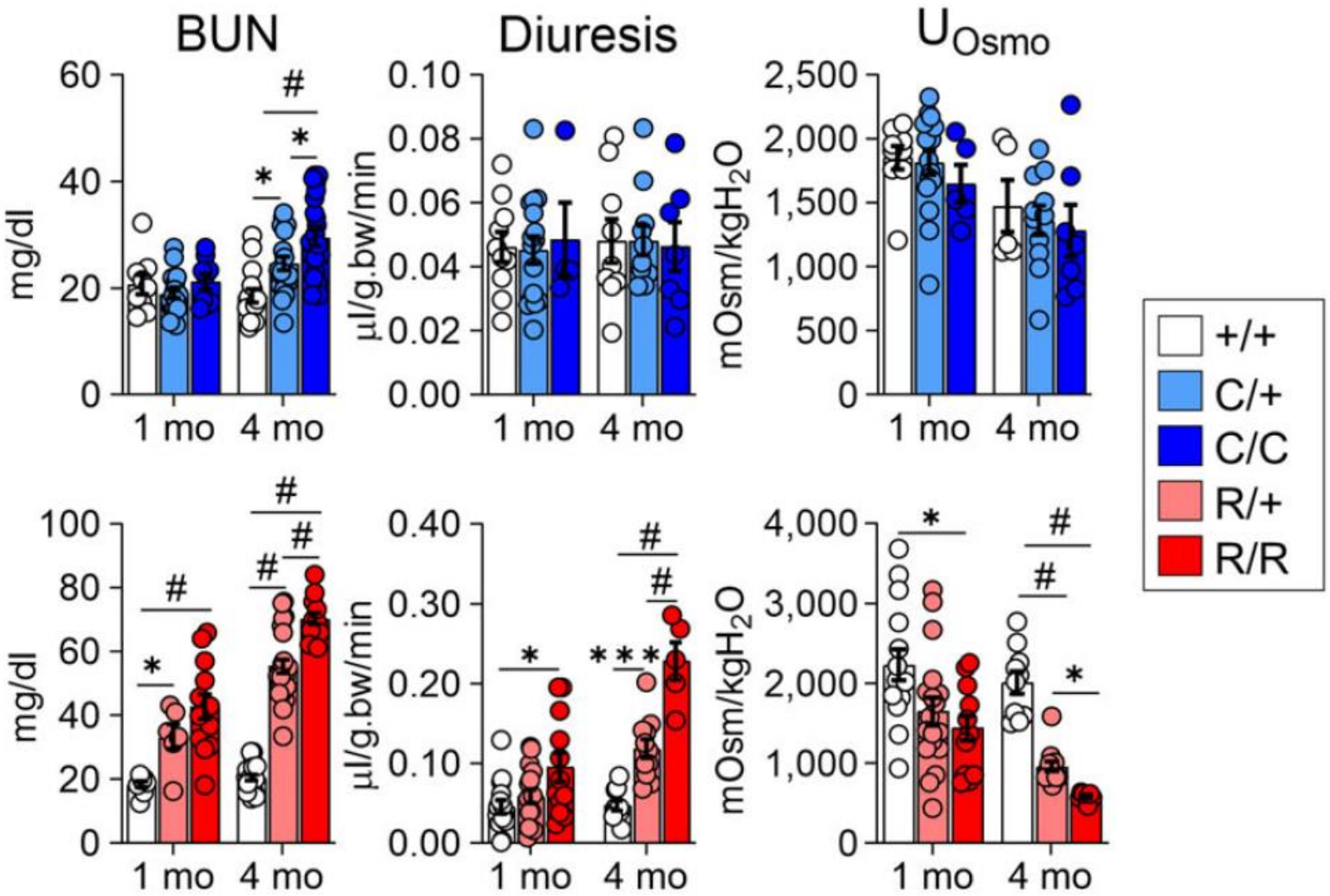
Schiano, et al. *EMBO Mol Med* 2023

Inflammation and Fibrosis in Kidneys from *Umod* KI Mice



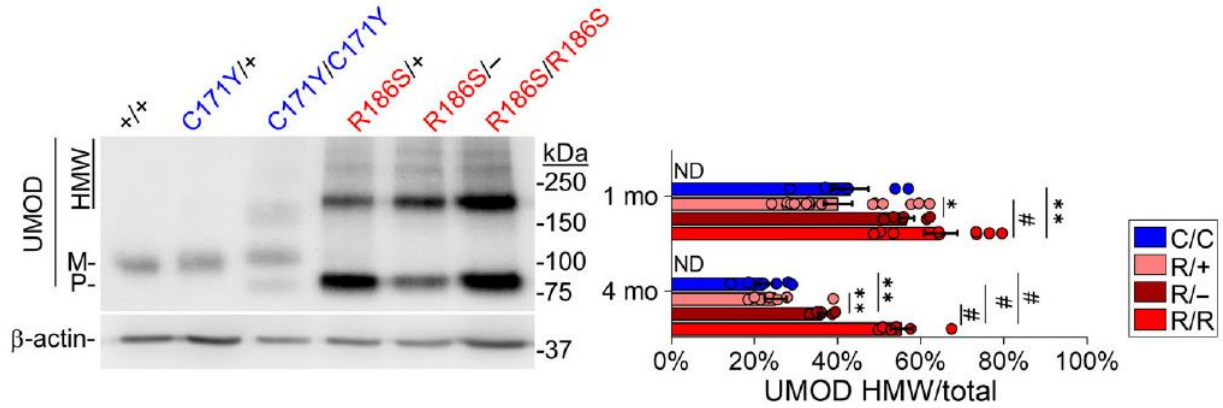
Schiano, et al. *EMBO Mol Med* 2023

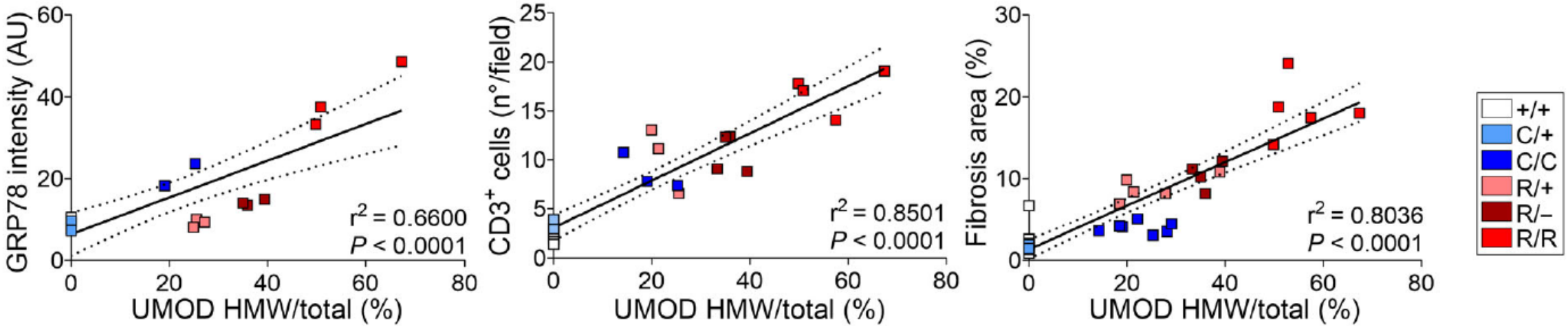
Allelic and Gene Dosage Effects on Kidney Function Parameters



Schiano, et al. *EMBO Mol Med* 2023

Uromodulin Aggregates Drive ADTKD-*UMOD* Progression

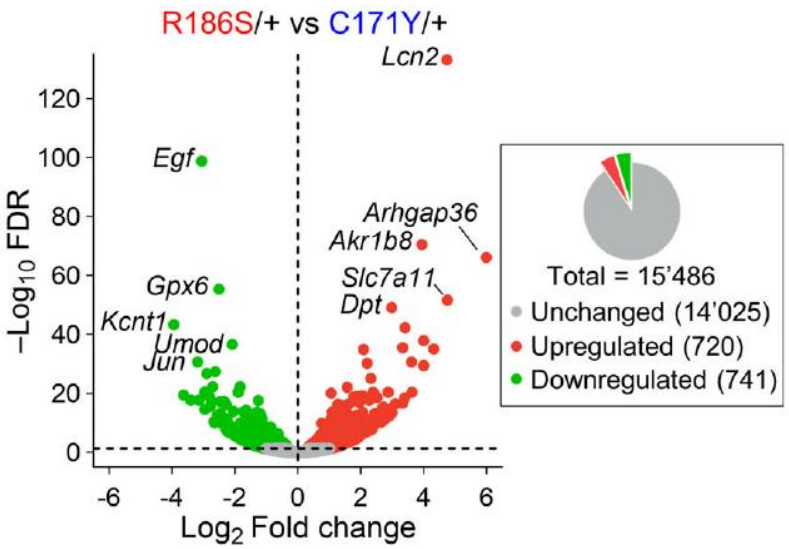


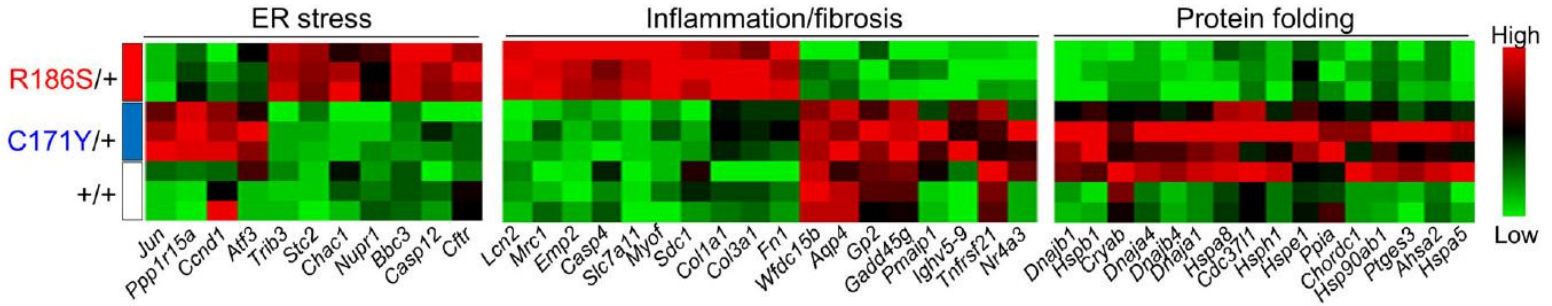


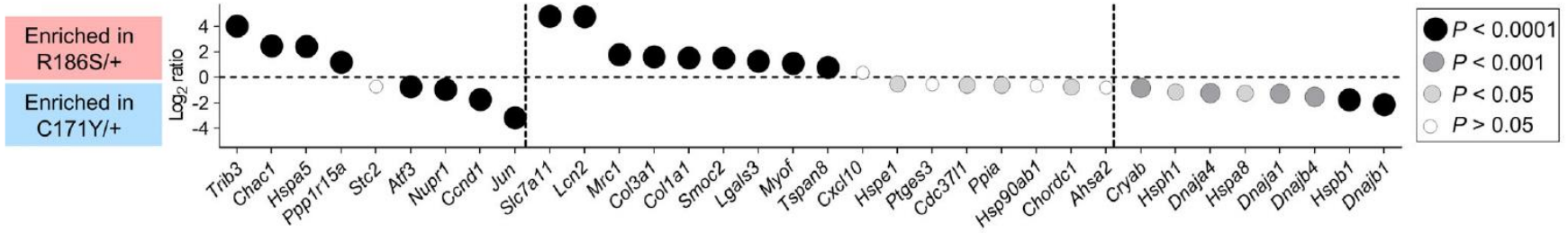
➢ *ER stress, inflammation and fibrosis correlate with the levels of uromodulin aggregates*

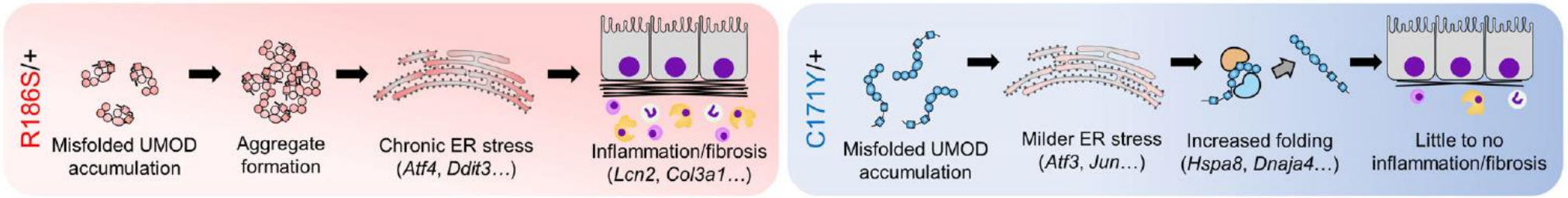
Schiano, et al. *EMBO Mol Med* 2023

Distinct Pathways activated in *Umod* KI Kidneys





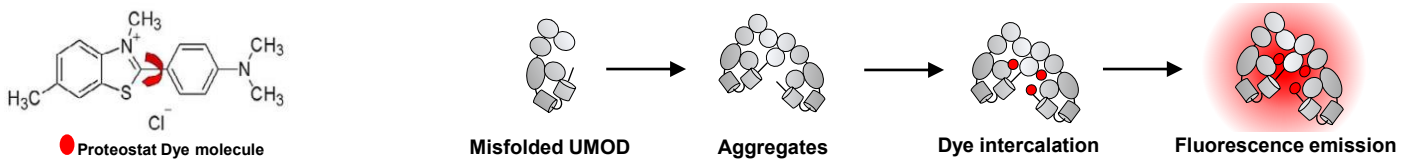


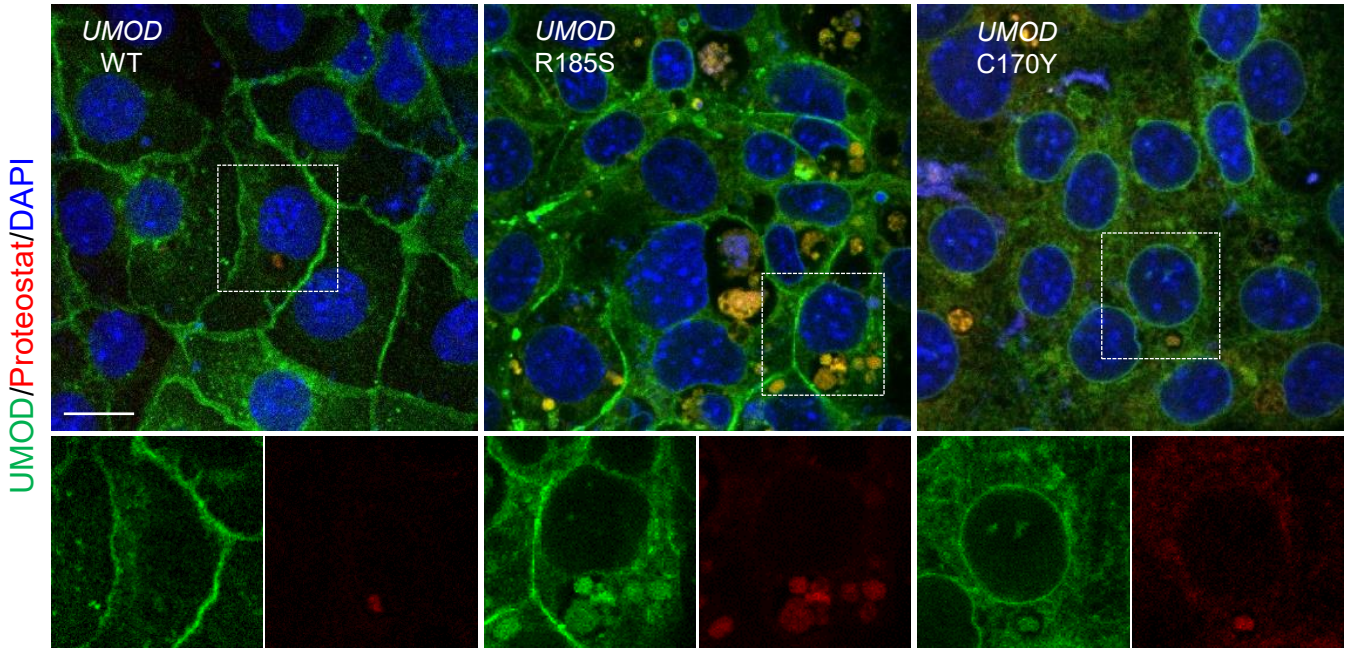


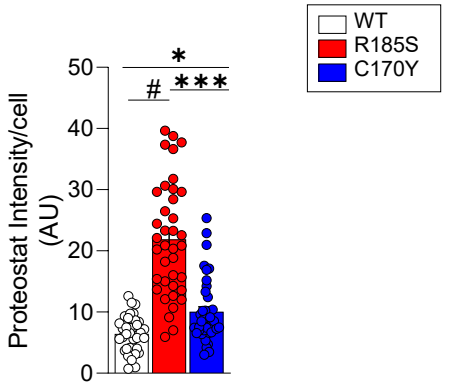
- *Umod*$^{R186S/+}$ kidneys: upregulation of chronic ER stress, inflammation and fibrosis
- *Umod*$^{C171Y/+}$ kidneys: milder ER stress response, induction of protein folding genes

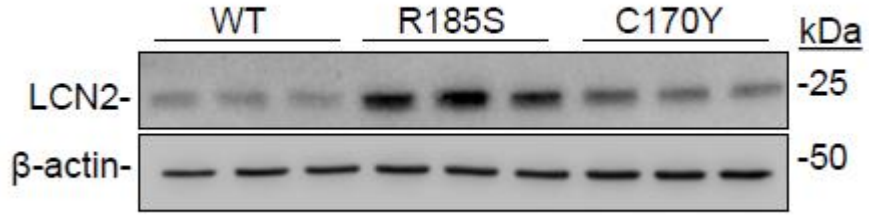
Schiano, et al. *EMBO Mol Med* 2023

Uromodulin Aggregates and ER Stress in mIMCD Cells





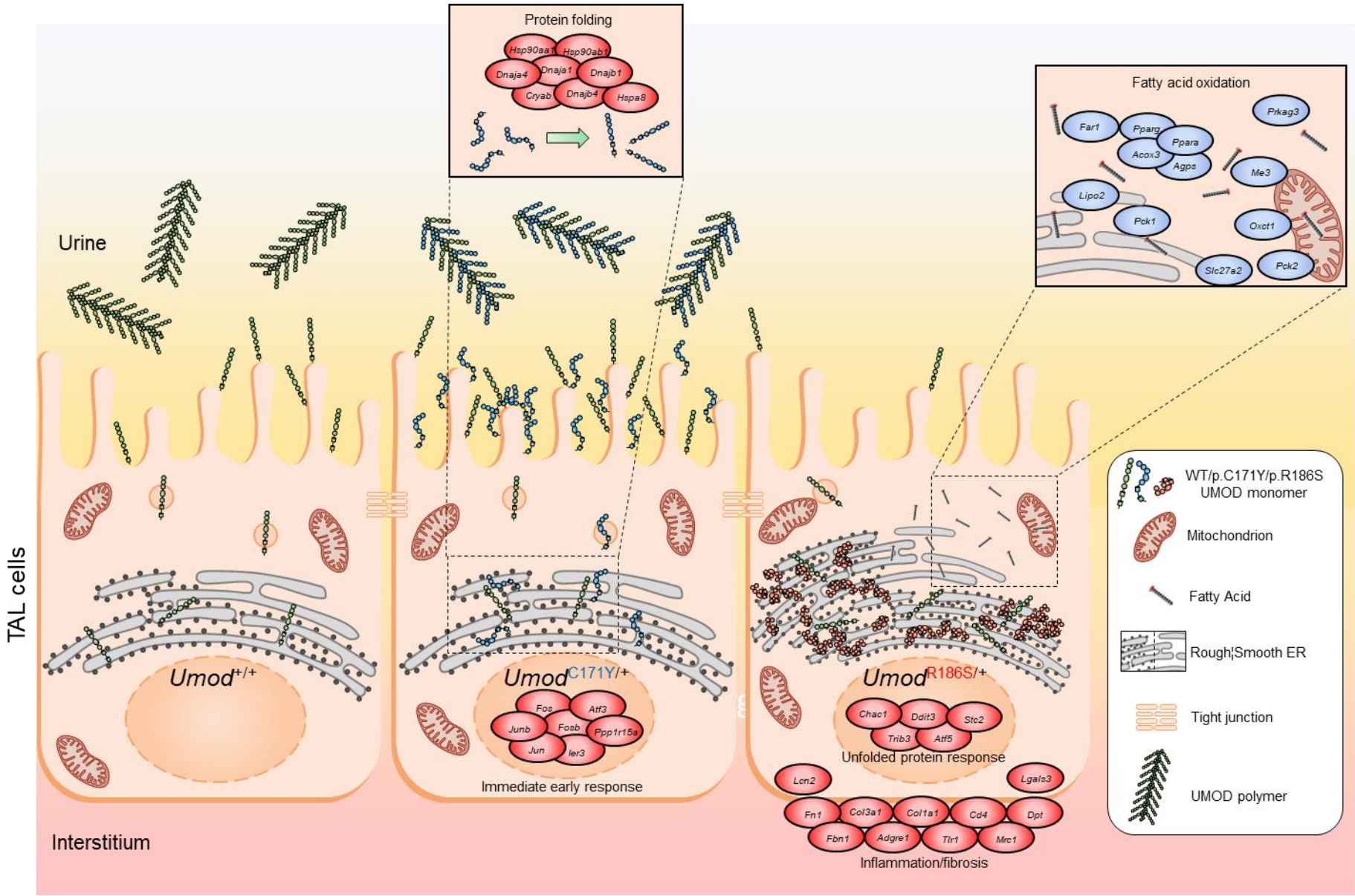




- Mutant uromodulin is detected in Proteostat⁺ structures
- A stronger Proteostat signal is observed in *UMOD* R185S compared to the other cell lines

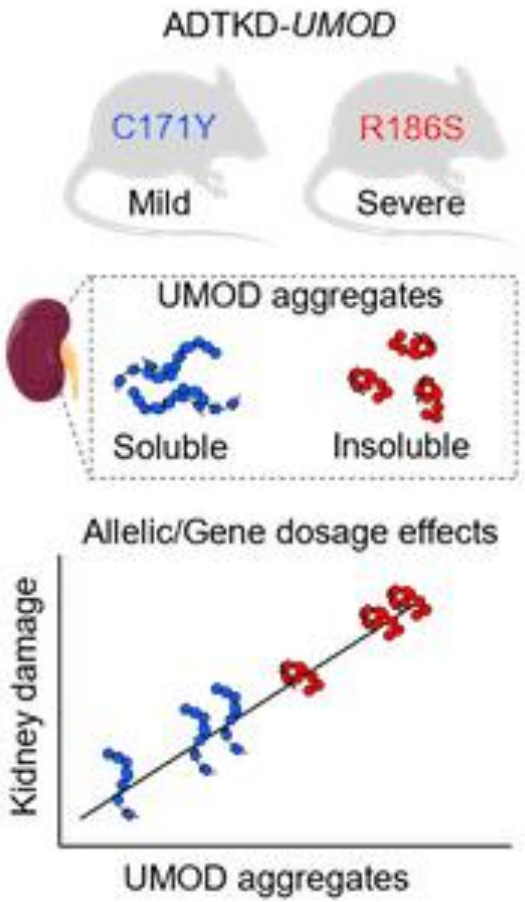
Schiano, Lake, Mariniello et al. *EMBO Mol Med* 2023

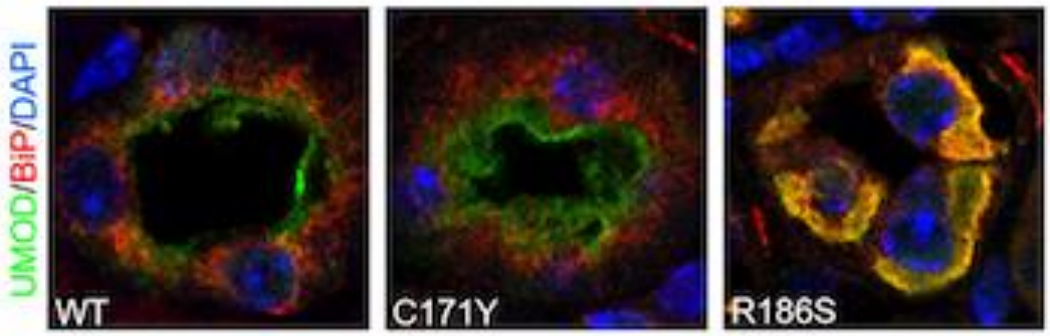
Mechanisms of Disease and Allelic Effects in ADTKD-*UMOD*

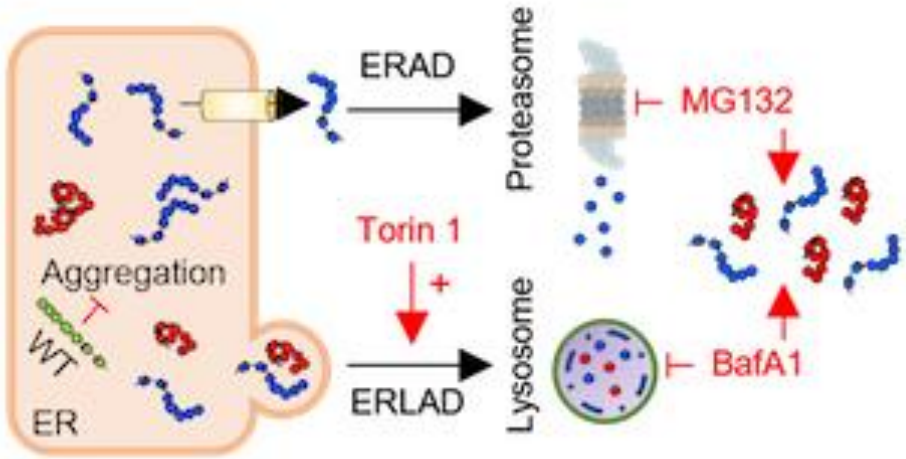


Proteinopathies: Not Restricted to Neurodegenerative Diseases

EMBO Molecular Medicine
EMBOpress
CURRENT ISSUE ABOU
Article | 26 October 2023 |

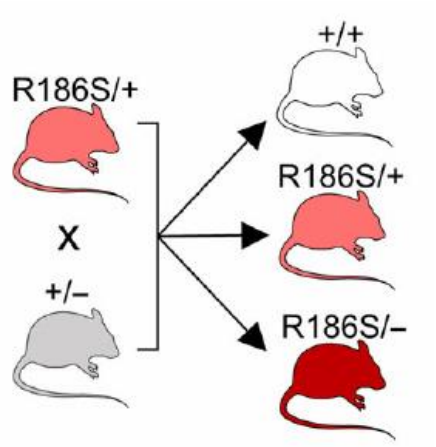


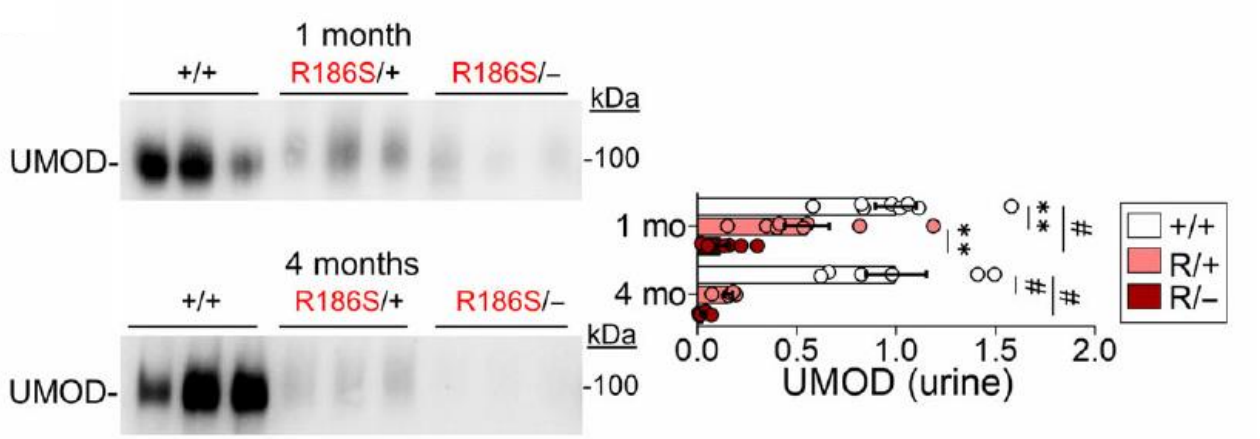


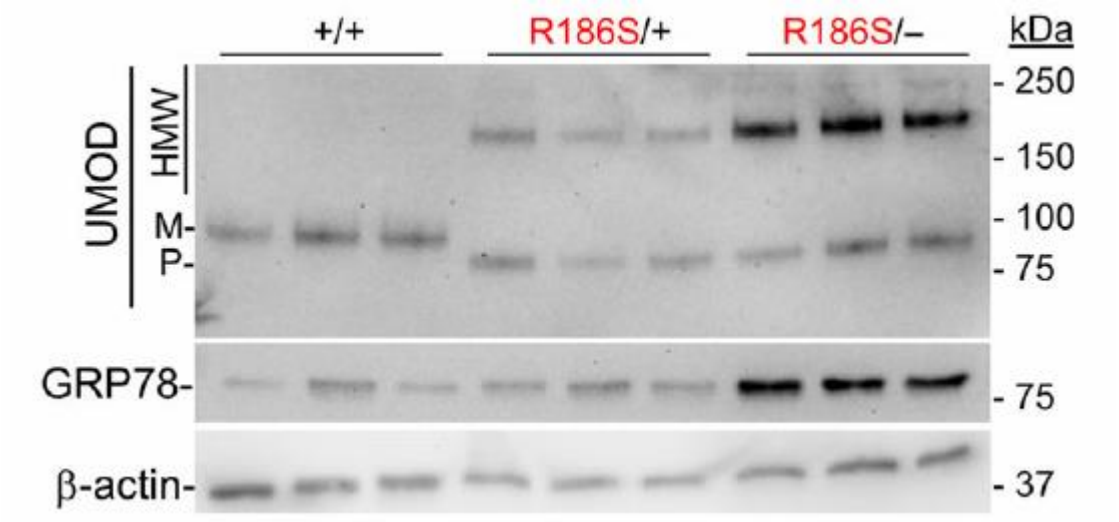


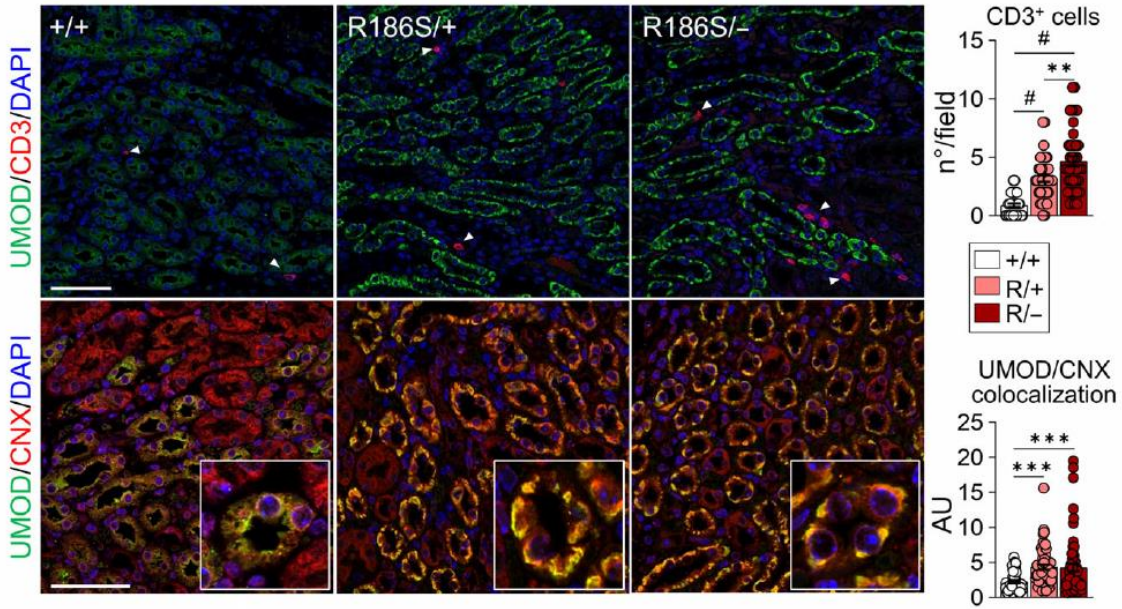
Schiano et al. *EMBO Mol Med* 2023

Deletion of Wild-type Uromodulin Increases Mutant Uromodulin Aggregation









Studies on Huntington disease (HD), also characterized by a toxic gain of function, reported a similar protective role of wild-type huntingtin (Htt) protein in the disease: the absence of wild-type protein in HD mutant mouse and Drosophila models of Htt toxicity leads to a more severe phenotype (Van Raamsdonk et al, 2005; Zhang et al, 2009). The protective role of the wild-type allele may be to facilitate the trafficking of mutant protein to the plasma membrane or, alternatively, to balance the propensity of mutant uromodulin to form aggregates.

The Journal of Neuroscience, April 20, 2005 • 25(16):4169–4180 • 4169

Neurobiology of Disease

Cognitive Dysfunction Precedes Neuropathology and Motor Abnormalities in the YAC128 Mouse Model of Huntington's Disease

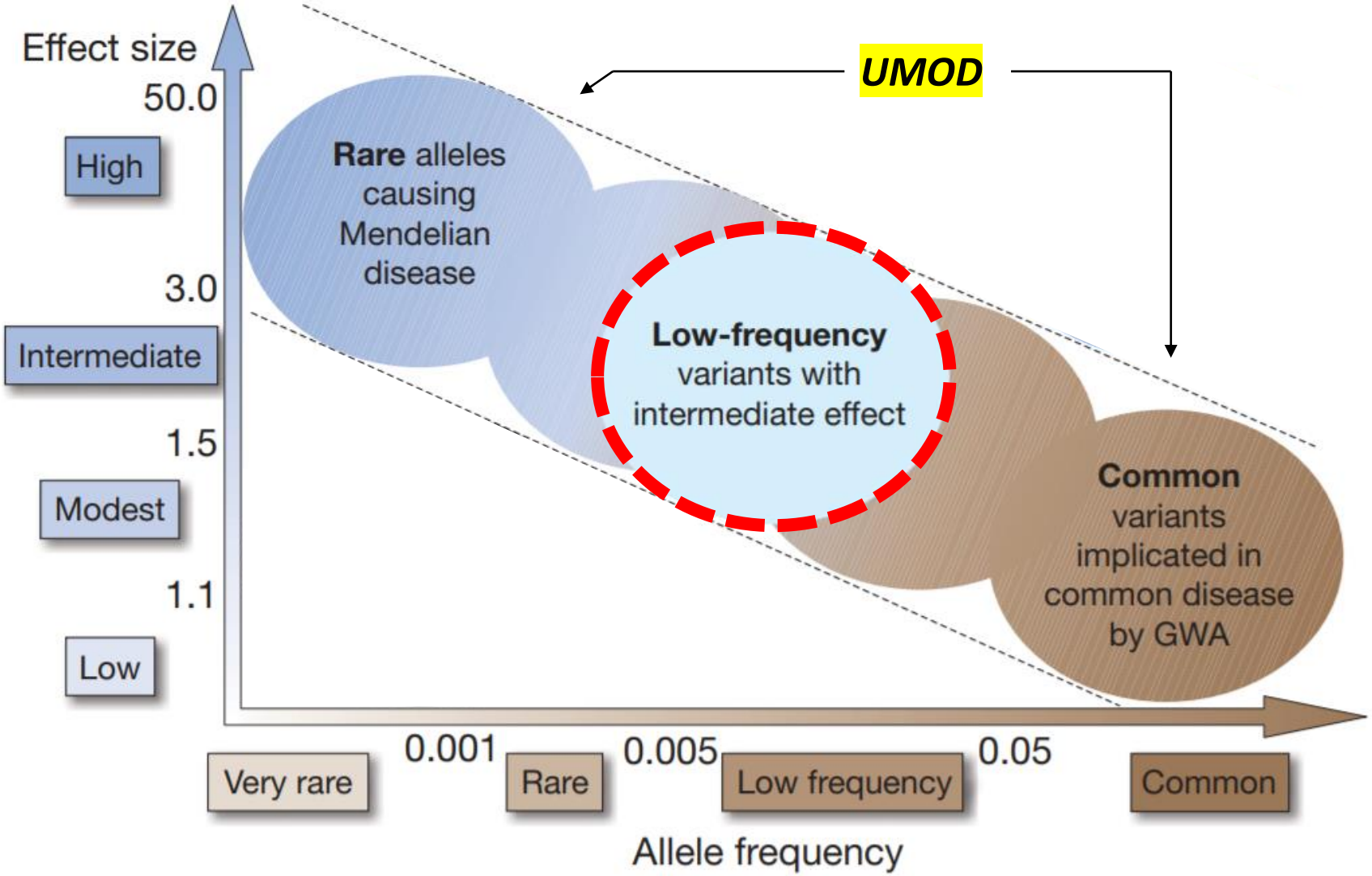
Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder caused by an abnormal expansion of a polyglutamine (polyQ) tract at the N-terminus of a large cytoplasmic protein, huntingtin (Htt). The polyQ tract contains between 6 and 35 repeats in the wild-type Htt protein, whereas it is expanded to beyond 36 repeats in HD. Numerous studies have demonstrated that mutant Htt containing an expanded polyQ tract is toxic to neurons

Disease Models & Mechanisms 2, 247-266 (2009) doi:10.1242/dmm.000653

RESEARCH ARTICLE

Inactivation of Drosophila Huntingtin affects long-term adult functioning and the pathogenesis of a Huntington's disease model

The Spectrum of *UMOD*-associated Kidney Diseases



Adapted from Manolio TA et al. Nature, 2009

RESEARCH ARTICLE | MEDICAL SCIENCES |

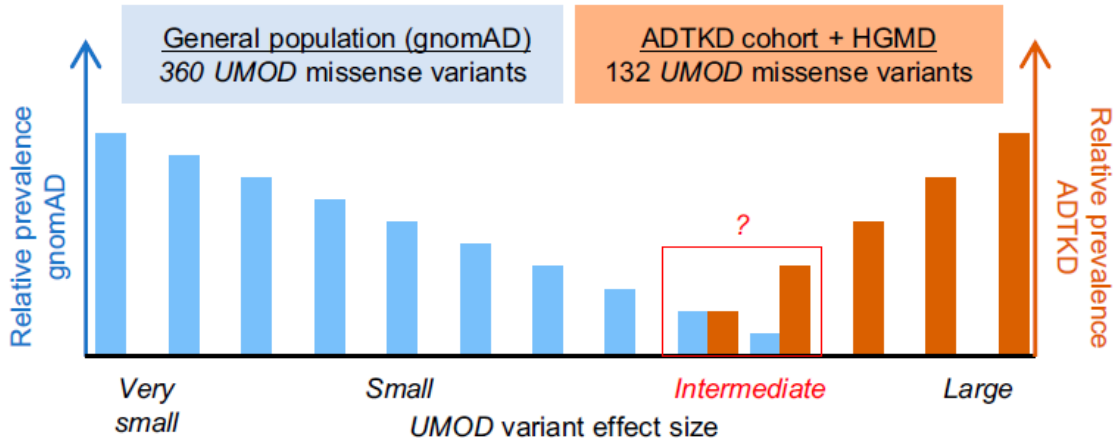
PNAS

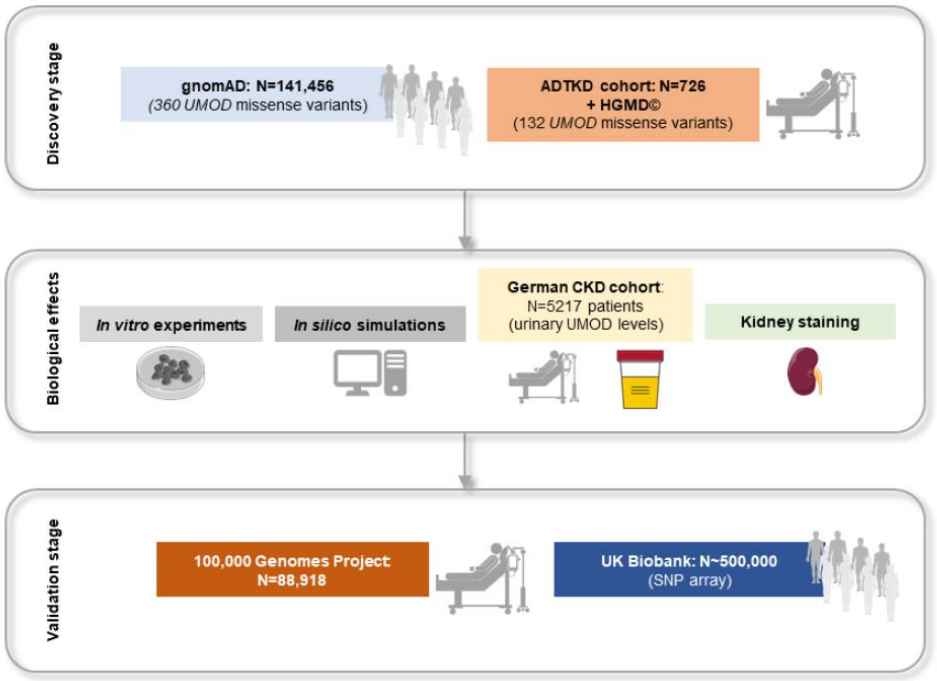
An intermediate-effect size variant in *UMOD* confers risk for chronic kidney disease

Eric Olinger, Céline Schaeffer, Kendrah Kidd, +21, and Olivier Devuyst Authors Info & Affiliations

Edited by Martin Pollak, Beth Israel Deaconess Medical Center, Brookline, MA; received September 3, 2021; accepted May 4, 2022

August 10, 2022 | 119 (33) e2114734119 | https://doi.org/10.1073/pnas.2114734119



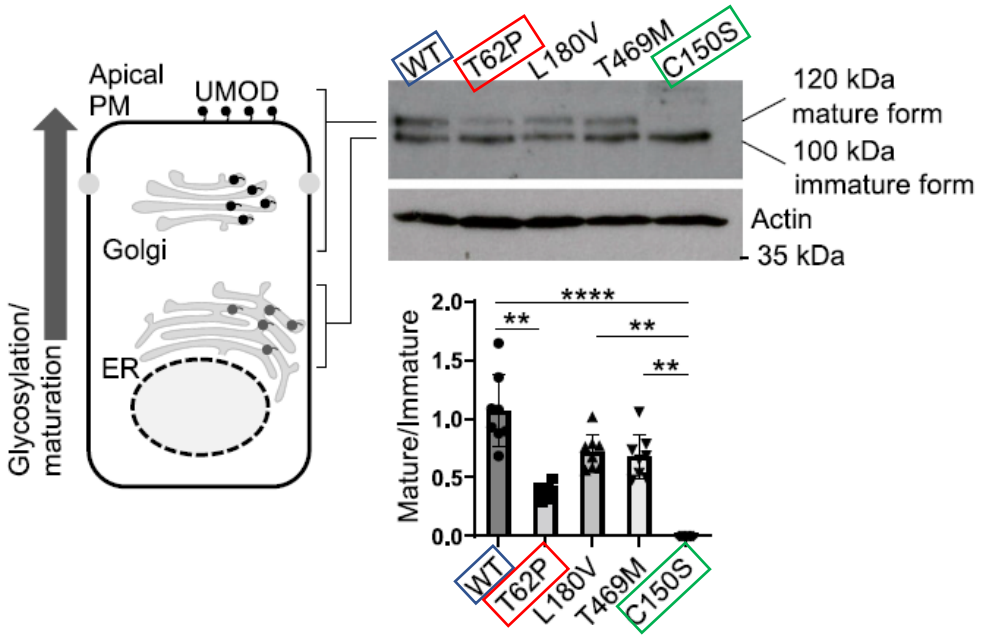


UMOD p.Thr62Pro confers 4-fold higher risk for kidney failure in UK Biobank

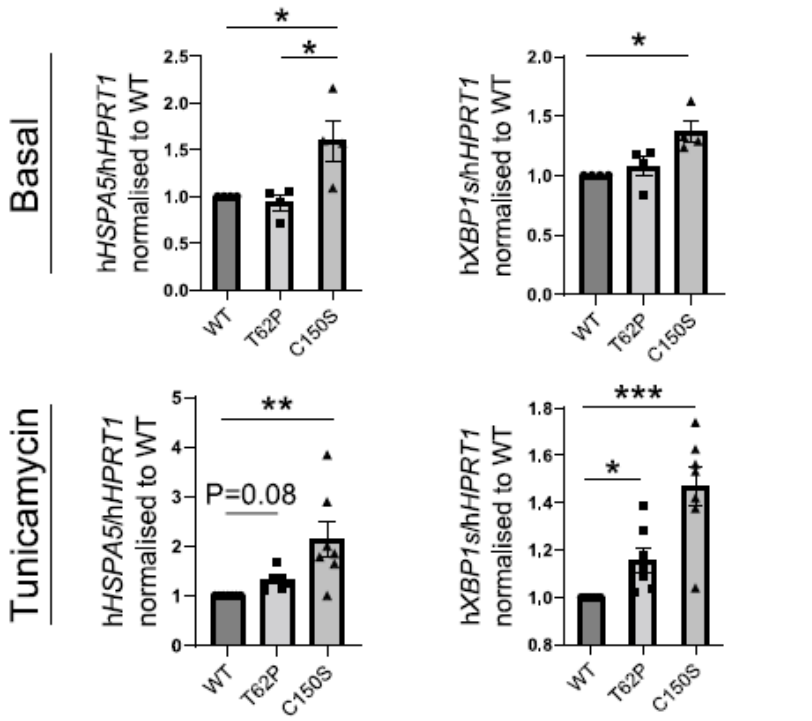
The 100,000 Genomes Project

biobank uk

UMOD p.Thr62Pro Shows an Intermediate Trafficking Defect & ER Stress



Western blot analysis of UMOD expression in HEK293 cells 6 h after transfection of the indicated UMOD isoforms. The graph represents the ratio of Golgi glycosylated form (mature) to ER glycosylated form (immature).



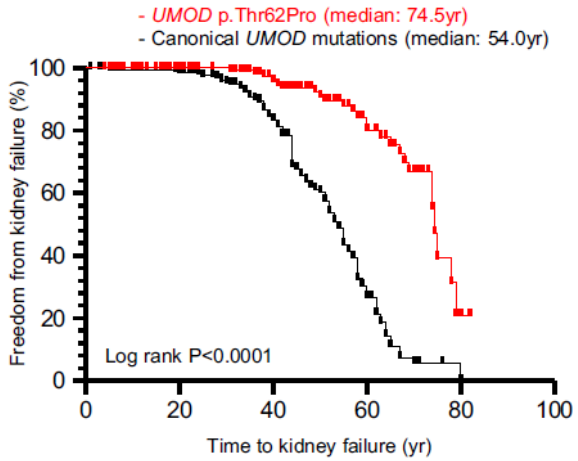
GRP78 (HSPA5) and spliced XBP1 (XBP1s) expression in HEK293 cells expressing indicated UMOD isoforms in the basal condition (Upper) or after 12 h with a low dose of tunicamycin.

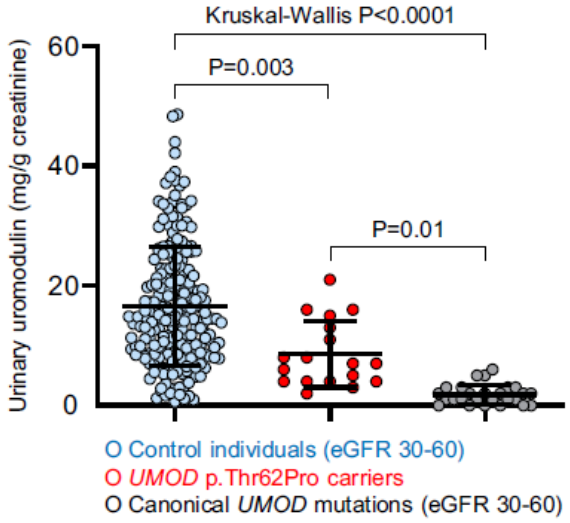
UMOD variant p.Thr62Pro shows an intermediate defect in processing from the ER to Golgi, and intermediate ER stress vs. wild type and a typical ADTKD mutant – under mild stress conditions (Tunicamycin).

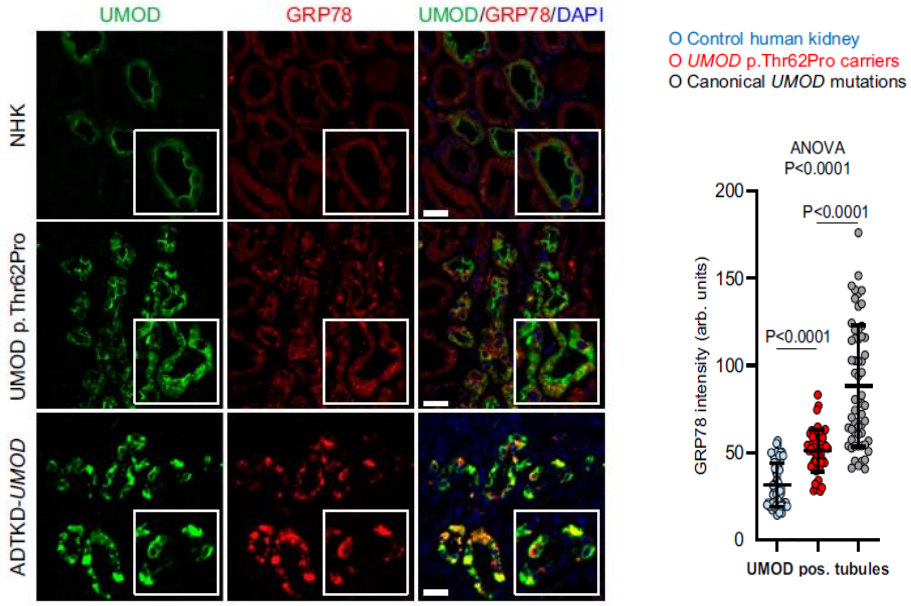
Milder Phenotype in *UMOD* p.Thr62Pro Carriers with Kidney Disease

T62P variant:

- In 20 families with ADTKD – no other genetic cause
- Incomplete penetrance/segregation
- MAF 4% in ADTKD (>100x in gnomAD)
- 157 carriers in CKD cohorts vs. 225 (canonical *UMOD* mutations)
- Intermediate disease progression – trafficking defect & ER stress

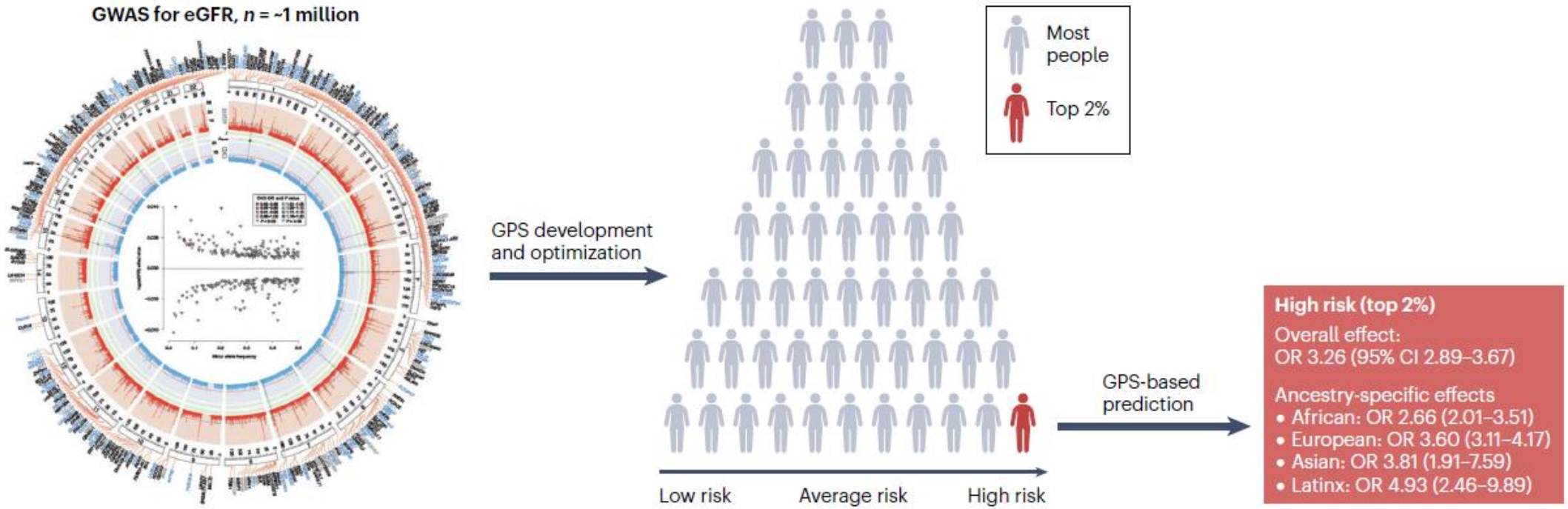




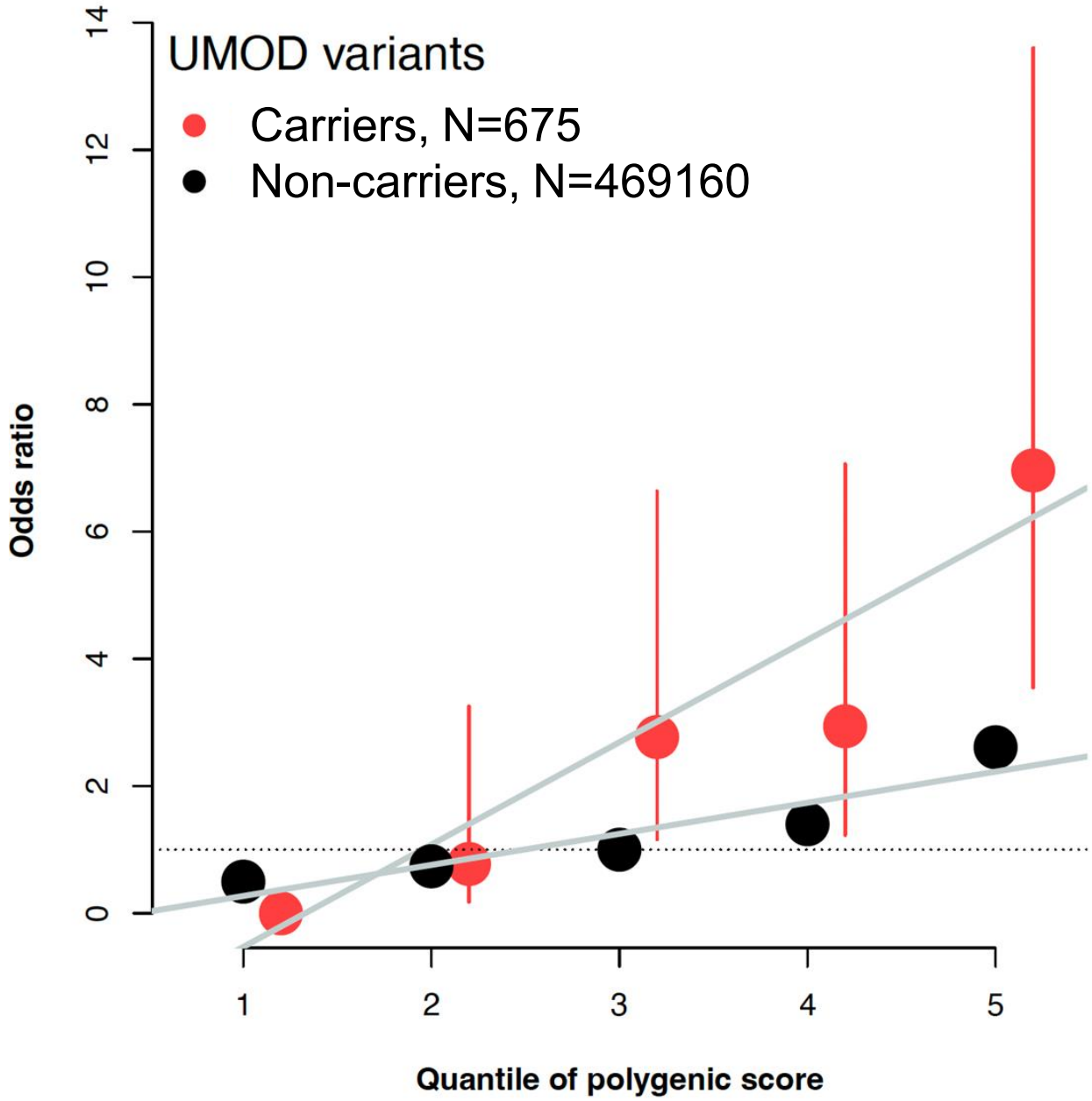


Polygenic scores and their applications in kidney disease

Atlas Khan & Krzysztof Kiryluk



Effect of p.Thr62Pro *UMOD* variant carrier in UKBB and CKD Polygenic Risk Score



Coll. A. Khan & K. Kiryluk

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

uk biobank

Acknowledgements

UZH, Zurich
S. Youhanna, H. Debaix, N. Nagele
E. Olinger, G. Schiano, J. Lake, M. Mariniello
B. Herzog, F. Verrey
B. Glaudemans, J. Loffing
A. Yoshifuji, M. Harvent

San Raffaele Institute, Milan
L. Rampoldi, C. Schaeffer

ETH Zurich
R. Glockshuber, M. Aebi
M. Pilhofer, J.S. Stanisich

Wake Forest, Winston Salem, NC
A. Bleier, K. Kidd, S. Kmoch

UCLouvain, Brussels
Y. Pirson, E. Goffin, V. Gillion

Lausanne – Bern - Zürich
M. Bochud, COLAUS & SKIPOGH
D. Fuster, O. Bonny, A. Kistler

MRC- University of Edinburgh
N. Hastie, C. Hayward

Columbia University
A. Khan, K. Kiryluk

NIH, NHLBI
C. Fox, M. Olden

Indiana University
D.S. Hains

German CKD Cohort
K-U. Eckardt, A. Köttgen, M. Wiesener

University Ferrara
G. Barbujani

Newcastle University
J. A. Sayer