Hereditary and Congenital Diseases of the Kidney

Classification

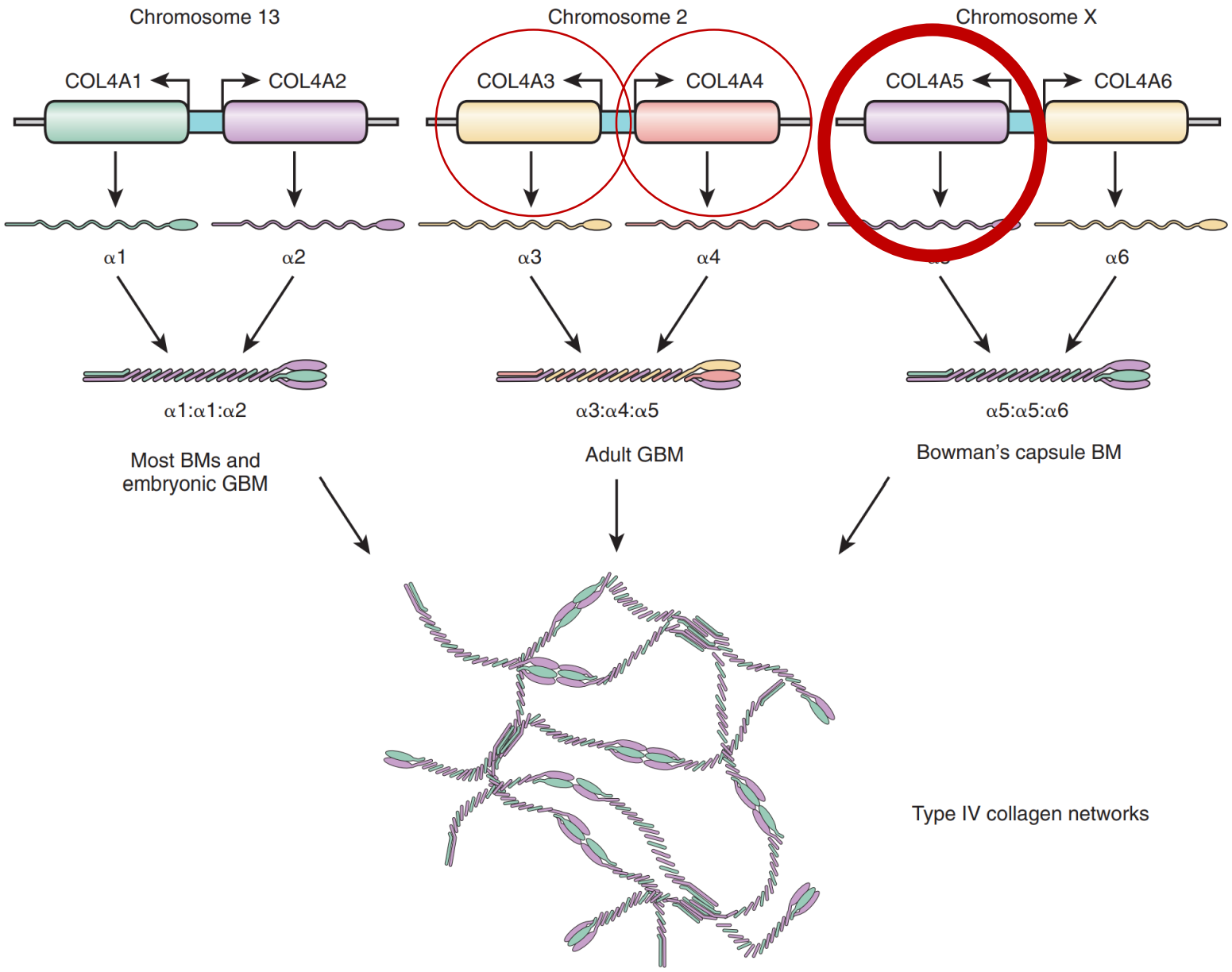
- Monogenic disorders
  - ADPKD
  - ARPKD
  - Alport syndrome
  - Fabry disease
  - Bartter and Gitelman syndromes
  - von Hippel-Lindau disease
  - Nephrogenic diabetes insipidus
  - Nephronophtysis
- Complex or multifactorial disorders
  - CAKUT - Congenital anomalies of the kidney and urinary tract

Kidney disorder or syndrome	Genes	Proteins/Products
Alport syndrome (X linked)	COL4A5	Type IV collagen α5 chain
Alport Syndrome (autosomal recessive)	COL4A3 or	Type IV collagen α3 chain
	OL4A4	Type IV collagen α4 chain
Alport syndrome with leiomyomatosis (X linked)	COL4A5 and COL4A6	Type IV collagen α5 and α6 chain
Benign familial hematuria (autosomal dominant)	COL4A4	Type IV collagen α4 chain
Autosomal dominant polycystic kidney disease 1 (PKD1)	PKD1	Polycystin 1
Autosomal dominant polycystic kidney disease 2 (PKD2)	PKD2	Polycystin 2
Autosomal recessive PKD	PKD3	Polycystin ?
VonLippel-Lindau (VHL) disease	TSC/VHL	VHL protein
Nephrogenic diabetes insipidus (X- linked)	ADHRV2	Vasopresin receptor V2
Nephrogenic diabetes insipidus (autosomal recessive)	AQP2	Aquaporin 2
Familial hypocalcuric hypercalcemia	CASR	Ca^{2+} sensing receptor
X- linked recessive nephrolithiasis	CLCN5	Cl^- channel
X- linked recessive hypophosphatemic rickets	CLCN5	Cl^- channel
Fabry disease (X- linked)	GLA	α-galactosidaseA (α-galA)
Juvenile nephronophtysis	NPHP1	
Steroid resistant nephrotic syndrome	NPHS2	podocin

Alport syndrome

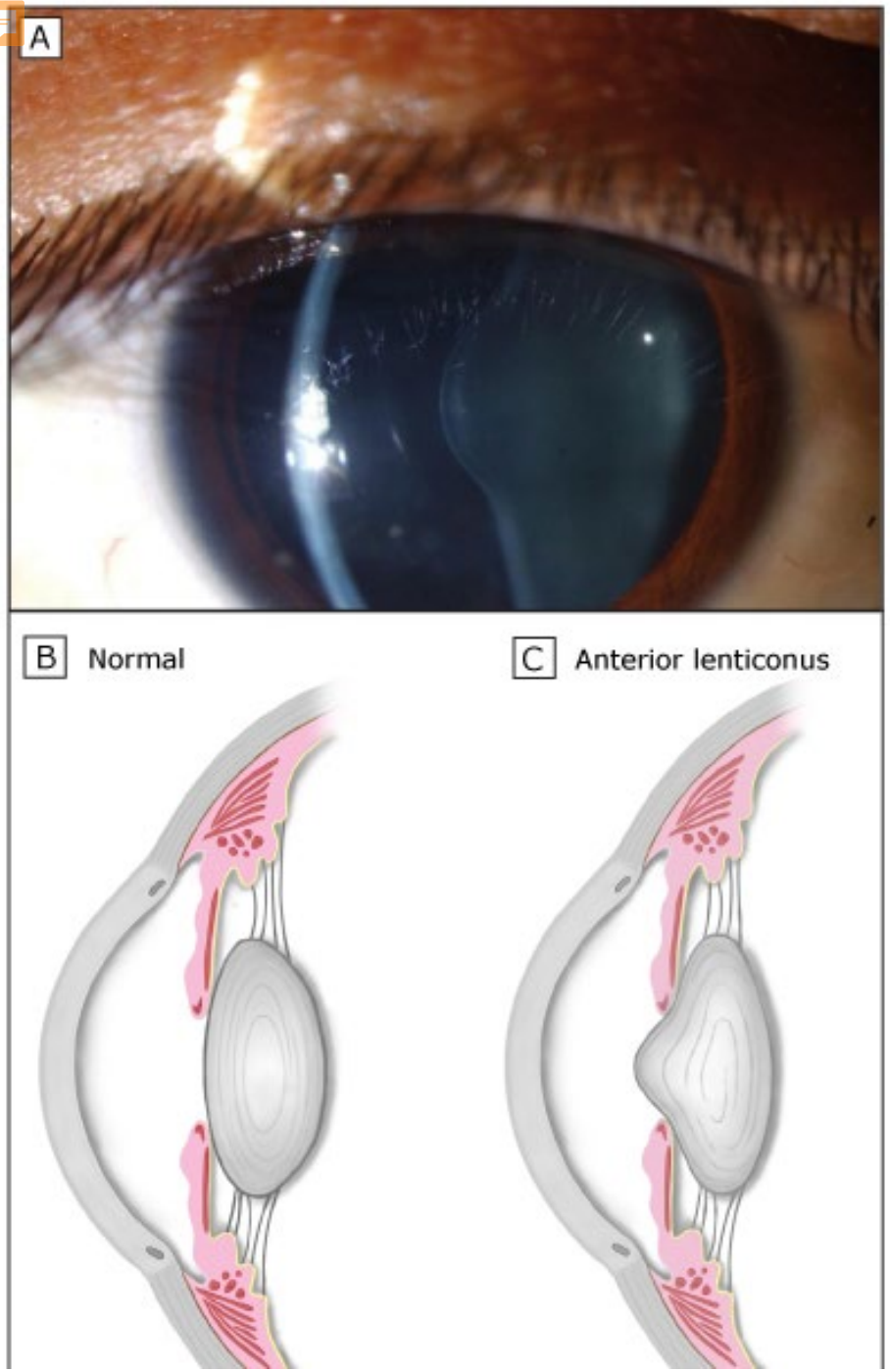
- Classically presents as a triad of:
  - Family history of progressive nephropathy.
  - Sensorineural deafness.
  - Ocular abnormalities
- Affects ~1 in 5,000 live births

- Defective basement membrane formation in the glomerulus, cochlea, and eye accounts for these findings.
- Although inheritance is varied, an X-linked inherited mutation in the *COL4A5* gene (>200 described) that encodes α5 type IV collagen accounts for 80% of cases.
- This leads to afflicted ♂, with ♀ carriers.
- Autosomal recessive forms account for~15% and autosomal dominant (AD) for ~5% (gene: *COL4A3*/*COL4A4* on chromosome 2).


Chromosome 13
Chromosome 2
Chromosome X
COL4A1
COL4A2
COL4A3
COL4A4
COL4A5
COL4A6
α1
α2
α3
α4
α6
α1:α1:α2
α3:α4:α5
α5:α5:α6
Most BMs and embryonic GBM
Adult GBM
Bowman's capsule BM
Type IV collagen networks

Clinical signs and symptoms

- Proteinuria (often nephrotic range) and ↑ BP usually present by adolescence. Progressive CKD → ESRD by the 3rd to 4th decade (~2% of an ESRD program).
  - Severity is often consistent within a family.
  - High-tone sensorineural deafness (in the majority) and anterior lenticonus (conical, rather than spherical, lens, leading to distorted vision: ~ 20%).
  - X-linked ♀ carriers often have microscopic hematuria alone. However, proteinuria and progression to ESRD by 5th decade in ~10 – 15%.
- The AR form is clinically similar to disease in X-linked ♂. The AD form is clinically very heterogeneous



Ocular manifestations of Alport syndrome

From: Al-Mahmood AM, Al-Swailem SA, Al-Khalaf A, Al-Binali GY. Progressive lenticonus in a patient with Alport syndrome. Middle East Afr J Ophthalmol 2010; 17(4):379-81. DOI:

Investigations

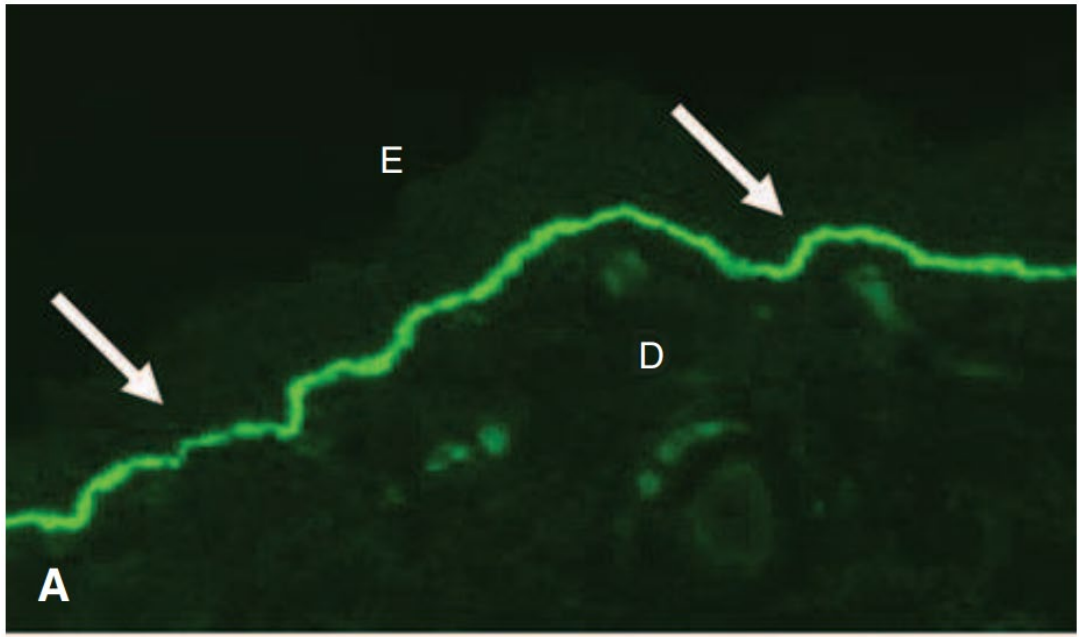
- Documentation of inheritance may be very helpful: AD inheritance of hematuria, with no proteinuria, CKD, or extrarenal manifestations, suggests TMD (although a confirmatory biopsy in at least one family member is desirable).
- Urinalysis + microscopy, uPCR or uACR. SCr, eGFR, U&E, albumin.
- Audiometry for subclinical hearing deficits and ophthalmic assessment.
- Skin biopsy with negative α5 type IV collagen staining is much less invasive than a renal biopsy and may be helpful in the assessment of possible X-linked Alport syndrome.

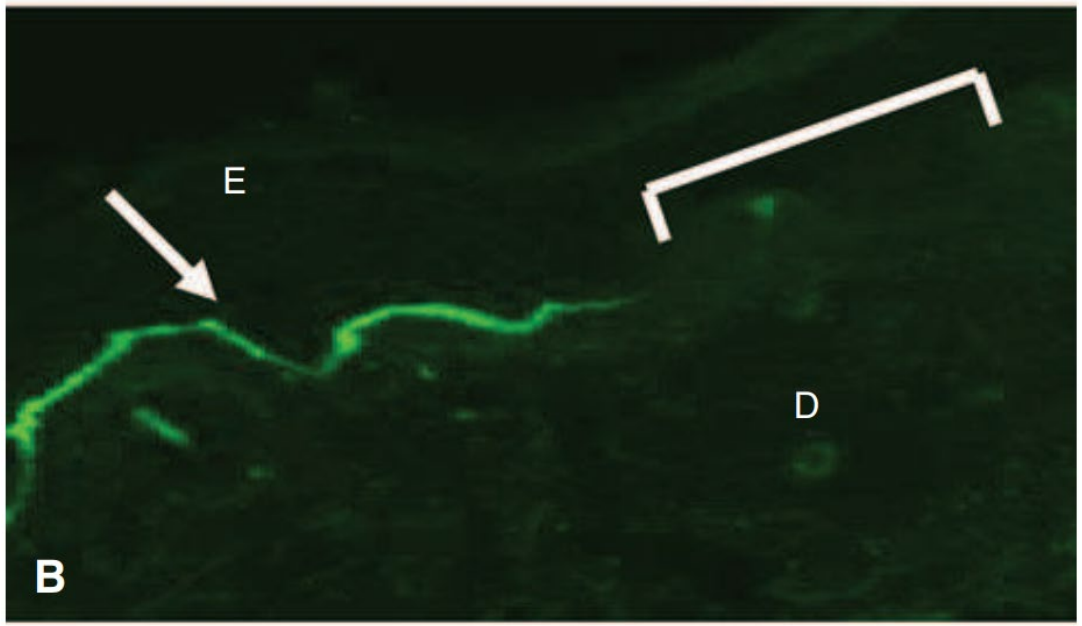
Molecular genetic testing

- The diagnostic procedure of choice because it is noninvasive and can be extremely accurate.
- Since the rate of progression of renal disease may be dependent upon the underlying specific mutation, molecular analysis may eventually provide more prognostic data than either renal or skin biopsy.
- Next generation sequencing allows simultaneous analysis of the *COL4A3*, *COL4A4*, and *COL4A5* genes and offers advantages in screening time and cost.
- The large size and high GC content of the *COL4A5* gene render direct mutational analysis of genomic DNA technically difficult. In addition, the analysis of genomic DNA may not detect large gene rearrangements or splice site mutations.

Renal biopsy

- *Alport ' s*: non-specific glomerulosclerosis and tubulointerstitial scarring on LM (esp. if ↑ SCr). A thin GBM on EM.
- Staining of the GBM for the α chain of type IV collagen is instructive.
  - In X-linked and AR Alport syndrome, the α3, α4, and α5 chains are absent (with a mosaic pattern of expression in ♀ carriers);
  - In AD Alport syndrome, the α4 and α5 chains are absent, whereas, in TMN, normal α chain distribution is preserved.


E
D
A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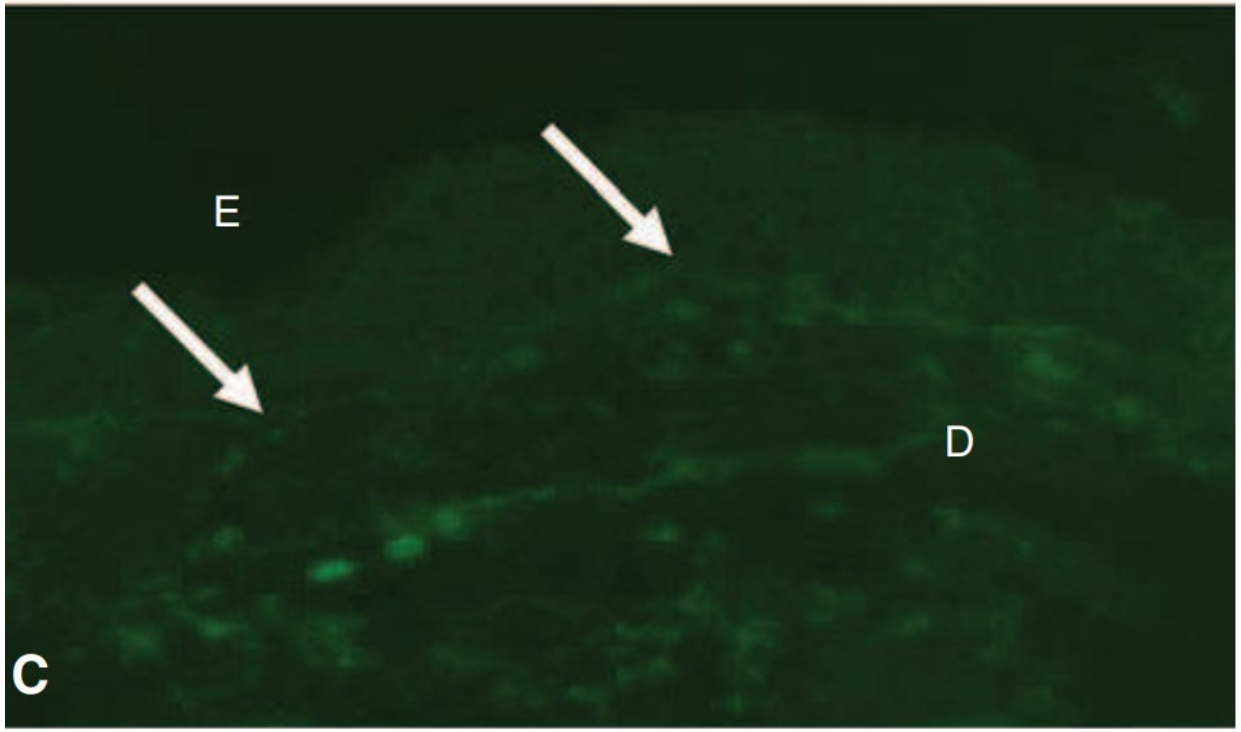
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Diagnostic evaluation for Alport syndrome

Management of Alport Syndrome

- No specific treatment for Alport syndrome. As with all progressive nephropathies, good control of BP, use of ACE-I/ARB, and proteinuria
- Annual monitoring for microalbuminuria and proteinuria as soon as the diagnosis of Alport syndrome is made or beginning at one year of age for at-risk children.
- Angiotensin blockade therapy is initiated when patients develop overt proteinuria
- Angiotensin blockade therapy is provided for male patients in whom there is a high risk of end-stage renal disease (ESRD) by 30 years of age
- Supportive measures are initiated to prevent and treat complications of chronic kidney disease
- Kidney transplantation is the preferred option over dialysis for patients who develop ESRD
- Supportive measures are used for hearing loss (eg, hearing aids) and ocular impairment as there are no interventions that correct hearing loss and ocular defects.

Management

- In <5%, transplanted Alport patients may develop *de novo* anti-GBM antibodies that cause an RPGN; i.e. donor α5 type IV collagen is recognized as non-self.
  - However, it is not a contraindication to transplantation.
- Family members should be screened for hematuria and ↑BP.
- Offer genetic counselling.

Thin basement membrane nephropathy

- A common AD inherited (occasionally sporadic) familial condition, presenting with microscopic hematuria, almost always with normal renal function.
- TBMN was previously known as ‘benign familial hematuria’.
- The normal GBM is ± 350nm thick—but, in TMD, it is often less than 200nm (although otherwise structurally normal)

Thin basement membrane nephropathy. Epidemiology.

- It is present in ~5% of post-mortem studies and is a relatively common finding during the assessment of potential live kidney donors.
- Studies on kidneys used for kidney transplantation suggest that the frequency of thin GBM in the general population may be as high as 5 to 9 percent.
- However, TBMN is clinically diagnosed in less than 1 percent of the population.

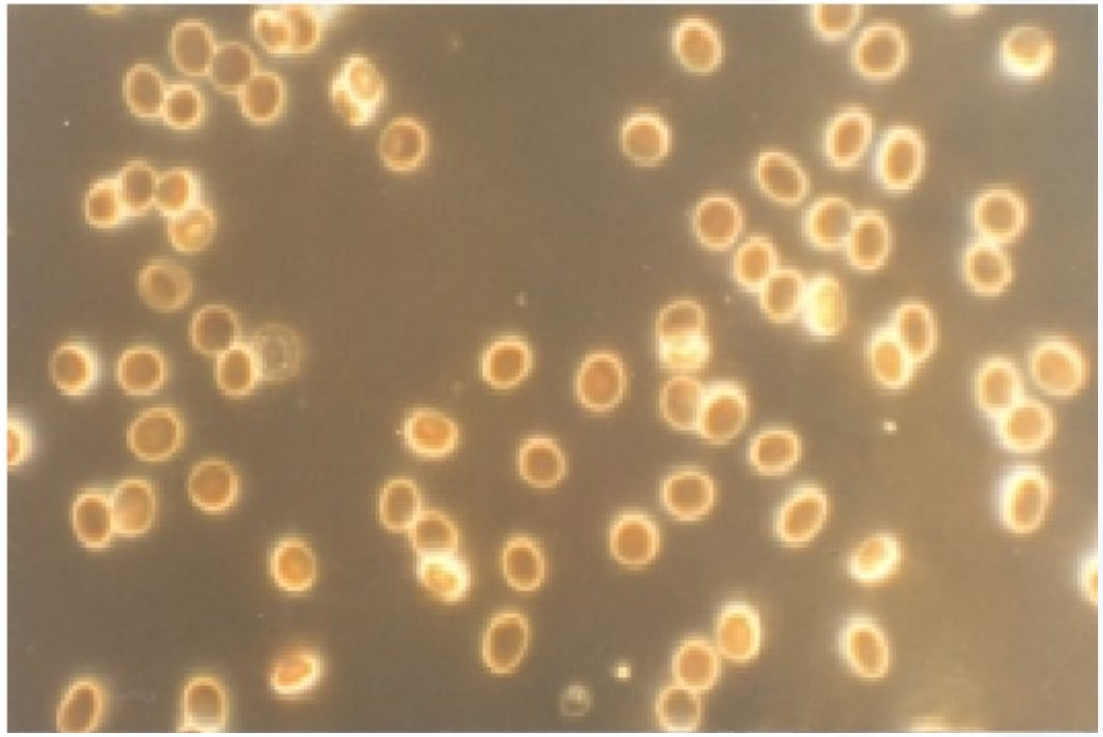
TBMN pathogenesis

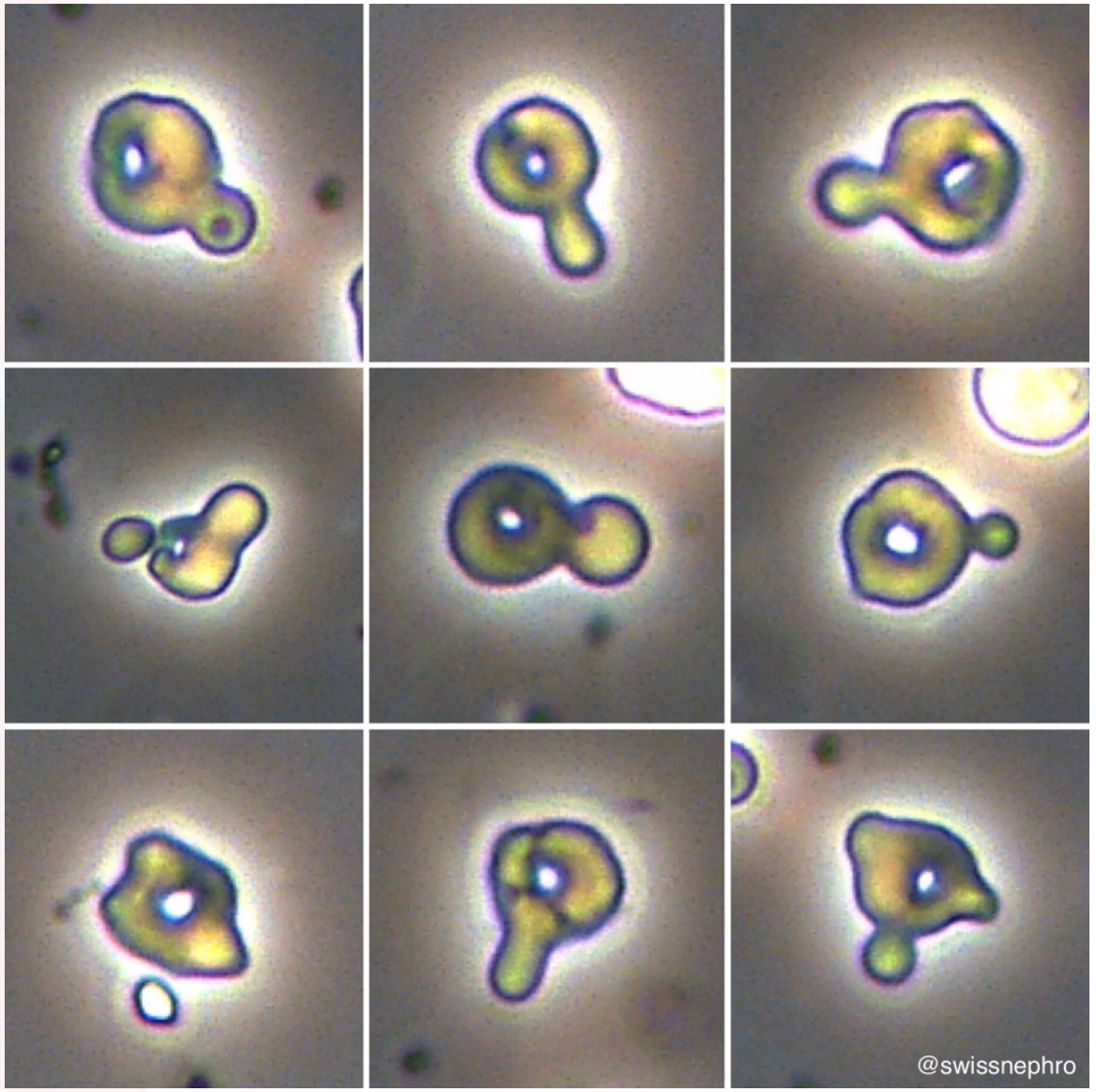
- It had been suspected that the genetic defect in TBMN would be similar to that in hereditary nephritis (Alport syndrome) since patients with the latter group of disorders also have thin GBM early in the course of the disease
- Patients with TBMN who have heterozygous *COL4A3/COL4A4* mutations are considered "carriers" of autosomal recessive Alport syndrome by some clinicians since mutations in both alleles of *COL4A3* or *COL4A4* cause autosomal recessive Alport syndrome.
- Approximately 40 to 50 percent of heterozygous carriers of a *COL4A3* or *COL4A4* mutation in Alport families exhibit microhematuria

- The underlying defect probably affects type IV collagen integration into the GBM and results in a partial failure of basement membrane function.
- 40% of families have mutations in *COL4A3*/*COL4A4* (>20 described, usually a single nucleotide substitution associated with a single family).
- These probably represent the benign end of the spectrum of Alport syndrome.
- The additional TMD genetic loci have not yet been identified.

TBMN.
Symptoms and signs

- Probably accounts for ~25% of all microscopic hematuria presenting to a renal clinic (the majority of whom will not undergo a renal biopsy).
- Macroscopic hematuria in ~20%.
- Proteinuria, ↑ BP, and renal impairment are rare.
- TBMN has no extrarenal manifestations.




@swissnephro

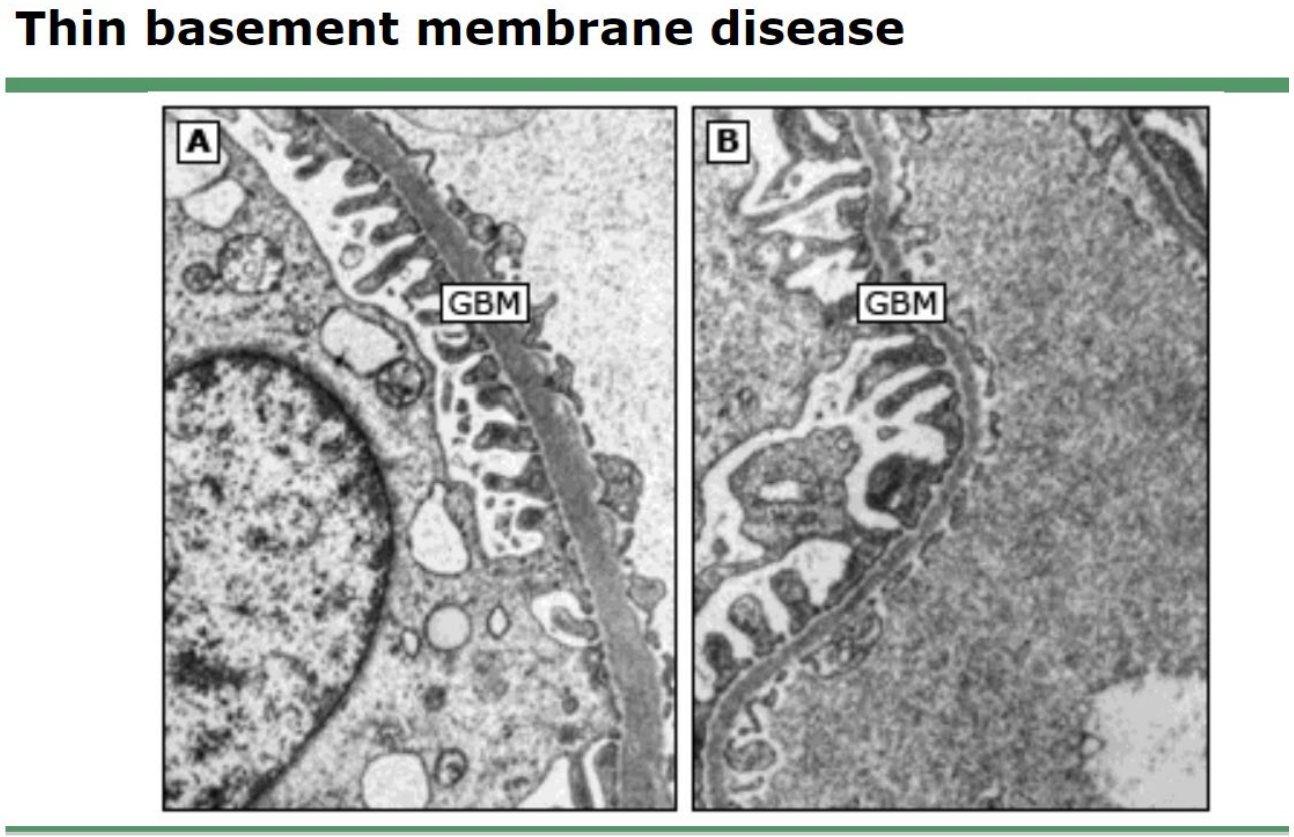
- Often a diagnosis of exclusion.
- The diagnosis of TBMN is usually inferred from
  - the benign presentation and course,
  - the positive family history of hematuria,
  - the negative family history of kidney failure.
- Kidney biopsy is generally **not** performed in patients who present with familial isolated glomerular hematuria, no or minimal proteinuria, normal kidney function, and no family history of kidney failure.
- The prognosis is excellent

Indications for kidney biopsy

- Suspected TBMN with proteinuria
- Or if hematuria alone and:
  - Is the patient being considered as a kidney donor?
  - Is marriage to another individual with isolated hematuria being planned?

Microscopy

- *TMD:* normal light microscopy. EM demonstrates reduction in GBM thickness.



Management

- Patients with uncomplicated TMD can be reassured but should be followed up at annual intervals (urinalysis ± uPCR, BP, and eGFR).
- If proteinuria
  - ACE inhibitor or angiotensin II receptor blocker

TMD vs Alport

	TMD	Alport
Hematuria	+ to +++	++
Proteinuria	±	+++ (>3 g/day)
↑ Blood pressure	-	+++
Renal dysfunction	±	+++
Deafness/lenticonus	-	++
History of ESRD	-	+
Father-to-son transmission	+	- (if X-linked)

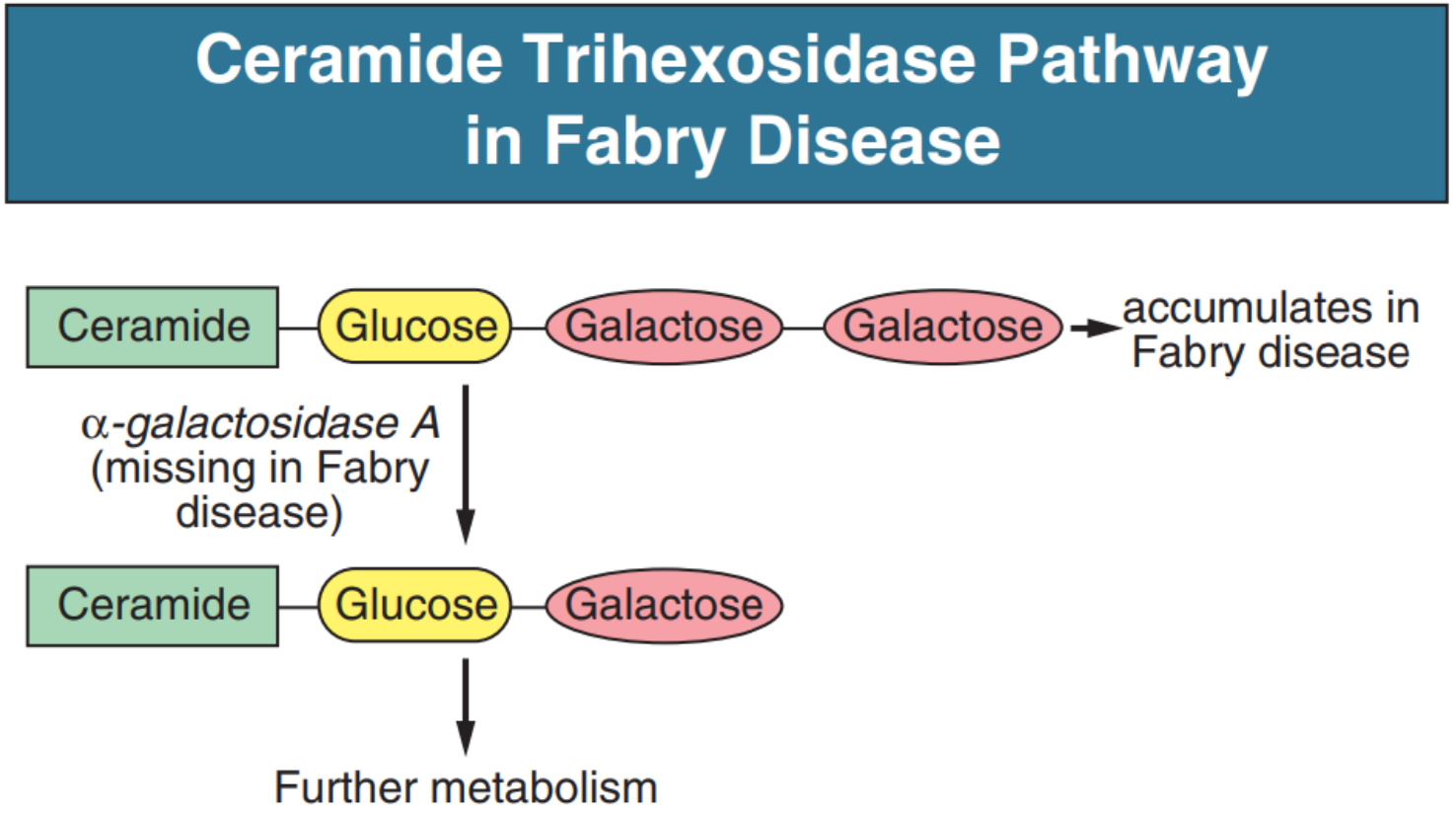
Fabry disease

- caused by hereditary deficiency of the enzyme **α-galactosidase A** (α-Gal A)

- resulting in the intracellular accumulation of neutral glycosphingolipids with terminal α-linked galactosyl moieties

Pathogenesis

- >500 mutations causing Fabry disease have been identified in *GLA,* the gene for α-Gal A, which is located on the X chromosome

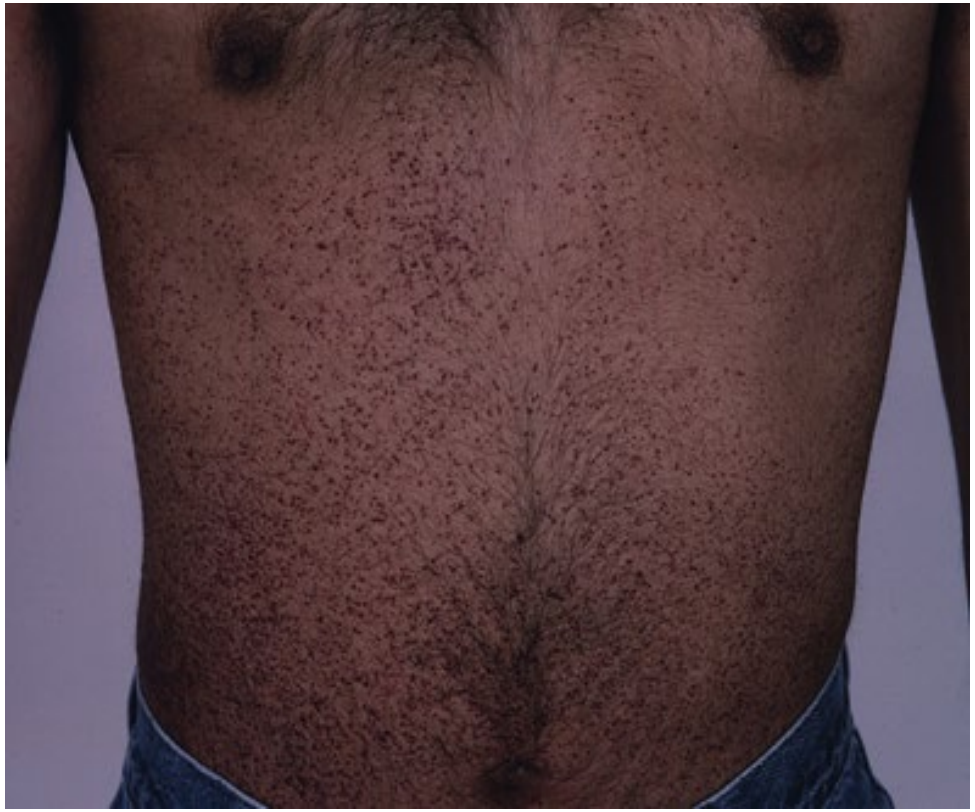


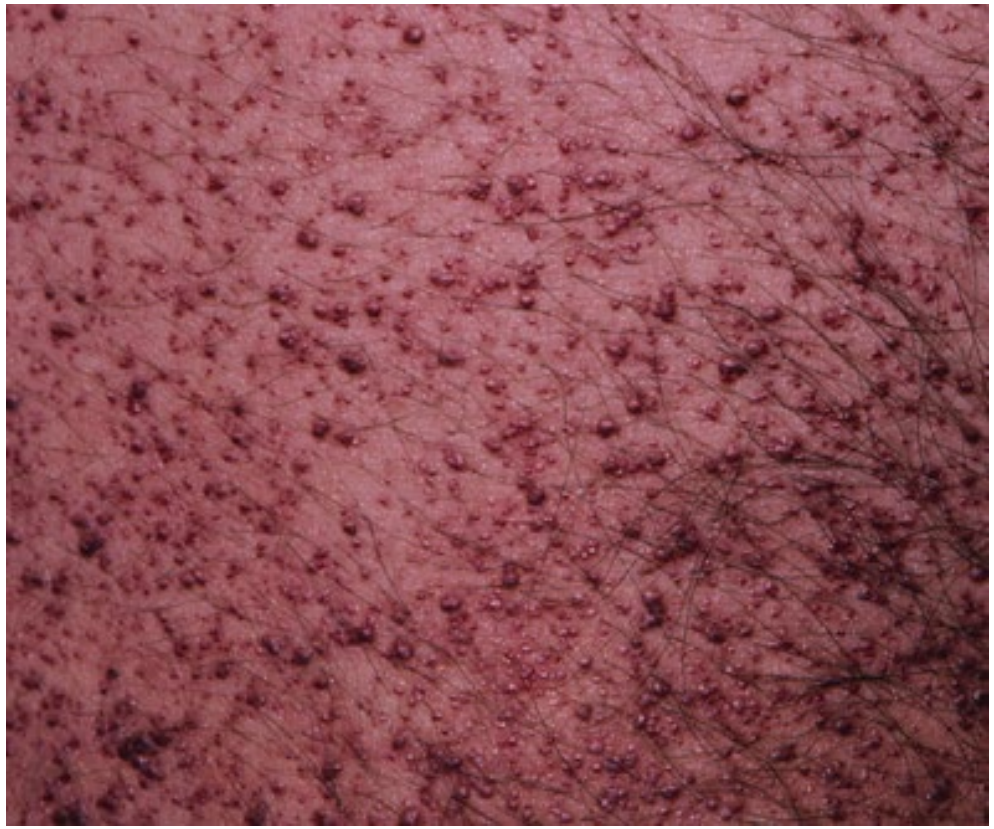
Clinical manifestations

multisystem disorder

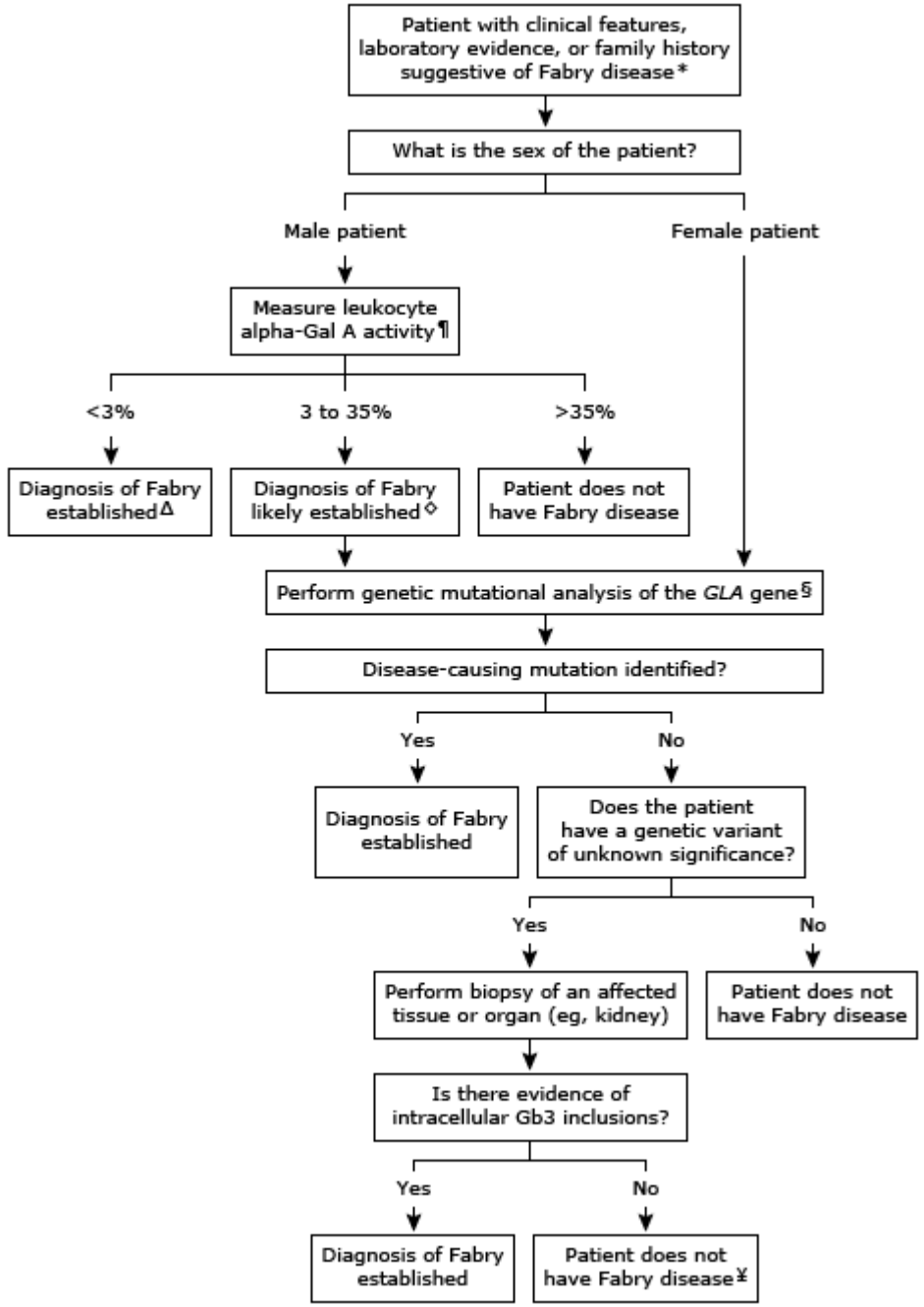
Childhood
Acroparesthesia, may be severe
Telangiectasias on ears, conjunctiva
Hypohidrosis, poor exercise and heat tolerance
Nausea, diarrhea, and abdominal pain
Raynaud phenomenon
Ophthalmologic abnormalities (cornea verticillata)
Early adulthood
Extensive angiokeratomas, telangiectasias
Albuminuria, hematuria, oval fat bodies in urine
Nausea, diarrhea, and abdominal pain
Fever, heat collapse, anhidrosis
Proteinuria
Cornea verticillata, conjunctival vessel tortuosity, and lymphedema
30 to 40 years of age
Cardiac disease: Left ventricular hypertrophy, conduction and rhythm abnormalities, valvular disease, small coronary vessel disease
Renal insufficiency usually with proteinuria
Ischemic cerebrovascular stroke or TIAs
Progressive length-dependent small-fiber nephropathy: Acroparesthesia, loss of cold and warm perception
Nausea, diarrhea, and abdominal pain

Angiokeratomas are distributed in a typical symmetrical fashion on the torso





Diagnosis of Fabry disease



Management

- enzyme replacement therapy with recombinant human α-Gal A (**agalsidase**)
  - IV: 1 mg/kg every 2 weeks
    - 5 mg (per each): $1,040.40
  - The estimated retail cost of therapy with Fabrazyme for one year is approximately USD $300,000 in the United States and Europe
- Migalastat
  - Oral pharmacologic chaperone that binds to and stabilizes specific mutant forms of alpha-galactosidase
  - Facilitates proper trafficking of the enzyme to lysosomes and increasing enzyme activity

Non-specific treatment

- ACE inhibitors and ARBs
- Dialysis
- Transplantation

Prognosis

- Survival is substantially reduced in males with classic Fabry disease.
- Before dialysis was commonly available, such patients usually died in the fourth decade of life, and the availability of dialysis prolonged survival into the fifth decade.
- Median cumulative survival was 50 years, with very few individuals alive after the age of 60 years.

Bartter and Gitelman syndromes

- also called *tubular hypomagnesemia-hypokalemia with hypocalciuria*
- **autosomal recessive** disorders with characteristic sets of metabolic abnormalities:
  - hypokalemia,
  - metabolic alkalosis,
  - hyperreninemia,
  - hyperplasia of the juxtaglomerular apparatus (the source of renin in the kidney),
  - hyperaldosteronism.

PREVALENCE

- Gitelman syndrome is a much more common disease than Bartter syndrome
- The prevalence of Gitelman syndrome has been estimated to be between 1 to 10 in 40,000
  - compared with 1 in 1,000,000 for Bartter syndrome
    - The lower prevalence of Bartter syndrome in the population may be due at least in part to prenatal or neonatal death resulting from the disorder before it could be diagnosed

Disorder	Gene affected	Gene product	Clinical presentation	Functional studies
Bartter syndrome type I	SLC12A1 Autosomal Recessive	NKCC2	Antenatal Bartter syndrome (hyperprostaglandin E syndrome), polyhydramnios, prematurity, and nephrocalcinosis	Concentrating capacity reduced and diluting capacity reduced
Bartter syndrome type II	KCNJ1 Autosomal Recessive	ROMK	Antenatal Bartter syndrome, polyhydramnios, prematurity, nephrocalcinosis, and transient hyerkalemia	Concentrating capacity reduced and diluting capacity reduced
Bartter syndrome type III	CLCNKB Autosomal Recessive	CLC-Kb	Classic Bartter syndrome	Concentrating capacity reduced and diluting capacity reduced
Bartter syndrome type IVA	BSND Autosomal Recessive	Barttin (beta-subunit of CLC-Ka and CLC-Kb)	Antenatal Bartter syndrome (hyperprostaglandin E syndrome), sensorineural deafness,* polyhydramnios, and prematurity	Concentrating capacity reduced and diluting capacity reduced
Bartter syndrome type IVB	CLCNKA and CLCNKB Autosomal Recessive	CLC-Ka and CLC-Kb	Antenatal Bartter syndrome (hyperprostaglandin E syndrome) and sensorineural deafness*	Concentrating capacity reduced and diluting capacity reduced
MAGED2 mutation Bartter syndrome	MAGED2	Melanoma-associated antigen D2	Antenatal Bartter syndrome, transient salt wasting in surviving children, extrarenal manifestations, polydyramnios, and transient salt wasting	Renal tubule defects improve or resolve in surviving infants
Hypocalcemia with renal salt wasting	CASR Autosomal Dominant	CaSR	Bartter syndrome with hypocalcemia	Concentrating capacity reduced and diluting capacity reduced
Gitelman syndrome	SLC12A3 Autosomal Recessive	NCC	Gitelman syndrome	Concentrating capacity normal/near normal and diluting capacity reduced

Diagnosis

- suspected in patients with unexplained hypokalemia, metabolic alkalosis, and a normal or low blood pressure.
- Exclusion diagnosis

Treatment

- tubular defects cannot be corrected
- treatment is aimed at minimizing the effects of extracellular volume depletion (and the resulting increases in renin, aldosterone, and, in some patients, prostaglandins), as well as correcting the volume deficit and electrolyte abnormalities.
- Sodium, potassium, and magnesium supplements
- NSAIDs and drugs that block distal tubule sodium-potassium exchange
- Angiotensin inhibitors
- Kidney transplantation – correct the tubular defect

von Hippel-Lindau

- An inherited, autosomal dominant syndrome manifested by a variety of benign and malignant tumors.
- Affected 1 in 36,000 people

- The initial manifestations of disease can occur in childhood or adolescence, or later (mean age approximately 26 years).
- The spectrum of vHL-associated tumors includes:
  - Hemangioblastomas of the central nervous system
  - Retinal hemangioblastomas
  - Clear cell renal cell carcinomas
  - Pheochromocytomas
  - Endolymphatic sac tumors of the middle ear
  - Serous cystadenomas and neuroendocrine tumors of the pancreas
  - Papillary cystadenomas of the epididymis and broad ligament

Two types of vHL disease

- based upon the likelihood of developing pheochromocytoma.
  - **Type 1** –have a substantially lower risk of developing pheochromocytomas (type 1A) and a lower risk of both pheochromocytomas and renal cell carcinoma (RCC; type 1B)
  - **Type 2** – Kindreds with type 2 disease are at high risk for developing pheochromocytoma.
    - Type 2 disease is subdivided based upon the risk of developing RCC.
    - Type 2A and 2B families have a low and high incidence of RCC, respectively, while type 2C kindreds are characterized by the development of pheochromocytomas only, without RCC or hemangioblastoma.

Management

- Surgery to remove RCC
  - Nephron sparing surgery is the procedure of choice when possible
- Bilateral nephrectomy and renal transplantation may be an acceptable alternative
- Drugs that inhibit the pVHL-HIF-VEGF pathway, such as the multiple tyrosine kinase inhibitors, sunitinib, sorafenib, and pazopanib, and the monoclonal anti-VEGF antibody bevacizumab, have a proven role for sporadic RCC and may be therapeutically useful in VHL-related hemangioblastomas and RCC

Nephronophthisis

- a clinical condition caused by a group of autosomal recessive cystic kidney disorders that typically progresses to end-stage renal disease
- caused by mutations in a large number of genes that encode proteins involved in the function of primary cilia, basal bodies, and centrosomes, resulting in renal disease and extrarenal manifestations

Gene mutations and affected proteins linked to nephronophthisis and other associated syndromes

Gene	Protein	Clinical features/syndrome
NPHP1	Nephrocystin-1	NPH, SLS, JBTS
NPHP2/INVS	Inversin	NPH, SLS, HF, situs inversus
NPHP3	Nephrocystin-3	NPH, SLS, HF, MKS
NPHP4	Nephrocystin-4/Nephroretinin	NPH, SLS
NPHP5/IQCB1	Nephrocystin-5/IQ motif containing B1	NPH, SLS, LCA
NPHP6/CEP290	Centrosomal protein 290	NPH, SLS, LCA, JBTS, MKS,
NPHP7/GLIS2	GLI similar 2	NPH
NPHP8/RPGRIP1L/MKS5	RPGRIP1-like	NPH, SLS, JBTS, MKS
NPHP9/NEK8	NIMA-related kinase 8	NPH, SLS
NPHP10/SDCCAG8/SLSN7	Serologically defined colon cancer antigen 8	NPH, SLS, BBS-like
NPHP11/TMEM67/MKS3	Transmembrane protein 67	NPH, JBTS, MKS, HF
NPHP12/TTC21B	Intraflagellar transport protein 139	NPH, JBTS, JATD, BBS
NPHP13/WDR19	WD repear domain 19/IFT protein 144	NPH, JATD, SBS
NPHP14/ZNF423	Zing finger protein 423	NPH, JBTS
NPHP15/CEP164	Centrosomal protein 164	NPH, SLS, JBTS, BBS
NPHPL1/XPNPEP3	X-prolyl aminopeptidase 3	NPH
TMEM216/JBTS2/MKS2	Tranbsmembrane protein 216	NPH, JBTS, MKS
AH11/JBTS3	Jouberin	NPH, JBTS
CC2D2A/MKS6	Coiled coil and C2 domain containing 2A	NPH, JBTS, MKS
ATXN10	Ataxin 10	NPH, JBTS, HF
IFT43	Intraflagellar transport protein 43	NPH, SBS
IFT122	Intraflagellar transport protein 122	NPH, SBS
IFT140	Intraflagellar transport protein 140	NPH, JATD, SMS
CEP41	Centrosomal protein 41	NPH, JBTS

- Three clinical variants have been described based upon the median age of onset of ESRD:
  - Infantile − 1 year of age
  - Juvenile − 13 years of age
  - Adolescent − 19 years of age
- The diagnosis of NPHP is suggested by characteristic clinical findings and confirmed by a positive genetic test

- There is no specific therapy for NPHP.
- Supportive treatment
  - focused on maintaining fluid and electrolyte balance,
  - treating anemia,
  - promoting normal growth.
- Renal transplantation is the preferred replacement therapy because outcome is excellent, as tubular injury does not recur in the transplanted kidney

Congenital anomalies of the kidney and urinary tract

- CAKUT constitute approximately 20 to 30 percent of all anomalies identified in the prenatal period.
- Defects can be bilateral or unilateral, and different defects often coexist in an individual child.

Type of renal malformation
Dilatation of upper tract
Unilateral multicystic dysplastic kidney
Unilateral renal agenesis
Bilateral renal agenesis/dysgenesis
Polycystic kidney disease
Supernumerary kidney
Ectopic kidney
Posterior urethral valves
Solitary cyst
Bladder exstrophy
Multiple malformations

Under development technologies

- **Gene therapy**
  - introduction of an exogenous gene or genes into one or more autologous or allogeneic cell types
- **Gene editing**
  - CRISPR-Cas9
- **Gene silencing**
  - reduction of the expression of a gene (or genes)