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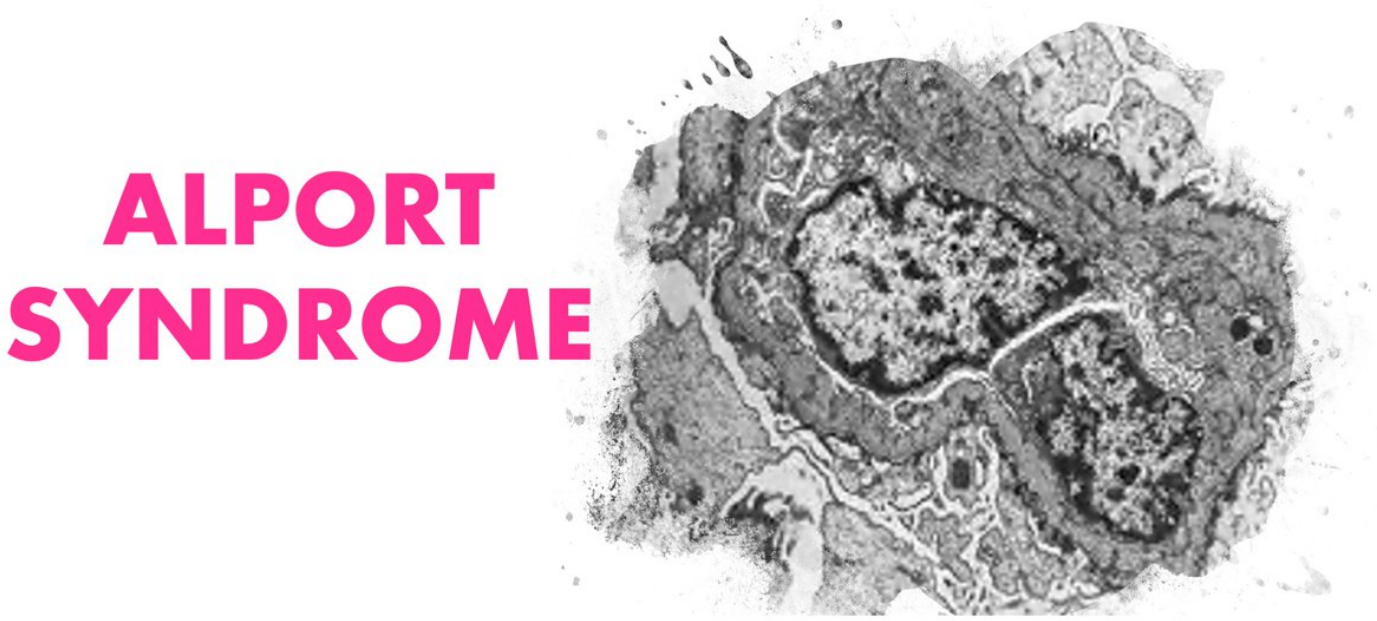
24 Tweets • 2021-03-30 15:04:09 UTC • See on Twitter

rattibha.com ♥

📢Hello, #MedTwitter

⚡This month's @ASPNeph Renal Pathology Webinar was all about 🌟#Hereditary nephritis
Here are some important "facts" I learned!

#Medtweetorial #nephtwitter
#AlportSyndrome



Let’s start with an interesting fact

Who was the first doctor🕵️ to identify ALPORT SYNDROME (AS)❓

💥Ans: Dr. Cecil A. Alport first identified the condition. In 1927, he published a study of his findings and noted that family members👨‍👨‍👧‍👧 were more susceptible to kidney damage.
📍

https://www.alportsyndrome.org/cecil-alport-naming-the-syndrome/

🌟As per USRDS [approx 0.2 % of all adults and 3 % of all children with ESRD have AS.

🧬Gene frequency is estimated to be 1:5000 to 10,000.

📌

https://www.sciencedirect.com/science/article/

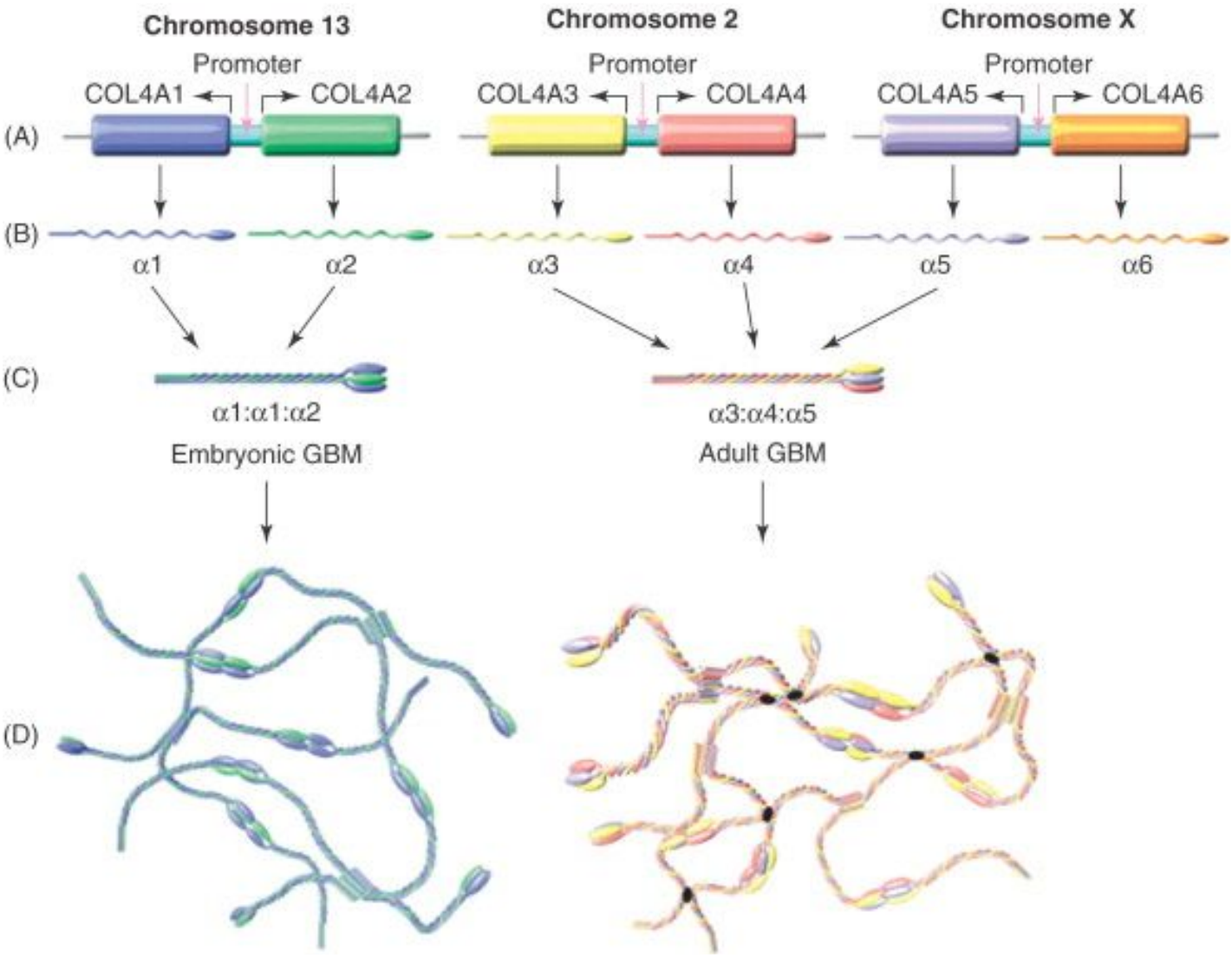
Abnormalities in which collagen🧬 is a/w pathogenesis of AS❓

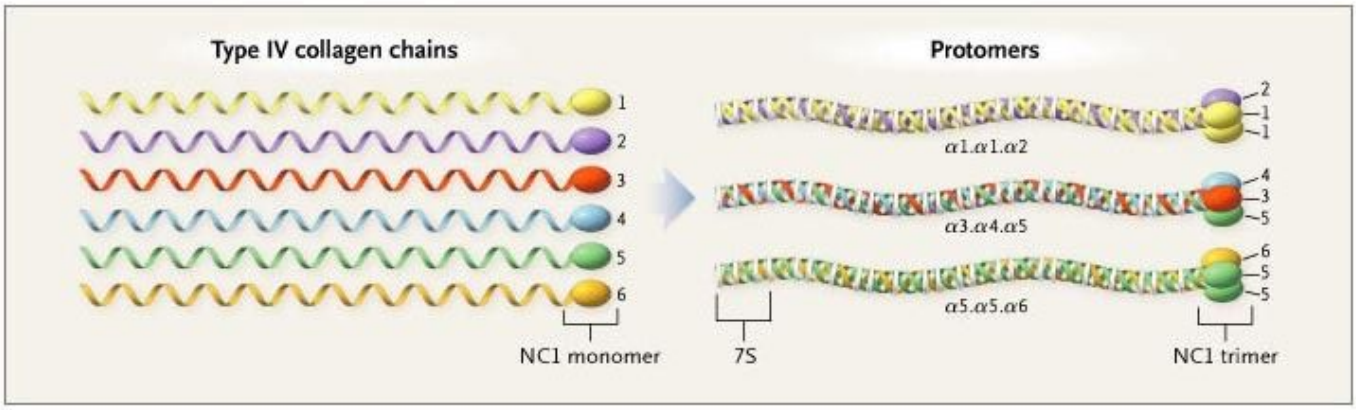
Yes! It is✨ Collagen IV.
Type IV collagen has 6 α chains
α1 to α6, to form triple helix structures

💥In the GBM, cochlea BM, and base of the ocular lens : triplet α3–α4–α5
💥Bowman's capsule and skin BM: α5–α5–α6

📍

https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/type-iv-collagen





Which one is the most common genetic type of Alport Syndrome ?

❄️M/C genetic🧬 types of AS are

💫80% XLAS
💫15% ARAS
💫5% ADAS

📌

https://www.kidneymedicinejournal.org/article/S2590-0595(20)30160-6/fulltext

Table 1. New Classification Scheme Categorizes Genetic Diseases of *COL4A3*, *COL4A4*, and *COL4A5* Into 3 Types of Alport Syndrome: X-linked, Autosomal, and Digenic

Inheritance	Affected Gene(s)	Allelic State	Mutation Phenotype
X-linked	*COL4A5*	Hemizygous (males)	NA
		Heterozygous (females)	NA
Autosomal	*COL4A3* or *COL4A4*	Homozygous or compound heterozygous	Recessive
		Heterozygous	Dominant
Digenic	*COL4A3*, *COL4A4*, and *COL4A5*	Variable	

Abbreviation: NA, not applicable.
Data from Kashtan et al.[1]

💥Ever wondered what is different in women affected with AS❓

💫Females are mostly undiagnosed
💫15%–30% develop ESRD by 60 yrs
💫Hearing loss by middle age.
💫½ of their sons and daughters are affected

📌
📍

https://pdfs.semanticscholar.org/

Features	X-Linked Alport Syndrome in Females	Autosomal Recessive Alport Syndrome in Females
Frequency	1 in 5000; M/F = 1:2	1 in 40,000, M/F = 1:1
Family history	Women are affected twice as often as men but usually have less severe disease	Men and women are affected equally often, and equally severely
Inheritance pattern	Disease occurs in several generations of the same family, appears to skip a generation where a woman is undiagnosed	Single generation only
Gene mutations	Heterozygous mutation in *COL4A5*	Two mutations in *COL4A3* or *COL4A4 in trans*
Hematuria	At least 95%	Probably all
Proteinuria	Common from early adulthood	Common from adolescence
Renal impairment	Prevalence and age not known	Probably all
ESRD	15%–30% by the age of 60 yr	Probably the majority by middle age
Hearing loss	Common from middle age	Common earlier than middle age
Corneal opacities	Often undetected, occurs even with normal renal function	Not known
Lenticonus	Very uncommon	Common
Central fleck retinopathy	30%	85%
Retinal thinning (on OCT)	50% of hospital-based females	Not known, but probably more common than in women with X-linked disease
Macular hole	Uncommon but occurs	Uncommon, maybe 5%
Peripheral retinopathy	50%	Nearly all
Leiomyomatosis	Not common but all women with *COL4A5-COL4A6* deletions	Not reported

Please refer to manuscript for references. M/F, Male/Female; OCT, optical coherence tomography.

💥Diagnosis🧐: Symptomatic children with AS are usually diagnosed within their 1st decade of life, at which time they are typically oligosymptomatic, with mild haematuria and low-grade proteinuria

✨ Pathogenesis:

💫Assembly of the α3α4α5 heterotrimer does not occur, resulting in ⏬ mechanical stability.
Mutant collagen IV leads to splitting of the GBM, podocyte effacement, glomerulosclerosis with ECM deposition, kidney fibrosis ⏩ ESRD

📌

https://pubmed.ncbi.nlm.nih.gov/23165304/

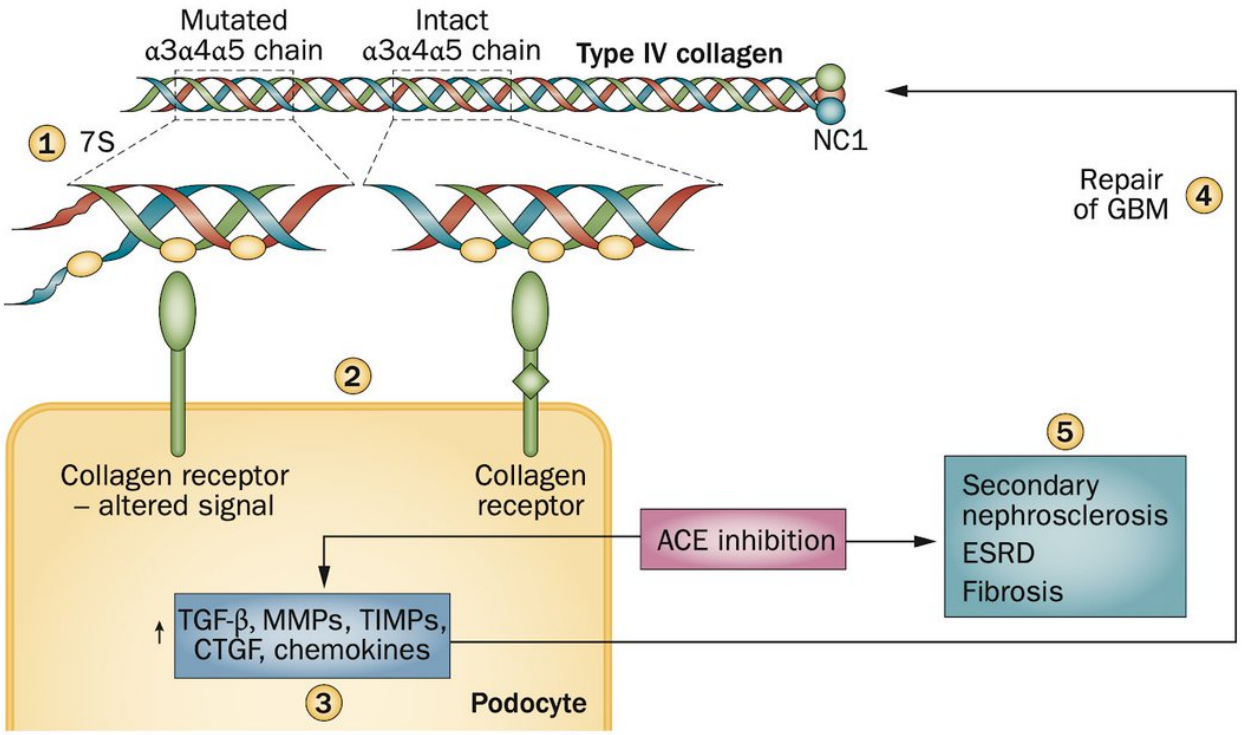


Figure 1 | Potential mechanisms underlying chronic renal disease occurring in Alport syndrome. (1) Mutations in the α3α4α5 chains of type IV collagen in the GBM cause

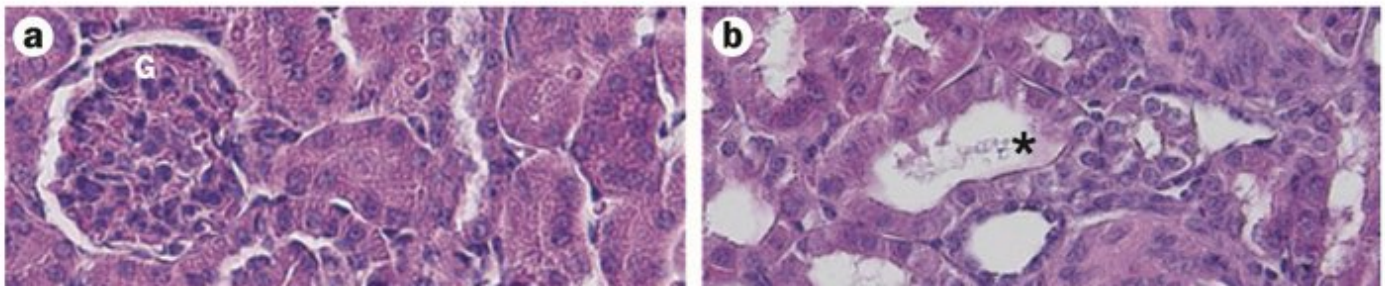
🔎HISTOLOGY: Usually nonspecific (can be glomerular hypercellularity, FSGS, tubular atrophy, foam cell formation, or interstitial fibrosis)

💥

https://pubmed.ncbi.nlm.nih.gov/23165304/

Box 1 | Stages in the development of Alport syndrome

- Stage 0: microscopic haematuria (<30 mg albumin per g creatinine or per day)
- Stage 1: microalbuminuria (30–300 mg albumin per g creatinine or per day)
- Stage 2: gross proteinuria (>300 mg albumin per g creatinine or per day)
- Stage 3: impaired renal function (GFR <60 ml/min/1.73 m^2)
- Stage 4: end-stage renal disease



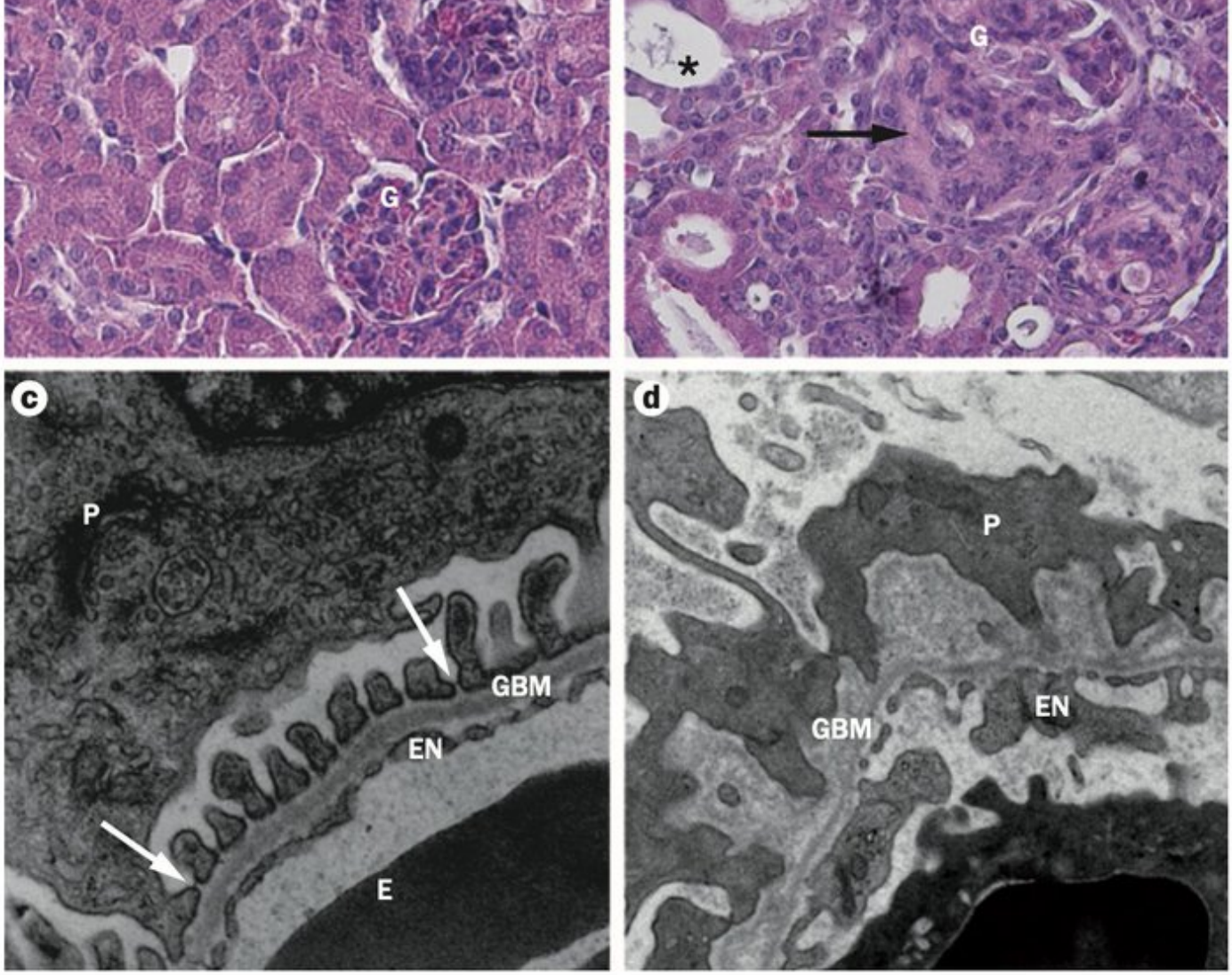


Figure 2 | Kidney pathology in Alport syndrome. **a** | Light microscopy images of kidneys from 9-week-old normal mice. **b** | Light microscopy images of kidneys from 9-week-old *COL4A3*$^{-/-}$ mice. The *COL4A3*$^{-/-}$ mice have focal segmental glomerulosclerosis (black arrow) as well as enlarged and partially destroyed tubuli (asterisks). **c** | Electron microscopy images of glomeruli from 9-week-old normal mice show a normal GBM, podocytes with foot processes, and slit diaphragms (white arrows) as well as fenestrated endothelium. **d** | Electron microscopy images of glomeruli from 9-week-old Alport mice show typical diagnostic findings of wave-like thickening and splitting of the GBM, and podocyte effacement typical of Alport syndrome. Abbreviations: E, erythrocyte; EN, endothelium; G, glomerulus; GBM, glomerular basement membrane; P, podocyte.

🔍 EM

⚡ Diffuse thinning of GBM

⚡So-called “basket-weave pattern” irregular thin/thickened areas with splintered and irregular multi-laminated lamina densa,with short stubs of fibrils right angles to GBM

Irregular lucent areas interspersed with thickened areas of lamina densa

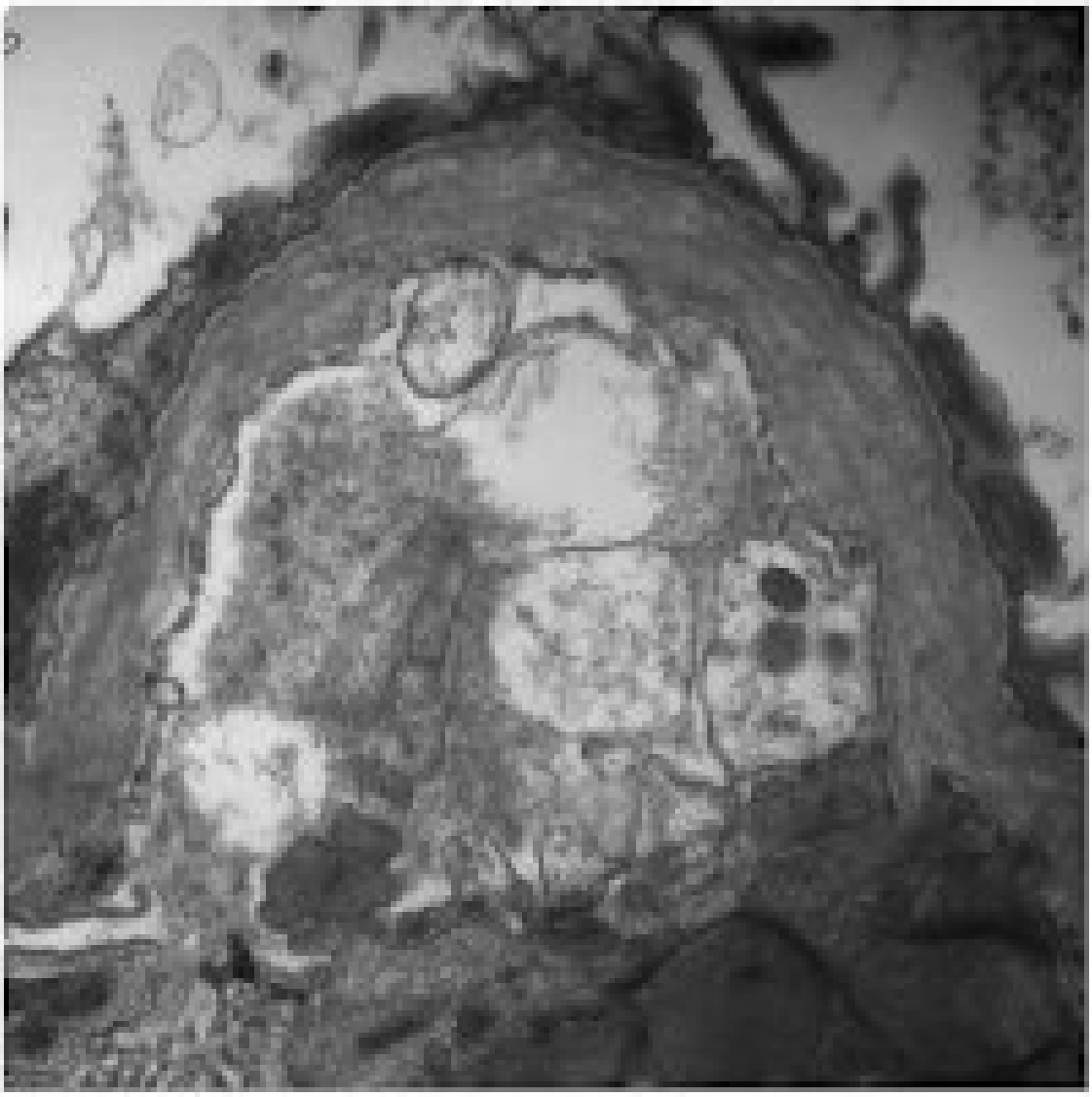


Figure 5. Alport syndrome with basket-weave and lamellated appearance of the glomerular basement membrane (electron microscopy).

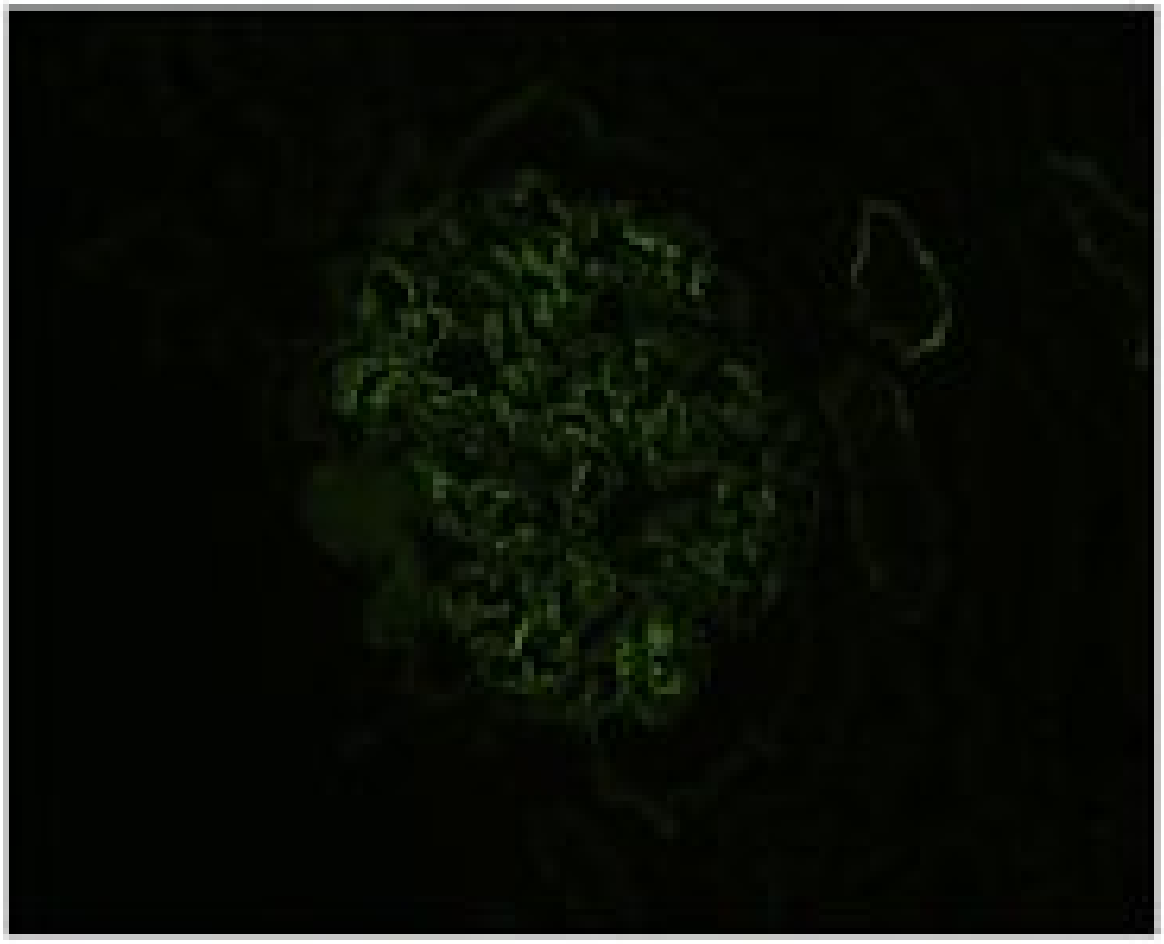


Figure 3. Alport syndrome with discontinuous staining for alpha 5 subtype of collagen type IV along glomerular basement membranes, Bowman's capsule, and distal tubule basement membranes, consistent with a carrier state of X-linked Alport syndrome in a female patient (immunofluorescence microscopy; alpha 5 subtype of collagen type IV staining).

🤔Can a skin biopsy diagnose Alport syndrome ❓

⚡The absence of the α5 chain from collagen type IV in skin BM s/o a diagnosis of X-AS

✨But it is less effective in the diagnosis of AS with COL4A3 or COL4A4 mutation.

Table 323.3 Tissue distribution of type IV collagen chains in basement membranes

Type IV collagen Disease	GBM	Bowman's capsule	Collecting duct basement membrane	Epidermal basement membrane
Normal	+	+/–	–	–
α3/α4 (IV)	+	+	+	+
α5(IV)				
X-linked Alport in males	–	–	–	–
α3/α4 (IV)	–	–	–	–
α5(IV)				
X-linked Alport in females	Mosaic			–
α3/α4 (IV)	Mosaic			Mosaic
α5(IV)				
Autosomal recessive Alport syndrome	–	–	–	–
α3/α4(IV)	–	+	+	+
α5(IV)				

❄️Diagnostic workup:

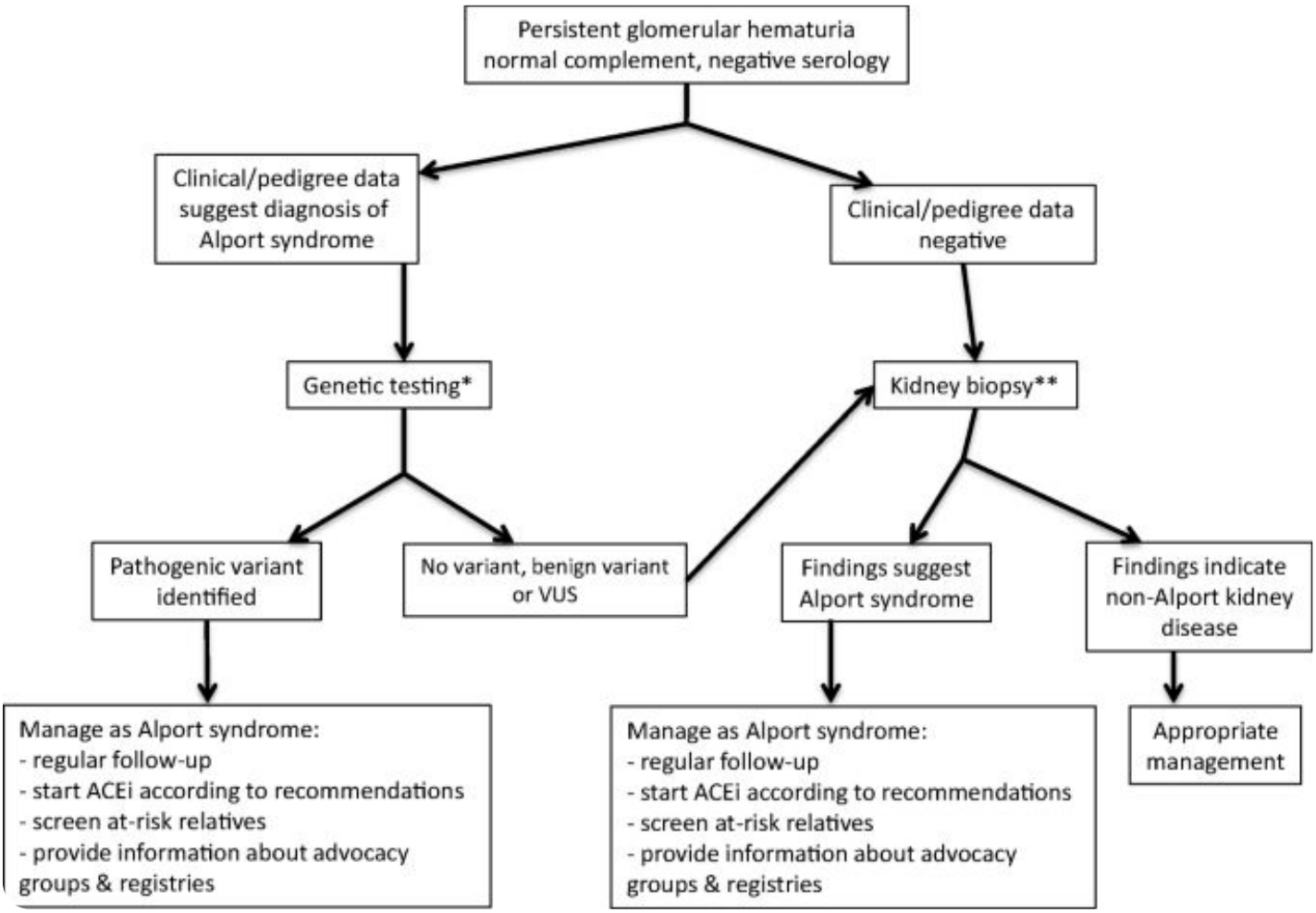
obtain a family history

🌟Urine analysis : presence of dysmorphic RBC, acanthocytes and proteinuria

🌟Eye examination, including a slit lamp inspection for lenticonus

🌟Hearing test for SNHL

Genetic testing is the gold standard



What are the ophthalmic👁️ manifestations found in AS❓

⚡Common 👁️eye problems are

Corneal opacities, anterior lenticonus, fleck retinopathy, and temporal retinal thinning. (Usually do not affect vision)

⚡Rare findings: Posterior polymorphous corneal dystrophy, giant macular hole, and maculopathy (can cause visual loss)

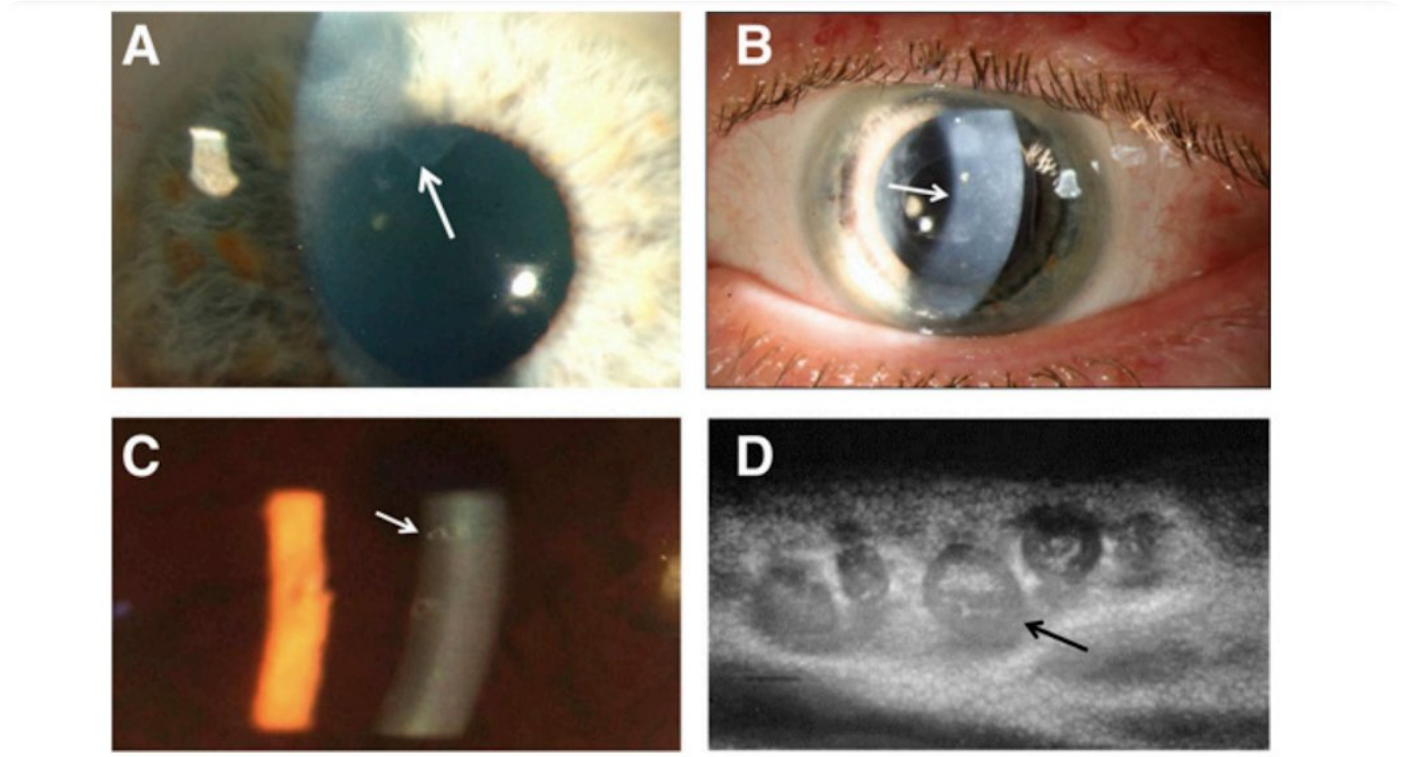


Figure 2. | Corneal abnormalities. (A) Mild scarring caused by recurrent corneal erosions shown on slit-lamp examination in a man with X-linked Alport syndrome (arrow), renal failure, and perimacular retinopathy. The patient's mother is also affected with renal disease

Table 1. Prevalence of ocular features in X-linked and autosomal recessive Alport syndrome

Ocular Feature	X-Linked Alport Syndrome (%)		Autosomal Recessive Alport Syndrome (%)
	Men	Women	
Recurrent corneal erosions	<10	<10	Not described
Posterior polymorphous corneal dystrophy	Rare	Rare	Not described
Lenticonus	50	<5	75 (52)
Central or perimacular fleck retinopathy	70	20	75 (52)
Peripheral retinopathy	80	50	75 (52)
Temporal retinal thinning	55	30	90
Lamellar macular hole	<5	Not described	<5
Other maculopathies	<5	<5	Not described

Lamellar and Giant Macular Holes

Lamellar or partial-thickness macular holes are uncommon in men with X-linked Alport syndrome and men and

Clinical Usefulness of Ophthalmic Features

The ocular features of Alport syndrome are explained b distribution of the collagen IV α3α4α5 network in bas

✨Coming on to SNHL👂:

💫Mostly high frequency, b/l, symmetrical, and usually progressive.

💫Can precede or even occurs in the absence of renal affections

💫Result of altered cochlear micromechanics.

💥Histology : BM separation from the cells of the organ of Corti, outer and inner hair cell loss, and cellular infilling of the tunnel and EC spaces of the organ of Corti.

📍

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6119774/

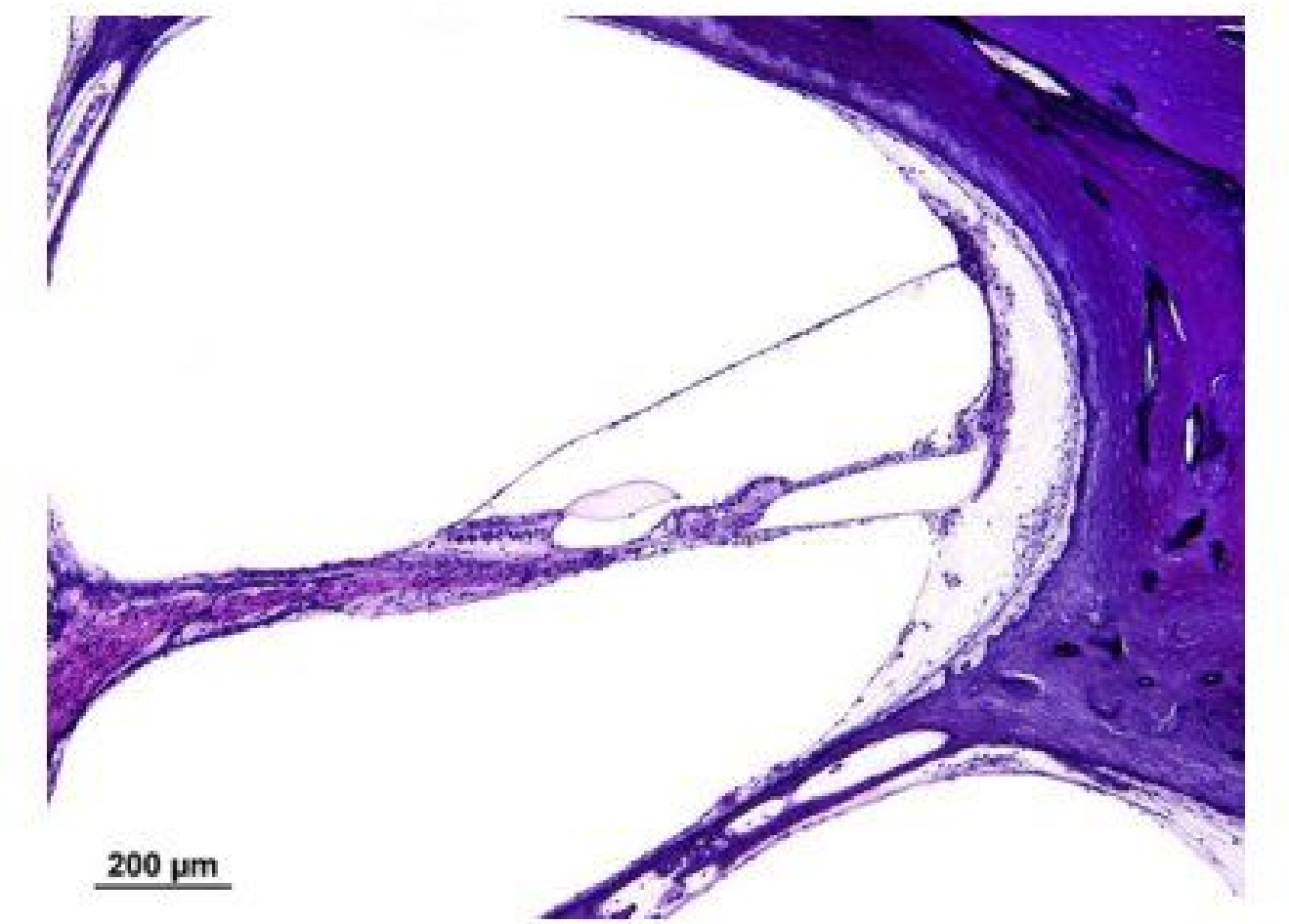


Fig. 2. Right middle cochlear duct turn. Horizontal section, light microscopy, Hematoxylin, and Eosin staining. A zone of separation between the organ of Corti and the basilar membrane extending along the bottom surface of the Deiter cells, Hensen cells, Claudius cells, and external sulcus cells is clearly seen.

🌟Can u guess what are the other causes (D/D) of characteristic features of Alport syndrome?

🧐Take a look at this chart

📌JASN '13.

https://doi.org/10.1681/ASN.2012020148

Table 2. Other causes of the characteristic features of Alport syndrome

Clinical Feature	Causes
Persistent familial hematuria	Glomerular hematuria
	TBMN
	Familial IgA disease
	MYH9-related disorders (Fechtner, Epstein syndromes)
	Membranoproliferative GN type 2 (dense deposit disease)
	Familial hemolytic uremic syndrome
	C3 nephropathy
	Nonglomerular hematuria
	Autosomal dominant polycystic kidney disease
	Sickle cell disease or trait
	Familial hypercalciuria, other familial forms of urolithiasis
Renal failure plus hearing loss	*MYH9*-related disorders (Fechtner syndrome)
	Nephronophthisis
	Bartter syndrome
	Distal renal tubular acidosis
	MELAS syndrome
	Fabry disease
	Branchio-oto-renal syndrome
	Townes-Brock syndrome
	CHARGE syndrome
	Kallmann syndrome
	Alstrom disease
	Muckle-Wells syndrome
Hearing loss	Middle-ear infections
	Age
	Industrial noise exposure
	Ototoxic drugs
	Renal failure, dialysis
Retinal flecks	Membranoproliferative GN type 2
	IgA disease, systemic lupus erythematosus, and some other forms of GN
	Severe hypertension (macular star)
	C3 nephropathy
Lamellated GBM	Focal damage
	MYH9-related disorders (Fechtner, Epstein syndromes)
	Pierson syndrome
	Nail-patella syndrome
	Mutations in the tetraspanin (*CD151*) gene
	Frasier syndrome
	Galloway-Mowat syndrome

MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke; CHARGE, coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies.

🔥Finally,

Can we do anything to prevent ESKD in AS patients ❓

❄️Animal models suggested multiple potentially effective therapies, but none seems to be effective🙄.
❄️Angiotensin inhibition: antiproteinuric cytokine, collagen production and tubulointerstitial fibrogenesis.

Therapy	Reduction of proteinuria		Delay of renal failure		Optimal start of therapy	
	Human	Animal	Human	Animal	Human	Animal
***ACE inhibition [6, 8–11]**	**(+++) (A)**	**(+++) (A)**	**ND**	**(+++) (A)**	**ND**** (microalbuminuria?)	**Hematuria (A)**
***AT1 antagonist [7]**	**(++) (D)**	**(++) (A)**	**ND**	**(++) (A)**	**ND**** (microalbuminuria?)	**Hematuria (A)**
***Aldosterone antagonist [12]**	**(+) (D)**	**(+) (D)**	**ND**	**ND**	**ND** (proteinuria?)	**ND**
***HMG-CoenzymeA inhibition [20]**	**(+) (D)**	**(+) (A)**	**ND**	**(+) (A)**	**ND**** (nephr. syndrome)	**Nephr. syndrome (A)**
***Cyclosporine [13–15]**	**(++) (B)**	**(++) (A)**	**NS (harm?)**	**(+) (A)**	**No therapy?**	**Unknown**
***Vasopeptidase inhibition [18]	(+++) (D)	(+++) (A)	**ND**	(+++) (A)	ND (microalbuminuria)	Hematuria (A)
***TGFβ-antagonist [16]	ND	(+) (A)	**ND**	(+) NS (A)	ND	ND
***BMP7 [21]	ND	Yes (A)	**ND**	ND (A)	ND	ND
***Gene therapy [22]	ND	(++) (A)	ND	(+) (A)	ND	ND
***Bone marrow cells [23–25]	ND	NS (A)	ND	ND, NS (A)	ND	ND
***Mesenchymal stem cells [26]	ND	NS (A)	ND	ND, NS (A)	ND	ND
Endothelin receptor *	ND	(++) (A)	ND	(+) (A)	ND	ND
***Chemokine receptor [19]	ND	(++) (A)	ND	(+) (A)	ND	ND
Collagen receptor **	ND	(++) (A)	ND	(+) (A)	ND	ND

🔥🔥Let's summarize,
AS is a hereditary disease characterized by hematuria, kidney failure, hearing loss, lenticonus, and retinal flecks; a lamellated GBM with an abnormal collagen IV composition; mutations in the COL4A5 or COL4A3/COL4A4 genes.

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