

Other Glomerular Diseases

IgA nephropathy • Alport spectrum disorders

Morphology | Pathogenesis | Clinicopathologic diagnosis

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Learning outcomes

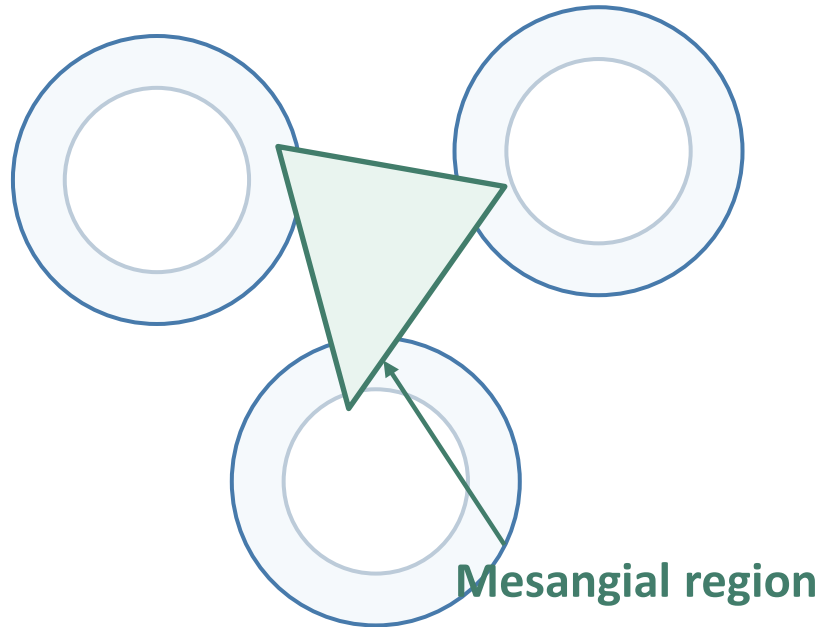
- Distinguish immune-complex glomerular injury from inherited basement-membrane disease.
- Explain the multistep pathogenesis and mesangial morphology of IgA nephropathy.
- Interpret IgA immunofluorescence and electron-microscopy patterns.
- Relate type IV collagen defects to Alport renal and extrarenal manifestations.
- Use integrated clinical, family-history, LM, IF, and EM findings in differential diagnosis.

Two pathways to glomerular hematuria

Feature	IgA nephropathy	Alport spectrum disorders
Primary mechanism	Aberrantly glycosylated IgA1; immune complexes	Inherited defects of type IV collagen
Main initial site	Mesangial immune deposits	Glomerular basement membrane network
Defining evidence	Mesangial IgA on IF	Collagen-IV–associated ultrastructural/genetic findings
Shared manifestations	Hematuria; variable proteinuria	Hematuria; later proteinuria

Glomerular compartments relevant to diagnosis

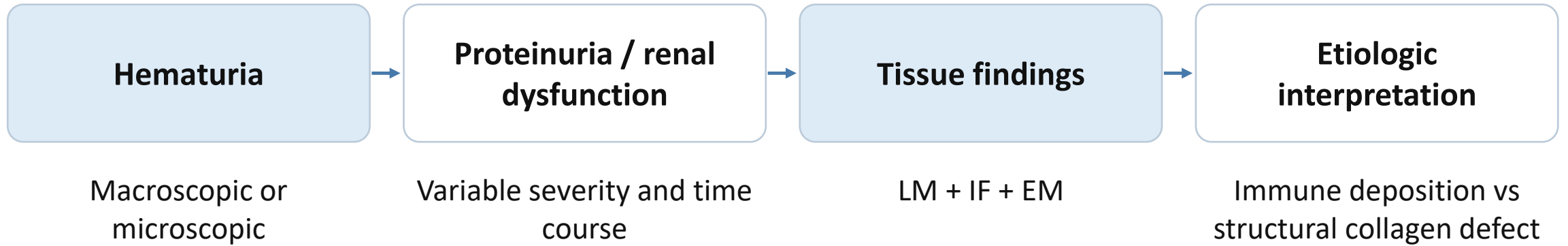
Capillary loops



What each modality resolves

- LM: Proliferation and scarring
- IF: Immunoglobulin identity and location
- EM: Electron-dense deposits or GBM defects

Clinical phenotype directs the tissue question



The same urinary phenotype may reflect very different mechanisms.

Core mechanisms are not interchangeable

IgA nephropathy

- Abnormal IgA1 and immune complexes
- Mesangial deposition and activation
- IF identifies mesangial IgA

Alport disorders

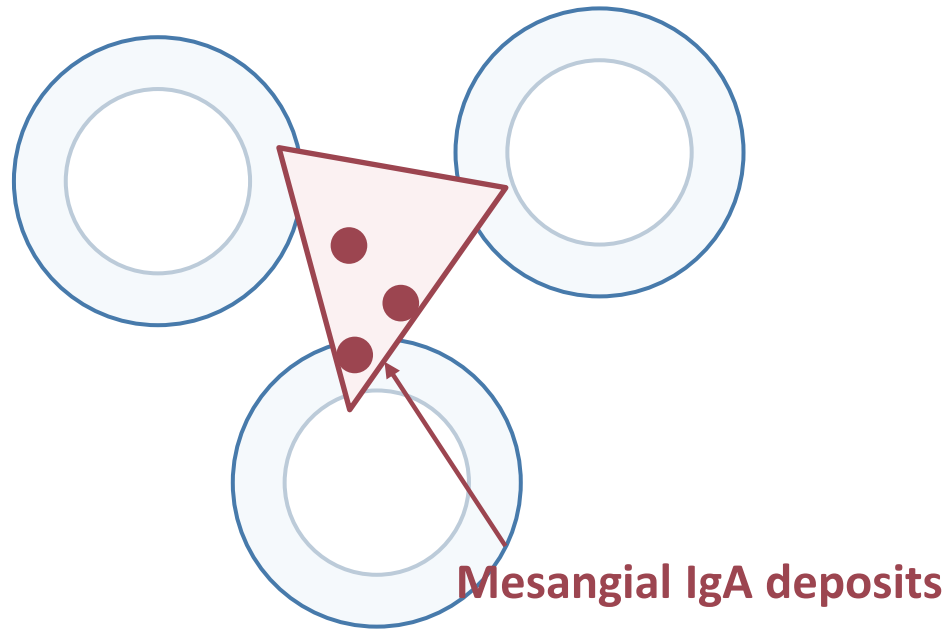
- Inherited collagen-IV defects
- Basement-membrane instability
- EM / collagen staining / genetics assist

IgA nephropathy: Defining features

- Prominent IgA deposits in the glomerular mesangium are required for diagnosis.
- Recurrent hematuria is characteristic; Proteinuria is often mild.
- It is as the most common glomerulonephritis worldwide.
- Severe podocyte injury may occasionally produce nephrotic syndrome.
- Crescentic glomerulonephritis is an uncommon presentation.

Mesangial localization is the central clue

Capillary loops



Source-defined hallmark

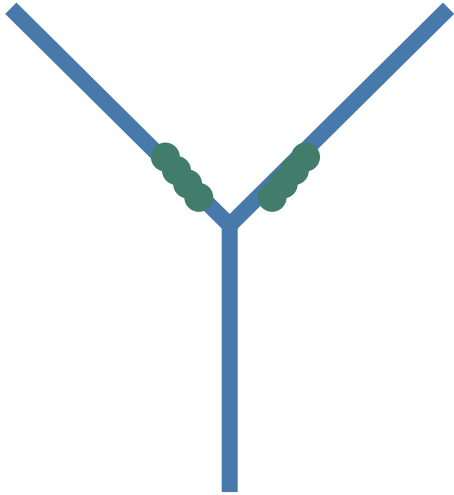
- IgA deposits in mesangial regions
- Possible associated C3 staining
- LM alone may underestimate disease

Normal IgA handling provides mechanistic context

- IgA is the principal immunoglobulin in mucosal secretions.
- Circulating IgA is mainly monomeric and relatively low in concentration.
- Polymeric IgA is normally catabolized in the liver.
- In IgA nephropathy, circulating polymeric IgA increases, but increased production alone does not explain injury.

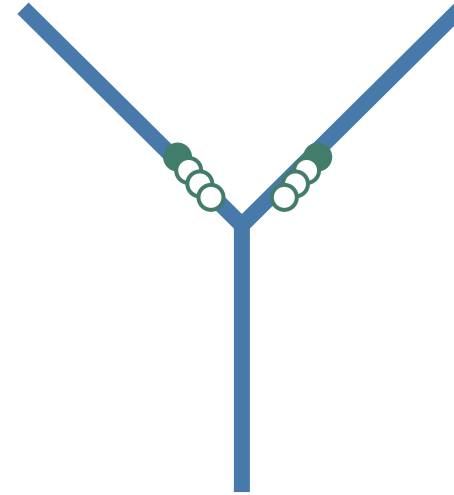
Abnormal IgA1 hinge-region glycosylation

Normal IgA1



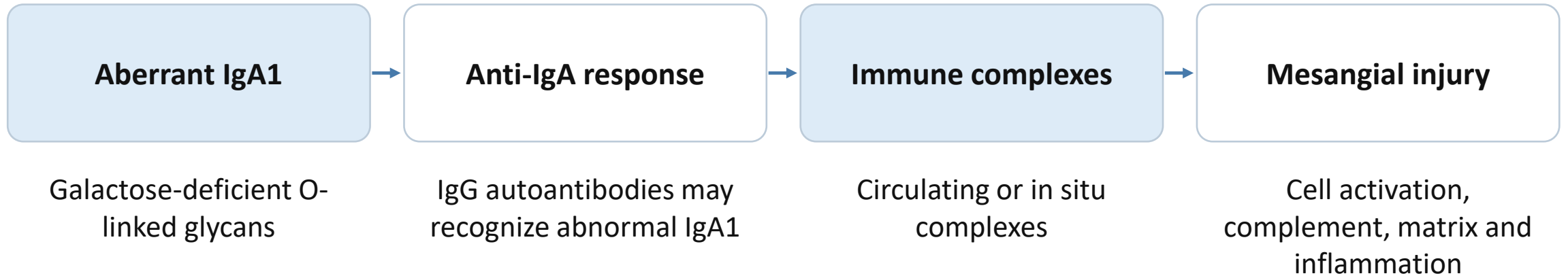
Galactose-bearing O-glycans

Galactose-deficient IgA1



Reduced galactose-bearing O-glycans

IgA nephropathy: The proposed multihit sequence



Robbins frames this sequence as the favored model, not as a fully resolved initiating cause.

A glycosylation defect is not simply IgA overproduction

- Glomerular deposits contain predominantly polymeric IgA with abnormal glycans.
- A key proposed defect concerns galactose-bearing O-linked glycans on the IgA1 hinge region.
- The defect may be hereditary or acquired.
- Abnormally glycosylated IgA provides a substrate for mesangial deposition and autoantibody recognition.

Autoantibodies amplify the initial IgA abnormality

- IgG autoantibodies may target structurally abnormal IgA1.
- IgG–IgA interactions can generate circulating immune complexes.
- The model explains why elevated IgA production alone is insufficient.
- The source also allows mesangial deposition of abnormal IgA before local complex formation.

Two routes to mesangial immune complexes

Circulating deposition

- Aberrant IgA1 reacts with IgG
- Preformed complexes circulate
- Complexes become trapped in mesangium

In situ formation

- Aberrant IgA1 deposits first
- Antibody then binds deposited IgA1
- Complex forms within mesangium

Complement involvement in IgA nephropathy

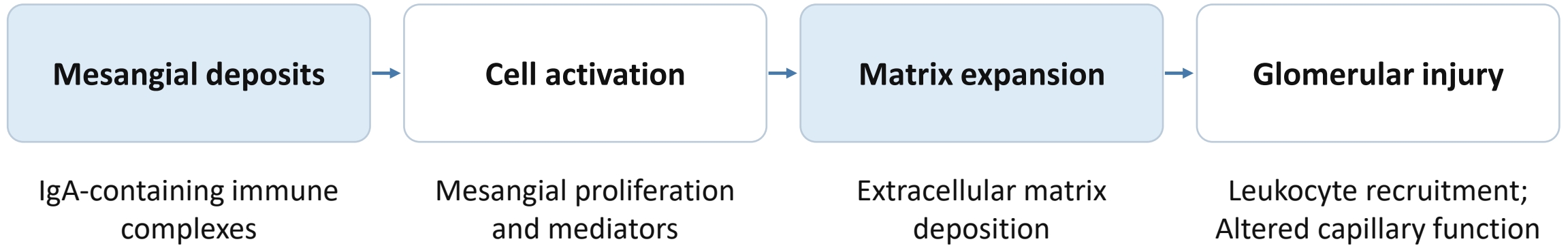
Typical IgA-nephropathy IF

- IgA: Mesangial dominant deposition
- C3 and properdin: Often present
- IgG or IgM: May be weaker

Usually absent or not prominent

- C1q: Usually absent
- C4: Usually absent
- Supports alternative-pathway involvement

Deposits translate into mesangial injury



A mesangial deposit is a stimulus for cellular and matrix responses, not merely a passive stain.

Inflammatory amplification affects lesion severity

- Activated mesangial cells release cytokines and growth factors.
- These mediators further stimulate mesangial cells and recruit inflammatory cells.
- Leukocytes contribute to injury but also aid clearance of immune complexes.
- The balance between injury and repair helps explain heterogeneous biopsy patterns.

Genetic susceptibility modifies risk

- Familial occurrence and affected HLA-identical siblings support inherited susceptibility.
- Associations have been reported with certain HLA and complement genotypes.
- Genome-wide studies implicate MHC class II loci.
- Genetic susceptibility does not identify a single obligatory initiating antigen.

Mucosal exposures may influence abnormal IgA production

- Respiratory and gastrointestinal exposure to environmental agents may increase abnormal IgA synthesis.
- Viruses, bacteria, and dietary antigens have been implicated.
- The precise initiating antigen remains unknown in the source account.
- This context helps explain hematuria episodes temporally related to infection.

Secondary IgA deposition: Relevant systemic settings

Clinical context	Source-supported rationale
Chronic liver disease	Defective hepatobiliary clearance of IgA complexes
Celiac disease	Increased frequency with altered intestinal mucosal barrier
Other intestinal disorders	Secondary IgA nephropathy may occur
Staphylococcal infection	Infection-associated IgA deposition may occur

Primary and secondary IgA disease

Primary renal disease

- Often an isolated glomerular process
- Recurrent hematuria is frequent
- Mesangial IgA remains the defining tissue feature

Secondary IgA disease

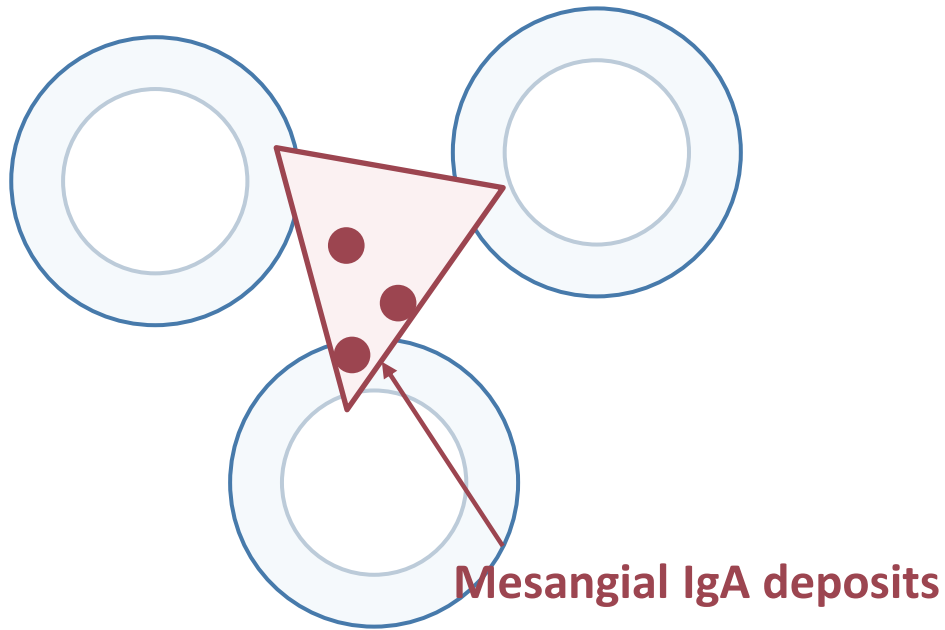
- Associated with liver/intestinal disorders or infection
- Systemic context can influence interpretation
- IgA deposits alone do not establish primary disease

Light microscopy: Wide morphologic spectrum

Observed pattern	Potential interpretation
Normal-appearing glomeruli	LM may fail to reveal the immune-deposition process
Mesangial expansion	More cells, matrix, deposits, or combinations
Endocapillary proliferation	Inflammatory/proliferative activity
Focal or segmental proliferation	Involves only some glomeruli or tuft segments
Crescentic lesion	Rare severe proliferative injury

Mesangial expansion: More than one substrate

Capillary loops



Mesangial widening arises from

- Increased mesangial-cell number
- Extracellular matrix accumulation
- Immune deposits or mixed causes

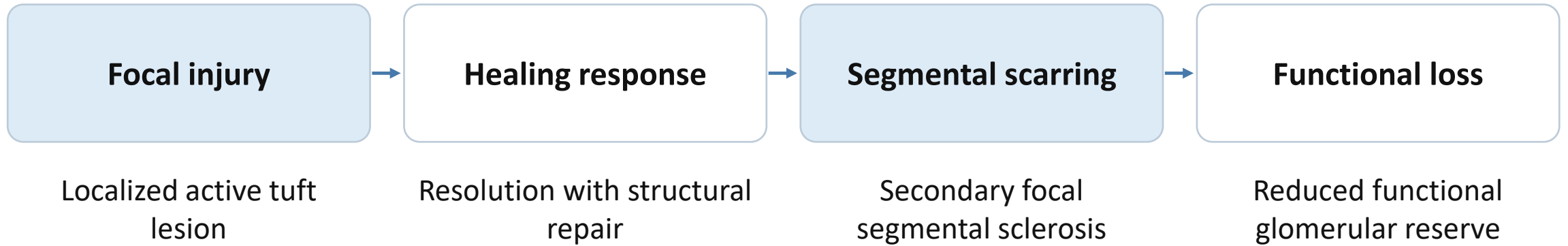
Endocapillary and segmental activity

- Endocapillary proliferation may accompany mesangial changes.
- Focal proliferative lesions involve only some glomeruli.
- Segmental disease may affect part of the tuft rather than its entirety.
- The number of intracapillary leukocytes varies from case to case.

Crescents identify an unusually severe phenotype

- Crescentic glomerulonephritis is uncommon in ordinary IgA nephropathy.
- Its appearance correlates with a rapidly progressive nephritic presentation in some patients.
- Severity cannot be inferred from mesangial IgA staining alone.
- Interpret crescents together with the entire injury pattern and clinical trajectory.

Proliferative injury can leave a sclerotic residue



Current biopsy activity and chronic scarring provide different kinds of information.

Immunofluorescence establishes the diagnosis

- Mesangial IgA deposition is characteristic and is required for the diagnosis.
- C3 and properdin are frequently detected together with IgA.
- IgG or IgM can be present in lower abundance.
- Early complement components are usually absent.

IgA immunofluorescence: Interpret the full panel

Target	Typical biopsy observation	Inference
IgA	Prominent mesangial staining	Defining immune deposit
C3 / properdin	Often present	Alternative-pathway involvement
IgG / IgM	May be present in lesser amounts	Mixed immune-component deposition
C1q / C4	Usually absent	Early complement pathway not typically prominent

Electron microscopy confirms deposit localization

- Electron-dense immune deposits are predominantly mesangial.
- Capillary-wall deposits can occur but are usually sparse.
- Electron microscopy complements rather than replaces IF identification of IgA.
- LM and EM heterogeneity should be reconciled with the immune staining pattern.

Three microscopy modalities answer different questions

Light microscopy

- Normal → proliferative
- Mesangial / endocapillary
- Rare crescents

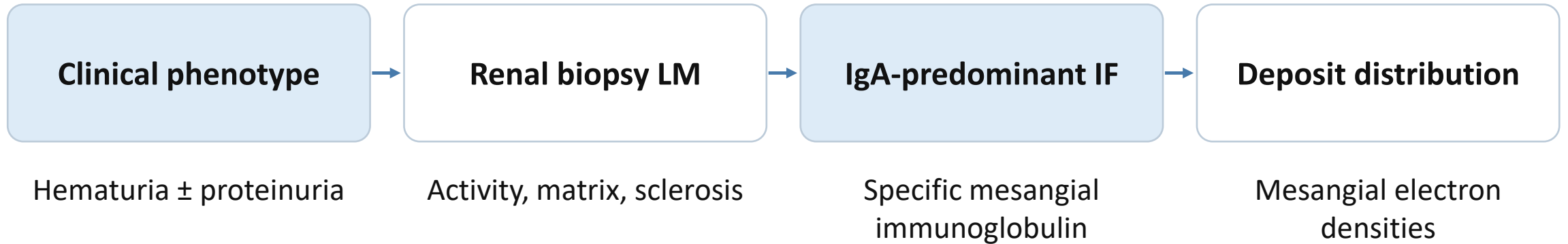
Immunofluorescence

- Mesangial IgA
- Often C3, properdin
- Early complement usually absent

Electron microscopy

- Electron-dense deposits
- Predominantly mesangial
- Sparse capillary deposits

IgA diagnostic synthesis

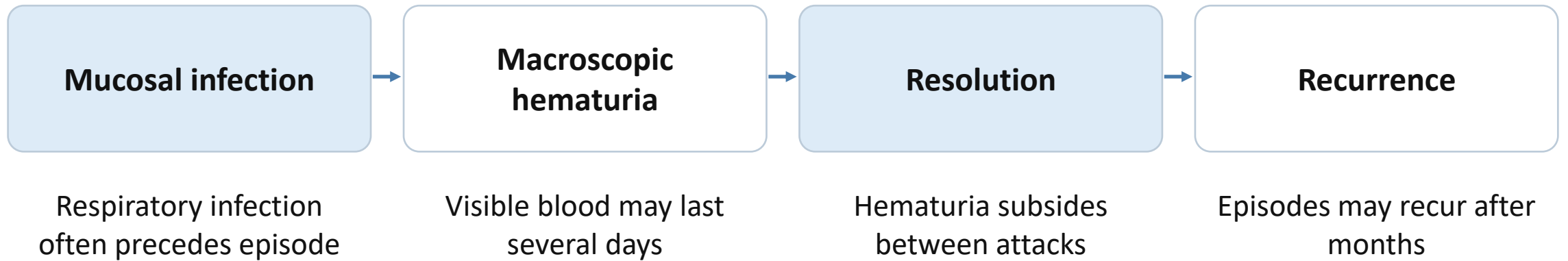


Biopsy findings are interpreted with secondary causes and clinical context in mind.

Clinical expression ranges from silent to severe

- Some patients have microscopic hematuria detected incidentally.
- Others experience episodic gross hematuria after mucosal infection.
- Proteinuria ranges from mild to nephrotic-range in severe podocyte injury.
- A small minority present with acute nephritic or rapidly progressive disease.

Recurrent hematuria can follow a relapsing course



Microscopic hematuria is a frequent presentation

- Microscopic hematuria alone in about 30%–40% of patients.
- Proteinuria may be present or absent in this group.
- Detection depends on urinalysis rather than visible change in urine.
- An initially mild presentation does not eliminate the need to assess longitudinal renal risk.

Nephritic and nephrotic expressions are distinct

- Acute nephritic syndrome in approximately 5%–10% of cases.
- Rapidly progressive glomerulonephritis may occur in a subgroup with severe injury.
- The nephrotic syndrome is less common and may reflect extensive podocyte damage.
- The clinical syndrome and biopsy lesion should be described separately.

Age and episodic symptoms provide diagnostic context

- IgA nephropathy can affect any age group.
- Older children and young adults are most commonly affected.
- Gross hematuria may follow respiratory, gastrointestinal, or urinary tract infection.
- Visible hematuria usually resolves over several days and may recur months later.

Why prognosis is heterogeneous

Relatively preserved course

- Many patients maintain stable renal function for decades
- Hematuria may recur without immediate failure
- Clinical follow-up distinguishes the trajectory

Progressive course

- Sustained proteinuria and hypertension increase concern
- Glomerulosclerosis indicates established structural injury
- Progression may be prolonged rather than abrupt

Long-term renal outcomes cohort

- Chronic renal failure in 15%–40% of patients over about 20 years.
- This is a historical textbook estimate rather than a personalized prediction.
- Many patients maintain normal renal function for decades.
- The observed course reflects marked heterogeneity in activity and chronic injury.

Markers of greater progression risk

Feature	Clinicopathologic rationale
Older age at onset	Textbook-associated adverse course
Heavy proteinuria	More severe glomerular barrier injury
Hypertension	Concomitant clinical injury burden
More glomerulosclerosis	Established irreversible structural damage

IgA deposits can recur after renal transplantation

- IgA deposition in transplanted kidneys is frequent in the source account.
- A recurrent deposit is not automatically equivalent to clinically progressive dysfunction.
- That approximately 15% of patients with recurrent IgA deposits follow a similarly progressive course.
- Histologic recurrence and clinically important recurrence should be distinguished.

IgA nephropathy versus systemic IgA vasculitis

Feature	IgA nephropathy	IgA vasculitis (Henoch–Schönlein)
Distribution	Typically isolated renal disease	Skin, gastrointestinal tract, joints, kidneys
Renal deposits	Mesangial IgA	Often analogous mesangial IgA
Clinical clue	Episodic hematuria	Purpura with systemic manifestations
Mechanistic overlap	IgA-driven immune processes	Overlapping IgA-driven immune processes

Apply the IgA pathway to a clinical vignette

Fictional teaching vignette

- An older child has brief recurrent gross hematuria after respiratory illness.
- Urinalysis also detects mild proteinuria.
- Biopsy IF is dominated by mesangial IgA.

Questions

- Which compartment is involved?
- Which antibody class is essential to the diagnosis?
- Why may LM show varied degrees of proliferation?

Interpret the IgA vignette

Fictional teaching vignette

- Recurrent post-infectious hematuria is compatible with the clinical pattern.
- Mesangial IgA provides the decisive immunopathologic clue.
- Activity and scar burden must still be documented.

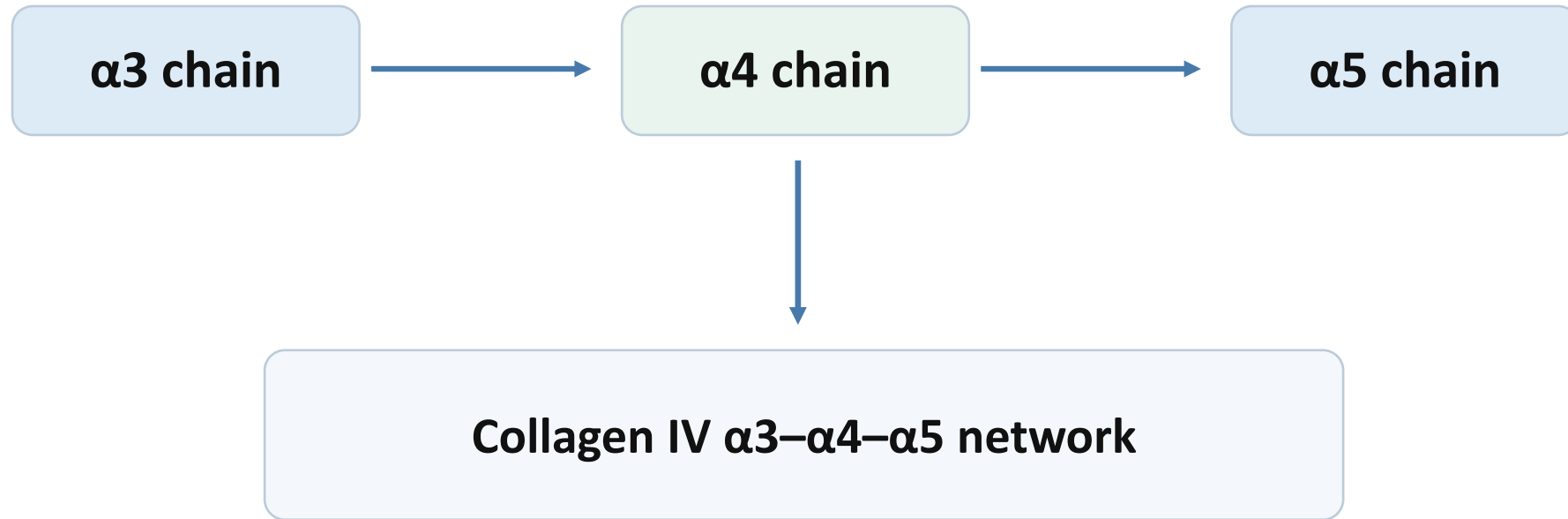
Interpretation

- Mesangium is the main deposit compartment.
- IgA immunofluorescence is defining.
- Mesangial activation, immune deposits, matrix and leukocytes vary.

Alport spectrum: A structural glomerular disorder

- Alport disorders are familial nephropathies associated with basement-membrane component mutations.
- Classic severe Alport syndrome reflects defective type IV collagen assembly.
- Hematuria is the common initial renal manifestation.
- The full phenotype may combine progressive kidney injury, sensorineural hearing loss, and ocular changes.

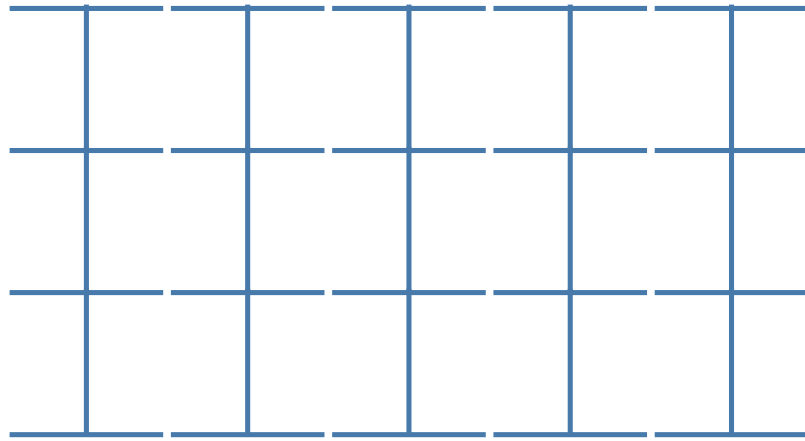
The glomerular collagen IV network requires $\alpha 3$, $\alpha 4$ and $\alpha 5$



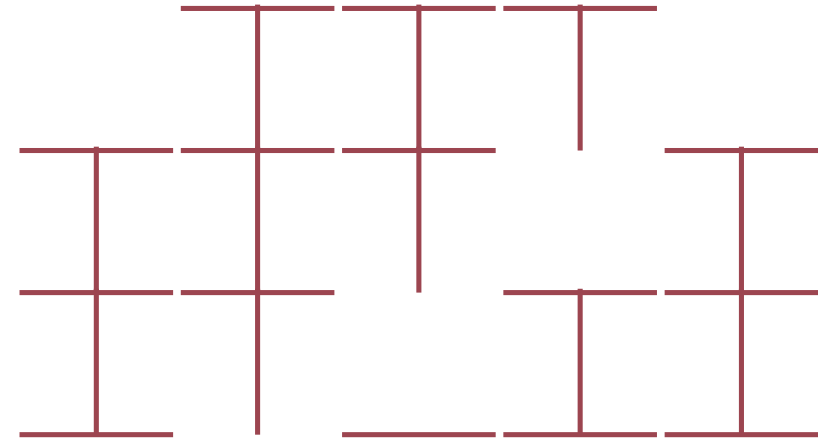
Variant affecting one essential chain → defective network assembly

A defective chain compromises network assembly

Intact collagen IV network



Disordered network



Collagen-IV mutations produce multisystem effects

- The $\alpha3$ – $\alpha4$ – $\alpha5$ collagen IV network is central to glomerular basement-membrane function.
- Collagen IV also supports specialized basement membranes in the inner ear and eye.
- Missense, splice-site, insertion and deletion variants are described.
- The inheritance pattern depends on which collagen-IV gene is affected.

Inheritance patterns in the Alport spectrum

Mode	Typical implications
X-linked	Majority of classic cases in Robbins; often severe disease in affected males
Autosomal recessive	Both sexes can manifest the full syndrome
Autosomal dominant / heterozygous	Often milder hematuria spectrum; progression remains possible

X-linked Alport disease is frequently more severe in males

- The textbook attributes approximately 85% of cases to X-linked inheritance.
- Affected males often manifest the complete renal and extrarenal syndrome.
- Heterozygous females commonly present with hematuria, but require surveillance.
- Phenotype varies with the pathogenic variant; Not every carrier remains clinically mild.

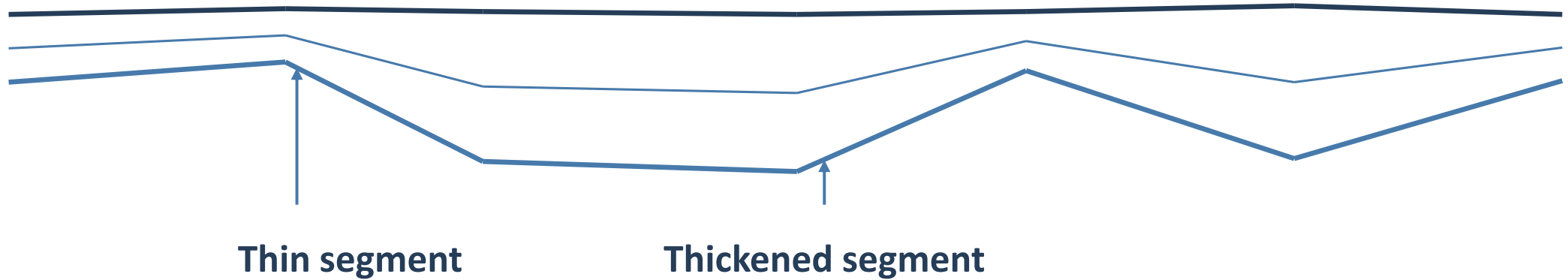
Penetrance and renal risk require contextual interpretation

- Complete penetrance for classic X-linked Alport syndrome.
- It reports that about 90% of affected males develop end-stage renal disease by age 40.
- These figures describe the textbook's reported cohorts and are not individualized predictions.
- Less severe phenotypes occur within the broader collagen-IV disease spectrum.

Early light microscopy may be deceptively normal

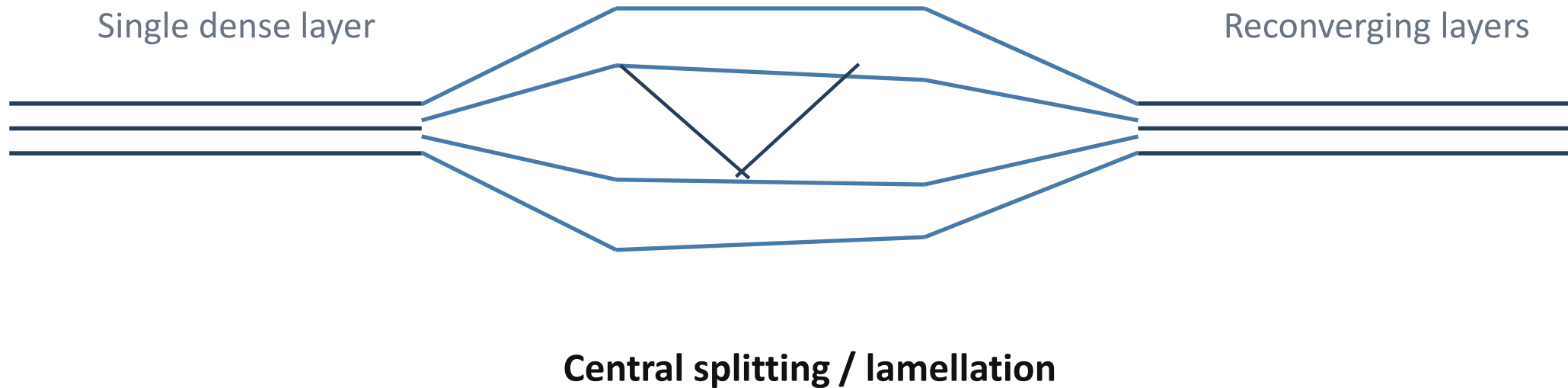
- Glomeruli may appear normal by light microscopy early in Alport disease.
- Early urinary blood loss reflects a molecular structural defect rather than required immune deposits.
- Light microscopy becomes more abnormal as chronic scarring develops.
- An unremarkable LM sample does not exclude inherited collagen-IV disease.

Alternating GBM thinning and thickening



Irregular alternation of attenuated and expanded GBM regions

Lamina-densa splitting creates a basket-weave pattern



Layer separation produces the characteristic basket-weave description

Electron microscopy provides structural evidence

- Fully developed disease may show irregular GBM thickening alternating with attenuation.
- Splitting and lamellation of the lamina densa can create a basket-weave appearance.
- Similar basement-membrane alterations may occur in tubules.
- These features are most informative within the clinical and familial context.

Late Alport lesions evolve toward chronic scarring

- Focal segmental glomerulosclerosis can occur as disease progresses.
- Global glomerulosclerosis reflects more extensive permanent injury.
- Tubular atrophy, interstitial fibrosis and vascular sclerosis may accompany late disease.
- Underlying basement-membrane instability may increase podocyte vulnerability.

Collagen IV staining complements morphology

Tissue/target	Textbook observation	Interpretive role
Glomerular / tubular BM	Classic X-linked disease may lack $\alpha 3$, $\alpha 4$, $\alpha 5$ staining	Supports disturbed collagen-IV network
Skin biopsy	Loss of $\alpha 5$ staining may be seen	Ancillary evidence in classic X-linked disease
Electron microscopy	Thinning, thickening, lamellation	Structural evidence of glomerular BM disorder

The classic Alport phenotype spans three organ systems

Kidney

Hematuria → proteinuria →
declining function

Inner ear

Sensorineural hearing loss

Eye

Lens, cataract and corneal
abnormalities

One inherited basement-membrane network can affect multiple organs.

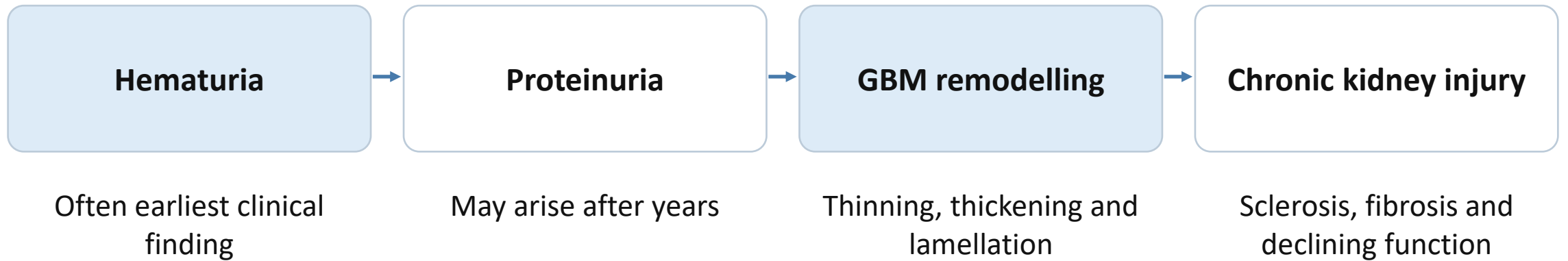
Sensorineural hearing loss may be clinically subtle

- Cochlear basement-membrane dysfunction produces sensorineural hearing deficits.
- Auditory involvement can be mild or initially overlooked.
- Sensitive auditory testing may be required.
- Hearing impairment provides an important extrarenal clue to renal hematuria.

Ocular lesions broaden the diagnostic phenotype

- Lens dislocation and posterior cataracts.
- Corneal dystrophy is another reported manifestation.
- Eye findings reflect the role of collagen IV in ocular basement membranes.
- Their coexistence with hematuria and hearing loss strengthens clinical suspicion.

Alport renal presentation can evolve over years



Conceptual progression; Timing and penetrance vary across variants

Typical ages and chronology in classic disease

- Urinary hematuria is often first detected between ages 5 and 20 years.
- Proteinuria may arise later in the disease course.
- Overt male renal failure between approximately ages 20 and 50 years.
- A later-onset, milder course is possible within the spectrum.

COL4A5 variant type can influence severity

- The source associates large deletions affecting COL4A5 with earlier end-stage kidney disease in X-linked cases.
- Type IV collagen assembly is impaired by different pathogenic variant classes.
- Genotype–phenotype correlations vary and must not replace phenotype assessment.
- Genetic findings support inheritance counseling and longitudinal follow-up.

Mild Alport variants and thin GBM findings

Domain	Source-supported features
Clinical	Familial hematuria; sometimes mild or moderate proteinuria
Ultrastructure	Diffuse or segmental GBM attenuation; focal lack of lamina densa
Genetic background	Often heterozygous type IV collagen-related variants
Long-term outcome	May remain stable or develop renal decline and FSGS

Basement-membrane thickness in the source text

Condition	Illustrative adult GBM width
Thin basement-membrane phenotype	Approximately 150–225 nm
Healthy adult reference in Robbins	Approximately 300–400 nm

Textbook ranges require careful EM processing and laboratory interpretation.

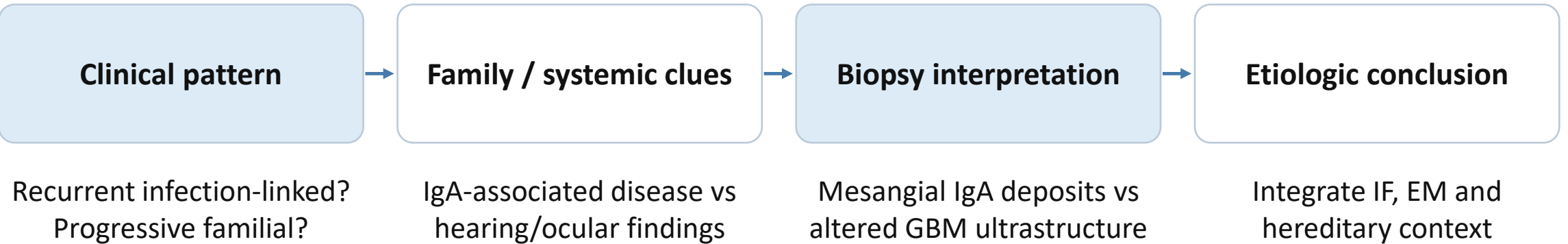
A disease spectrum requires family-based interpretation

- Milder heterozygous X-linked and autosomal variants may share clinical features with severe Alport syndrome.
- Some relatives with apparently isolated familial hematuria may have severe disease.
- Thin basement-membrane nephropathy overlaps genetically with collagen-IV disorders.
- Genetic counseling and sustained clinical follow-up are important across the spectrum.

IgA nephropathy versus Alport spectrum

Dimension	IgA nephropathy	Alport spectrum
Fundamental defect	Immune-complex deposition	Inherited collagen-IV network defect
Initial anatomic focus	Mesangium	GBM
IF	Mesangial IgA	Collagen-IV staining may be abnormal
EM	Mesangial electron-dense deposits	GBM thinning, thickening, lamellation
Extrarenal clues	Mucosal illness; secondary settings	Hearing loss; ocular anomalies; family history

Diagnostic reasoning for persistent hematuria



No single routine light-microscopic pattern distinguishes every patient.

Compare two hematuria presentations

Fictional teaching vignette

- Case A: Recurrent hematuria after respiratory illnesses; Mesangial IgA staining.
- Case B: Familial hematuria with hearing impairment; EM reveals lamellated GBM.

Interpretation

- Case A: IgA nephropathy is favored.
- Case B: Alport-spectrum disease is favored.
- Which test establishes each mechanism?

Synthesis: Link mechanism to diagnostic observation

Disease group	Causal lesion	Best differentiating clue
IgA nephropathy	Aberrant IgA1 → immune complexes → mesangial activation	Mesangial IgA by immunofluorescence
Alport spectrum	Type IV collagen defect → GBM network instability	GBM ultrastructure, collagen-IV studies and family/genetic context
Both	Variable glomerular barrier injury and hematuria	Clinical phenotype alone may overlap

Clinical reasoning check

- Which source-supported lesion explains mesangial IgA with recurrent gross hematuria?
- Why is isolated hematuria compatible with early Alport disease despite normal LM?
- Which biopsy modality directly demonstrates lamina-densa lamellation?
- Which Alport-associated extrarenal findings should be actively sought?
- Why must secondary contexts be considered before labeling IgA nephropathy primary?

Answers: Core discriminating principles

- IgA immune-complex deposition and mesangial activation.
- The primary collagen-IV structural defect can precede light-microscopic scarring.
- Electron microscopy identifies GBM thickness changes and lamellation.
- Sensorineural hearing abnormalities and characteristic ocular changes.
- Liver, intestinal, and infection-associated conditions may cause secondary IgA deposition.

Primary reading

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Renal chapter: glomerular diseases; IgA nephropathy and Alport spectrum disorders.
- Core diagnostic framework: clinical findings together with LM, IF, EM and genetic/family context.
- Schematic drawings in this lecture are conceptual, editable and not patient images.