

Epidermolysis Bullosa and Porphyria

Noninflammatory blistering disorders

Mechanical failure of skin adhesion and porphyrin-associated cutaneous injury

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

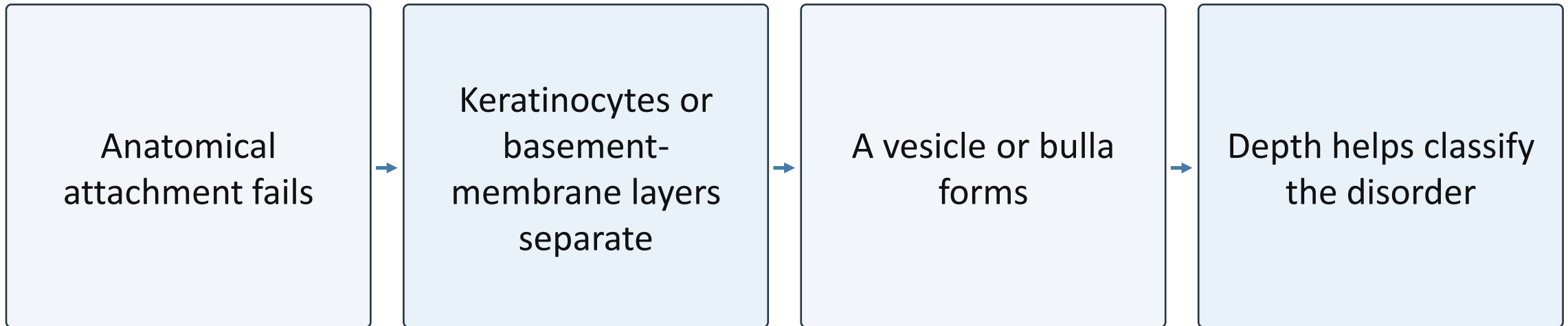
www.abusuraihsakhri.com

Learning objectives

- Localize a blister to the epidermis, lamina lucida, or sublamina-densa compartment.
- Explain how KRT5/KRT14, laminin, BPAG2, and COL7A1 defects produce distinct EB forms.
- Recognize the cutaneous and microscopic findings described for porphyria.
- Distinguish inherited and metabolic bullous disease from autoimmune blistering disorders.

Why the blister plane matters

A blister is a structural lesion with a localizable level.



Localize first; Infer mechanism second.

Skin adhesion: Five relevant compartments

Upper epidermis

Basal keratinocytes

Lamina lucida

Lamina densa

Anchoring fibrils / dermis

- Basal keratinocytes contain intracellular keratin filaments.
- Hemidesmosomes attach basal cells to the underlying basement membrane.
- Lamina lucida, lamina densa, and anchoring fibrils transmit the attachment toward dermis.

Simplified anatomical schematic

Two routes to skin fragility

Mechanical route

- Inherited structural-protein defect
- Pressure or friction triggers cleavage
- Epidermolysis bullosa

Metabolic route

- Porphyrin-metabolism disturbance
- Sunlight exacerbates the cutaneous reaction
- Porphyria-associated blistering

Inherited disease versus autoantibody disease

The same attachment system can fail through genetic or immunologic mechanisms.

Disorder	Dominant mechanism	Representative target
Epidermolysis bullosa	Inherited structural weakness	Keratin / laminin / collagen VII
Bullous pemphigoid	Autoantibody to attachment proteins	BPAG2
Pemphigus	Autoantibody-mediated cell-cell detachment	Desmogleins
Dermatitis herpetiformis	IgA-associated subepidermal injury	Anchoring-region components

Clinical provocation: Friction or light?

Pressure / rubbing

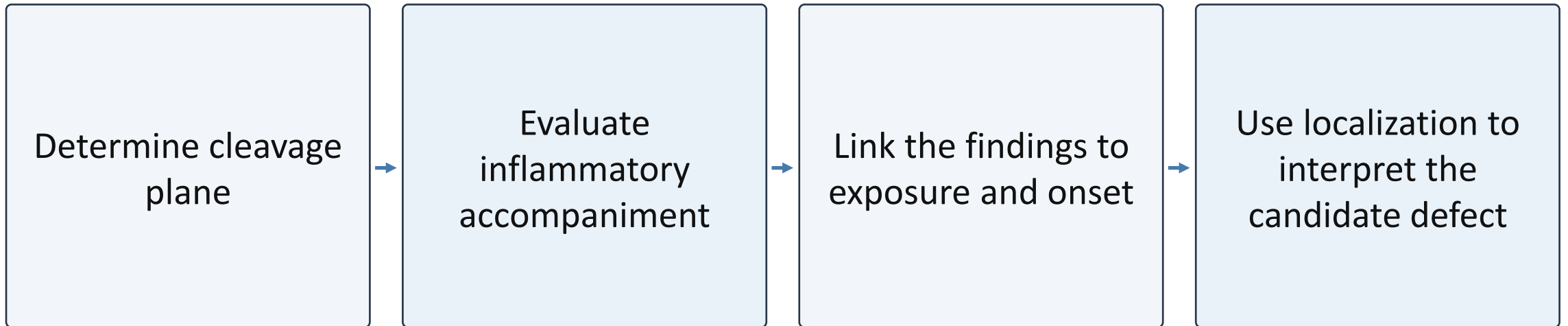
- Characteristic of inherited EB
- Onset at or soon after birth
- Mechanical sites are especially vulnerable

Sun exposure

- Exacerbates porphyria-associated lesions
- May accompany urticaria and vesicles
- Scarring may follow

A structured morphology approach

Subepidermal location alone is not specific to a single disease.



Epidermolysis bullosa: Disease definition

- An umbrella term for inherited defects in proteins essential for skin mechanical stability.
- The shared phenotype is blistering after minor pressure, rubbing, or trauma.
- The various forms are defined in large part by the level and molecular basis of cleavage.

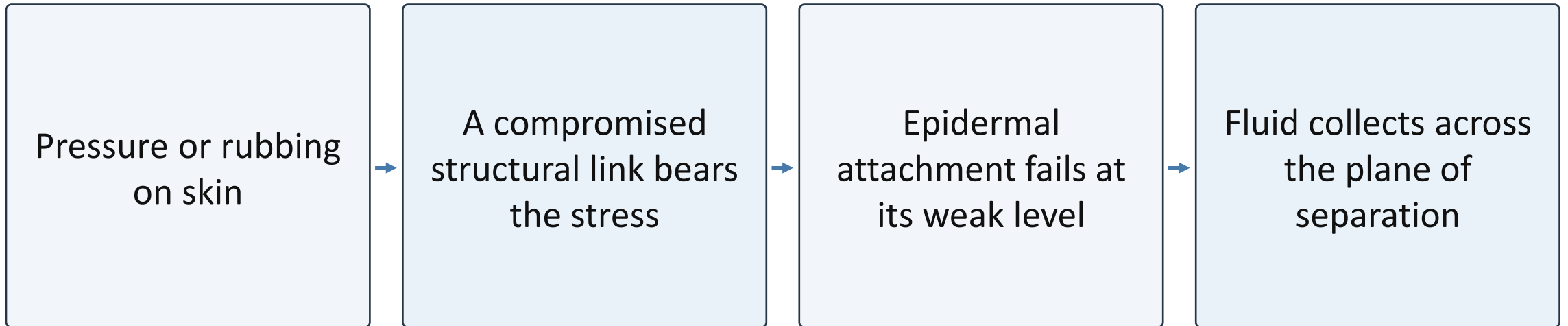
Presentation at or soon after birth

A clinical clue, not a genotype.

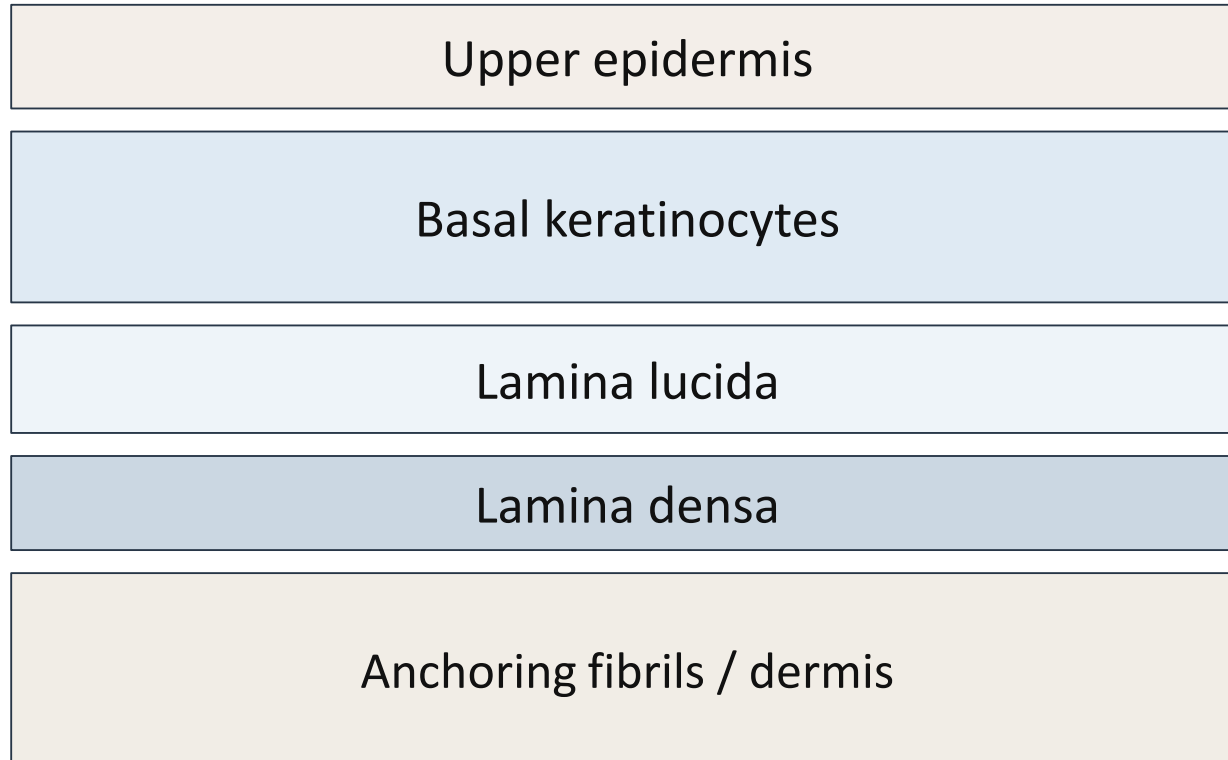
- Characteristic blister susceptibility is present at or shortly after birth.
- Minor trauma can have a disproportionate effect in structurally fragile skin.
- Early onset supports a hereditary fragility mechanism but does not identify the subtype.

From mechanical force to a blister

Different mutated proteins create different cleavage planes.



Major EB forms map to different layers



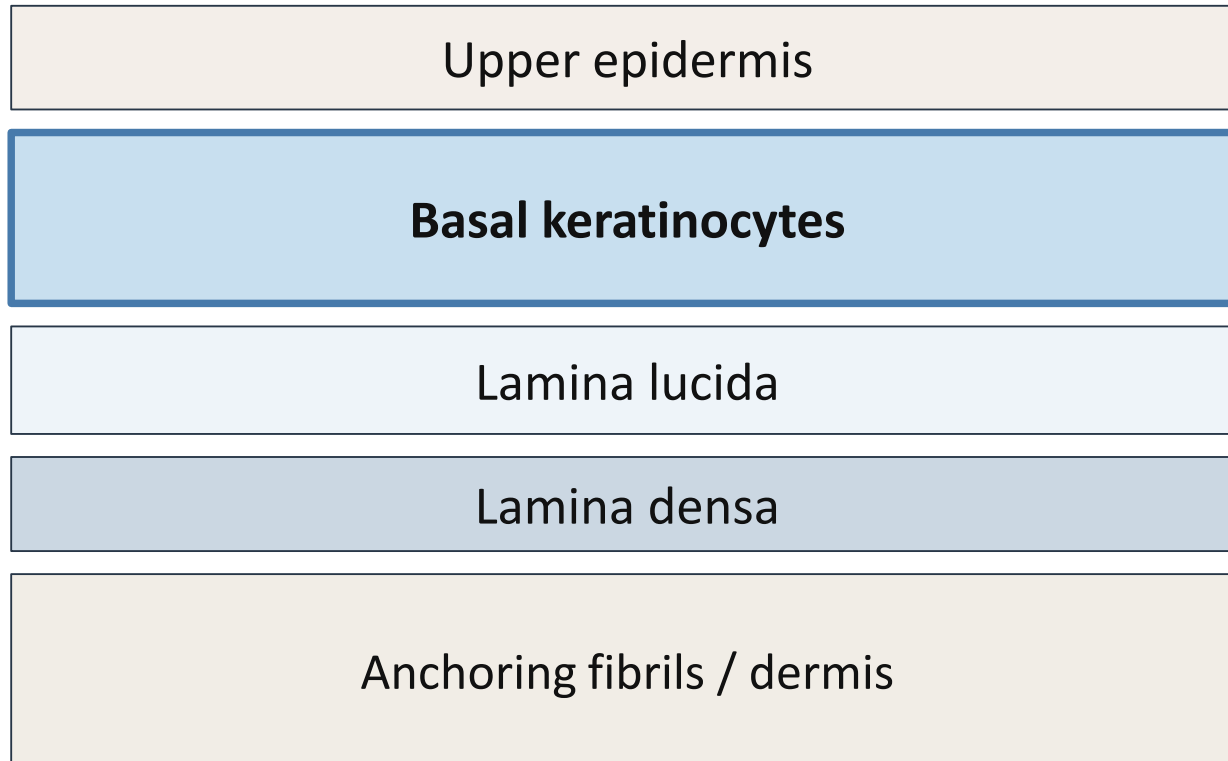
- Simplex: Defect within basal epidermal keratinocytes.

- Junctional: Cleavage at the lamina lucida.

- Dystrophic: Cleavage beneath the lamina densa.

Simplified anatomical schematic

EB simplex: Basal-layer cleavage

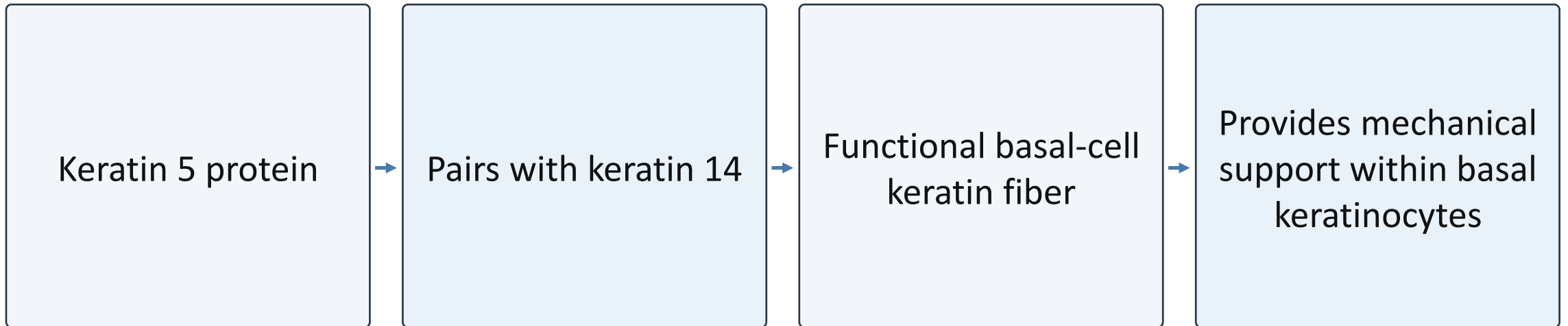


- Defect affects the basal cell layer of the epidermis.
- Keratin 5 and keratin 14 are the principal gene products identified.
- The disturbance is intracellular rather than a lamina-lucida split.

Simplified anatomical schematic

Keratin 5 and keratin 14 function as a pair

The two partners are required to build the same structural apparatus.



Why either KRT5 or KRT14 can cause EB simplex

A shared fiber explains overlapping clinical effects.

KRT5 mutation

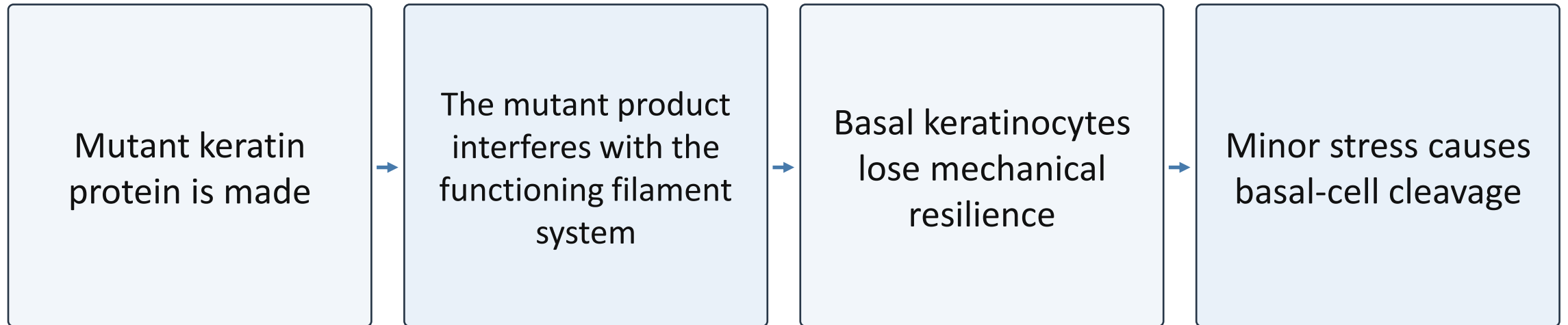
- Alters a partner of the basal keratin pair
- Disrupts keratin-fiber function

KRT14 mutation

- Alters the other partner of the same pair
- Can produce a similar phenotype

Dominant-negative keratin effect

Dominant-negative activity as the basis of common dominant transmission.



Inheritance of classic EB simplex

Typical pattern

Autosomal dominant

Molecular explanation

Dominant-negative activity
of mutant keratin

Clinical implication

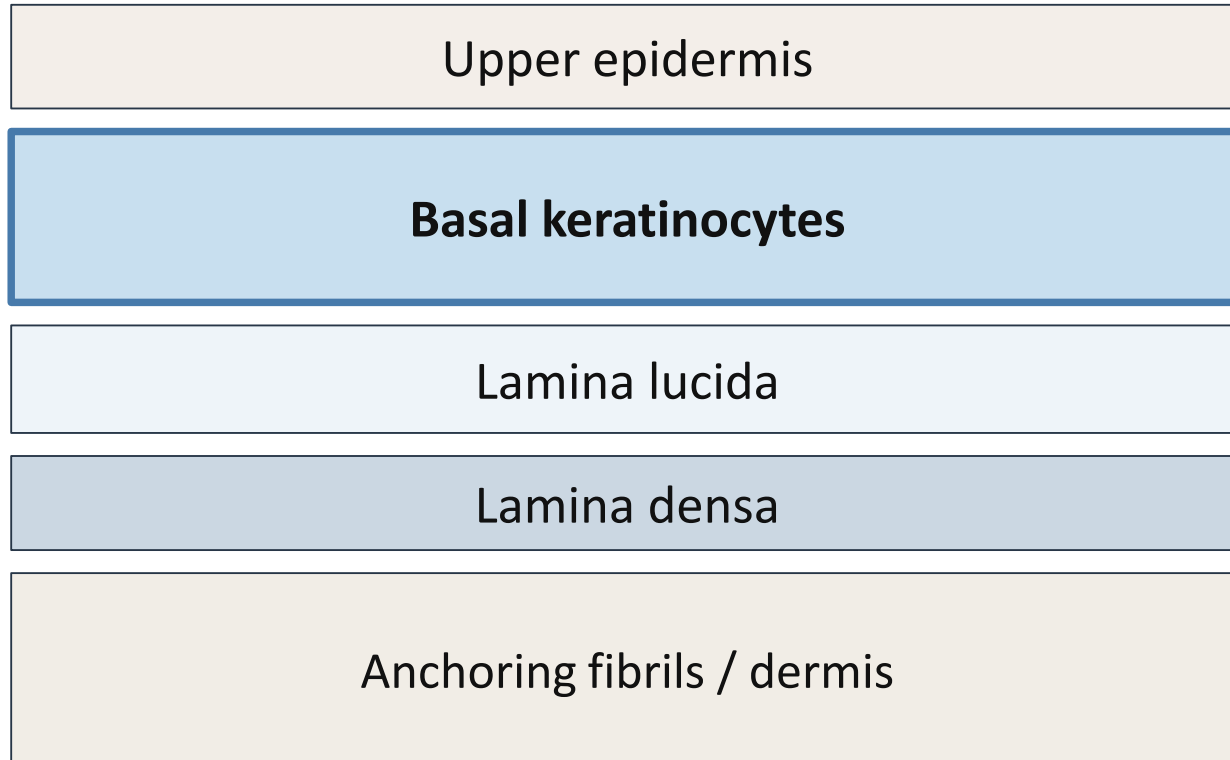
A single pathogenic allele
may disrupt a shared
filament system

EB simplex is the most common EB group

Textbook frequency: Subtype proportion, not population incidence.

- Robbins assigns approximately 75%–85% of EB cases to the simplex type.
- The common molecular basis is mutation of keratin 5 or 14.
- Frequency does not replace cleavage-plane or molecular assessment in an individual case.

Recognizing basal-cell injury in EB simplex



- The cleavage localizes to the basal epidermal compartment.
- The level is distinct from lamina-lucida or sublamina-densa failure.
- Very subtle findings may require ultrastructural characterization.

Simplified anatomical schematic

Basal-cell versus basement-membrane failure

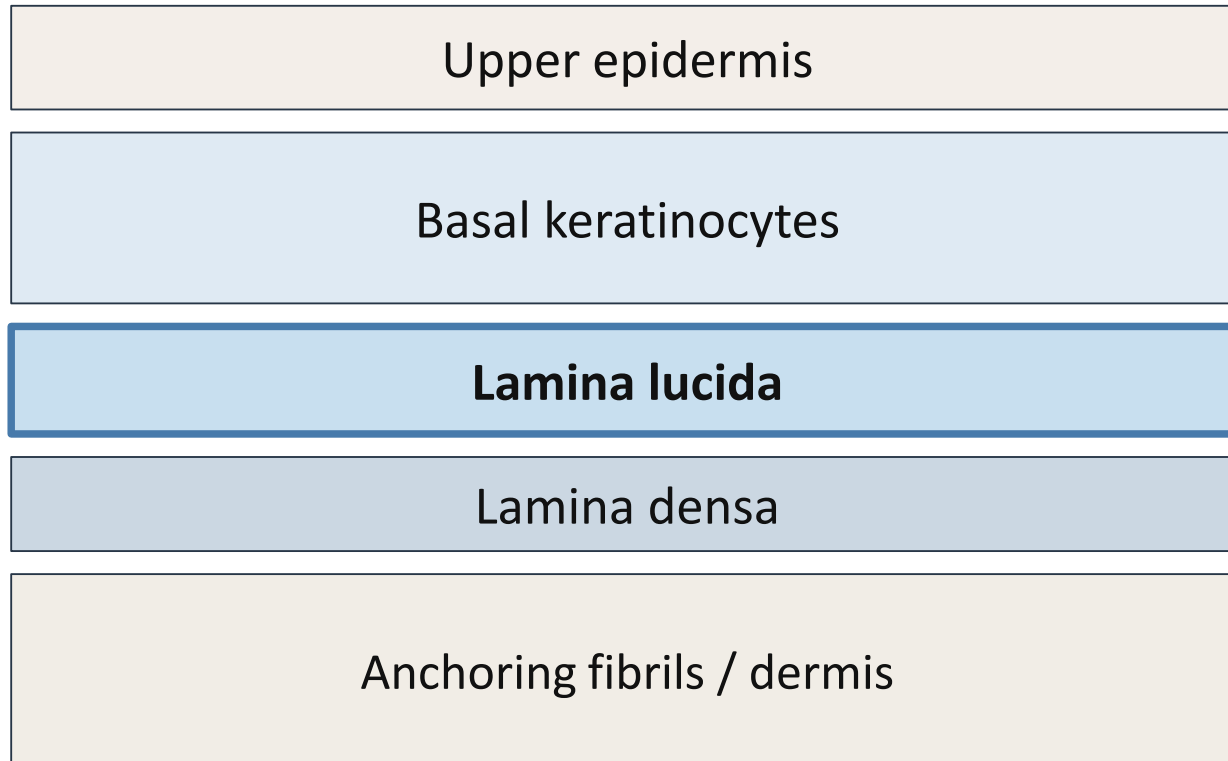
Intracellular keratin defect

- KRT5/KRT14
- Simplex EB
- Basal epidermis

Extracellular attachment defect

- Laminin or type VII collagen
- Junctional or dystrophic EB
- Basement-membrane region

Junctional EB: Lamina-lucida cleavage



- The separation occurs at the level of the lamina lucida.
- Overlying skin may appear otherwise histologically normal.
- Subepidermal separation need not be accompanied by inflammation.

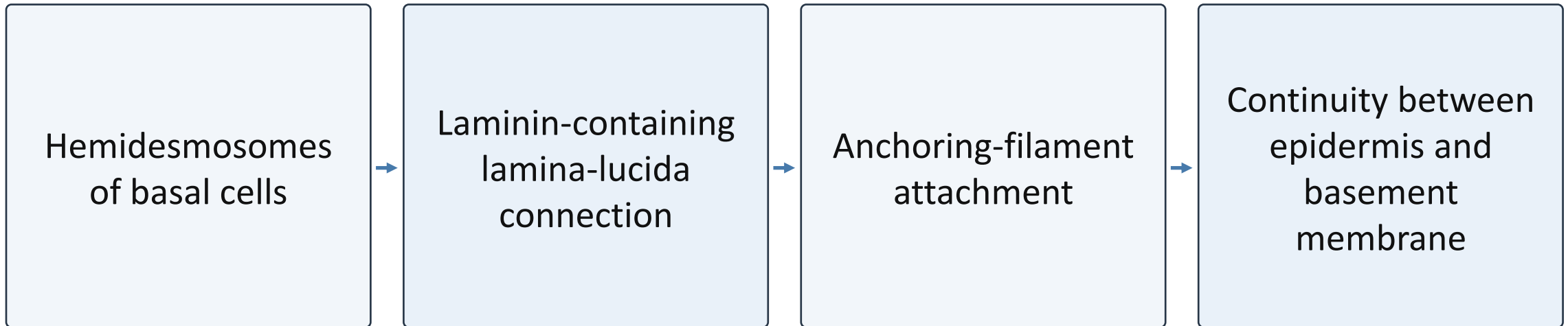
Simplified anatomical schematic

The lamina lucida as a junctional interface

- It is a specialized compartment beneath basal keratinocytes.
- Laminin contributes to binding hemidesmosomes and anchoring filaments.
- Defective links here permit the epidermis to separate despite otherwise preserved epidermal architecture.

Laminin bridges the epidermal attachment apparatus

Loss of laminin function weakens the junctional adhesive bridge.



Laminin-subunit mutations in junctional EB

- Most junctional EB cases in the source result from laminin-subunit defects.
- These defects are usually inherited in an autosomal recessive pattern.
- The relevant dysfunction occurs at the level of the lamina lucida.

BPAG2 mutations: An alternative junctional cause

- BPAG2 mutations in a subset of junctional EB.
- BPAG2 is a hemidesmosomal structural protein.
- Genetic loss of function and antibody targeting of the same protein have different etiologic bases.

BPAG2 illustrates genetic and immune mechanisms

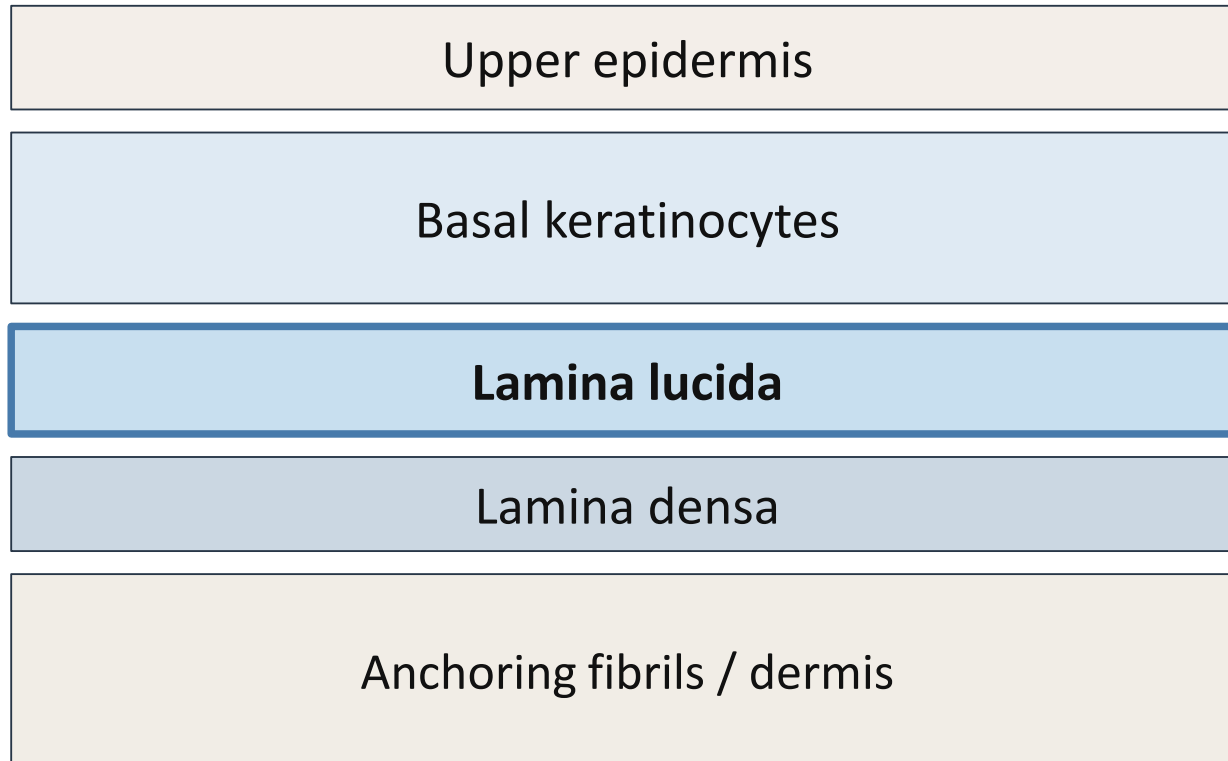
Junctional epidermolysis bullosa

- Inherited BPAG2 defect
- Structural adhesion weakness
- Blistering without a necessary inflammatory autoimmune mechanism

Bullous pemphigoid

- Autoantibodies to BPAG2
- Complement and inflammatory recruitment
- Subepidermal blister

Junctional EB: Characteristic noninflammatory split



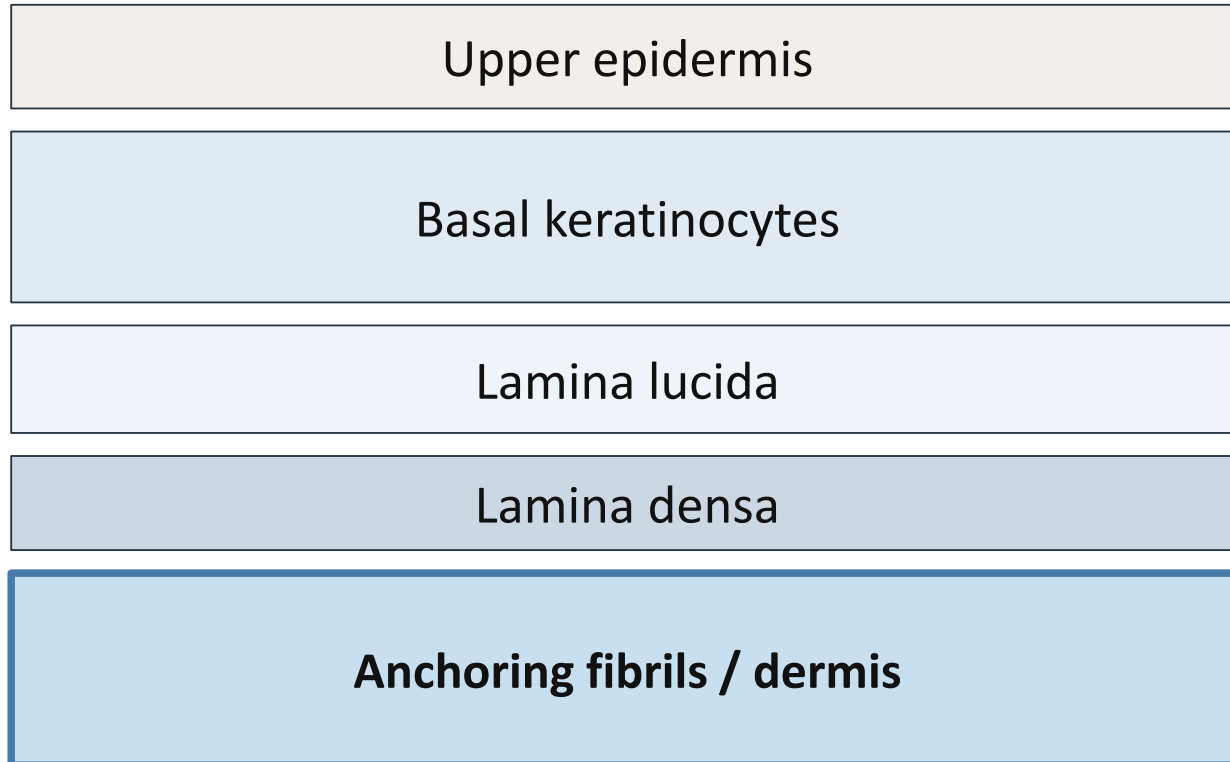
Simplified anatomical schematic

- A subepidermal blister at the lamina lucida.
- The illustrated lesion has no associated inflammation.
- Absence of inflammation supports a structural disease mechanism in this context.

Clinical morphology of junctional EB

- An illustrative Robbins case shows erosions in flexural creases.
- Erosions are compatible with mechanically fragile skin exposed to friction.
- Clinical distribution helps identify vulnerable regions but is not a precise cleavage-plane test.

Dystrophic EB: A deeper cleavage plane



- Blisters form beneath the lamina densa.
- The associated anchoring fibrils are rudimentary or defective.
- This deeper defect is associated with scarring forms of EB.

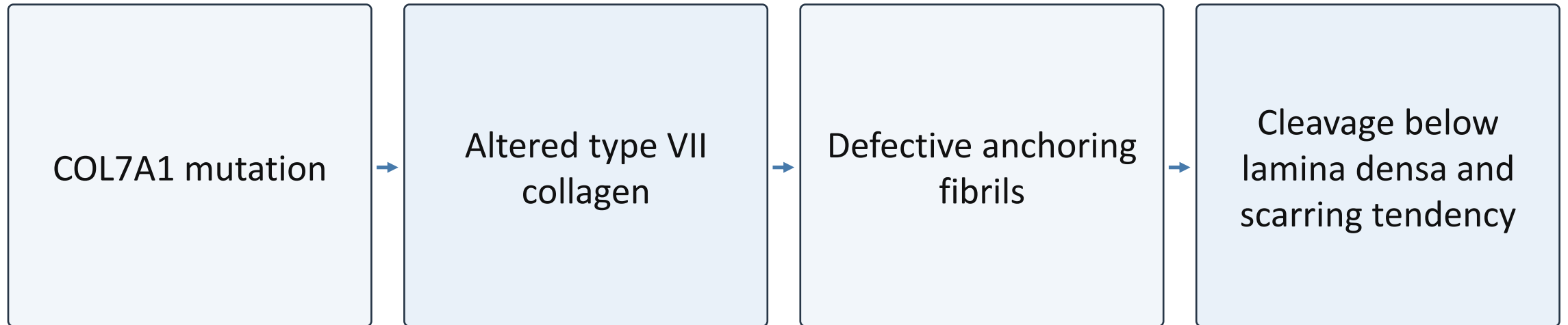
Simplified anatomical schematic

Anchoring fibrils secure epidermis to dermis

- Anchoring fibrils extend below the lamina densa into dermal attachment structures.
- Type VII collagen is a major component of these fibrils.
- Deficiency shifts the weak point beneath the dense basement-membrane layer.

COL7A1 to dystrophic EB

A direct gene → structural protein → cleavage-plane relationship.



Dystrophic EB can have two inheritance modes

The inheritance mode is mutation-dependent; Do not assume one pattern for all dystrophic EB.

Dominant dystrophic EB

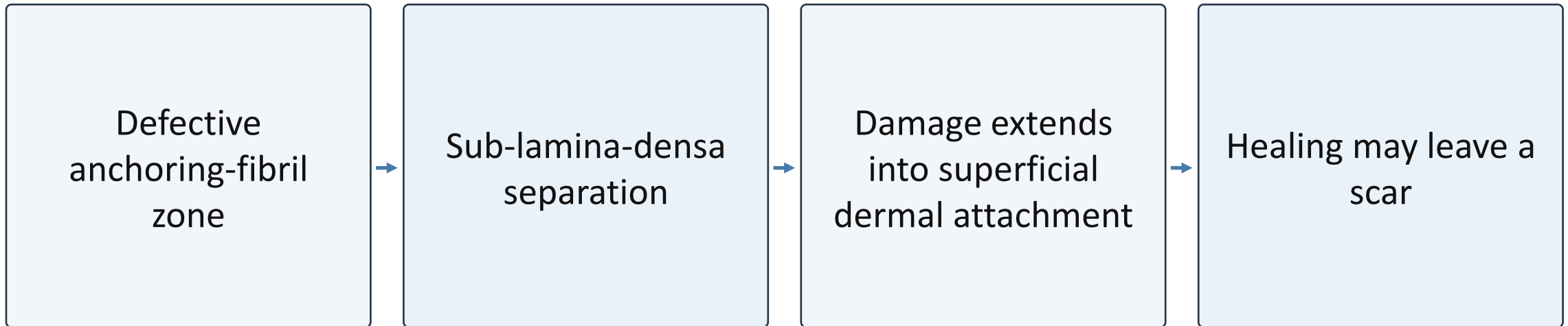
- Certain COL7A1 mutations
- Autosomal dominant transmission

Recessive dystrophic EB

- Other COL7A1 mutations
- Autosomal recessive transmission

Why deeper separation may be associated with scarring

The textbook specifically associates dystrophic EB with scarring.



Junctional versus dystrophic EB

Junctional

- Lamina-lucida cleavage
- Laminin or BPAG2 defects
- Often autosomal recessive laminin lesions

Dystrophic

- Cleavage below lamina densa
- COL7A1 / type VII collagen
- Dominant or recessive

Mixed EB forms are recognized

- Not all inherited EB falls cleanly within one single plane.
- Mixed types show defects at several anatomical levels.
- A simple three-category scheme is a useful first model, not an exhaustive description of every case.

EB anatomy-to-gene synthesis

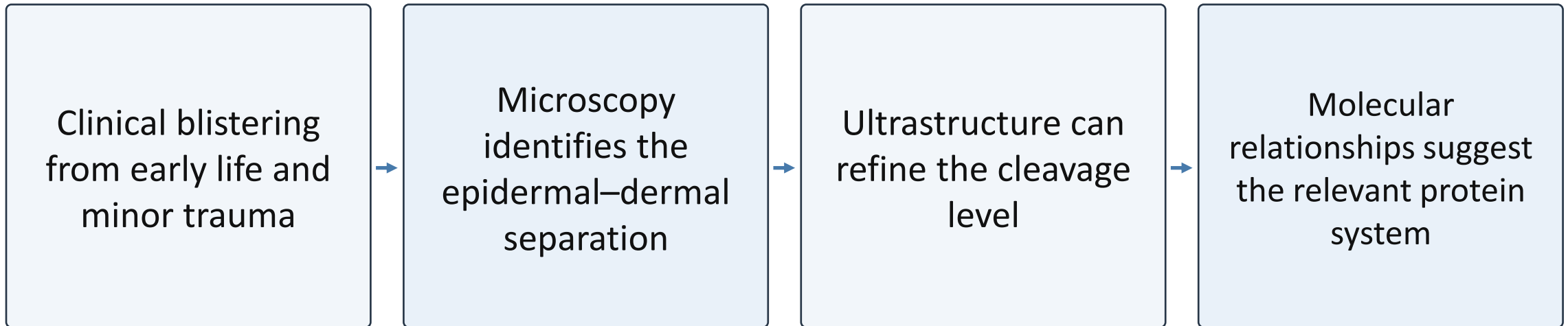
Subtype	Weak compartment	Representative molecular lesion	Inheritance described
Simplex	Basal cell layer	KRT5 or KRT14	Usually AD
Junctional	Lamina lucida	Laminin subunits; Sometimes BPAG2	Usually AR for laminin defects
Dystrophic	Below lamina densa	COL7A1 (collagen VII)	AD or AR
Mixed	Multiple levels	Not specified in excerpt	Not specified

Why routine histology may not subtype EB

- Histologic changes can be extremely subtle.
- Cleavage-depth distinctions may require electron microscopy.
- A generic “subepidermal blister” report may not distinguish lamina lucida from below-lamina-densa separation.

Logical interpretation of an EB specimen

This is an explanatory framework, not a substitute for a formal diagnostic testing protocol.



Case: A basal keratin defect

Constructed teaching vignette

An infant develops blisters at points of rubbing. A pathogenic KRT14 variant is identified.

Which attachment compartment is primarily impaired?

Interpretation **Basal keratinocyte filament system**

KRT14 pairs with keratin 5 in EB simplex.

Case: Lamina-lucida cleavage

Constructed teaching vignette

A skin sample shows a noninflammatory separation at the lamina lucida.

Which EB class and molecular system best fit?

Interpretation **Junctional EB; Laminin or selected hemidesmosomal proteins**

The cleavage plane corresponds to the lamina lucida.

Case: Type VII collagen

Constructed teaching vignette

Inherited skin fragility is accompanied by a COL7A1 variant and sublamina-densa blistering.

Which EB type is implicated?

Interpretation **Dystrophic EB**

Type VII collagen forms basement-membrane anchoring fibrils.

Porphyria: The central definition

- Porphyrias are uncommon inherited or acquired disturbances of porphyrin metabolism.
- They are biochemical disease groups that may include important cutaneous manifestations.
- The skin pathology is considered separately from inherited defects of adhesion proteins.

Where porphyrins normally participate

These three physiological contexts for porphyrins.

Hemoglobin

Porphyrin-containing heme supports oxygen transport.

Myoglobin

The heme group participates in oxygen binding in muscle.

Cytochromes

Heme-containing proteins support electron transfer.

Porphyria may be inherited or acquired

Inherited metabolic disturbance

- An inborn disturbance of porphyrin metabolism
- Part of the porphyria spectrum

Acquired metabolic disturbance

- A disturbance arising without a primary inherited defect
- Also within the porphyria spectrum

Classification is clinical and biochemical

- Robbins explicitly uses both clinical and biochemical features to classify porphyrias.
- The named categories are not defined solely by skin histology.
- Cutaneous blistering is one disease manifestation; The biochemical phenotype remains central.

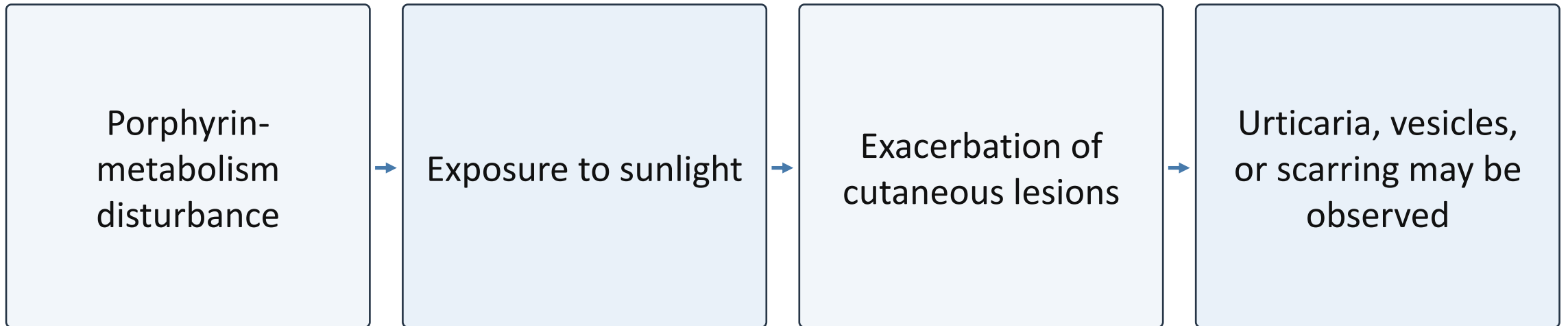
Five major porphyria groups

These are the textbook categories, not an independently updated taxonomy.

Textbook category	Teaching distinction
Congenital erythropoietic porphyria	One of the five groups identified in the text
Erythrohepatic protoporphyria	Textbook terminology retained as printed
Acute intermittent porphyria	Included in classification; Skin findings are not asserted for every case
Porphyria cutanea tarda	Cutaneous name within the classified group
Mixed porphyria	Classification category in the source

Sunlight is a key cutaneous exacerbating factor

The detailed mechanism of the described microscopic alterations is uncertain.



Clinical cutaneous manifestations of porphyria

- Urticarial lesions may occur.
- Vesicles are a characteristic cutaneous manifestation in the chapter.
- Scarring can accompany the lesions.
- Sun exposure exacerbates these manifestations.

Clinical blister and scar are different observations

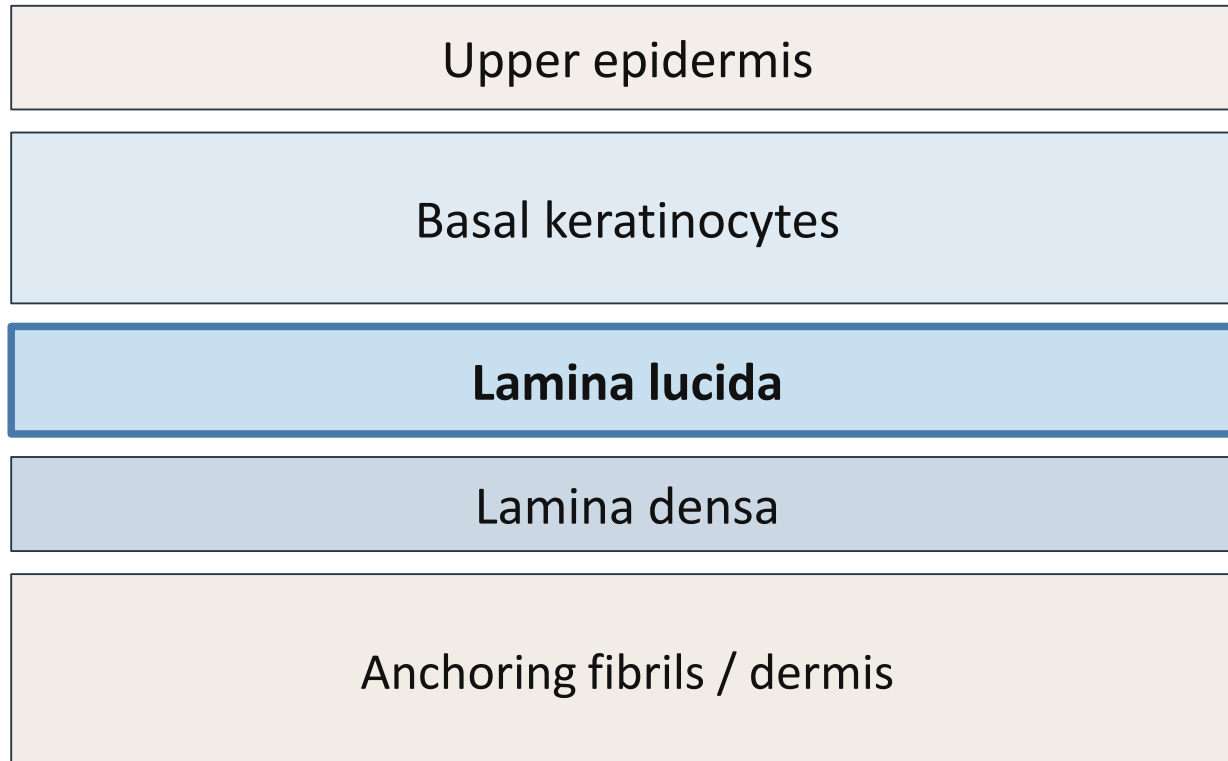
Active lesion

- Vesicle or bulla
- Focal fluid-filled separation
- A temporal indicator of ongoing injury

Healed lesion

- Scarring may persist
- Evidence of preceding injury
- Neither appearance alone identifies the metabolic subgroup

Porphyria blisters are subepidermal



Simplified anatomical schematic

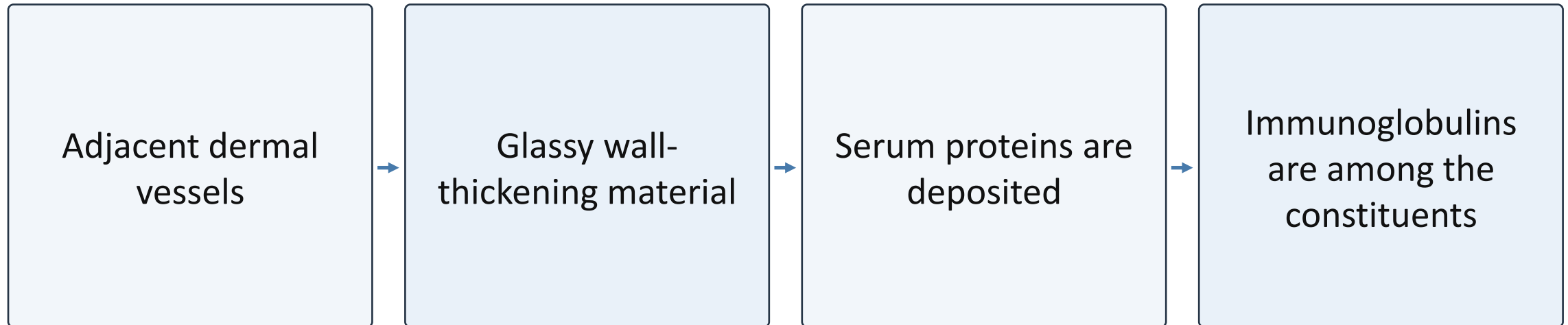
- Robbins locates the vesicles beneath the epidermis.
- The separation plane is shared by multiple bullous diseases.
- Associated dermal vascular alterations help interpret this pattern.

A distinct dermal vascular feature

- Dermal vessels adjacent to porphyric blisters have thickened walls.
- The thickening has a glassy or hyaline appearance.
- This associated finding adds diagnostic context beyond the blister plane.

What accumulates in thickened vessel walls?

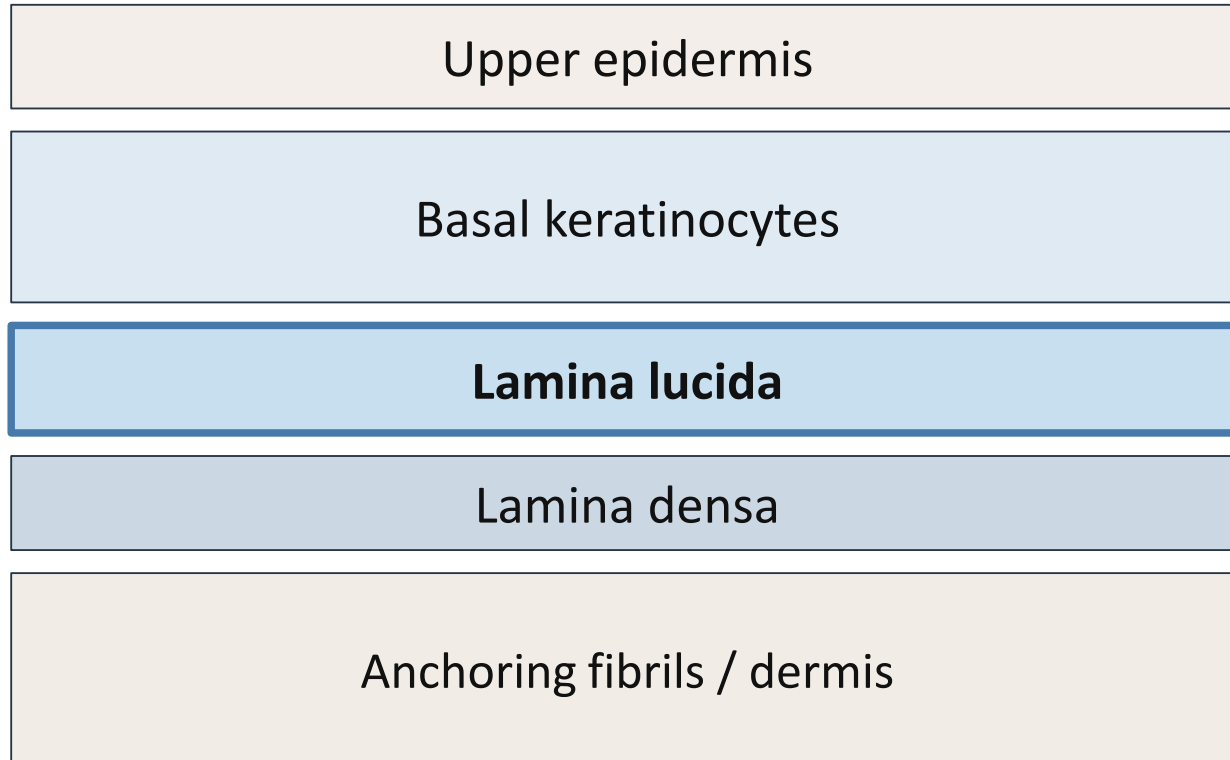
A vascular-wall deposit should not automatically be interpreted as pathogenic autoantibody targeting.



Mechanistic uncertainty must be retained

- The pathogenesis of the described porphyria skin alterations is not understood.
- Sunlight exacerbation is an observation, not a fully specified molecular sequence in this source.
- Do not infer a defined antibody-mediated blister mechanism solely from vascular immunoglobulin deposits.

Pattern recognition: Porphyria-associated bulla



Simplified anatomical schematic

- Subepidermal blister is the principal separation pattern.
- Dermal papillae at the base may appear relatively rigid.
- Adjacent vessel walls are thickened by glassy proteinaceous material.

EB versus porphyria: Principal distinctions

Feature	Epidermolysis bullosa	Porphyria
Primary mechanism	Inherited structural-protein defect	Porphyrin-metabolism disturbance
Typical provocation	Friction, pressure, trauma	Sunlight exacerbation
Age / timing	At or soon after birth (typical)	Not specified as one pattern
Histologic emphasis	Precise cleavage level	Subepidermal blister; Glassy dermal vessel walls

Contrast with autoimmune blistering disease

Entity	Mechanism	Typical plane / clue
Pemphigus	Anti-desmoglein IgG; Acantholysis	Subcorneal or suprabasal
Bullous pemphigoid	Anti-BPAG; Inflammatory injury	Subepidermal; Eosinophils; Linear complement
Dermatitis herpetiformis	IgA-associated injury	Subepidermal; Papillary neutrophils / granular IgA
EB	Inherited structural defect	Basal, lamina lucida, or deeper
Porphyria	Metabolic disturbance	Subepidermal; Hyaline dermal vessels

Bullous pemphigoid: Key differential features

Related Robbins section, pp. 1055–1056.

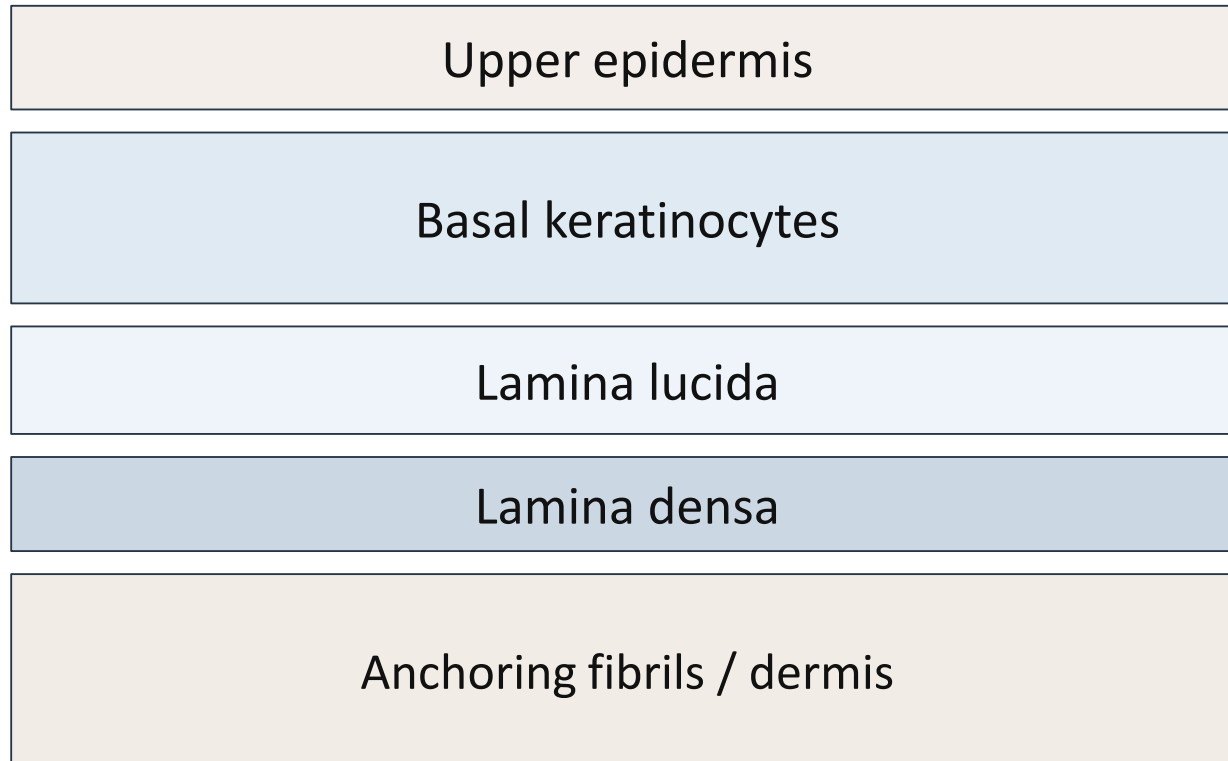
- Bullous pemphigoid is an autoimmune disease of epidermal attachment.
- Its subepidermal blisters can contain eosinophils and other inflammatory cells.
- Linear basement-membrane complement deposition is.
- BPAG2 links its target biology to genetic junctional EB.

Dermatitis herpetiformis: Contrasting pattern

Related Robbins section, p. 1055.

- Characteristically presents with grouped, intensely pruritic vesicles.
- Neutrophilic microabscesses occur at tips of dermal papillae.
- Direct immunofluorescence shows granular IgA at papillary tips.
- It shares a subepidermal plane but not the same etiology as EB or porphyria.

A shared cleavage plane does not imply shared cause



Simplified anatomical schematic

- Subepidermal blisters arise in junctional EB, porphyria, and immune-mediated bullous disease.
- Identify the exact compartment and associated tissue reaction.
- Timing, exposure, inflammation, and protein/genetic context supply discrimination.

Case: Sunlight-associated vesicles

Constructed teaching vignette

A person develops sun-exacerbated cutaneous vesicles. A biopsy shows a subepidermal split and glassy thickening of dermal vessels.

Which disease group is favored by the combination?

Interpretation **Porphyria-associated cutaneous disease**

Sunlight provocation plus glassy vessel walls is characteristic of the source description.

Case: Subepidermal blister is nonspecific

Constructed teaching vignette

A pathology report states only “subepidermal blister.” No exposure history or tissue-reaction details are given.

Is junctional EB established by the reported plane?

Interpretation **No; The information is insufficient.**

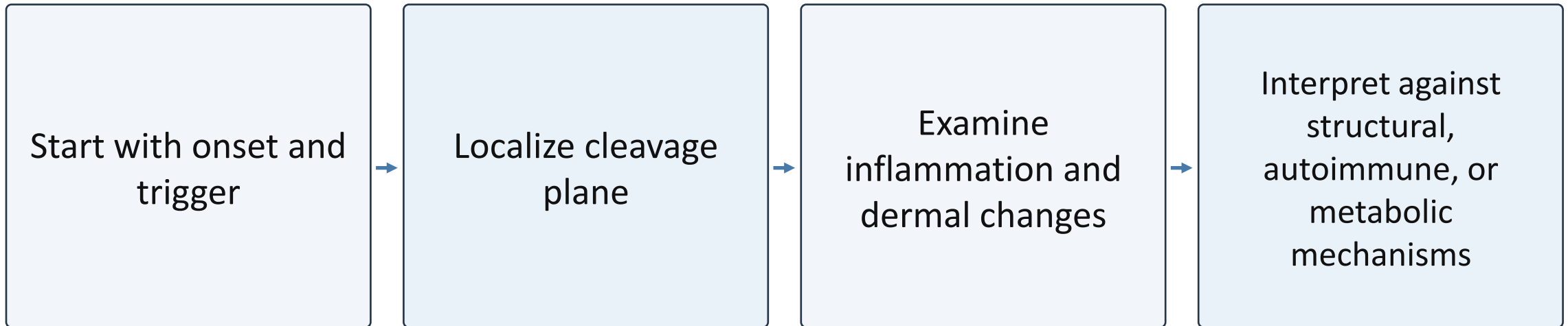
Porphyria, pemphigoid, and dermatitis herpetiformis may also split below the epidermis.

Common diagnostic reasoning errors

- Equating every subepidermal blister with one diagnosis ignores divergent etiologies.
- Assuming immunoglobulin-containing vascular deposits establish bullous pemphigoid is unjustified.
- Calling all EB autosomal recessive overlooks common dominant simplex and variable dystrophic forms.
- Assigning a complete molecular mechanism to porphyria skin injury exceeds the cited text.

Integrating a blistering-disorder differential

Precise localization and causal reasoning are complementary, not interchangeable.



EB: Three associations to retain

Basal epidermis

KRT5 / KRT14 — EB simplex

Lamina lucida

Laminin; Sometimes BPAG2
— junctional EB

Below lamina densa

COL7A1 / collagen VII —
dystrophic EB

Porphyria: Three associations to retain

Clinical

Sun-exacerbated urticaria,
vesicles, and scarring

Histology

Subepidermal blister

Dermis

Glassy thickening of vessel
walls with serum proteins

Reference and interpretation

Core reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. 2026. Chapter 25, The Skin; noninflammatory blistering disorders, pp. 1055–1058.

Adjacent Robbins sections on pemphigus, bullous pemphigoid, and dermatitis herpetiformis provide the differential context.

Original source figures 25.27, 25.28, 25.34, and 25.35 informed the compartmental descriptions; no textbook figure images have been reproduced.