

TYPE IV COLLAGEN NEPHROPATHY

WHEN RARE BECOMES COMMON

Tim Van Damme | October 12, 2024 | Ghent, Belgium

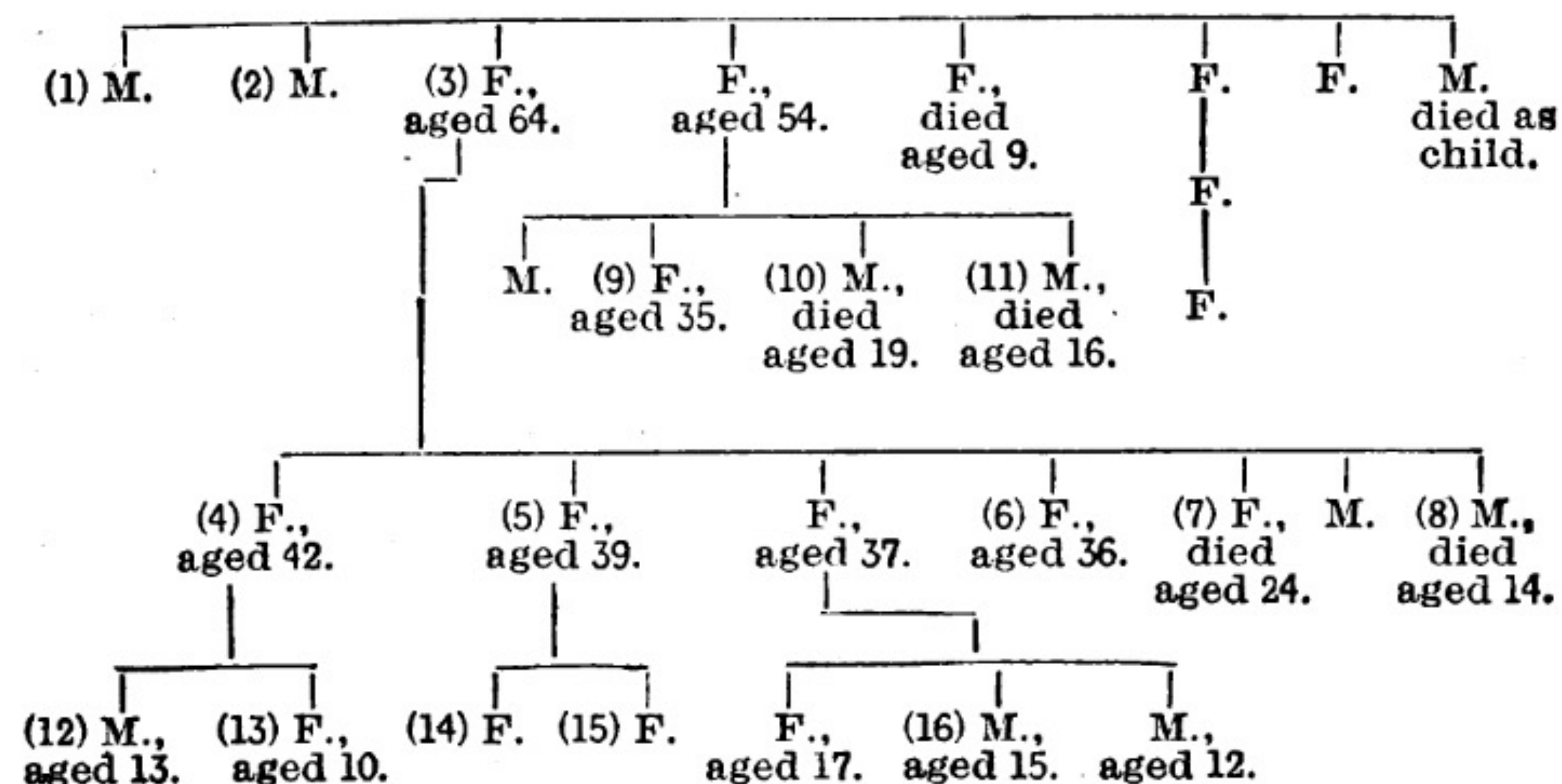


HEREDITARY FAMILIAL CONGENITAL HAEMORRHAGIC NEPHRITIS.

BY

A. CECIL ALPORT, M.D.ED., M.R.C.P.LOND.,
MEDICAL UNIT, ST. MARY'S HOSPITAL, PADDINGTON.

Genealogical Tree (Hurst).



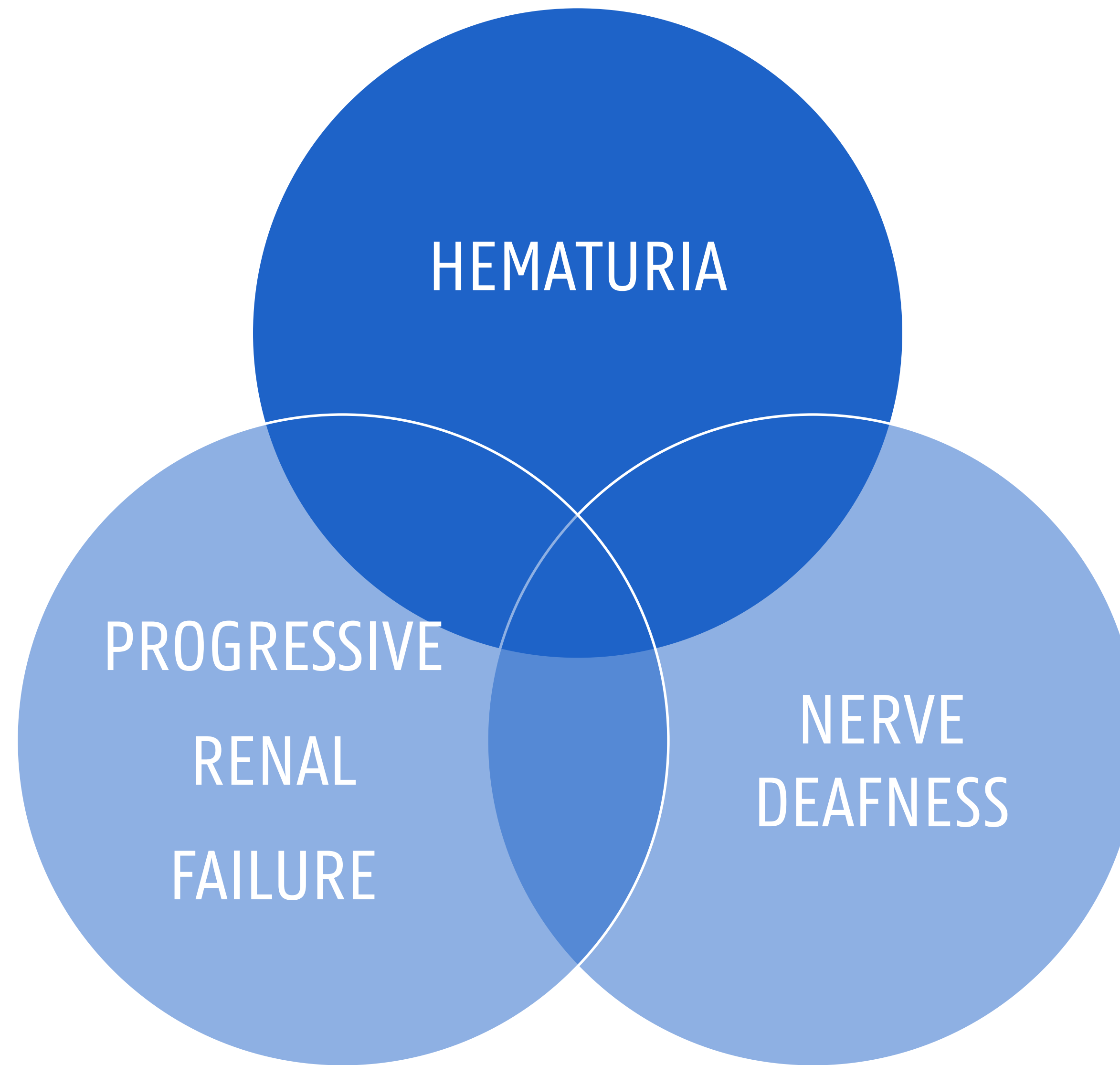
HEREDITARY FAMILIAL CONGENITAL HAEMORRHAGIC NEPHRITIS.

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- ▶ 1. Hereditary familial or congenital nephritis is a definite entity, and the kidneys in these patients are more susceptible to damage by the toxin of an unknown organism [...]
- ▶ 5. Deafness is a marked feature in nearly all these cases.[...]
- ▶ 6. The male members of a family tend to develop nephritis and deafness and do not as a rule survive. The females have deafness and haematuria and live to old age.[...]

'ALPORT'S SYNDROME' EST. 1961



'ALPORT'S SYNDROME' – AN X-LINKED RECESSIVE (?) DISORDER

RENAL

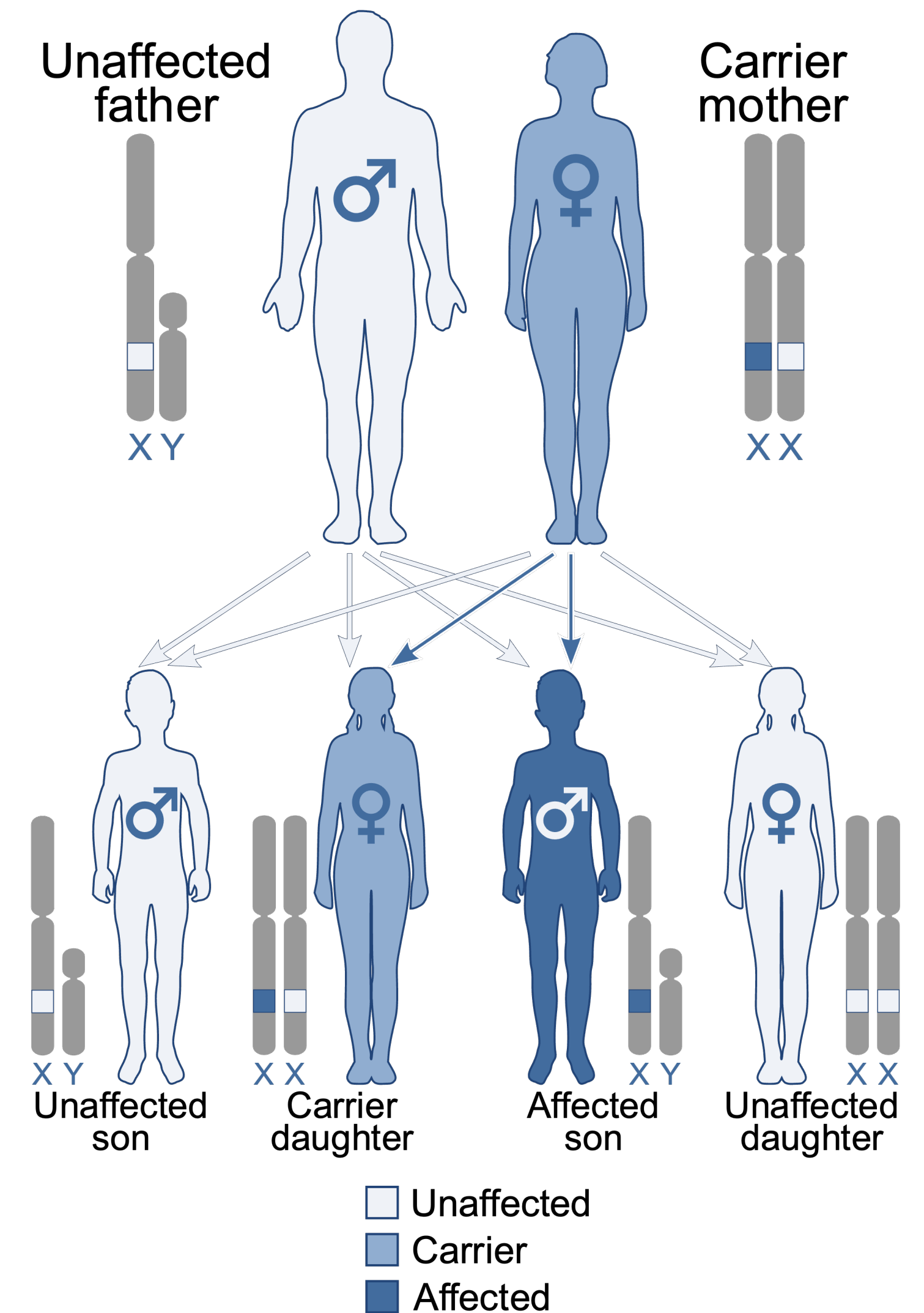
- ▶ micro- and macroscopic hematuria
- ▶ ESRD, mostly in adults, rarely in children

EXTRARENAL

- ▶ high frequency sensorineural hearing loss
- ▶ (anterior) lenticonus
- ▶ aortic valve insufficiency and BAV?
- ▶ aortic aneurysm/dissection?

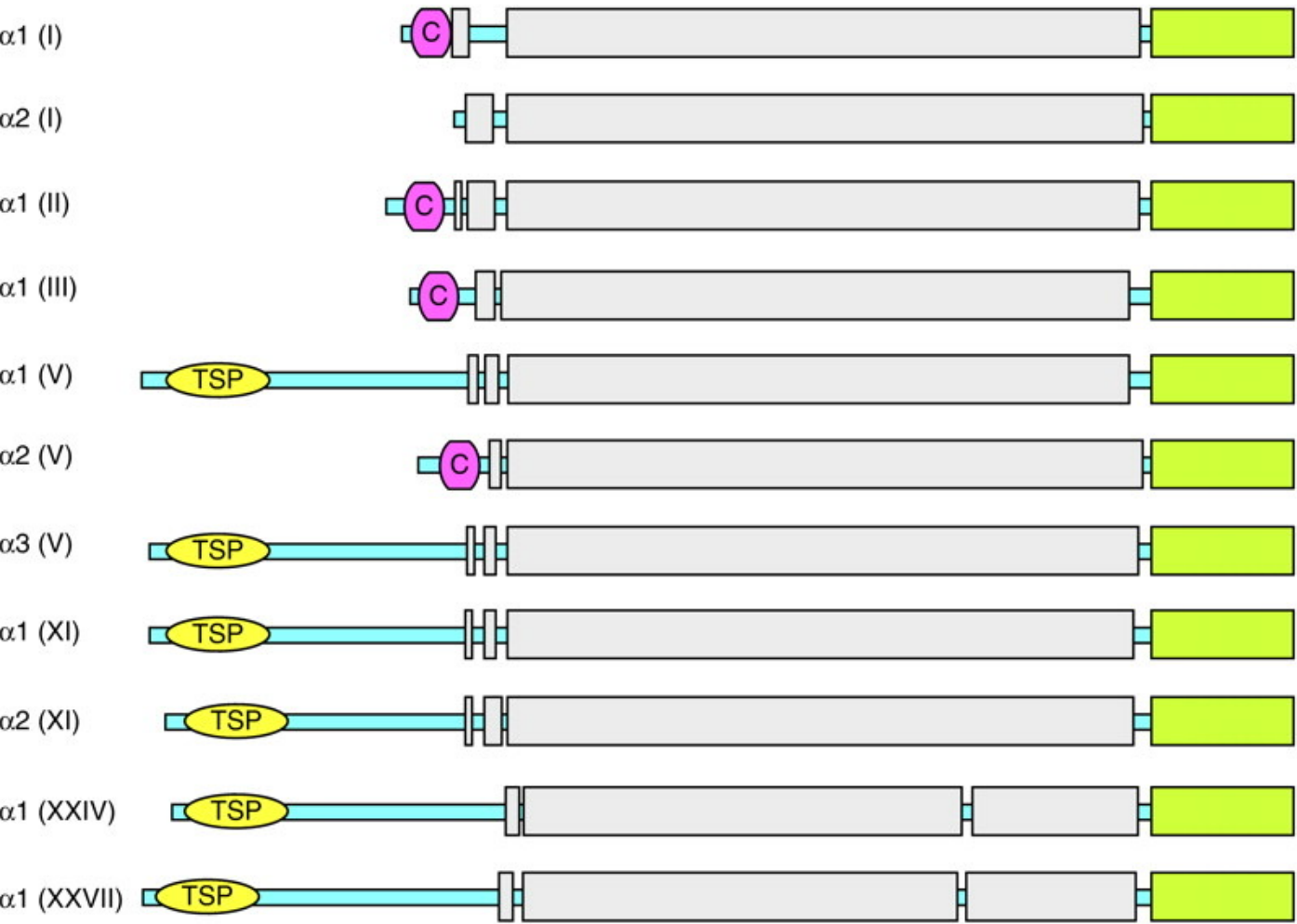
GENETICS

- ▶ *COL4A5* hemizygous pathogenic variants

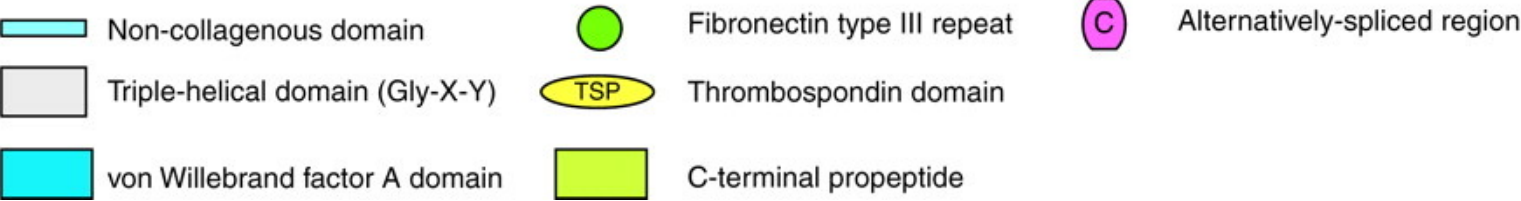
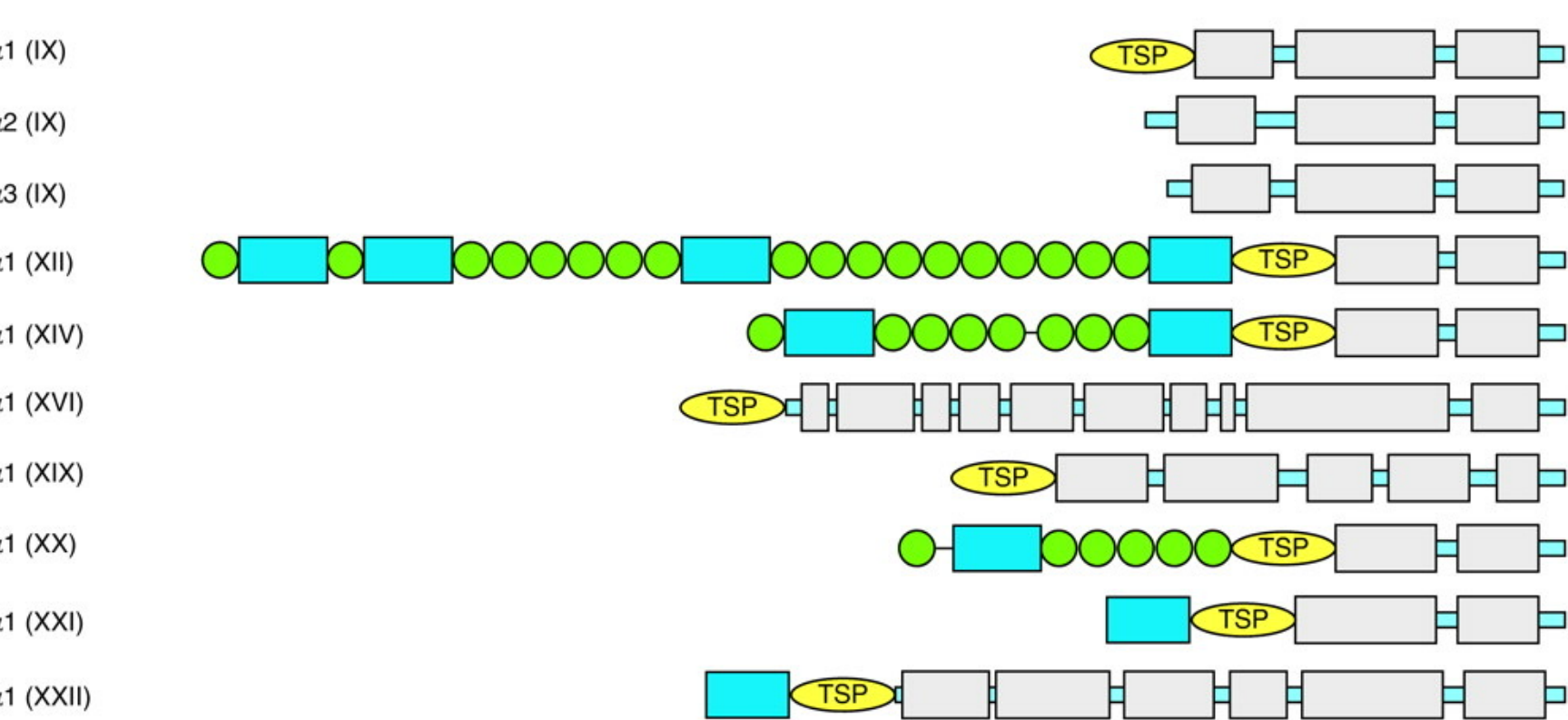


THE COLLAGEN SUPERFAMILY

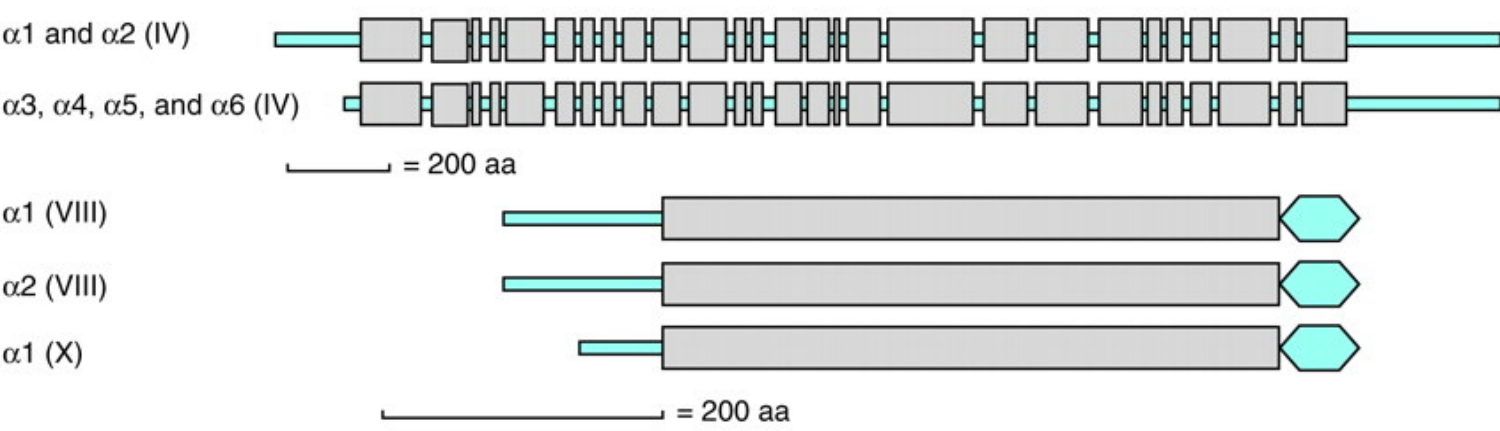
Fibril-forming collagens



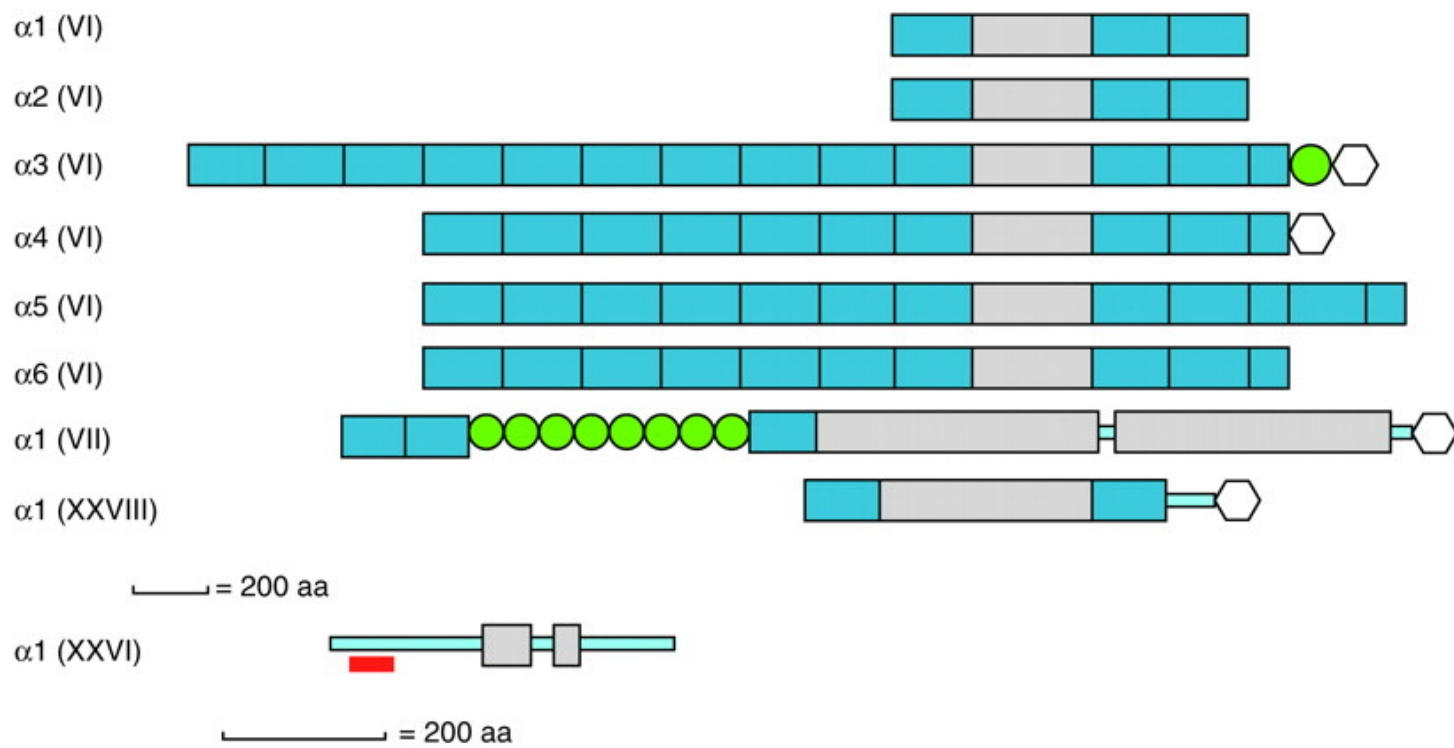
Fibril-associated collagens with interrupted triple helices



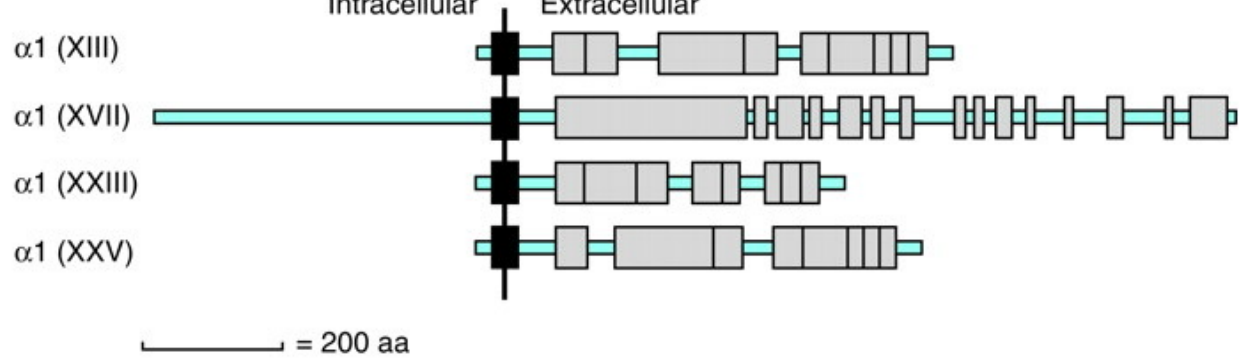
Network-forming collagens



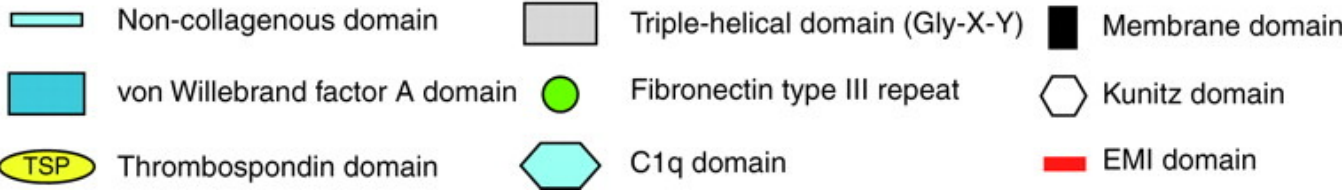
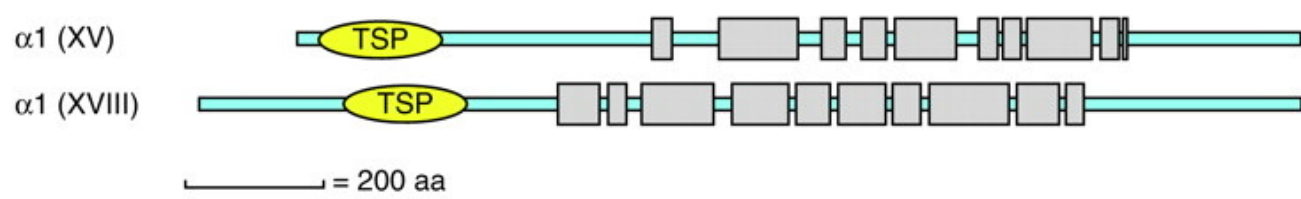
Collagens VI, VII, XXVI, and XXVIII



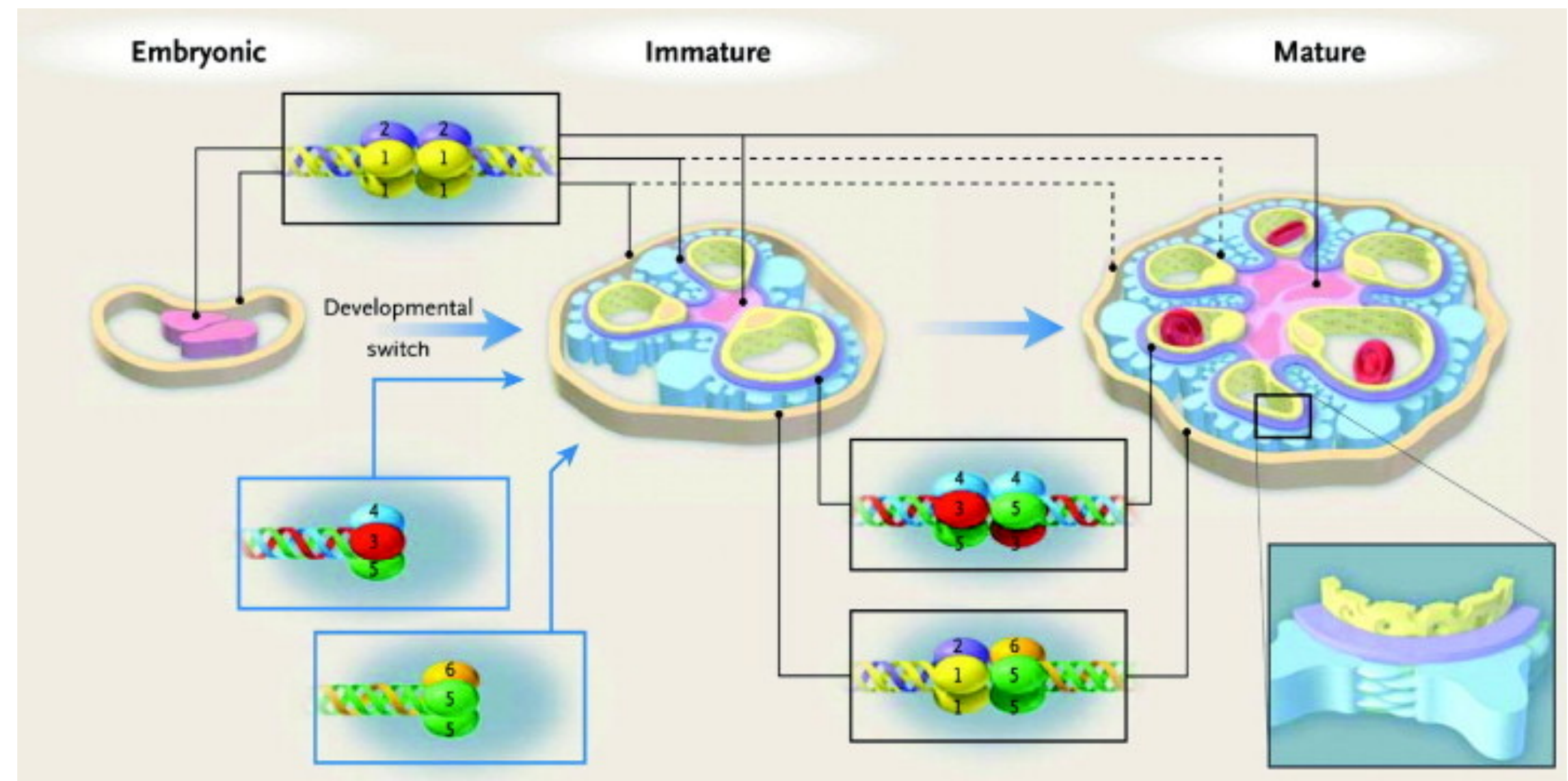
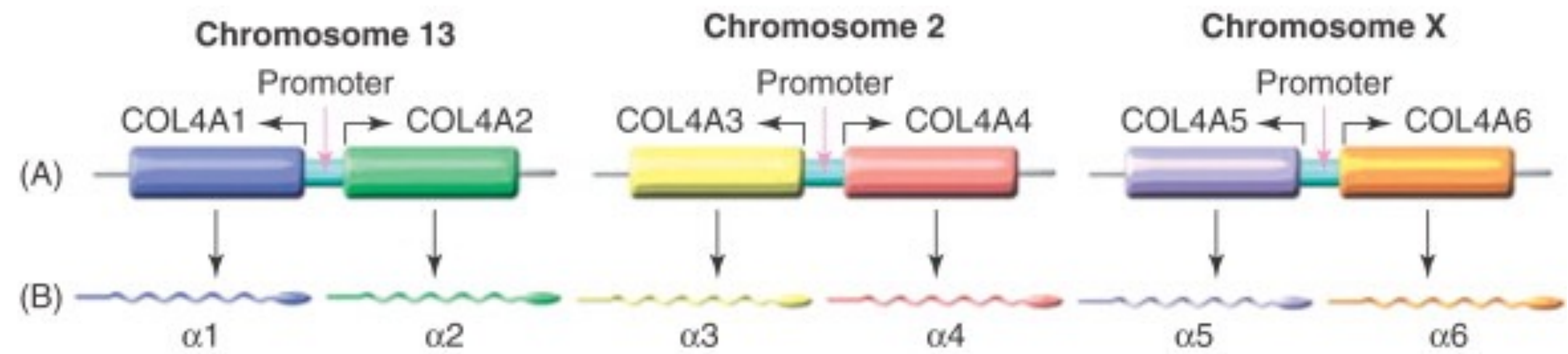
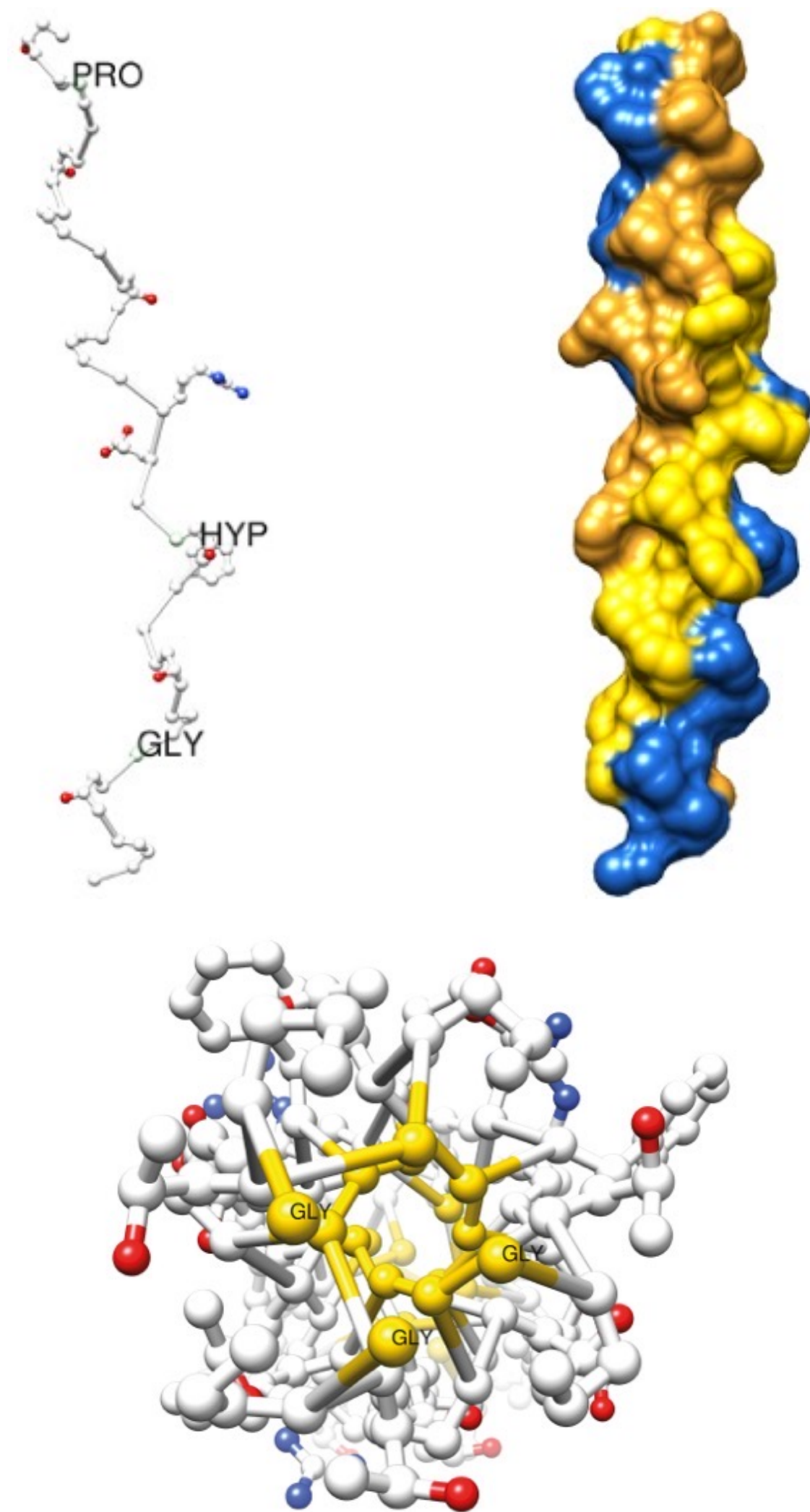
Membrane collagens



Multiplexins (collagens XV and XVIII)



TYPE IV COLLAGEN



'ALPORT'S SYNDROME' – AN AUTOSOMAL RECESSIVE / DIGENIC DISORDER

RENAL

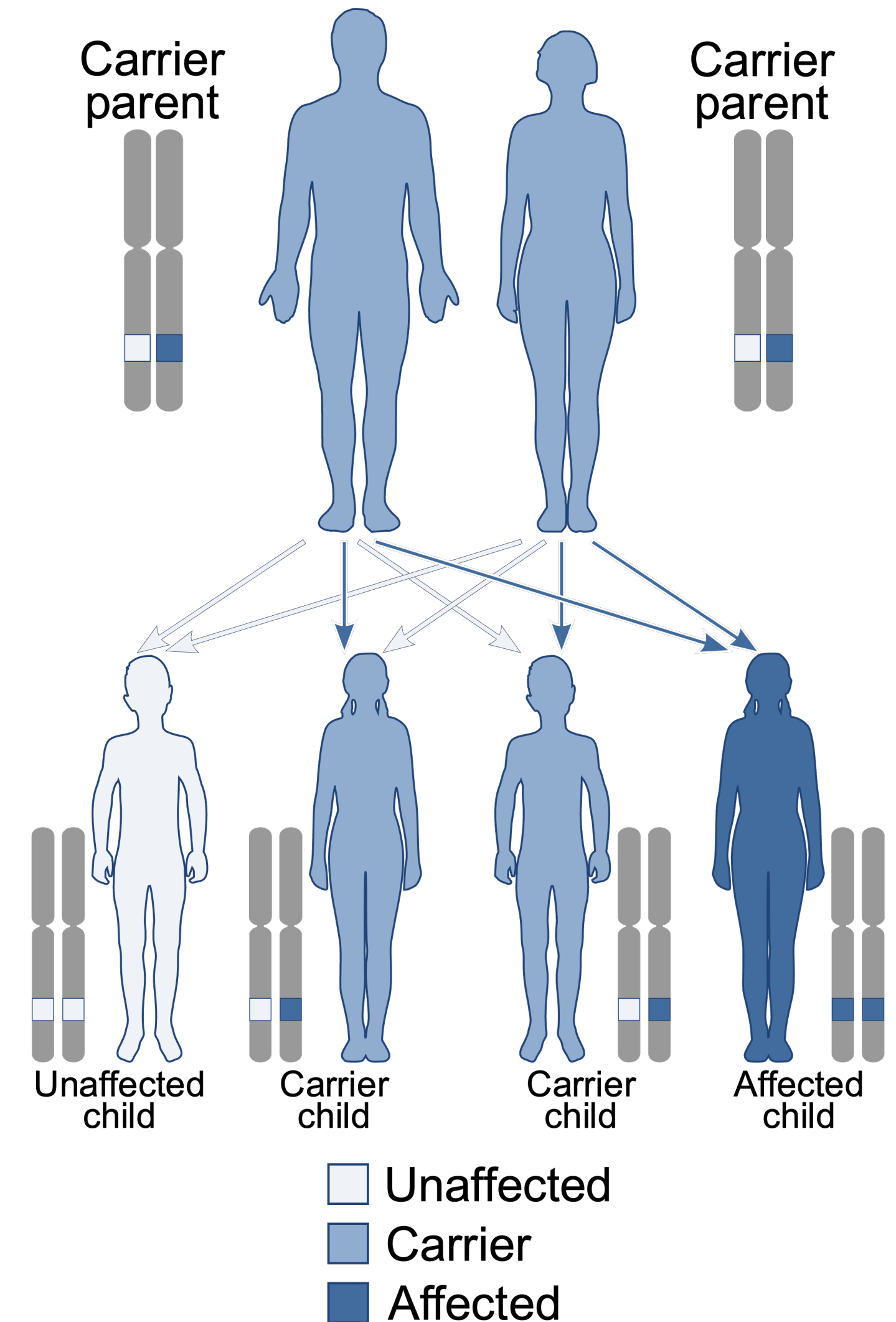
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- ▶ aortic aneurysm/dissection?

GENETICS

- ▶ *COL4A5* hemizygous pathogenic variants
- ▶ *COL4A3/4* bi-allelic or digenic pathogenic variants



X-LINKED RECESSIVE
AUTOSOMAL RECESSIVE
DIGENIC



**ALPORT SYNDROME &
RENAL FAILURE**

HETEROZYGOUS 'CARRIERS'

X-LINKED RECESSIVE
AUTOSOMAL RECESSIVE
DIGENIC



**ALPORT SYNDROME &
RENAL FAILURE**

HETEROZYGOUS 'CARRIERS'
(AUTOSOMAL DOMINANT)



**BENIGN FAMILIAL HEMATURIA
(THIN BASEMENT MEMBRANE DISEASE)**

X-LINKED RECESSIVE
AUTOSOMAL RECESSIVE
DIGENIC



**ALPORT SYNDROME &
RENAL FAILURE**

HETEROZYGOUS 'CARRIERS'
(AUTOSOMAL DOMINANT)



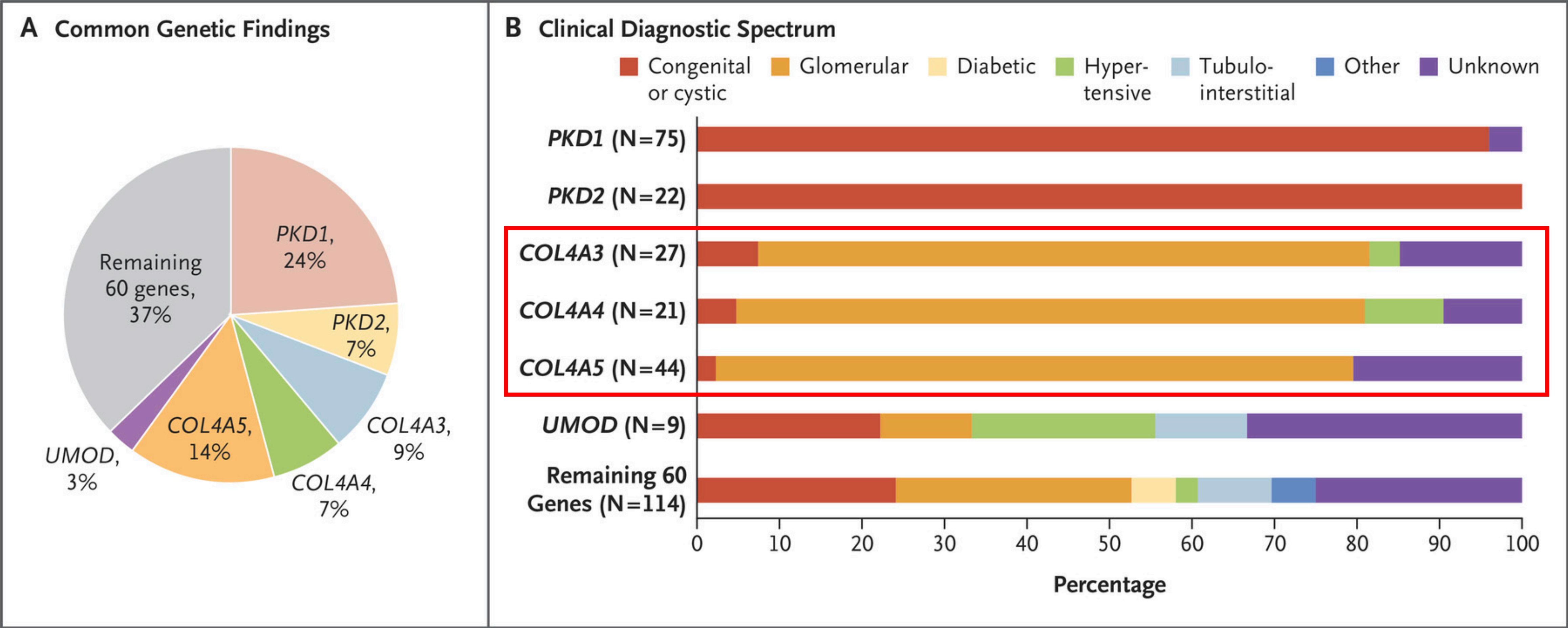
**BENIGN FAMILIAL HEMATURIA
(THIN BASEMENT MEMBRANE DISEASE)**

ORIGINAL ARTICLE

Diagnostic Utility of Exome Sequencing for Kidney Disease

E.E. Groopman, M. Marasa, S. Cameron-Christie, S. Petrovski, V.S. Aggarwal,
H. Milo-Rasouly, Y. Li, J. Zhang, J. Nestor, P. Krithivasan, W.Y. Lam, A. Mitrotti,
S. Piva, B.H. Kil, D. Chatterjee, R. Reingold, D. Bradbury, M. DiVecchia,
H. Snyder, X. Mu, K. Mehl, O. Balderes, D.A. Fasel, C. Weng, J. Radhakrishnan,
P. Canetta, G.B. Appel, A.S. Bomback, W. Ahn, N.S. Uy, S. Alam, D.J. Cohen,
R.J. Crew, G.K. Dube, M.K. Rao, S. Kamalakaran, B. Copeland, Z. Ren, J. Bridgers,
C.D. Malone, C.M. Mebane, N. Dagaonkar, B.C. Fellström, C. Haefliger,
S. Mohan, S. Sanna-Cherchi, K. Kiryluk, J. Fleckner, R. March, A. Platt,
D.B. Goldstein, and A.G. Gharavi

DIAGNOSTIC UTILITY OF EXOME SEQUENCING FOR KIDNEY DISEASE



PREVALENCE ESTIMATES OF PREDICTED PATHOGENIC *COL4A3-5* VARIANTS IN A POPULATION SEQUENCING DATABASE

COL4A5

▶ 1:2320

COL4A3/4

▶ 1:106

▶ ~ estimated prevalence of persistent hematuria and thin basement membrane nephropathy in normal donor kidney biopsy specimens

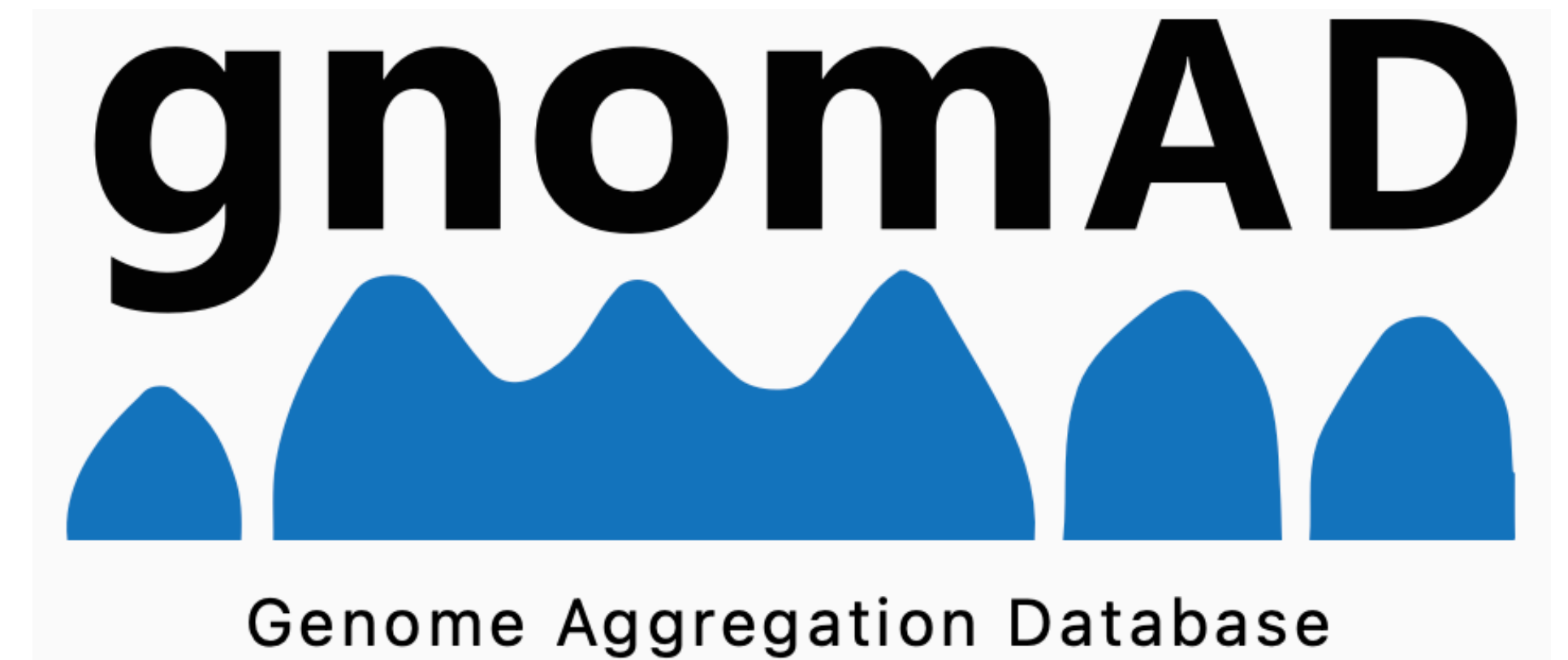


AR ALPORT SYNDROME

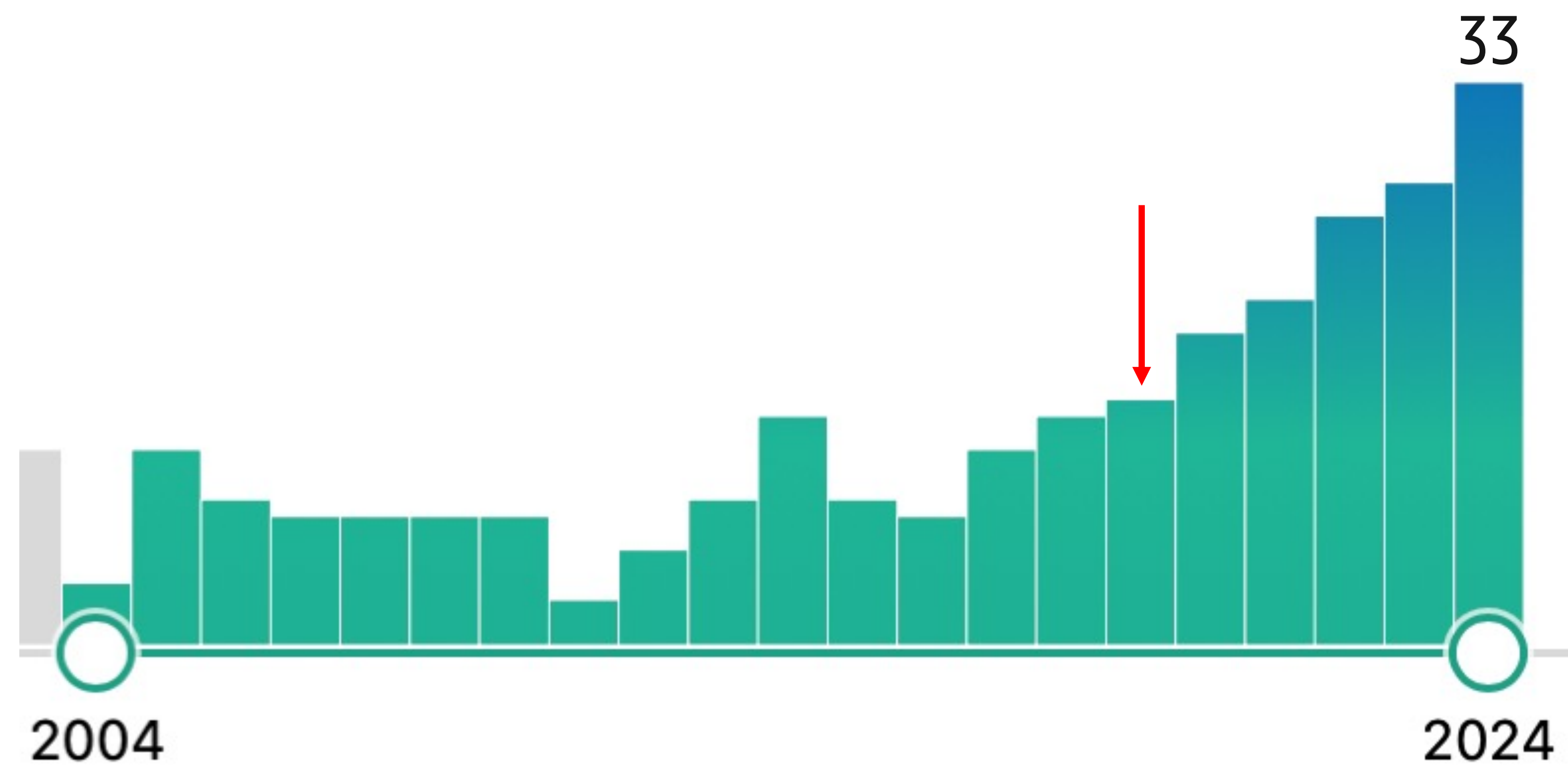
▶ 1:88,866

DIGENIC ALPORT SYNDROME

▶ 1:44,793



DIAGNOSTIC UTILITY OF EXOME SEQUENCING FOR KIDNEY DISEASE



Groopman EE, Marasa M, Cameron-Christie S, et al. New Engl J Med 2019;380(2):142–51.

HETEROZYGOUS PATHOGENIC *COL4A3-5* VARIANTS AND FSGS

> [Nephrol Dial Transplant](#). 2009 Sep;24(9):2721-9. doi: 10.1093/ndt/gfp158. Epub 2009 Apr 8.

Clinico-pathological correlations in 127 patients in 11 large pedigrees, segregating one of three heterozygous mutations in the COL4A3/ COL4A4 genes associated with familial haematuria and significant late progression to proteinuria and chronic kidney disease from focal segmental glomerulosclerosis

Alkis Pierides ¹, Konstantinos Voskarides, Yiannis Athanasiou, Kyriacos Ioannou, Loukas Damianou, Maria Arsali, Michalis Zavros, Michael Pierides, Vasilios Vargemezis, Charalambos Patsias, Ioanna Zouvani, Avraam Elia, Kyriacos Kyriacou, Constantinos Deltas

Affiliations + expand

PMID: 19357112 DOI: [10.1093/ndt/gfp158](https://doi.org/10.1093/ndt/gfp158)

Abstract

Background: Heterozygous mutations in the COL4A3/ COL4A4 genes are currently thought to be responsible for familial benign microscopic haematuria and maintenance of normal long-term kidney function.

SELECTED WORKS FROM 2024...

Kidney Cysts in Children With **Alport** Syndrome: A Report of 3 Cases.

Chang YW, Hwang DY, Chen TY, Lin CC, Tseng MH, Tsai JD.

Kidney Med. 2024 Mar 25;6(5):100815. doi: 10.1016/j.xkme.2024.100815. eCollection 2024 May.

PMID: 38680391 **Free PMC article.**

Alport syndrome (AS) is a progressive hereditary kidney disease characterized by hematuria, proteinuria, and progressive kidney dysfunction accompanied by sensorineural hearing loss and ocular abnormalities. ...The patient in case 1 was initially diagnosed with **IgA** ...

Analyzing three pedigrees in X-linked **Alport** syndrome with the presentation of nephrotic syndrome.

Zhang JH, Liu J, Ruan DD, Chen Q, Yang J, Wu M, Yu HP, Liao LS, Zheng XL, Luo JW, Zhang L.

Front Genet. 2024 Aug 9;15:1419154. doi: 10.3389/fgene.2024.1419154. eCollection 2024.

PMID: 39184349 **Free PMC article.**

BACKGROUND: **Alport** syndrome (AS) is a common cause of end-stage renal disease (ESRD) with various clinical symptoms and incomplete manifestation. Patients with AS and other renal disorders are often misdiagnosed. This study reported three X-linked **dominant Alport** ...

First patient diagnosed with lipoprotein glomerulopathy and **Alport** syndrome.

Yang L, Yang G, Guo H.

Nephrology (Carlton). 2024 Sep 27. doi: 10.1111/nep.14399. Online ahead of print.

PMID: 39328028

Alport syndrome (AS) is one of the most common inherited kidney disorders, involving pathogenic variants of COL4A3, COL4A4 and COL4A5 genes that lead to disruption of the normal structure of collagen IV protein through improper chain or heterotrimer folding or degradation ...

A Novel COL4A5 Pathogenic Variant Joins the Dots in a Family with a Synchronous Diagnosis of Alport Syndrome and Polycystic Kidney Disease.

Graziani L, Minotti C, Carriero ML, Bengala M, Lai S, Terracciano A, Novelli A, Novelli G.

Genes (Basel). 2024 May 8;15(5):597. doi: 10.3390/genes15050597.

PMID: 38790225 **Free PMC article.**

Polycystic kidney disease (PKD), which is most frequently associated with Autosomal Dominant PKD (ADPKD) due to PKD1 and PKD2 **heterozygous** variants, is emerging as a possible clinical manifestation in COL4A3-A5 patients. ...(Leu366ValfsTer45)), which was associated with AS ...

Genetic Characterization of Kidney Failure of Unknown Etiology in Spain: Findings From the GENSEN Study.

Blasco M, Quiroga B, García-Aznar JM, Castro-Alonso C, Fernández-Granados SJ, Luna E, Fernández Fresnedo G, Ossorio M, Izquierdo MJ, Sanchez-Ospina D, Castañeda-Infante L, Mouzo R, Cao M, Besada-Cerecedo ML, Pan-Lizcano R, Torra R, Ortiz A, de Sequera P; GENSEN Study Investigators.

Am J Kidney Dis. 2024 Jul 6:S0272-6386(24)00844-8. doi: 10.1053/j.ajkd.2024.04.021. Online ahead of print.

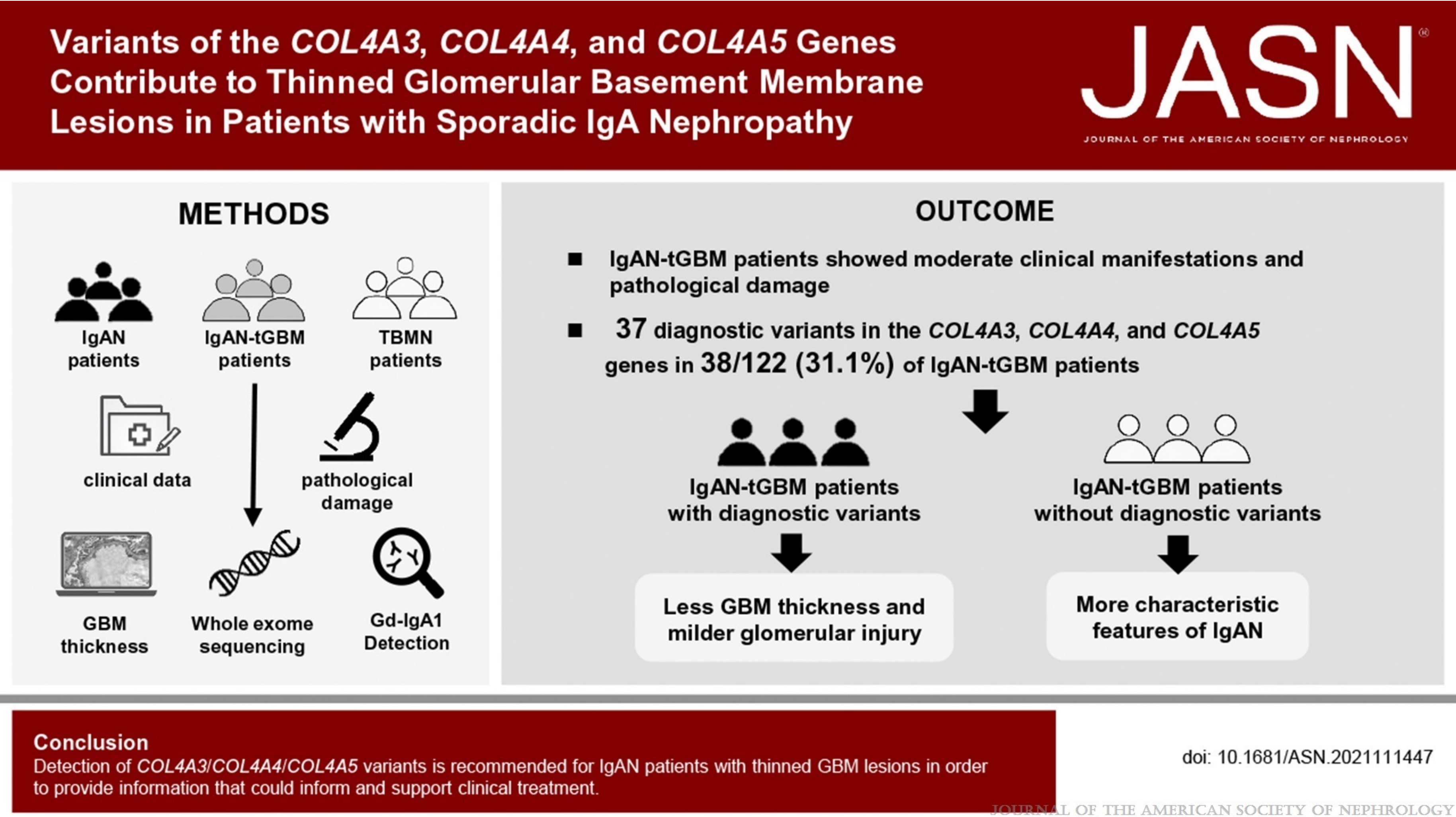
PMID: 38972501

The top 5 most common previously undiagnosed diseases were **Alport** syndrome spectrum (35% of total positive reports), genetic podocytopathies (19%), nephronophthisis (11%), autosomal **dominant** tubulointerstitial kidney disease (7%), and congenital anomalies of the kid ...

(NON)CAUSAL ASSOCIATION?

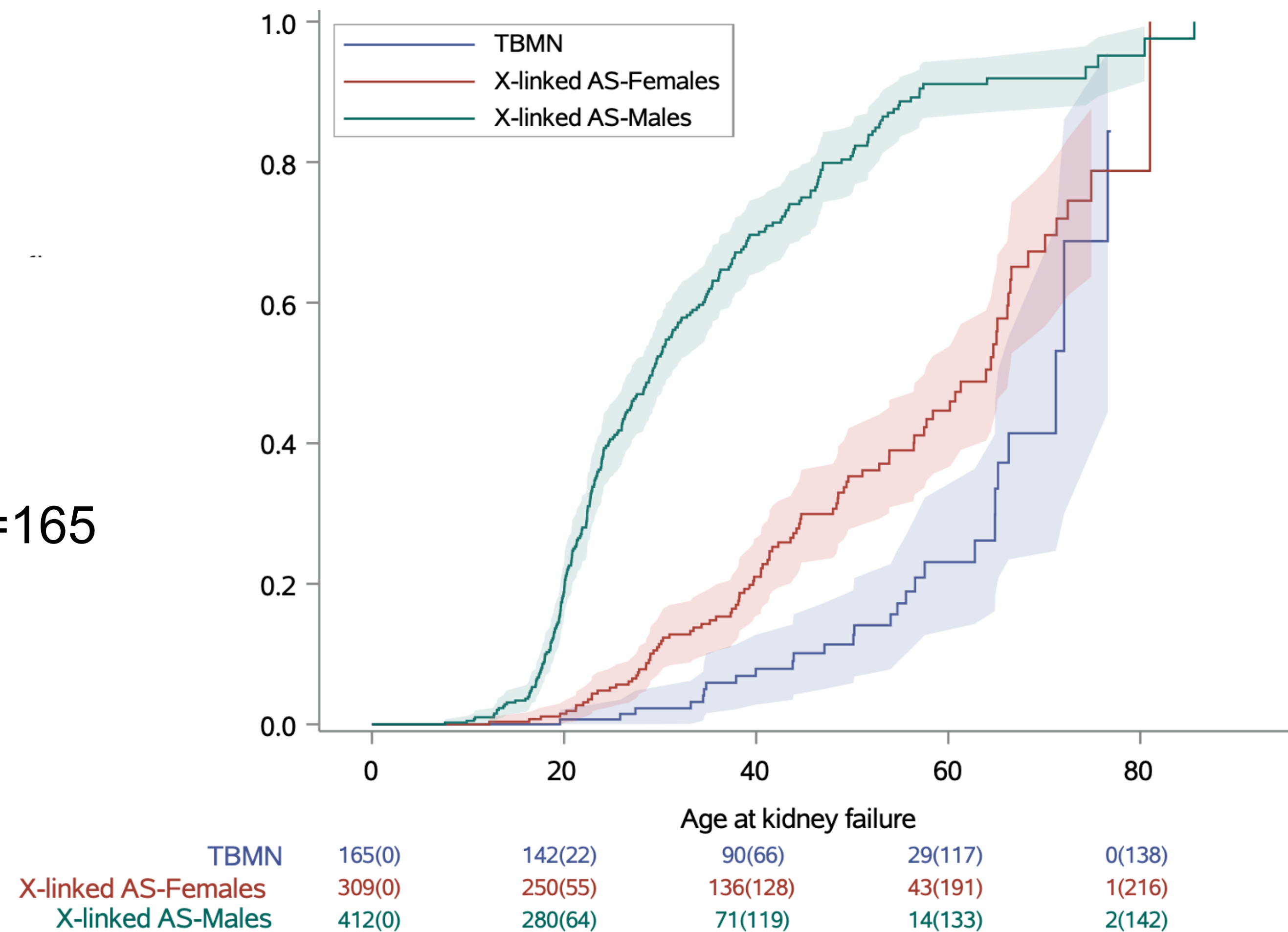


HETEROZYGOUS PATHOGENIC *COL4A3-5* VARIANTS AND IGA NEPHROPATHY

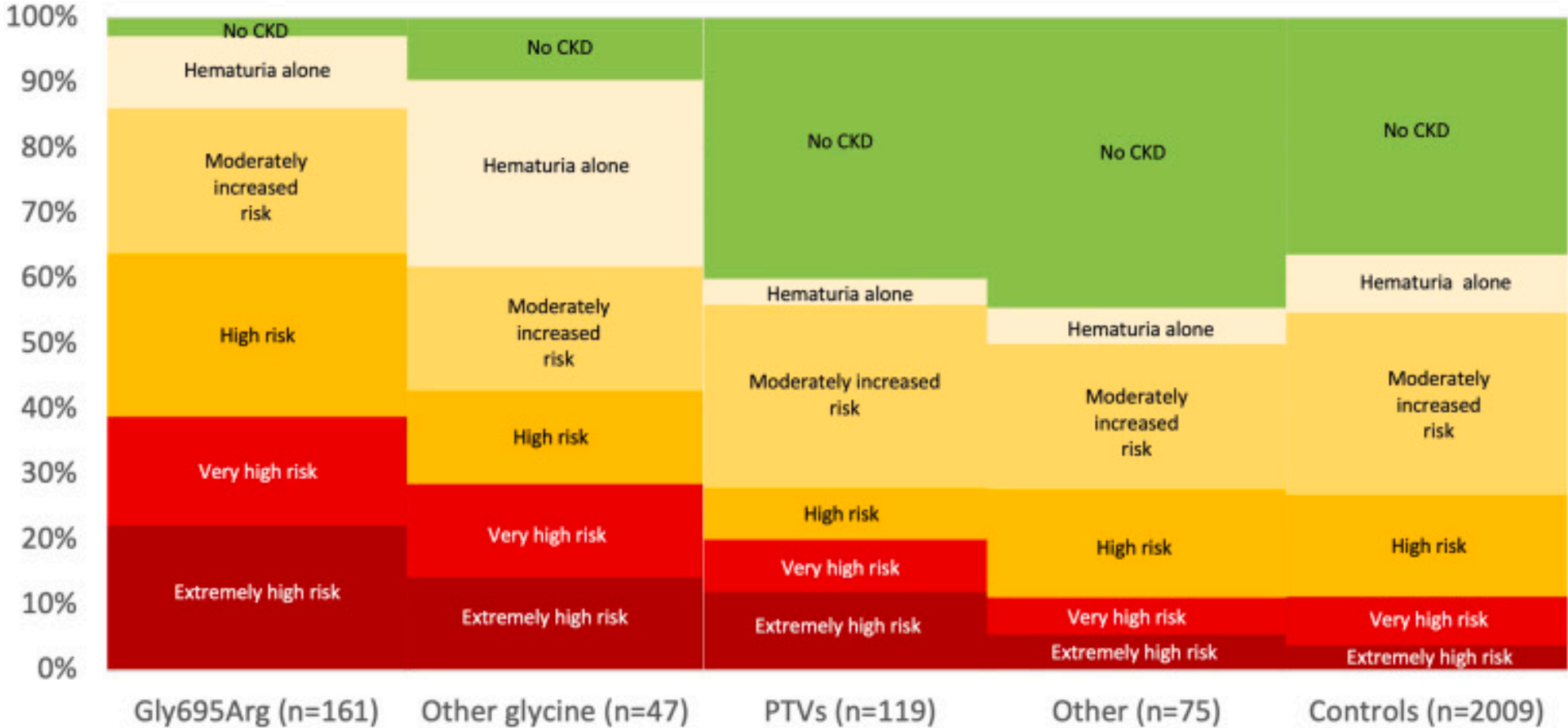
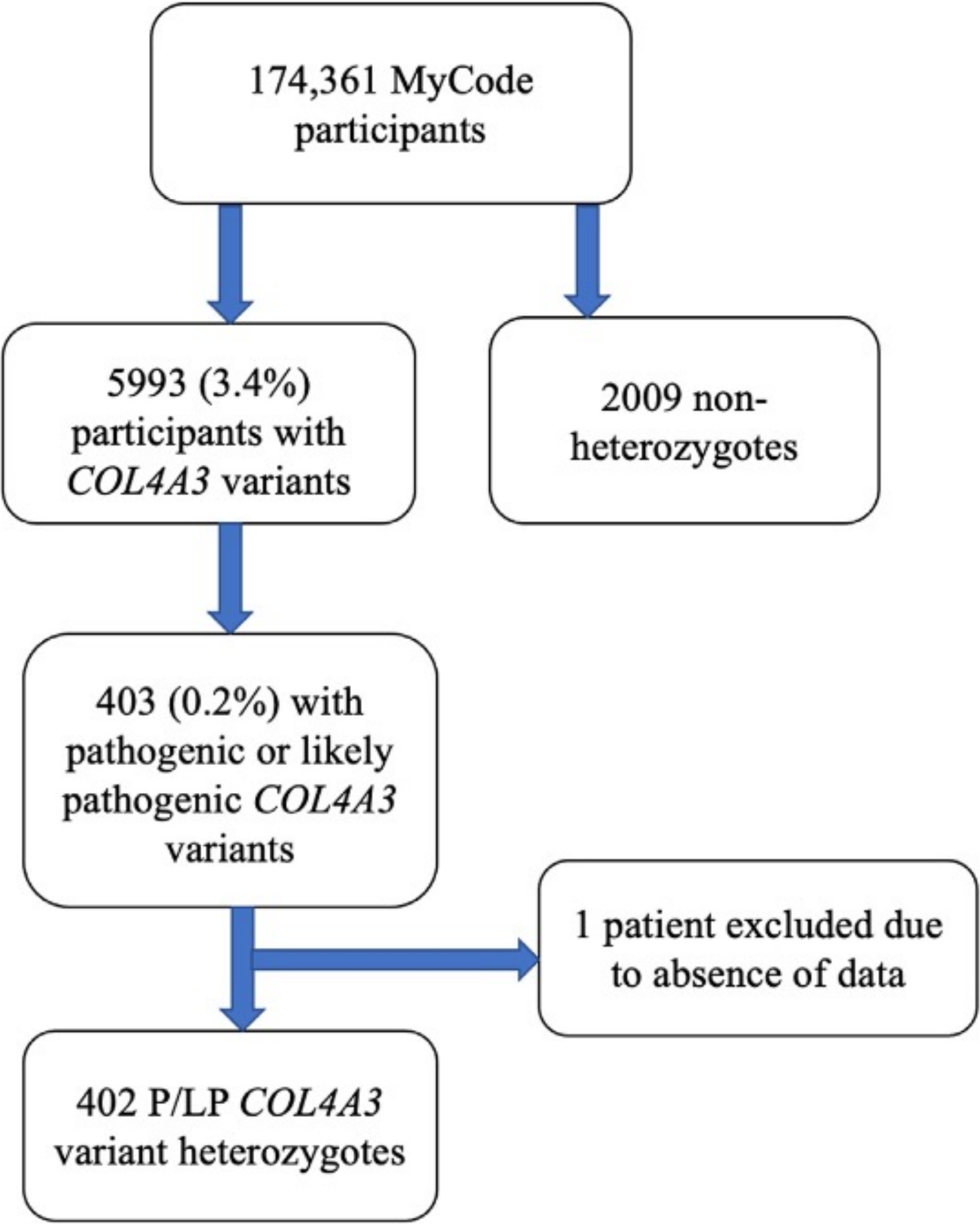


EFFECTS OF RARE KIDNEY DISEASES ON KIDNEY FAILURE: A LONGITUDINAL ANALYSIS OF THE UK NATIONAL REGISTRY OF RARE KIDNEY DISEASES COHORT

- ▶ XLAS males n=412
- ▶ XLAS females n=309
- ▶ TBMN (COL4A3-4 heterozygotes?) n=165



THE PHENOTYPIC SPECTRUM OF COL4A3 HETEROZYGOTES



- p.Gly695Arg
- ▶ hematuria OR 9.5 (95% CI: 6.32, 14.28)
 - ▶ kidney failure OR 7.02 (95% CI: 3.48, 14.16)
- PTV
- ▶ hematuria OR 1.64 (95% CI: 1.03, 2.59)
 - ▶ kidney failure OR 7.02 (95% CI: 1.28, 9.2)

				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GUIDELINES FOR GENETIC TESTING AND MANAGEMENT OF ALPORT SYNDROME

MANAGEMENT

- ▶ Individuals with a heterozygous pathogenic *COL4A3* or *COL4A4* variant should be treated with RAAS blockade from the onset of microalbuminuria, hypertension, or kidney impairment.
- ▶ These recommendations are the same for children and for adults.

KIDNEY TRANSPLANTATION AND DONATION

- ▶ Potential donors suspected of having *COL4A3*-*COL4A5* variants should undergo genetic testing prior to kidney transplantation to confirm the diagnosis and determine the mode of inheritance and any variant characteristics associated with a poor prognosis.
- ▶ Women who have a *COL4A5* variant should not act as kidney donors because of their own risk of kidney impairment and of further deterioration after donation.
- ▶ Individuals with a heterozygous *COL4A3* or *COL4A4* variant should also not act as kidney donors because of their own risk of kidney impairment and of a further deterioration after donation.

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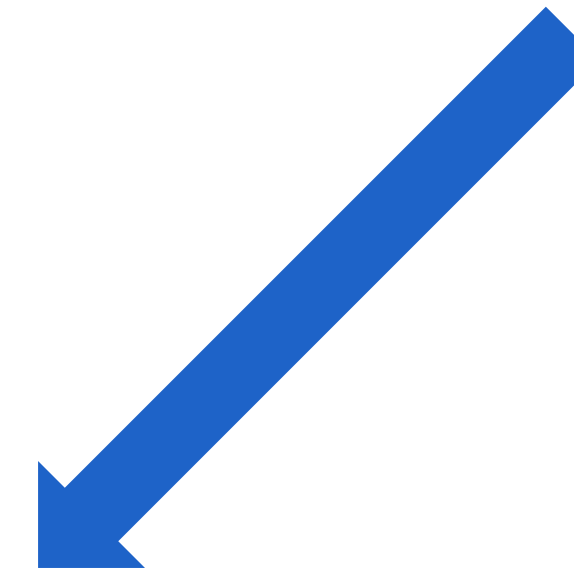
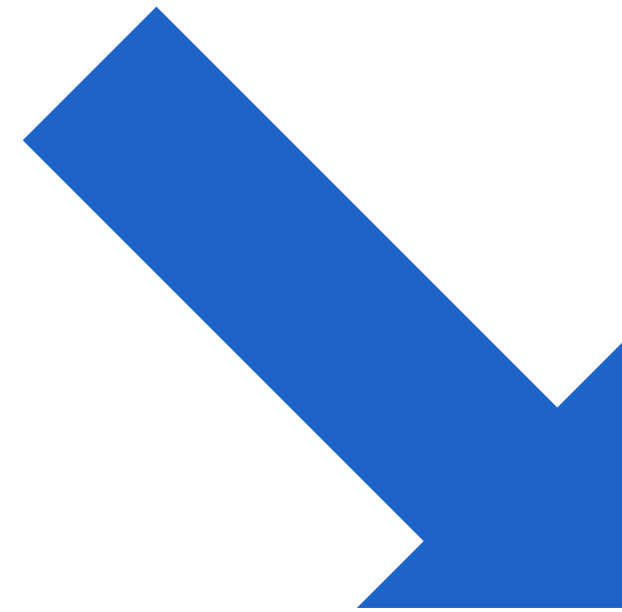
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MEDICAL UNIT, ST. MARY'S HOSPITAL, PADDINGTON.

Alport syndrome is a definite entity with variable severity, and the kidneys in these patients are more susceptible to damage due to one or more pathogenic variants in *COL4A3-5*.

X-LINKED RECESSIVE
AUTOSOMAL RECESSIVE
DIGENIC

AUTOSOMAL DOMINANT
X-LINKED DOMINANT



**ALPORT SYNDROME &
RENAL FAILURE**

~~**BENIGN FAMILIAL HEMATURIA**~~

X-LINKED RECESSIVE
AUTOSOMAL RECESSIVE
DIGENIC

AUTOSOMAL DOMINANT
X-LINKED DOMINANT



MONOGENIC



MULTIFACTORIAL

**ALPORT SYNDROME &
RENAL FAILURE**

~~BENIGN FAMILIAL HEMATURIA~~

X-LINKED RECESSIVE
AUTOSOMAL RECESSIVE
DIGENIC

AUTOSOMAL DOMINANT
X-LINKED DOMINANT



COUNSELING

MONOGENIC

MULTIFACTORIAL

**ALPORT SYNDROME &
RENAL FAILURE**

~~BENIGN FAMILIAL HEMATURIA~~

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