Welcome to

ERKNet/ERA Educational Webinars on
Pediatric Nephrology & Rare Kidney Diseases

Collagenopathies

WEBINAR

03/05/22

Speaker: Roser Torra (Barcelona, Spain)

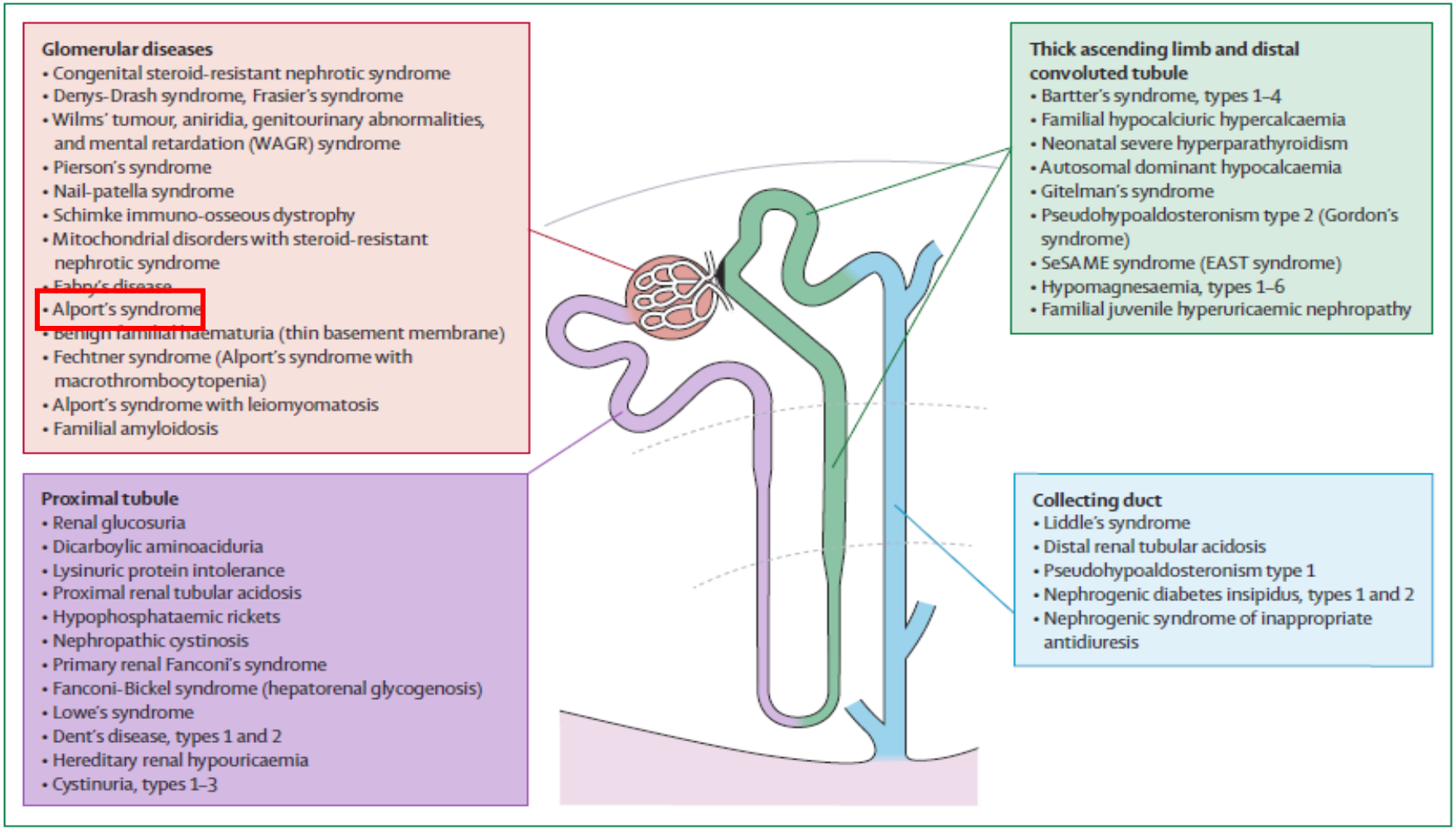
Patient's voice: Susie Gear & Heidi Zealey (Alport UK)

Moderator: Francesco Emma (Rome, Italy)

ERKNet
The European
Rare Kidney Disease
Reference Network

ERA
LEADING EUROPEAN NEPHROLOGY

Inherited Kidney Disorders: Segmental Distribution



Devuyst O, et al. Lancet **383**, 2014

Inherited hematuric diseases

Disease	Causing gene
HANAC	COL4A1 13q34
ALPORT	COL4A3 2q36.3, COL4A4 2q36.3, COL4A5 Xq22.3
ALPORT + leiomyomatosis (CGS)	COL4A6 Xq22.3
Complement Factor H-related	CFHR5 1q32
MYH9 related diseases	MYH9 22q11.2
Fibronectin 1	FN1 2q35
Ig A	???..non-mendelian

GLOMERULAR FILTRATION BARRIER

Epithelia: podocytes

Glomerular Basement Membrane

Endothelium

Collagen type IV network
α3.α4.α5

GLOMERULAR FILTRATION BARRIER: the GBM

- The GBM is a unique type of basement membrane because of its great thickness (300–350nm) and its position between two cell layers, podocytes and endothelial cells.

- The GBM has a specific role in maintenance of the glomerular filtration barrier by:

  - Providing **mechanical support** for the glomerular capillaries. Supports the **highest capillary pressure in the body (45 mmHg)**

  - **Ultrafiltration** of circulating blood
    - **Size-selective**
    - **Charge-selective** (prevents anionic molecules leakage)

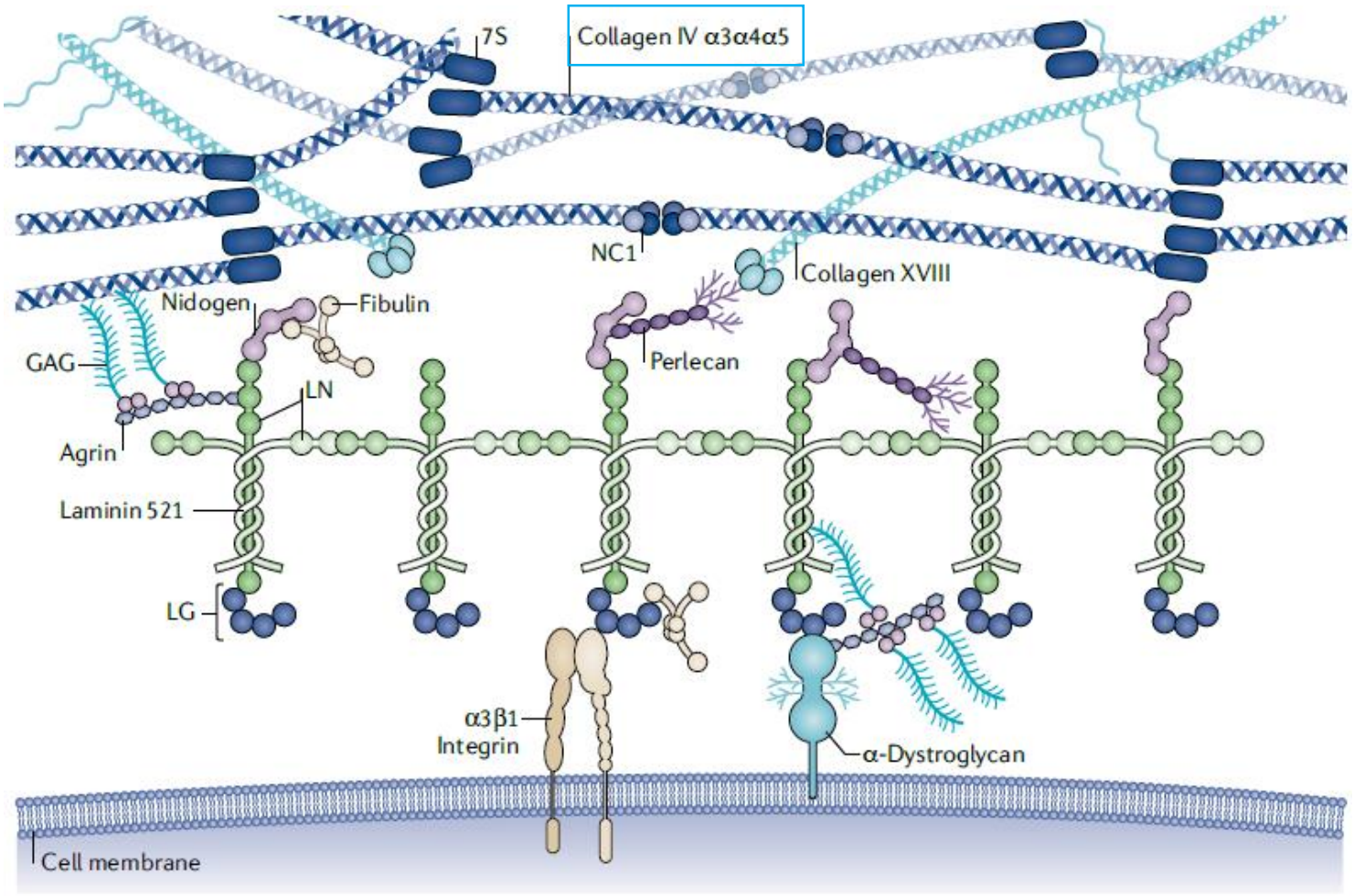
  - Blocking the passage of **cellular components** and large proteins from entering the urinary space.

Components of the GBM

Produced by endothelial cells and podocytes (initally double layer):

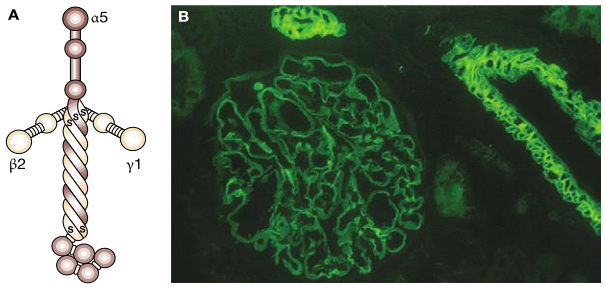
- Collagen IV
- Laminin
- Integrins
- Heparan sulfate proteoglycan
- Nidogen

MAJOR COMPONENTS OF THE GLOMERULAR BASEMENT MEMBRANE

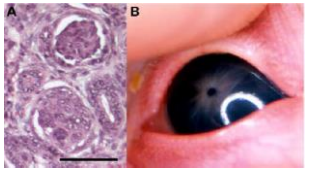


Naylor RW et al Nat Rev 2021

Laminins



- Heterotrimeric molecules:one α, one β, and one γ chain, with a cruciform organization.
- **laminin β2** chain is expressed at high levels in the GBM
- Essential for the **structural assembly of basement membranes, and interact with type IV collagen via nidogen.**
- Indispensable for the **intial formation of GBM**
- Mutations in *LAMB2* causes Pirson Syndrome



Gubler MC, Nature Clin Pract 2007

Integrins

- Transmembrane αβ heterodimers
- Integrin α3β1 is the predominant integrin normally present on the basal surface of podocytes
- The binding of laminin to integrin is essential for the **formation of the typical glomerular capillary loop structure**

Other components of the GBM

Nidogen is a ubiquitous basement membrane component that **'bridges' the collagen IV and laminin networks**

HSPGs (Heparan Sulfate Proteoglycans) **charge selectivity of the GFB.**

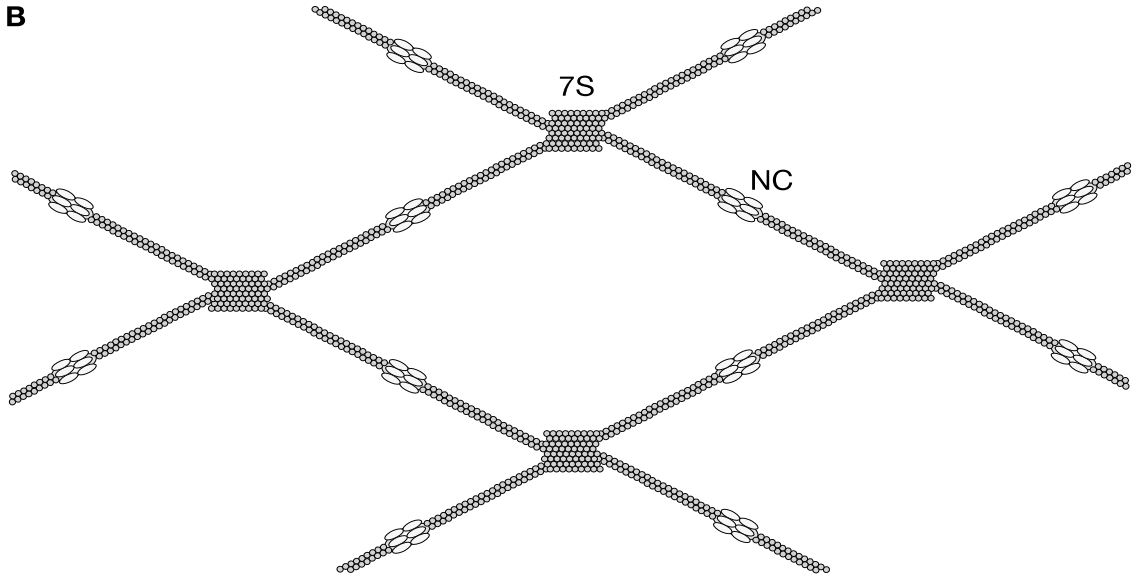
Agrin is the major HSPG in the GBM.

Perlecan is exclusively present on the endothelial side of the GBM and in the mesangial matrix.

Type IV collagen

- Is the most abundant protein found in basement membranes (50% of the mass)
- Collagen IV protomers are assembled inside the endoplasmic reticulum and secreted into the extracellular space
- Self- polymerize into a ‘chicken-wire-like’ network

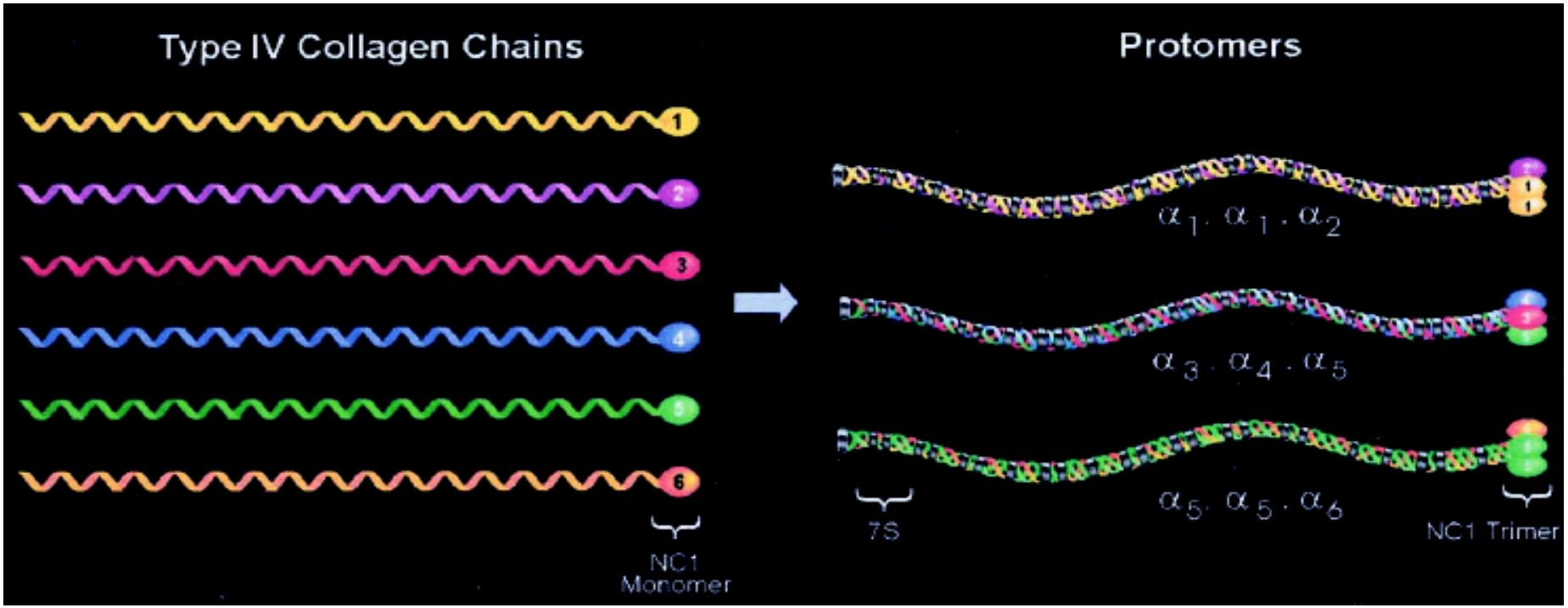
Organization of a type IV collagen network



Two molecules unite via their noncollagenous domains, and four molecules via their 7S domains.

Gubler MC, Nature Clin Pract 2007

COLLAGEN IV CHAINS



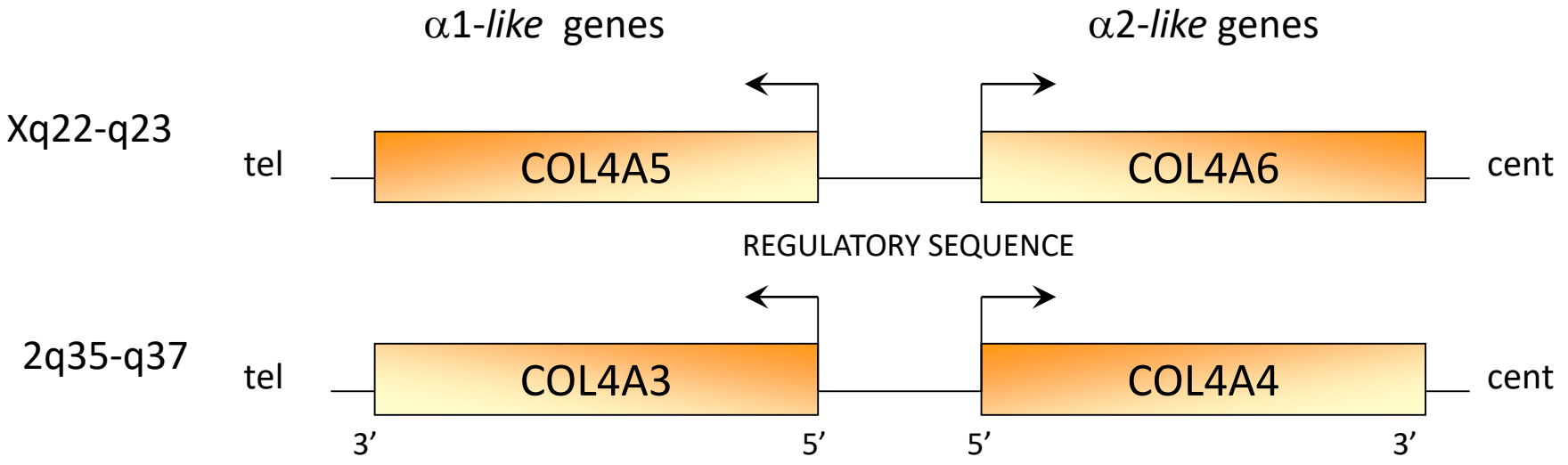
Collagen IV chains

Gene	Chromos	Protein	prot expression	Disease
COL4A1	13q34	α1 (IV)	All BM	HANAC
COL4A2	13q34	α2 (IV)	All MB	
COL4A3	2q35-37	α3 (IV)	Kidney, eye, ear	ARAS, ADAS
COL4A4	2q35-37	α4 (IV)	Kidney, eye, ear	ARAS, ADAS
COL4A5	Xq22	α5 (IV)	Kidney, eye, ear, skin	XLAS
COL4A6	Xq22	α6 (IV)	Kidney, eye, ear, skin	(XLAS+LM)

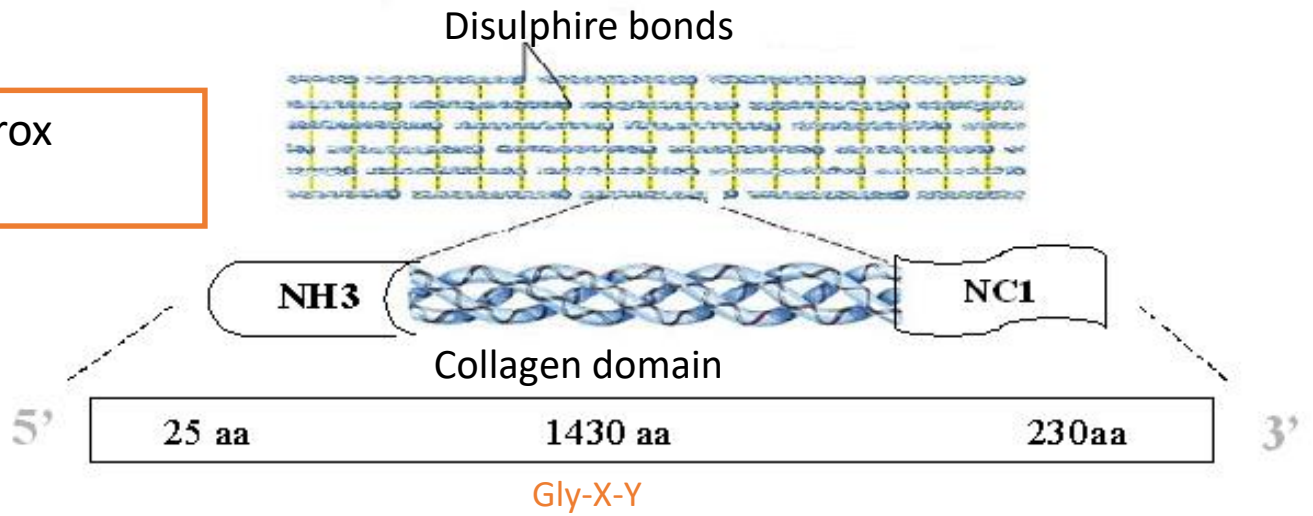
HANAC

- HANAC syndrome is an infrequent systemic basement-membrane disease
- Heterozygous mutations in *COL4A1*.
- Clinical features:
  - Hereditary Angiopathy
  - Nephropathy (microhemautria, cysts, renal failure)
  - Aneurysms
  - Muscle Cramps
- Electron microscopy shows thickening and splitting on the basement membranes (including tubules, capillaries and GBM).

Structure of collagen IV genes implicated in AS



50 exons per gene aprox
Large sized introns



Substitution of glycines in the collagen domain

GLY-X-Y

- The most common mutations: **missense**

- **Glycine** is the smallest AA
  - **only one that fits into the folds** within the narrow triple helix structure

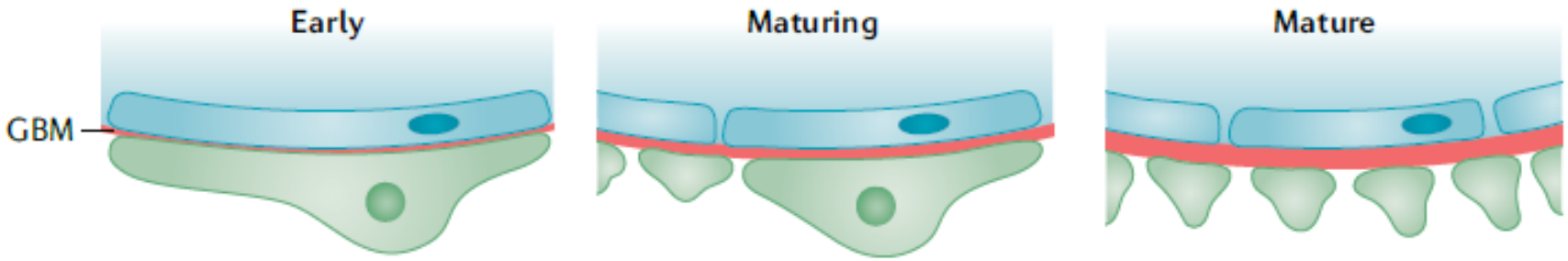
- Some of the substitutions will totally prevent the formation of the triple helix, while others will have a minimal effect on the folding of the chains.
  - Less severe when involving exons 1 to 20.
  - Ala <Ser <Cys <Arg <Val <Glu <Asp <Trp

- Substituting a **Gly for an alanine** could give rise to a phenotype so **mild** or so late in appearance that it could escape diagnosis.

- Substitution of any of the **X and Y positions will always have less impact** than the smaller of the glycine substitutions

GBM development

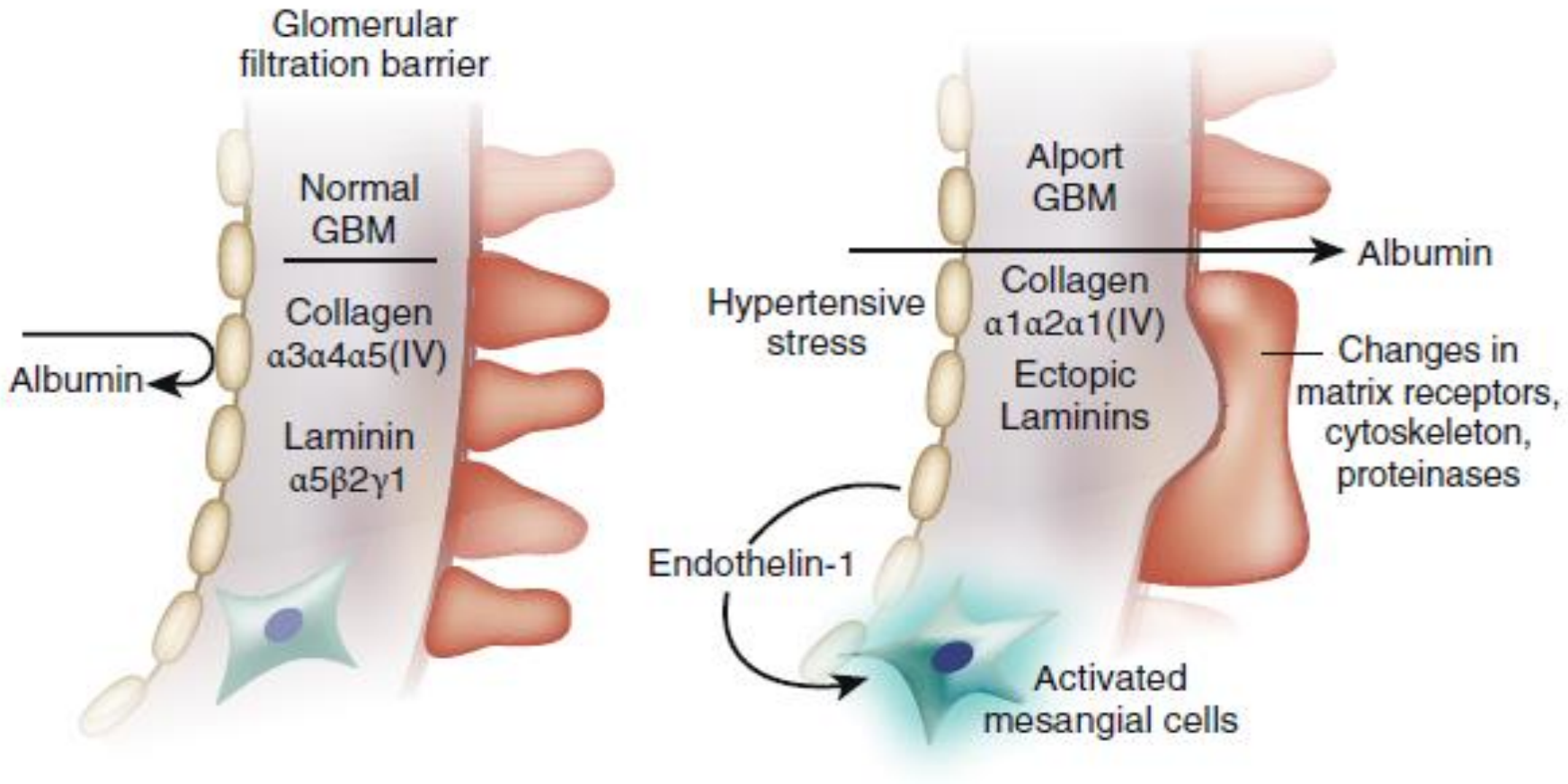
Switch!!



	Early	Maturing	Mature
GBM composition	Laminin 111 col(IV) α1α2α1	Laminin 511 col(IV) α1α2α1/α3α4α5	Laminin 521 Mainly α3α4α5; some α1α2α1 persists
Podocyte maturation	Primary inter-digitations, fusion with endothelial basement membrane	Switch from col(IV) α1α2α1 to col(IV) α3α4α5, formation of the slit diaphragm	Deposition of more matrix proteins into the GBM, complex inter-digitation
Endothelial maturation	Invasion of haemangioblasts into the distal cleft	Initial fenestrations form	Multiple fenestrations present

Naylor RW et al Nat Rev 2021

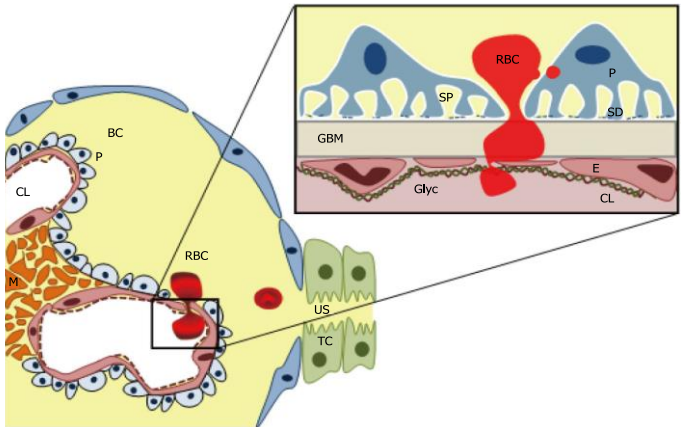
HYPOTHESIS FOR PROTEINURIA



Abrahamson et al KI 2016

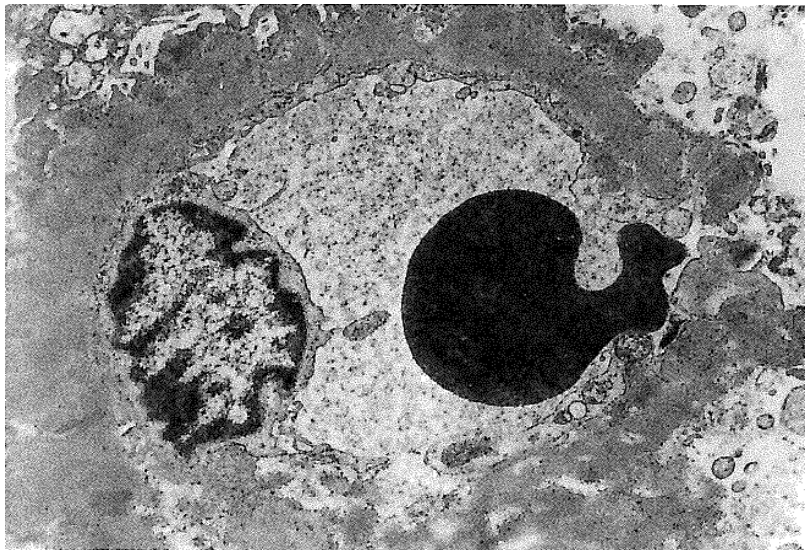
Physiopathology of microhematuria

- The precise pathogenic mechanisms responsible of glomerular haematuria remain to be elucidated
- Under physiological conditions, the endothelium with its **fenestrations (50-100 nm)** acts as molecular size sieve, self-sufficient to maintain the **RBCs (6.2-8.2 µm)** away from the GBM.
- How the **RBCs,100-fold bigger** than the glomerular endothelium's pore, cross the GFB remains unclear.

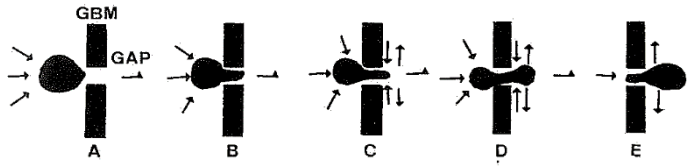


Yuste C et al WJN 2015

Physiopathology of microhematuria

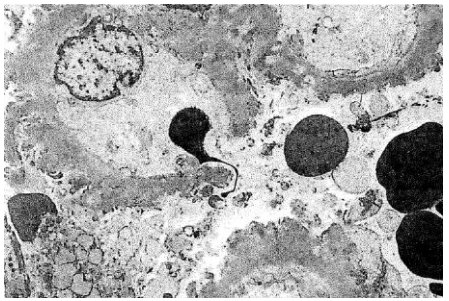


A red blood cell of normal electron density is about to enter the gap between endothelial cells. The size of gap is 1,57 mm
X7.200



GBM stretches and retracts
Disruptions of GMB to allow RBC go though?
RBC very elastic and deformable

Pulses of capillary circulation + contractility of GBM
Squeeze the cell though the GAP



Jai-Trung L et al, Nephron 1983

ALPORT SYNDROME

- Rare disease:
  - XLAS estimated 1:10,000 1:5,000 to 1:57,000
  - ARAS estimated to 1:50 000)
  - ADAS unknown but underdiagnosed……..

1927

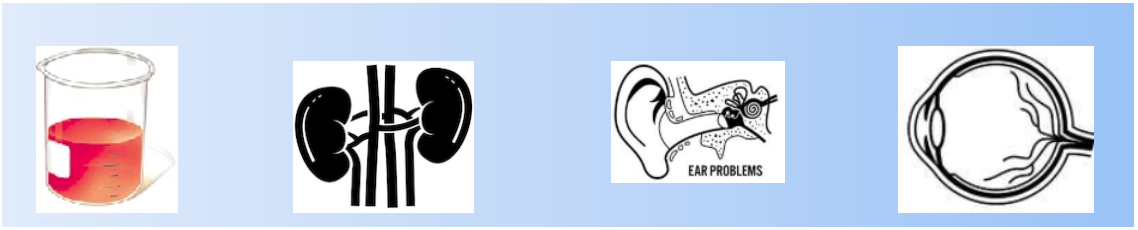
- In Europe, **untreated patients XLAS/ARAS** reach end-stage renal disease with a median age of **22 years** (Gross, 2012)

- More than 500 different mutations have been described, mostly linked to X-chromosome

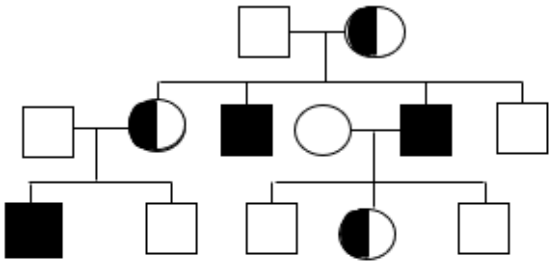
AS: DIAGNOSTIC CRITERIA

- **Family history** of nephritis or hematuria in first degree relative or in a male relative via maternal transmission**.**
- Persistent **hematuria** without evidence of another cause of hematuria (stones, ADPKD, IgA)
- Bilateral **sensorineural hearing loss** (2,000-8,000 Hz), absent in childhood and generally established before age 30.
- **Mutation** in any of these genes: *COL4A3 / 4/5*
- **Immunohistochemical** evidence of lack of Alport epitope in glomerular or epidermal basement membranes.
- **Ultrastructural changes of the GBM**: thinning, thickening, lamellation.
- **Eye** lesions: anterior lenticonus, posterior subcapsular cataract
- **ESRD** in the proband or in at least 2 relatives.
- Diffuse **leiomyomatosis** of the esophagus, female genitalia or both

ALPORT SYNDROME

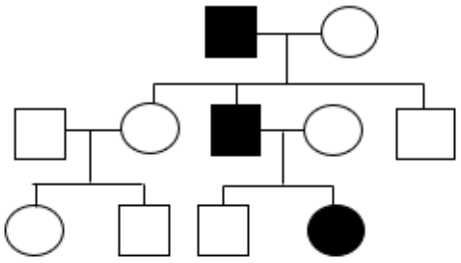


X LINKED



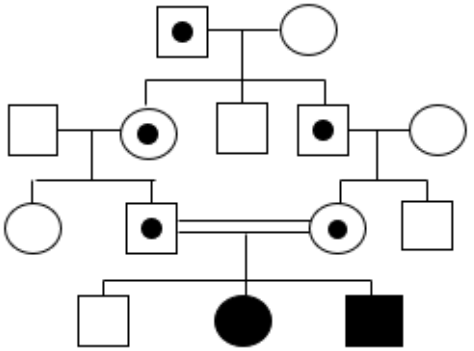
COL4A5 pathogenic variant

AUTOSOMAL DOMINANT

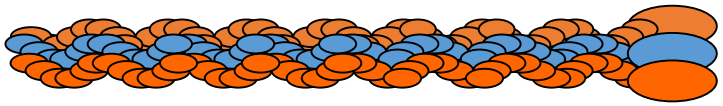
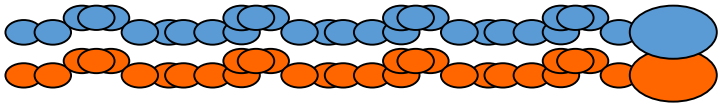
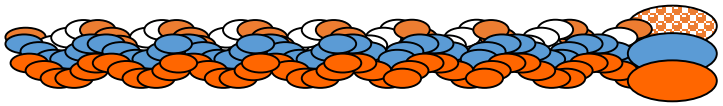
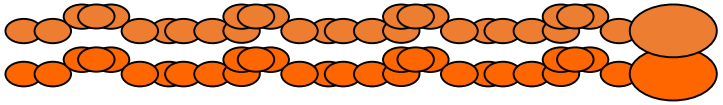
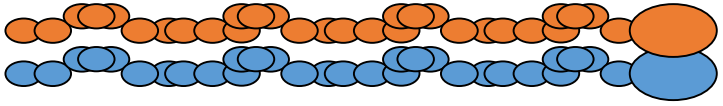
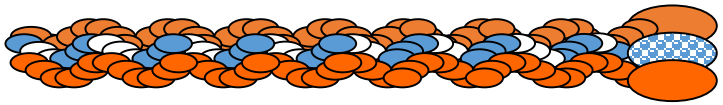
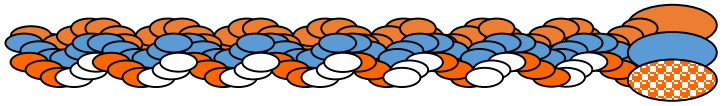
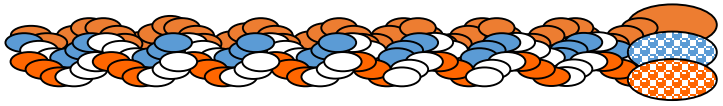
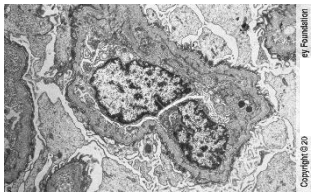


One *COL4A3/4* pathogenic variant

AUTOSOMAL RECESSIVE

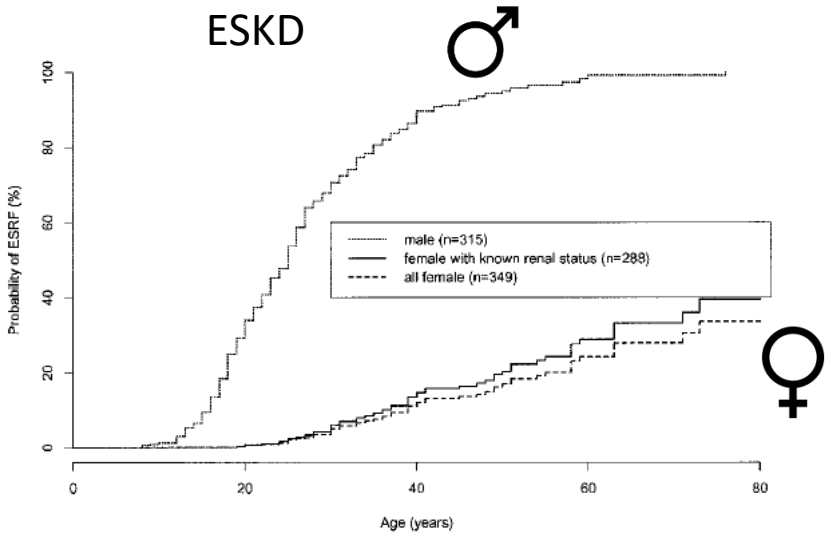


Two *COL4A3/4* pathogenic variants

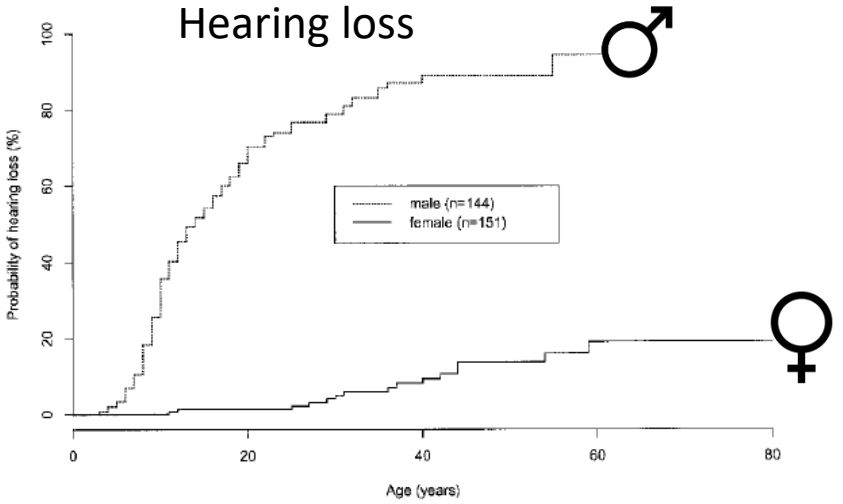
TRIPLE HELIX COLLAGEN IV	MOLECULAR DEFECT	PHENOTYPE
 α5(IV) α3(IV) α4(IV)	-	NORMAL GBM
 α3(IV) α4(IV)	1 MUTACIÓN *COL4A5* XY	Males more affected Early ESR- XLAS
 α5(IV) α3(IV) α4(IV)	1 MUTACIÓN *COL4A5* XX	Affected/carrier woman XLAS
 α5(IV) α4(IV)	2 MUTACIONES *COL4A3*	ARAS Early ESRD
 α5(IV) α3(IV)	2 MUTACIONES *COL4A4*	
 α5(IV) α3(IV) α4(IV)	1 MUTACIÓN *COL4A3*	COLLAGEN IV NEPHROPATHY (α3,α4) Variable evolution 
 α5(IV) α3(IV) α4(IV)	1 MUTACIÓN *COL4A4*	
 α5(IV) α3(IV) α4(IV)	1 MUTACIÓN *COL4A4* 1 MUTACIÓN *COL4A3*	

XLAS: males more severely affected than females

ESKD

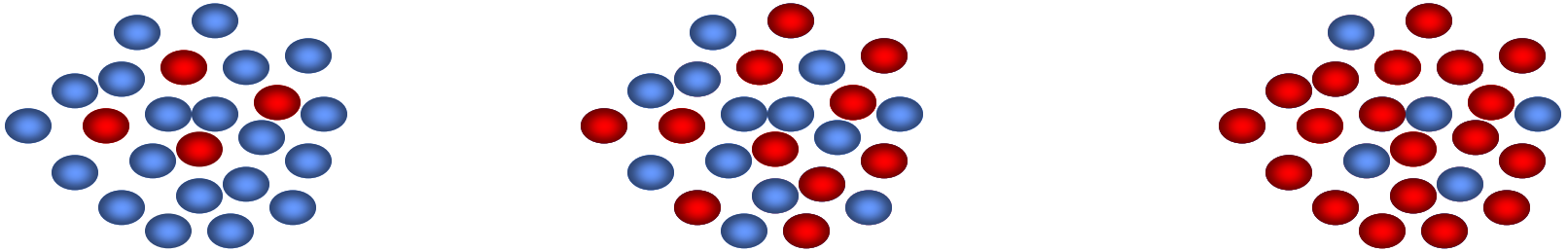


Hearing loss

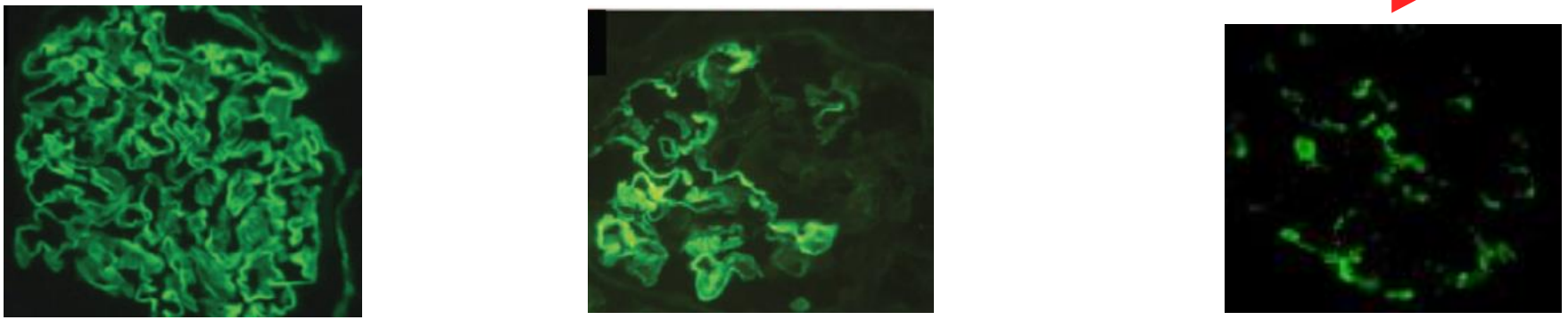


Jais JP et al JASN 2003

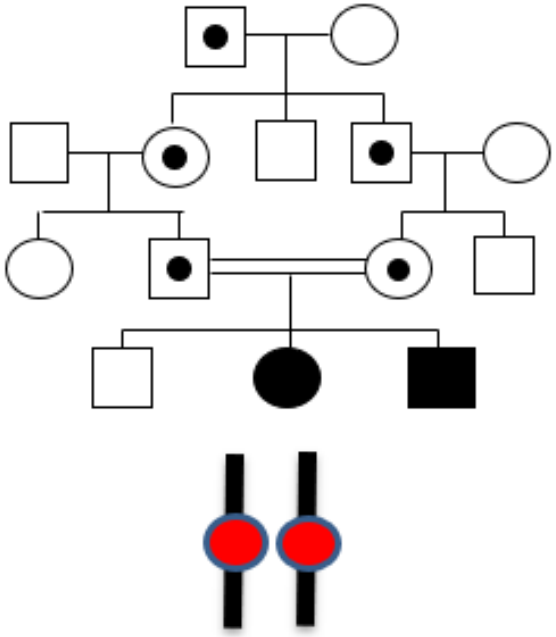
LYONISATION: inactivation mosaicism



‘skewed X inactivation’

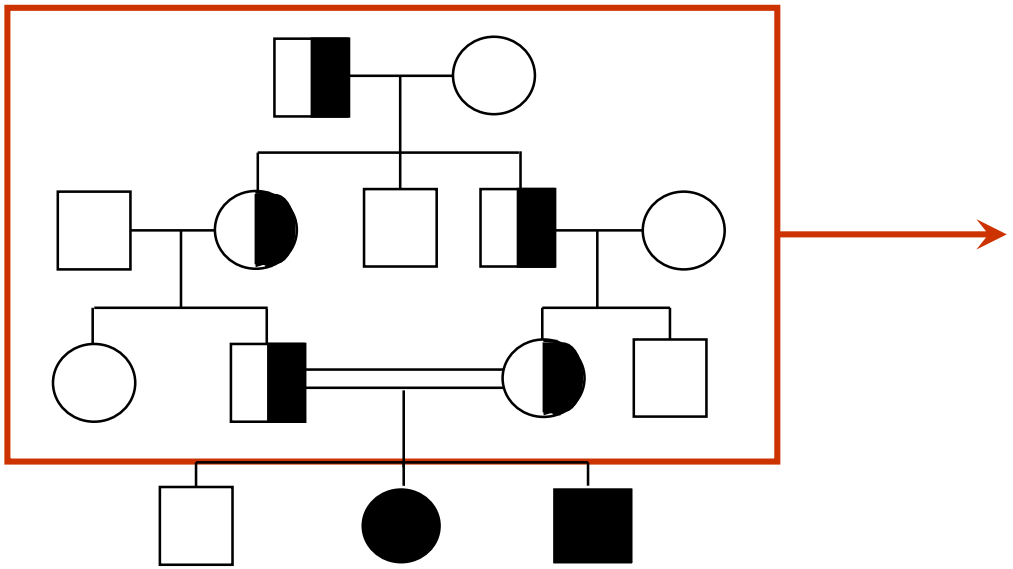


ARAS: males equally affected than females



As severe as XLAS in males. Frequent hipoacusia, eye involvement

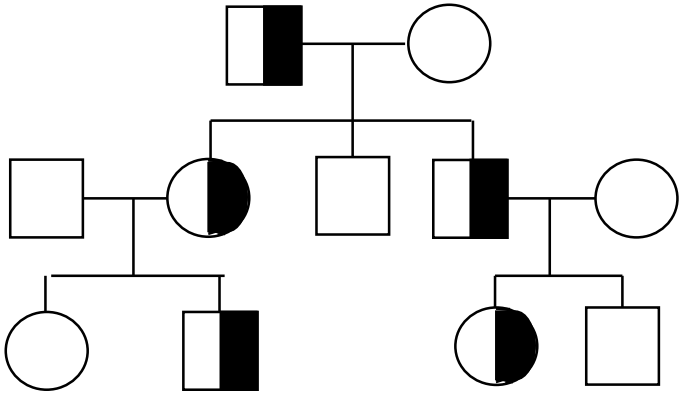
AUTOSOMAL RECESSIVE AS (ARAS)



14%

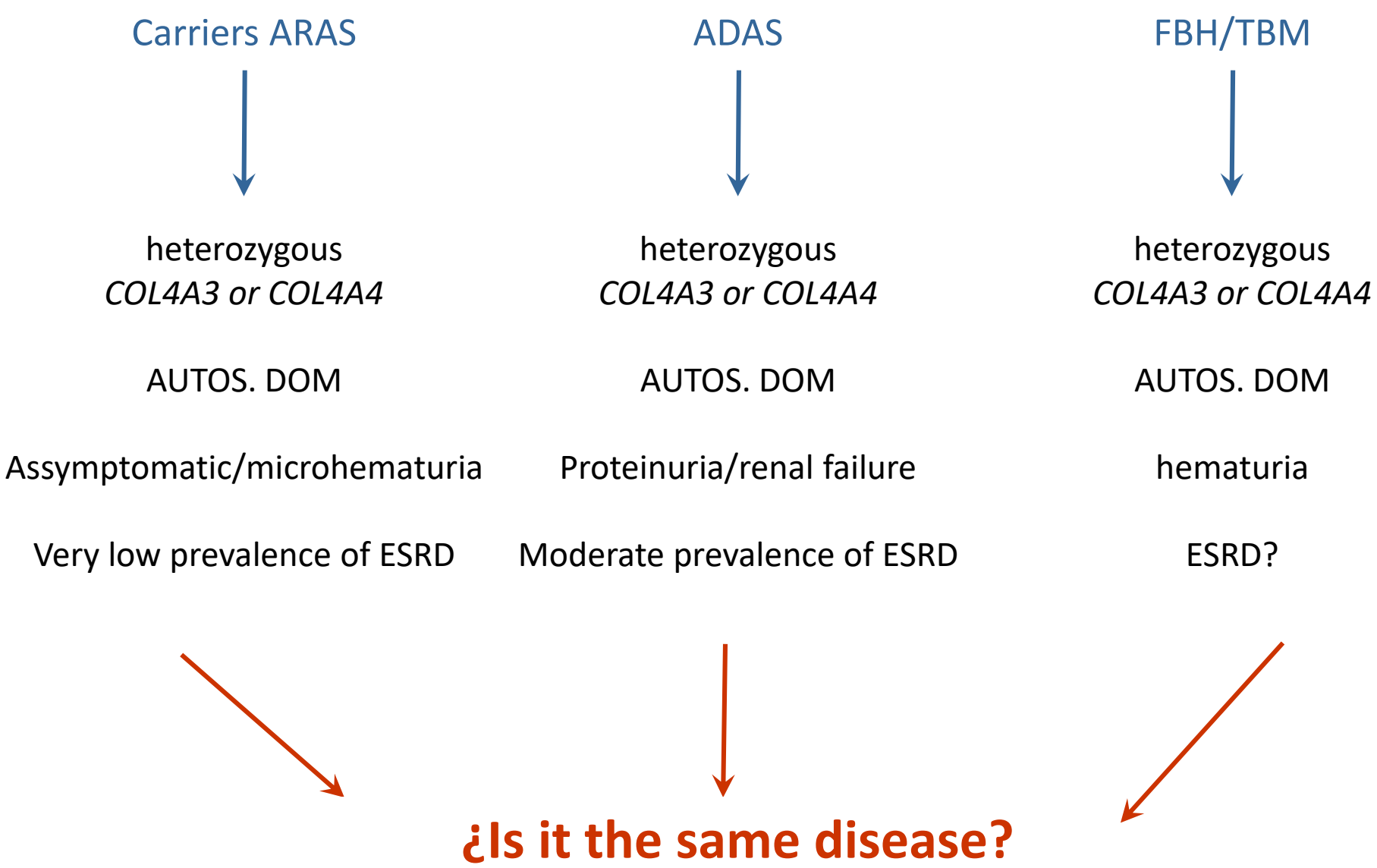
Men and women equally affected
2 mutations *COL4A3* or *COL4A4*

- Frequent Consanguinity
- Girls ESRD < 20 years



CARRIERS ARAS
HETEROZYGOTS
mutations *COL4A3 or COL4A4*

Microhematuria
Pattern of inheritance
AUTOS. DOMINANT


Carriers ARAS
ADAS
FBH/TBM
heterozygous
COL4A3 or COL4A4
AUTOS. DOM
Assymptomatic/microhematuria
Very low prevalence of ESRD
heterozygous
COL4A3 or COL4A4
AUTOS. DOM
Proteinuria/renal failure
Moderate prevalence of ESRD
heterozygous
COL4A3 or COL4A4
AUTOS. DOM
hematuria
ESRD?
¿Is it the same disease?

Nephrol Dial Transplant (2004) 19: 2429–2432
doi:10.1093/ndt/gfh435
Advance Access publication 27 July 2004

Editorial Comments

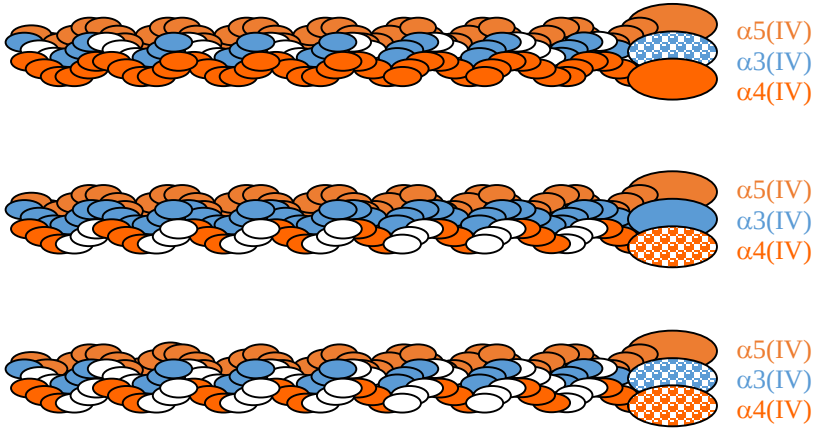
Nephrology
Dialysis
Transplantation

Collagen type IV (α3–α4) nephropathy: from isolated haematuria to renal failure

Roser Torra, Bárbara Tazón-Vega, Elisabet Ars and José Ballarín

Fundació Puigvert, Barcelona, Spain

COLLAGEN IV NEPHROPATHY (α3-α4)/ADAS



VARIABLE
OUTCOME

AUTOSOMAL DOMINANT ALPORT SYNDROME

- PROS:
  - Single name for a disease caused by a mutation in either *COL4A3* or *COL4A4*
  - These patients will have access to RCT

- CONS:
  - Scaring diagnosis
  - Physicians need to be educated

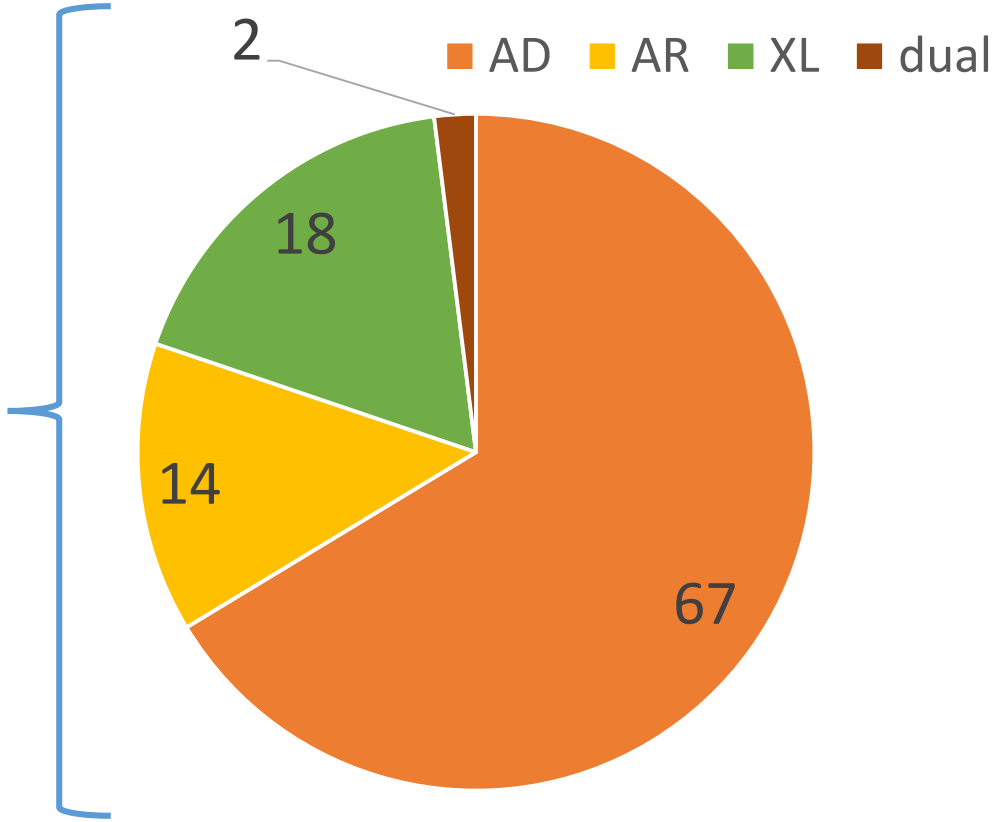
Will become a much more frequent disease

Diagnostic Utility of Exome Sequencing for Kidney Disease

3315 patients with CKD (64% KRT)
91.6% >21 years
35.5% non-European ancenstry

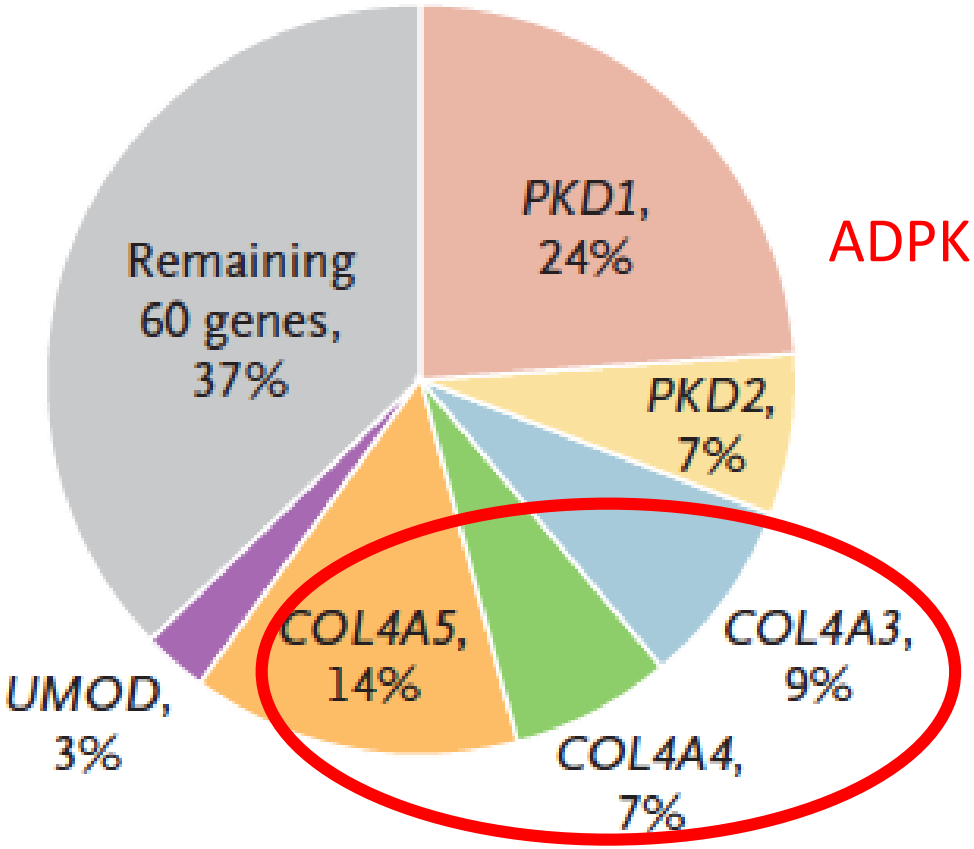
9.3% had a diagnostic variant for a **monogenic** renal disease

- 59% variants found in a single patient



Groopman et al NEJM 2018

Collagen IV genes are (at least) the second cause of monogenic renal disease



ADPKD: 31%

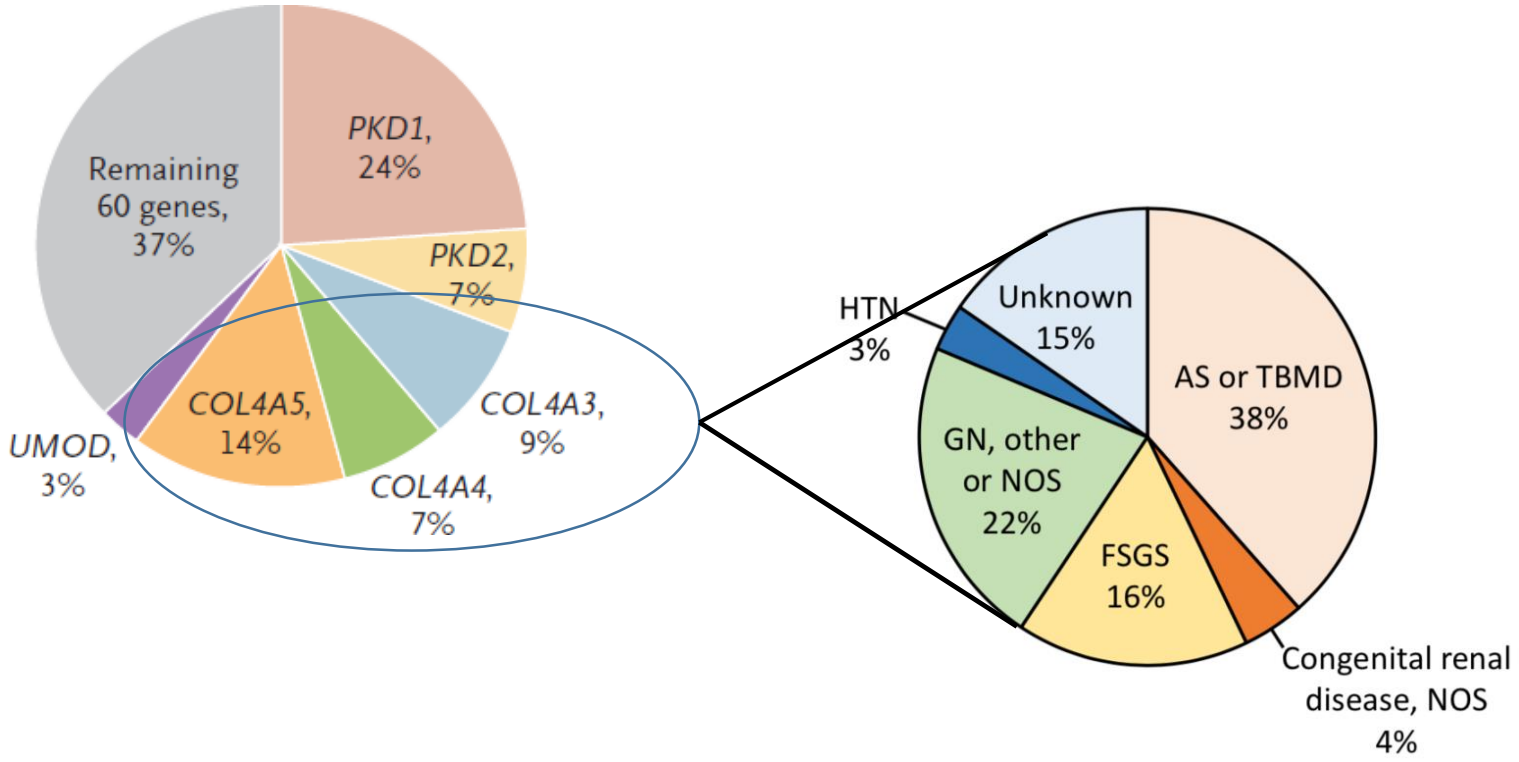
Collagen 4: 30%

But many ADAS patients may only show microhematuria and not KRT:
AS probably more frequent than ADPKD

Groopman et al NEJM 2018

PREVIOUS DIAGNOSIS IN PATIENTS WITH AS

Only 35 of the 91 patients (**38%**) with diagnostic variants in *COL4A3* , *COL4A4* , or *COL4A5* had a clinical diagnosis of AS or TBMD



Groopman et al NEJM 2018

ADAS: FROM MICROHEMATURIA

J Am Soc Nephrol 13: 1248–1254, 2002

Mutations in the *COL4A4* and *COL4A3* Genes Cause Familial Benign Hematuria

CÈLIA BADENAS,*† MANUEL PRAGA,‡ BÁRBARA TAZÓN,*†
LAURENCE HEIDET,§ CHRISTELLE ARRONDEL,§ ANNA ARMENGOL,*†
AMADO ANDRÉS,‡ ENRIQUE MORALES,‡ JUAN ANTONIO CAMACHO,¶
XOSE LENS,# SONIA DÁVILA,‡ MONTSE MILÀ,† CORINNE ANTIGNAC,§
ALEJANDRO DARNELL,* and ROSER TORRA*

**Nephrology and †Genetics Departments, Hospital Clínic, Barcelona, Spain; ‡Nephrology Department, Hospital 12 de Octubre, Madrid, Spain; §Nephrology Department, Inserm U423, Université René Descartes, Hôpital Necker-Enfants Malades, Paris, France; ¶Hospital Sant Joan de Déu, Barcelona, Spain; and #Nephrology Department, Hospital Clínico Universitario, Santiago de Compostela, Spain.*

TO FSGS

Rare hereditary COL4A3/COL4A4 variants may be mistaken for familial focal segmental glomerulosclerosis

KI 2014

Andrew F. Malone[1,2], Paul J. Phelan[1,2], Gentzon Hall[1,2], Umran Cetincelik[3], Alison Homstad[1,4], Andrea S. Alonso[1,4], Ruiji Jiang[1,4], Thomas B. Lindsey[1], Guanghong Wu[1], Matthew A. Sparks[2], Stephen R. Smith[2], Nicholas J.A. Webb[5], Philip A. Kalra[6], Adebowale A. Adeyemo[7], Andrey S. Shaw[8], Peter J. Conlon[9], J. Charles Jennette[10], David N. Howell[11], Michelle P. Winn[1,2] and Rasheed A. Gbadegesin[1,4]

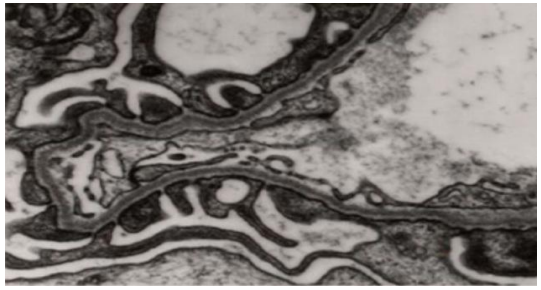
Nephrol Dial Transplant (2016) 31: 961–970
doi: 10.1093/ndt/gfv325
Advance Access publication 7 September 2015

Collagen (*COL4A*) mutations are the most frequent mutations underlying adult focal segmental glomerulosclerosis

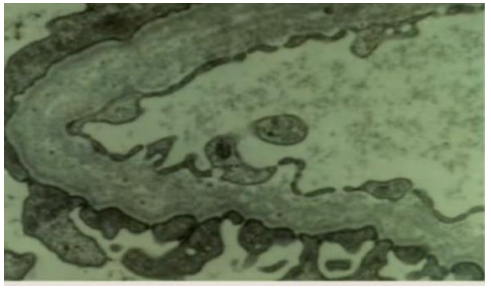
Christine Gast[1,2], Reuben J. Pengelly[2], Matthew Lyon[3], David J. Bunyan[3], Eleanor G. Seaby[2], Nikki Graham[2], Gopalakrishnan Venkat-Raman[1] and Sarah Ennis[2]

[1]Wessex Kidney Centre, Portsmouth Hospitals NHS Trust, Portsmouth, UK, [2]Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton, Southampton, UK and [3]Wessex Regional Genetics Laboratory, Salisbury District Hospital, Salisbury, UK

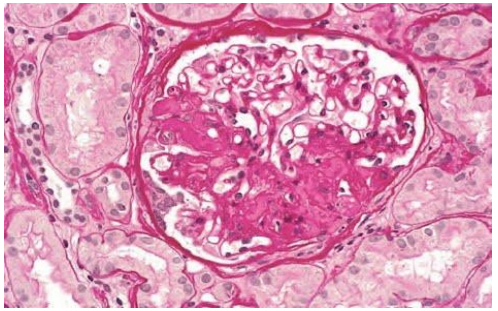
SURPRISED?? AS: PROGRESSION OF LESIONS



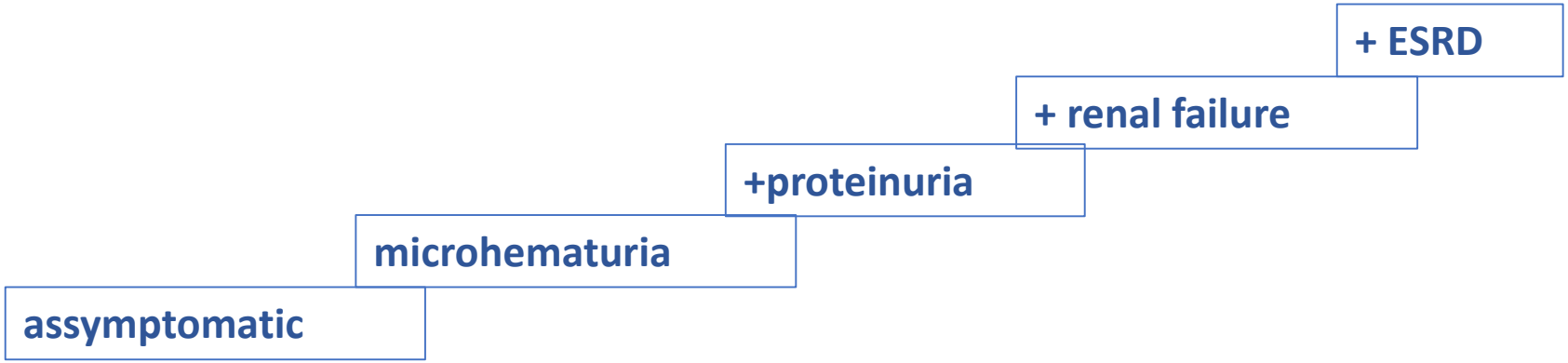
Thinning of GBM
Nomal podocyte foot processes



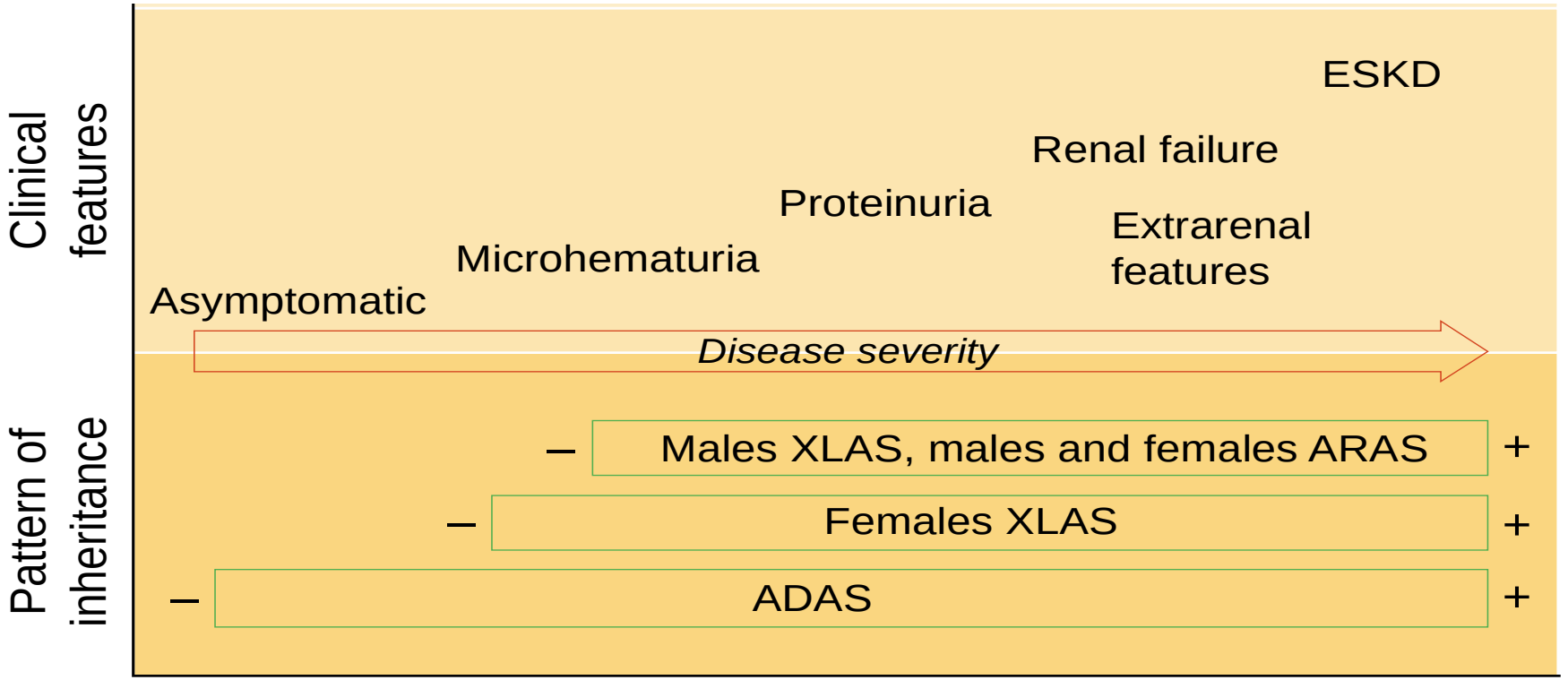
Thickening of GBM
Basket-weaving
Scalloping of epithelial surface
Podocyte effacement
FOAM CELLS



FSGS



AS HAS A WIDE PHENOTYPIC SPECTRUM



Torra and Furlano, NDT 2019

AUTOSOMAL DOMINANT ALPORT SYNDROME: cohort study

Probably the most frequent inherited nephropathy

BIAS

Retrospective cohort study

n = 252 patients
n = 82 families

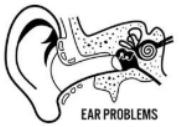
92,1 % microhematuria

Spanish hospitals

Extrarenal features are rare

Heterozygous disease-causing variants in *COL4A3* and *COL4A4*

- *COL4A4* 53% (134/252)
- *COL4A3* 42% (106/252)
- *Digenic Inheritance* 5% (12/252)



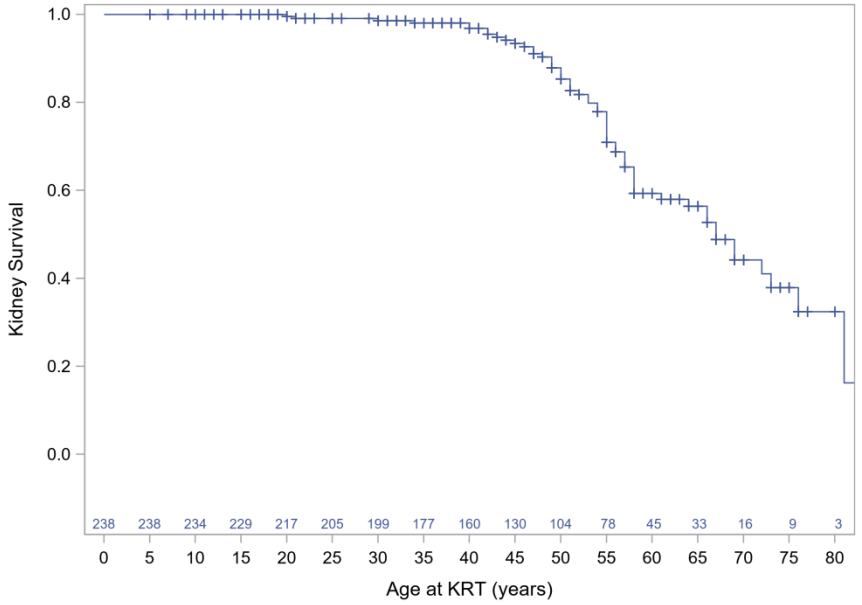
8%

2.5 %

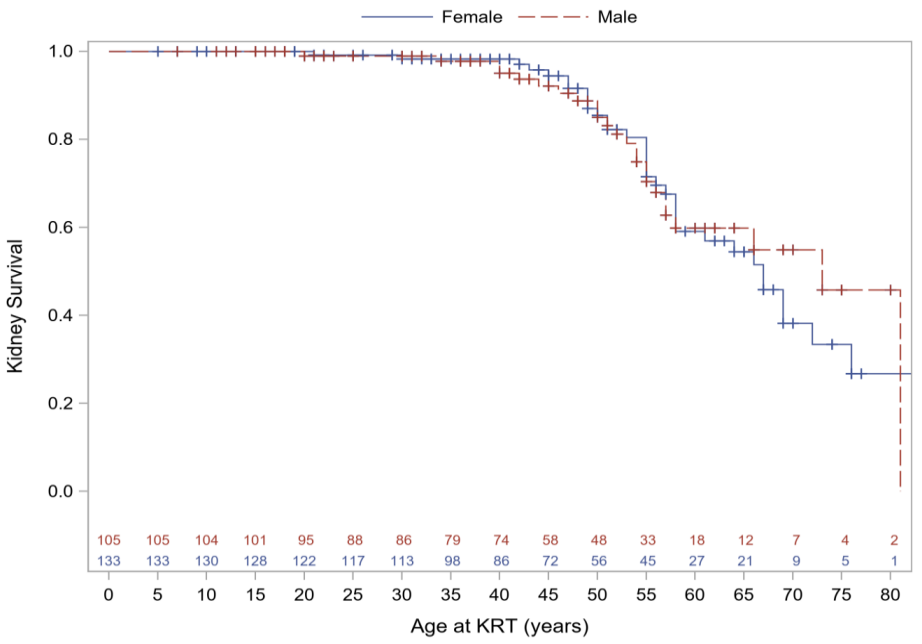
Furlano M, et al, AJKD 2021

KIDNEY SURVIVAL IN ADAS

BIAS



67 years (IC, 58–76)



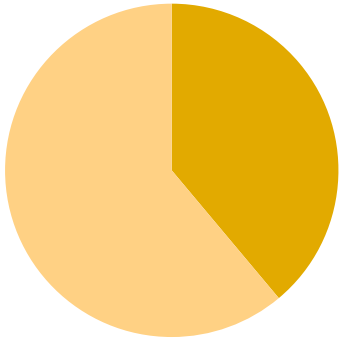
p = 0.77

Furlano M, et al, AJKD 2021

PROTEINURIA IN ADAS

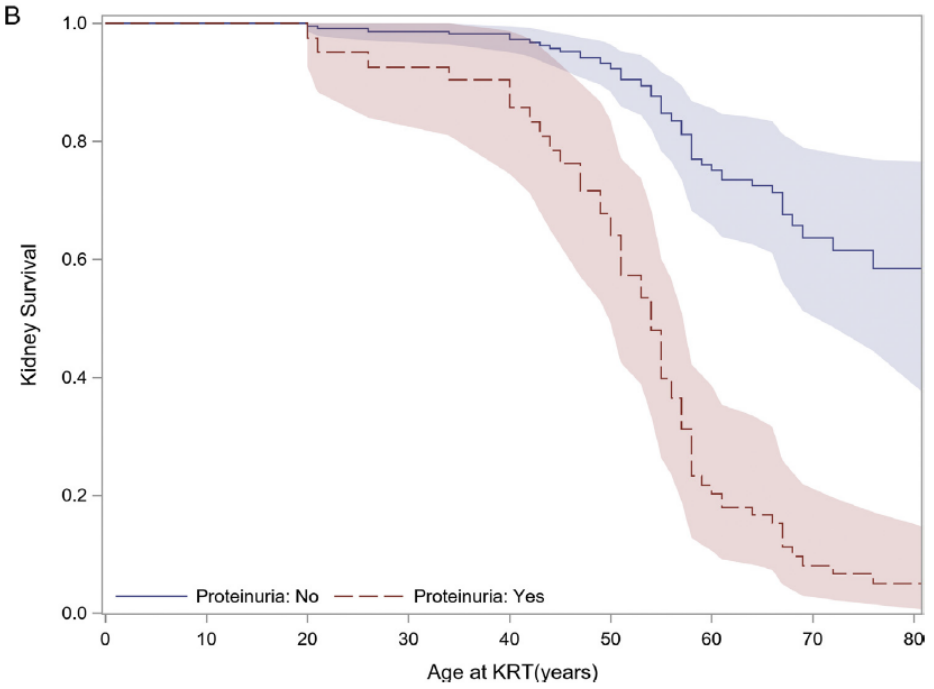
BIAS

Proteinuria and kidney replacement therapy (KRT)



KRT 38,9 % (61/157)

No KRT 61,10 % (96/157)



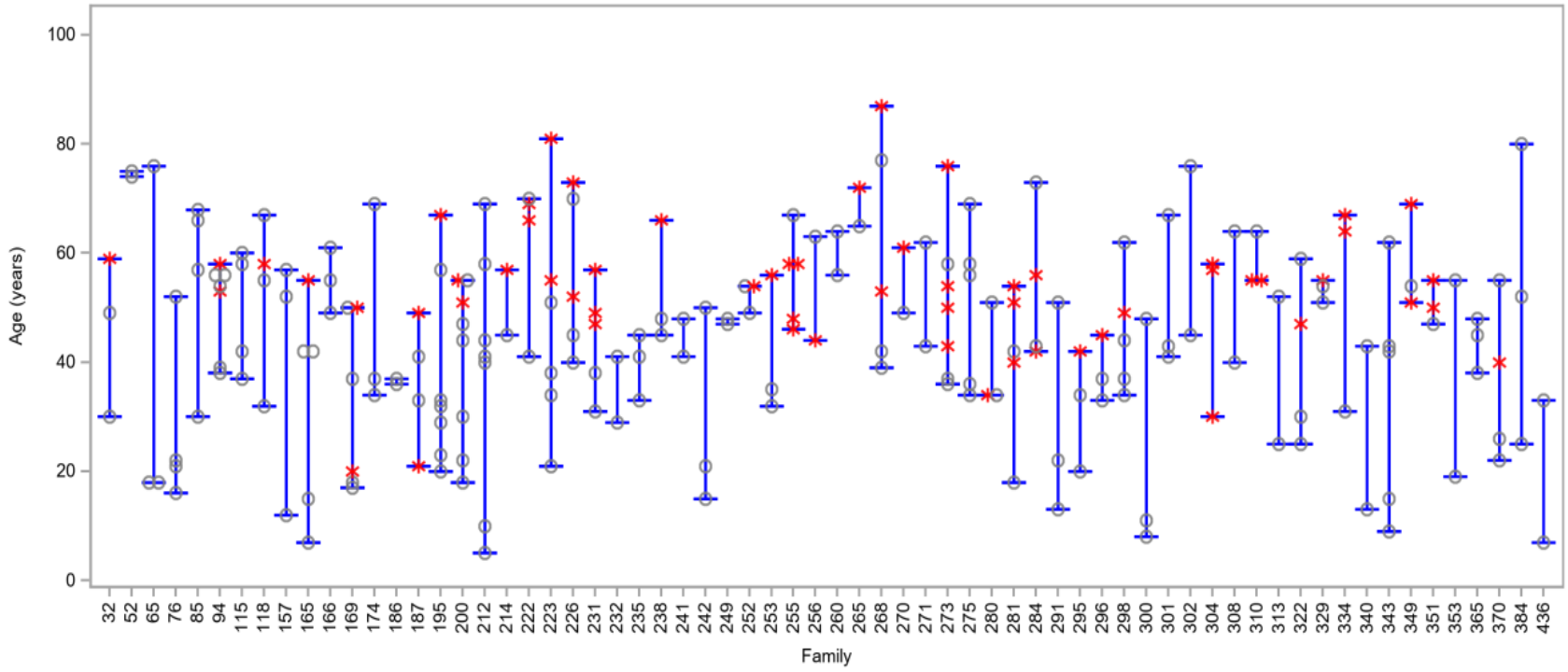
P < 0.001

No patients without proteinuria developed chronic kidney disease

But many has just microalbuminuria

Furlano M, et al, AJKD 2021

INTER- INTRAFAMILIAL VARIABILITY

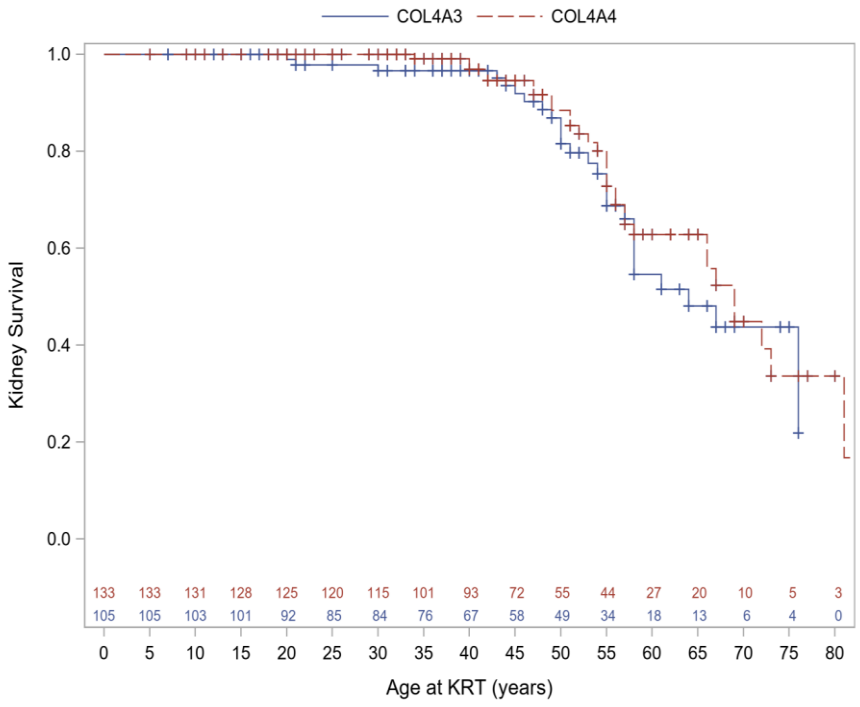


Age at KRT

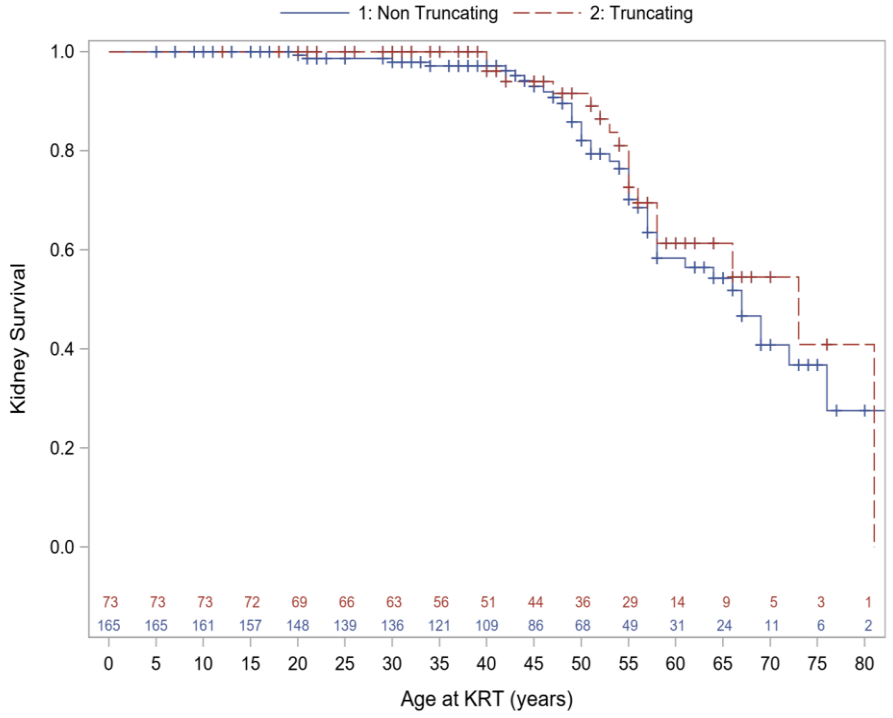
Age of patientes without KRT

Furlano M, et al, AJKD 2021

KIDNEY SURVIVAL BY GENE AND GENETIC VARIANTS



p = 0.51



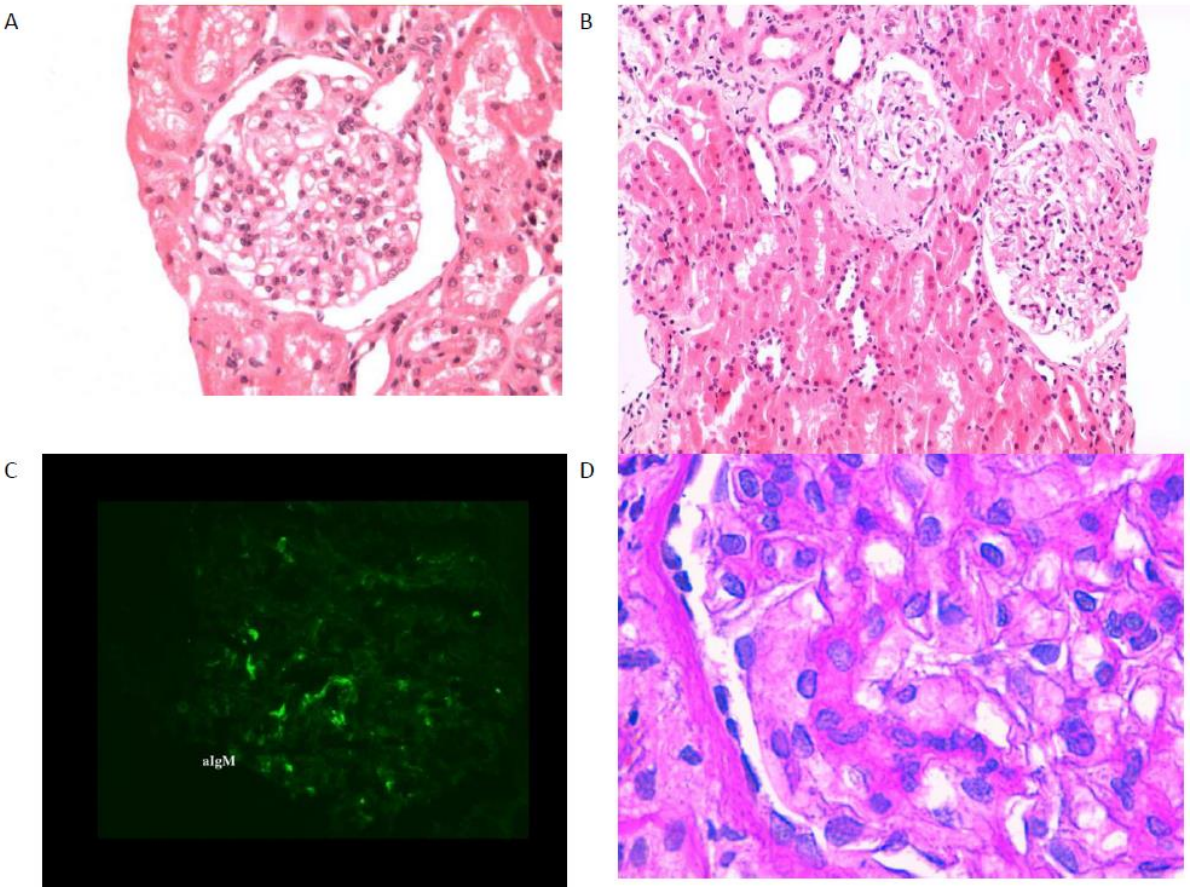
p = 0.37

Cohort size!!

Furlano M, et al, AJKD 2021

KIDNEY LESIONS IN ADAS

A) No glomerular abnormality



B) FSGS

C) expansion of the mesangial matrix with unspecific IgM IF staining

D) expansion of the mesangial matrix with negative IF staining

Furlano M, et al, AJKD 2021

IS IT THAT FREQUENT?

Prevalence Estimates of Predicted Pathogenic COL4A3 - COL4A5 Variants in a Population Sequencing Database and Their Implications for Alport Syndrome

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Joel Gibson, Rachel Fieldhouse, Melanie Chan, Omid Sadeghi-Alavijeh, Leslie Burnett, Valerio Izzi, Anton Persikov, Daniel Gale, Helen Storey and Judy Savige

JASN June 2021, ASN.2020071065; DOI: https://doi.org/10.1681/ASN.2020071065

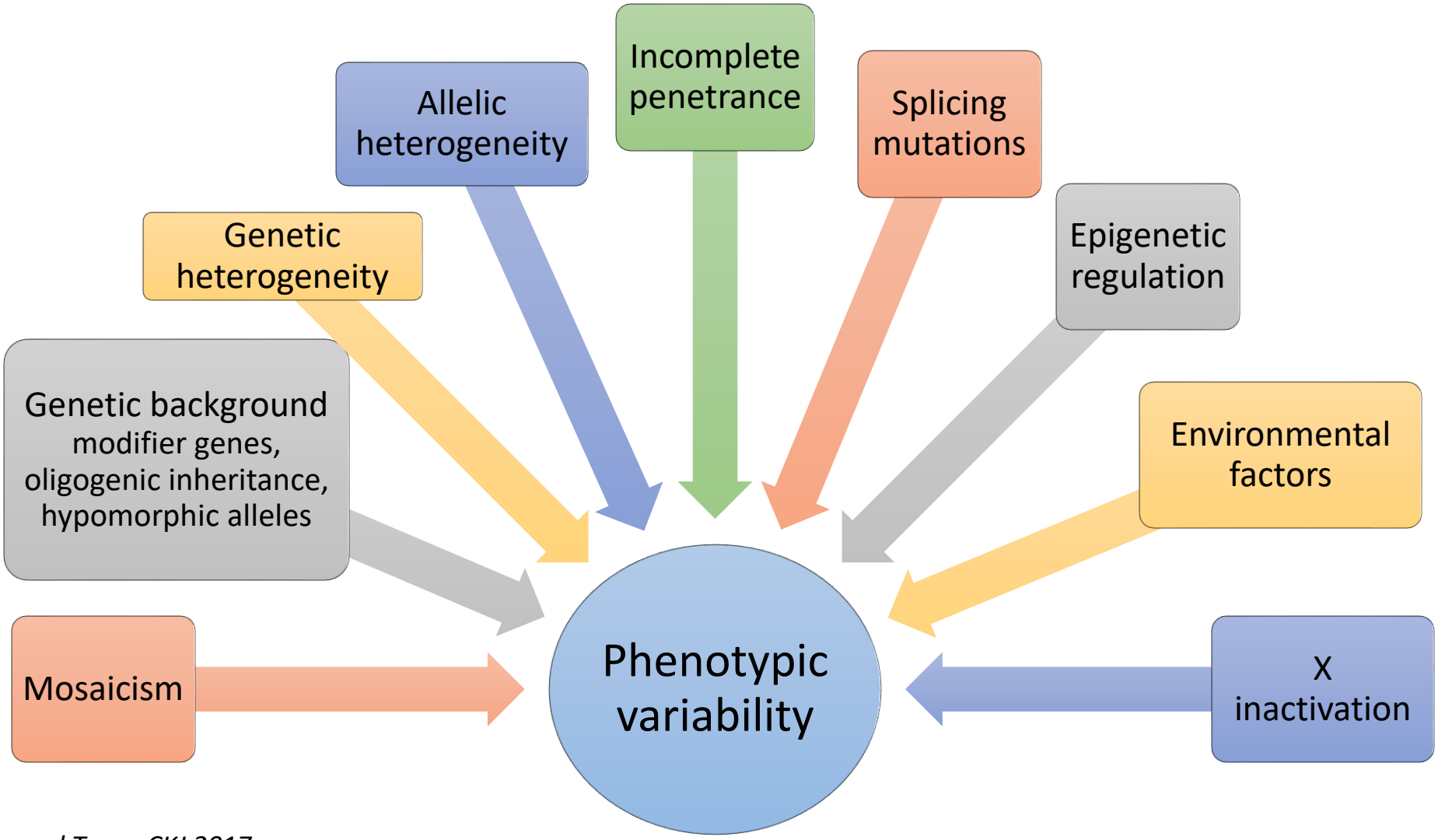
Background: This study **estimated the frequencies of predicted pathogenic *COL4A3- COL4A5*** *variants in sequencing databases of populations* ***without known kidney disease***

Results:

- Predicted pathogenic heterozygous *COL4A3-4 variants affected* ……***1 in 106 individuals***
- Predicted pathogenic *COL4A5* variants were found in at least……. **1 in 2320**
- *Digenic variants in at least* ……***1 in 44,793***.
- *Predicted pathogenic compound heterozygous variants*…….***1 in 88,866***

Conclusions: The frequencies of predicted pathogenic *COL4A3-COL4A5 variants must be adjusted for the disease penetrance of individual variants, as well as the likelihood of already diagnosed disease and non-Gly substitutions.* ***Disease penetrance may depend on biochemical features.***

Reasons for extreme phenotypes



Ars and Torra. CKJ 2017

Genetic testing in Alport Syndrome

Pediatric Nephrology
https://doi.org/10.1007/s00467-018-3985-4

REVIEW

Expert consensus guidelines for the genetic diagnosis of Alport syndrome

Judy Savige[1] · Francesca Ariani[2] · Francesca Mari[2] · Mirella Bruttini[2] · Alessandra Renieri[2] · Oliver Gross[3] · Constantinos Deltas[4] · Frances Flinter[5] · Jie Ding[6] · Daniel P. Gale[7] · Mato Nagel[8] · Michael Yau[9] · Lev Shagam[10] · Roser Torra[11] · Elisabet Ars[12] · Julia Hoefele[13] · Guido Garosi[14] · Helen Storey[9]

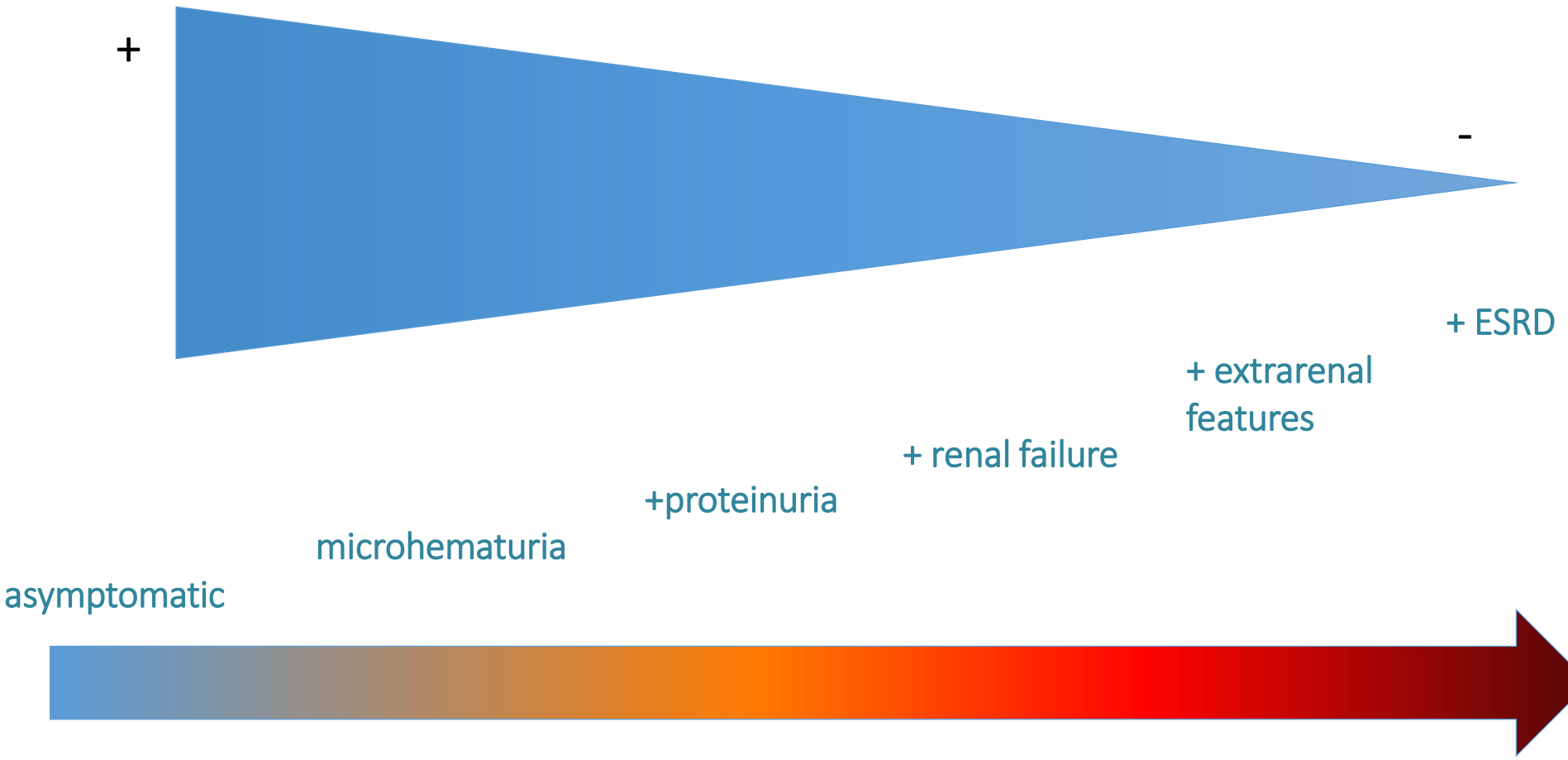
Received: 10 January 2018 / Revised: 22 February 2018 / Accepted: 10 May 2018

- **Genetic testing** is the **gold standard** for the **diagnosis of Alport syndrome** since it is **more sensitive and specific than renal biopsy** and provides some **predictive information** about disease severity.

- Individuals with **suspected Alport syndrome** should be offered genetic testing for mutations in all three Alport syndrome genes (***COL4A3, COL4A4, COL4A5***) and, if negative, analysis of **podocyte-related genes** is recommended. PANEL!

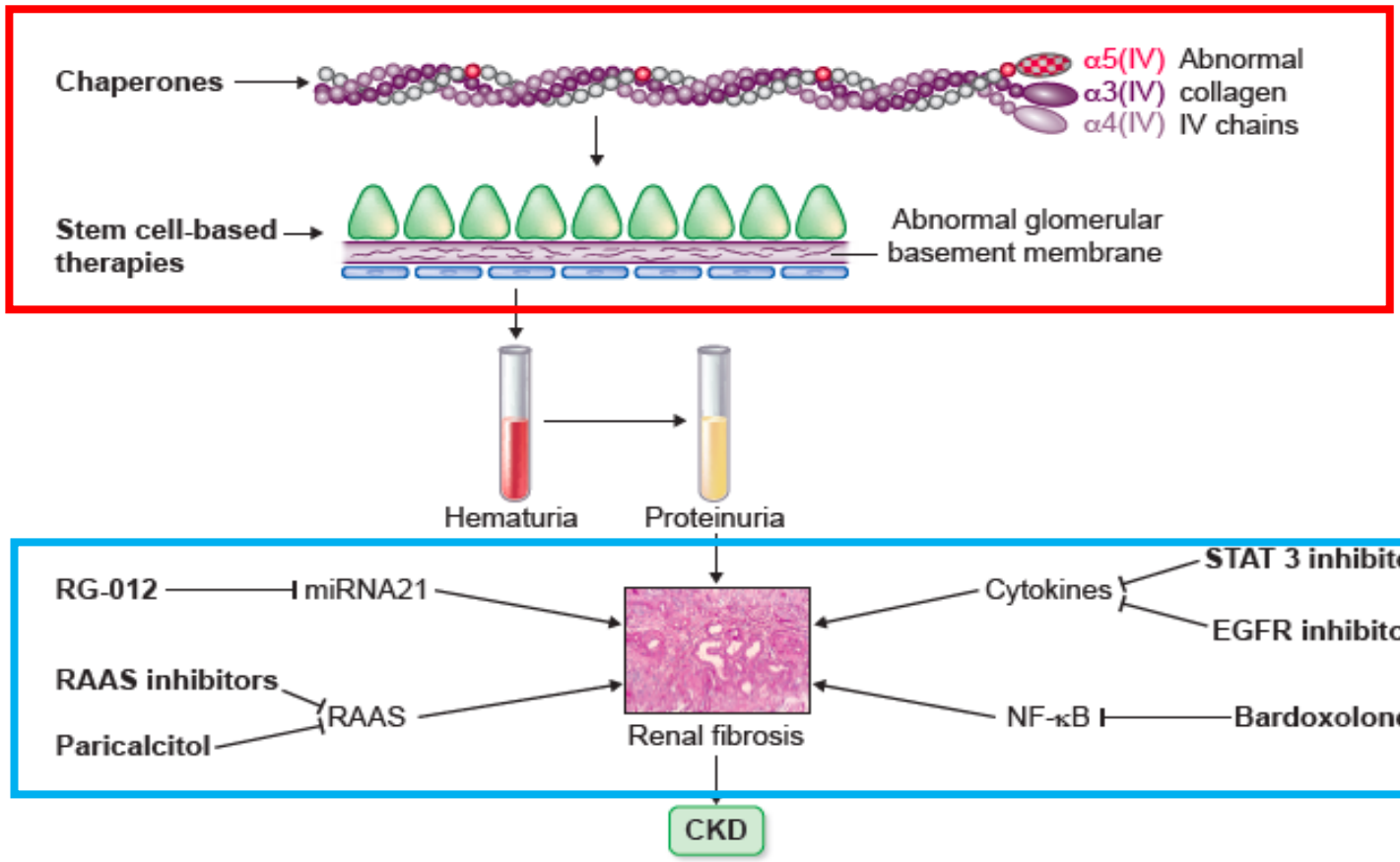
- Individuals with **focal segmental glomerulosclerosis** should also be offered genetic testing for mutations in **Alport genes** in addition to **podocyte-related genes**.

IMPACT OF TREATMENT



Therapeutic targets for AS

SPECIFIC



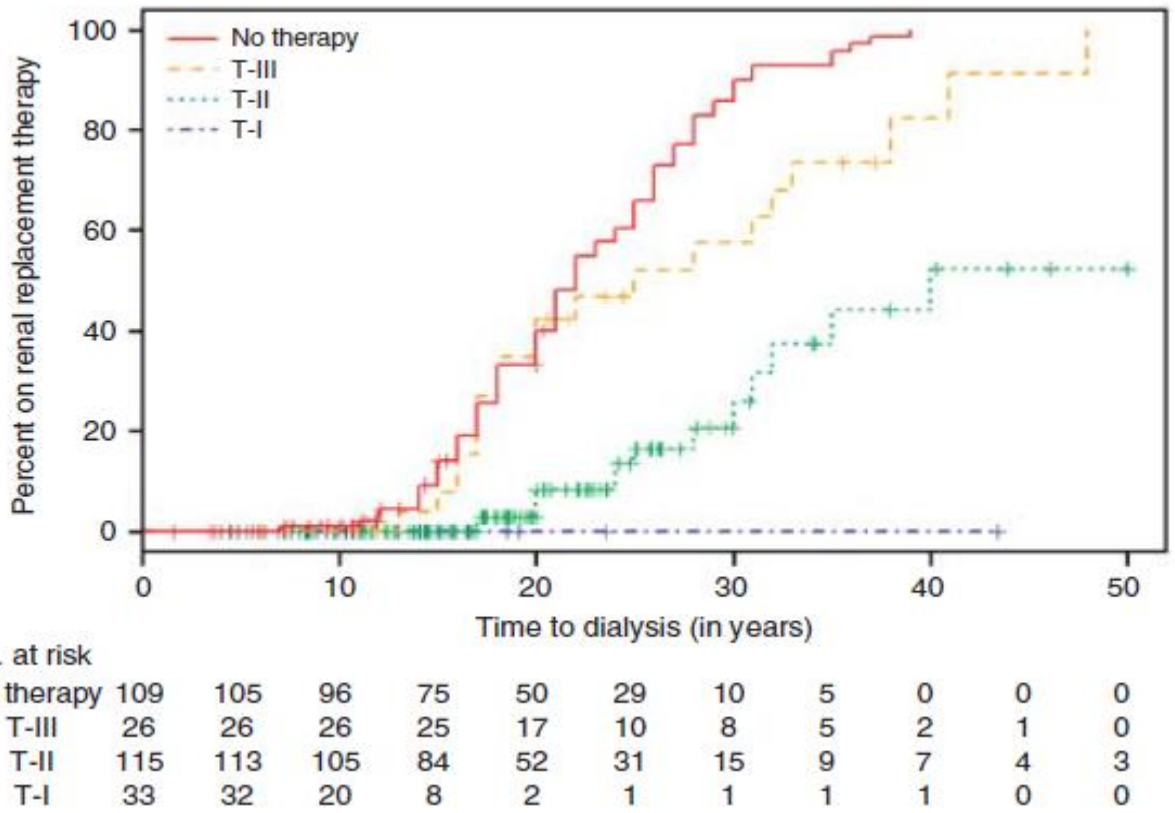
Torra & Furlano NDT 2019

TREATMENT WITH ACEI - XLAS males or children with ARAS

Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy

Oliver Gross[1], Christoph Licht[2], Hans J. Anders[3], Bernd Hoppe[4], Bodo Beck[4], Burkhard Tönshoff[5], Britta Höcker[5], Simone Wygoda[6], Jochen H.H. Ehrich[7], Lars Pape[7], Martin Konrad[8], Wolfgang Rascher[9], Jörg Dötsch[4], Dirk E. Müller-Wiefel[10], Peter Hoyer[11], and Study Group Members of the Gesellschaft für Pädiatrische Nephrologie (GPN), Bertrand Knebelmann[12], Yves Pirson[13], Jean-Pierre Grunfeld[12], Patrick Niaudet[14], Pierre Cochat[15], Laurence Heidet[16], Said Lebbah[16], Roser Torra[17], Tim Friede[18], Katharina Lange[18], Gerhard A. Müller[1,20] and Manfred Weber[19,20]

Antipoteinuric/atifibrotic effect



No. at risk											
No therapy	109	105	96	75	50	29	10	5	0	0	0
T-III	26	26	26	25	17	10	8	5	2	1	0
T-II	115	113	105	84	52	31	15	9	7	4	3
T-I	33	32	20	8	2	1	1	1	1	0	0

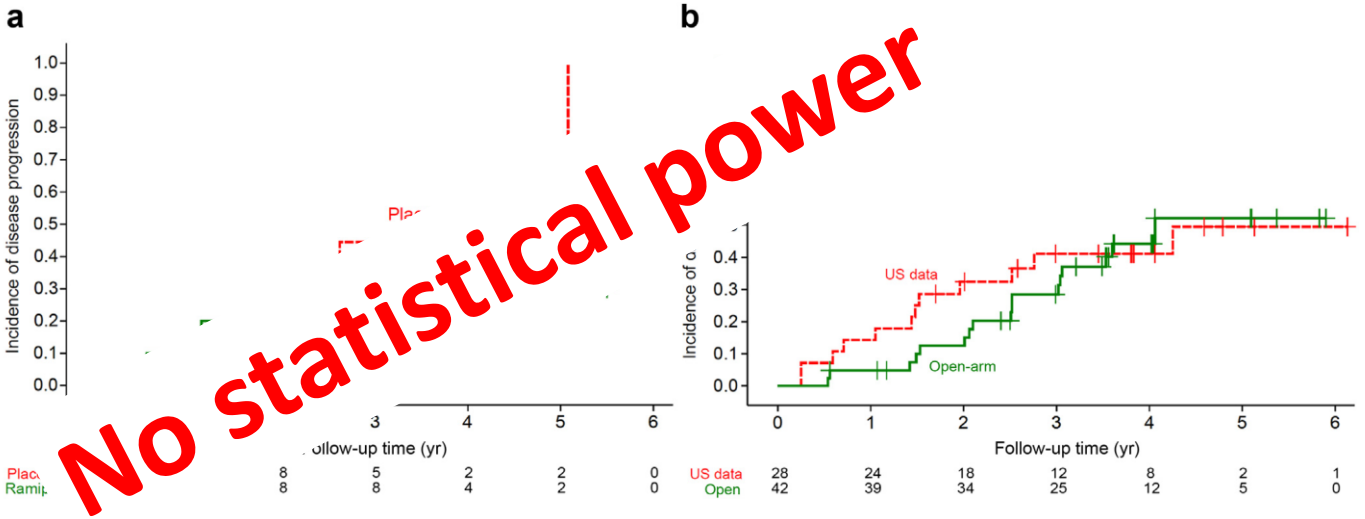
T-1: Inicio de tratamiento con microhemturia o MAU
T-2: Inicio de tratamiento con proteinuria>0.3 g/d
T-3: Inicio de tratamiento en ERC estadios 3-4
No T: sin tratamiento antes de diálisis o TR

Gross O et al , KI 2011

ACEI in children

Gross O, Institut fuer anwendungsorientierte Forschung und klinische Studien GmbH

Early prospective Therapy Trial to Delay Renal Failure in Children with Alport Syndrome Ramipril versus Placebo

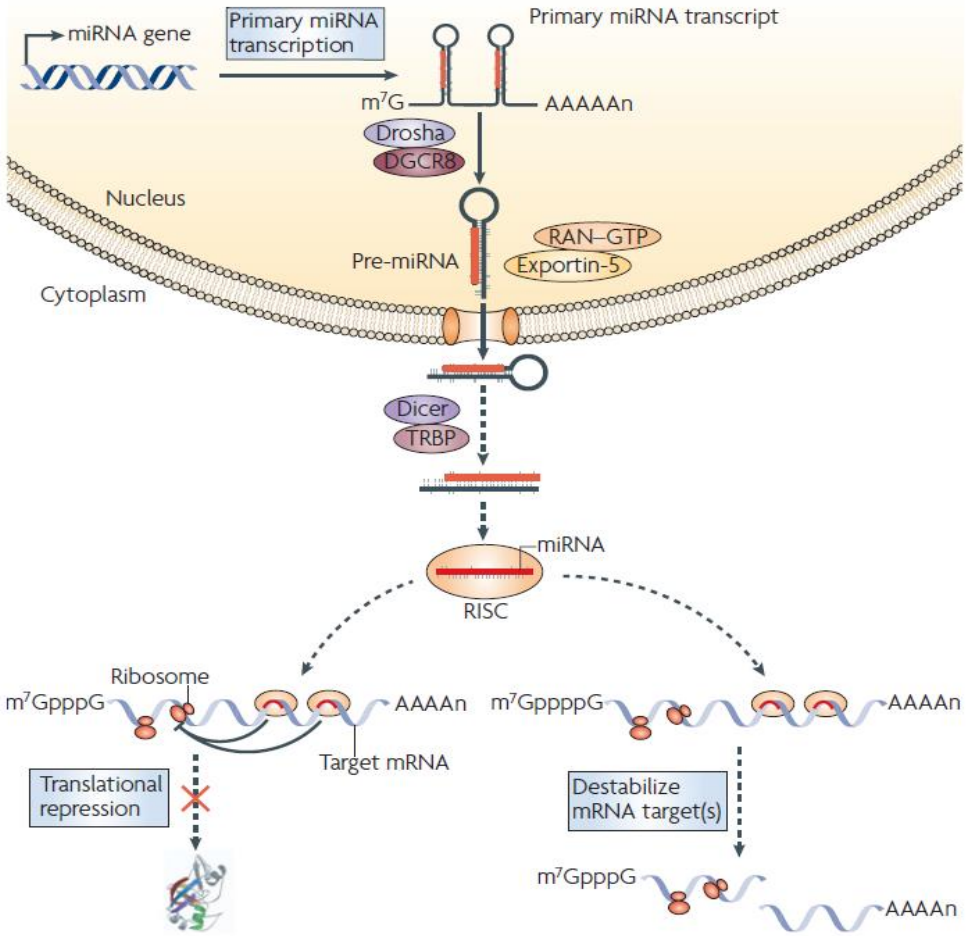


No statistical power

Gross et al, Kidney International (2020) 97, 1275–1286

microRNA (miRNA)

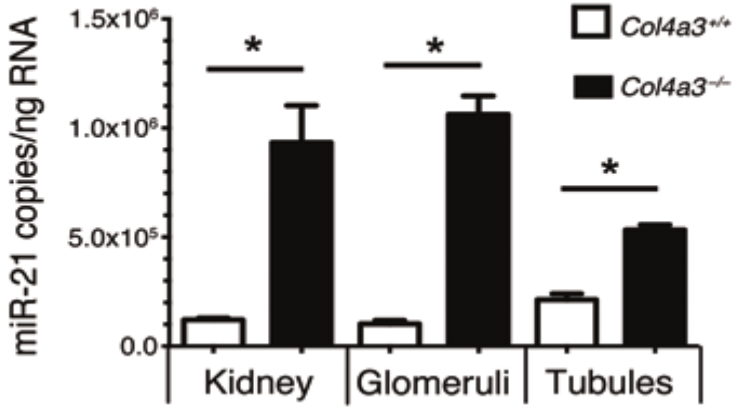
microRNAs (miRNAs): small non-coding RNAs that can regulate gene expression post-transcriptionally by affecting the degradation and translation of target mRNAs



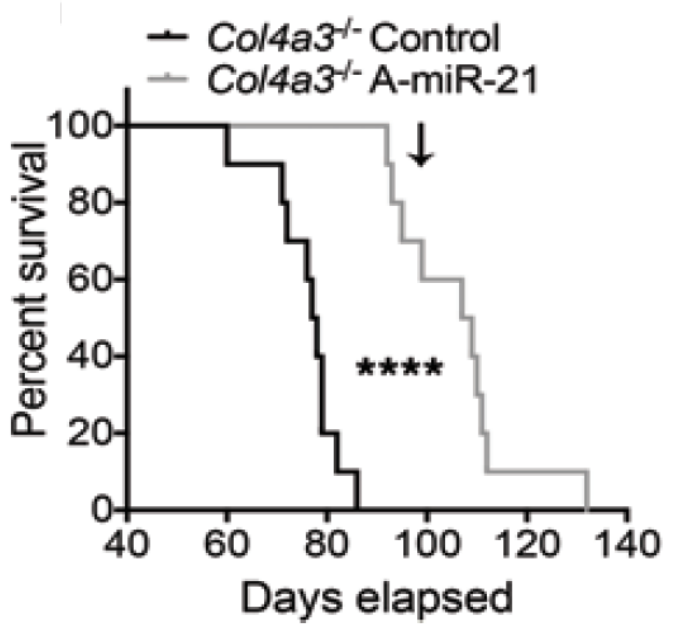
Lodish et al Nat Rev Immunol 2008

Anti-miRNA-21 prevents Alport nephropathy progression

miR-21 contributes to the pathogenesis of fibrogenic diseases in multiple organs, including the kidneys, by silencing metabolic pathways that are critical for cellular ATP generation, ROS production, and inflammatory signaling.

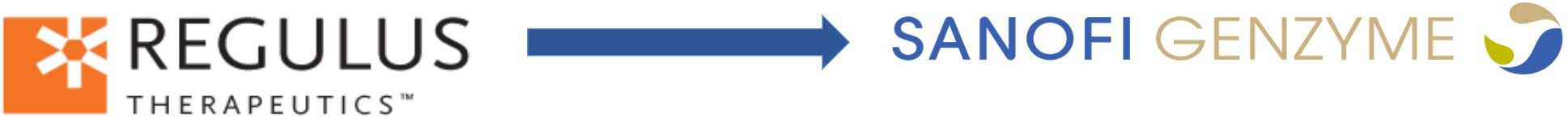


mRNA 21 is upregulated in AS mice



Gomez I et al JCI 2015

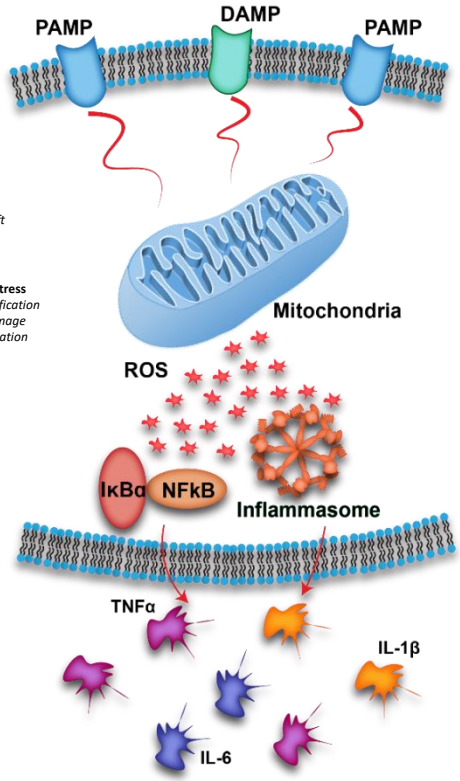
anti-miRNA-21



- Orphan drug designation
- Observational study: ATHENA
- Phase 1: Good safety profile but investigating unexpected mouse chronic toxicity. Investigations in primates.
- Sanofi taking over Phase 2 trial: HERA ongoing

Disease Triggers

Autoimmunity, Mutations, Cellular damage (DAMPs), Infection (PAMPs), Cytokines



Increased Energy Production

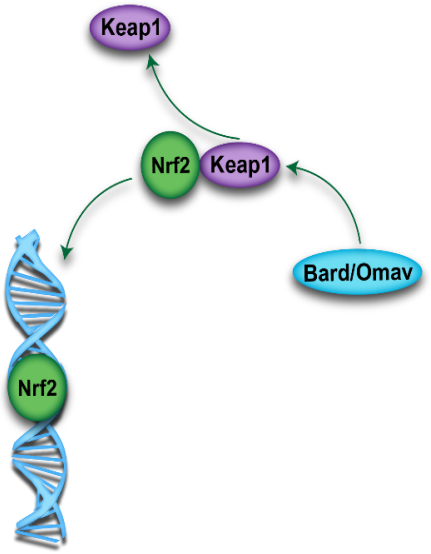
- *Increased ATP,NADH, $FADH_2$, production*
- *Mitochondrial biogenesis*
- *Anti-inflammatory metabolic shift*

Antioxidant activity

- *Glutathione & NADPH*
- *SOD, TRX, GRX, PRX, GPX*
- *NLRP3 inhibition*
- *Redox homeostasis*

Anti-inflammatory activity

- *IκBα/NF-κB & NLRP3 inhibition*
- *Cytokine suppression*
- *(TNFα, IL-1ß, IL-6, MCP1)*
- *Resolution of inflammation*



Disease Deficits

Acute

Decreased 6MWD
Decreased eGFR
Decreased muscular function
proliferation
Tissue remodeling
Fibrosis (TGFß)

Chronic

Abnormal

Potential Amelioration of Acute and Chronic Disease Deficits

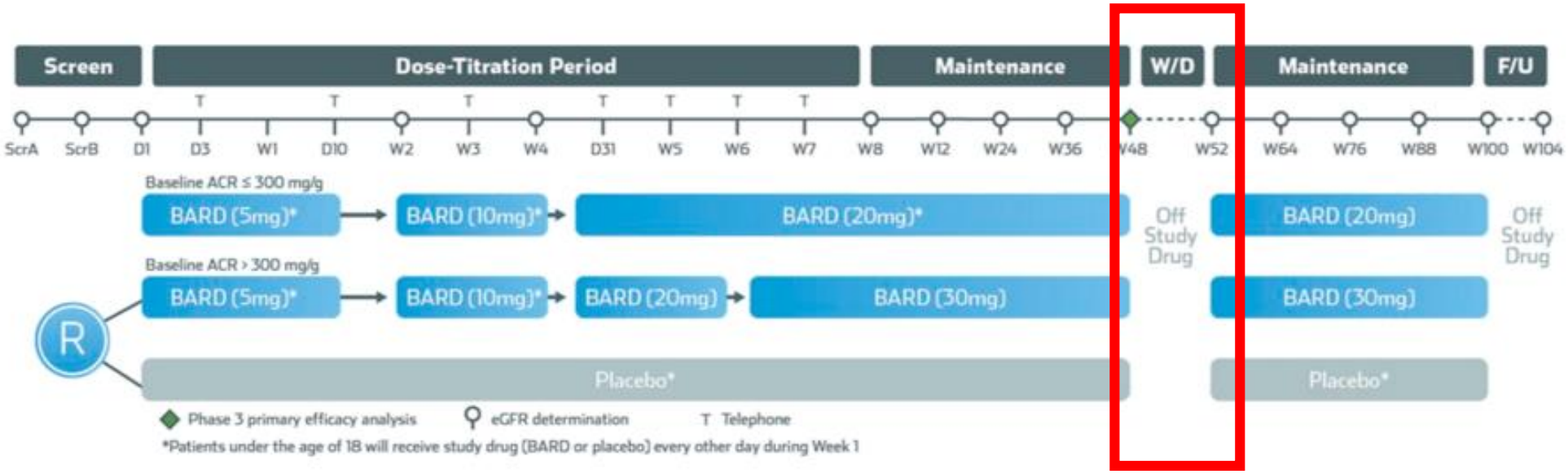
Physiological

- May acutely improve organ function
- May chronically reduce fibrosis and remodeling

BARDOXOLONE

CARDINAL: fase 3.

- International, doubke blind, randomized, 12-70 years, GFR 30-90
- Bardoxolone methyl (n=77) or placebo (n=80).



FDA U.S. FOOD & DRUG ADMINISTRATION

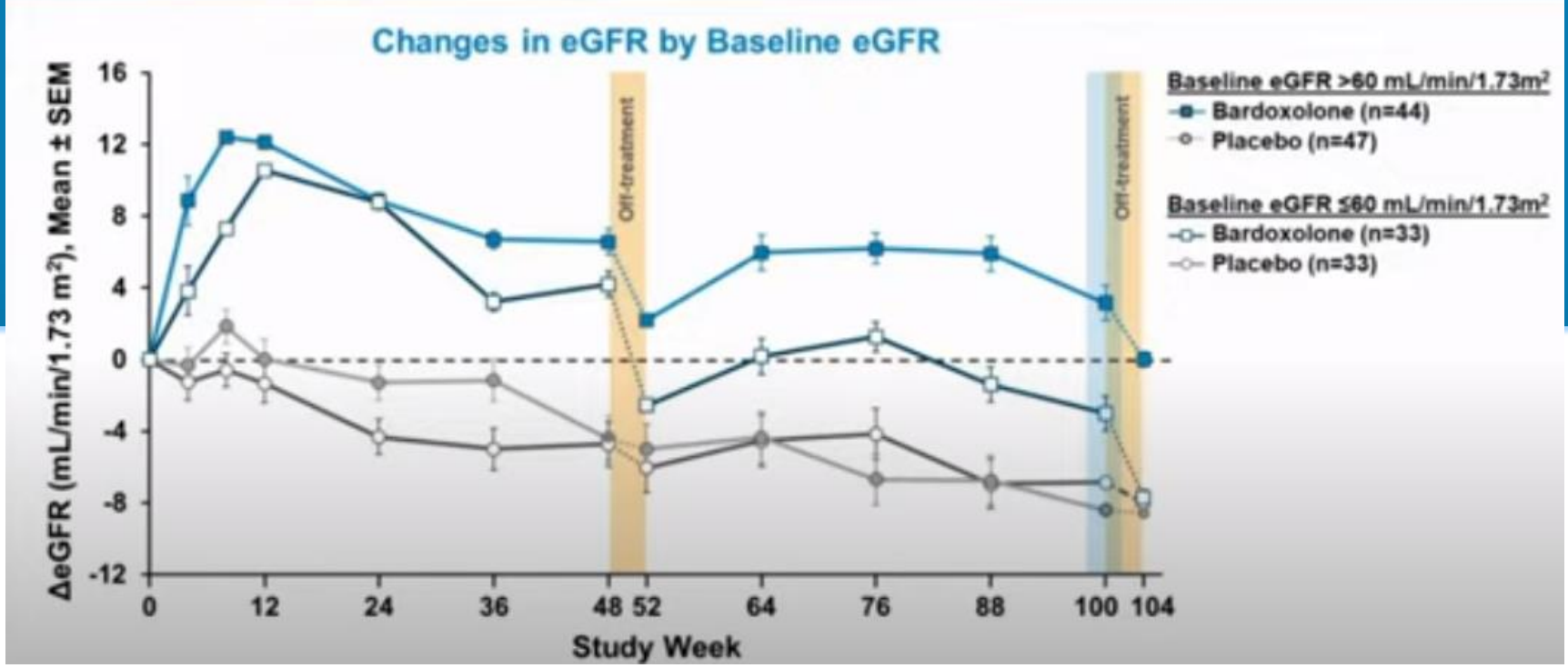
What You Will Hear Today

Medical Need	Urgent need in this rare, serious and rapidly progressive kidney disease
Study Design	Appropriate design and off-treatment duration
Efficacy	Robust, consistent, clinically meaningful slowing of CKD progression
Safety	Safety and tolerability profile well defined, clinically manageable
Benefit/Risk	Positive benefit/risk in patients with Alport syndrome

FDA U.S. FOOD & DRUG ADMINISTRATION

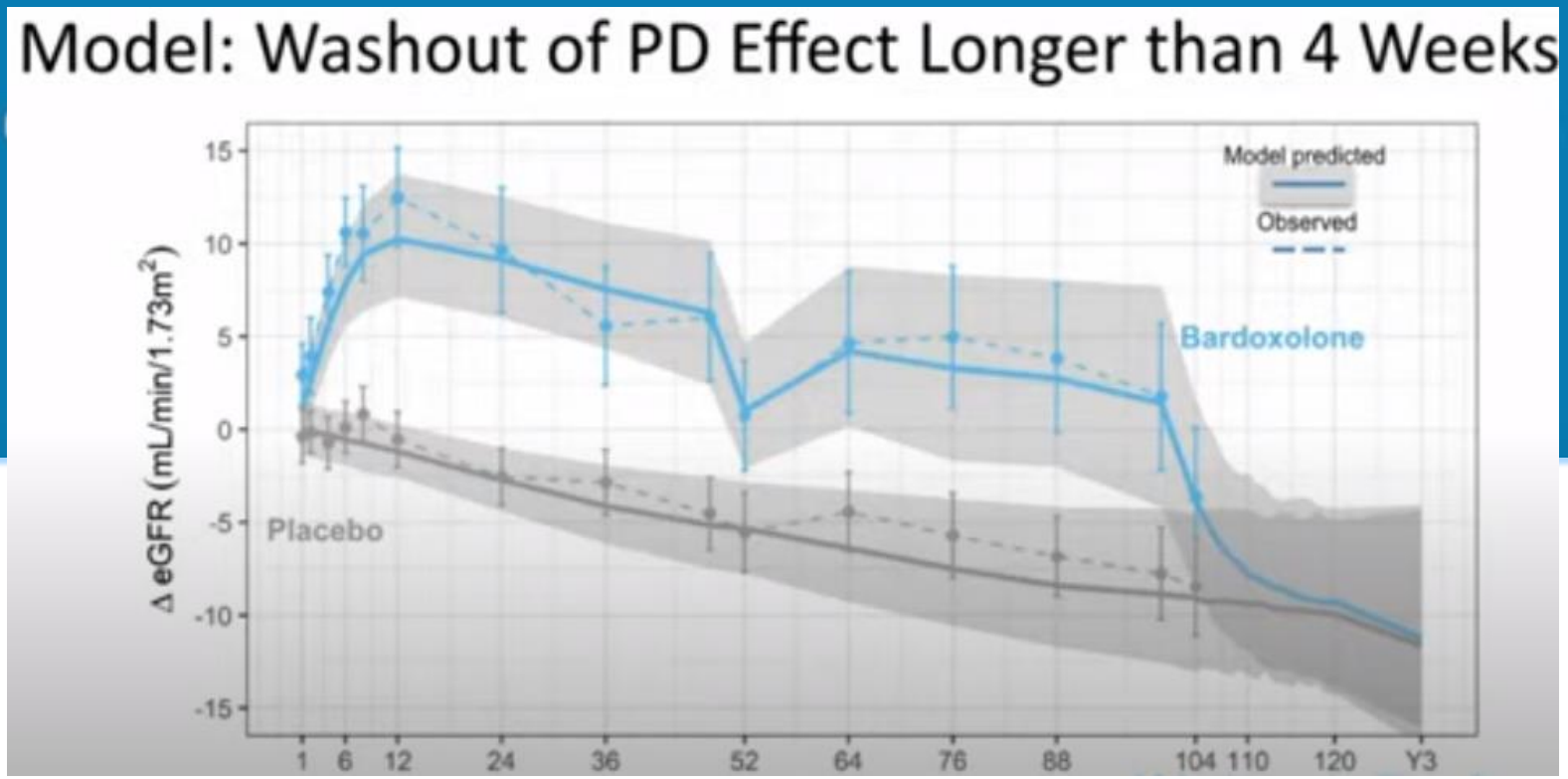
eGFR Summary by Baseline eGFR

Study 1603 Phase 3



FDA U.S. FOOD & DRUG ADMINISTRATION

Model: Washout of PD Effect Longer than 4 Weeks



U.S Food and Drug Administration

February 2022

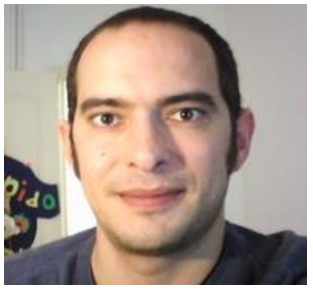
- The **FDA cannot approve the new drug application in its present form**. Based on its review, the FDA concluded that it **does not believe** the submitted data demonstrates that bardoxolone is **effective in slowing the loss of kidney function in patients with Alport syndrome** and reducing the risk of progression to kidney failure and has requested additional data to support the efficacy and safety of bardoxolone.
- Major **efficacy** concerns:
  - adequacy of off-treatment duration to assess resolution of **acute pharmacodynamic effect**
  - **lack of divergence** in on-treatment eGFR change from baseline between Week 48 and Week 100
- Major **safety** concerns:
  - Clinically relevant effect on the **QT interval**
  - **Lack of weight gain** in adolescents and possible **impact on growth**
- **Reata** will continue to seek FDA advice regarding the path forward for BRD in AS, in ADPKD and will continue to enroll patients in FALCON and continue to dose patients with AS and ADPKD in EAGLE (the extended access study).

Take home messages

- The GBM is a major contributor to the size selectivity of the glomerular filter
- The composition of the GBM changes during glomerulogenesis to permit proper development and filtration function.
- Mutations in collagen IV genes give rise to a wide spectrum of disease ranging from microhematuria to ESKD with/without extrarenal features (eye, ear).
- Pathogenic *COL4A5* variants are highly penetrant for hematuria and renal failure in males and for hematuria in females.
- The penetrance of persistent hematuria with *COL4A3* and *COL4A4* variants is about 70% and the penetrance of a thinned GBM, FSGS, and renal impairment are not known.
- AS phenotype ADAS is underdiagnosed, but women with XLAS also
- AS is the second (???) more prevalent genetic kidney disease after ADPKD.
- It should be suspected in familial proteinuric-hematuric nephropathies, non immunological-non secondary FSGS (specially if there is hematuria).
- Genetic testing is the only certain diagnostic tool for the disease.

Thanks!

Elisabet Ars



Marc Pybus

Laura Lorente

Andrea Domingo

Melissa Pilco

Mónica Furlano

Anna Matamala

ERKNet
The European Rare Kidney Disease Reference Network

HOSPITAL DE LA SANTA CREU I SANT PAU
FUNDACIÓ DE GESTIÓ SANITÀRIA
UNIVERSITAT AUTÒNOMA DE BARCELONA

Fundació Puigvert

era edta
LEADING EUROPEAN NEPHROLOGY

isc Instituto de Salud Carlos III

INSTITUTO "REINA SOFIA" DE INVESTIGACION NEFROLOGICA
FUNDACIÓN RENAL

Red de Investigación Renal
redinren iscIII

Sociedad Española de Nefrología

ASK THE EXPERT

Virtual session on **Wednesday, 11th May**

5:00-6:30 PM (CET)

Several ERKNet experts address questions in following areas:
17:00-17:35 **Glomerulopathies**
17:35 -17:50 **Tubulopathies**
17:50-18:05 **Atypical haemolytic-uraemic syndrome**
18:05-18:15 **ADPKD**
18:15-18:30 **Congenital anomalies of the kidney and the urinary tract (CAKUT)**

Questions will be **translated** into all major European languages

Please **forward** this invitation to other patients and families with rare kidney diseases that might be interested in our experts' opinions and advice!

Subscribe our Newsletter
Or follow us on Twitter
@EuRefNetwork

ERKNet The European Rare Kidney Disease Reference Network
european society for paediatric nephrology
WGIKD Working Group on Inherited Kidney Disorders
IPNA

NEXT WEBINARS

17/05/22

Reno-vascular hypertension
Jelena Stojanovic (London, UK)

14/06/22

When to perform genetic testing in CAKUT (and what to test)?
Nine Knoers (Groningen, Netherlands)

28/06/22

Gitelman – adult view
Tom Nijenhuis (Nijmegen, Netherlands)

Subscribe our Newsletter
Or follow us on Twitter
@EuRefNetwork

ERKNet The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

WGIKD Working Group on Inherited Kidney Disorders

IPNA