Role of genetics in renal diagnosis - Genetic renal diseases

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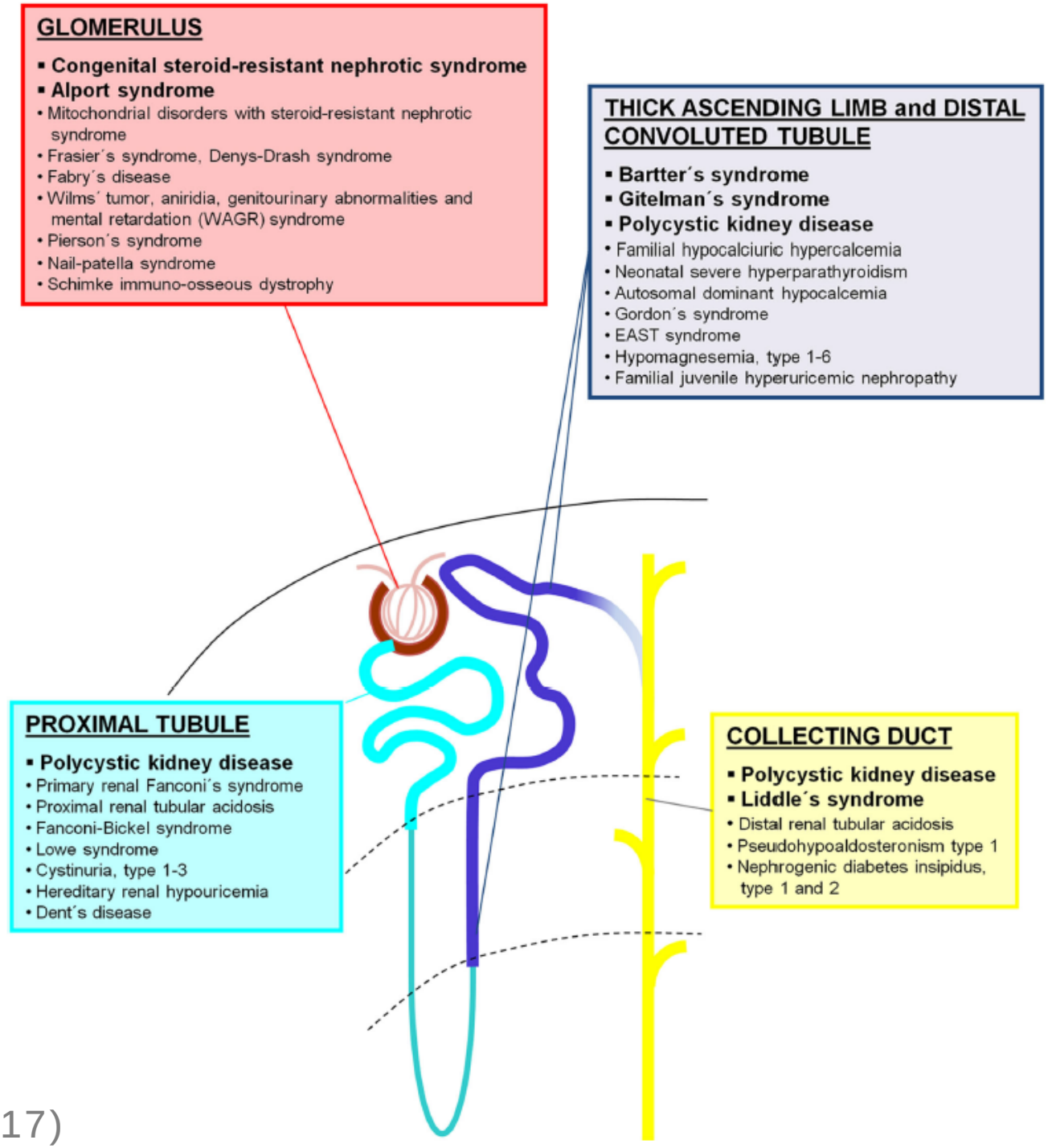
Genetic renal diseases – The journey begins



PKD,
ADTKD,
Nephro-
nophthisis

(Hofmeister et al, 2017)

Role of genetics in renal diagnosis- Genetic renal disease

- **Congenital steroid-resistant nephrotic syndrome (CNS):**
  NPHS1, NPHS2, TRPC6, ACTN4, INF2, WT-1

- **Collagen type IV associated diseases**
  (thin basement GN, Alport`s disease)

- **Polycystic kidney disease (PKD):**
  Autosomal dominant and recessive polycystic kidney disease (ADPKD, ARPKD)

- **Autosomal dominant and recessive tubulointerstitial kidney disease** (ADTKD, nephronophthisis)

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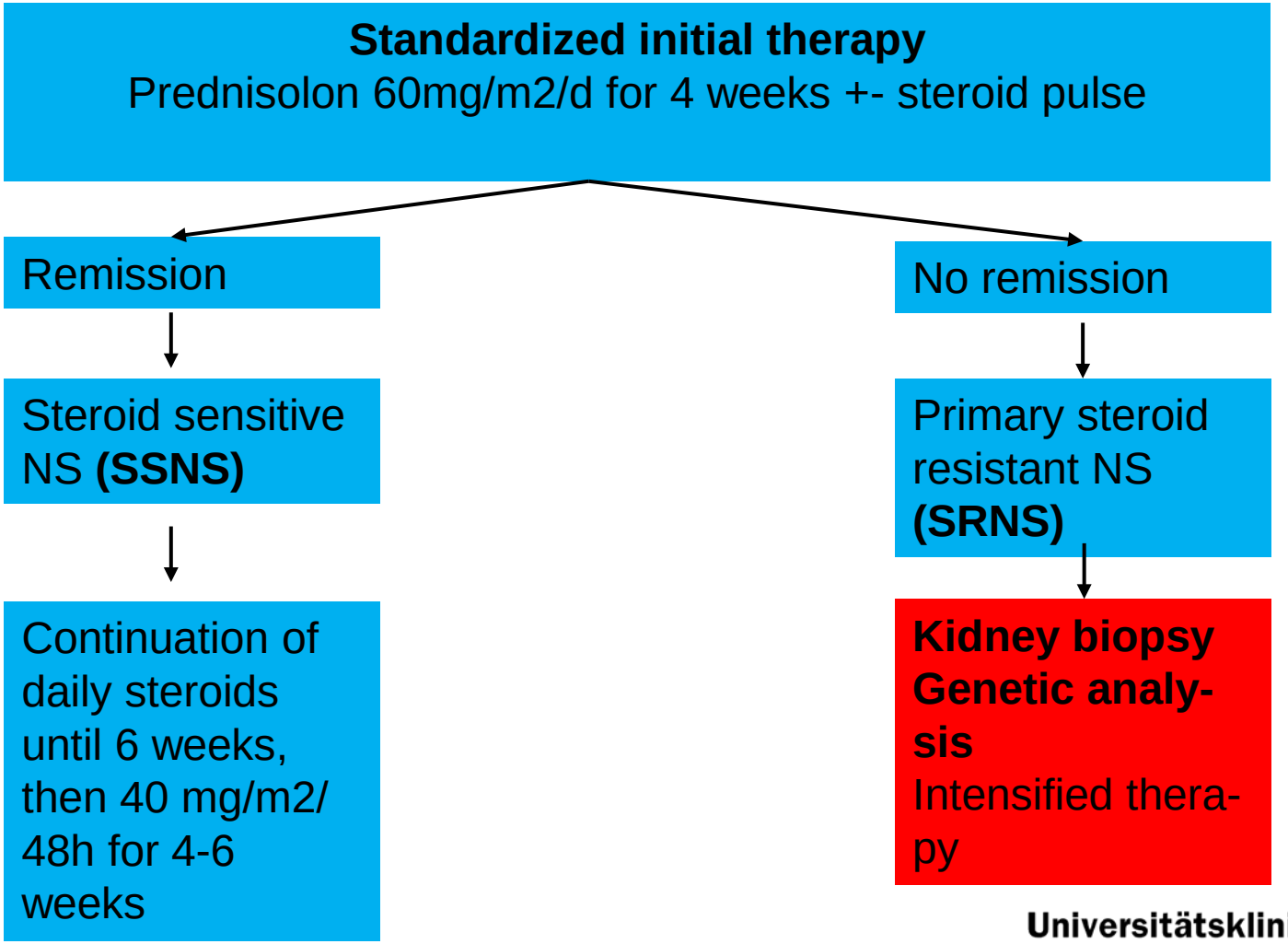
Standardized approach to nephrotic syndrome (NS) in newborns and children



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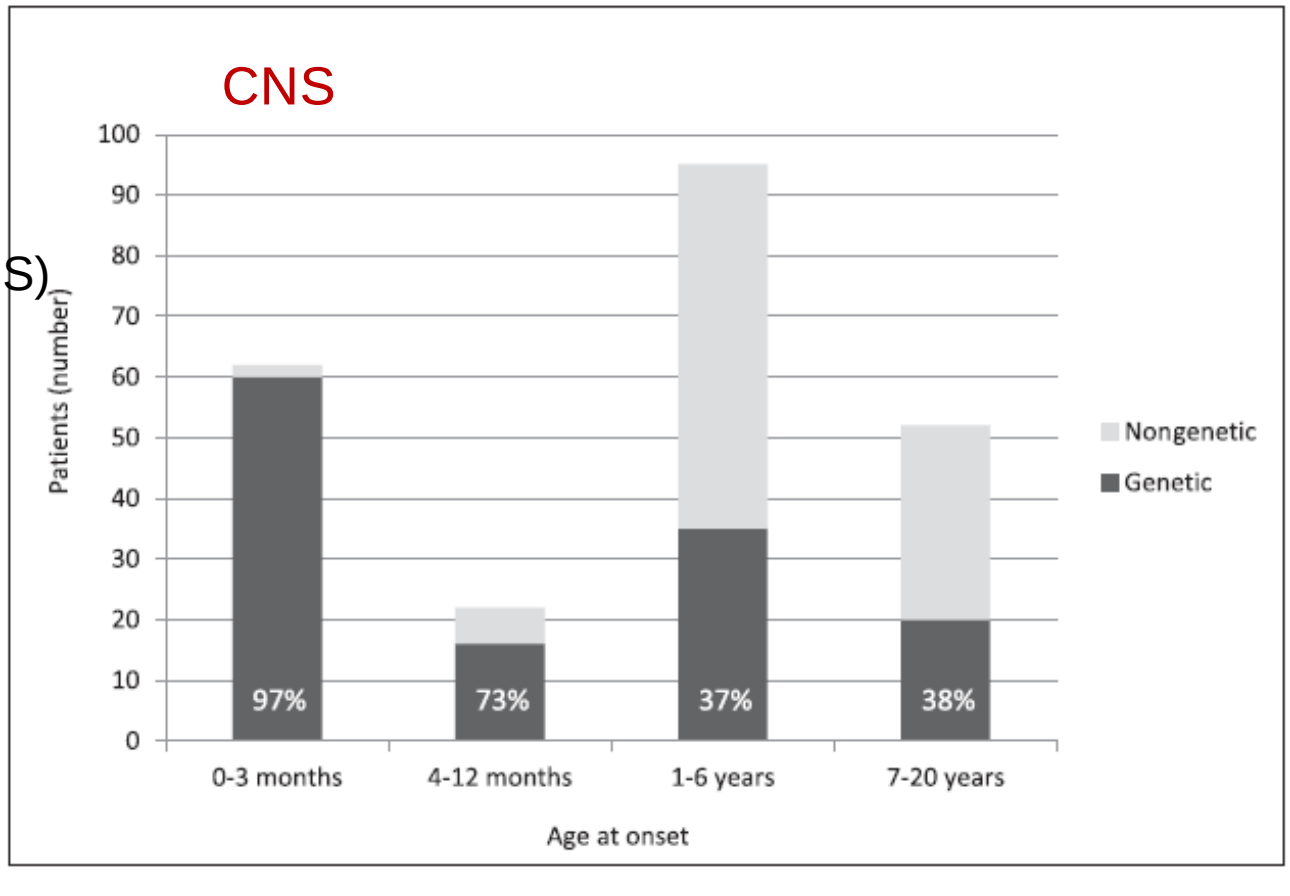
Rapid Response to Cyclosporin A and Favorable Renal Outcome in Nongenetic Versus Genetic Steroid–Resistant Nephrotic Syndrome

Anja K. Büscher, Bodo B. Beck,† Anette Melk,‡ Julia Hoefele,§ Birgitta Kranz,‖ Daniel Bamborschke,† Sabrina Baig,‡ Bärbel Lange-Sperandio,¶ Theresa Jungraithmayr,** Lutz T. Weber,†† Markus J. Kemper,‡‡ Burkhard Tönshoff,§§ Peter F. Hoyer,* Martin Konrad,‖ and Stefanie Weber* for the German Pediatric Nephrology Association (GPN)*

231 patients with CNS/ SRNS

57% with genetic disease (97% in CNS,14% in SRNS)

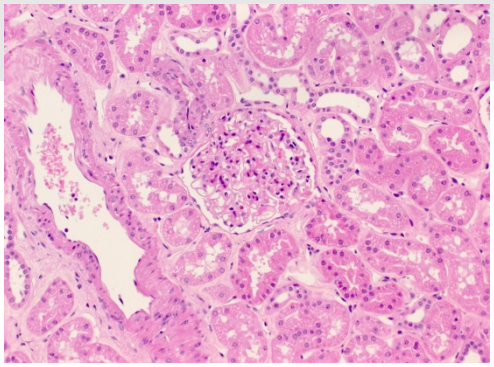


Renal Biopsy in CNS and SRNS

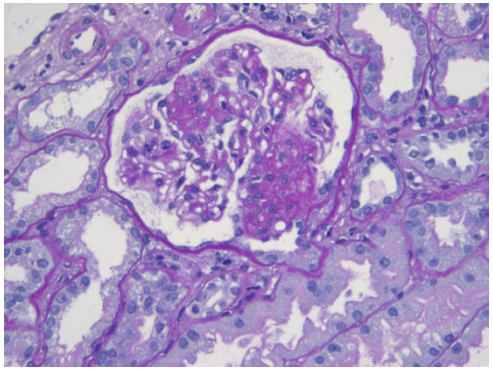
- **Nongenetic disease:**
  - 23% MCN
  - 69% FSGS
- **Genetic disease (CNS vs SRNS):**
  - 21% and 66% **FSGS**
  - 40% and 14 % **DMS** (→ suspicious for genetic origin)
- In patients with FSGS and MCN the prognostic value of renal histology is limited

  → genetic testing:

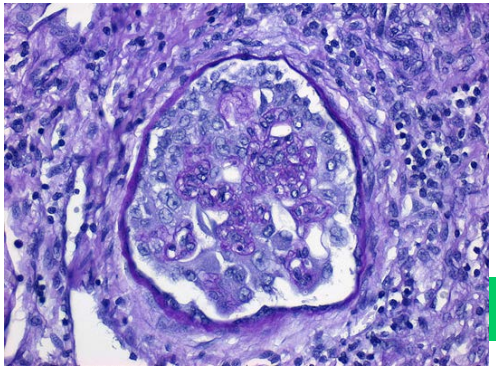
  - genetic forms of FSGS are often resistant to steroid treatment
  - genetic forms of FSGS carry a low risk of recurrence after renal tx



MCN



FSGS



DMS

(Büschges et al. CJASN 2016)

Rapid Response to Cyclosporin A and Favorable Renal Outcome in Nongenetic Versus Genetic Steroid–Resistant Nephrotic Syndrome

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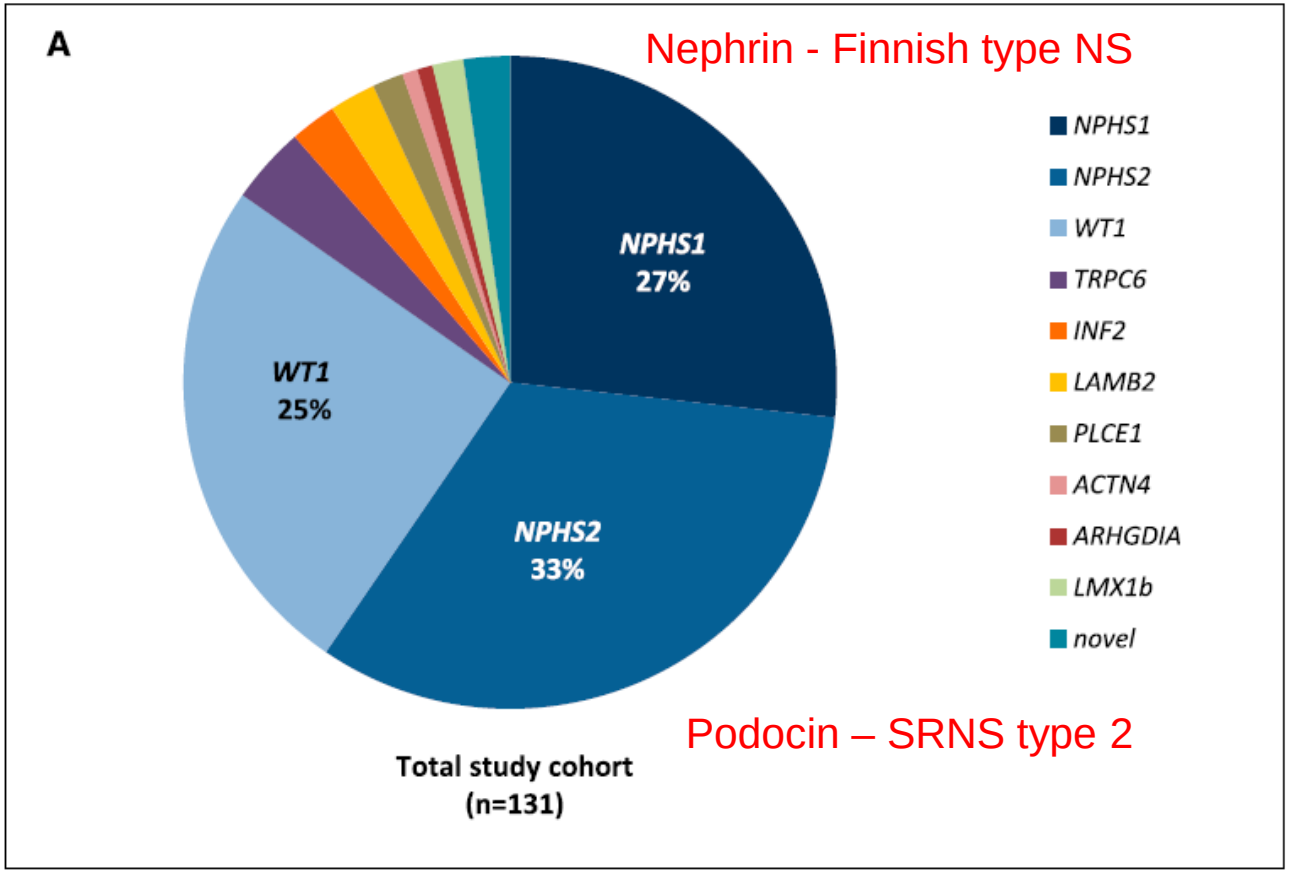
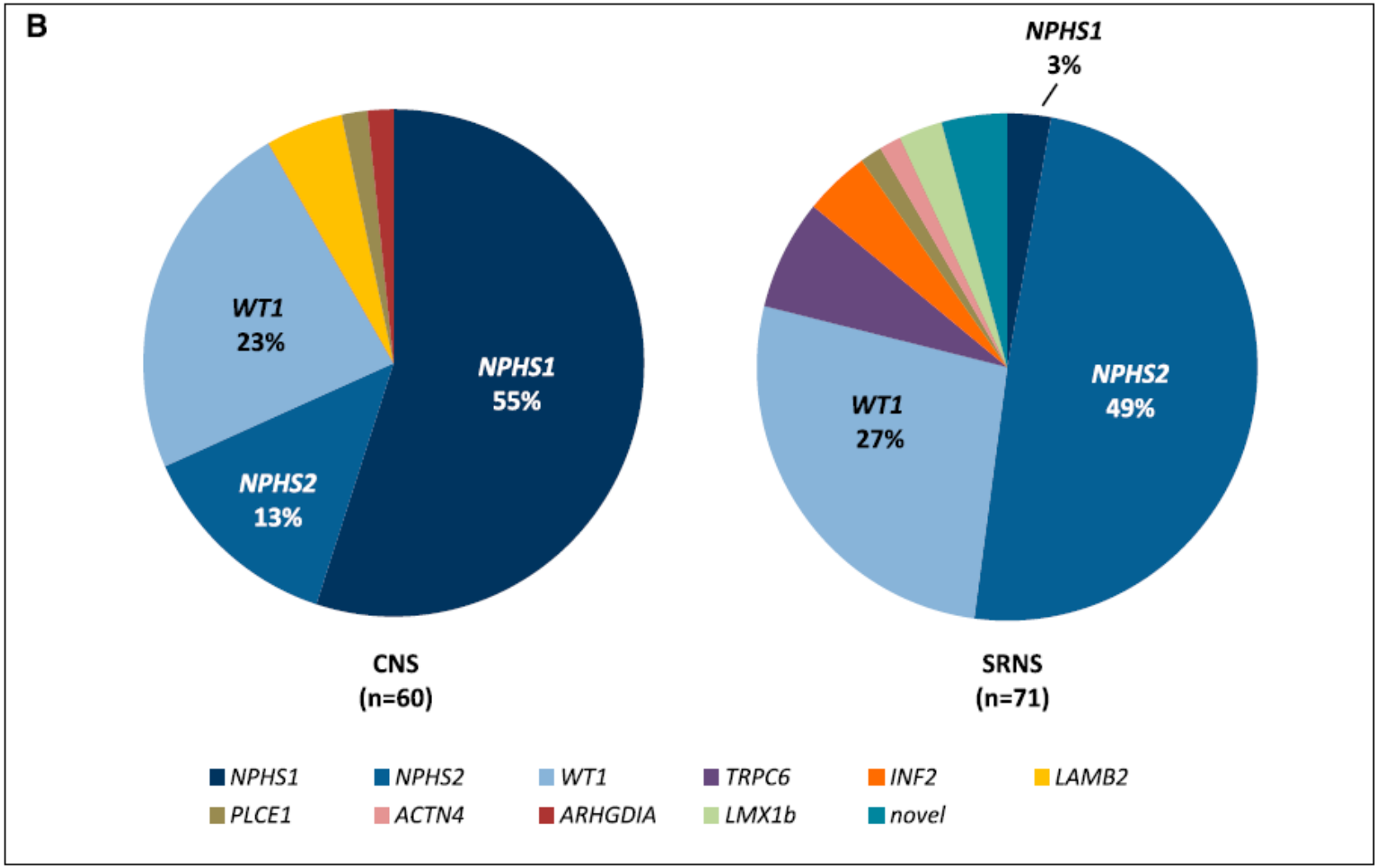
- 50 different genes causing FSGS
- 3 major genes cover 85%

WT1→ DMS (Denys-Drash)
FSGS (Frasier)
+-nephroblastoma



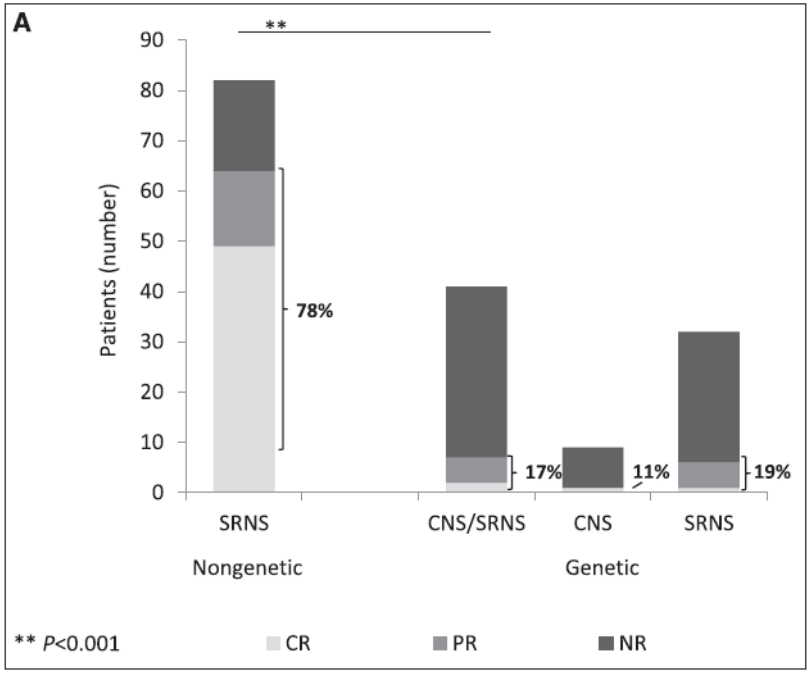
(CJASN 2016)

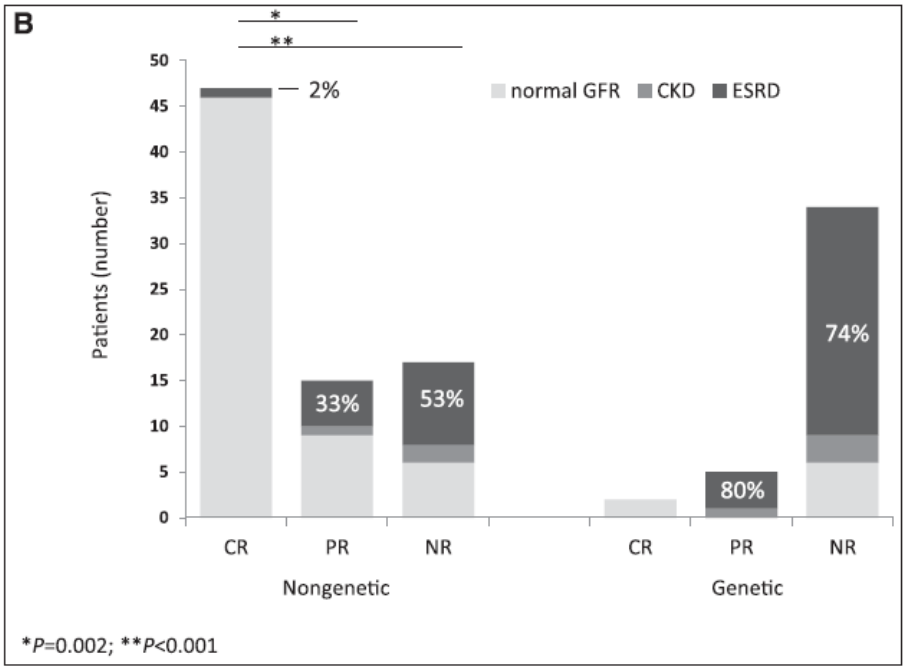
Congenital nephrotic syndrome (CNS) versus Steroid-resistant nephrotic syndrome (SRNS)



(Büschges et al. CJASN 2016)

Response to cyclosporin A (CsA) treatment (A) and renal outcome (B) in either nongenetic or genetic disease





→Genetic diseases respond differentially:

- sig. lower rate of complete remission (CR)
- sig. higher rate of ESRD

(Büschges et al. CJASN 2016)

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Role of genetics in renal diagnosis- Genetic renal disease

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- Autosomal dominant and recessive tubulointerstitial kidney disease (ADTKD, nephronophthisis)

MECHANISMS OF DISEASE

Alport's Syndrome, Goodpasture's Syndrome, and Type IV Collagen

Billy G. Hudson, Ph.D., Karl Tryggvason, M.D., Ph.D.,
Munirathinam Sundaramoorthy, Ph.D., and Eric G. Neilson, M.D.

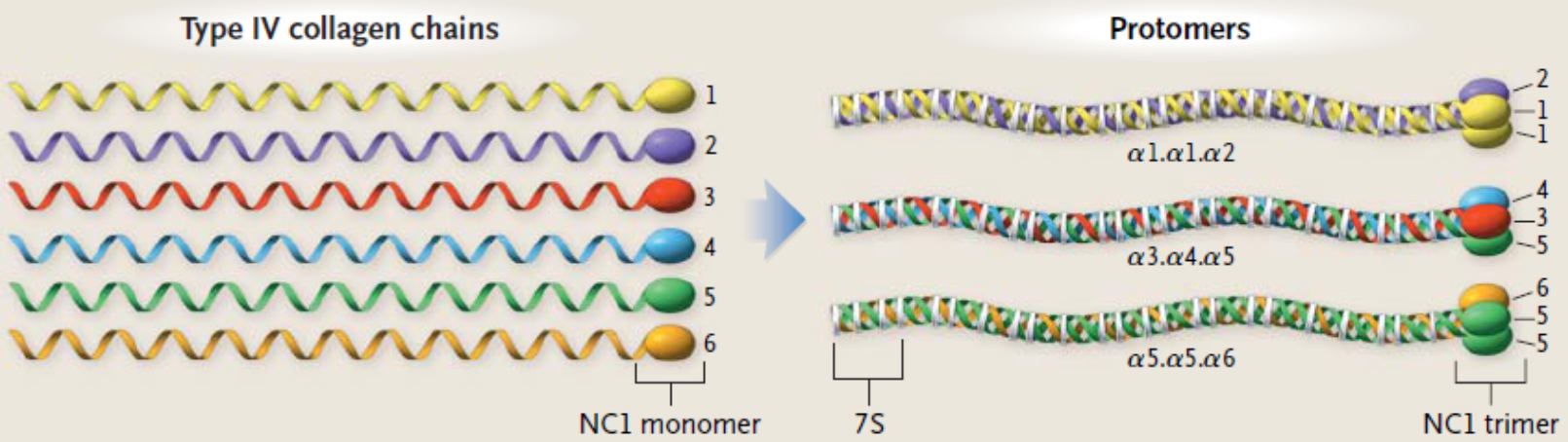


Figure 1. Triple Helical Organization of the Type IV Collagen Family.

Six genetically distinct α chains are arranged into three triple helical protomers that differ in their chain composition. Each protomer has a 7S triple helical domain at the N-terminal; a long, triple helical, collagenous domain in the middle of the molecule; and a noncollagenous (NC1) trimer at the C-terminal. Interruptions in the Gly–Xaa–Yaa amino acid sequence at multiple sites along the collagenous domain (white rings) confer flexibility, allowing for looping and supercoiling of protomers into networks. The selection of α chains for association into trimeric protomers is governed by molecular recognition sequences encoded within the hypervariable regions of NC1 domains.[35,37]

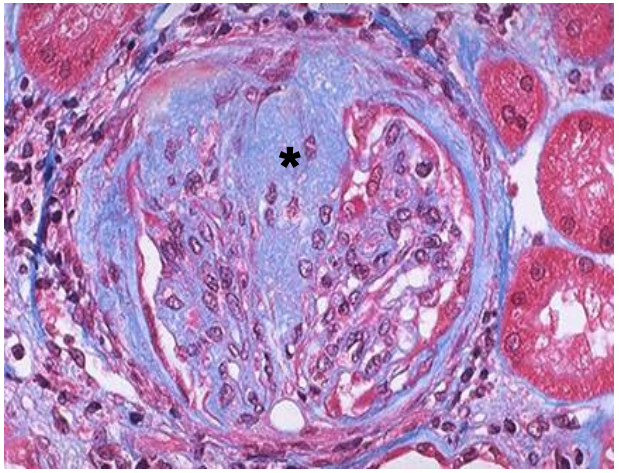
1927: first description by Cecil Alport

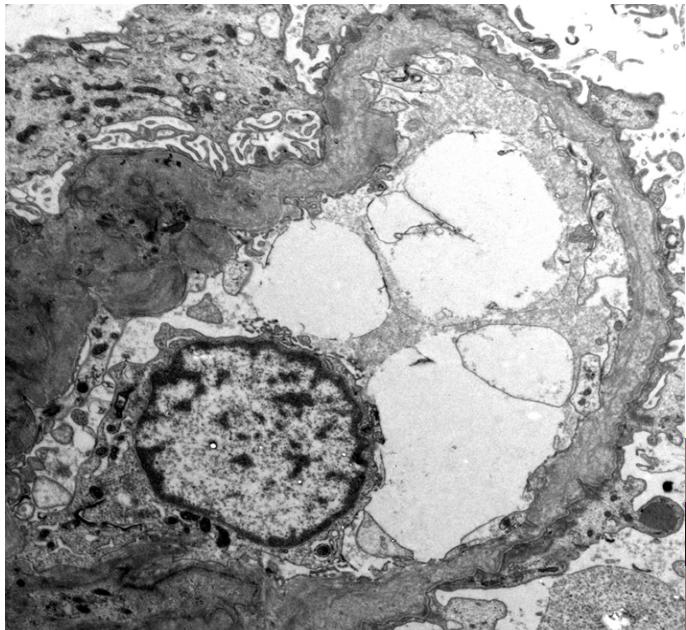
(NEJM 2003)

Clinical pathophysiology of Alport`s syndrome

Table 1. Clinical Pathophysiology of Alport's and Goodpasture's Syndromes.

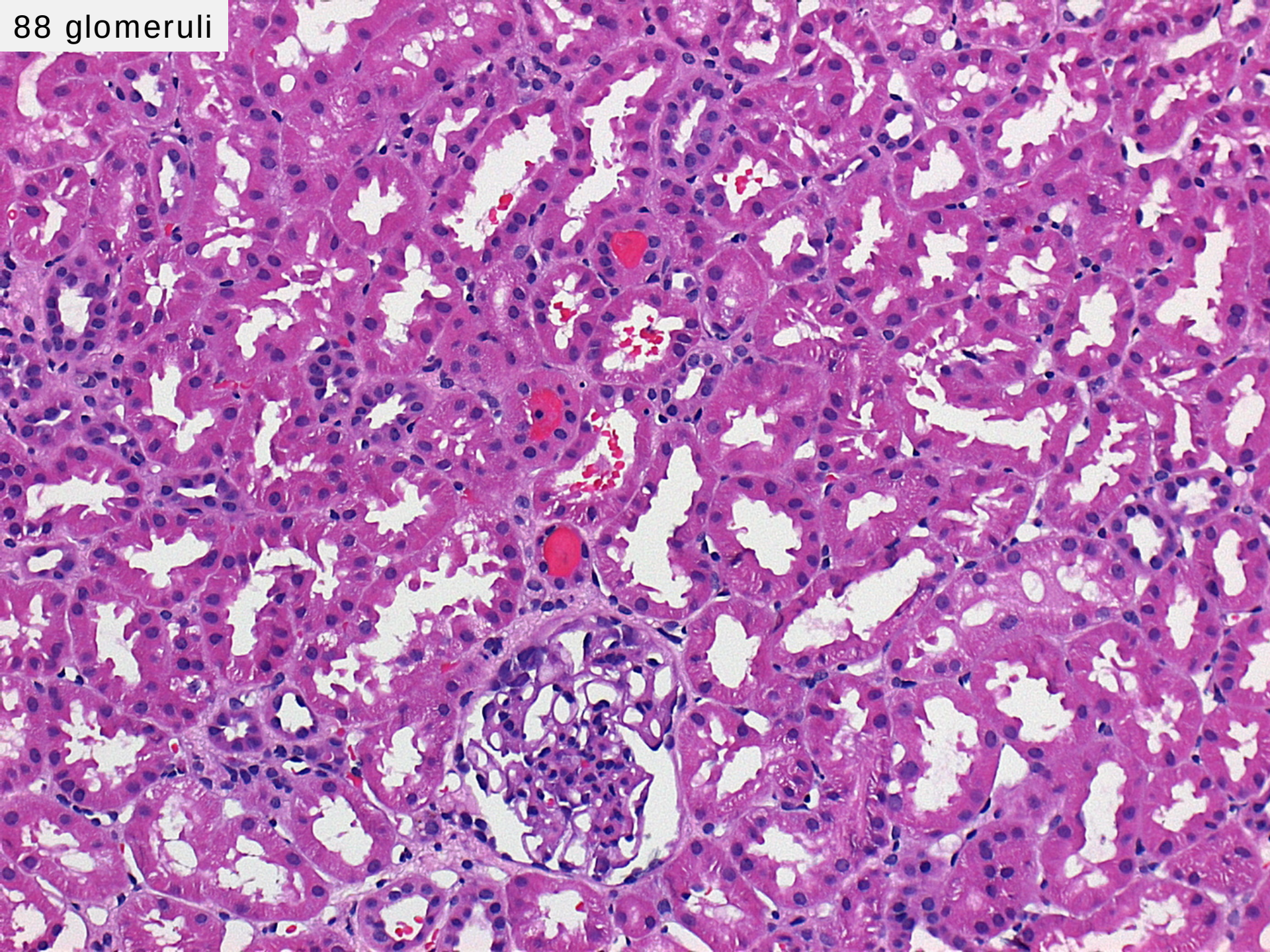
Disease	Mechanism	Clinical Description
Alport's syndromes		
X-linked		
Adult	Some missense mutations or splice variants in the *COL4A5* gene, producing a reduction or distortion in $\alpha3.\alpha4.\alpha5$(IV) and $\alpha5.\alpha5.\alpha6$(IV) networks	Delayed onset of renal failure (>30 yr of age), with mild deafness in men; less severe in female carriers
Juvenile	Deletions, nonsense mutations, or missense mutations in the *COL4A5* gene, producing a loss of $\alpha3.\alpha4.\alpha5$(IV) and $\alpha5.\alpha5.\alpha6$(IV) networks	Early onset of renal failure (<30 yr of age) in men, with frank deafness and often lenticonus
Leiomyomatosis	Deletions from the *COL4A5* gene through to the second exon of the *COL4A6* gene, producing a loss of $\alpha3.\alpha4.\alpha5$(IV) and $\alpha5.\alpha5.\alpha6$(IV) networks and smooth-muscle tumors	Early onset of renal failure, with esophageal dysfunction, genital leiomyomas, and occasional posterior cataract
Recessive	Homozygous or compound heterozygous nonsense mutations, missense mutations, frame shifts, small deletions, or splice variants in *COL4A3* or *COL4A4* gene, producing a loss of the $\alpha3.\alpha4.\alpha5$(IV) network	Early onset of renal failure (<30 yr of age) in both sexes
Dominant	Missense mutation in the *COL4A4* gene; splice variants or short in-frame deletions of the collagenous region; or shortened signal-peptide sequences in the *COL4A3* gene; defects produce aberrations in the $\alpha3.\alpha4.\alpha5$(IV) network	Renal failure of varying severity
Benign familial hematuria	Missense mutations in the *COL4A3* gene or splice variants, frame shifts, or missense mutations in the *COL4A4* gene, inherited in an autosomal dominant fashion, producing a subtle decrease in the $\alpha3.\alpha4.\alpha5$(IV) network	Mild hematuria with thin basement membranes and rare hypertension or proteinuria that is nonprogressive; findings on kidney biopsy have been relatively normal
Nail–patella syndrome	Autosomal dominant mutation in the LMX1B transcription factor, which regulates the *COL4A3* or *COL4A4* gene as well as the genes encoding nephrin, podocin, and *CD2*-associated protein	Variable penetrance, but some children have nephrotic syndrome and skeletal and nail dysplasias

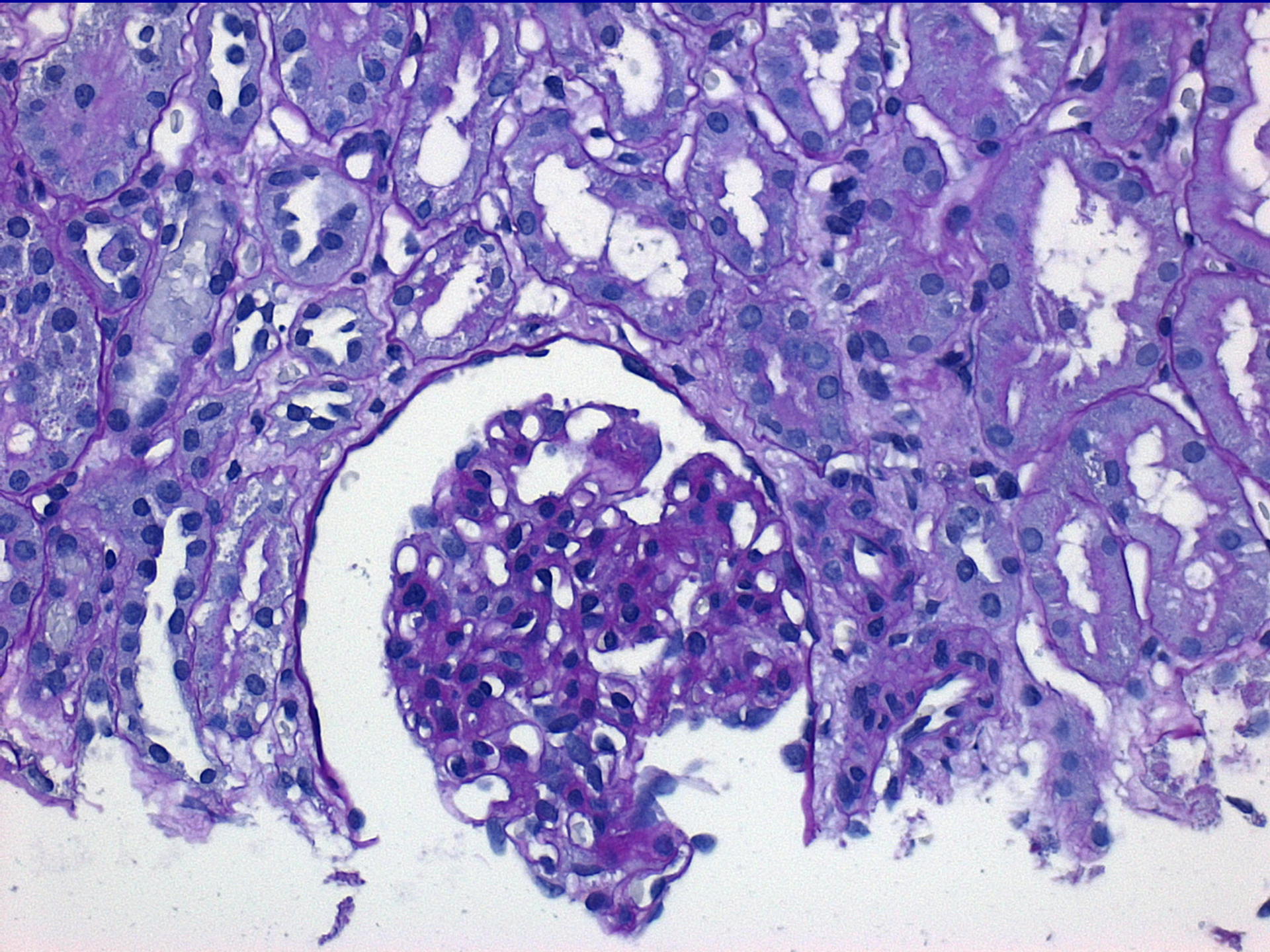


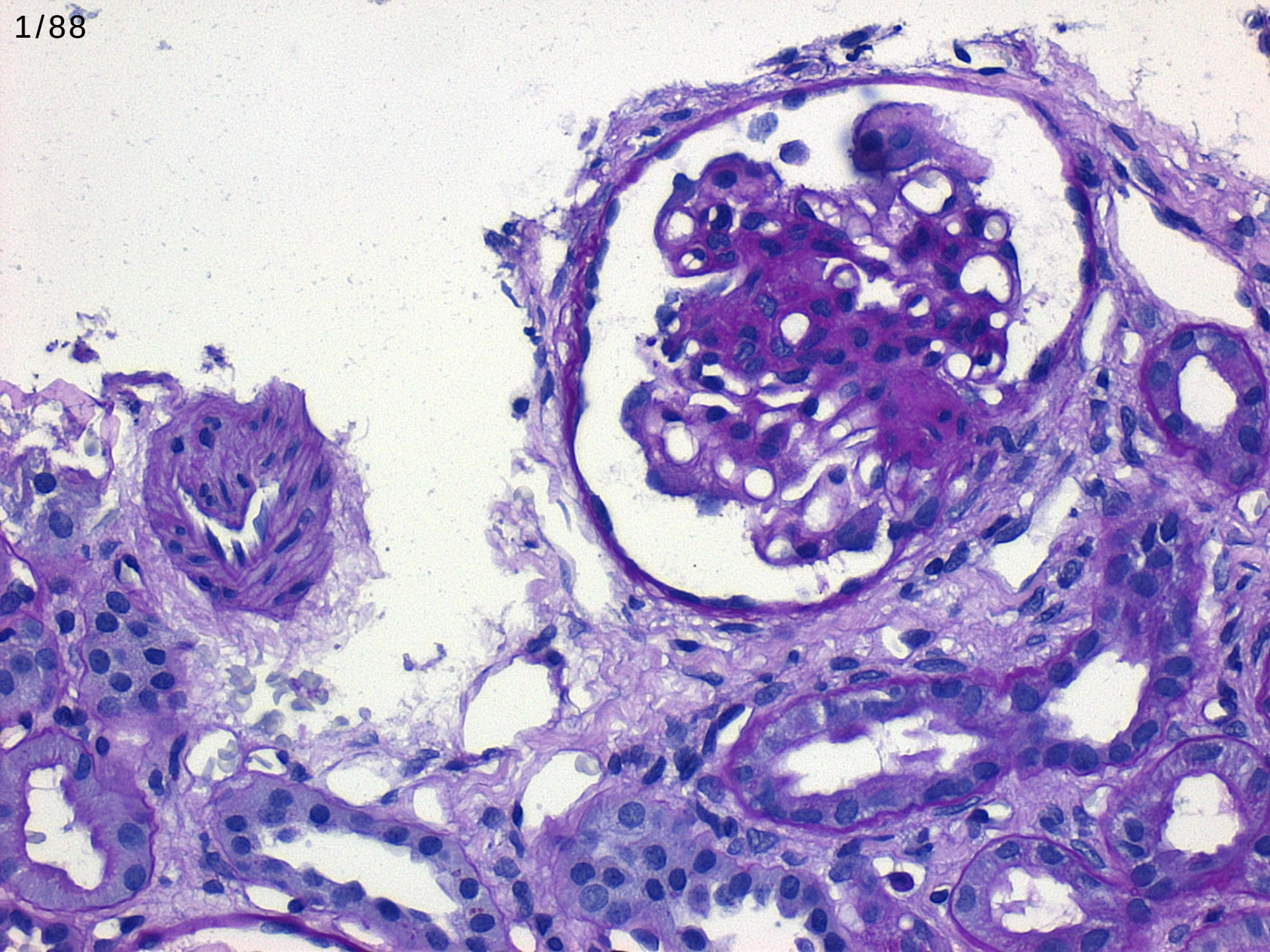


(NEJM 2003)

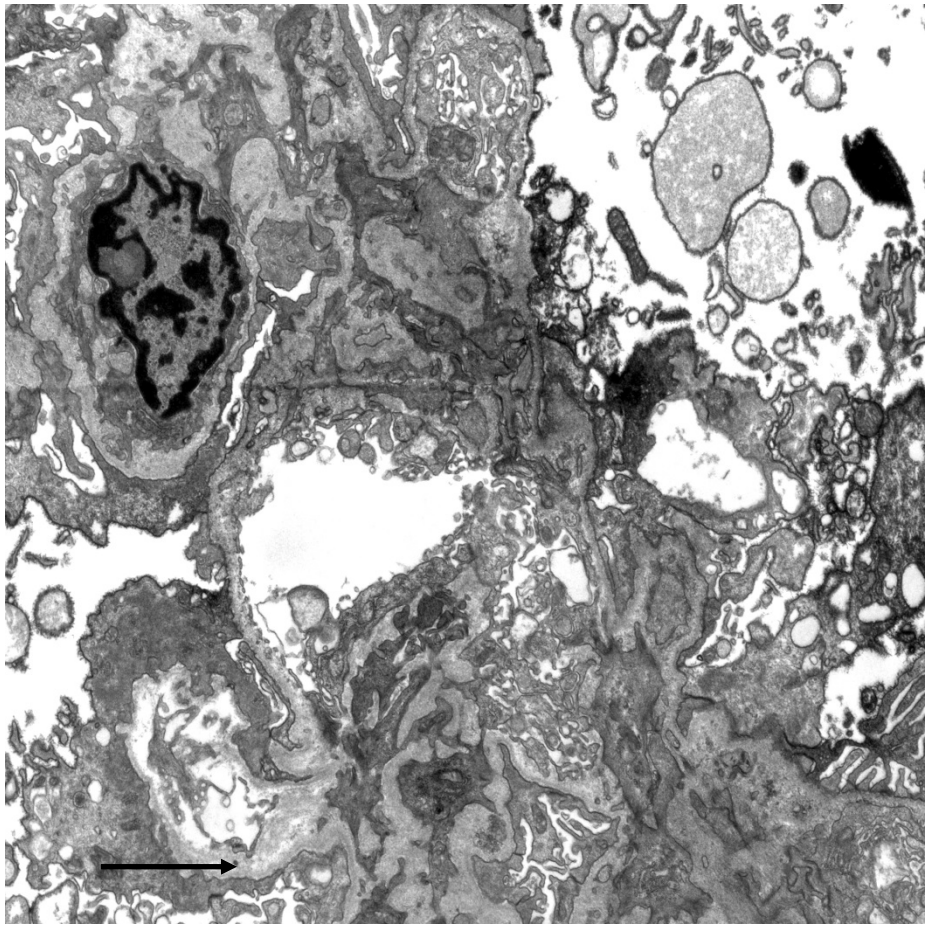
The interesting case

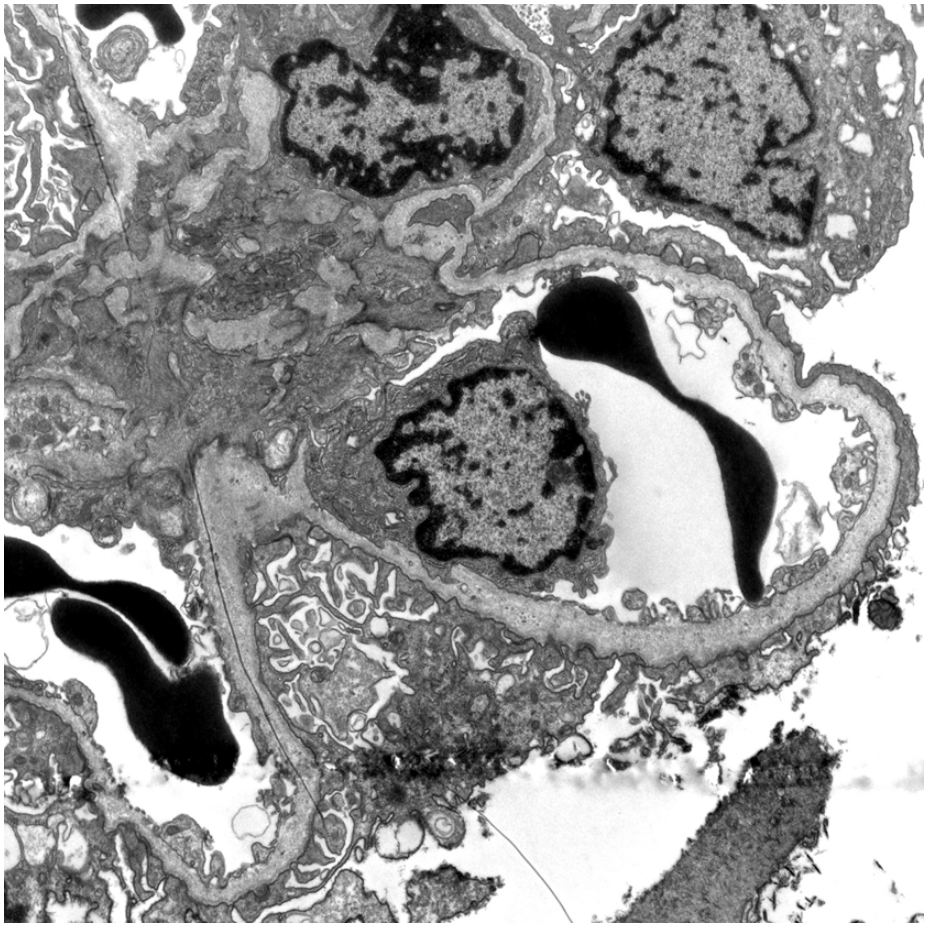

88 glomeruli





Electron microscopy





Diagnosis

- Global (2/88) and focal-segmental (1/88) glomerulosclerosis
- EM:
  glomerular basement thickness 135-889 µm
  structural alterations: lamellation and splicing

→ despite negative genetics highly suggestive for Alports disease (DD: MYH9-defect)

- **Additional information:**
  genetic testing was performed 11 ys ago and was now repeated yielding a novel disease causing mutation in COL4A5….

Identification of 47 novel mutations in patients with Alport syndrome and thin basement membrane nephropathy

Stefanie Weber[1] · Katja Strasser[1] · Sabine Rath[2] · Achim Kittke[2] · Sonja Beicht[2] · Martin Alberer[3] · Bärbel Lange-Sperandio[4] · Peter F. Hoyer[1] · Marcus R. Benz[5] · Sabine Ponsel[4] · Lutz T. Weber[5] · Hanns-Georg Klein[2] · Julia Hoefele[2,6]

Table 4 Summary of different *COL4A3*, *COL4A4*, and *COL4A5* mutations found in this study

Type of mutation	*COL4A3*	*COL4A4*	*COL4A5*
Missense			
Glycine mutation	13	6	15
Other mutation	4	2	5
Nonsense	1	2	1
Silent	1	0	2
Splice site	0	0	11
Small insertion	0	2	3
Small deletion	2	3	3
Gross insertion	0	0	2
Gross deletion	0	0	1
Total	21	15	43

Gene	ARUP®	HGMD®	LOVD	Novel (identified in this study)	Percentage added (ARUP®/HGMD®/LOVD)
COL4A3	–	156	266	16	-/10/6
COL4A4	–	115	268	5	-/4/2
COL4A5	771	814	1168	26	3/3/2

Data are presented as the number of mutations, unless indicated otherwise

[a] Novel mutations (those found in this study) were compared with databases recording mutations causing Alport syndrome (ATS) and thin basement membrane nephropathy (TBMN): ARUP® (ARUP® Laboratories), HGMD® (Human Gene Mutation Database, professional release 2015.1, Cardiff, UK), and LOVD (Leiden Open Variation Database, last update December 2013, Leiden, The Netherlands)

→ genetic (re-)testing important to confirm morphological findings

(Ped Nephrol 2016)

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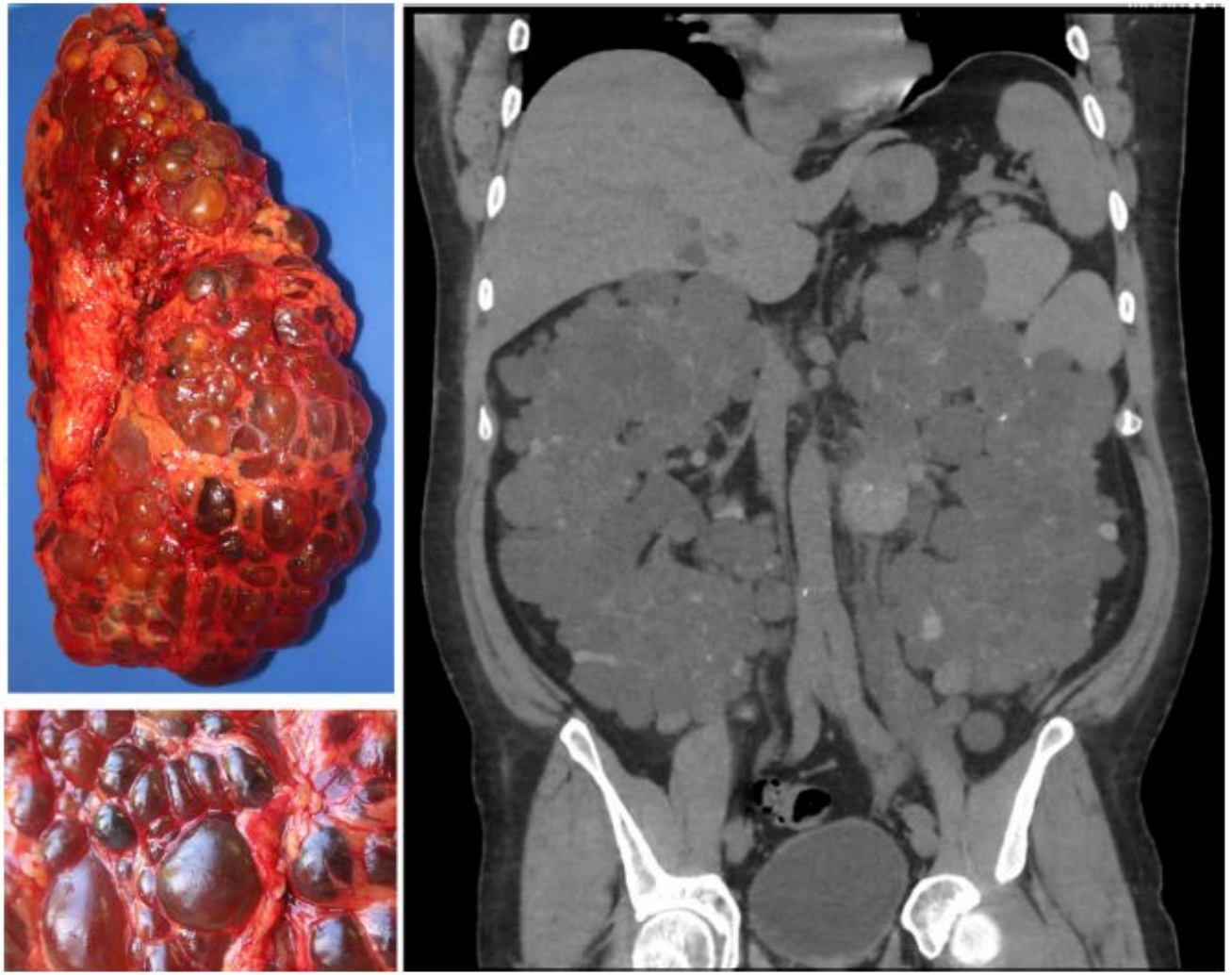
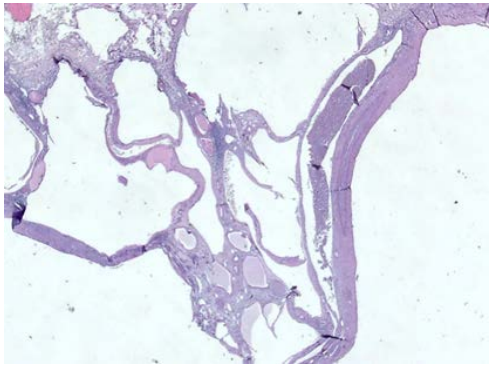
ADPKD – positive family history + presence of renal cysts on kidney imaging



(Rangan et al. 2015)

Autosomal dominant polycystic kidney disease (ADPKD)

- **most common monogenic (inherited) kidney disease** in Western countries (prevalence: 2.4/10,000 - 3.9/10,000) that accounts for 5-10% of ESRD in developed countries
- **systemic disease** resulting in deterioration in renal function
- mutations in two genes ***(PKD1* and *PKD2)***
- recently, the European Medicines Agency (EMA) approved the use of the **vasopressin V2 receptor antagonist tolvaptan** to slow the progression of cyst development and renal insuffi-ciency in adult ADPKD patients with CKD 1-3 at initiation of treatment with evidence of rapidly progressing disease.



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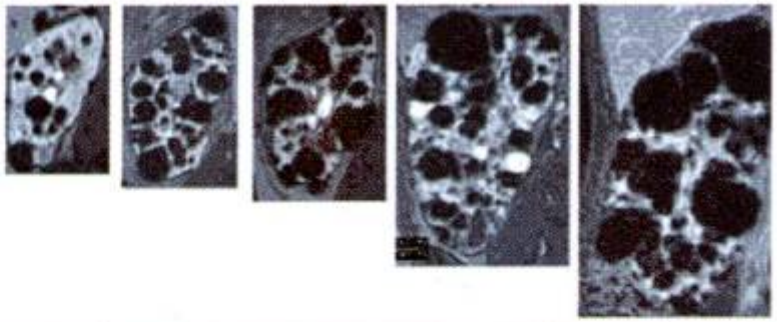
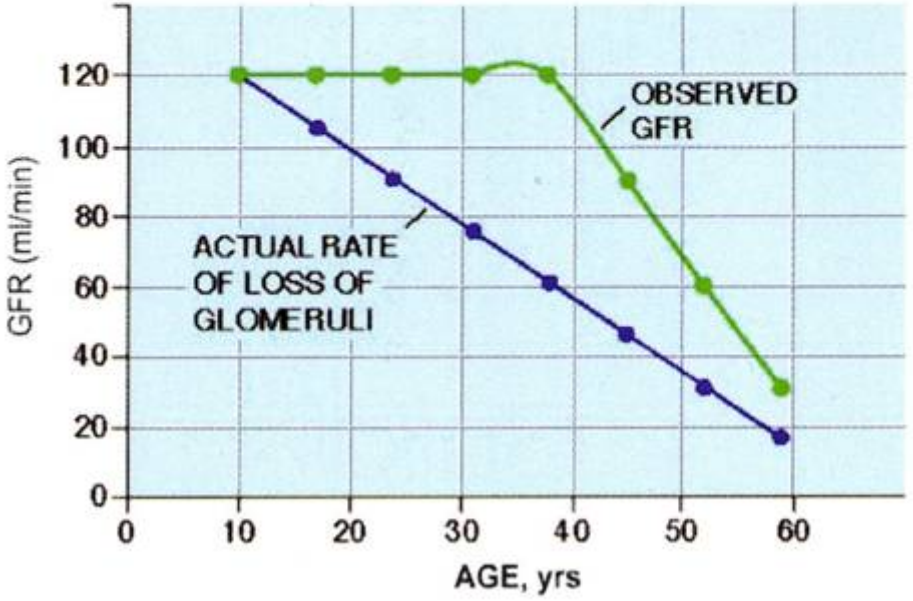
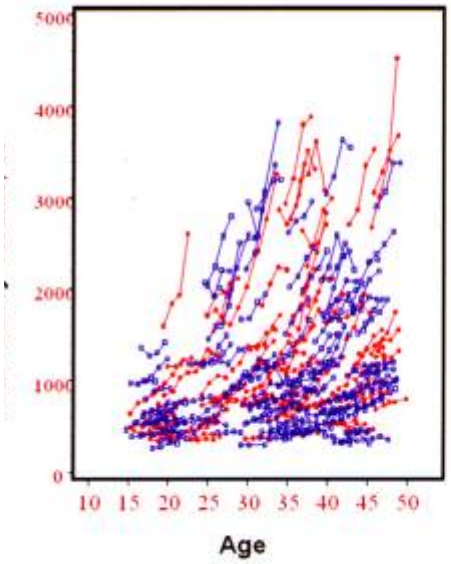
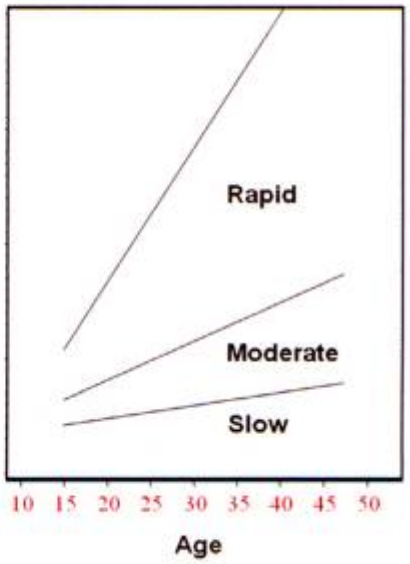
Monitoring of growth of cysts in ADPKD by MR









increase of kidney size: 5.27% per y

(Chapman 2007)

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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*

BACKGROUND

The course of autosomal dominant polycystic kidney disease (ADPKD) is often associated with pain, hypertension, and kidney failure. Preclinical studies indicated that vasopressin V_2-receptor antagonists inhibit cyst growth and slow the decline of kidney function.

2.8 vs 5.5. % per year

(03. November 2012)

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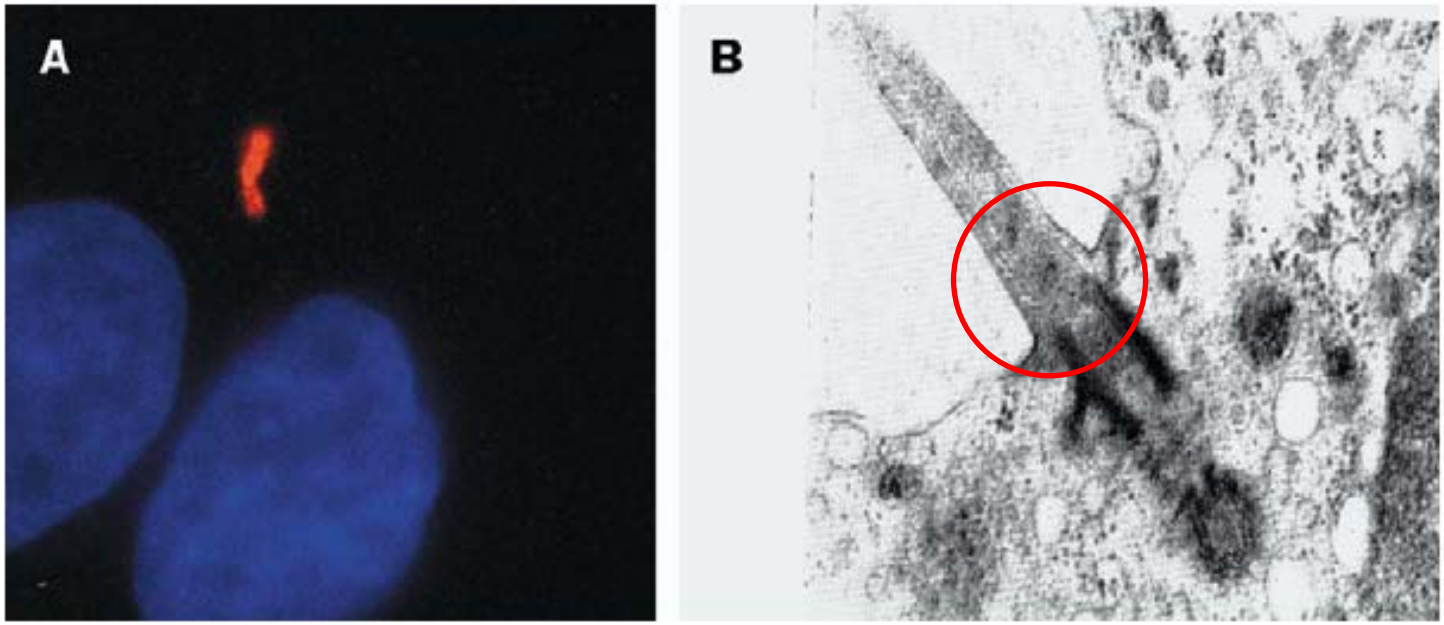
Rapid review

Polycystic kidney disease—the ciliary connection

Albert C M Ong, Denys N Wheatley

Polycystin → signaling pathways



structure of a primary cilia

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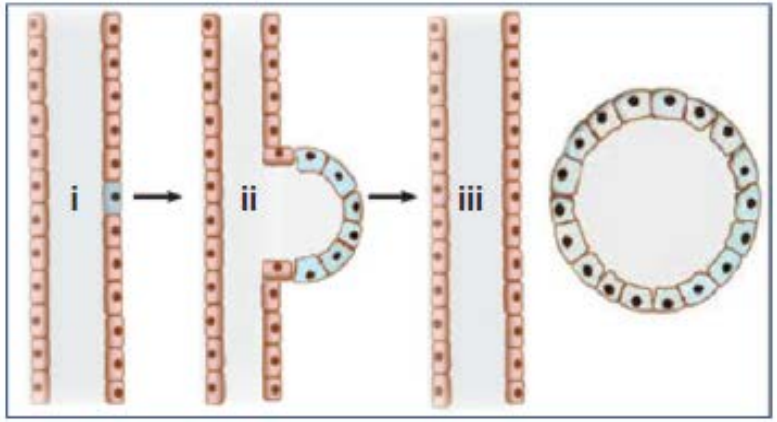
(Lancet 2003)

PATHOGENESIS

loss of heterocygosity of PKD in the distal nephron

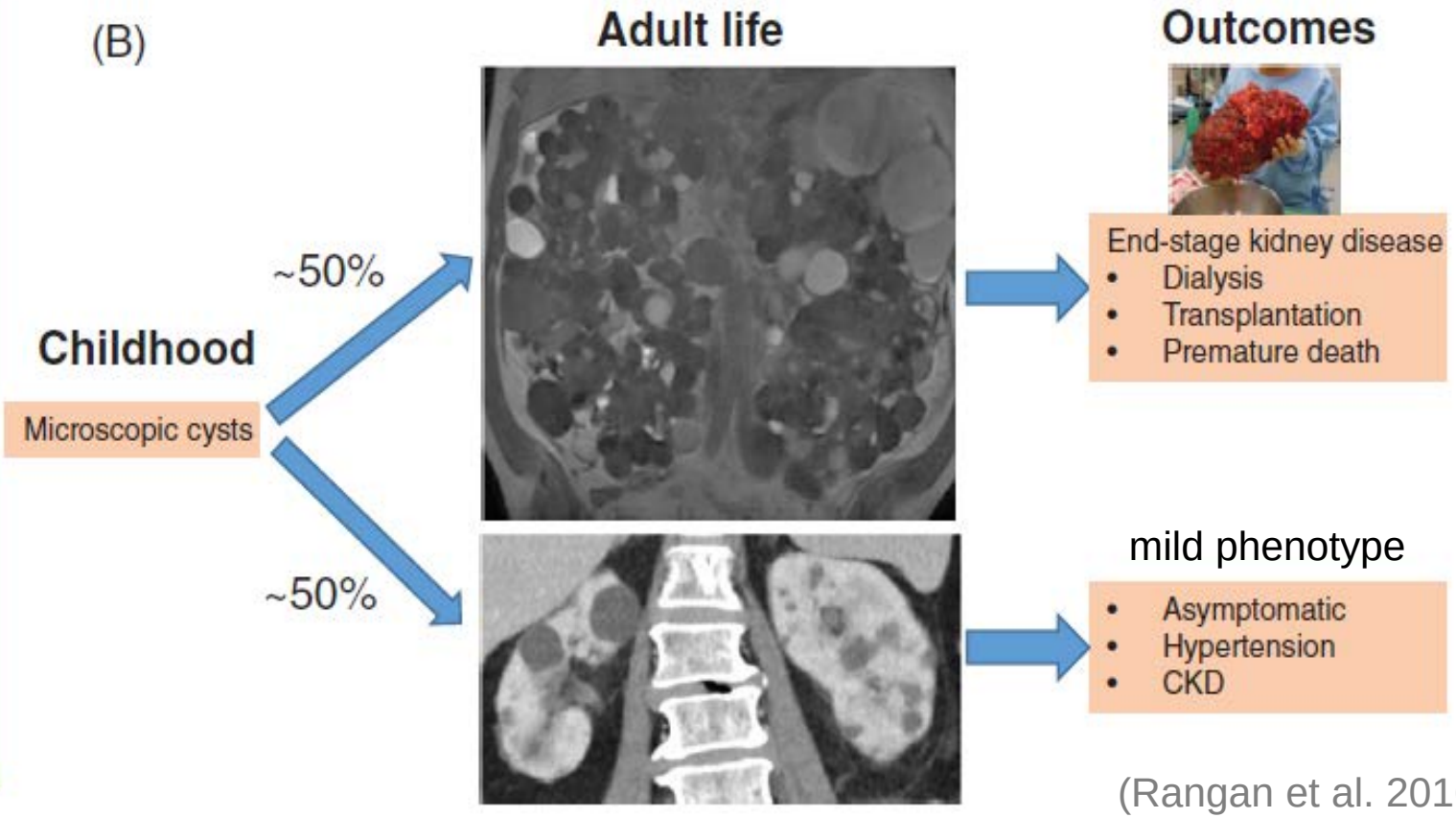
(A)



loss of cellular polarity, proliferation, transepithelial fluid secretion, ECM remodeling

NATURAL HISTORY

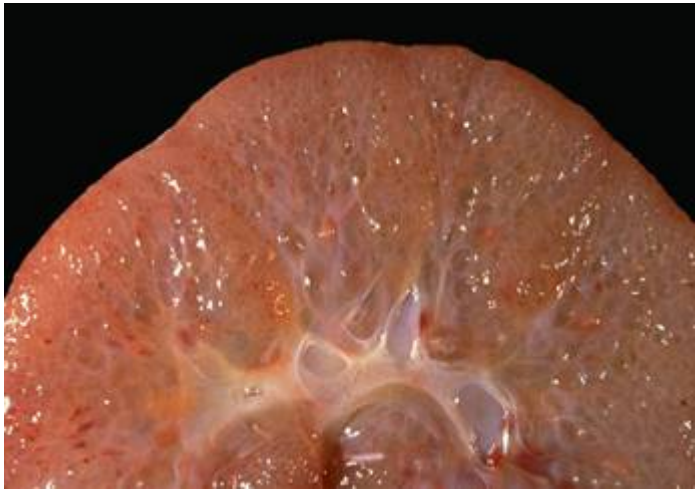
(B)

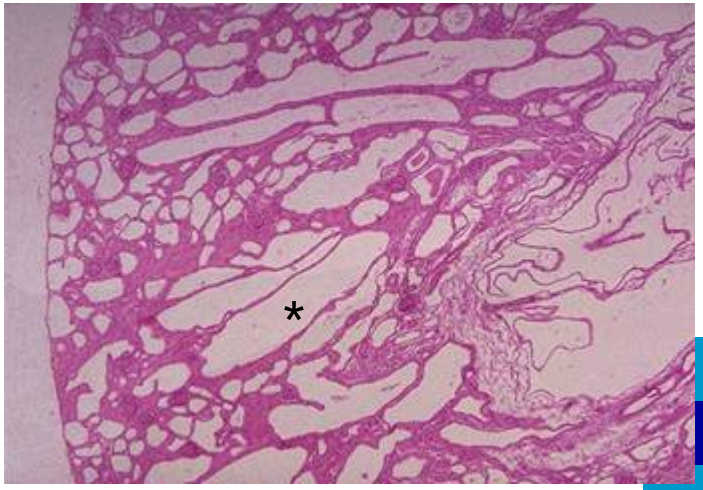


(Rangan et al. 2016)

Autosomal recessive polycystic kidney disease (ARPKD)

- Belongs to a group of **congenital hepatorenal fibrocystic syndromes** and is a cause of significant renal- and liver-related morbidity and mortality in children.
- > 300 mutations in the **PKHD1** gene (**fibrocystin**)
- The majority of individuals with ARPKD present in the **neonatal period** with enlarged echogenic kidneys.
- Renal disease is characterized by **nephromegaly, hypertension, and varying degrees of renal dysfunction**.
- >50% of affected individuals with ARPKD progress to **ESRD** within the first decade of life
- ESRD may require **kidney transplantation**.

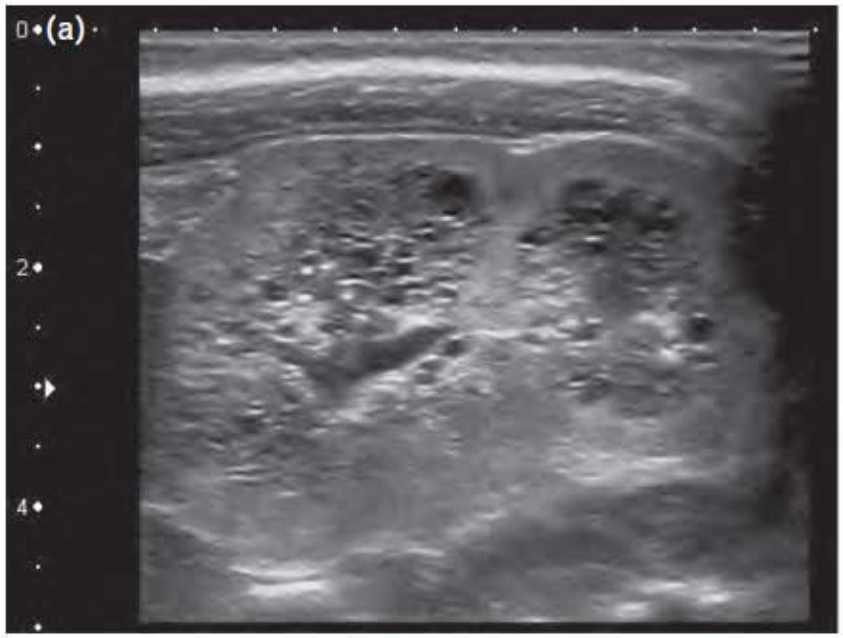




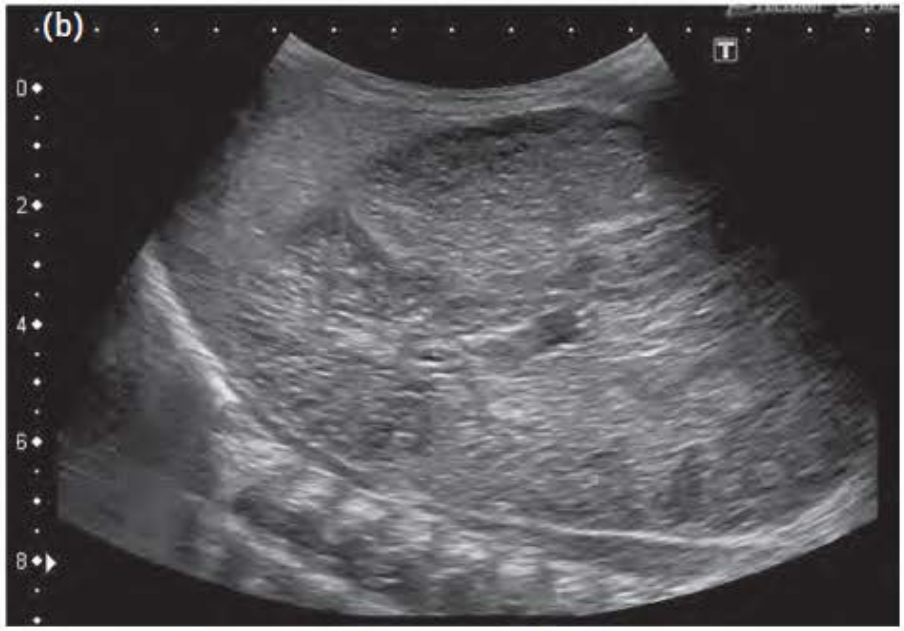
(Sweeney WE, Avner ED, 2016)

Clinical manifestations of autosomal recessive polycystic kidney disease

Peter F. Hoyer

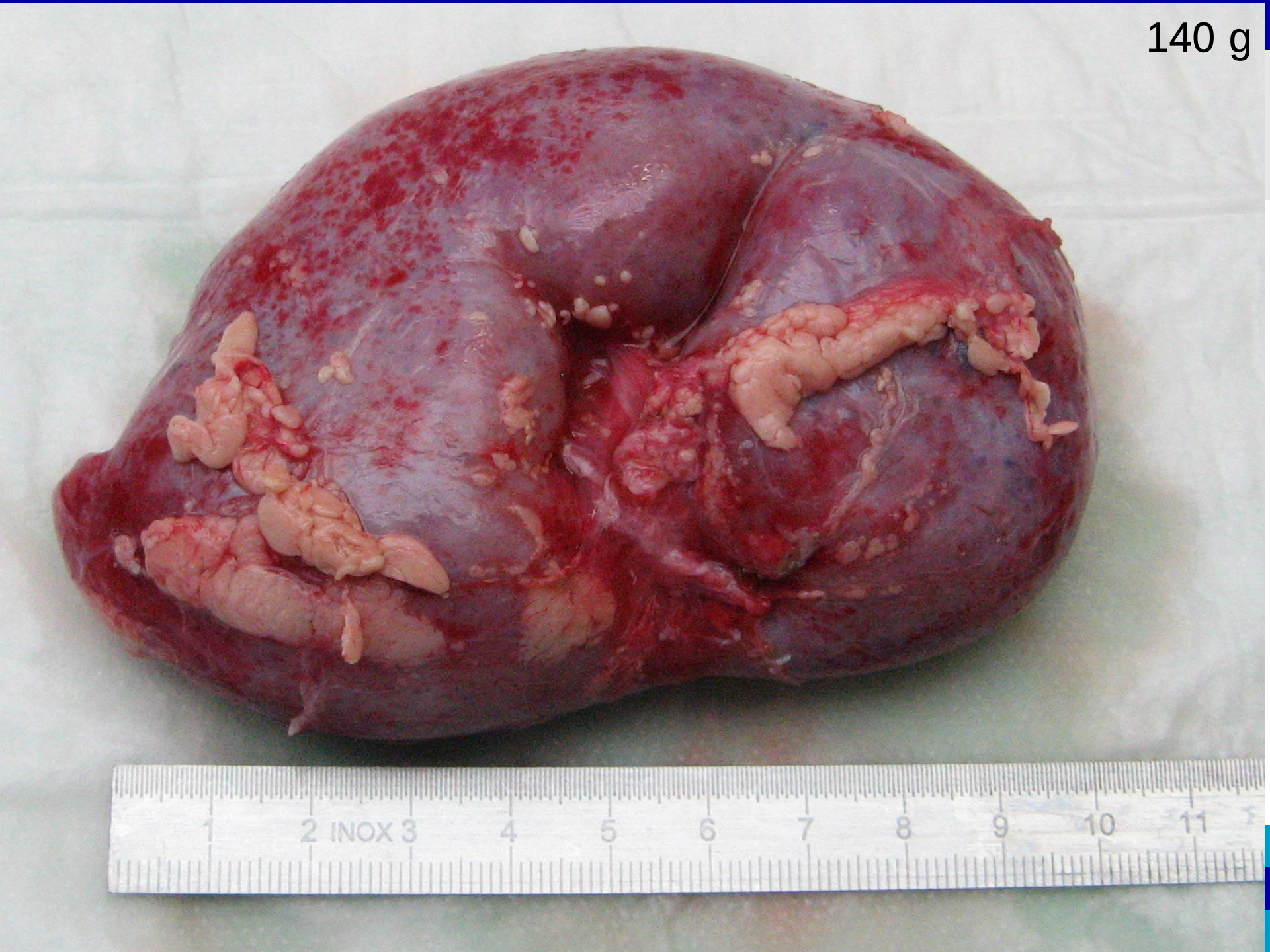


Predominantly medullary cyst distribution



Corticomedullary cyst distribution

Difficult case


140 g
1
2 INOX 3
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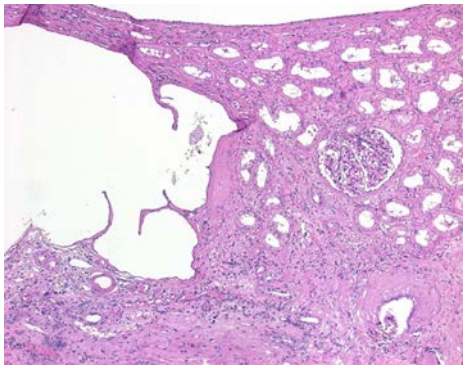
What is it ?

- ARPKD ?
- ADPKD
- Anything else ?

Extended family history: father with renal cysts….



Genetic testing:
sporadic mutations in both parents resulting in an ADPKD-like disease

Morphology important to detect findings or patterns that do not fit
→ genetic testing to confirm suspicion !

Role of genetics in renal diagnosis- Genetic renal disease

- Congenital steroid-resistant nephrotic syndrome (CNS): NPHS1, NPHS2, TRPC6, ACTN4, INF2, WT-1

- Collagen type IV associated diseases (thin basement GN, Alport`s disease)

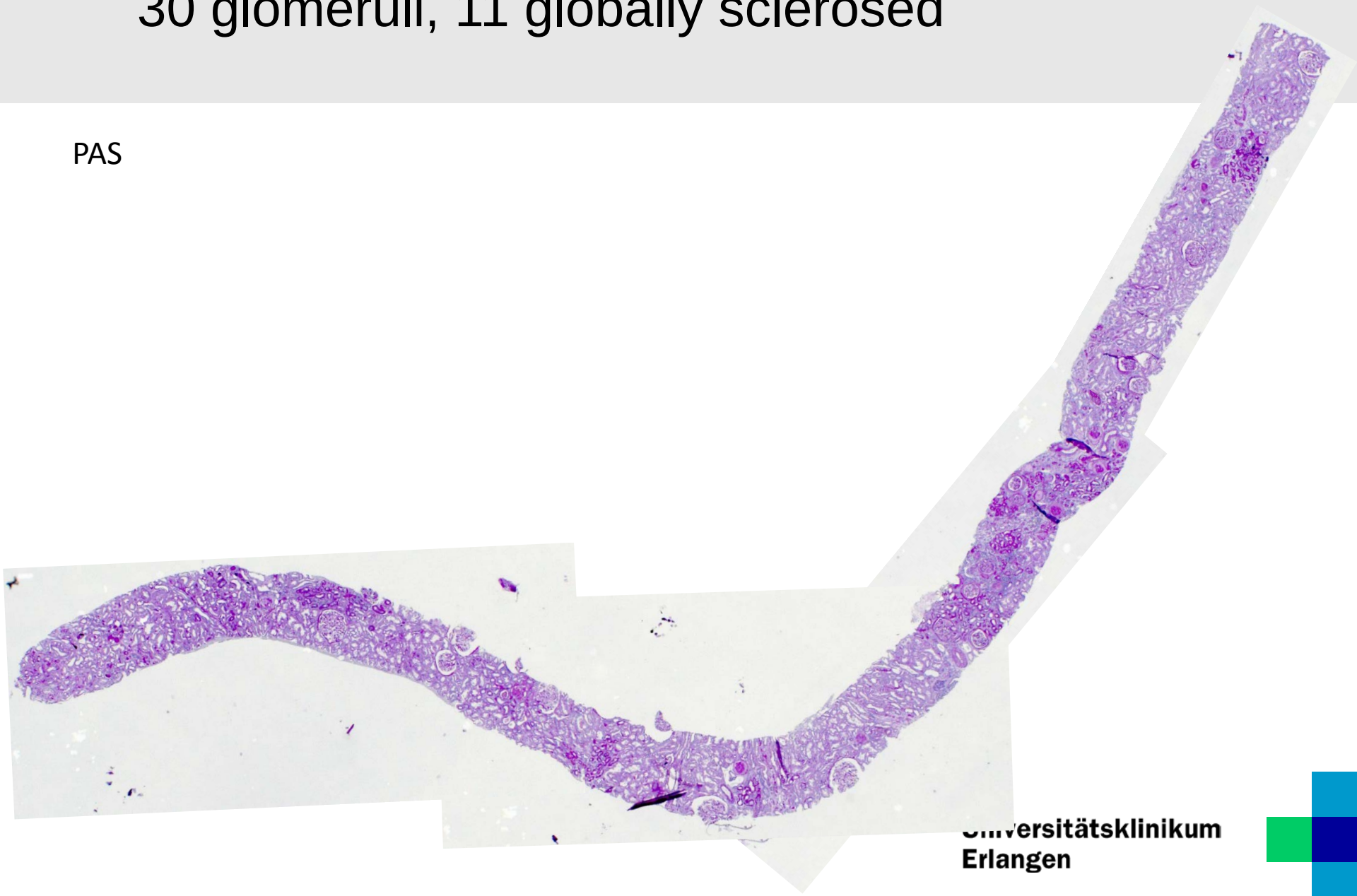
- Polycystic kidney disease (PKD):
  Autosomal dominant and recessive polycystic kidney disease (ADPKD, ARPKD)

- Autosomal dominant and recessive tubulointerstitial kidney disease (ADTKD, nephronophthisis)

Interesting case

30 glomeruli, 11 globally sclerosed

PAS



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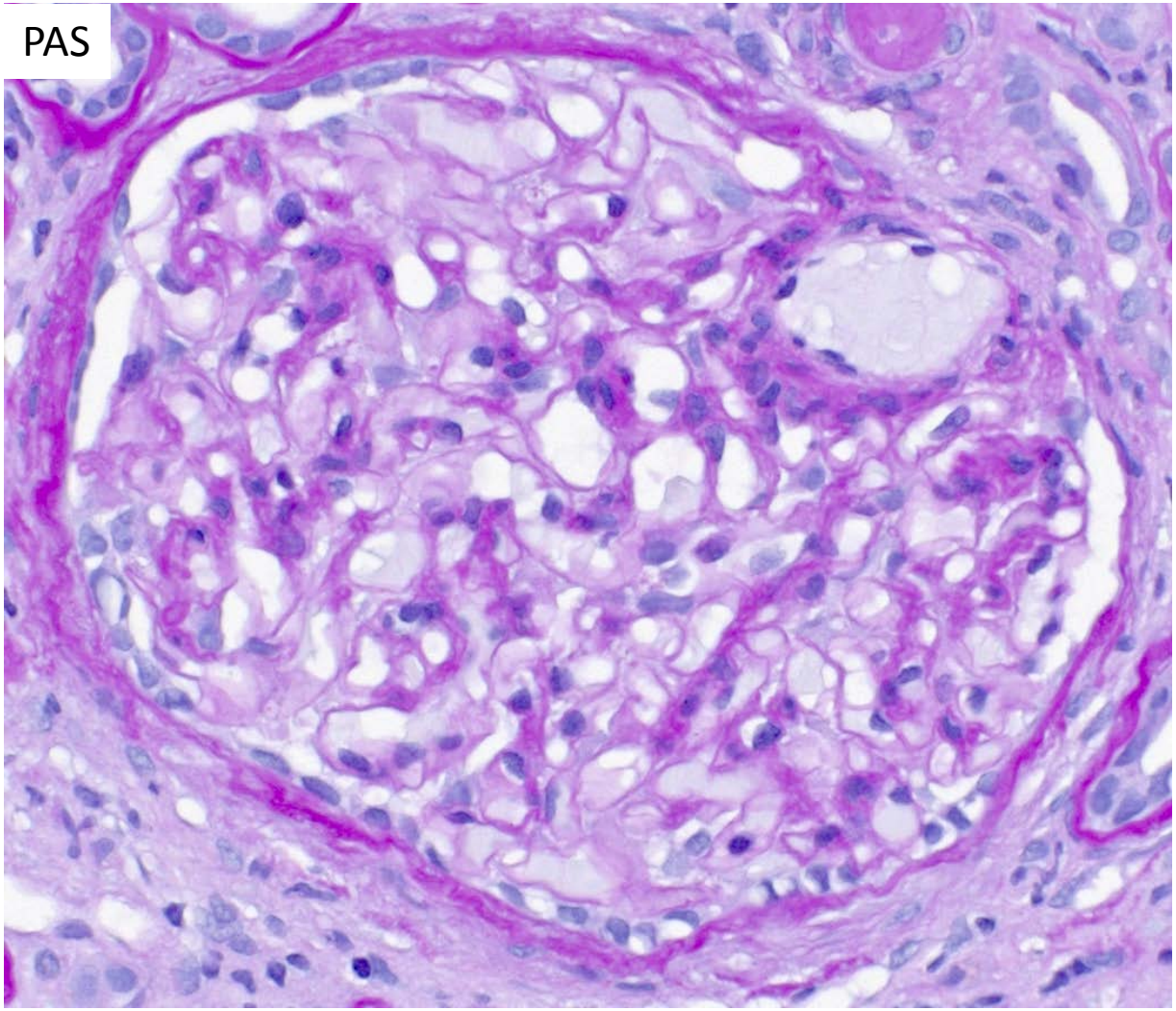
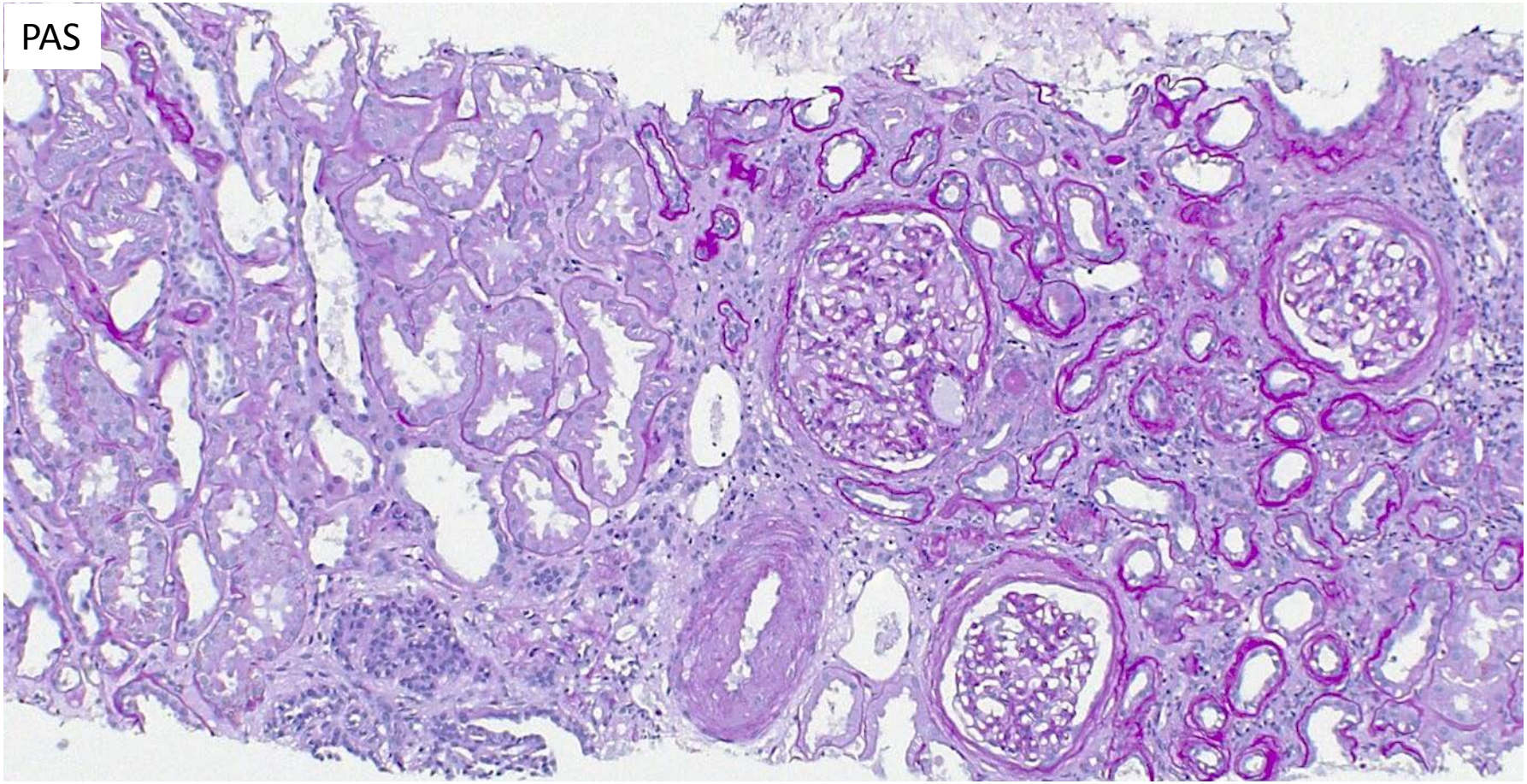
Erlangen

Other glomeruli normal.

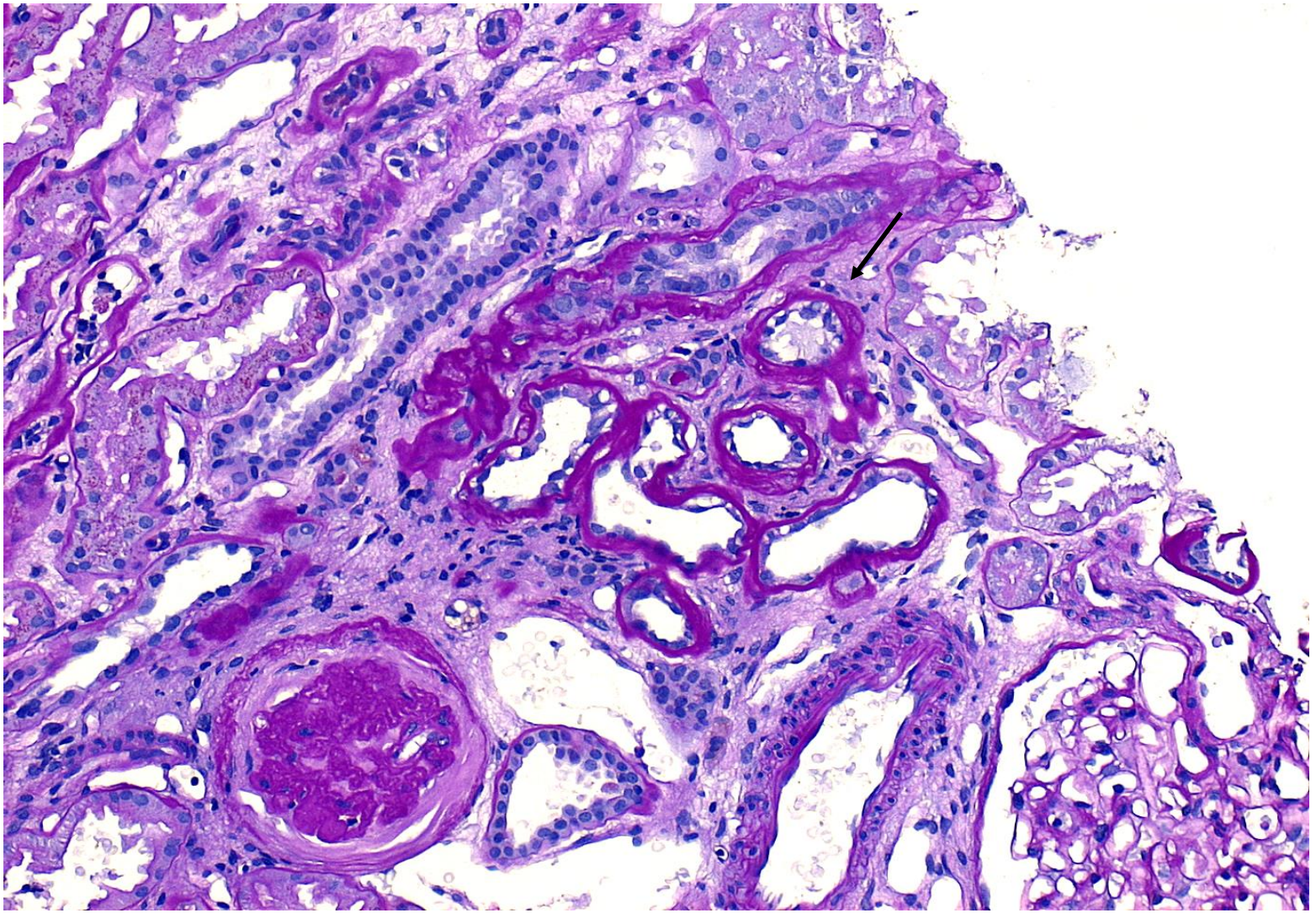


Acute tubular damage (ATN), 20-25 % IF/TA.



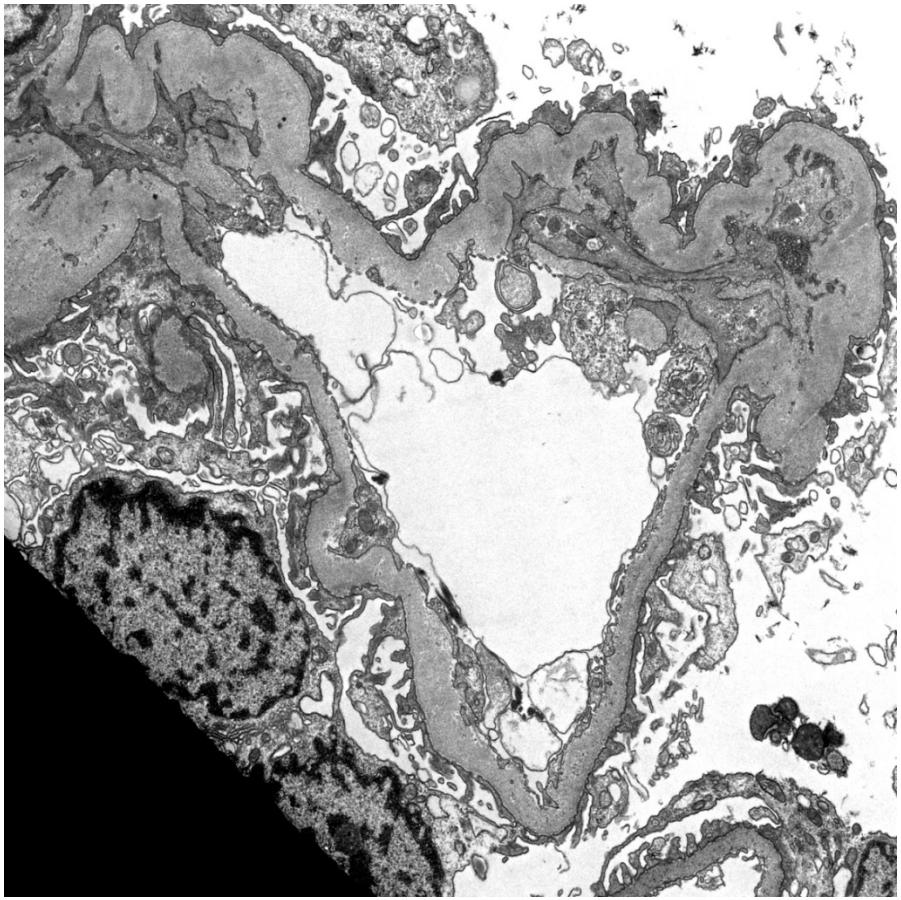
Thickened and lamellated tubular basement membranes

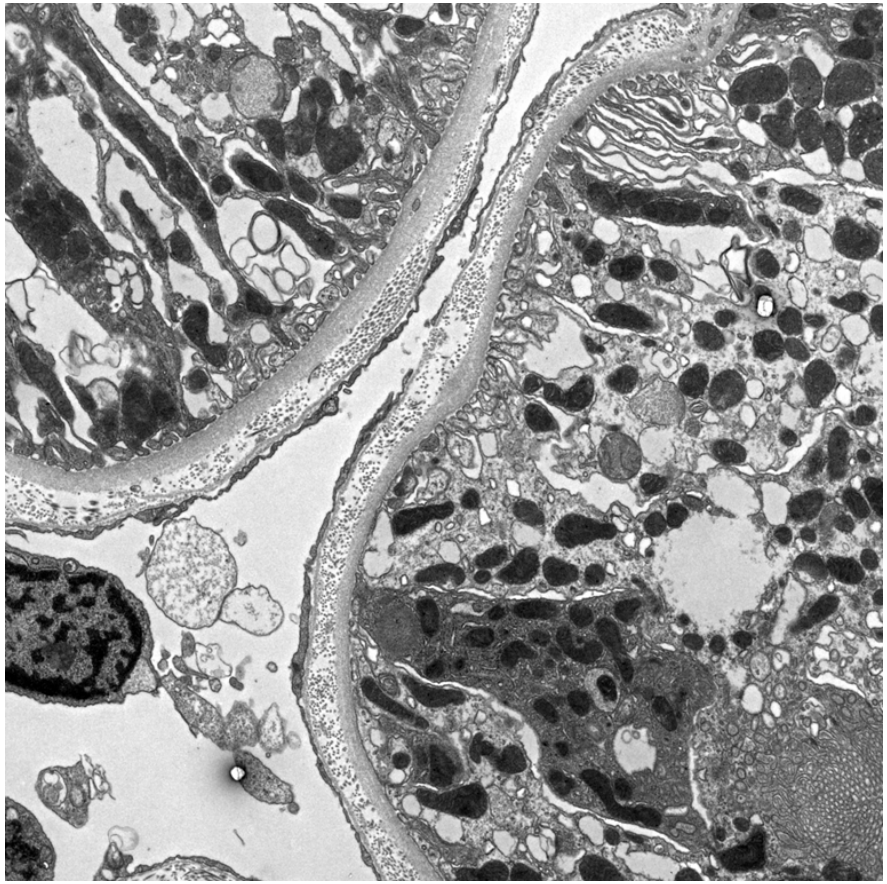
PAS



Electron microscopy:

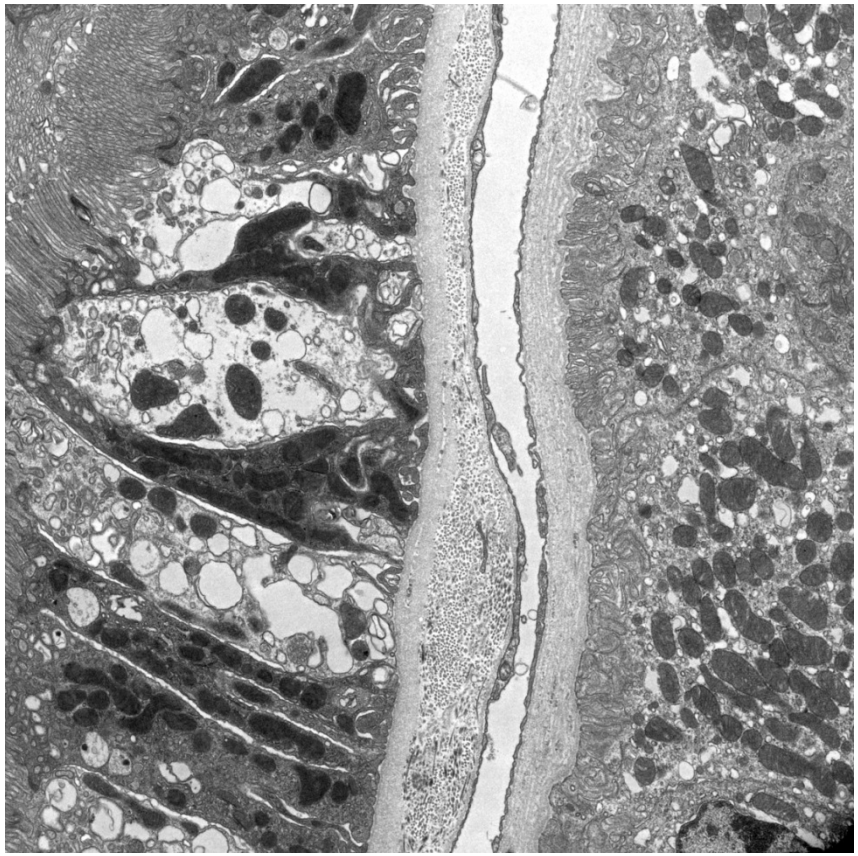
Mild thickening and wrinkling of glomerular and tubular basement membranes, lamellation of tubular basement membranes. No osmiophilic deposits, no fibrils.

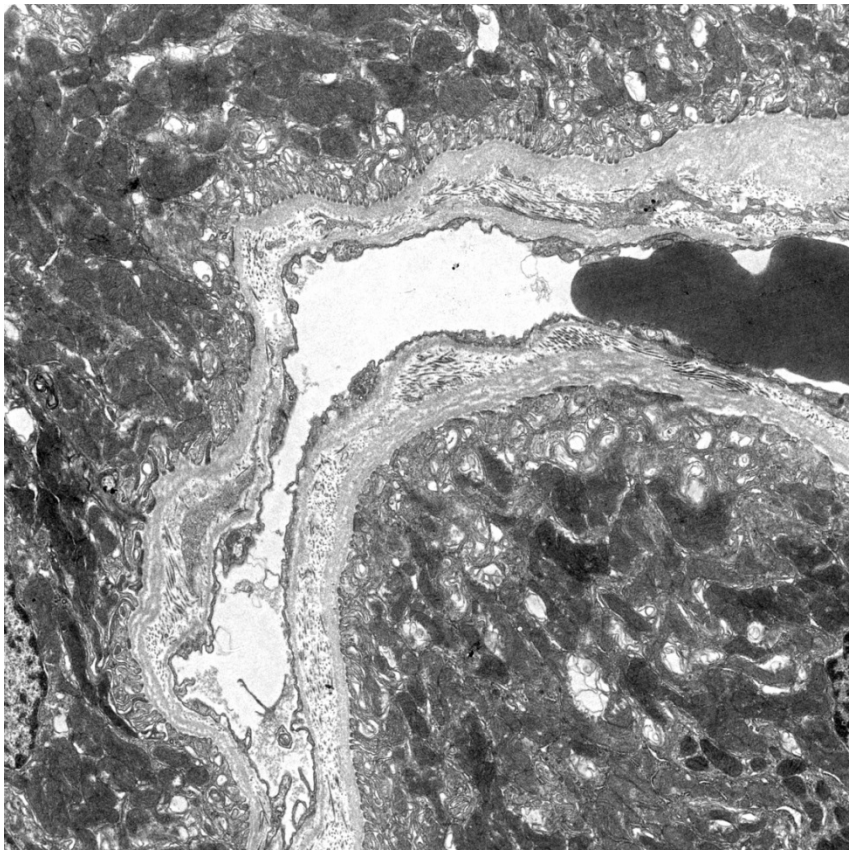




Electron microscopy:

Mild thickening and lamellation of tubular basement membranes.
No osmiophilic deposits, no fibrils.



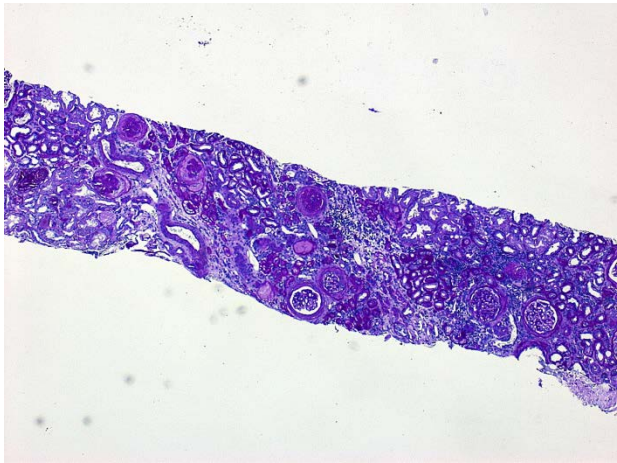


Diagnosis

- Global glomerulosclerosis (11/30)
- Ischemic glomerular damage and moderate arteriosclerosis (hypertension ?)
- 20-25 % IF/TA with thickened and lamellated tubular basement membranes

→ **In view of the positive family history highly suggestive for an autosomal dominant tubulointerstitial kidney disease (i.e. ADTKD-UMOD).**

→ Genetic testing:
Mutation in Uromodulin (Umod) was confirmed.



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

Abbreviations: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease; HNF1B, hepatocyte nuclear factor 1β; MUC1, mucin-1; NOS, not otherwise specified; REN, renin; UMOD, uromodulin.

[a]These terms may be easier to use in communicating with patients.

Clinical findings in ADTKD

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.

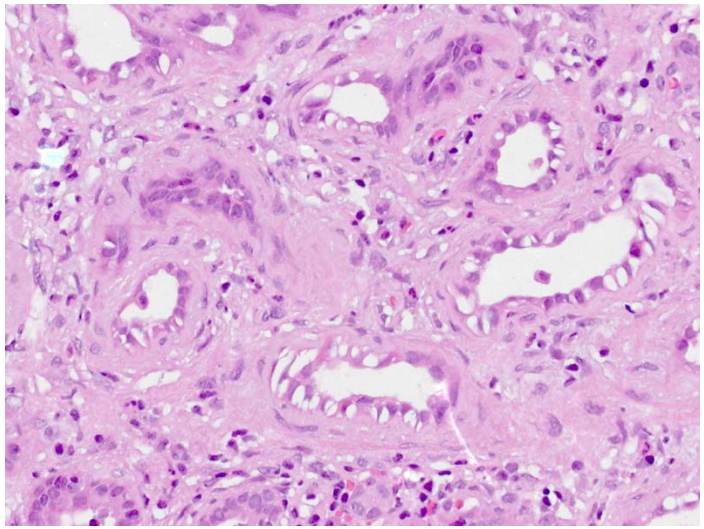
+ specific findings in each of the 4 different types of ADTKD
(i.e. hyperuricemia / gout in ADTKD-UMOD)

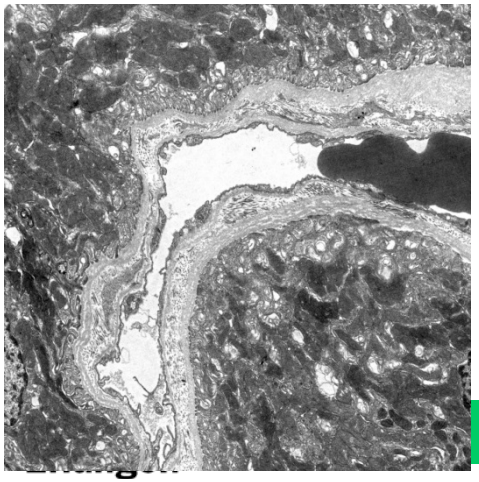
Typical histology in ADTKD ? – untypical and unspecific

- Interstitial fibrosis
- Tubular atrophy
- Thickening and lamellation of tubular basement membranes (→ EM)
- (cystic) tubular degeneration
- negative IH/- IF

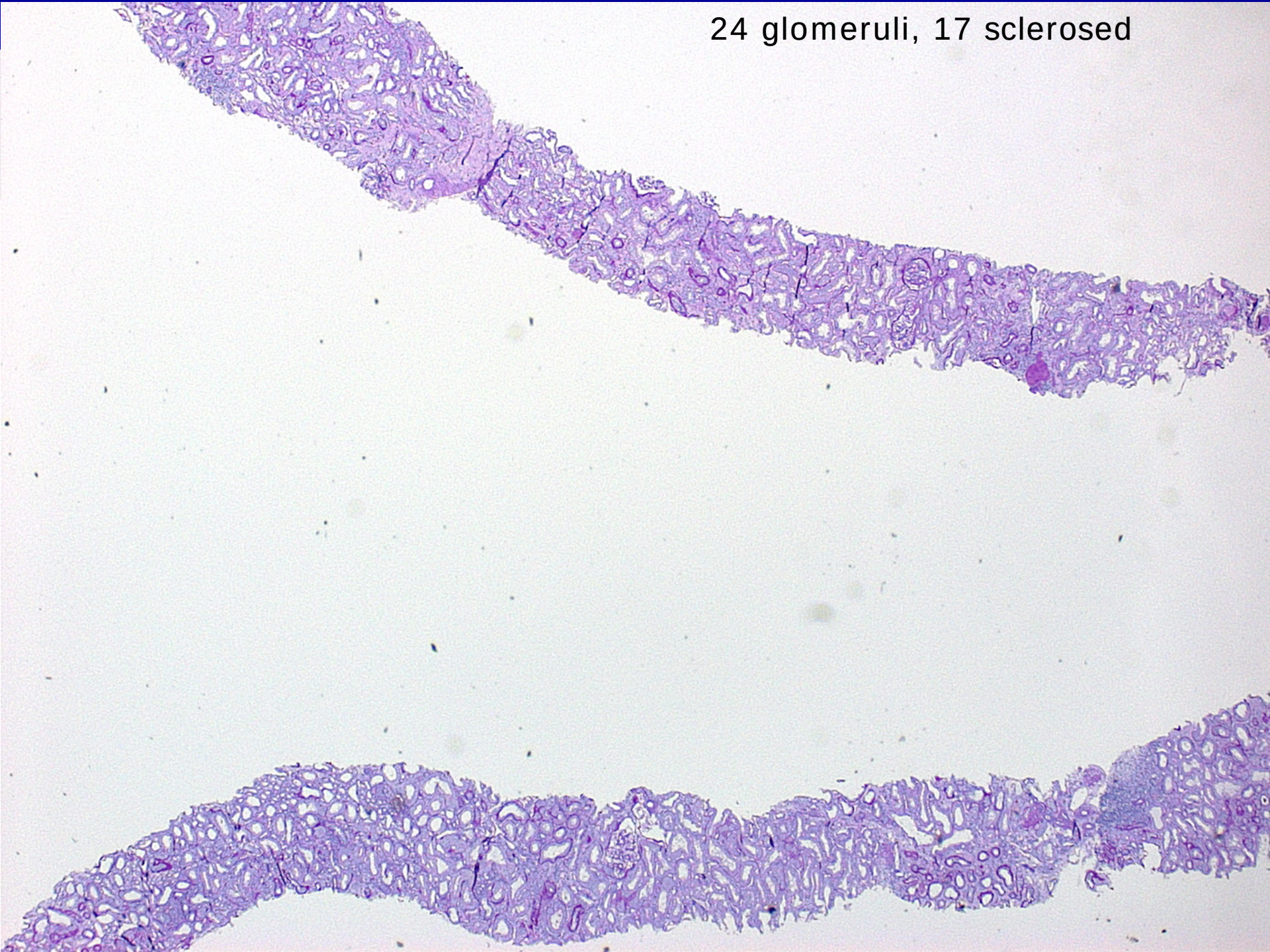
→ unspecific findings

→ family history and genetic testing

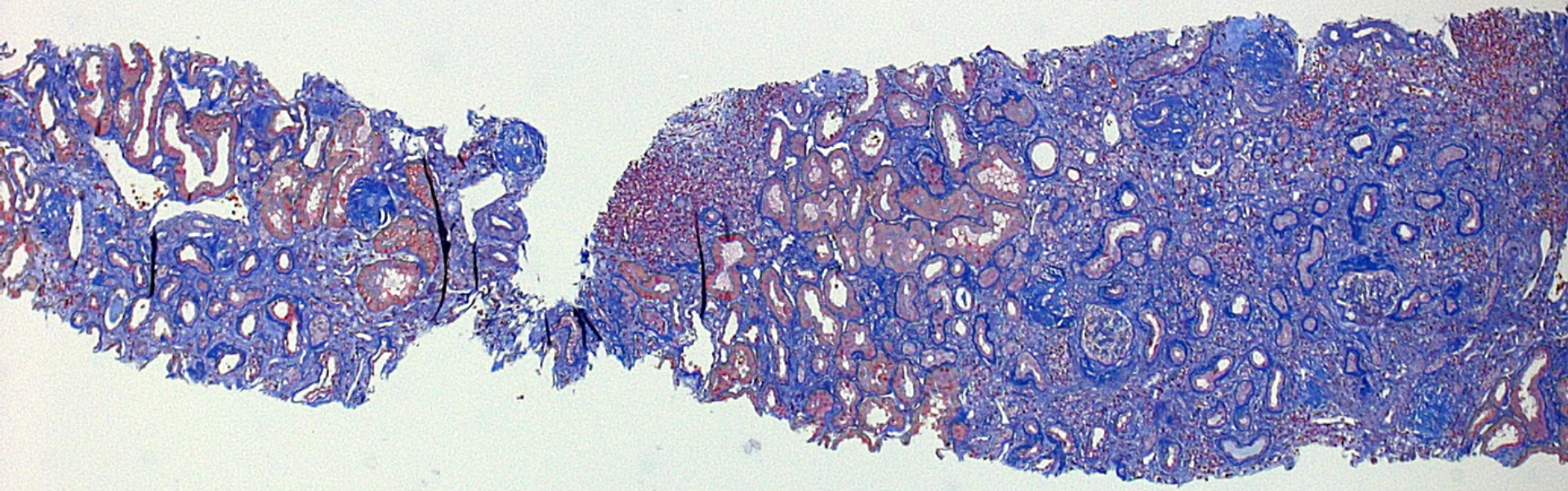


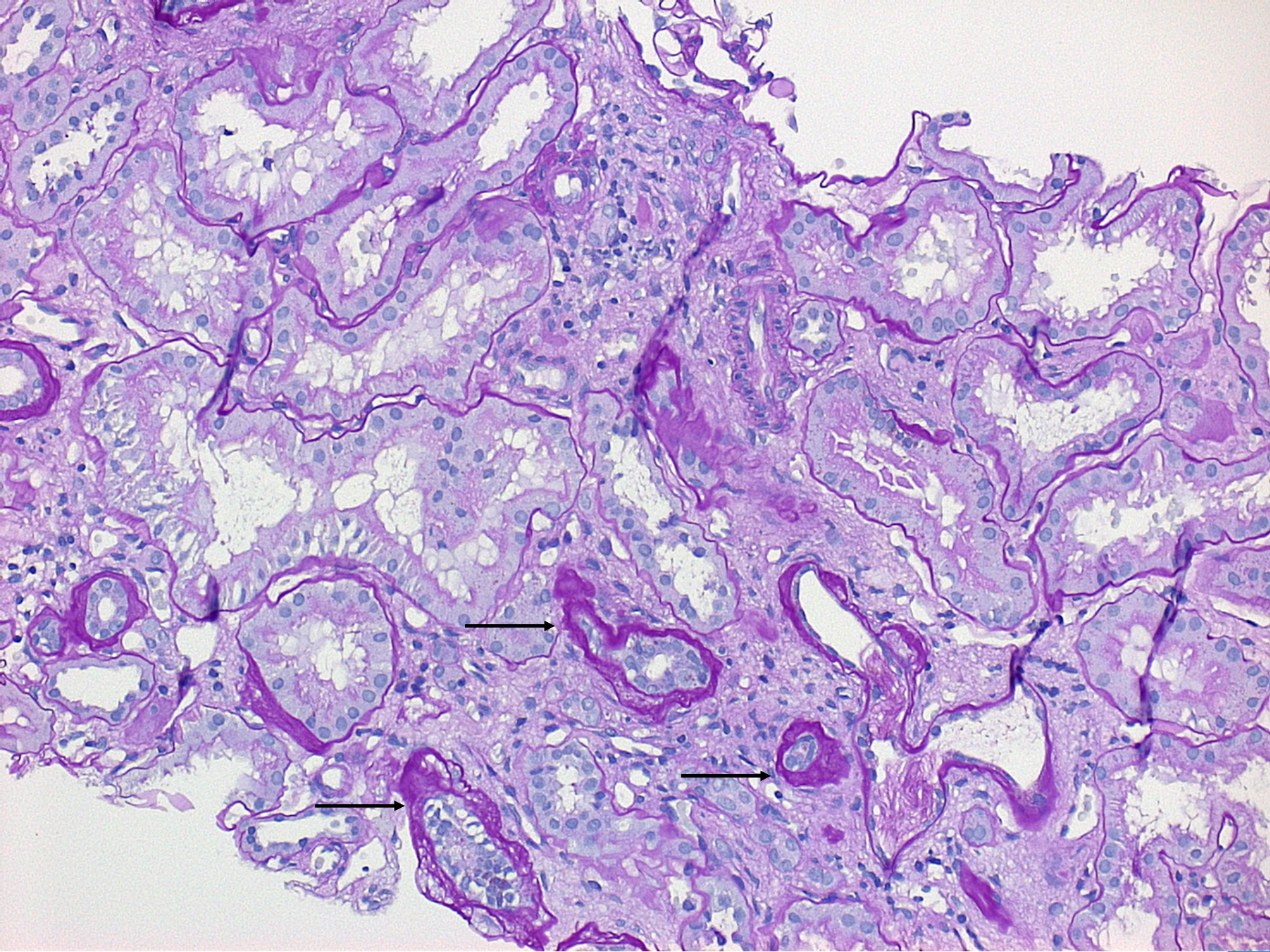


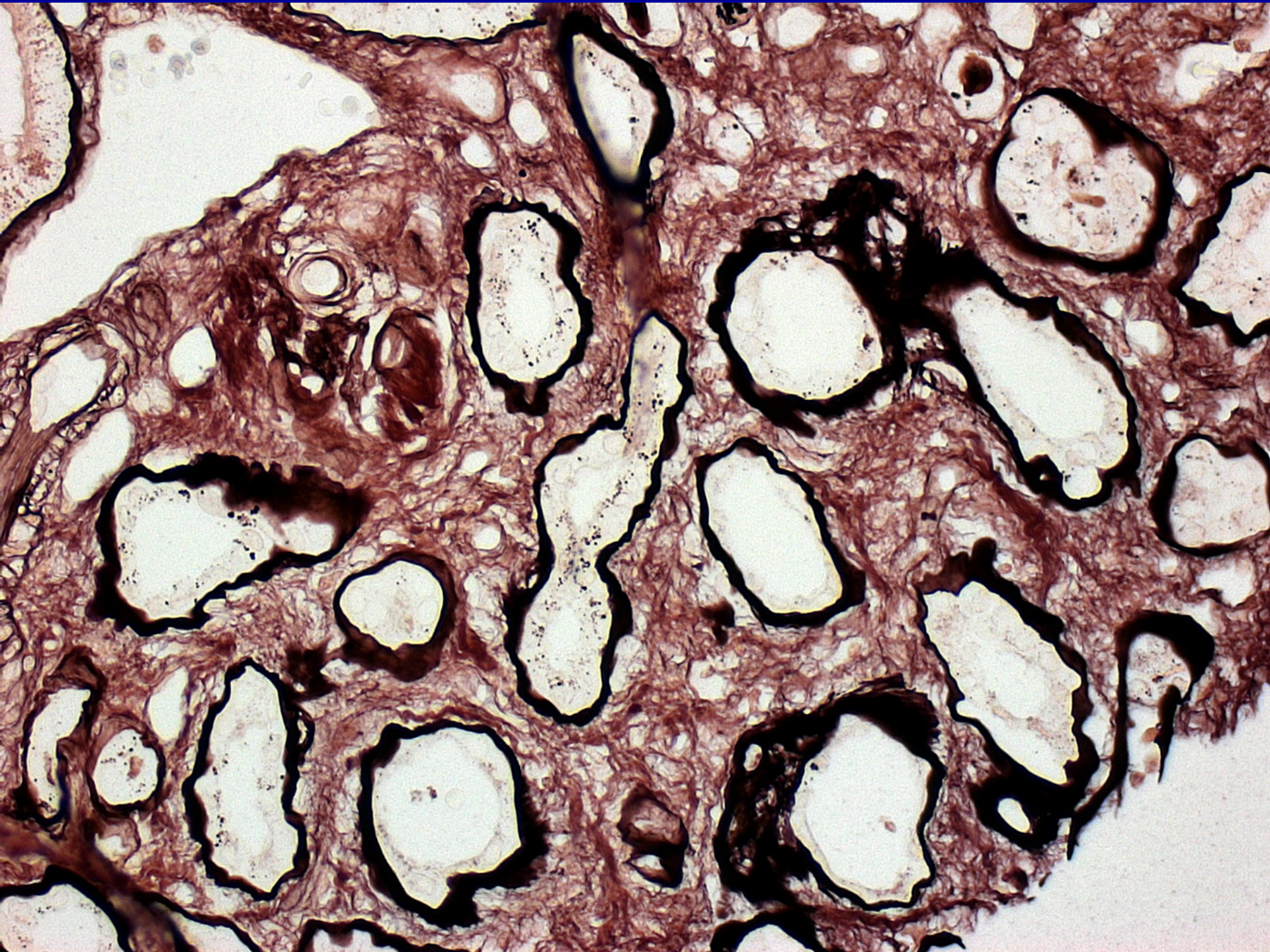
And now a very last case

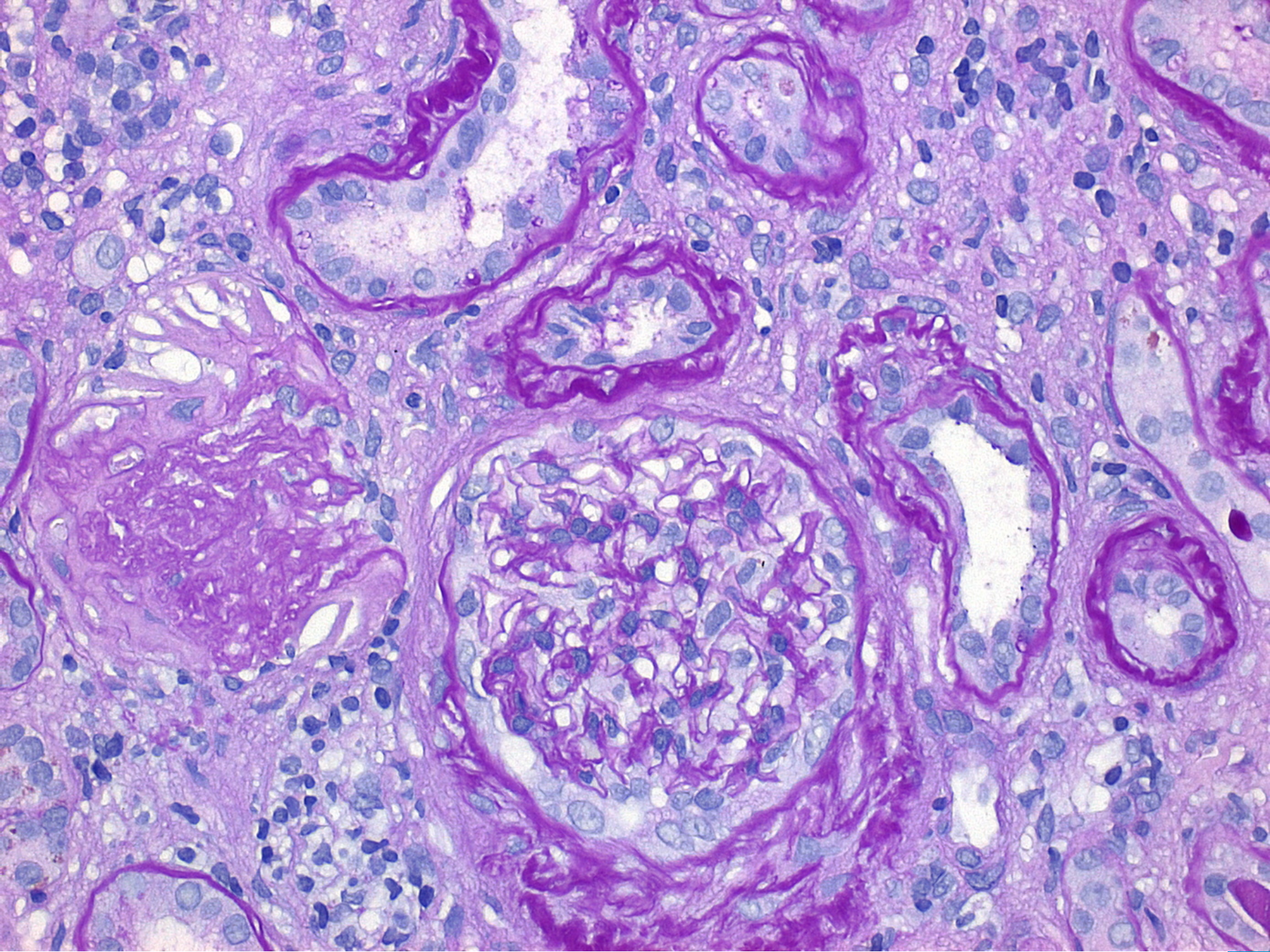

24 glomeruli, 17 sclerosed

approx. 20% IFTA









Diagnosis

- Advanced global glomerulosclerosis (17/24)
- Ca. 20 % IF/TA
- Mild arterio-arteriolosclerosis
- Moderate tubular damage
- Mild focal interstitial inflammation

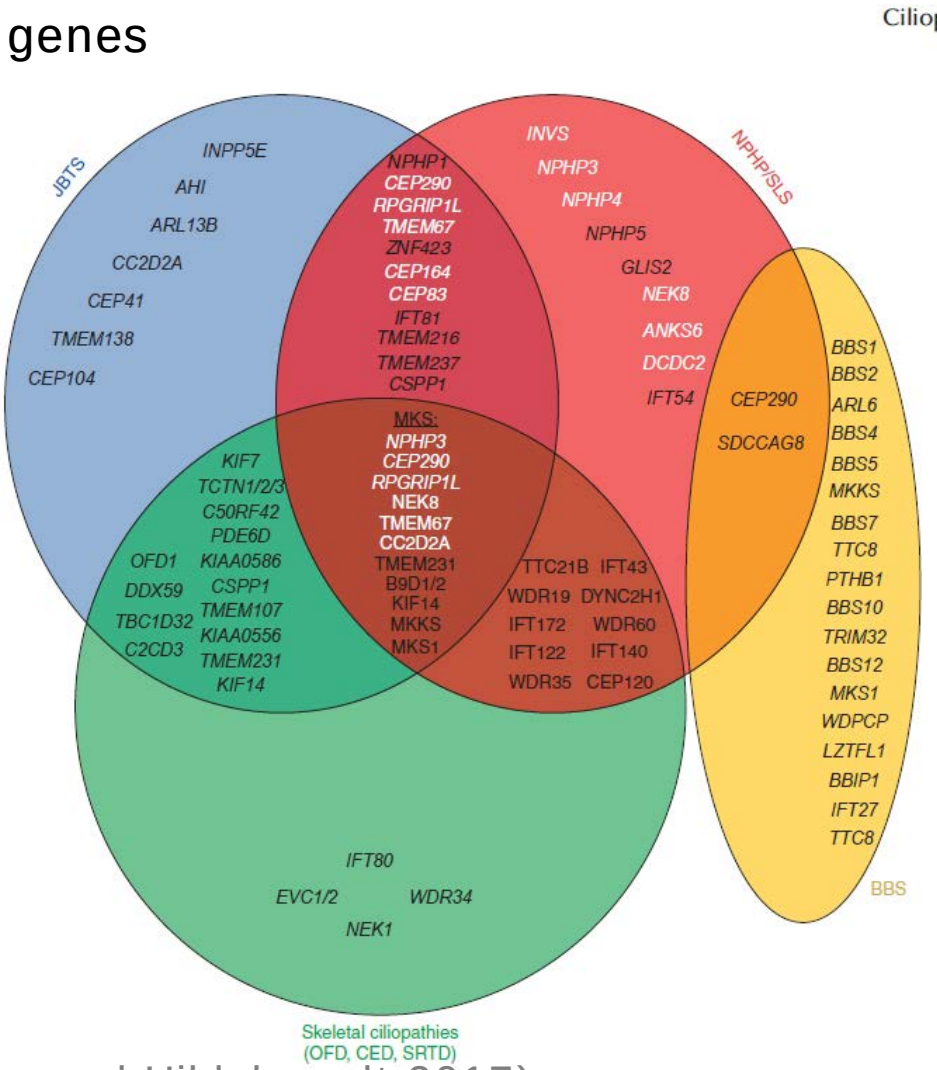
→ **Suspicous for autosomal dominant tubulointerstitial kidney disease (ADTKD)**

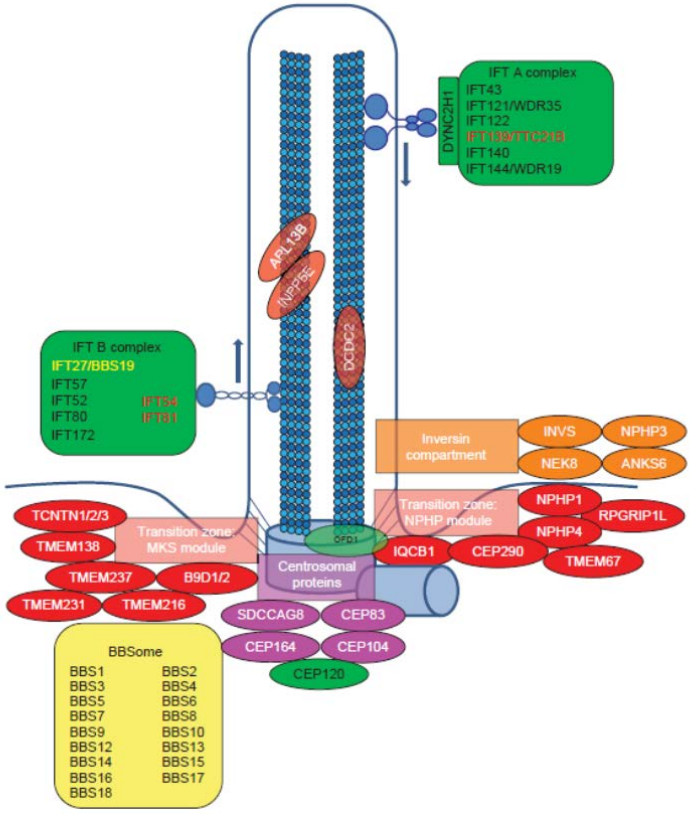
→ **Genetic testing**

- Counseling of pediatric nephrologist: history of polydipsia
- Genetic testing for nephronophthisis
- **positive for NPHP1 → nephronophthisis**

Monogenic genes of nephronophthisis-related ciliopathies (NPHP-RC)

>90 genes





(Braun and Hildebrandt 2017)

Universitätsklinikum Erlangen

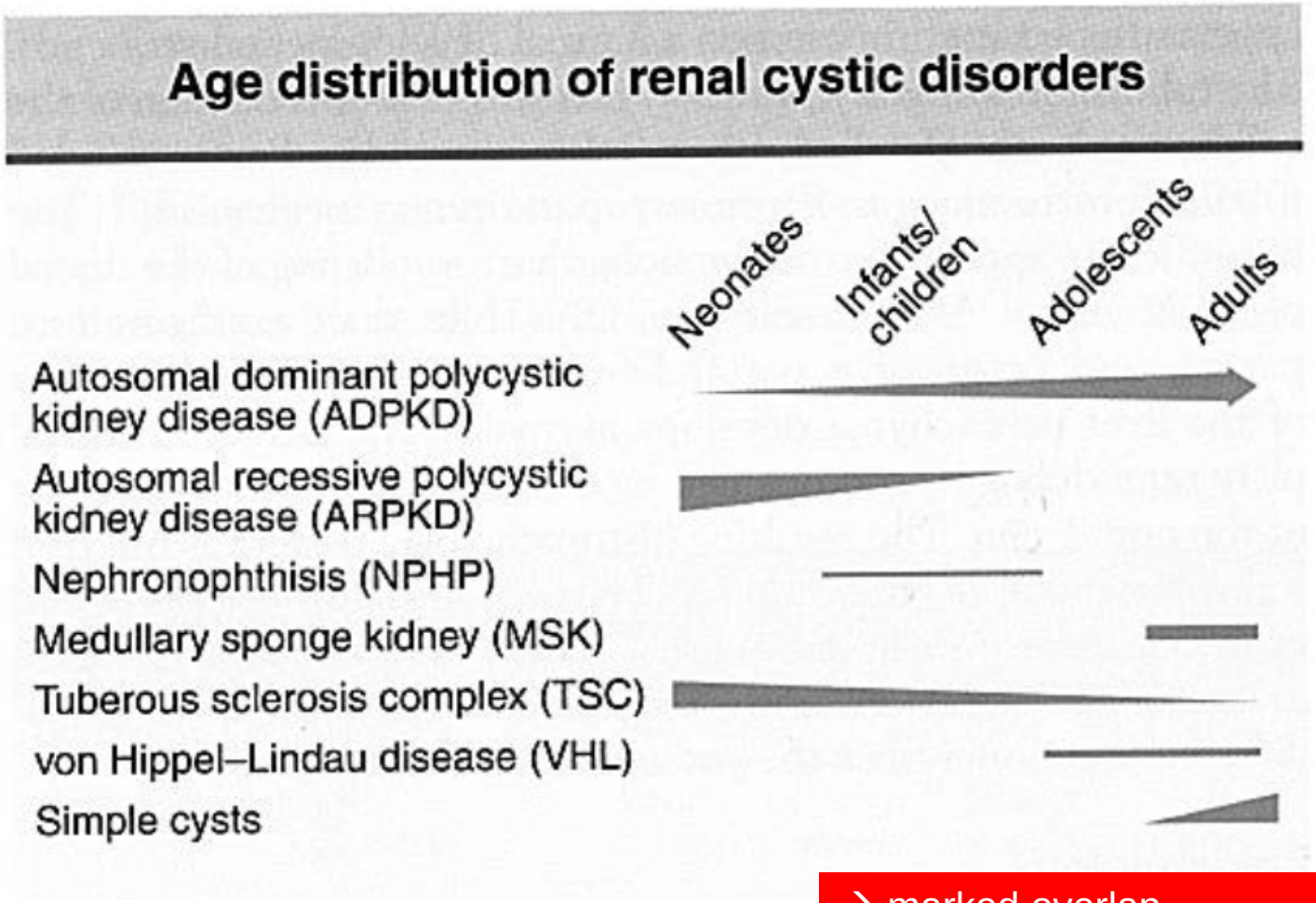
3 major phenotypes of NPH – most important cause of ESRD in children

Infantile NPH	3 years	oligohydramnios sequence
Juvenile NPH (most common form)	13 years	polydipsia and poly-uria, growth retarda-tion, chronic iron-re-sistant anemia, or other findings of CKD
Adolescent/ adult NPH	19 years	See above

Histologic findings:

tubulointerstitial fibrosis
thickened and disrupted tubular basement membrane
sporadic corticomedullary cysts
normal or reduced kidney size.

Age distribution of renal cystic disorders



→ marked overlap
→ additional genetic information helpful to correctly classify PKD !

(Comprehensive clinical nephrology, 3rd ed.)

Role of genetics in renal diagnosis

- Although of great importance, morphological information is sometimes limited, most likely due to limited reaction patterns of the body (i.e. the kidney)

  → molecular biology and genetics may help to better classify and treat renal diseases

- It is the pleasure and duty of the renal pathologist to ask for additional genetic tests where appropriate!