Autosomal Dominant Tubulointerstitial Kidney Diseases : ADTKD

B Knebelmann MD, PhD
Department of Adult Nephrology
Reference Center for Hereditary Kidney Diseases (MARHEA)
ERKNet Center
Necker Hospital, Paris Cité University

ANJH-20-05-2026

Hereditary TIN: not all are ADTKD

Hereditary Chronic Tubulointerstitial Nephritis

- **-Chronic Tubulointerstitial Nephritis**
  - -Nephronophthisis (Autosomal recessive)
  - -Autosomal Dominant Tubulointerstitial Diseases
- **-Crystalline Nephropathies** (Autosomal recessive)
  - -Cystinosis
  - -Primary hyperoxaluria
  - -2,8 dihydroadeninuria
- **-Tubular Transport Nephropathies**
  - -Dent's disease and Lowe's oculo-cerebral-renal syndrome (X-linked)
  - -Bartter's syndrome
- **-Miscellaneous**
  - -Systemic karyomegaly (FAN1; AR; liver and lung disease)
  - -Methylmalonic aciduria
  - -Mitochondrial cytopathies

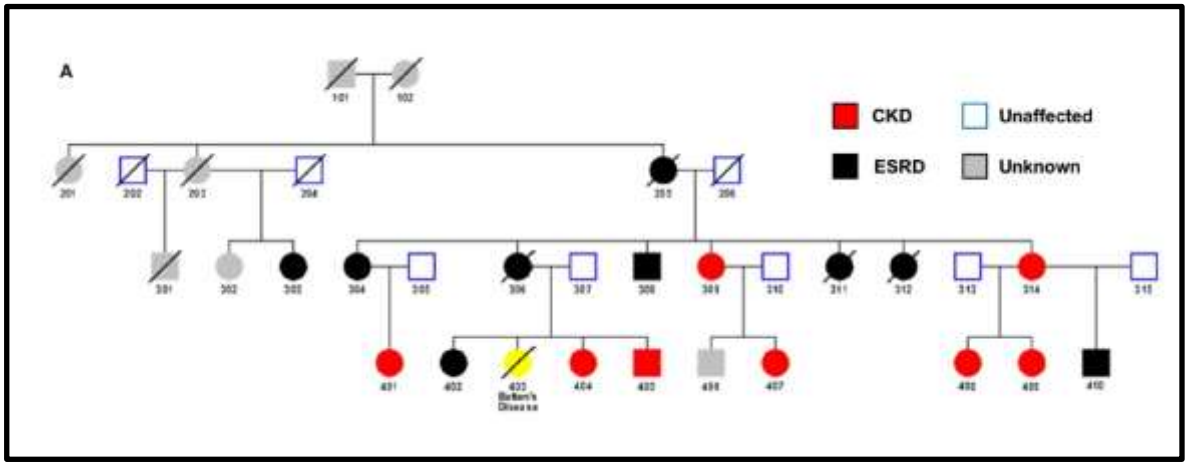
PLOS | GENETICS

RESEARCH ARTICLE

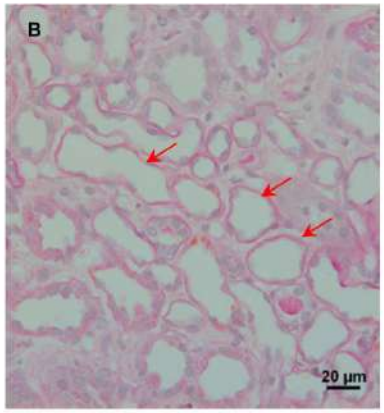
Mutations in mitochondrial DNA causing tubulointerstitial kidney disease

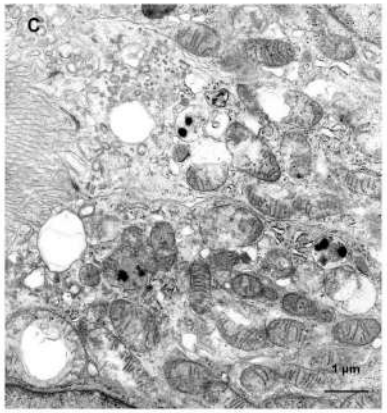
Thomas M. Connor[1*], Simon Hoer[2*], Andrew Mallett[3], Daniel P. Gale[4], Aurora Gomez-Duran[5], Viktor Posse[6], Robin Antrobus[3], Pablo Moreno[7], Marco Sciacovelli[7], Christian Frezza[7], Jennifer Duff[8], Neil S. Sheerin[8], John A. Sayer[9], Margaret Ashcroft[10], Michael S. Wiesener[11], Gavin Hudson[6], Claes M. Gustafsson[6], Patrick F. Chinnery[5], Patrick H. Maxwell[12]*

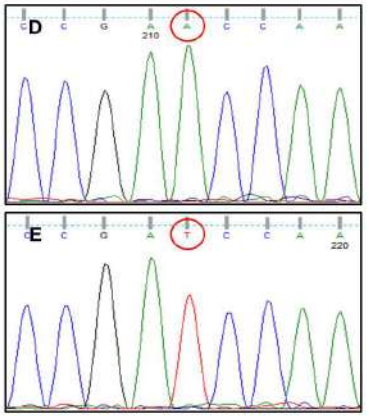
MI-TKD



Maternel Inheritance ++







homoplasmic m.547A>T Substitution (non coding region)

Fig 1. Pedigree with maternally inherited renal disease and m.547A>T substitution. (A) Pedigree of family showing individuals affected

In front of a TKD, when known causes have been excluded, Suspect

ADTKD

- Third cause of genetic kidney disease (after ADPKD and COLIV)
- 5% of monogenic kidney diseases

Estimated prevalence among CKD/ESRD cohorts:

- **0.13%** (7/ 5,217) extrapolated to the total GCKD cohort from a prevalence of 2,6% (7/271) of the selected (nephroangiosclerosis, uCKD, hereditary ckd, IgA!) sequenced cohort (Popp EJHG 2022)

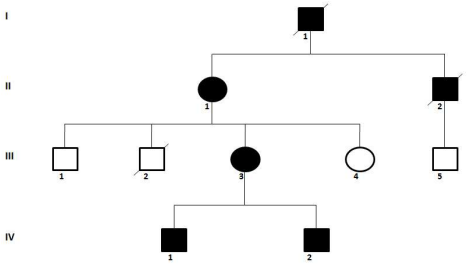
- **0.54%** in the complete ESKD cohort of Ireland

- **0,39%** (13/3000) CKD + ESKD cohorts (Groopman et al nejm 2019)

- **1%** of CKD and 2 % of ESKD (UK) (Gast BMC Nephrol 2018)

Popp et al, European Journal of Human Genetics (2022); Groopman E, nejm 2019

Hereditary TIN:
An old confusing Terminology simplified thanks to molecular genetics



Cysts, small kidneys ->	« Adult » Nephronophtisis	NPH
Cysts, medullary? →	Medullary Cystic Kidney Disease	MCKD (1,2)
Gout->	Familial Juvenile Hyperuricemic Nephropathy	FJHN (1-3)

Autosomal Dominant Tubulointersitial Kidney Diseases: ADTKD

Eckart KU et al, KDIGO 2015, Kidney Int

Table 2 | Usual clinical findings in patients with ADTKD

- Autosomal dominant inheritance
- Progressive loss of kidney function
- Bland urinary sediment
- Absent-to-mild albuminuria/proteinuria
- No severe hypertension during early stages
- No drug exposure potentially causing tubulointerstitial nephritis
- Normal or small-sized kidneys on ultrasound
- Nocturia or enuresis in children (owing to loss of renal concentration ability)

Abbreviation: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease.

Eckart KU et al, KDIGO 2015, Kidney Int

Autosomal Dominant Inheritance not always obvious…

- De novo mutations : lack of Familial history

  # 40% HNF1b; 10% UMOD ; rarely MUC1

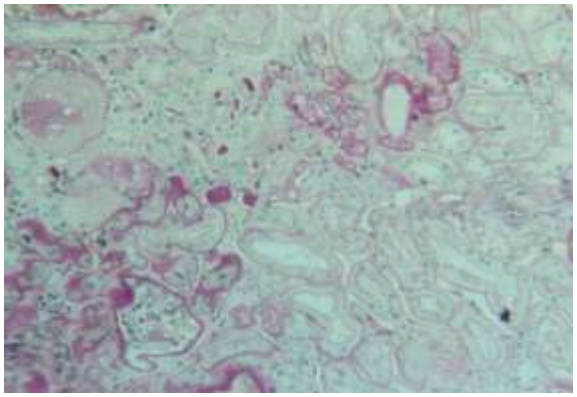
- Late /unknown phenotype in family members

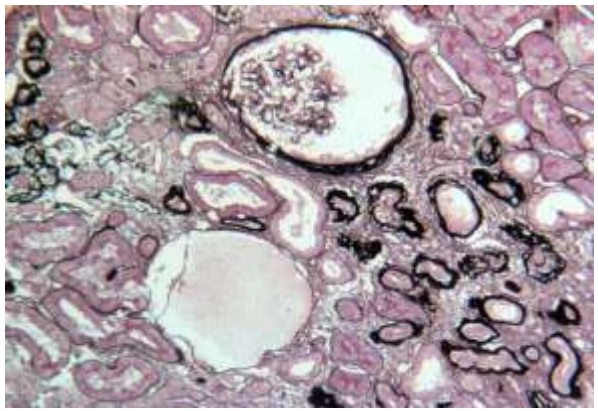
- Incomplete Penetrance (HNF1b>>UMOD/MUC1)

Table 3 | Usual findings on renal histology in patients with ADTKD : Often Non Specific

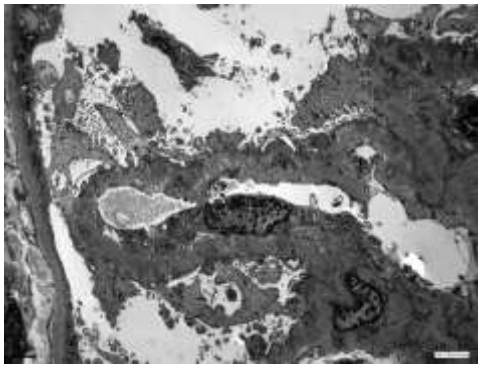
- Interstitial fibrosis (+/- inflamatory Cells)
- Tubular atrophy
- Thickening and lamellation of tubular basement membranes
- Possibly tubular dilatation (microcysts)
- Negative immunofluorescence for complement and immunoglobulins

◆ Non Specific Vascular lesions:
- « nephroangiosclerosis » was the main diagnosis in several cases….





Rarely Glomerular cyst



EM: look at ER

LH Noel, Necker Hospital

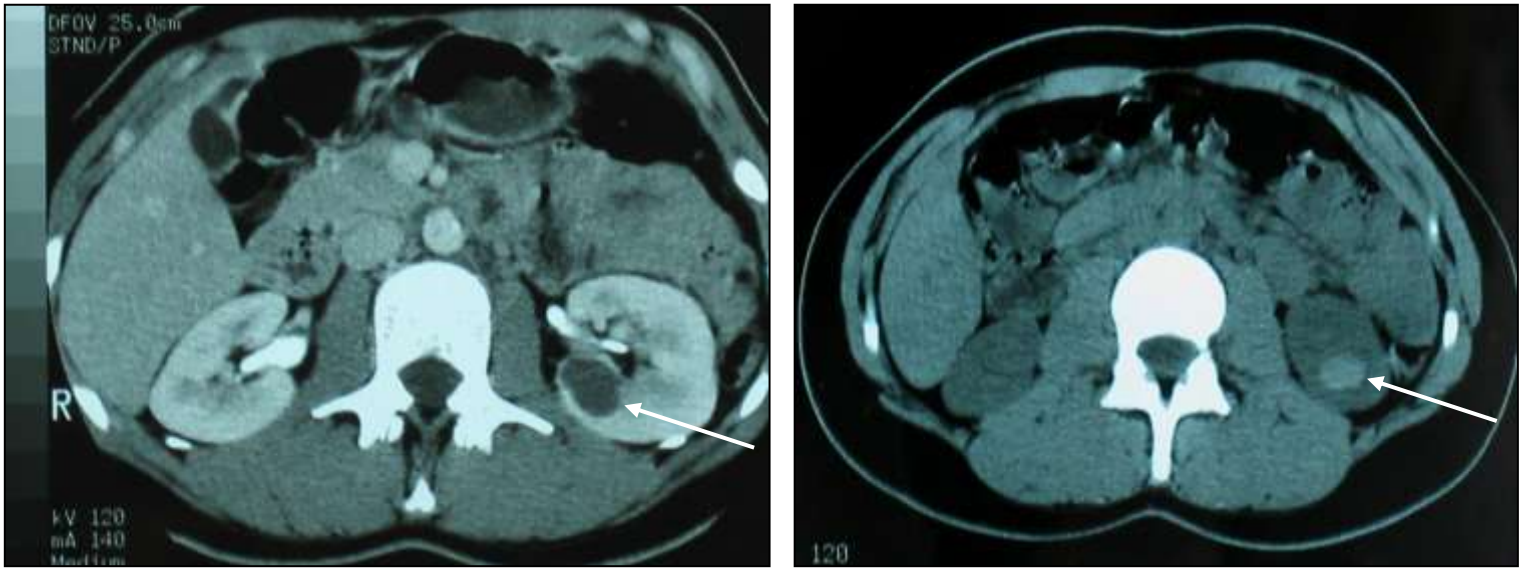
Eckart KU et al, KDIGO 2015, Kidney Int

Cysts can be present in ADTKD but only in 20-40%

- When present they are very rarely only medullary cysts

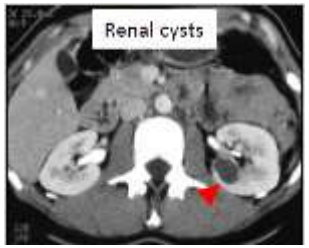
Medullary Cystic Kidney Disese (MCKD)= misleading name!

- Normal sized Kidneys (or small)



Early gout should alert!

- 29yr female referred for CKD
  - Gout at 18yrs
- Normal BP
- 2 kidneys cysts



High SUA : 505 umol/L

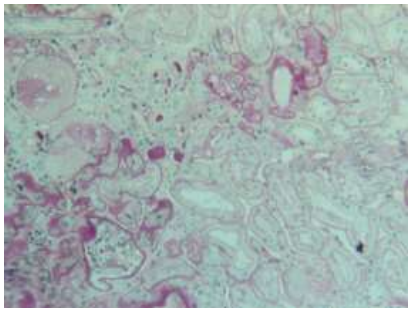
Low FEUA: 4,5%

Créatinine 102 µmol/l; eGFR = 59 ml/mn

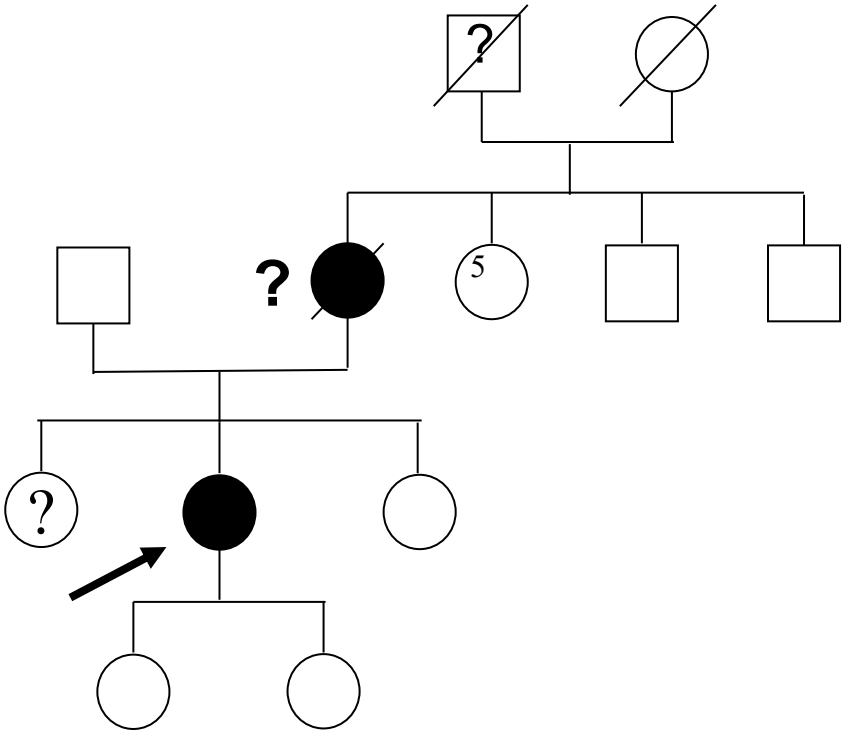
UPCR 0.27 g/g

No Hematuria , leucocyturia

KB: non specific TKD



Family History



Mother:

ESRD at 48 yrs

unknown cause

No gout

Molecular genetics:

Sanger sequencing of UMOD gene

→UMOD missense variant: Cys165Trp

- Heterozygote (AD)
- ACMG Class 5= pathogenic

Autosomal Dominant Tubulointerstitial Kidney Diseases ADTKD:

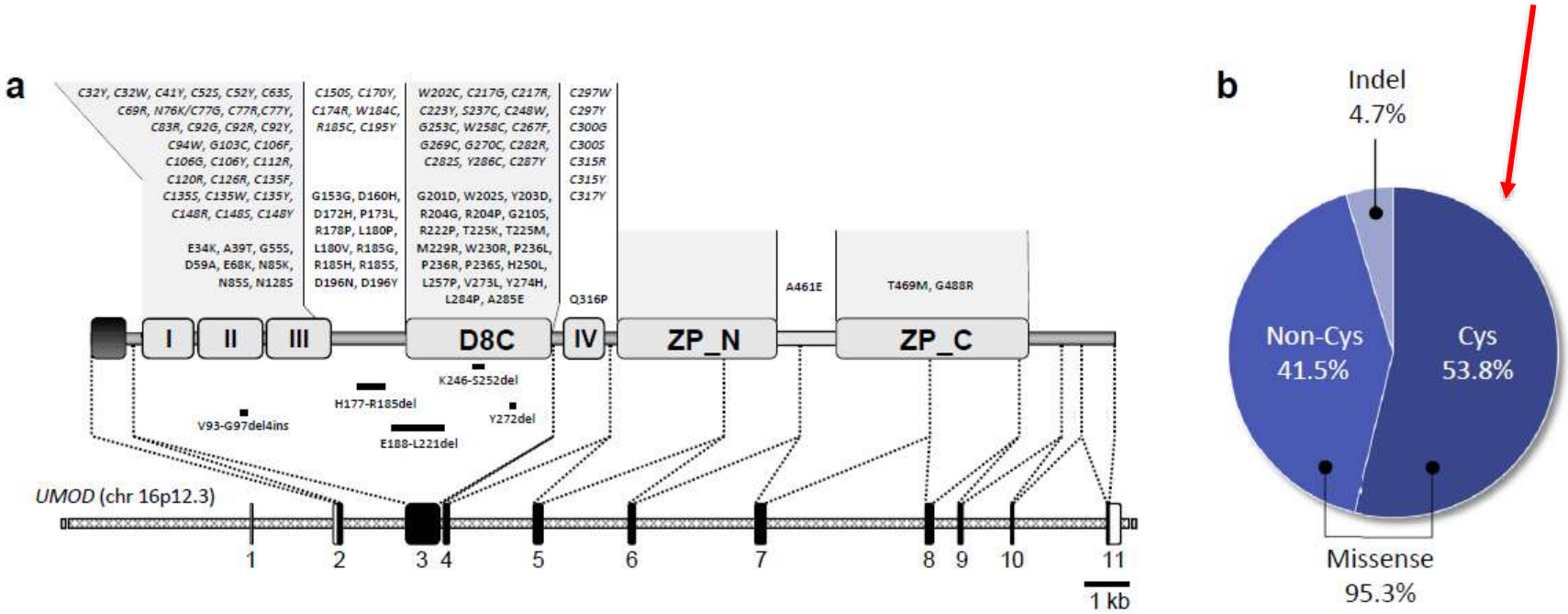
Gene-based Classification

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)
Not known; i.e., not otherwise specified (either not tested or genetic test without definitive result)	ADTKD—*NOS*	

Eckart KU et al, KDIGO 2015, Kidney Int

UMOD gene: Cystine missense mutations are the most frequent

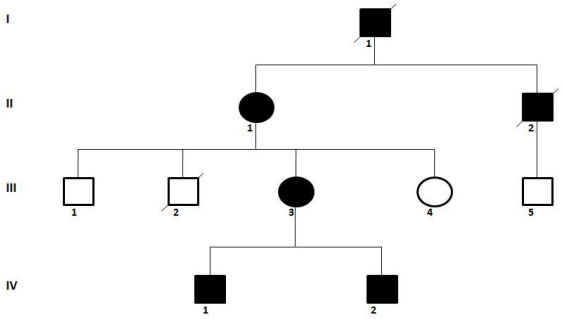


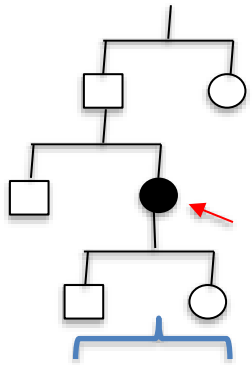
ADTKD-UMOD Phenotype

109 patients /45 families

(France and Belgium)

Positive Family History	No Family History
of gout and/or Renal disease 88%	(de novo mutation) 12%

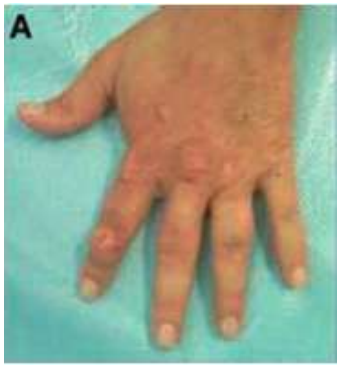




50% risk

Bollée et al CJASN 2011

ADTKD-UMOD:
Early Gout is not constant

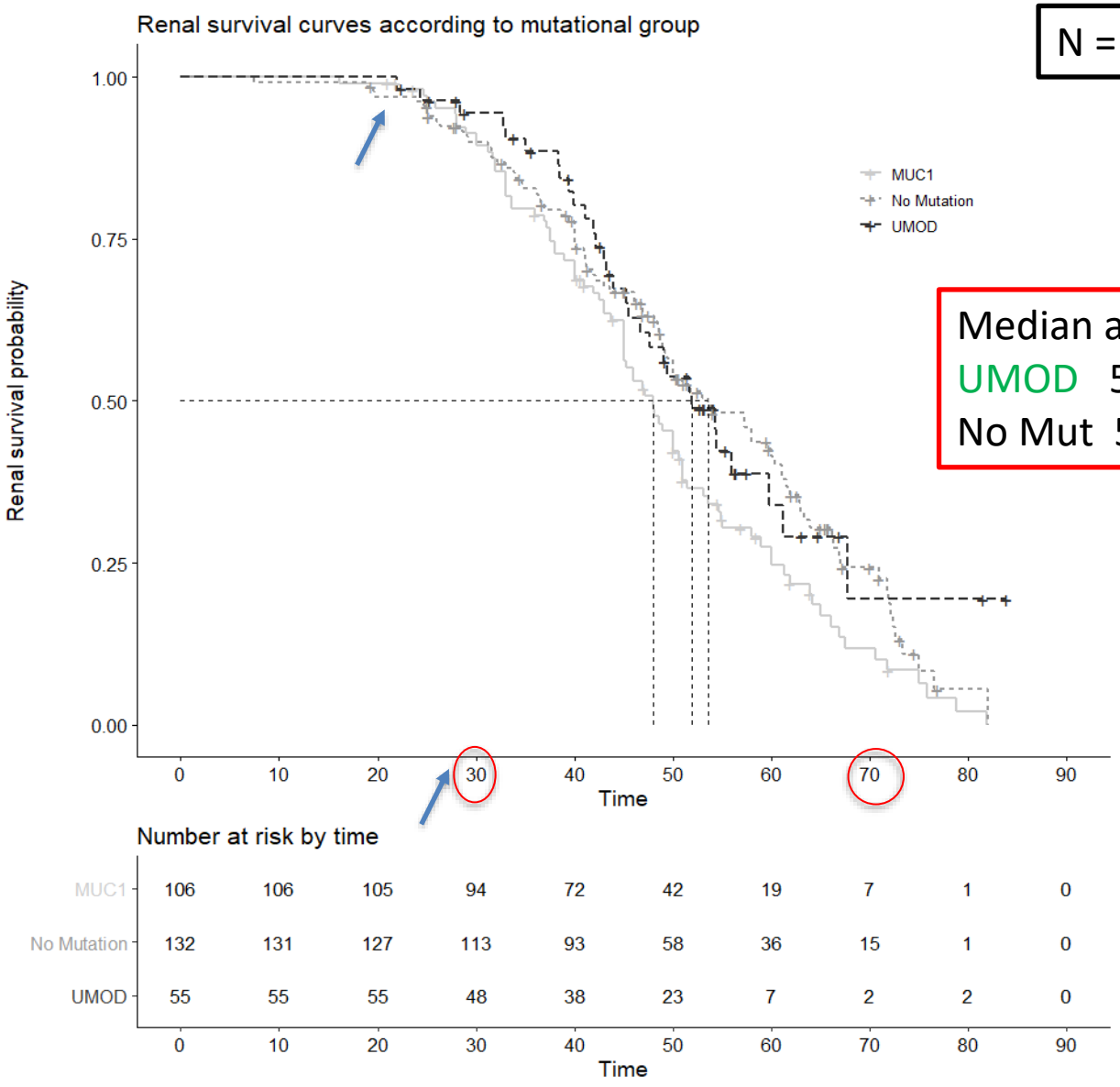


- history of gout in men 75%
- history of gout in women 50%
Total 65%

- age at first gout episode 21yrs (IQR 16-31)
Nearly **always Before 40yrs**
Non specific if GFR <30 +++

Bollée et al CJASN 2011

Renal Survival Curves in ADTKD-UMOD

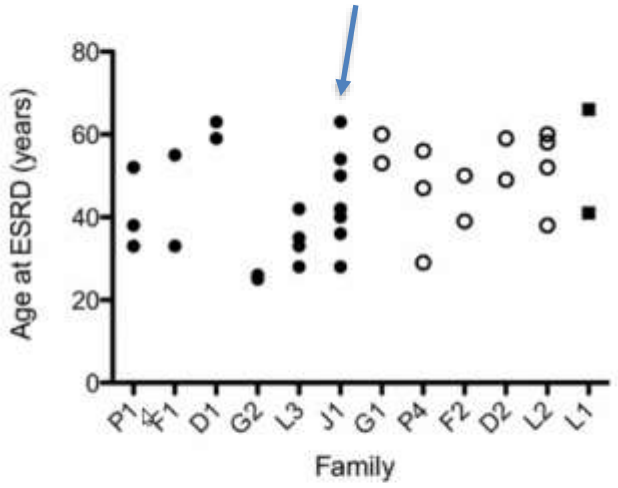


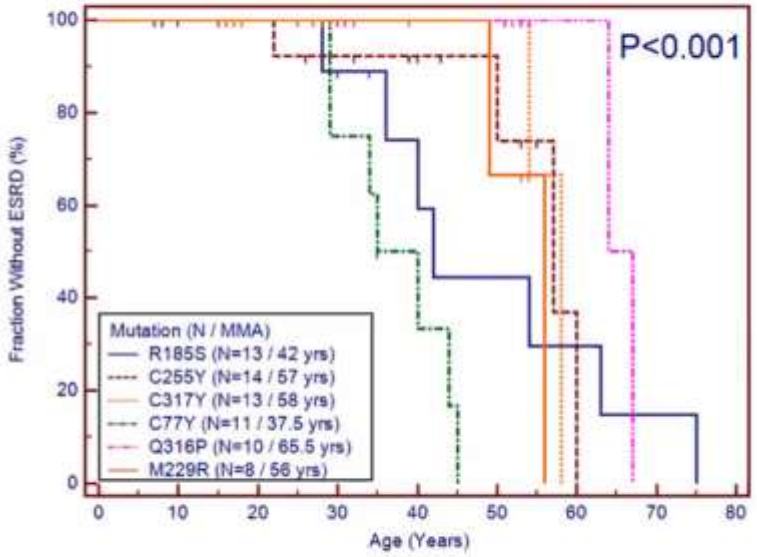
N = 204 ESRD pts

Median age at ESRD:
UMOD 52 yrs
No Mut 53.7 yrs

French cohort

Variable kidney disease progression in ADTKD-*UMOD*





Mutation-independent factors

Mutation-dependent factors

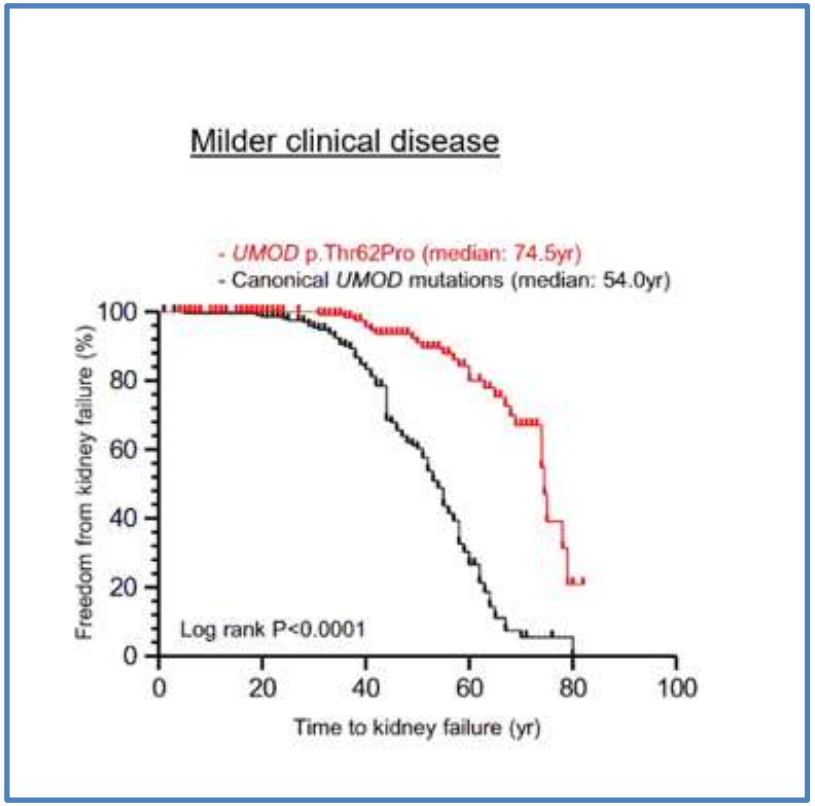
Bollée G et al. CJASN, 2011

Moskowitz JL et al. CJASN, 2013

Mutation-dependent Factors

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES OPEN ACCESS

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

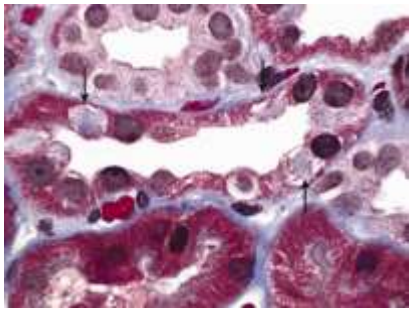


UMOD p.T62P: "non-mendelian" - clinical significance to be determined!

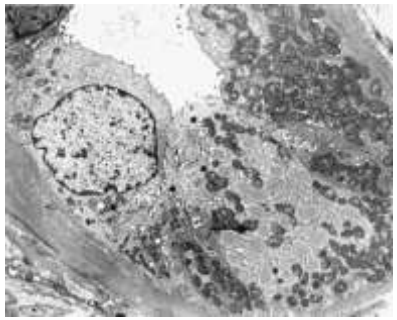
- Approx. 1/1,000 individuals of European ancestry
- Low penetrance – risk factor (kidney failure in the 100,000 Genomes Project: OR=3.99 [1.84 to 8.98] and the UK Biobank: OR=4.12 [1.32 to 12.85]

Ollinger E et al, PNAS, 2022

Renal biopsy findings in ADTKD-UMOD :
Classical histology often non specific



Focal intracytoplasmic inclusions in tubular cell *Nasr, Kidney Int, 2008*



EM: accumulation of material in the ER

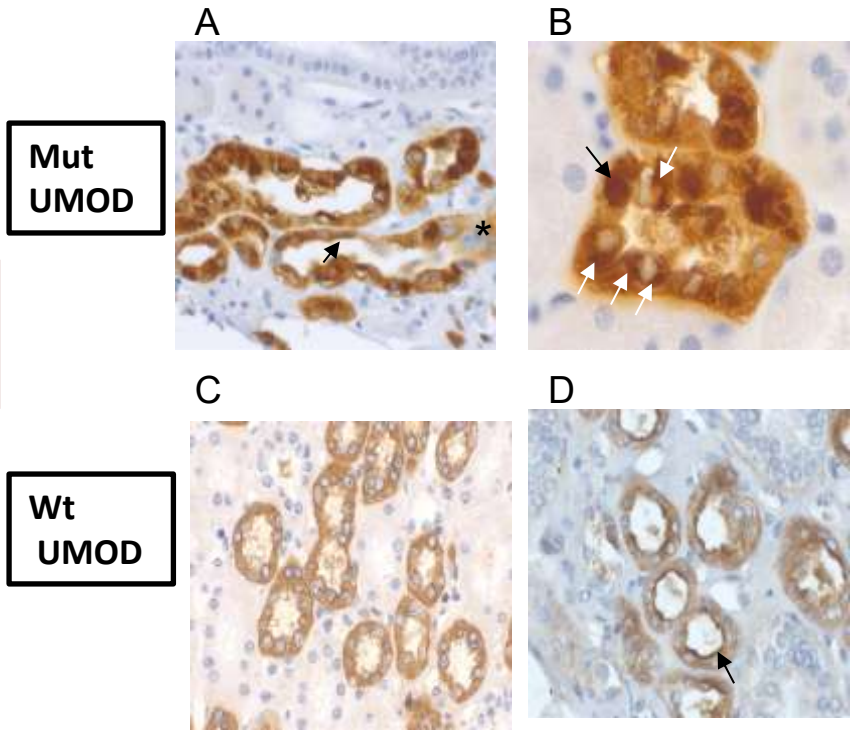
Renal biopsy findings in ADTKD-UMOD :

AJKD
Case Report

Endoplasmic Reticulum Stress in *UMOD*-Related Kidney Disease: A Human Pathologic Study

Julien Adam, MD,[1] Guillaume Bollée, MD, PhD,[2] Sophie Fougeray, PhD,[3] Laure-Hélène Noël, MD,[3] Corinne Antignac, MD, PhD,[4,5,6] Bertrand Knebelman, MD, PhD,[2] and Nicolas Pallet, MD, PhD[3,7]

Intracytoplasmic/ER retention of mutant Uromodulin

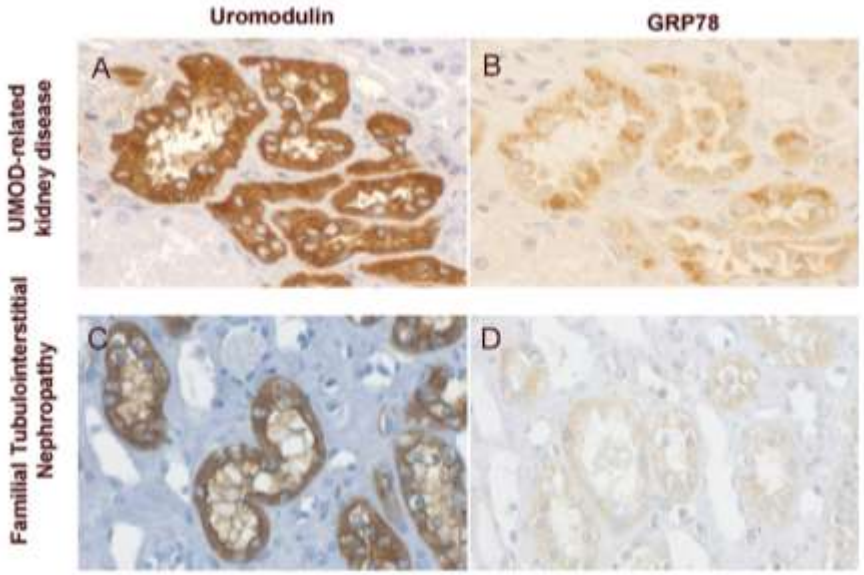


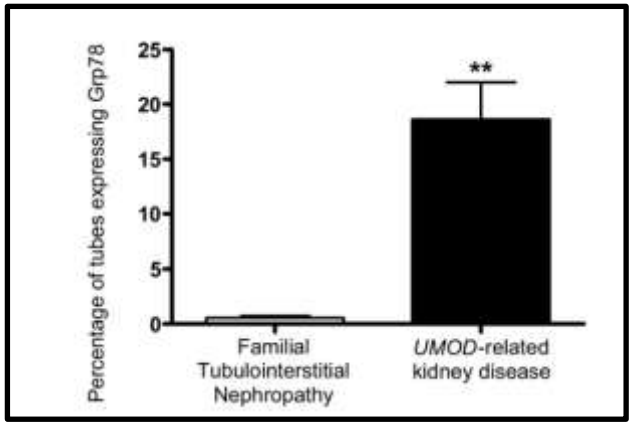
Dahan K et al JASN; Adam J et al, AJKD, 2011

AJKD
Case Report

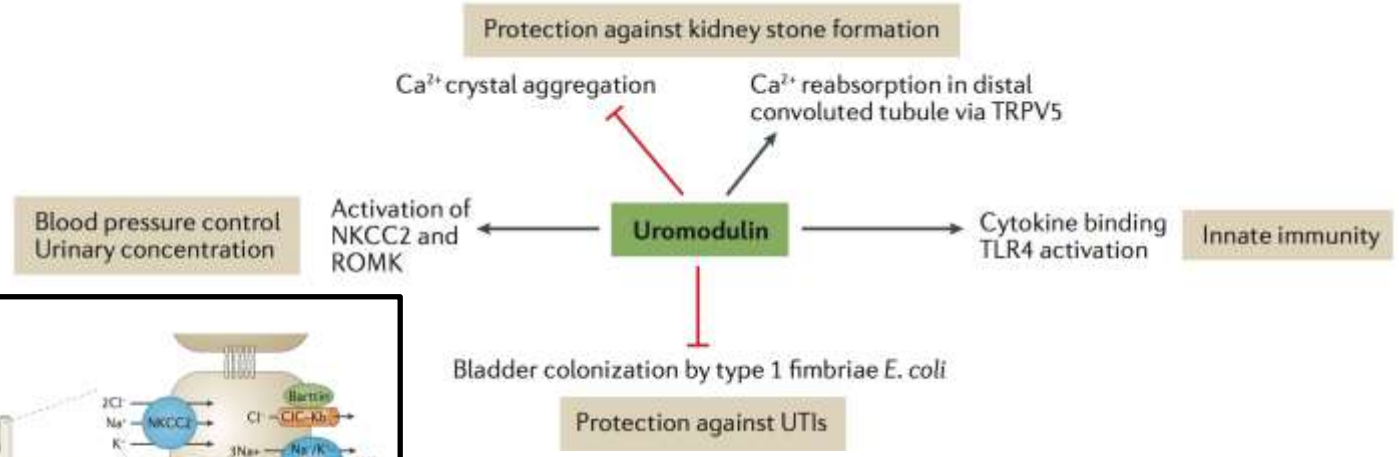
Endoplasmic Reticulum Stress in *UMOD*-Related Kidney Disease: A Human Pathologic Study

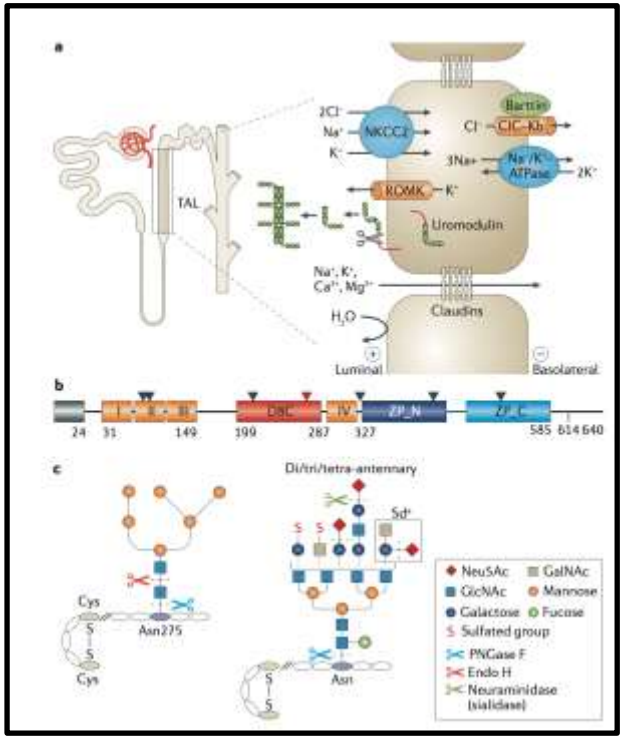
Julien Adam, MD,[1] Guillaume Bollée, MD, PhD,[2] Sophie Fougeray, PhD,[3] Laure-Hélène Noël, MD,[3] Corinne Antignac, MD, PhD,[4,5,6] Bertrand Knebelman, MD, PhD,[2] and Nicolas Pallet, MD, PhD[3,7]

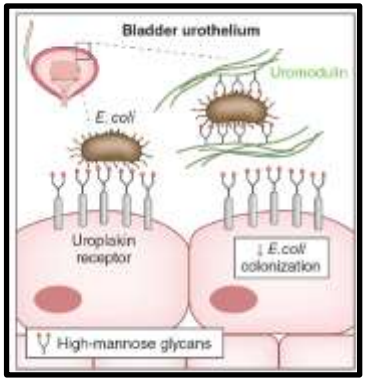


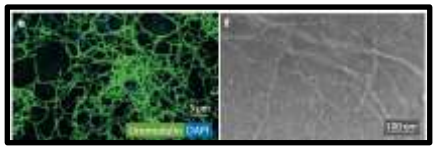


Roles of Uromodulin (Tamm Horsfall Protein)



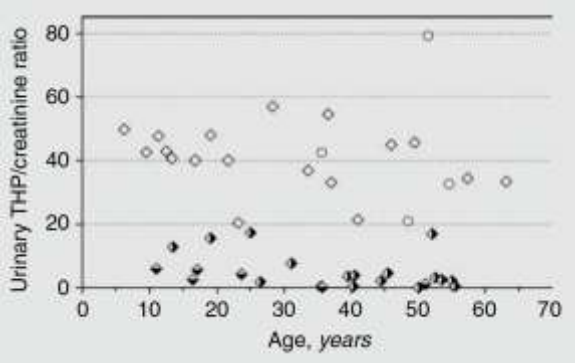






Devuyst et al, Nat Rev Neph 2017; Nat Rev Dis Primers 2019; Weiss et al, Science 2020

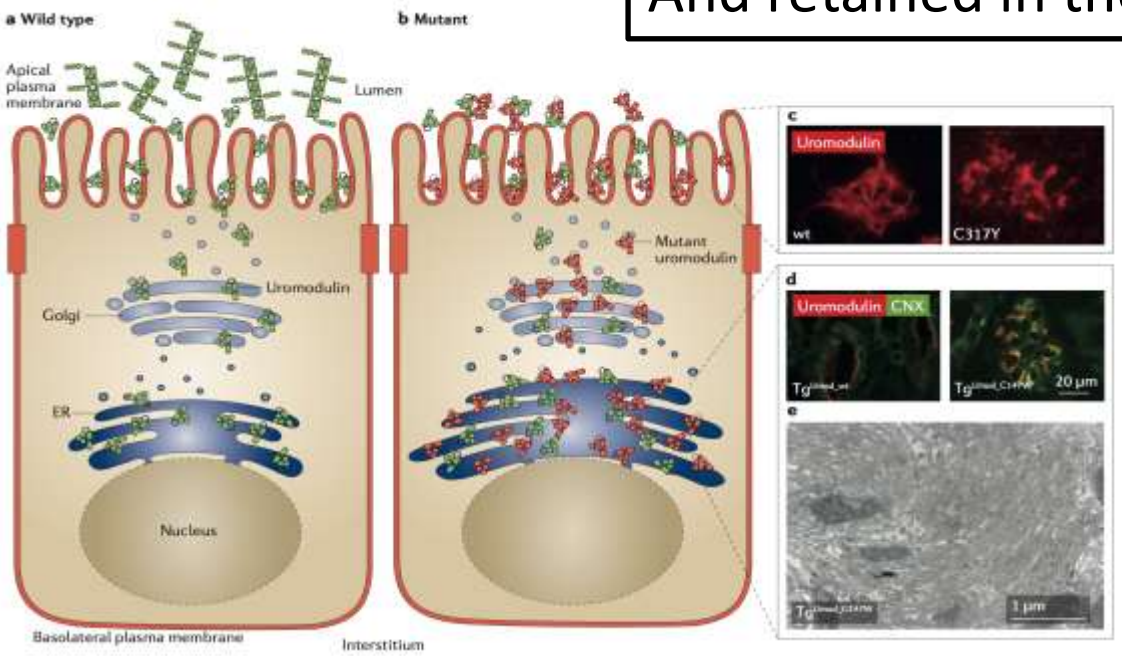
Pathophysiology of ADTKD-*UMOD*



Bleyer, Kidney Int 2004

Urinary uromodulin
is decreased
in ADTKD-*UMOD* pts

And retained in the ER



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

Devuyst, Nat Rev Neph 2017

Treatment for ADTKD-UMOD

- Hydratation > 2l/dy:
  - Salt loss if NKCC2 less expressed; increased UA proximal reabsorption
  - Diuretics should be avoided (early stage)
- XO inhibitors (Allopurinol, Febuxostat)
  - If Gout: Yes
  - In case of asymptomatic hyperuricemia?
    - Very Small retrospective study suggests protective effects (McBride 1998)
- Future ?

Nature Communications

https://doi.org/10.1038/s41467-026-72451-3

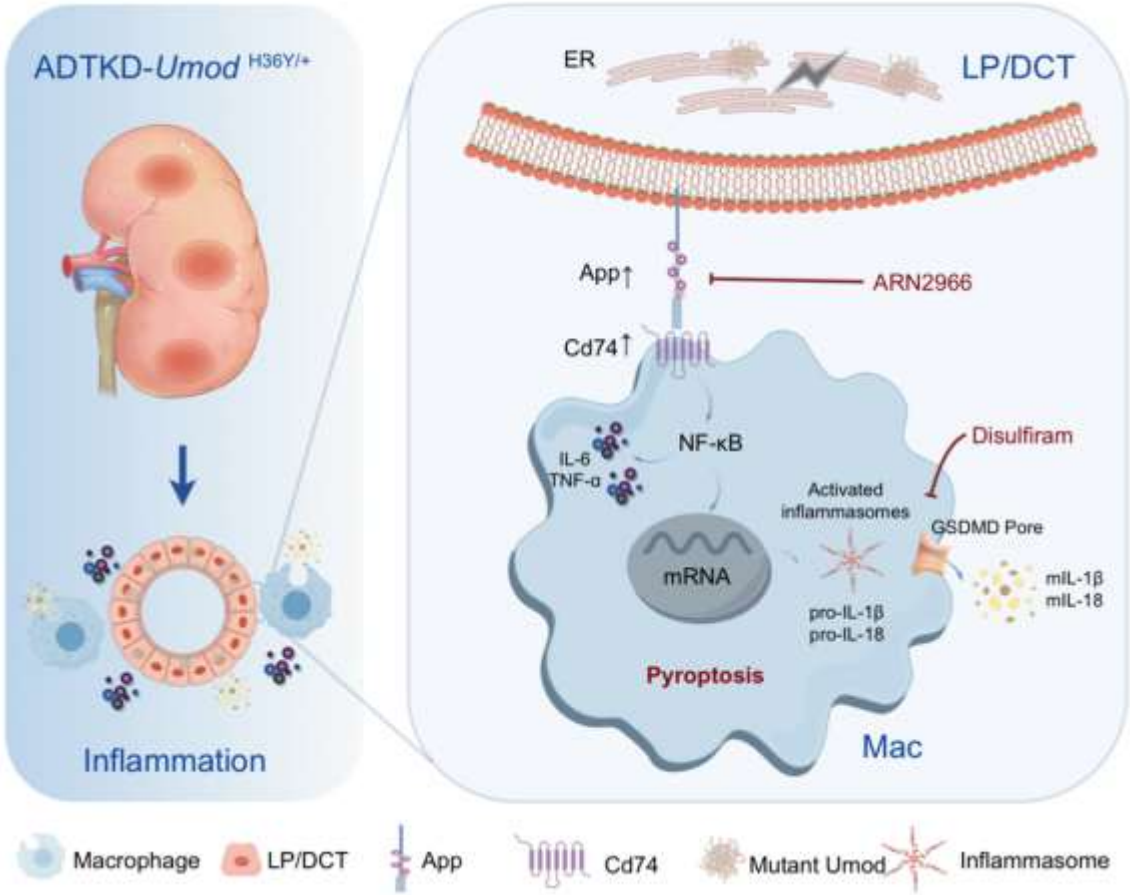
Article in Press

Uromodulin p.His36Tyr promotes macrophage pyroptosis via App-Cd74 signaling to drive renal inflammation in ADTKD

Received: 12 July 2025

Accepted: 15 April 2026

Cite this article as: Wu, Q.-Q., Peng, S.-Q., Zhang, Y.-L. *et al.* Uromodulin p.His36Tyr promotes macrophage pyroptosis via App-Cd74 signaling to drive renal inflammation in ADTKD. *Nat Commun* (2026). https://doi.org/10.1038/s41467-026-72451-3



NTIH.II

Homme de 35 ans,

marocain

Cs pour protéinurie 4g/g

de decouverte fortuite

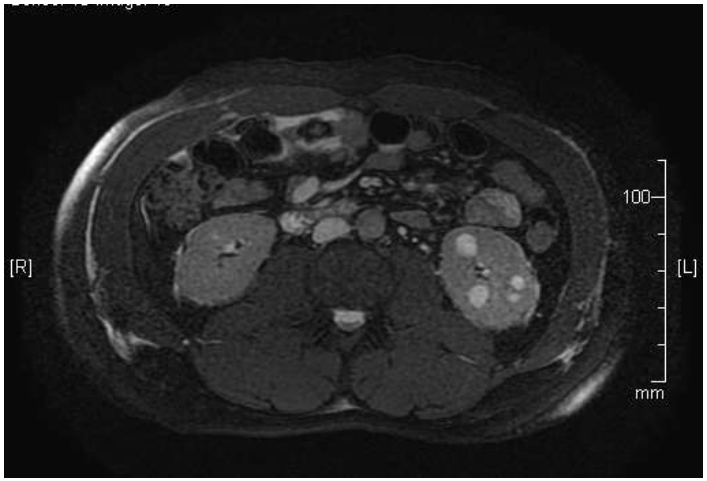
Pas d'Hématurie micro

Alb 27g/l

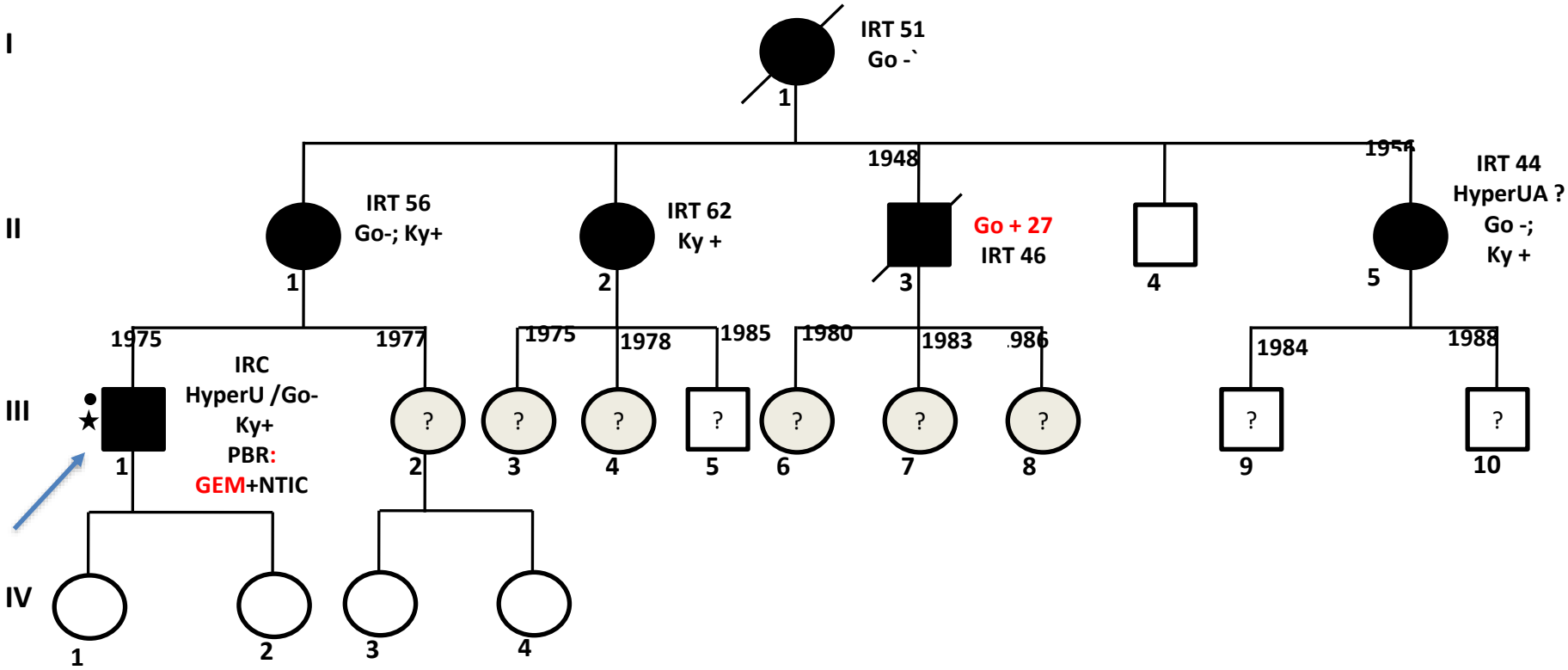
Creat 130 umol/l

- PBR: GEM; FIAT 25%
- Pas de cause retrouvée
- TRT:
  - Ponticelli : Co + Cyclophosphamide
- Evolution:
  - RC SN
  - Creat 145

MRI:
surprisingly many cysts



Family history of ESRD of unknown cause
(44 yrs to 62 yrs)
Hyperuricemia/gout in 2 pts



No mutations in

UMOD

REN

HNF1b

ADTKD-MUC1

Mutations causing medullary cystic kidney disease type 1 lie in a large VNTR in *MUC1* missed by massively parallel sequencing

Andrew Kirby[1,2], Andreas Gnirke[1], David B Jaffe[1], Veronika Barešová[3], Nathalie Pochet[1,4], Brendan Blumenstiel[1], Chun Ye[1], Daniel Aird[1], Christine Stevens[1], James T Robinson[1], Moran N Cabili[1,5], Irit Gat-Viks[1,6], Edward Kelliher[1], Riza Daza[1], Matthew DeFelice[1], Helena Hůlková[3], Jana Sovová[3], Petr Vylet'al[3], Corinne Antignac[7–9], Mitchell Guttman[1], Robert E Handsaker[1,10], Danielle Perrin[1], Scott Steelman[1], Snaevar Sigurdsson[1], Steven J Scheinman[11], Carrie Sougnez[1], Kristian Cibulskis[1], Melissa Parkin[1], Todd Green[1], Elizabeth Rossin[1], Michael C Zody[1], Ramnik J Xavier[1,12], Martin R Pollak[13,14], Seth L Alper[13,14], Kerstin Lindblad-Toh[1,15], Stacey Gabriel[1], P Suzanne Hart[16], Aviv Regev[1], Chad Nusbaum[1], Stanislav Kmoch[3], Anthony J Bleyer[17,18], Eric S Lander[1,18] & Mark J Daly[1,2,18]

nature genetics

6 « MCKD » Families

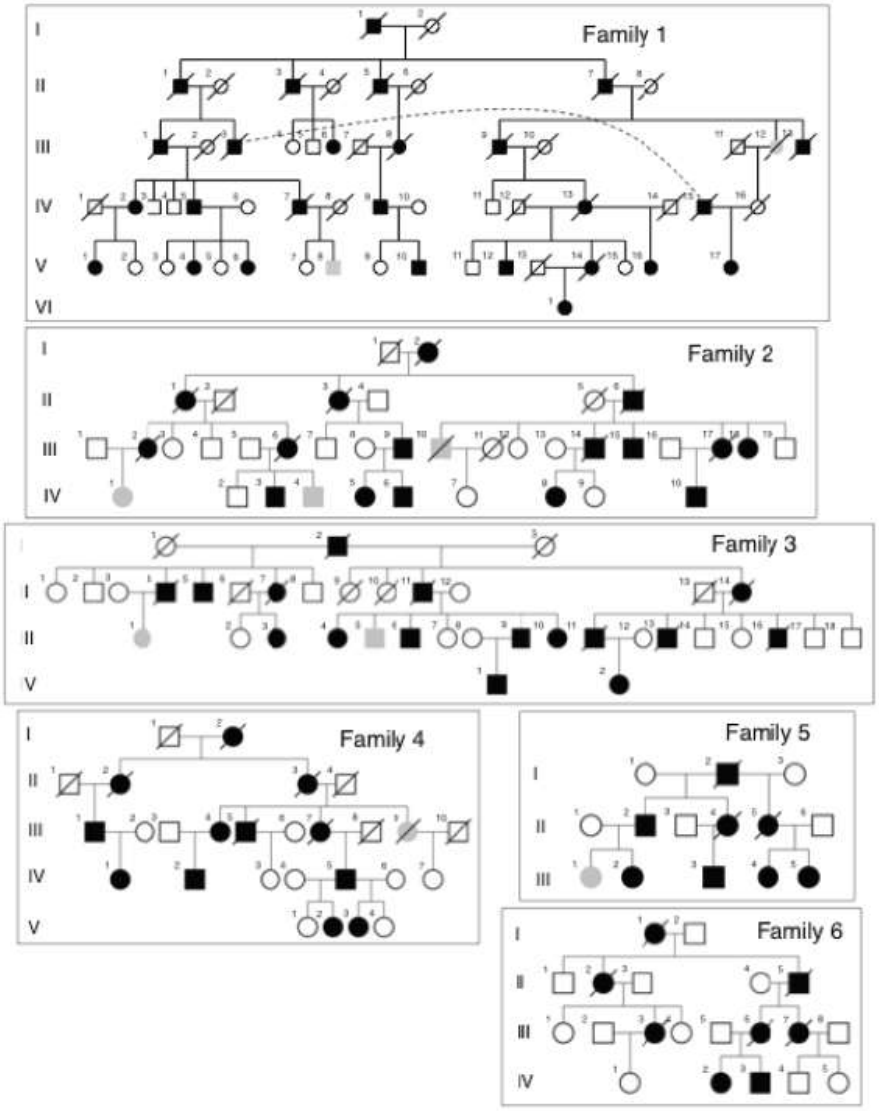
No gout/hyperuricemia

No or few renal cysts

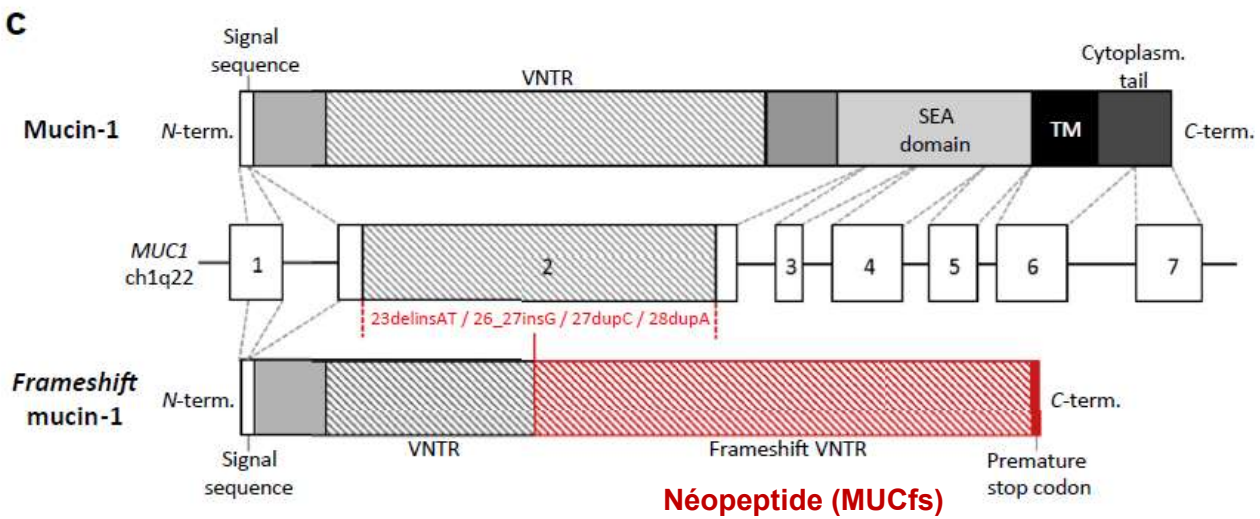
Linked to MCKD1 (1q21)

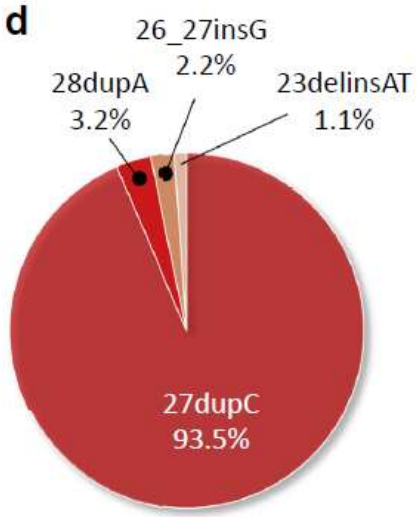
No gene identified by

- Sanger sequencing,
- WES
- WGS….!



MUC1 gene mutation = ADTKD-*MUC1*





Fam I: del 5C

N = 93 Families ; n = 104 patients

Normal: See the dog run
Frameshift: See eth edo gru n

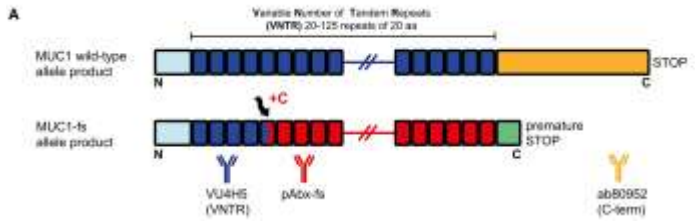
Olinger E et al. *Kidney Int* 98, 2020

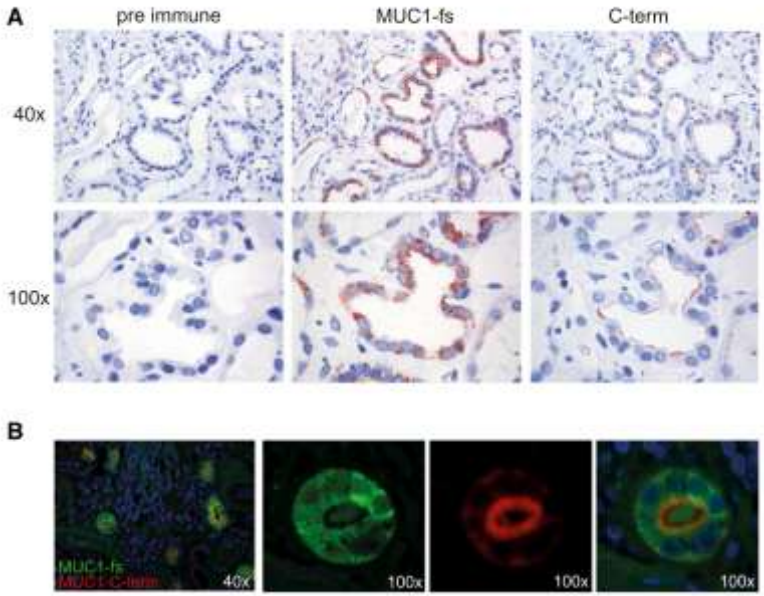
IHC can identify the Mutated MUC1 in Kidney Biopsies

BASIC RESEARCH www.jasn.org

Biallelic Expression of Mucin-1 in Autosomal Dominant Tubulointerstitial Kidney Disease: Implications for Nongenetic Disease Recognition

Karl X. Knaup,[1] Thomas Hackenbeck,[1] Bernt Popp,[2] Johanna Stoeckert,[1] Andrea Wenzel,[3] Meike Büttner-Herold,[4] Frederick Pfister,[4] Markus Schueler,[1] Didem Seven,[2,5] Annette M. May,[6] Jan Halbritter,[7] Hermann-Josef Gröne,[8] André Reis,[2] Bodo B. Beck,[3] Kerstin Amann,[4] Arif B. Ekici,[2] and Michael S. Wiesener[1]

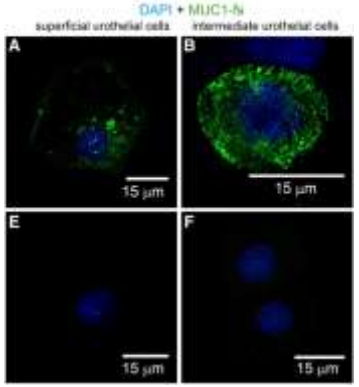




CLINICAL RESEARCH www.jasn.org

Noninvasive Immunohistochemical Diagnosis and Novel *MUC1* Mutations Causing Autosomal Dominant Tubulointerstitial Kidney Disease

Martina Zivná,[1] Kendrah Kidd,[2] Anna Pristoupilová,[1] Veronika Borešová,[1] Mathew DeFelice,[3] Brendan Blumenfeld,[3] Maegan Harden,[3] Peter Conlon,[4,5] Peter Lavin,[5] Dervla M. Connaughton,[4,6] Hana Hartmannová,[1] Kateřina Hodaňová,[1] Viktor Stránecký,[1] Alena Vrbacká,[1] Petr Vylet'al,[1] Jan Živný,[7] Miroslav Votruba,[1] Jana Sovová,[1] Helena Hůlková,[1,6] Victoria Robins,[2] Rebecca Perry,[2] Andrea Wenzel,[9,10] Bodo B. Beck,[9,10] Tomáš Seeman,[11] Ondřej Viklický,[12] Sylvie Rajnochová-Bloudíčková,[12] Gregory Papagregoriou,[13] Constantinos C. Deltas,[13] Seth L. Alper,[14] Anna Greka,[3,15,16] Anthony J. Bleyer,[1,2] and Stanislav Kmoch[1,2]

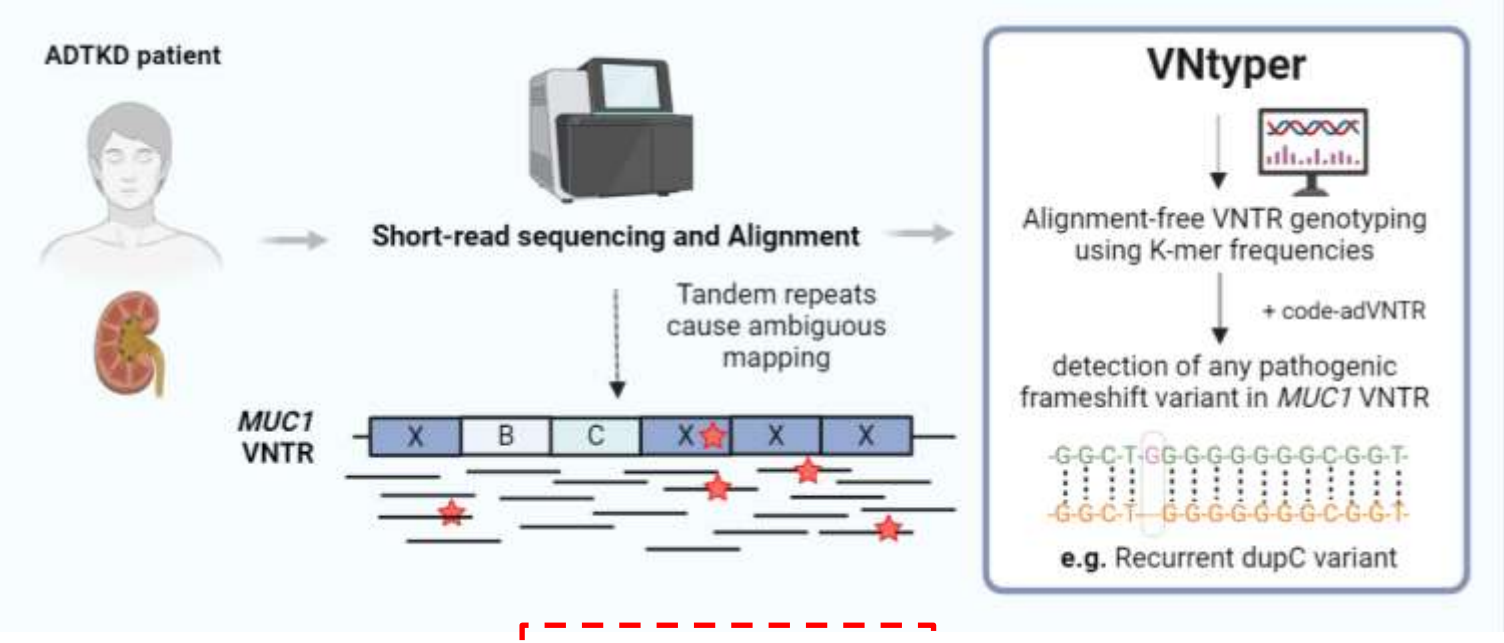


Urines smear

Sens 94,2%

Spe 88,6%

VNTyper, a computational pipeline to detect *MUC1* VNTR path variants



Starting from Short-read sequencing data

VNtyper tool (Genotyping using two independent methods)

Identify patients with pathogenic variation in the MUC1 gene coding-VNTR

H. Saei,…G. Dorval, *iScience*, 2023

Phenotypic Heterogeneity of ADTKD-*MUC1* Diagnosed Using VNtyper

Setting

- Cross-sectional observational study
- Single-center in Paris, France
- N = 4,040 patients
- 2017-2023
- Genetic testing for
  - glomerular disease
  - ciliopathy
  - CAKUT
  - ADTKD
  - CKD of unknown origin

Findings

VNtyper:
Novel genetic test for easier reliable detection of *MUC1* VNTR pathogenic variants

33 index patients

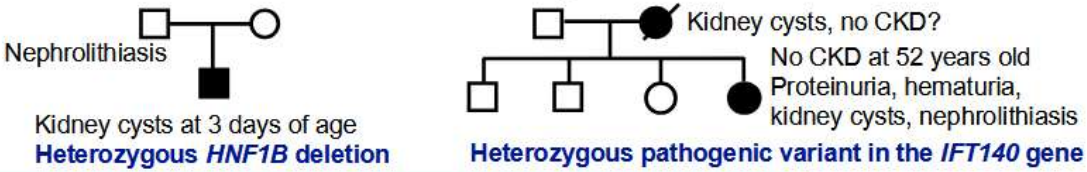
- 61%: ADTKD suspected
- 39%: ADTKD not suspected

ADTKD-*MUC1* detection rate: 0.4% (13/3608)

6 patients had no family history of kidney disease

↳ *De novo* ADTKD-*MUC1* confirmed in 2 patients

Patients with Two Genetic Diagnoses



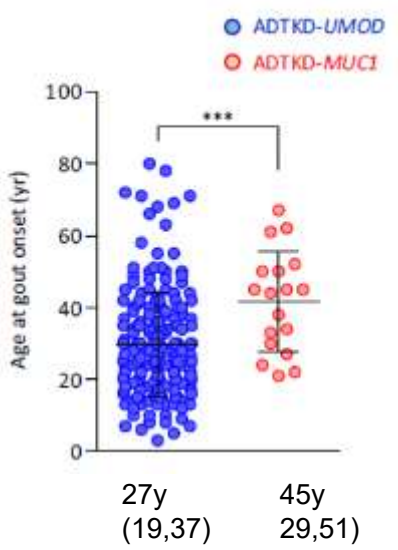
CONCLUSION: With VNtyper, we were able to diagnose new cases of ADTKD-*MUC1* in a large heterogeneous cohort of patients with various phenotypes.

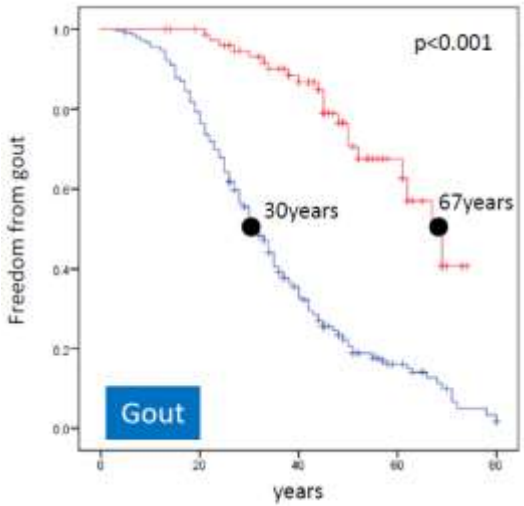
Jessica Kachmar, Hassan Saei, Vincent Morinière, et al

DOI: 10.1053/j.ajkd.2024.11.010

AJKD

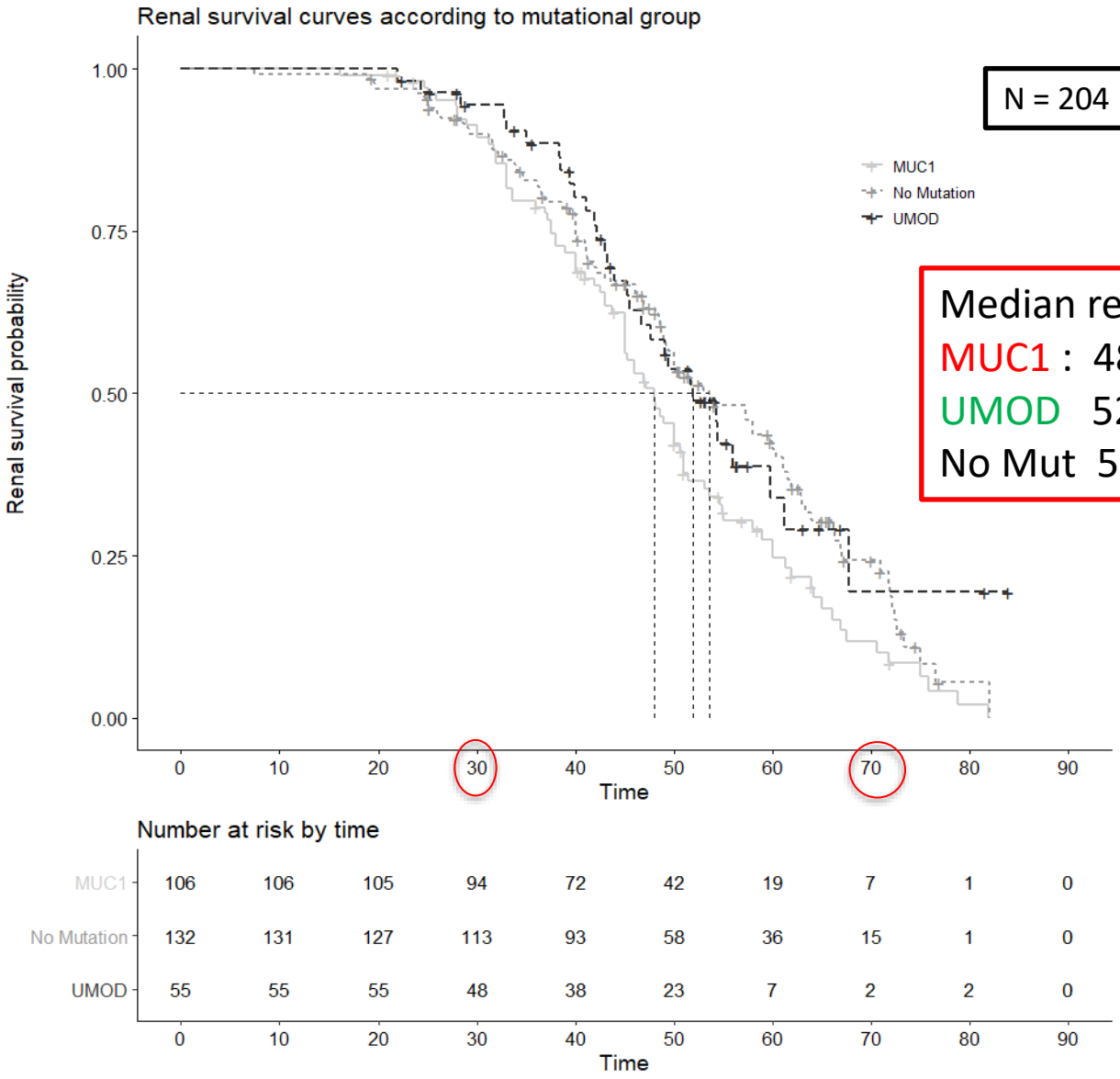
Gout is much less frequent in ADTKD-MUC1 Compared to ADTKD-UMOD





Olinger E et al, KI 2020

Renal Survival is similar in ADTKD-UMOD and ADTKD-MUC1



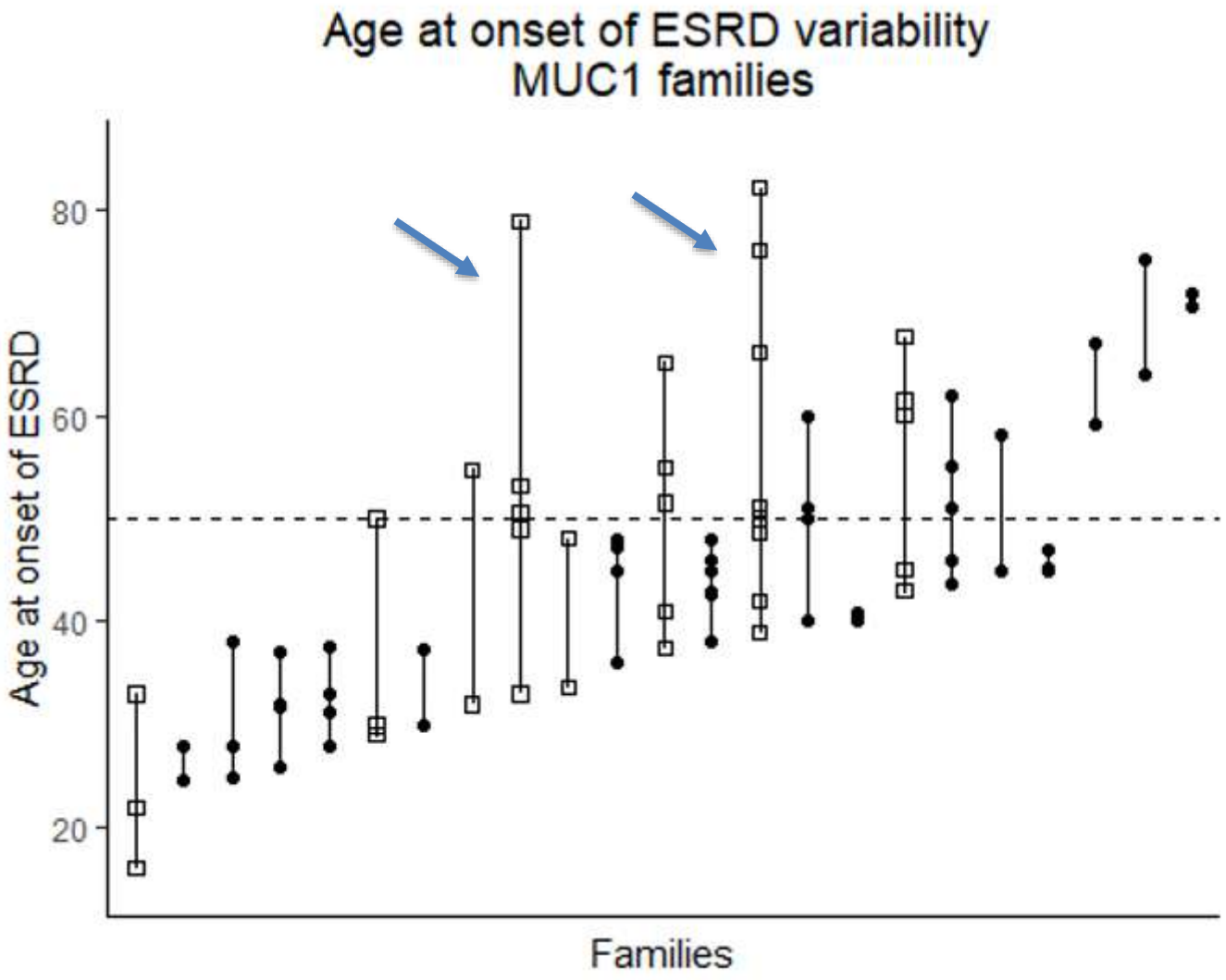
N = 204 ESRD pts

Median renal survival
MUC1 : 48 yrs
UMOD 52 yrs
No Mut 53.7 yrs

ADPKD: 58 ans

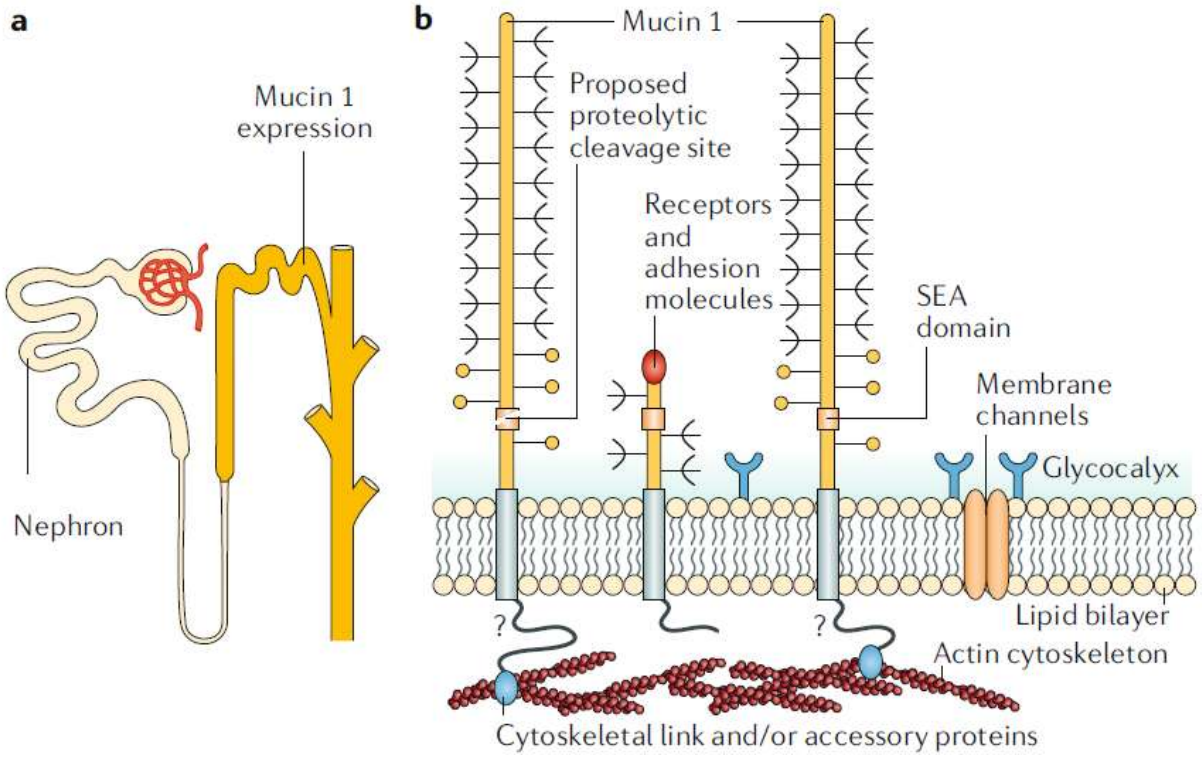
French cohort

Intrafamilial Variability of age at ESRD

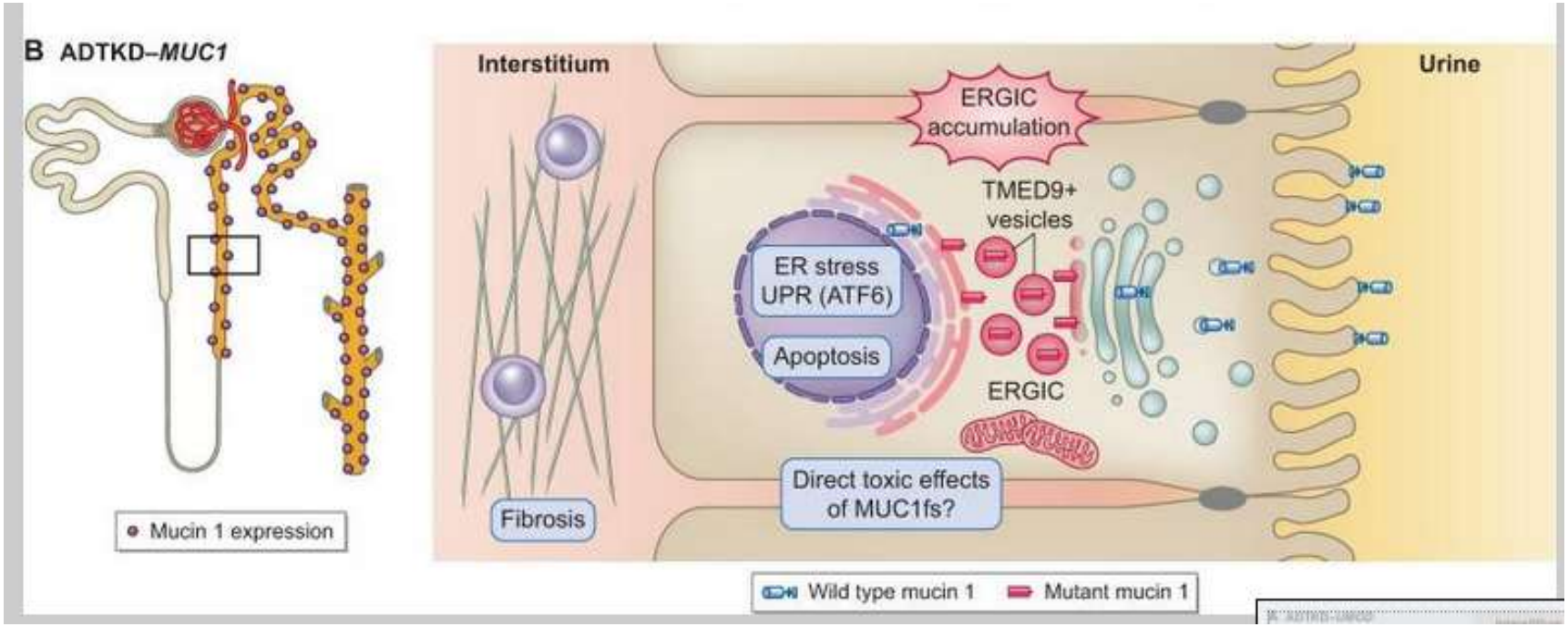


Onset of ESKD from 16 to > 80 years !

-**Mucin 1 belongs to a group of mucoproteins**
  -expressed on different epithelial tissues throughout the body
  -kidney expression: TAL, DCT and collecting ducts
-**In the kidney, Mucin 1 has**
  -a protective role in AKI models by transactivating the HIF1α and β- catenin pathways
  -a regulatory effect on calcium balance by stabilizing the TRPV5 calcium channel



ADTKD-MUC1 :Physiopathology

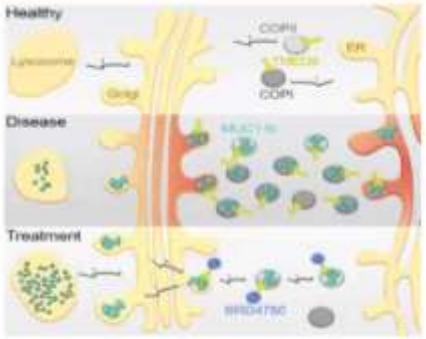


Mabillard NDT, 2023

Investigational Therapies for ADTKD-MUC1

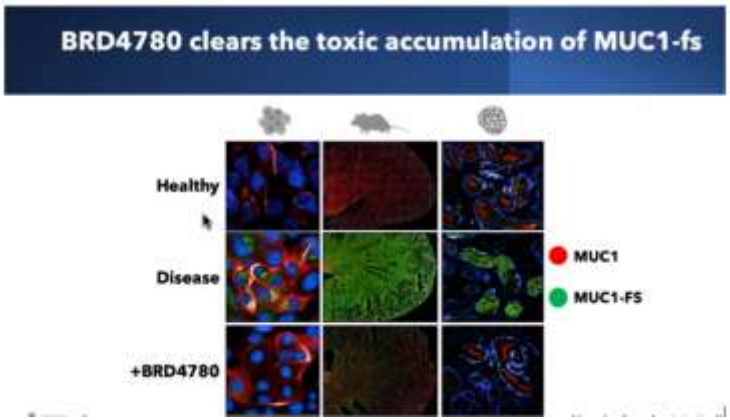
BRD4780 promotes MUC1-fs lysosomal degradation

- ✓ MUC1-fs accumulates in TMED9 positive vesicles
- ✓ BRD4780 promotes MUC1-fs lysosomal degradation
- ✓ TMED9 plays a role in MUC1-fs retention
- ✓ BRD4780 targets TMED9 or a TMED9 containing pathway



Dvela-Levitt et al, Cell 2019

….And improves
MUC1fs phenotype in mice



Investigational Therapies for ADTKD-MUC1

A Proof of Mechanism trial with Vit D to decrease MUC1/MUC1fs transcription

Une histoire d'anémie de l'enfance et de NTIC

Hb 6.8 g/dl
Endoscopies normales
Myélo: hypoplasie lignée rouge
EPO efficace

2 crises goutte

ASE

IRC
DFG 33

PBR:
Lesions TI minimes

DFG 55

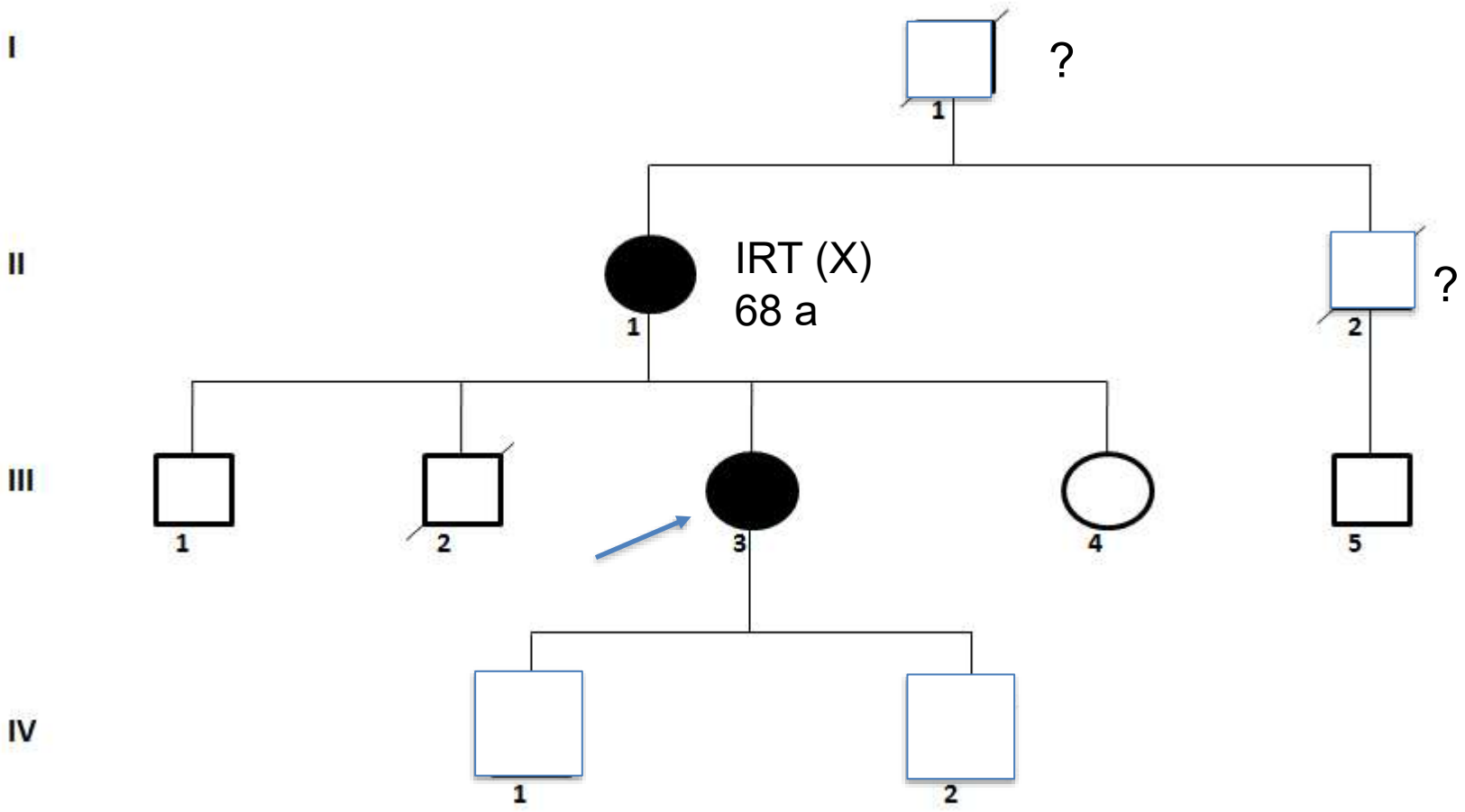
HyperU 480 µM
FeAU 5 %

K 5,7
RA 21 mM

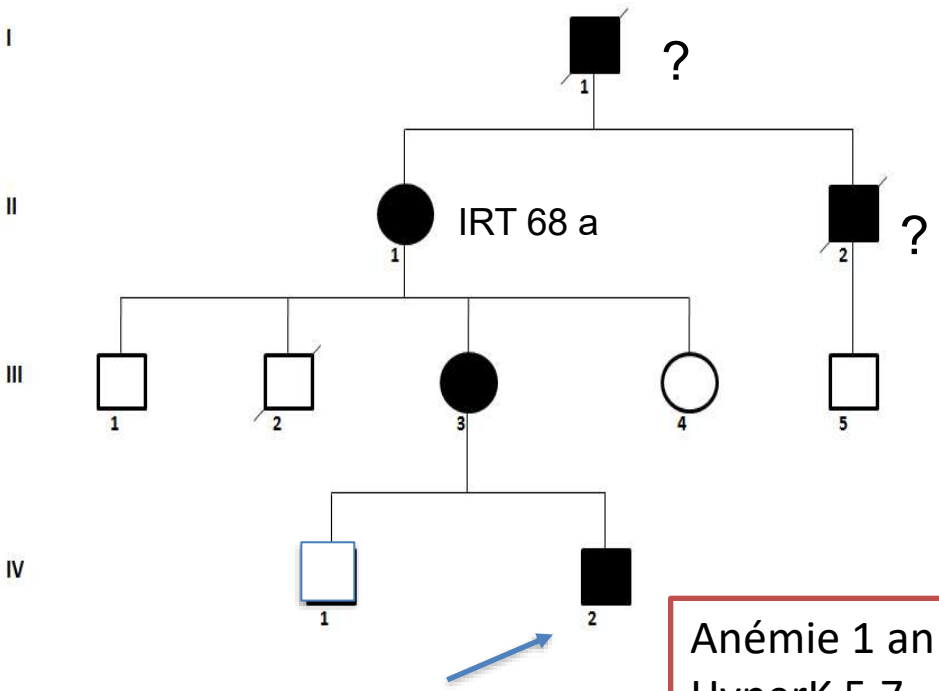
DFG 47
Creat
119µM

DFG 48
Creat
112µM

ATCD de néphropathie indeterminée chez sa mère

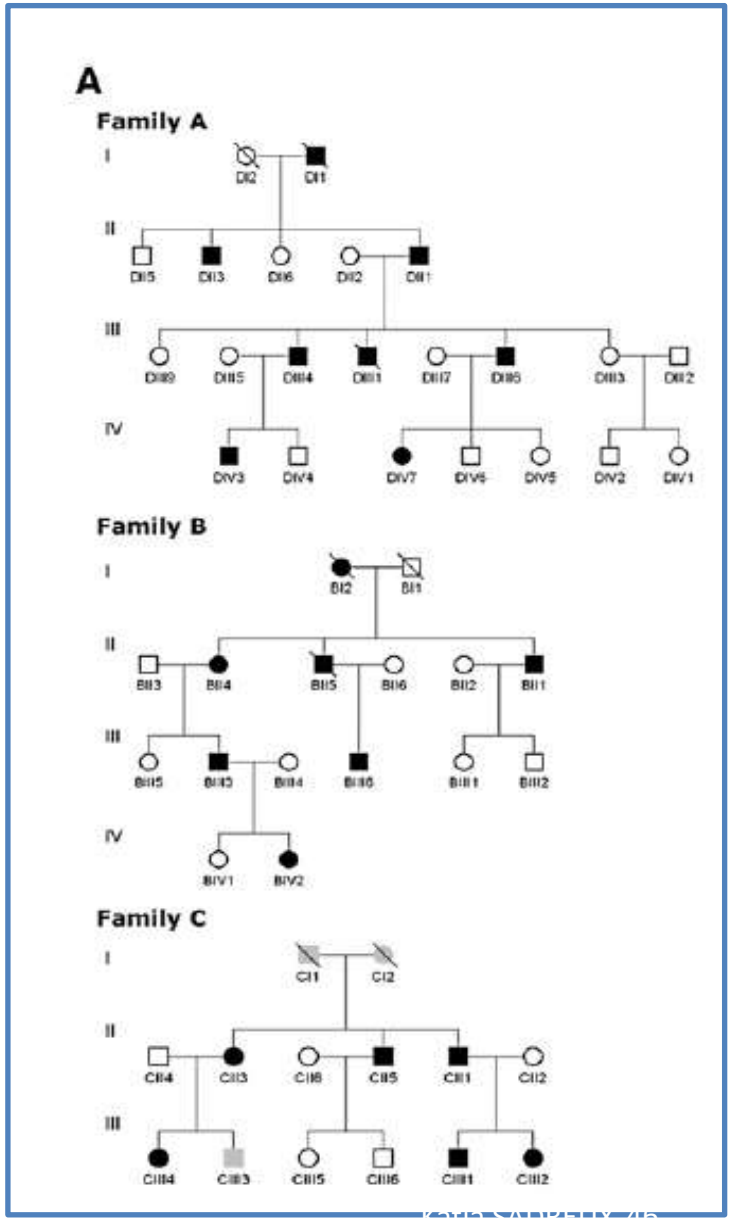


Son fils va développer la même maladie



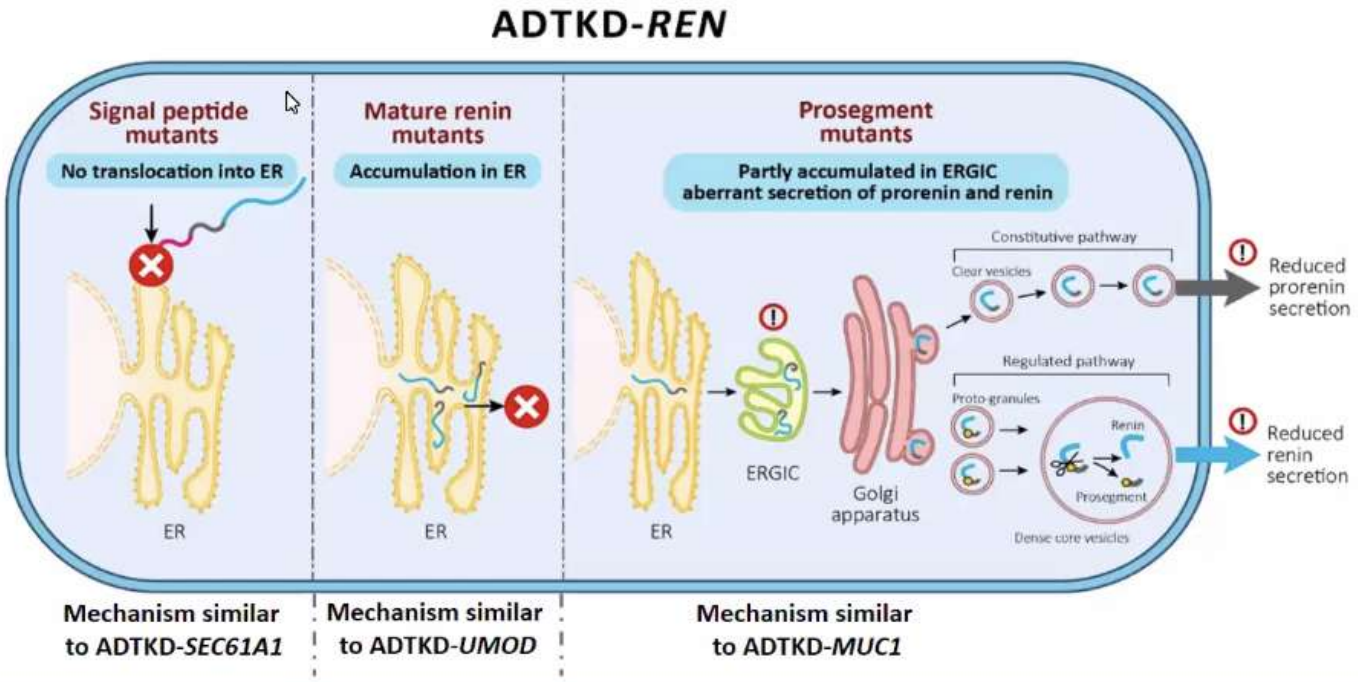
ADTKD-REN

- NTIC autosomique dominante
- **Anémie ++ (inconstante et transitoire)**
- **Hyperkaliémie**
- **Hyperuricémie/ goutte**
- Reins de petite taille (pas de kystes)
- Hypotension artérielle
- IRT Tardive (50-65 ans)



Hodanova, Kidney Int, 2005; Zivna, Am J Hum Genet 2009

Functional studies revealed three distinct pathogenetic mechanisms due to position of mutation in preprorenin



All of these three mechanisms activate ER stress of JGA cells, which leads to apoptosis and fibrosis

An International Cohort Study of Autosomal Dominant Tubulointerstitial Kidney Disease due to *REN* Mutations Identifies Distinct Clinical Subtypes

kidney INTERNATIONAL

Kidney Int. 2020 Aug 1
PMID: 32750457

Martina Živná PhD [1], Kendrah Kidd MS [1, 2], Mohamad Zaidan MD, PhD [3], Petr Vyleťal PhD [1], Veronika Barešová .... Stanislav Kmoch PhD [1, 2], Anthony J. Bleyer MD, MS [1, 2]

Clinical and biochemical investigations of ADTKD-*REN* revealed three distinct subtypes due to mutation position

The most severely affected patients

	Signal Peptide	Prosegment	Mature Renin	*P* value
Age of presentation	20±16	22±20	37±12	<0.001
Anemia as child (%)	91 %	69 %	0	<0.001
Age ESKD	53±11	51±18	64±8	<0.001
Develop gout (%)	56 %	65 %	64 %	ns

Much milder course campared to „signal peptide“ group

In all patients:

- Low mean plasma renin activity **0.5±0.8 ng/mL/h**

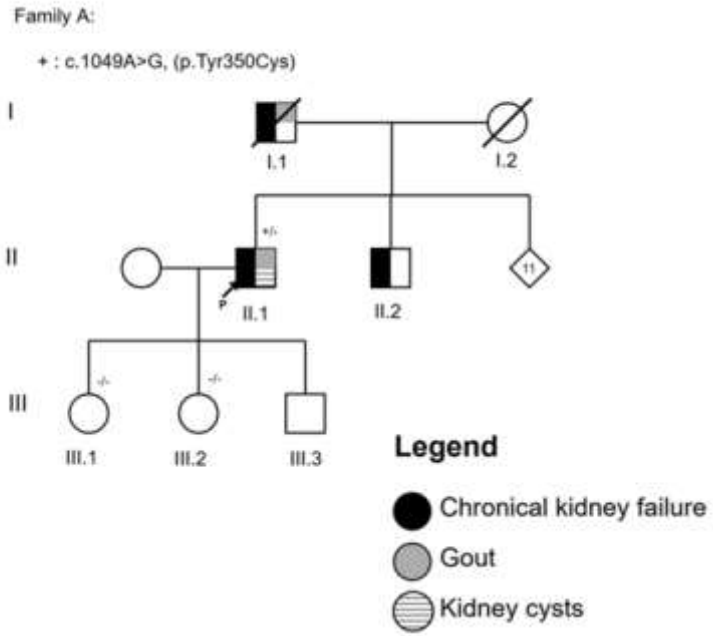
(normal range 2.9 to 24 ng/mL/h)

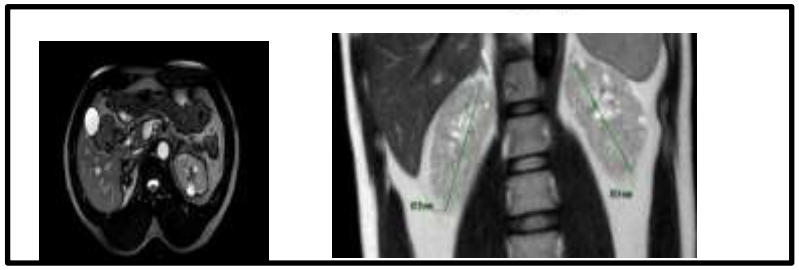
An International Cohort Study of Autosomal Dominant Tubulointerstitial Kidney Disease due to *REN* Mutations Identifies Distinct Clinical Subtypes

kidney INTERNATIONAL

Kidney Int. 2020 Aug 1
PMID: 32750457

Martina Živná PhD [1], Kendrah Kidd MS [1, 2], Mohamad Zaidan MD, PhD [3], Petr Vyletal PhD [1], Veronika Barešová .... Stanislav Kmoch PhD [1, 2], Anthony J. Bleyer MD, MS [1, 2]


Family A:
+ : c.1049A>G, (p.Tyr350Cys)
I
II
III
I.1
I.2
+/-
II.1
II.2
11
P
-/-
-/-
III.1
III.2
III.3
Legend
Chronical kidney failure
Gout
Kidney cysts



Genetic testing by next-generation sequencing was performed on the proband (AII.a) of family A, which revealed a heterozygous missense variant:

REN c.1049A>G, (p.Tyr350Cys), located in exon 9 (mature renin protein)

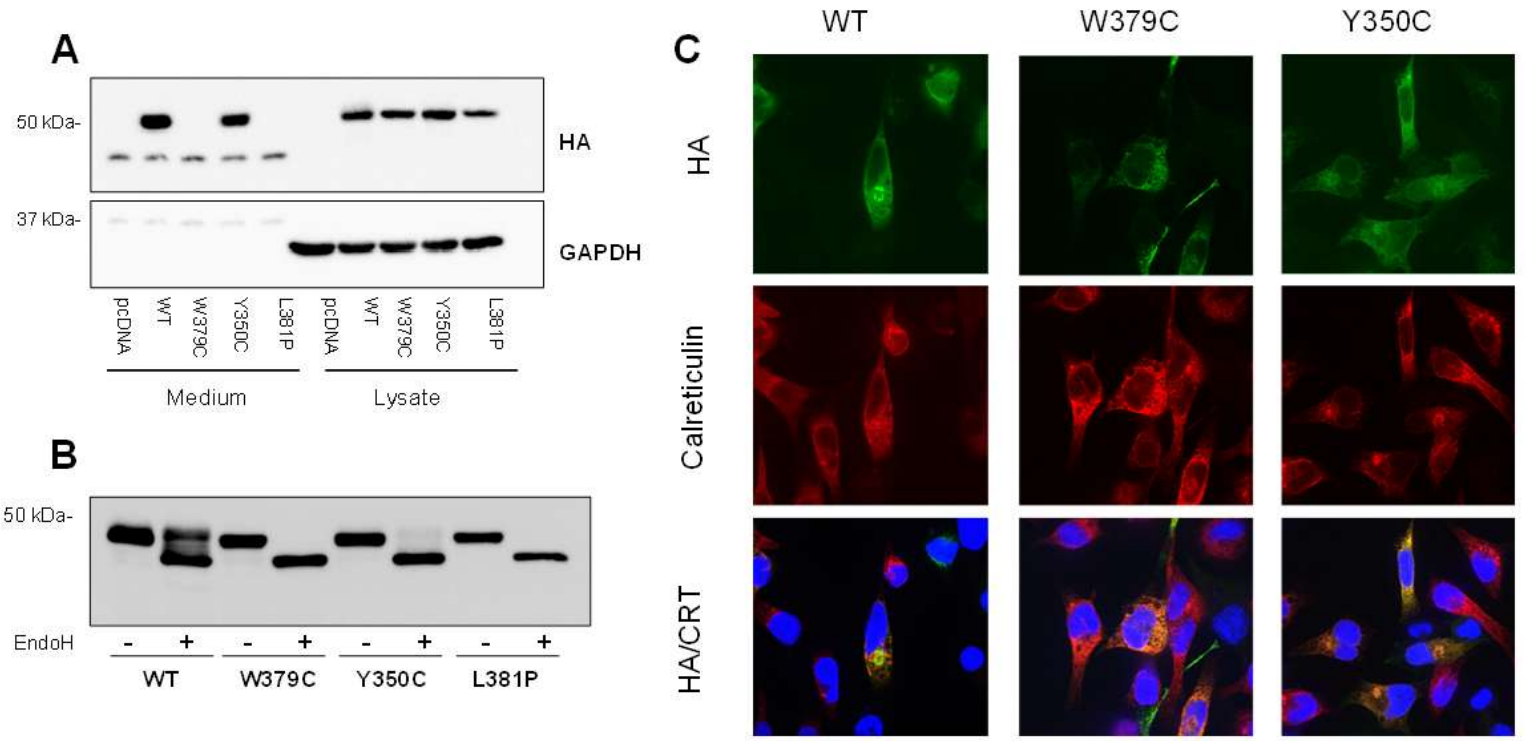
Gene	c.	p.	Polyphen 2	CADD	Alpha Missense	REVEL	SIFT
REN (NM_000537.4)	c.1049A>G	(p.Tyr350Cys)	1	25.8	0.872	0.724	0

This variant:

- has not been observed in general population (gnomAD, AllofUs, deCAF and UKBiobank)
- has not been previously reported on pathogenic databases like ClinVar or LOVD.
- -is located on the mature segment at a highly conserved residue and predicted to be deleterious by most *in silico* prediction tools (Table1).

According to the ACMG classification, the variant fulfilled the PM2 (absent from the general population) and PP3 (deleterious *in silico* predictions) criteria and was therefore classified as **variant of uncertain significance (VUS, class 3)** →

Functional Analysis of the YY350C UMOD variant



The Y350 C variant is likely pathogenic

L Rampoldi

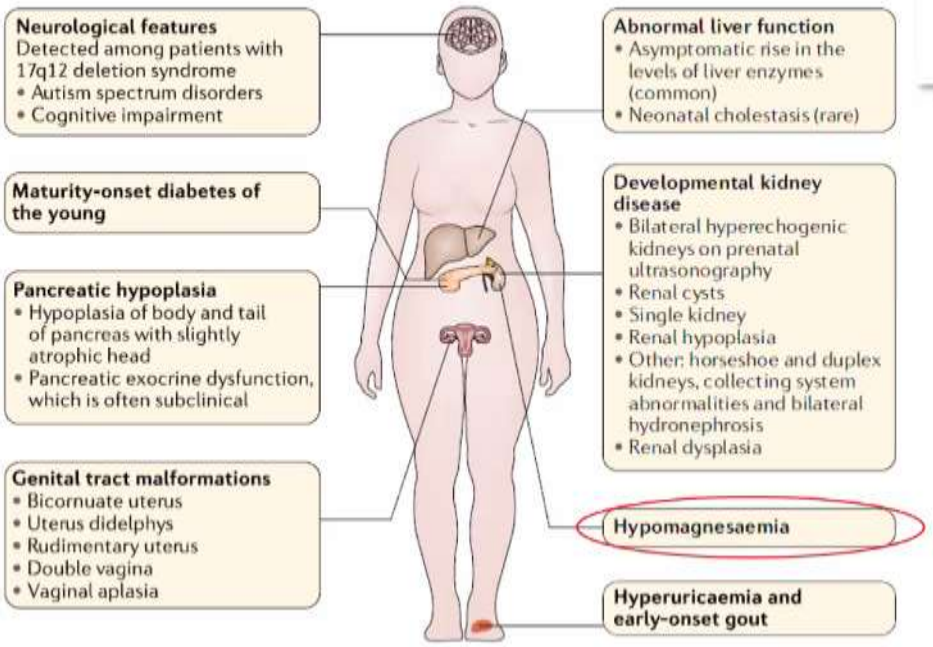
ADTKD-REN: Treatment

- Prevent dehydratation +++
- No low salt diet
- Avoid NSAID
- Allopurinol if gout

  (if asymptomatic hyperuricemia?)
- Fludrocortisone? (A Bleyer, case report)
  - Could decrease salt loss and Renin secretion/ER accumulation
- When High BP: avoid ACEI/ARBs/ Diuretics

ADTKD ?-HNF1b

Hepatocyte nuclear factor 1β (HNF1B)



KI REPORTS
KIReports.org

Variable Expressivity of HNF1B Nephropathy, From Renal Cysts and Diabetes to Medullary Sponge Kidney Through Tubulo-interstitial Kidney Disease

- *Presentations as isolated ADTKD probably rare*
- *Family history can be missing (de novo)*

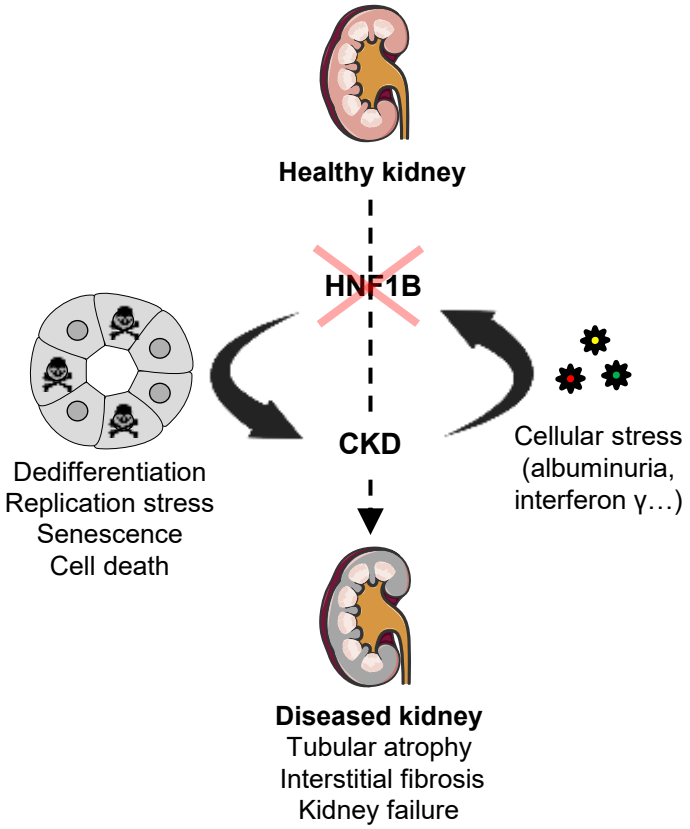
The two faces of HNF1B in kidney disease

A rare genetic renal disease

CAKUT:
Renal agenesis
Dysplasia
Tubular Cysts
Glomerular Cysts
Multicystic Hypodysplastic Kidneys

ADTKD:
Interstitial Fibrosis
Tubular Atrophy
Renal failure

Acquired HNF1B dysfunction in common CKD



Science
AAAS

Isnard P et al. Science 2026

Pediatric Nephrology (2025) 40:891–899
https://doi.org/10.1007/s00467-024-06562-8

REVIEW

Kidney and vascular involvement in Alagille syndrome

Bruno Ranchin[1] · Marie-Noelle Meaux[1,2] · Malo Freppel[1,2] · Mathias Ruiz[4] · Aurelie De Mul[1,2,3]

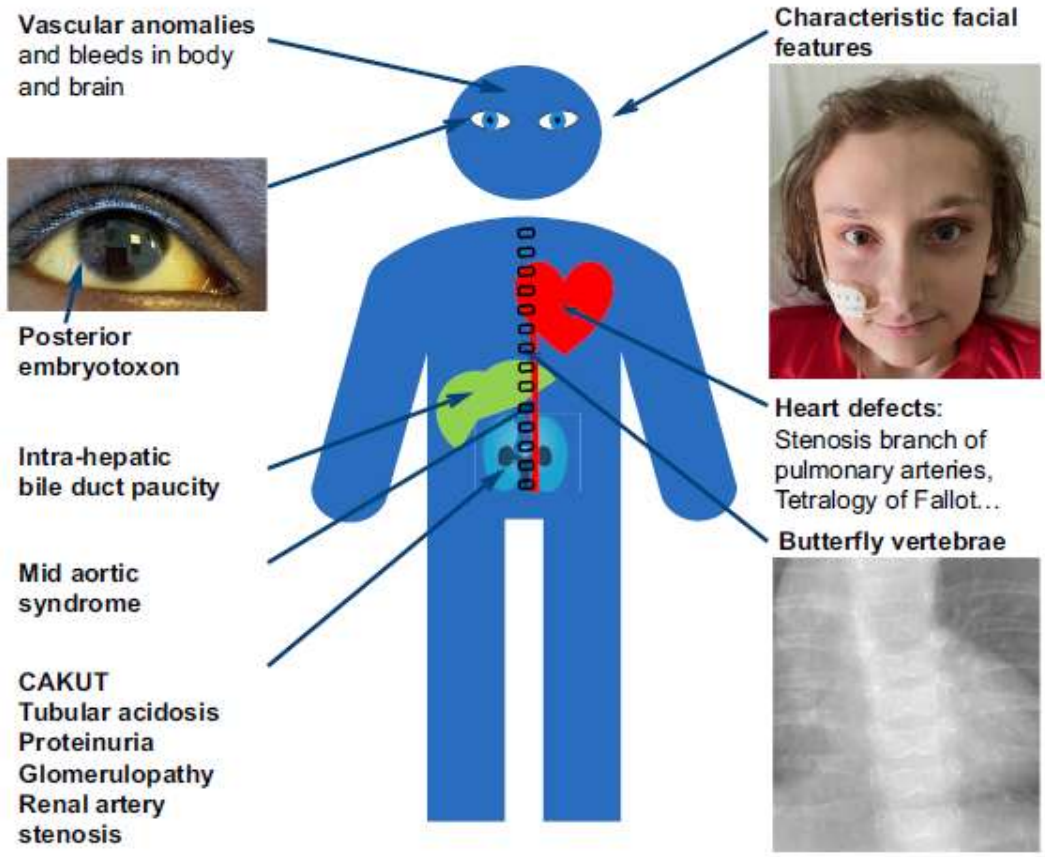


Fig. 1 Clinical features of Alagille syndrome. Written consent for publication of these images was obtained from the patients and their parents

ARTICLE IN PRESS
www.kidney-international.org clinical investigation

Mono-allelic pathogenic variants in *JAG1* cause autosomal dominant tubulo-interstitial kidney disease (ADTKD-*JAG1*)

Lucie Menguy[1], Laurent Hudier[2], Mohamad Zaidan[1], Bertrand Knebelmann[3], John A. Sayer[4,5,6], Juliana Arcila-Galvis[4], Christelle Arondel[1], Aurélie Hummel[2], Guillaume Dorval[1,7], Vincent Morinière[2], Landrine Fula-Pitu[1], Chiara Guerrera[8], David Buob[9], Maud Rabeyrin[10], Pierre Marijon[11], Nolwen Jean-Marcais[12], Chloé Fournier[13], Jean-Paul Duong Van Huyen[14], Corinne Antignac[1], Sophie Saunier[1,15] and Laurence Heidet[1,11,15,16]

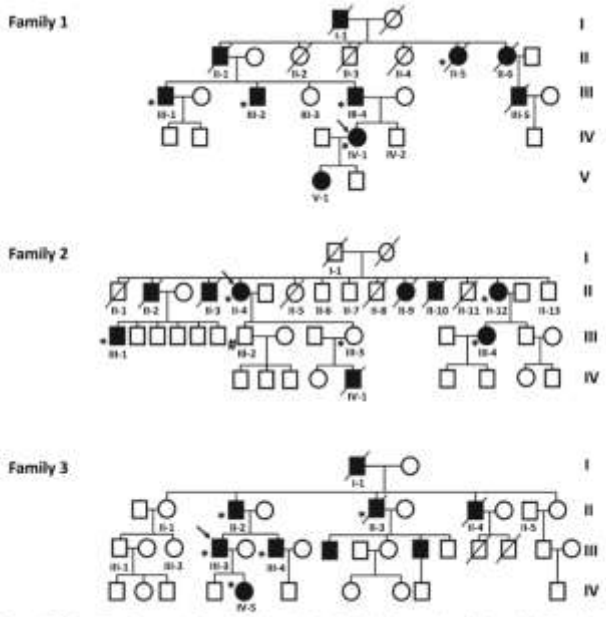
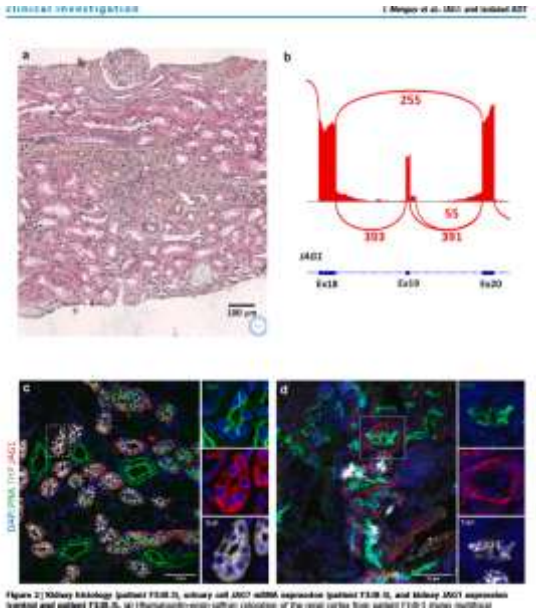


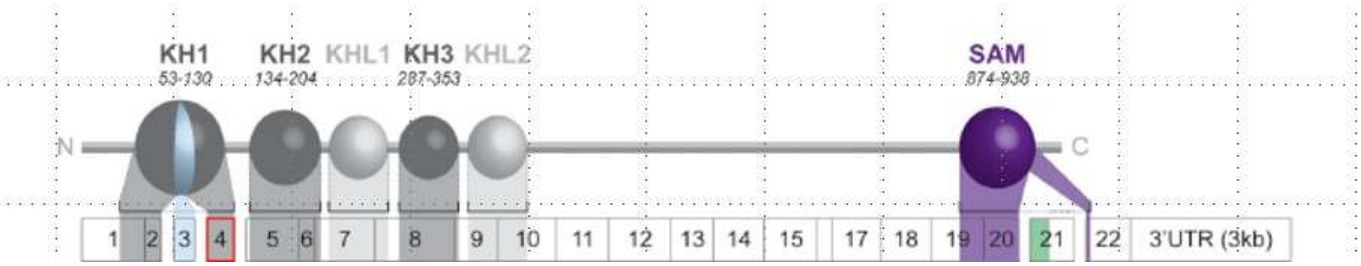
Figure 1 | Pedigree of the families. Squares: male family members, circles: female family members, black symbols: affected persons, white symbols: unaffected persons, star (*): JAG1 variant carriers, hash (#): noncarrier of the JAG1 variant, slashes: deceased family members, and arrows: the index cases.

«Rétrophénotyping »:
Pas de maladie glomérulaire
Pas de CAKUT (…)
Pas d'atteinte vasculaire
Pas d'acidose
Pas d'atteinte extra-rénale (cœur/œil/rachis/Ao….)



Pas de protéine anormale, haploinsuffisance (= idem syndrome d'Alagille), problème du conseil génétique ++++

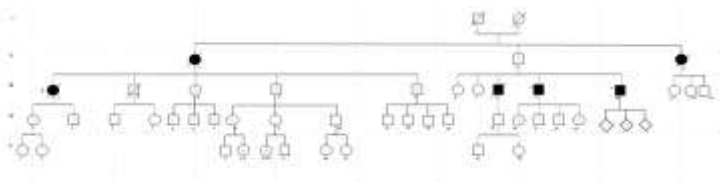
16 patients dans 13 familles avec maladies rénales et variants pathogènes BICC1 : des phénotypes variables selon localisation/zygosité des variants

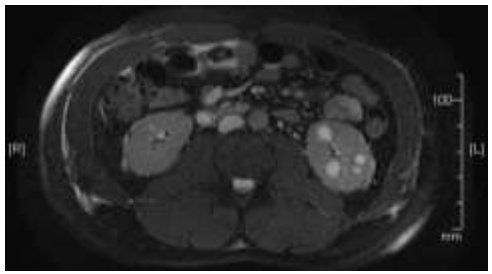


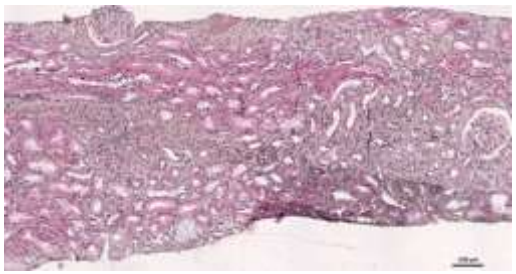
8 familles

Monoallélique
Tronquantes
C-ter

ADTKD

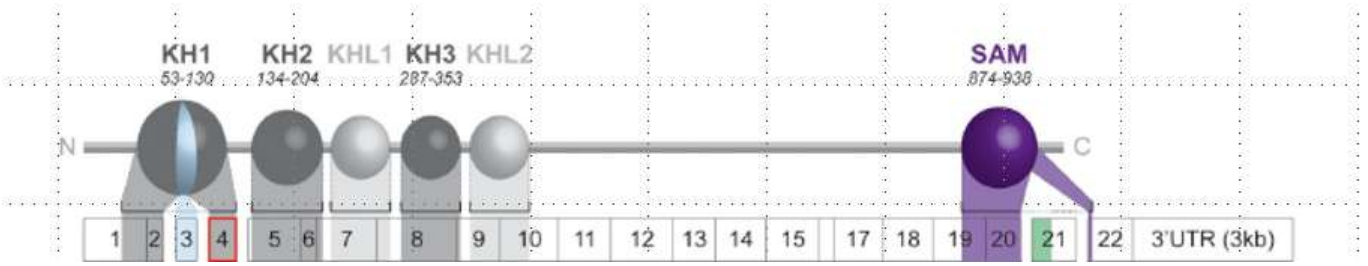


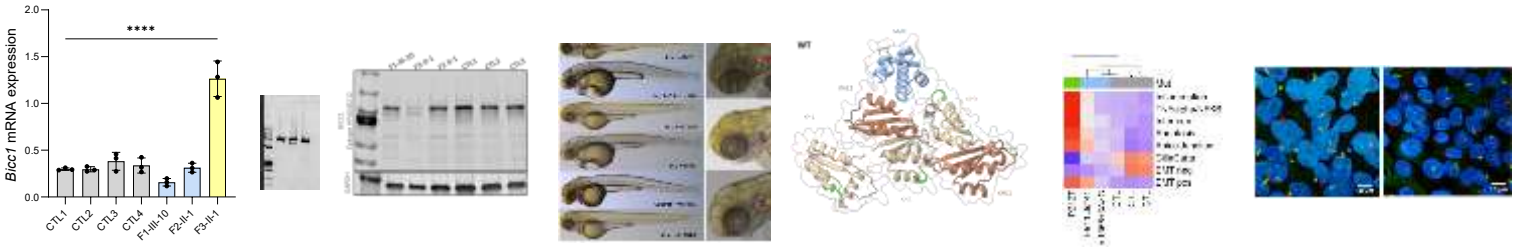




L heidet

16 patients dans 13 familles avec maladies rénales et variants pathogènes BICC1 : des phénotypes variables selon localisation/zygosité des variants





Hypothèses?

----------Fonction de BICC1----------

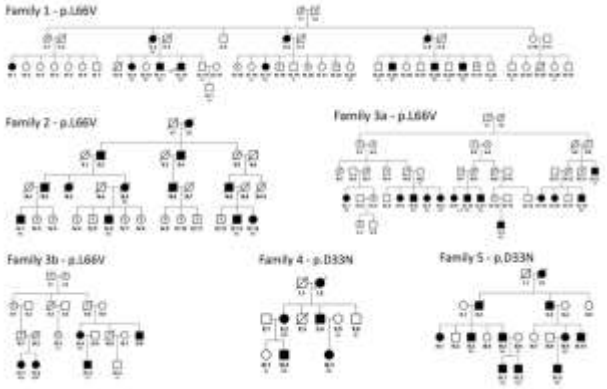
Maladie kystique Précoce sévère ..... **CAKUT** ..... **ADTKD**

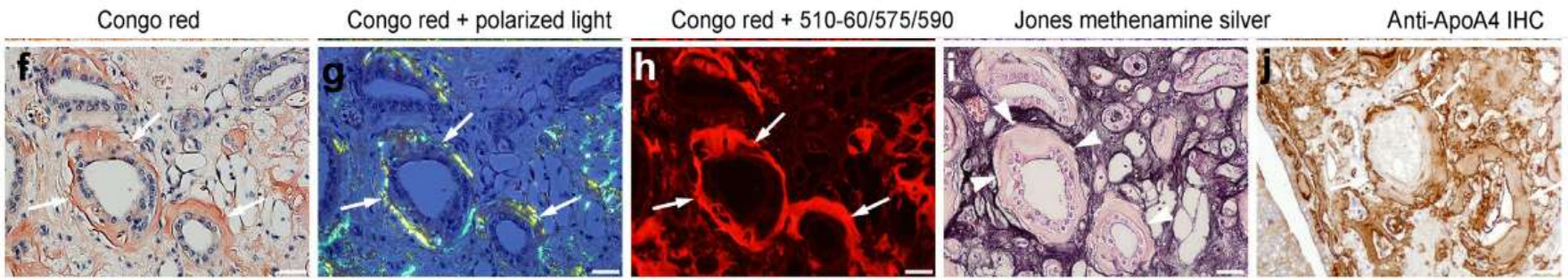
www.kidney-international.org clinical investigation

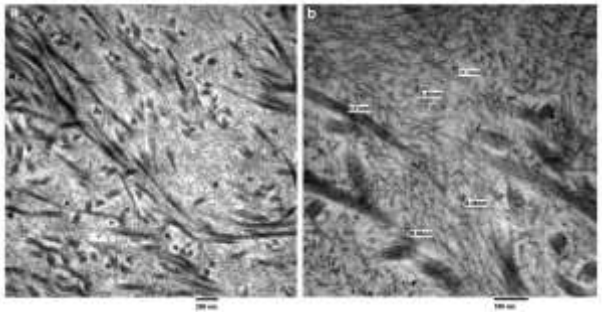
Autosomal dominant ApoA4 mutations present as tubulointerstitial kidney disease with medullary amyloidosis

see commentary on page 666

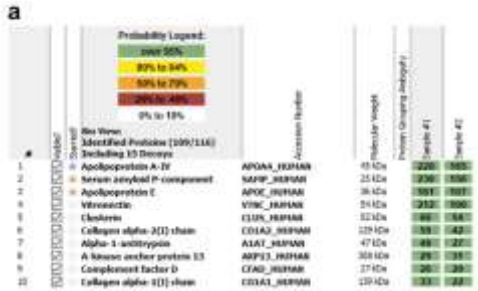
Tereza Kmochová[1,2†], Kendrah O. Kidd[1,2,23], Andrew Orr[3,4,23], Aleš Hnízda[1], Hana Hartmannová[1], Kateřina Hodaňová[1], Petr Vyletal[1], Karolína Naušová[1], Vítězslav Brinsa[1], Helena Trešlová[1], Jana Sovová[1], Veronika Barešová[1], Klára Svojšová[1], Alena Vrbacká[1], Viktor Stránecký[1], Victoria C. Robins[2], Abbigail Taylor[2], Lauren Martin[2], Ana Rivas-Chavez[2], Riley Payne[2], Heidi A. Bleyer[2], Adrienne Williams[2], Helmut G. Rennke[5], Astrid Weins[5], Patrick J. Short[6], Varun Agrawal[7], Leroy J. Storsley[8], Sushrut S. Waikar[9], Ellen D. McPhail[10], Surendra Dasari[11], Nelson Leung[12], Tom Hewlett[13], Jake Yorke[4], Daniel Gaston[4], Laurette Geldenhuys[4], Mark Samuels[3,4,15,16], Adam P. Levine[17], Michael West[13], Helena Hůlková[1,18], Petr Pompach[19], Petr Novák[19], Richard B. Weinberg[20,21], Karen Bedard[22], Martina Živná[1,2], Jakub Sikora[1,18], Anthony J. Bleyer Sr[1,2] and Stanislav Kmoch[1,2]







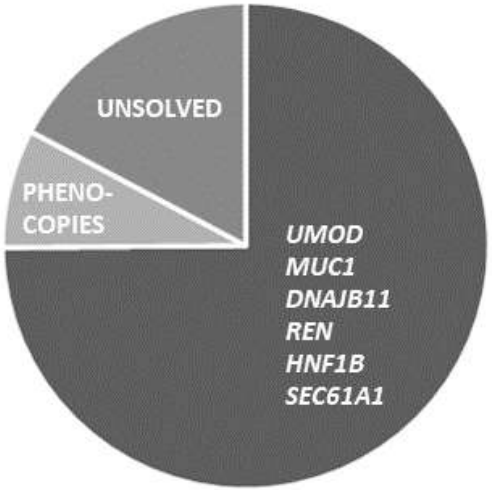
MS -→ APOA4



Familles génotypées à Necker entre 2017-2024

UMOD	*MUC1*	*REN*	*HNF1B* pat. (fam)	*SEC61A1/ DNAJB11*	PHENOCOPIES (*IFT140, SALL1, PAX2, OCRL, COL4, ALG5, PBX1*)
77	54	3	4?	14	16


Diverse molecular causes of unsolved autosomal dominant tubulointerstitial kidney diseases



17% unsolved

L Heidet, Necker/Imagine

Table 6 | Possible reasons for genetic testing of ADTKD

- Adults with CKD suspected to have ADTKD who wish to confirm the diagnosis
- Members of affected families with normal kidney function who wish to donate a kidney
- Healthy adult individuals at risk who are interested in establishing a genetic diagnosis
- Adults interested in undergoing preimplantation genetic diagnosis to avoid their child's inheritance of a disease-causing mutant allele
- Children suspected of having a *REN* mutation

- **Participate in Rare disease Registries (ERKNet, ADTKD-Net)**
- **Engage in novel therapeutical trials**

Eckart KU et al, KDIGO 2015, Kidney Int

ERKNet
The European Rare Kidney Disease Reference Network

for Physicians

About us | Our Experts | Disease Information | CPMS | Guidelines & Pathways | ERKReg & Registries | Education & Training

Research Project

Project Title:	ADTKD-Net
Project Type:	**Observational Study**, Enrolment not yet started Adjunct biobank: DNA, Serum, Plasma, Urine
Disease group(s):	AD structural kidney disorders
Project Summary:	EJP RD proposal on the Natural history of ADTKD with build-up of an ERKNet-based consortium
Lead principal Investigator(s):	Kai-Uwe Eckardt, Berlin Olivier Devuyst, Brussels Jan Halbritter, Berlin
Co-investigator(s):	Roser Torra, Barcelona Corinne Antignac, Paris Peter Conlon, Dublin Michael Wiesener, Erlangen John Sayer, Newcastle Eric Olinger, Brussels Luca Rampoldi, Milan
Project Period:	04/2024 - 05/2027
Sponsors:	EU

yann.nedelec@aphp.fr
johanna.nunez@institutimagine.org