

Autosomal Dominant Tubulointerstitial Kidney Disease

Genetic classification · tubular compartments · clinicopathologic interpretation

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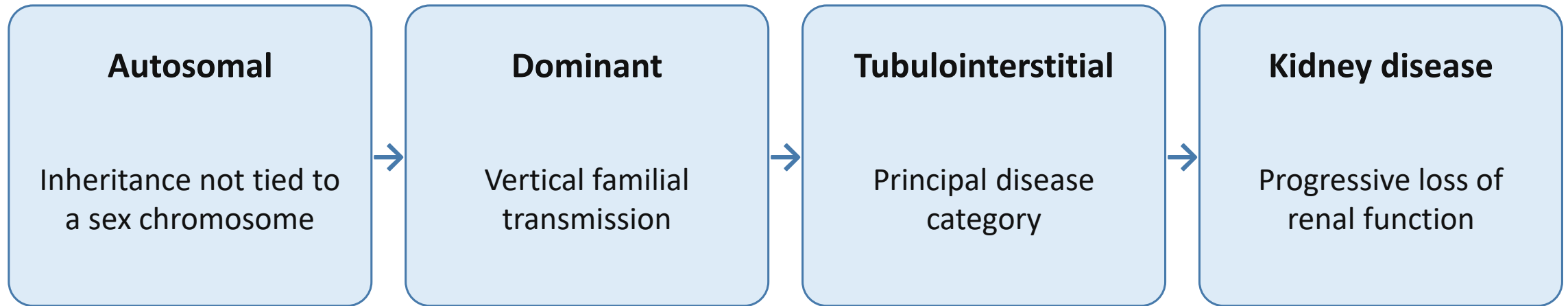
Learning objectives

- Explain the name change from medullary cystic kidney disease to ADTKD.
- Connect four implicated genes to their encoded proteins or functions.
- Interpret nonspecific renal findings and progressive adult-onset dysfunction.
- Recognize important limits of morphology, genetic detection, and mechanistic knowledge.

ADTKD: The defining description

- A hereditary renal disease transmitted in an autosomal dominant pattern.
- Grouped with tubulointerstitial disorders rather than defined by a single cyst pattern.
- Produces progressive renal failure during adult life.
- Clinical and pathologic abnormalities are nonspecific.

What each word in ADTKD contributes



This descriptive name is more durable than an imaging-only label.

Tubules and interstitium act together

- Robbins groups tubular and interstitial damage because they commonly coexist.
- Tubular epithelium performs transport; Adjacent interstitium supports the renal microenvironment.
- Disease involving one compartment can produce injury in the other.
- The general anatomic category does not specify a unique microscopic ADTKD lesion.

Primary compartment $\neq$ exclusive compartment

Early/primary emphasis

- A disease can be classified by the compartment in which it starts.
- Tubular dysfunction may predominate before advanced structural damage.

With chronic progression

- The interstitium, glomeruli, and vasculature may become secondarily affected.
- Late-stage kidney changes can obscure the initiating lesion.

The older name: “medullary cystic kidney disease”

- Earlier terminology placed cyst location and cyst formation at the center of the label.
- Robbins explicitly replaces this historical name with ADTKD.
- The new term foregrounds inherited tubulointerstitial disease.
- A historical label in an old record should not be treated as a distinct current diagnosis.

Why “cystic” is an unreliable gatekeeper

What the textbook establishes

- Cysts have variable presence in ADTKD.
- Some affected kidneys therefore need not show cysts.

What the reader must avoid

- Do not rule out ADTKD solely because no cyst is mentioned.
- Do not use cyst presence as a specific molecular marker.

Why “medullary” is an unreliable locator

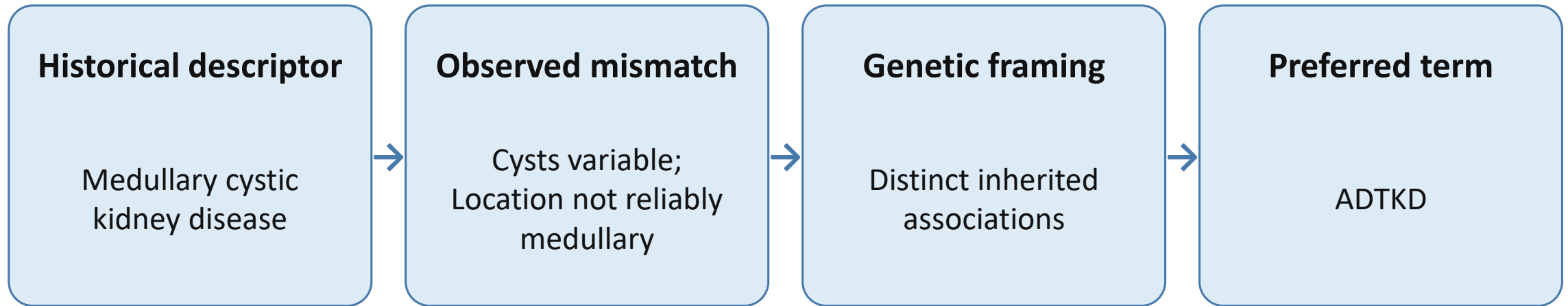
Observed naming problem

- When cysts are present, they are often not in the medulla.
- The historical location-specific label can mislead.

Diagnostic consequence

- Avoid inferring an obligatory medullary distribution.
- Separate lesion location from the underlying inherited category.

A nomenclature correction, not a new pathway



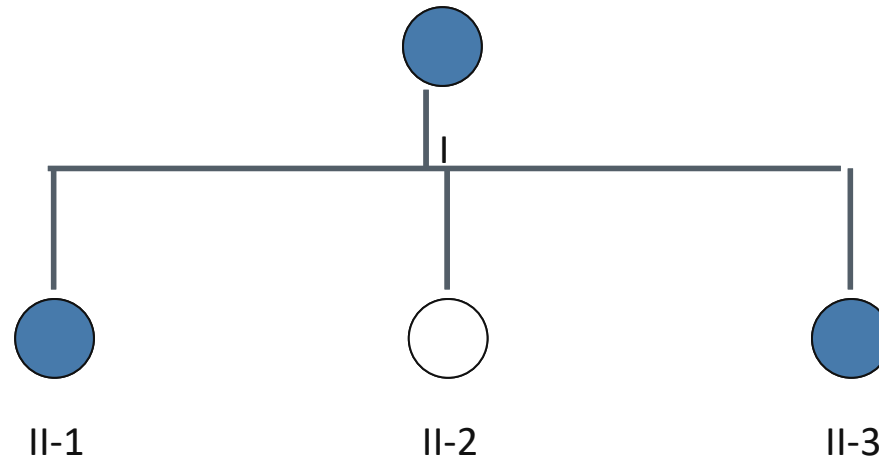
The term has changed because the former morphology-based name was insufficient.

Inherited renal disease: What is actually known

- Transmission is described as autosomal dominant.
- Multiple genes can be associated with a similar broad clinical category.
- Adult renal failure can emerge despite a familial pattern.
- Robbins does not provide gene-specific penetrance or progression rates in this section.

Autosomal dominant inheritance: Concept

An illustrative autosomal dominant family pattern



Vertical clustering can support dominant inheritance; The diagram alone does not establish a molecular diagnosis.

How to read a family history

Findings that increase suspicion

- Kidney disease recurring over generations.
- Adult relatives with progressive renal functional decline.

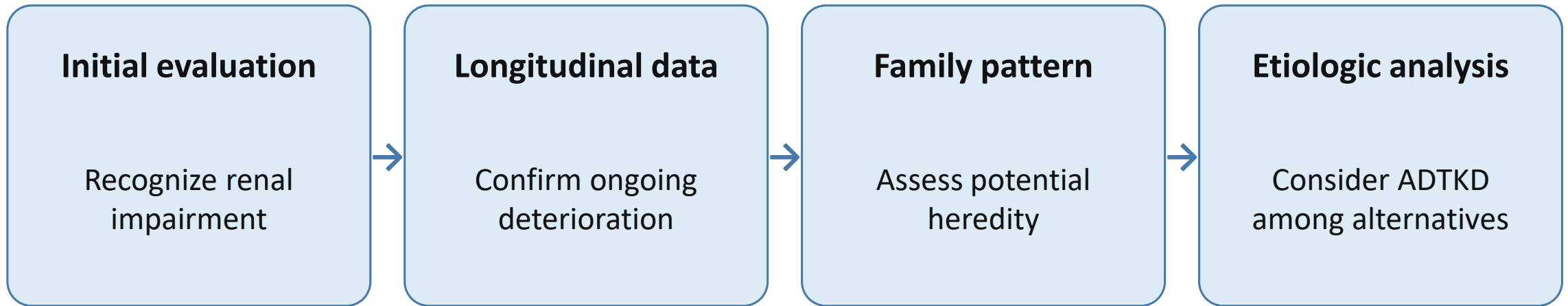
Findings that do not prove the cause

- Unspecified “kidney disease” in a relative.
- A dominant-looking pedigree without an established pathogenic variant.

Adult renal failure is the longitudinal signal

- Progressive renal failure in adult life.
- “Progressive” implies a time dimension, not an isolated abnormal result.
- End-stage or rapidly declining function at a single visit does not establish the original etiology.
- Do not infer age at onset, median ESKD age, or a rate of decline from this excerpt.

Interpreting progressive dysfunction



A clinical reasoning sequence—not a validated diagnostic rule or test threshold.

Nonspecific clinical findings

Positive textbook statement

- ADTKD produces nonspecific clinical findings.
- Progressive renal failure is emphasized.

Implication for interpretation

- No unique symptom is established in this excerpt.
- Symptoms alone cannot select a particular ADTKD gene.

Nonspecific pathologic findings

Positive textbook statement

- ADTKD produces nonspecific pathologic findings.
- The passage does not provide a pathognomonic microscopic lesion.

Implication for interpretation

- Histology should not be overinterpreted as subtype-specific.
- A pathology report requires clinical and genetic context.

What the ADTKD paragraph does not establish

- No diagnostic sensitivity or specificity for renal biopsy or imaging.
- No mandatory pattern of cysts, glomerular changes, or basement-membrane abnormalities.
- No gene-specific clinical timelines or treatment recommendations.
- No resolved common pathogenic mechanism.

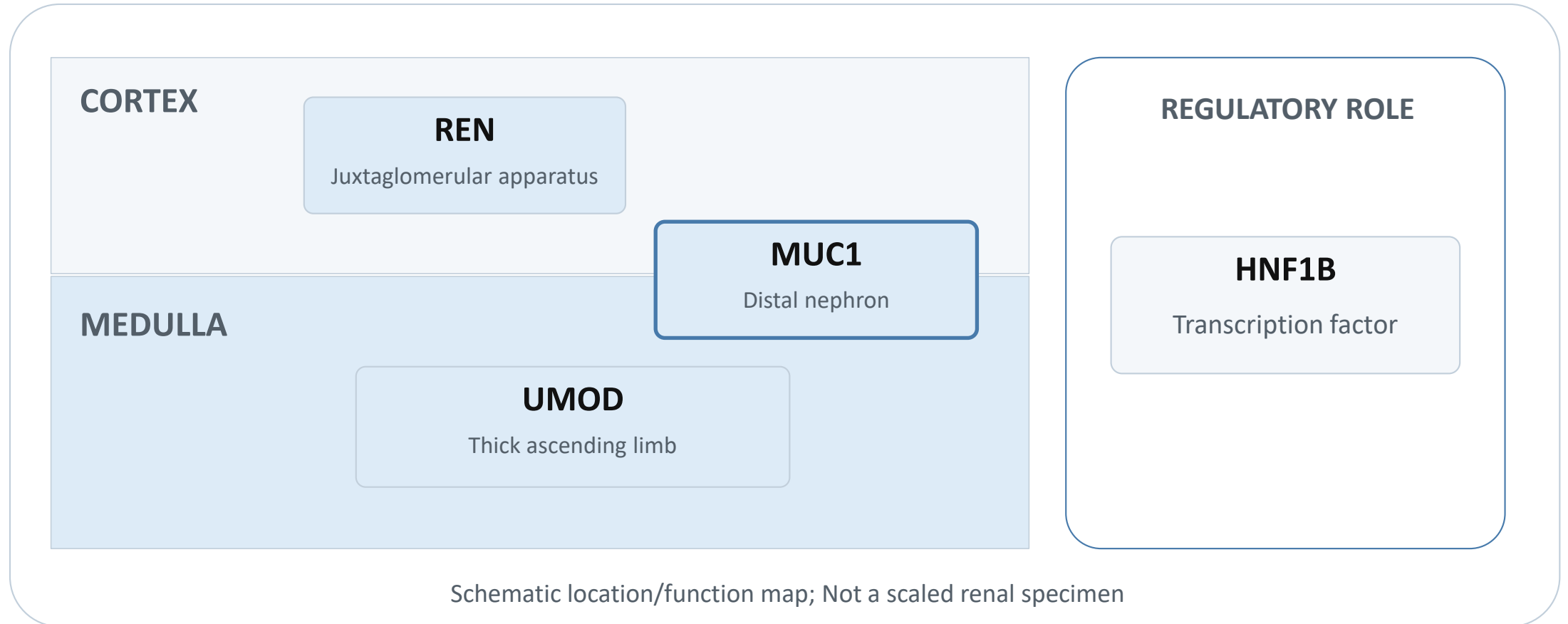
Genes named by Robbins

Gene	Encoded product / role	Stated renal localization
MUC1	Mucin-1	Distal nephrons
UMOD	Uromodulin	Thick ascending limb
REN	Preprorenin	Juxtaglomerular apparatus
HNF1B	HNF1 β transcription factor	Controls multiple genes, including UMOD

MUC1: Molecular identity

- The MUC1 gene encodes mucin-1.
- Mucin-1 expression in distal nephron segments.
- This identifies a protein and an anatomic context.
- The passage does not establish an exact MUC1 injury pathway.

MUC1: Locate the distal-nephron clue



MUC1: Evidence versus extrapolation

Supported association

- MUC1 mutations are associated with ADTKD.
- Mucin-1 expression is described in distal nephrons.

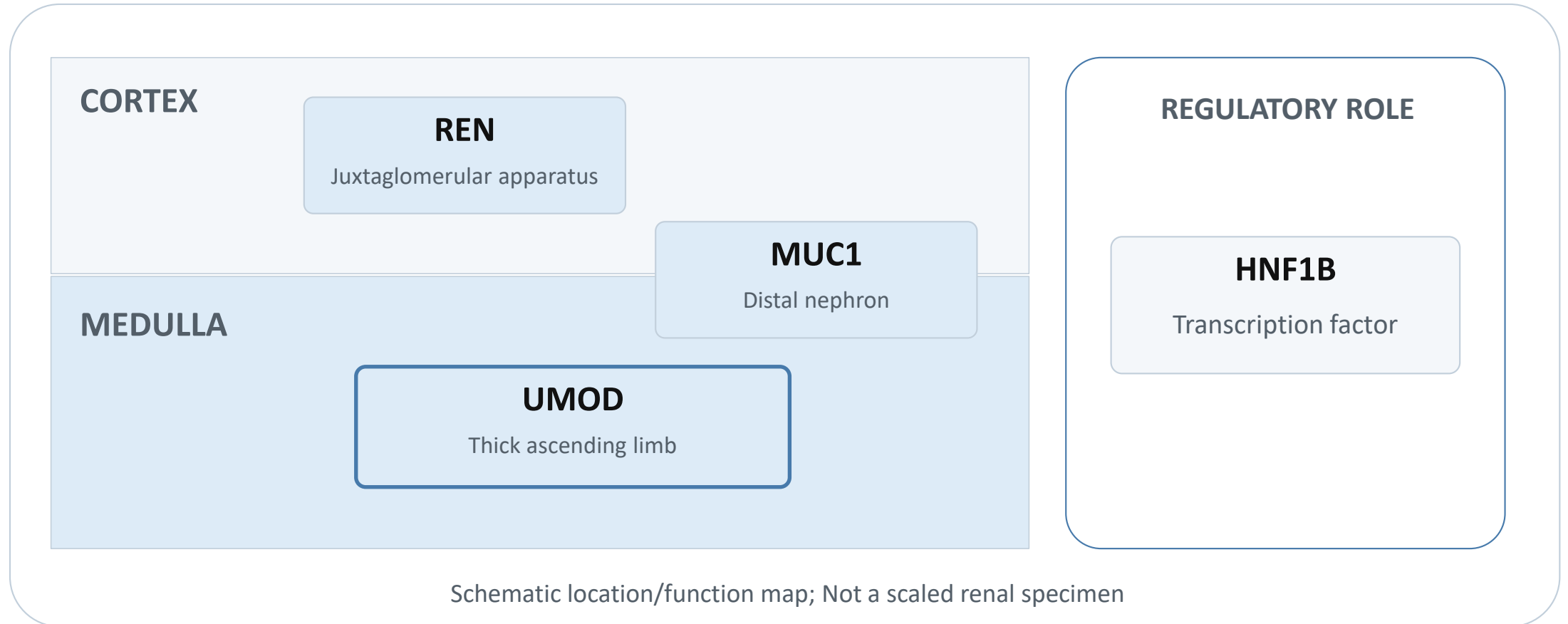
Unsupported from this section

- A specific cellular toxicity sequence.
- A unique biopsy stain pattern or age-of-onset prediction.

UMOD: Molecular identity

- The UMOD gene encodes uromodulin.
- Uromodulin is expressed in the thick ascending limb of the loop of Henle.
- The thick ascending limb is therefore the anatomical expression clue.
- Gene association does not itself describe every pathologic mechanism.

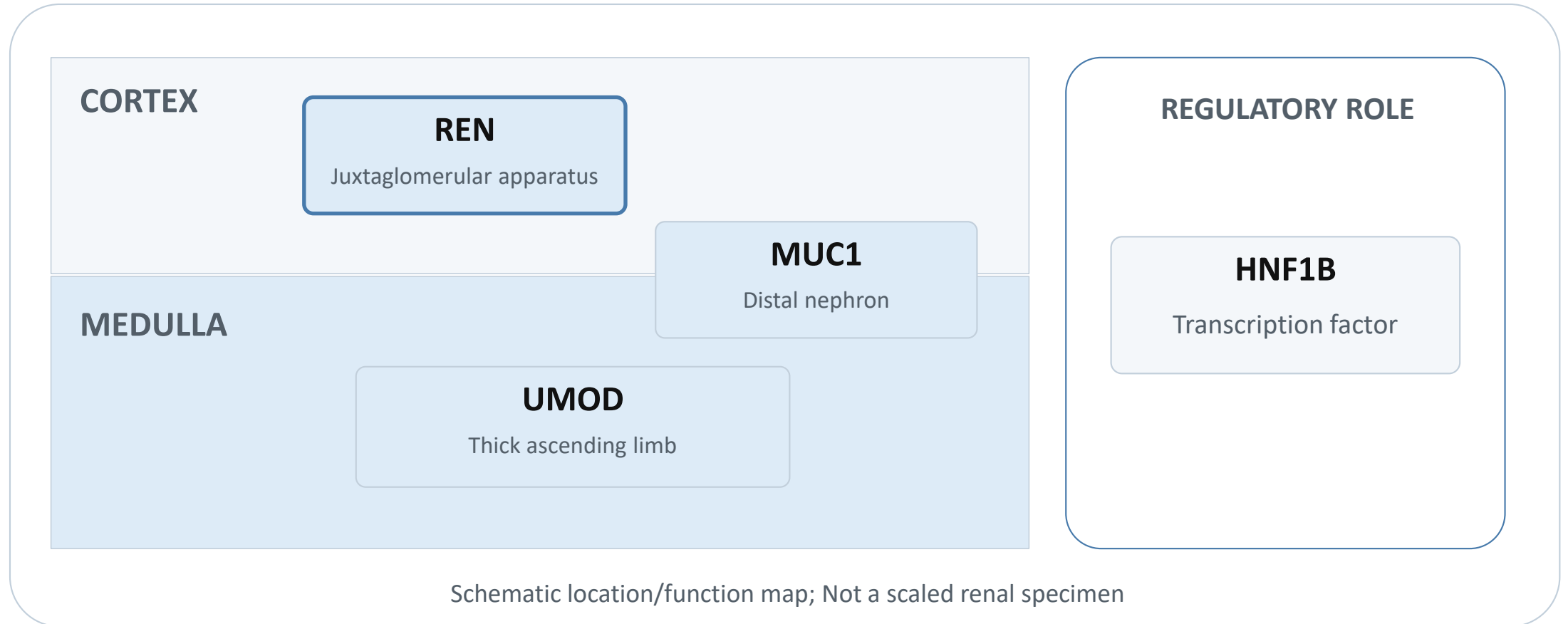
UMOD: Thick ascending limb highlighted



REN: Molecular identity

- The REN gene encodes preprorenin.
- Robbins localizes expression to the juxtaglomerular apparatus.
- The locus and expressed protein differ from the MUC1 and UMOD examples.
- The excerpt does not specify the manner by which REN variants damage the kidney.

REN: Juxtaglomerular expression



REN: Do not confuse physiologic role with proven disease mechanism

Established in the excerpt

- REN → preprorenin.
- Expression: Juxtaglomerular apparatus.

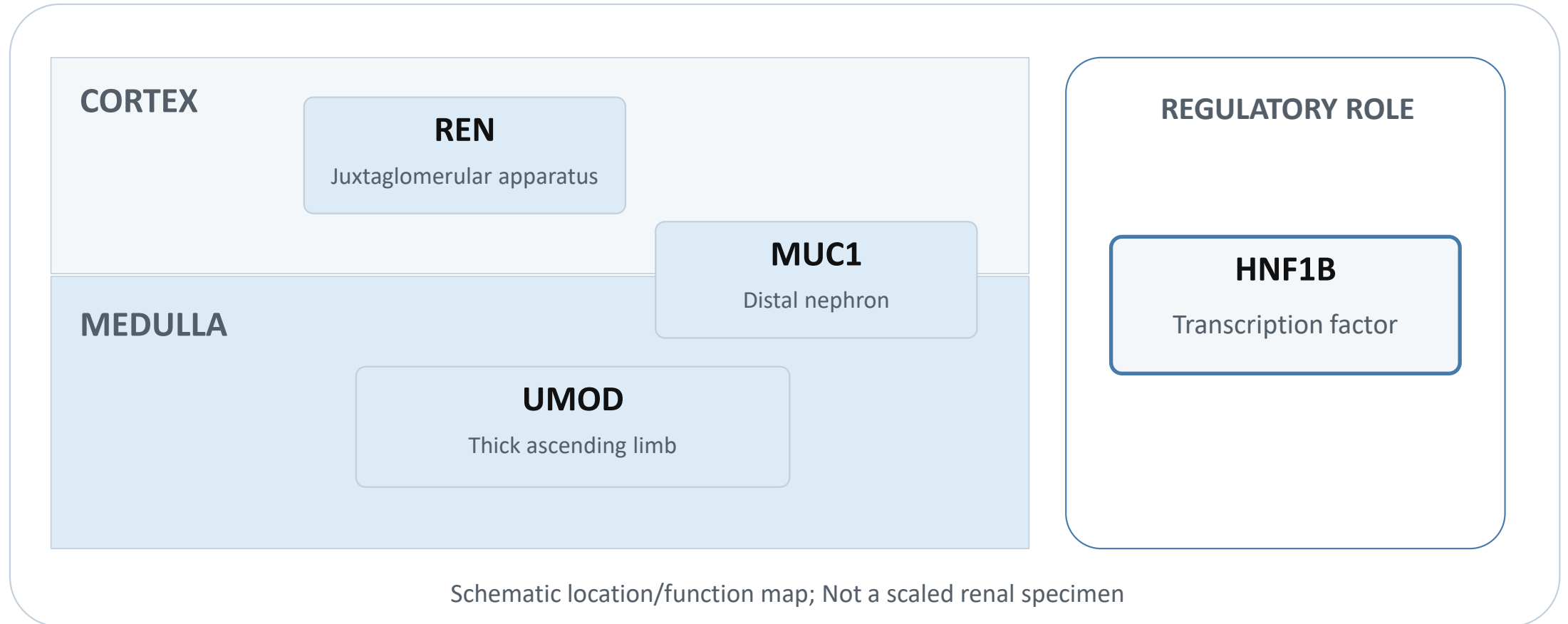
Not established here

- A particular renin concentration profile.
- A universal clinical blood-pressure pattern or therapy.

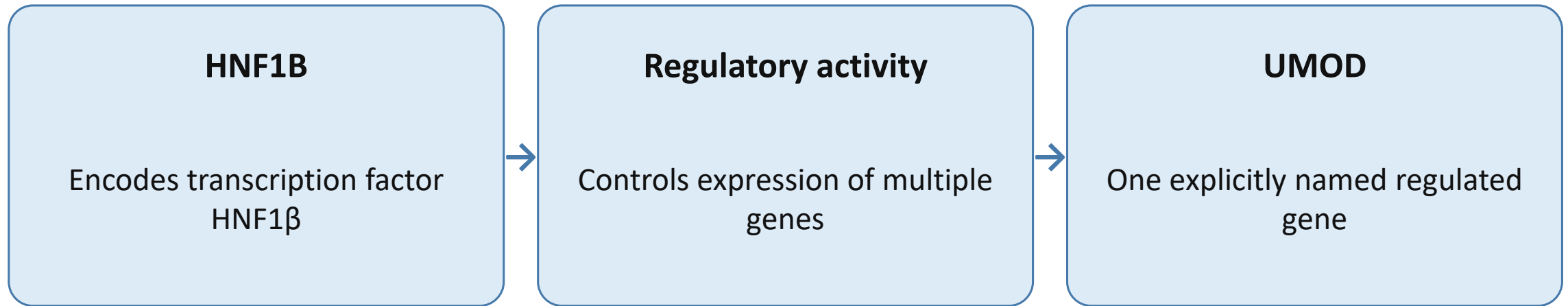
HNF1B: Molecular identity

- The HNF1B gene encodes hepatocyte nuclear factor 1 β .
- The protein is a transcription factor.
- It regulates multiple genes, including UMOD.
- A transcriptional regulator is not simply another nephron-segment protein.

HNF1B: A regulatory level, not a duct label



HNF1B–UMOD: Documented regulatory relationship



This is a gene-regulatory link, not proof of a complete injury cascade.

Direct expression versus transcriptional control

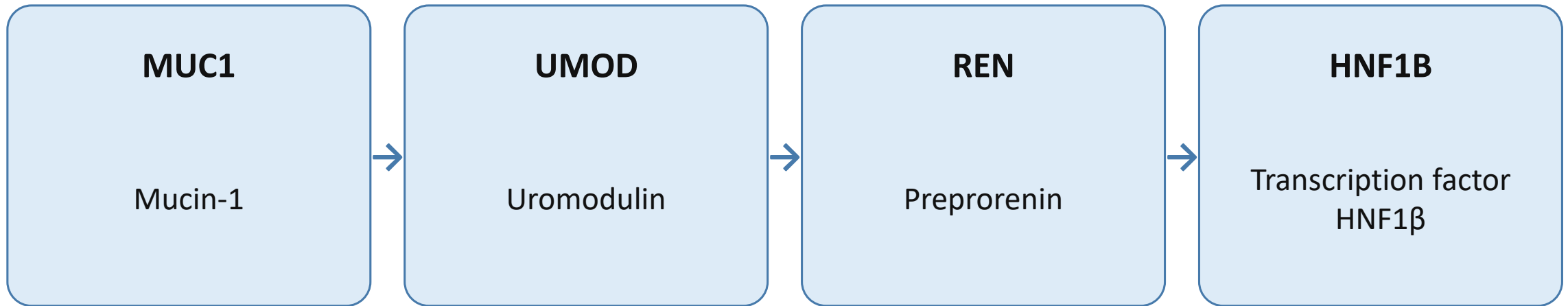
Location-first genes

- MUC1: Distal nephron.
- UMOD: Thick ascending limb.
- REN: Juxtaglomerular apparatus.

Regulatory factor

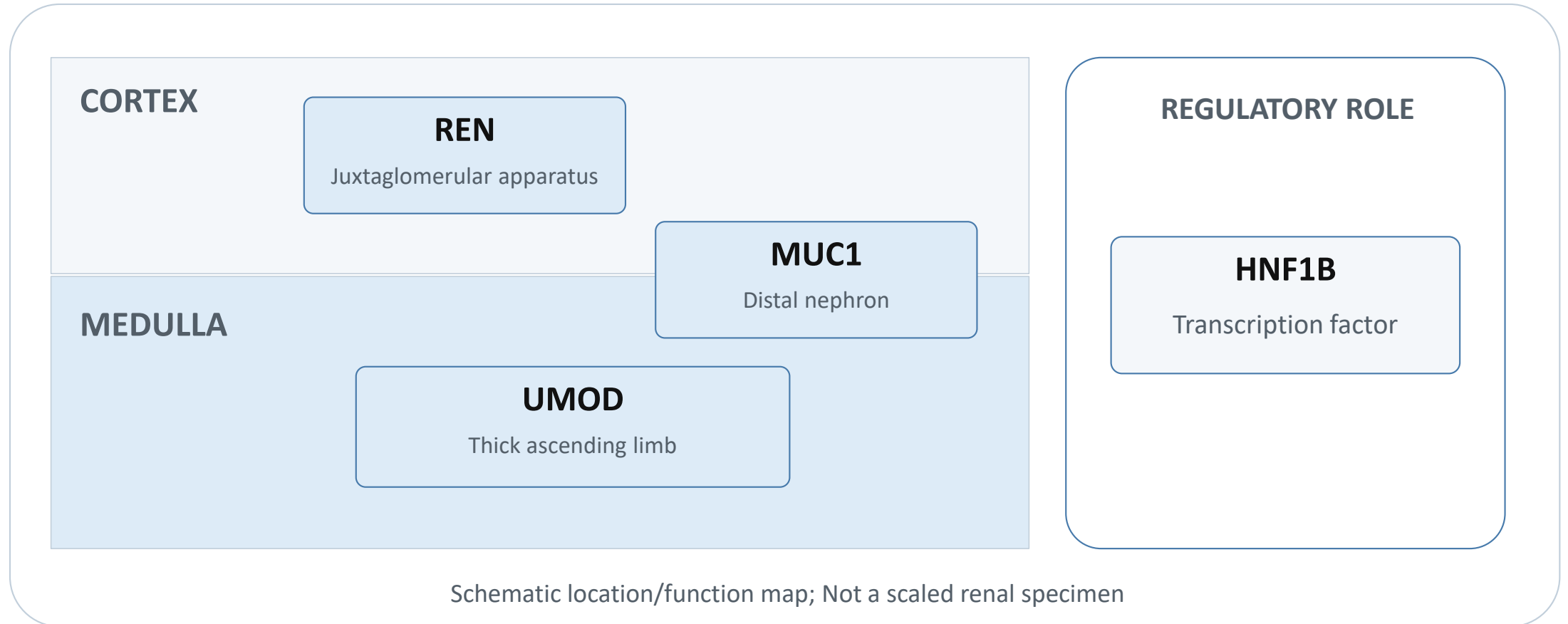
- HNF1B: Transcription factor.
- Its stated role spans multiple downstream genes.

Four loci, one broad disease category



The common clinical label does not imply identical gene products or a proven shared pathway.

Anatomic expression: Three locations + one regulator



Molecular clues: Do not interchange

Question	Answer from Robbins
Which product belongs to MUC1?	Mucin-1
Which gene encodes uromodulin?	UMOD
Where is preprorenin expressed?	Juxtaglomerular apparatus
Which factor regulates UMOD?	HNF1B

Genetic heterogeneity is integral to ADTKD

- ADTKD with four named genes.
- Different molecular starting points occur under a common diagnostic category.
- The affected protein or regulatory role can differ between families.
- A phenotype-based label need not identify the causal locus.

“Almost half” lack a detectable mutation

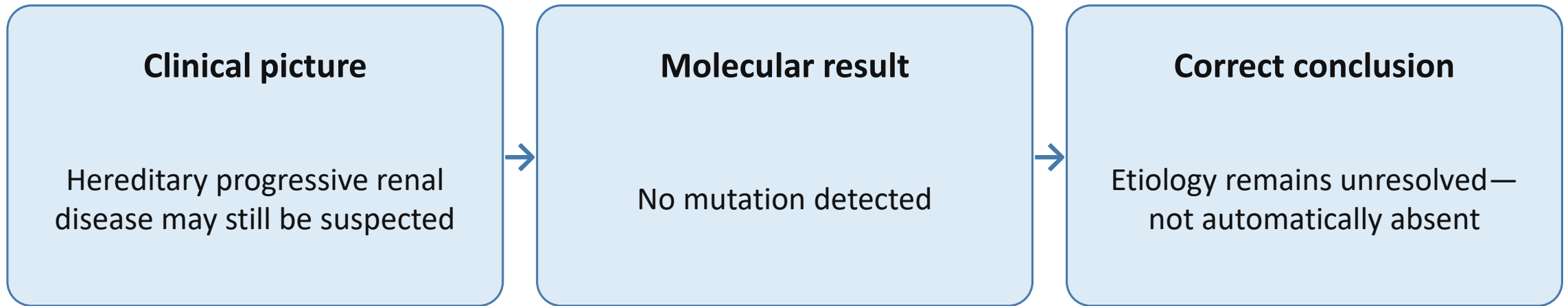
Exact source claim

- Almost half of ADTKDs do not have a detectable mutation.
- The passage does not state a test platform or cohort.

Interpretation guardrails

- Avoid converting “almost half” to an exact population estimate.
- Do not claim that a negative result disproves inherited disease.

A negative molecular result is not a clinical exclusion



No diagnostic algorithm or assay-performance estimate is asserted.

Known association versus unknown pathogenesis

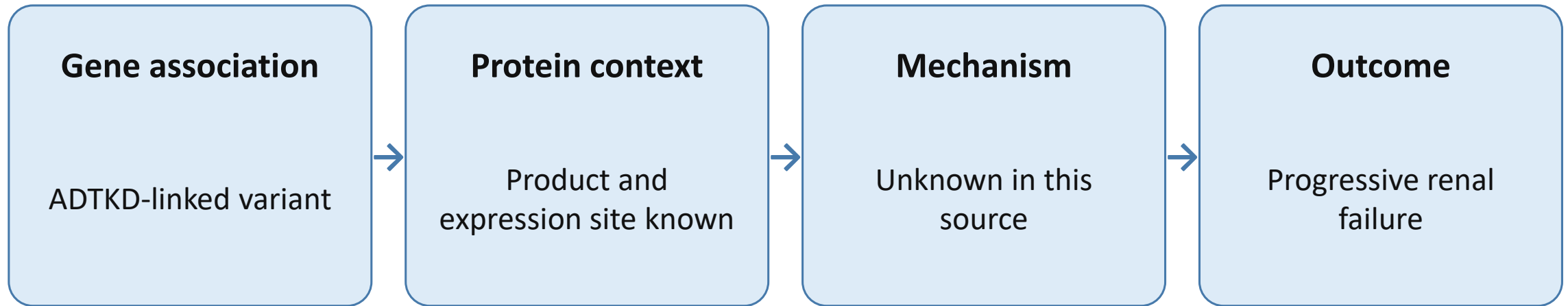
What is identified

- Genes and encoded products.
- Anatomic expression or transcriptional role.
- Dominant inheritance and progressive adult renal failure.

What remains unresolved

- The pathogenic mechanisms are described as unknown.
- A unified molecular-to-histologic causal sequence is not provided.

Do not fill the mechanistic gap with arrows



Conceptual chain with a deliberate knowledge gap; Not a verified pathway.

How strong is each level of evidence?

- Association: A gene is listed among those implicated in ADTKD.
- Localization: The corresponding protein is expressed in a named renal compartment.
- Regulation: HNF1B controls multiple genes including UMOD.
- Mechanism: The ADTKD paragraph explicitly states that this remains unknown.

A nonspecific biopsy can still be clinically important

It may establish

- Presence and extent of renal tissue damage.
- A chronic tubulointerstitial pattern, if actually observed.

It cannot establish from this source alone

- A particular ADTKD gene.
- A pathognomonic ADTKD histology pattern.

Tubular dysfunction: General parent-chapter context

- Tubulointerstitial disorders can impair urinary concentrating ability.
- They may show polyuria, nocturia, salt wasting, or acid excretion defects.
- These are general features of the tubulointerstitial disease group.
- Robbins does not require any individual feature to diagnose ADTKD.

Distinguishing tubular from glomerular syndromes

General tubulointerstitial context

- Absence of classic nephritic/nephrotic syndromes is a group-level hallmark.
- Tubular functional defects may be subtle.

Limits of classification

- Advanced diseases of either origin may look similar.
- Neither absence of nephrotic syndrome nor nocturia proves ADTKD.

Case 1: Family history changes the frame

CLINICOPATHOLOGIC VIGNETTE

An adult has slowly progressive renal impairment. A parent and an older sibling also developed chronic kidney disease.

What clue justifies considering an inherited tubulointerstitial disorder?

The vertical family history strengthens suspicion; No single gene can yet be assigned.

Case 2: No cysts reported

CLINICOPATHOLOGIC VIGNETTE

An adult with progressive renal dysfunction has a family history compatible with dominant inheritance, but renal imaging does not describe cysts.

Does that observation exclude ADTKD?

No. Cysts as variably present; Absence cannot be an absolute exclusion.

Case 3: Biopsy lacks a signature

CLINICOPATHOLOGIC VIGNETTE

A renal biopsy shows chronic damage described by the pathologist as nonspecific. Several relatives have progressive kidney disease.

Is the negative histologic specificity decisive?

No. Nonspecific pathological findings are part of the textbook ADTKD description.

Case 4: Genetic result unresolved

CLINICOPATHOLOGIC VIGNETTE

A family with a clinically suggestive dominant pattern has a molecular evaluation that identifies no mutation.

Which conclusion is most defensible from the textbook?

Unresolved molecular cause. No detectable mutation in almost half of cases.

Case 5: Incidental cyst and unrelated renal decline

CLINICOPATHOLOGIC VIGNETTE

A patient has a single cyst described on imaging and progressive kidney dysfunction without a clear family history.

Can the cyst alone establish ADTKD?

No. Cyst detection is neither a necessary nor a sufficient disease-specific marker.

ADTKD versus nephronophthisis

Dimension	ADTKD	Nephronophthisis
Inheritance	Autosomal dominant	Familial forms usually autosomal recessive
Typical clinical era	Progressive renal failure in adult life	Usually childhood/adolescence
Cyst description	Variable; not always medullary	Often corticomedullary/medullary
Genetic category	MUC1, UMOD, REN, HNF1B listed	Nephrocystin / ciliopathy genes described

ADTKD versus medullary sponge kidney

ADTKD

- Hereditary, autosomal dominant renal disorder.
- Progressive adult renal failure is emphasized.
- Cysts may be absent or nonmedullary.

Medullary sponge kidney

- Cystic dilation of medullary collecting ducts.
- Usually discovered radiographically in adults.
- Renal function is usually normal.

ADTKD versus classic adult polycystic kidney disease

ADTKD

- No obligatory large cyst burden in the disease definition.
- Cysts can vary in presence and distribution.

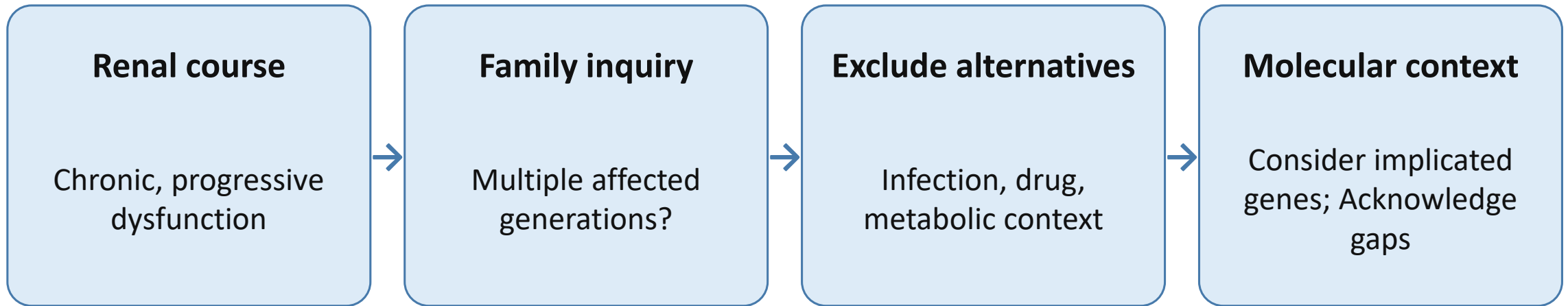
Autosomal dominant polycystic kidney disease

- Markedly enlarged kidneys with numerous cysts.
- A macrocystic gross pattern is a different diagnostic starting point.

Other chronic tubulointerstitial contexts

Competing context	Clue described by Robbins
Chronic pyelonephritis / reflux	History of infection/reflux; distorted calyces and scars
Drug-related interstitial disease	Drug exposure and immune or cumulative toxic injury
Urate nephropathy	Urate deposition and tubulointerstitial injury
Nephrocalcinosis	Calcium deposition with impaired concentrating ability
ADTKD	Dominant inheritance; listed genetic associations

Etiologic reasoning when the morphology is nonspecific



Interpretive framework only. Not a formally validated clinical diagnostic algorithm.

Case 6: A segment is not a diagnosis

CLINICOPATHOLOGIC VIGNETTE

An exam question states that a patient has an ADTKD-associated UMOD variant and asks which nephron segment expresses the product.

What is the source-supported answer?

The thick ascending limb of the loop of Henle.

Case 7: Distinguish product from regulator

CLINICOPATHOLOGIC VIGNETTE

A molecular report names HNF1B. A trainee labels it as the protein made by UMOD.

What is the correction?

HNF1B encodes a transcription factor; It regulates multiple genes, including UMOD.

Case 8: Renal failure timing

CLINICOPATHOLOGIC VIGNETTE

An adult develops progressive renal dysfunction. The family pedigree is consistent with dominant transmission; Biopsy changes are nonspecific.

Which combination is compatible with the textbook ADTKD profile?

Adult progressive renal failure + autosomal dominant pattern + nonspecific findings.

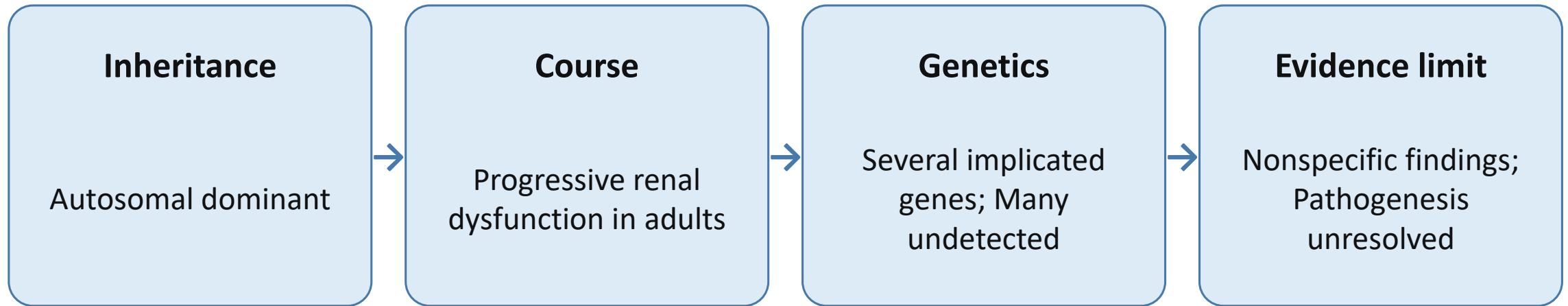
Four exam-level gene–product associations

If the prompt mentions...	Recall...
MUC1	Mucin-1; distal nephron
UMOD	Uromodulin; thick ascending limb
REN	Preprorenin; juxtaglomerular apparatus
HNF1B	Transcription factor; regulates UMOD among other genes

Diagnostic pitfalls that change the answer

- Using absence of cysts to rule out ADTKD.
- Treating an affected medulla as required by the old name.
- Claiming pathognomonic biopsy morphology despite the stated nonspecific findings.
- Interpreting an undetected mutation as proof against the diagnosis.
- Presenting a hypothetical molecular mechanism as established.

The defensible ADTKD mental model



Use a convergent interpretation—not a single imaging, histology, or test gate.

Five source-anchored conclusions

- ADTKD supersedes the historic medullary cystic kidney disease label.
- Cysts are variably present and frequently not medullary.
- MUC1, UMOD, REN, and HNF1B are implicated.
- Almost half lack a detectable mutation account.
- Adult progressive renal failure occurs with nonspecific findings; Mechanisms are unknown.

References and evidence boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).
- The ADTKD passage establishes nomenclature, genetic associations, inheritance, and adult progression.
- Renal disease comparisons draw on the surrounding tubulointerstitial and cystic-disease discussions.
- Illustrative pedigrees, vignettes and reasoning flows are educational schematics, not patient observations.
- The supplied source gives no ADTKD-specific microscopy or current testing guideline; neither is fabricated here.