Epidermolysis bullosa

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MSG Genetica, March 11, 2025

The skin

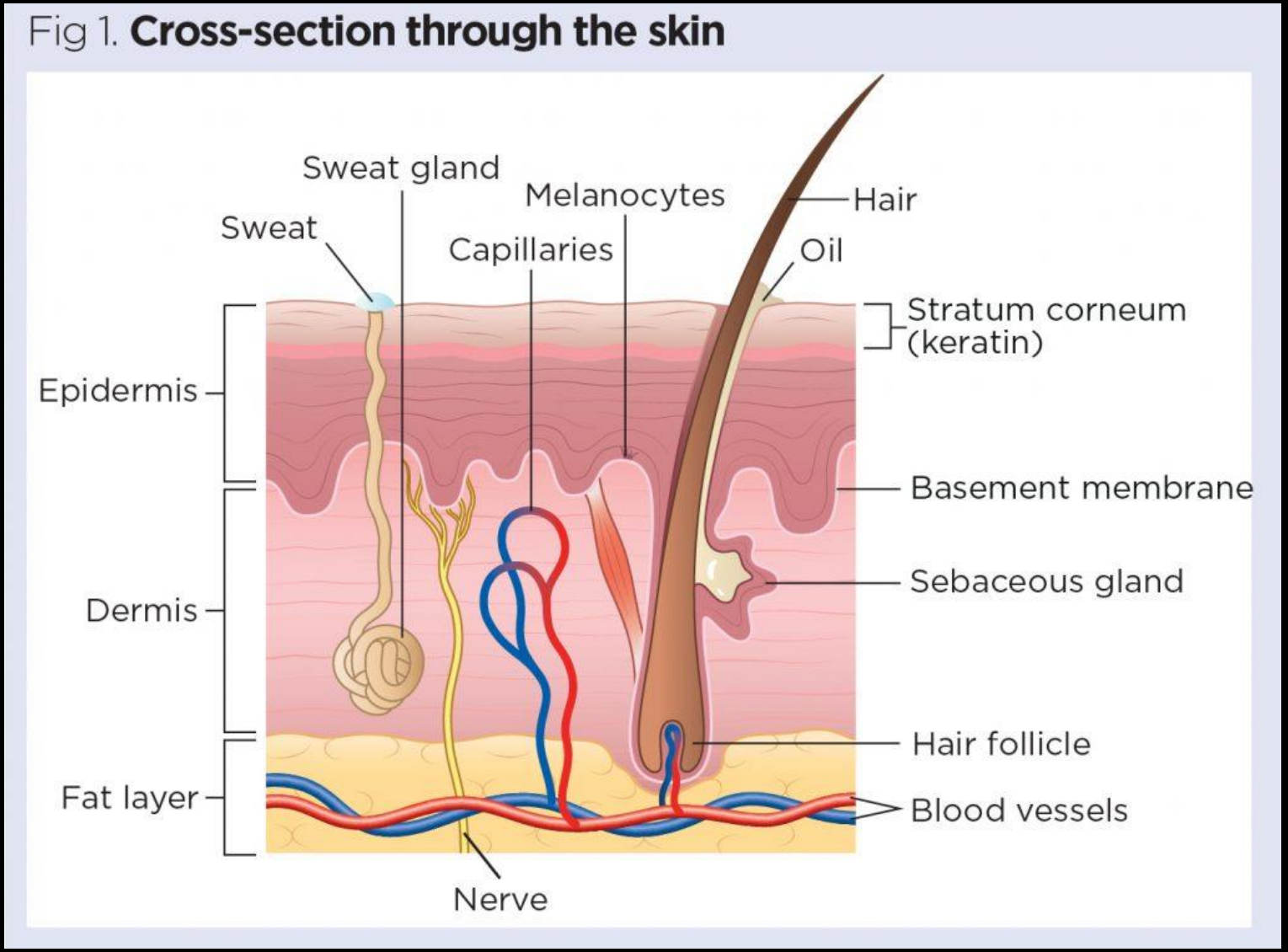
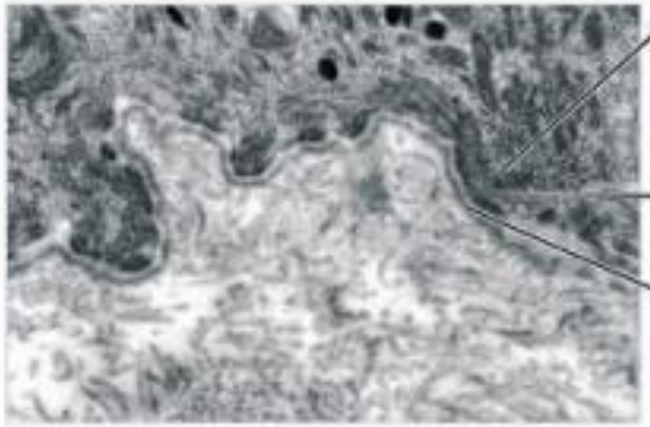
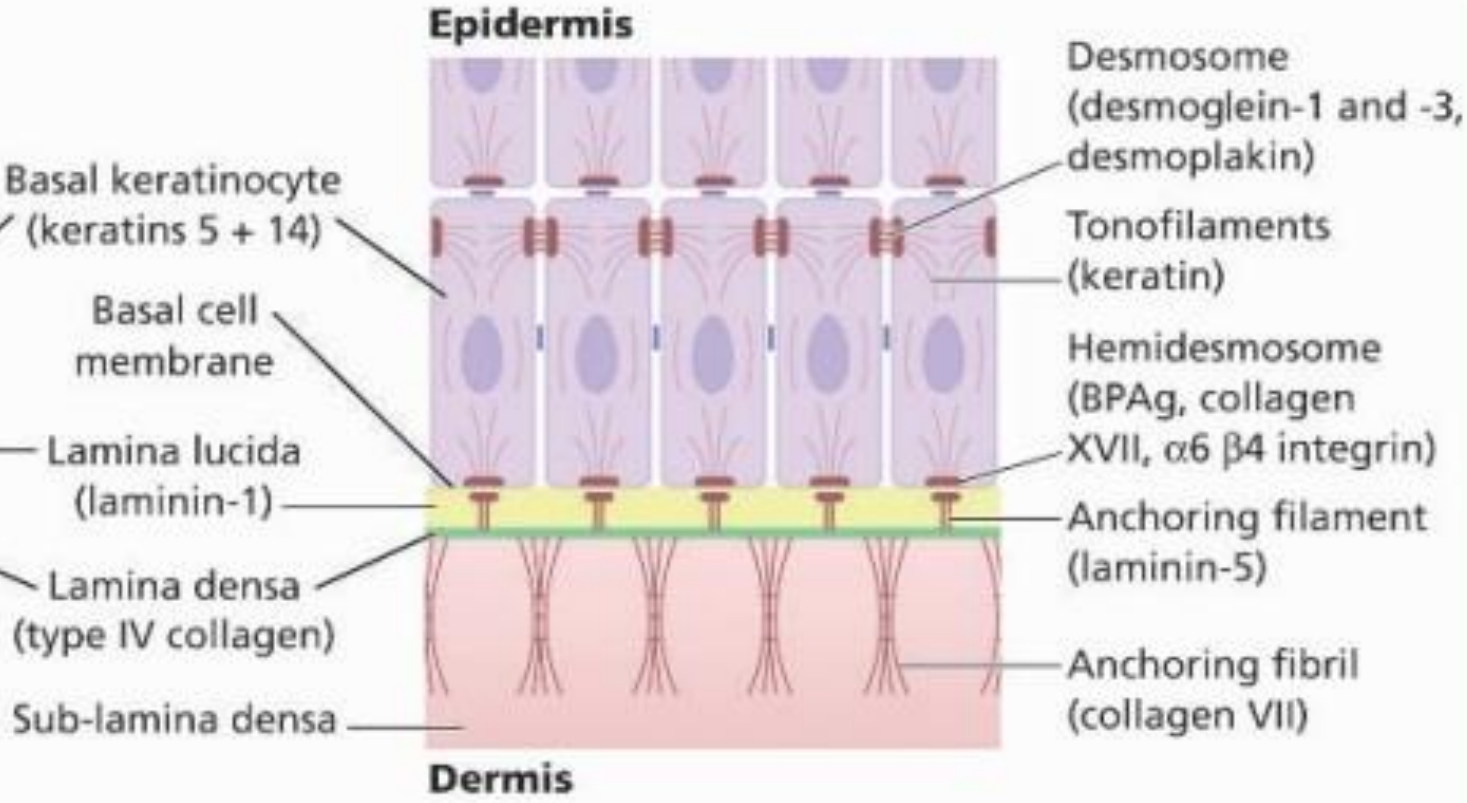


Fig 1. Cross-section through the skin
Sweat gland
Melanocytes
Hair
Sweat
Capillaries
Oil
Stratum corneum (keratin)
Epidermis
Basement membrane
Dermis
Sebaceous gland
Hair follicle
Fat layer
Blood vessels
Nerve

The dermo-epidermal junction



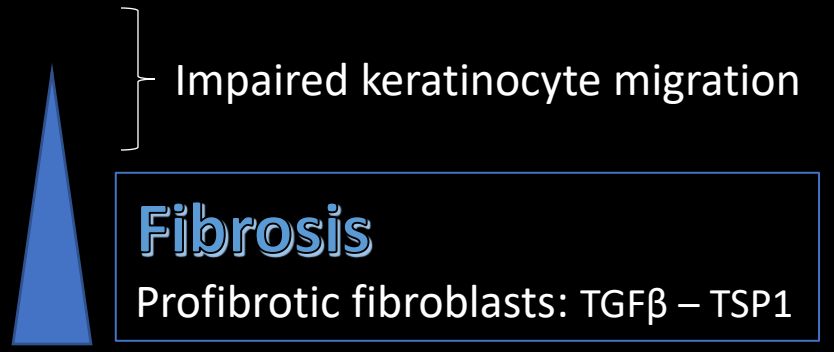


The dermo-epidermal junction

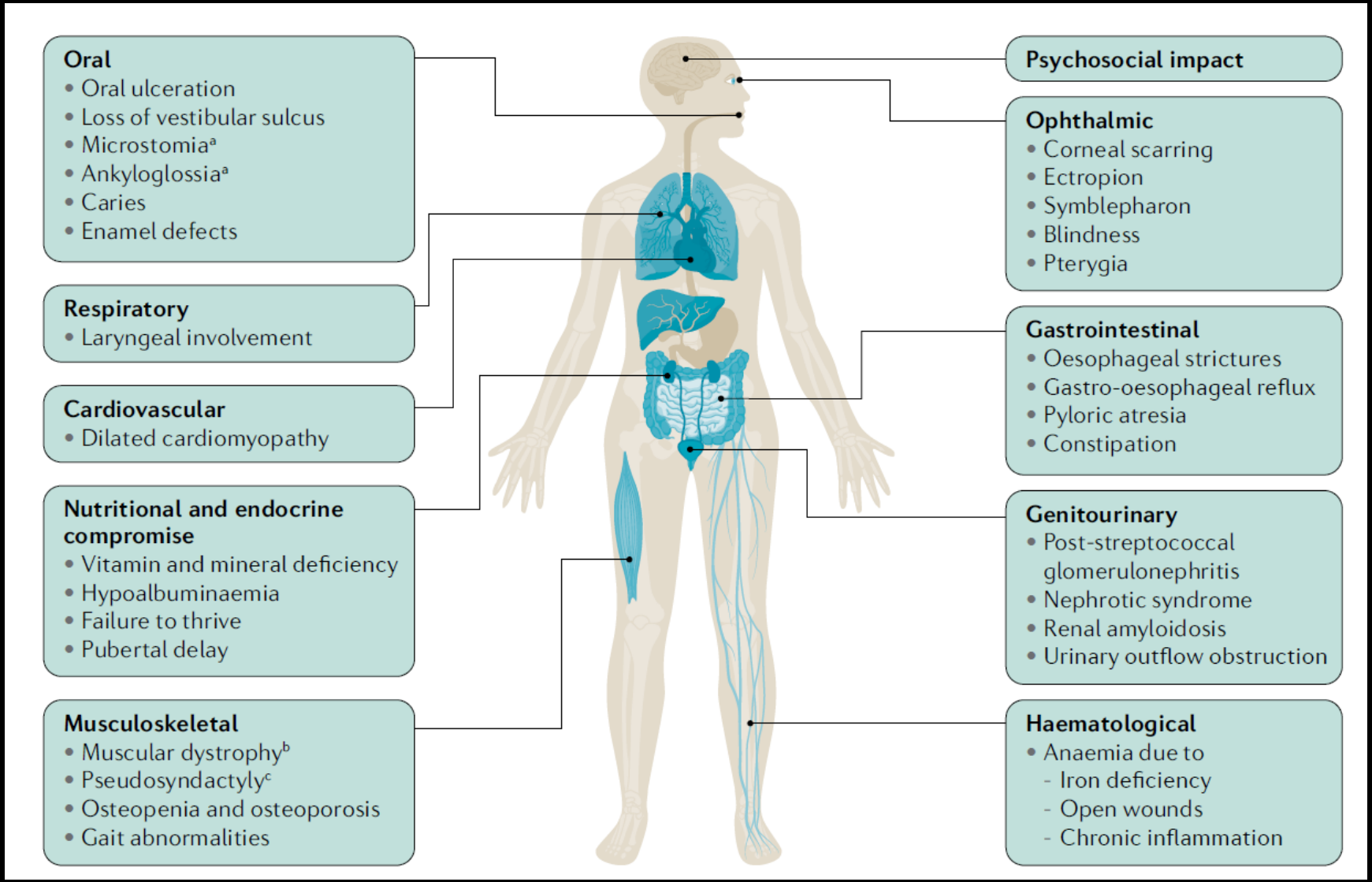
- Scaffold for cellular adhesion
- Selective permeable barrier for cells and molecules
- Template for repair: development, apoptosis, cell necrosis, and cell differentiation

Epidermolysis bullosa (EB)

- Mechanobullous disorder
- 1-2/100 000 live borns
- 4 types:
  - EB simplex (70%): epidermal fragility
  - Junctional EB: lamina lucida
  - Dystrophic EB: lamina densa
  - Kindler EB: splits at various levels
- *Multisystemic* disorder



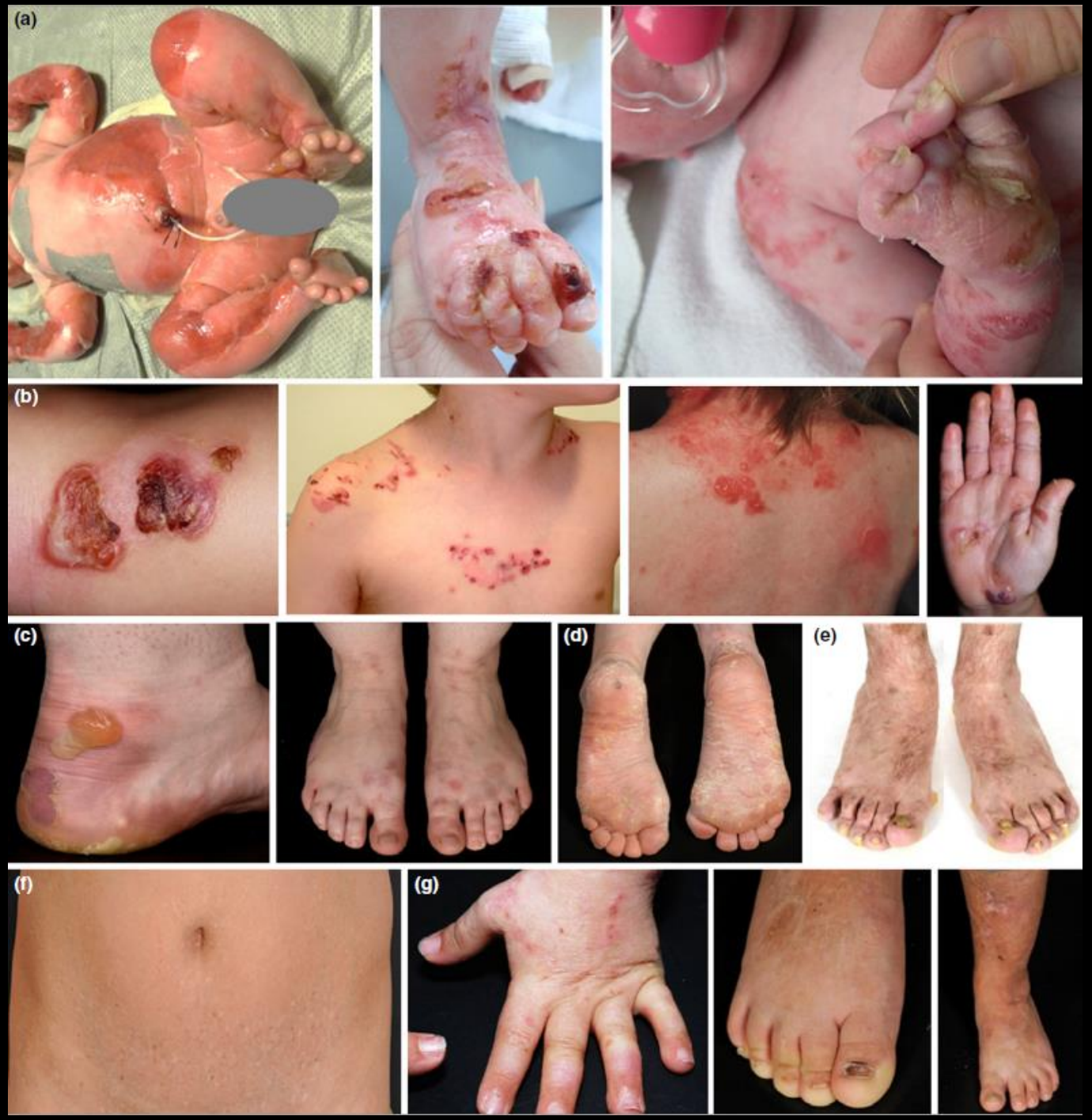
Multisystemic involvement



Bardhan et al, 2020
Nature Reviews Disease Primers

EB Simplex

- AD > AR
- Localized vs severe
- Tissue fragility
- Failure to thrive (sometimes): protein loss, larynx – esophagus involvement
- Neuropathic pain / itch
- Thick nails
- Mottled pigmentation
- Palmoplantar keratoderma

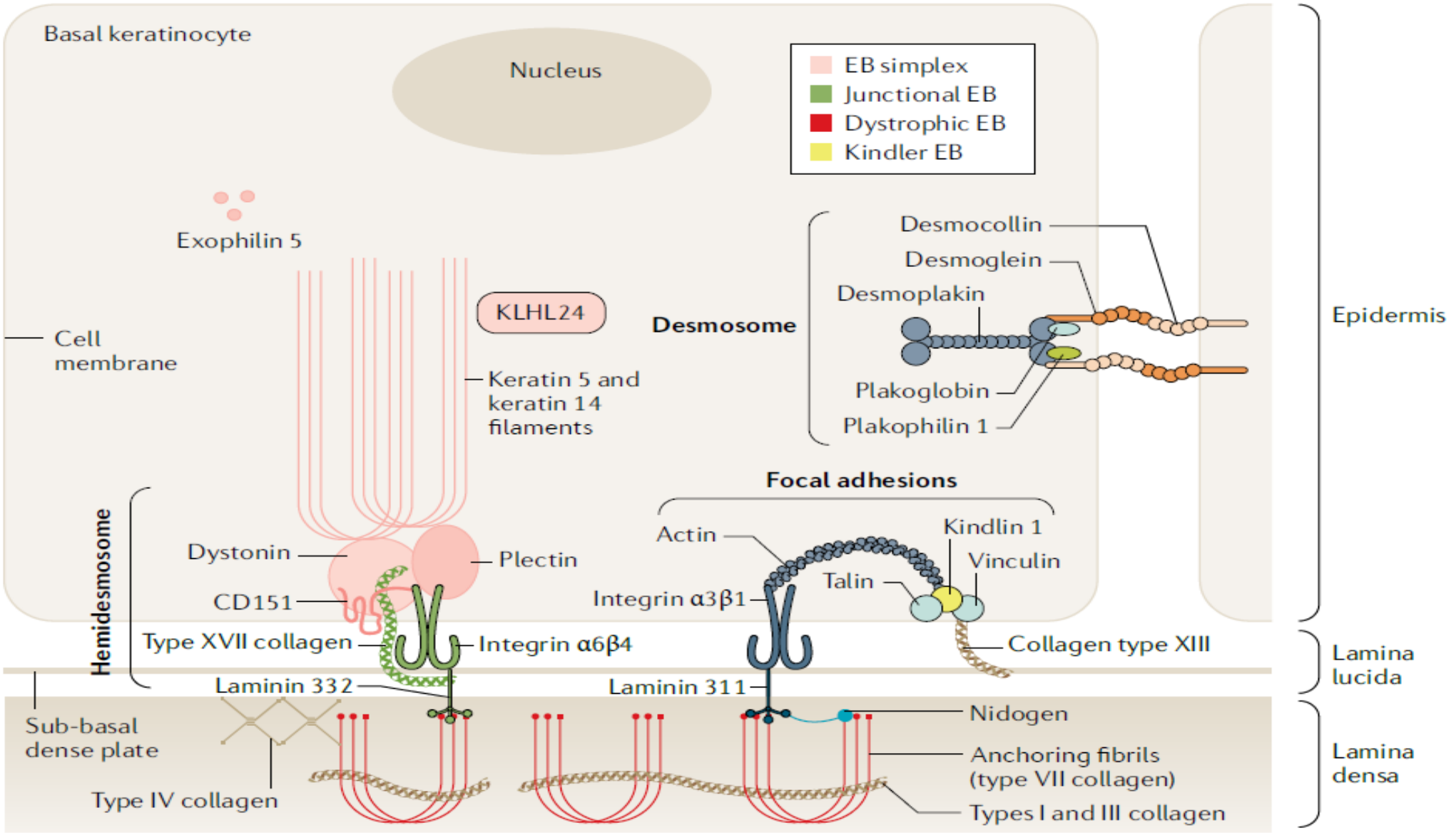


Localized vs severe
Palmoplantar keratoderma
Mottled pigmentation
Thickened nails

Has et al, 2020 Br J Dermatology

EB Simplex

- Keratin assembly and interactions
  - *KRT5 >> KRT14*
  - *Dominant negatief (heterodimers): → aggregates – Δ cytoplasmic stiffness → cytolysis*
- Hemidesmosomal proteins
  - *PLEC* (plectin) *(+/- muscular dystrophy/pyloric stenosis (AR))* : cytoskeletal linker protein
  - DST (dystonin): AR
  - *EXPH5* (exophilin 5) (exosome function, keratin transport)
  - *CD151* (+/- nephropathy): cell adhesion – transport of integrins
- Control of keratin proteostasis
  - *KLHL24: substrate adaptor for ubiquitin E3 ligases: prevents keratin 14 degradation*



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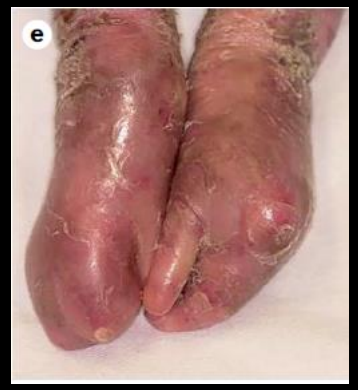
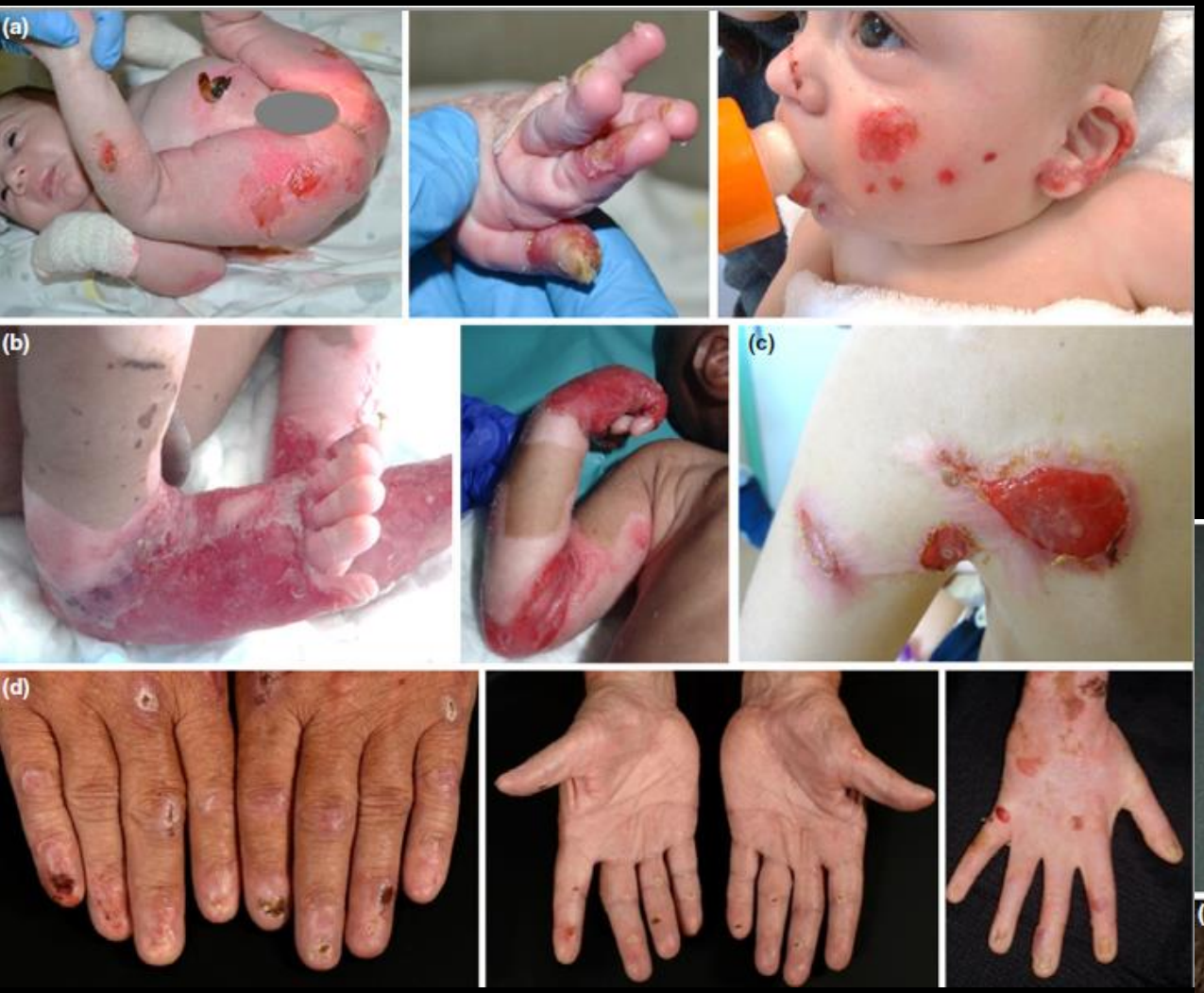
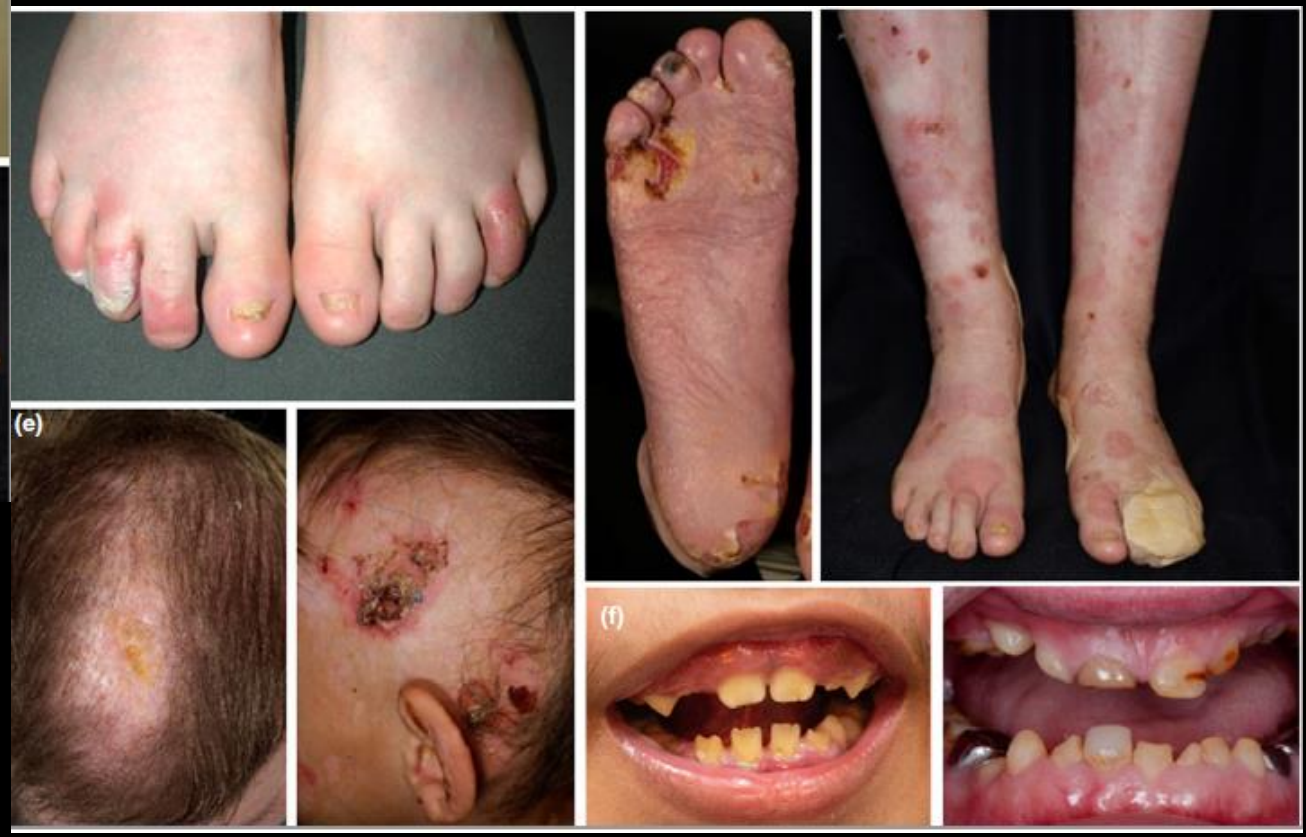
Junctional EB



- AR > AD
- Severe
- Mucosal involvement
- Mitten deformity (pseudosyndactyly)
- Dental enamel hypoplasia (note: also in carriers)
- Residual/partial functioning protein → milder disease
  - Intermediate (less granulation)
  - inversa (flexural areas)
  - late – onset
  - localized (acral)

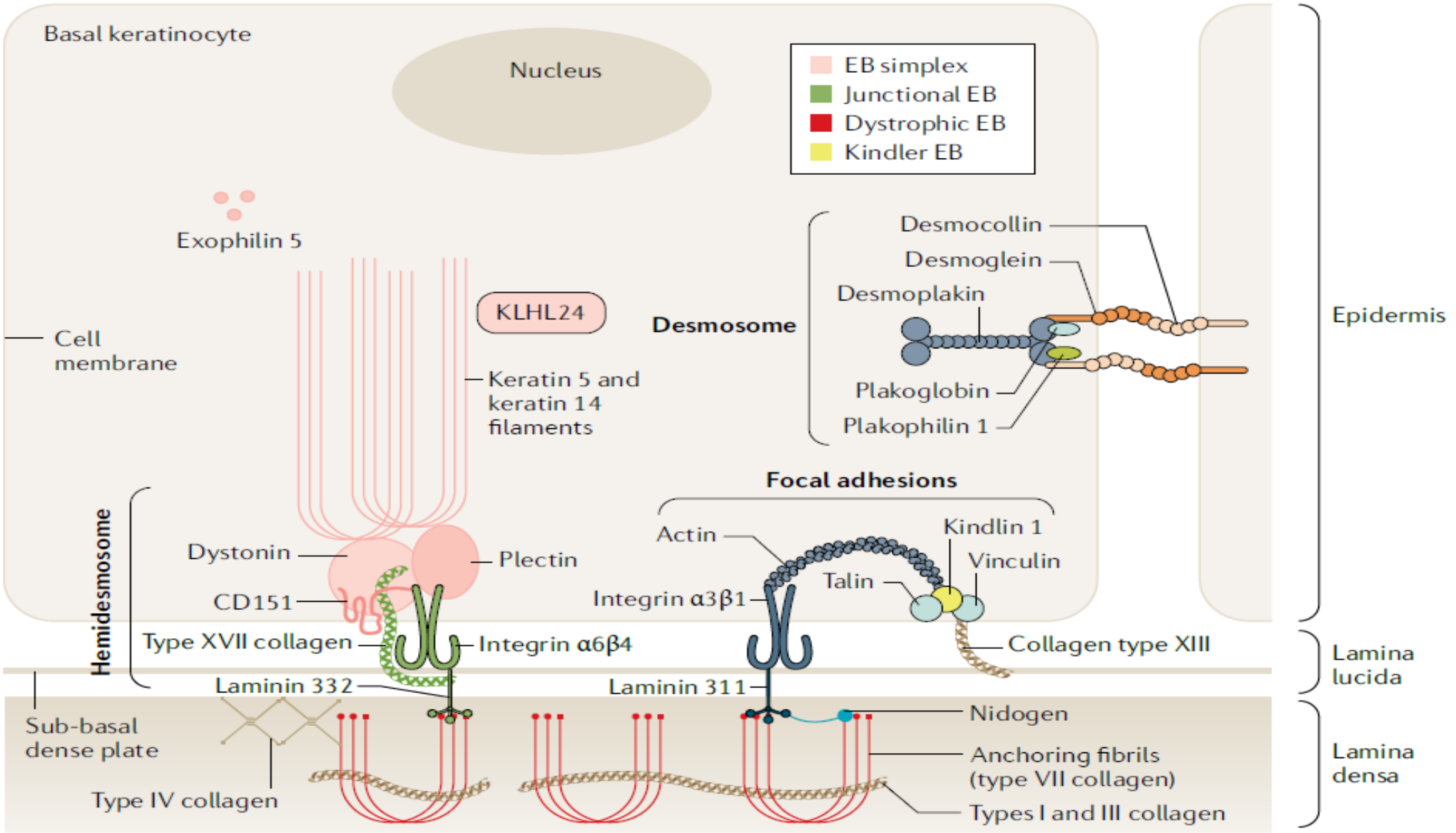




Has et al, 2020 Br J Dermatology

Junctional EB

- Anchorage of basal keratinocytes to the basement membrane
  - COL17A1 (homotrimer Collagen 17)
    - Skin atrophy, depigmentation, hair loss (*role of COL17 in follicle stem cells and melanocyte stemcells*)
    - Carcinogenesis (directed cell mobility)
  - Hemidesmosomes
    - Laminin 332 (*LAMA3, LAMB3, LAMC2*): anchorage lamina lucida
      extracutaneous – mucosal involvement – failure to thrive - cornea – kidney - lung
    - Integrin α6β4 (*ITGA6, ITGB4*)
      Pyloric stenosis, nail dystrophy
    - Integrin α3 (*ITGA3*)
      Lung disease – nephrotic syndrome (podocyte)



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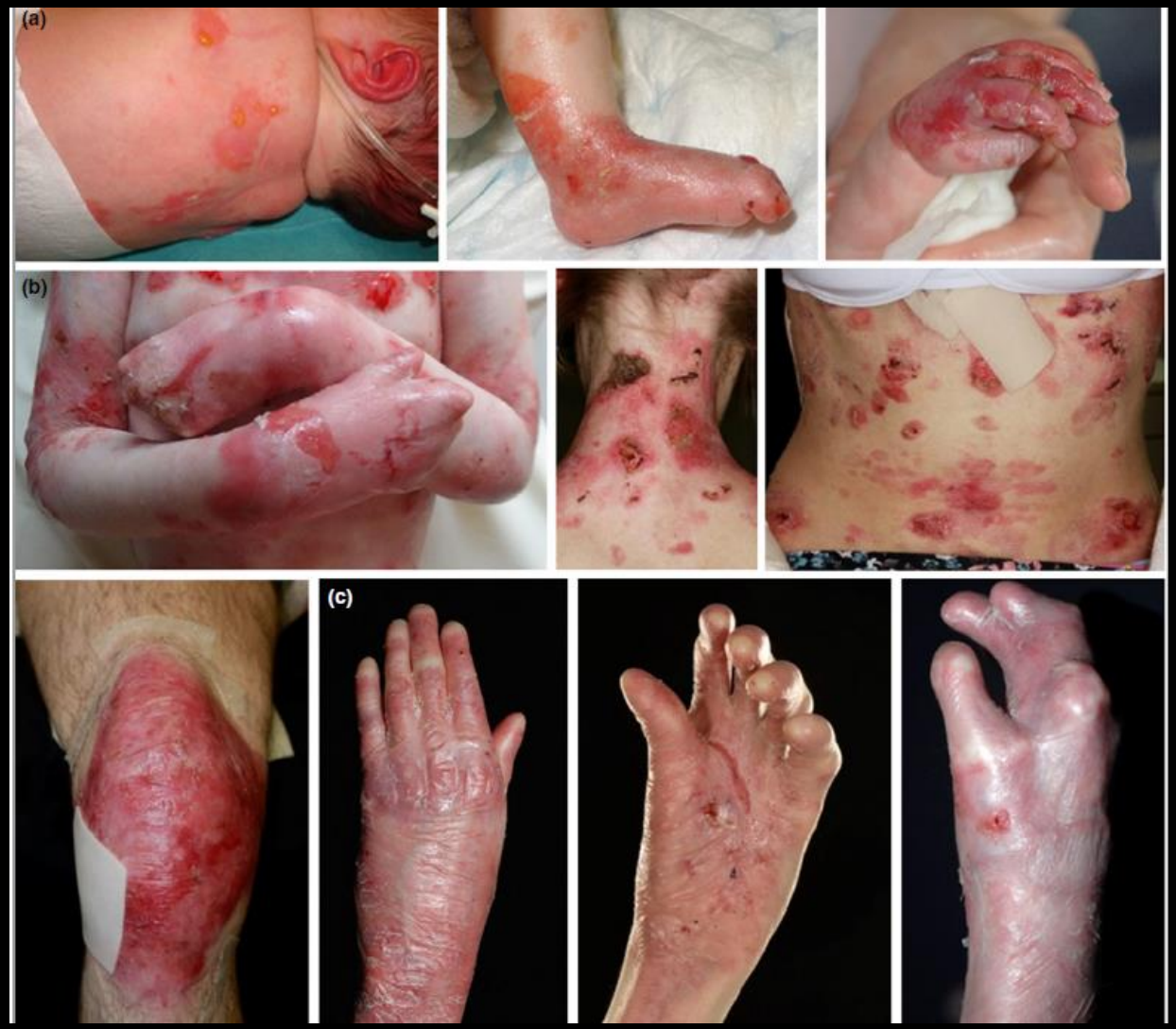
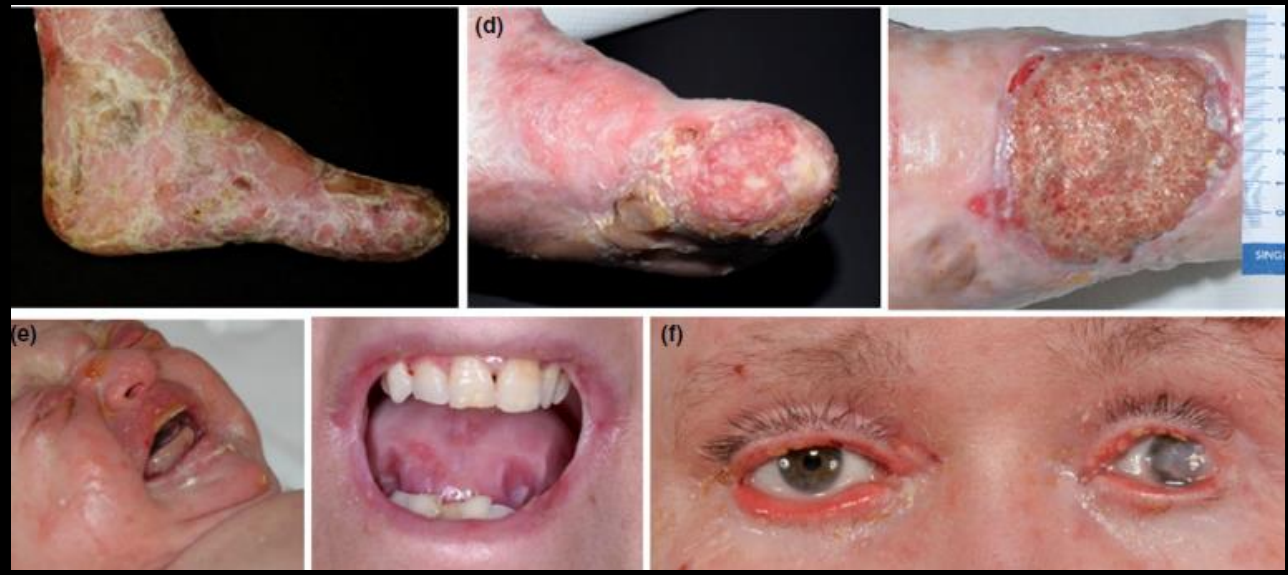
Dystrophic EB

- Blisters, fibrosis, scars, milia

- AD (often milder)
  - Intermediate (birth – mucous membranes: oral/esphageal)
  - Localized (acral) – nails
  - Pruriginosa: linear cords of papules – nails
  - Self-improving: resolution < 2y
- AR
  - >>Severe – mitten deformities
  - Intermediate (contractures)
  - Inversa: flexural
  - Localised
  - Pruriginosa
  - Self-improving





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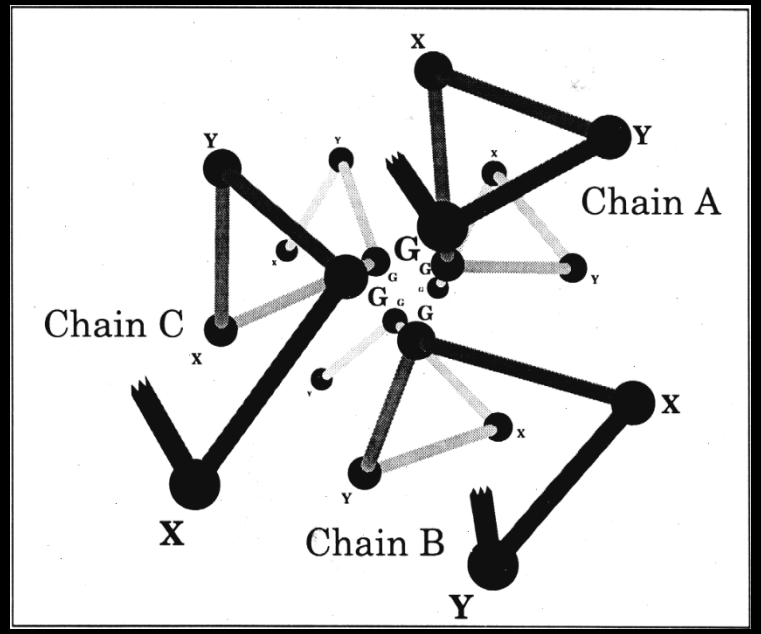
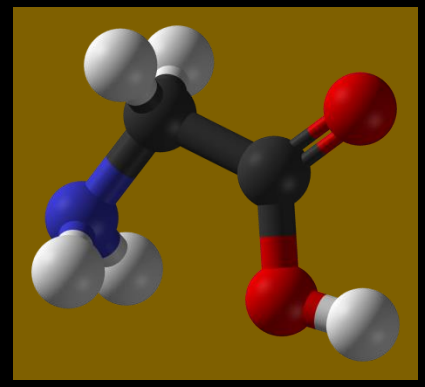
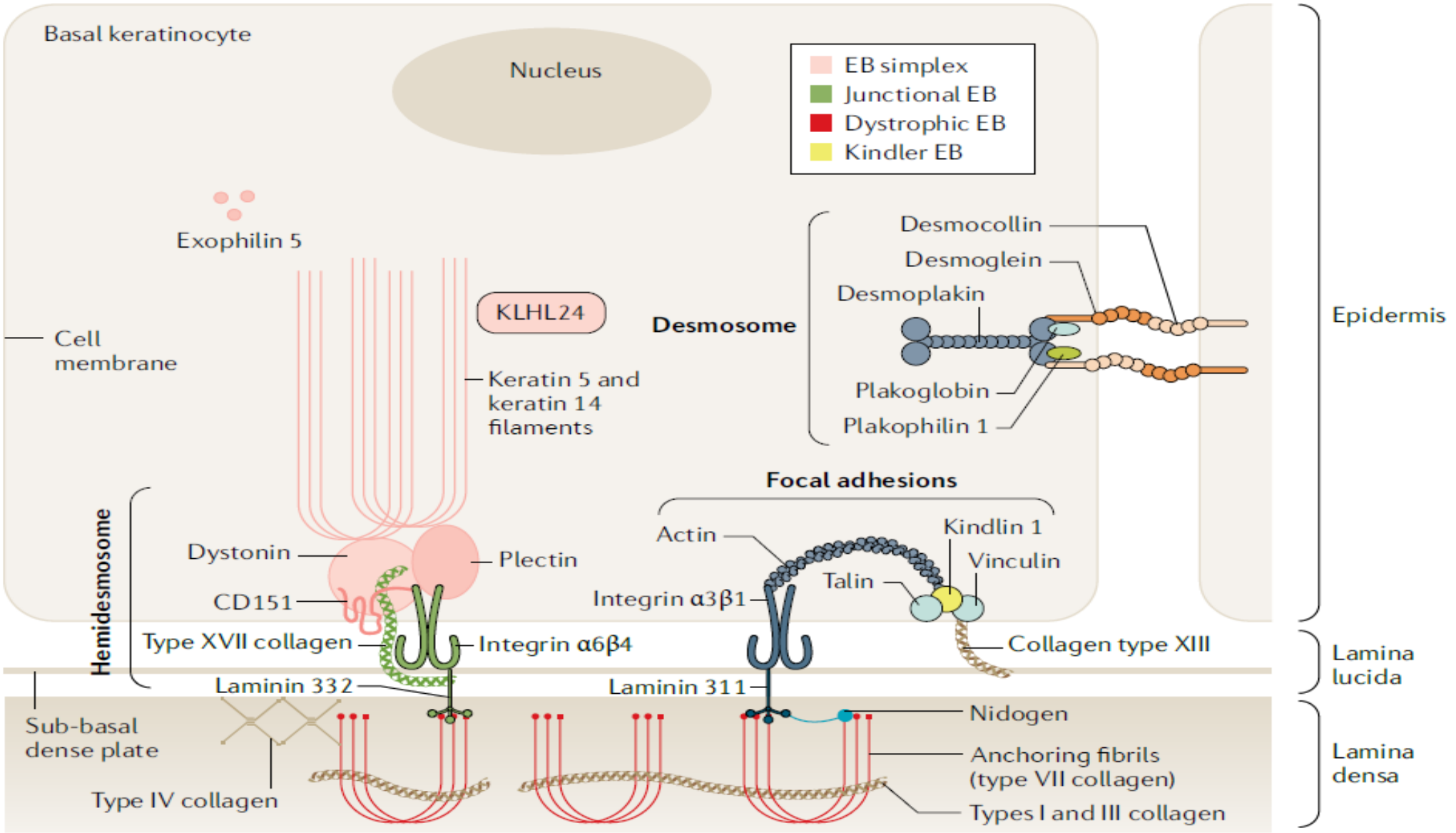
Dystrophic EB

- COL7A1: disruption of anchoring fibrils
  - Arise perpendicularly from the lamina densa and bridges laminin 332 with collagen fibrils in the superficial papillary dermis
  - AD: glycine substitutions: dominant negative effect
  - AR: PTC/missense variations



Glycine





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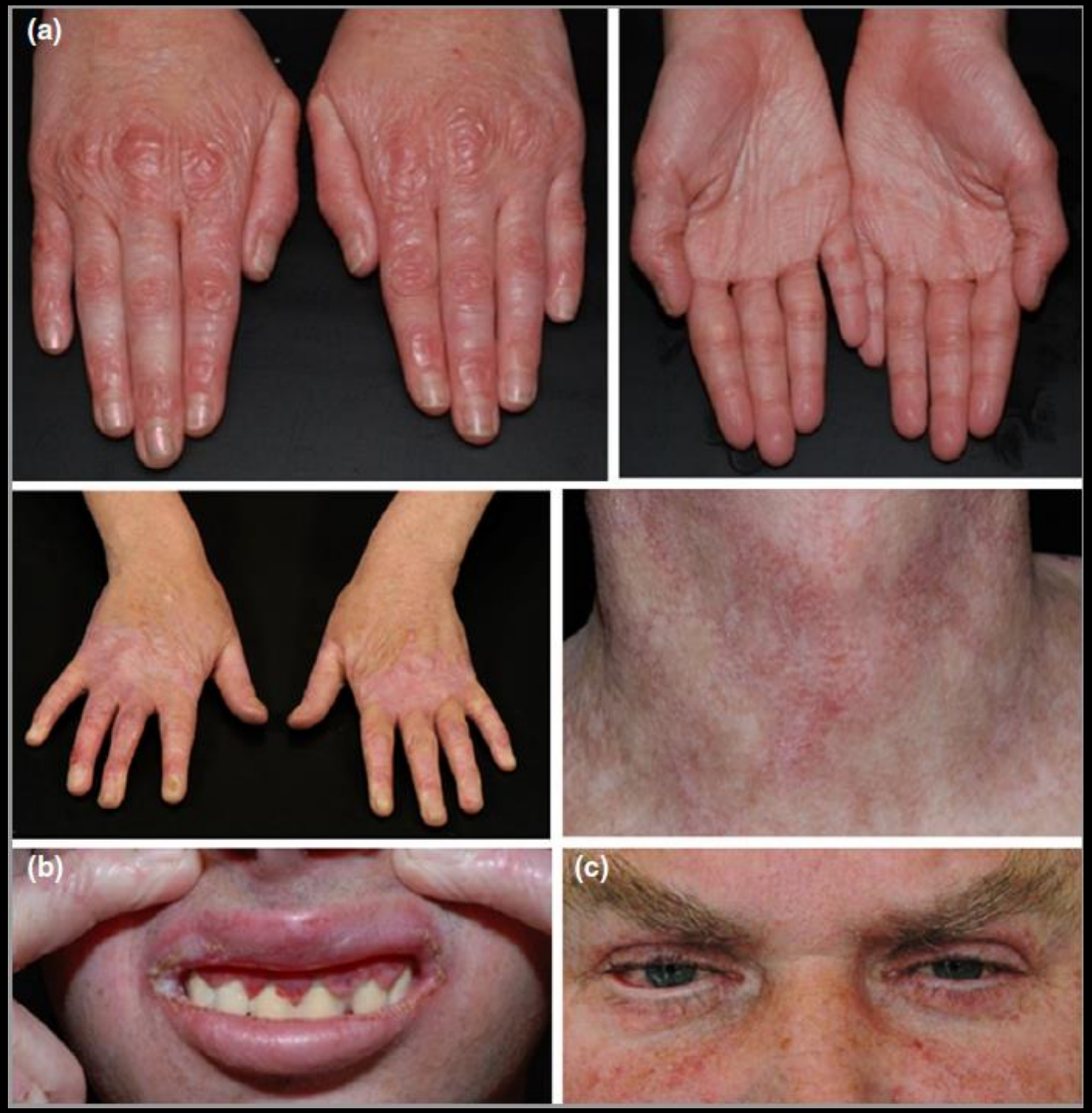
Kindler EB

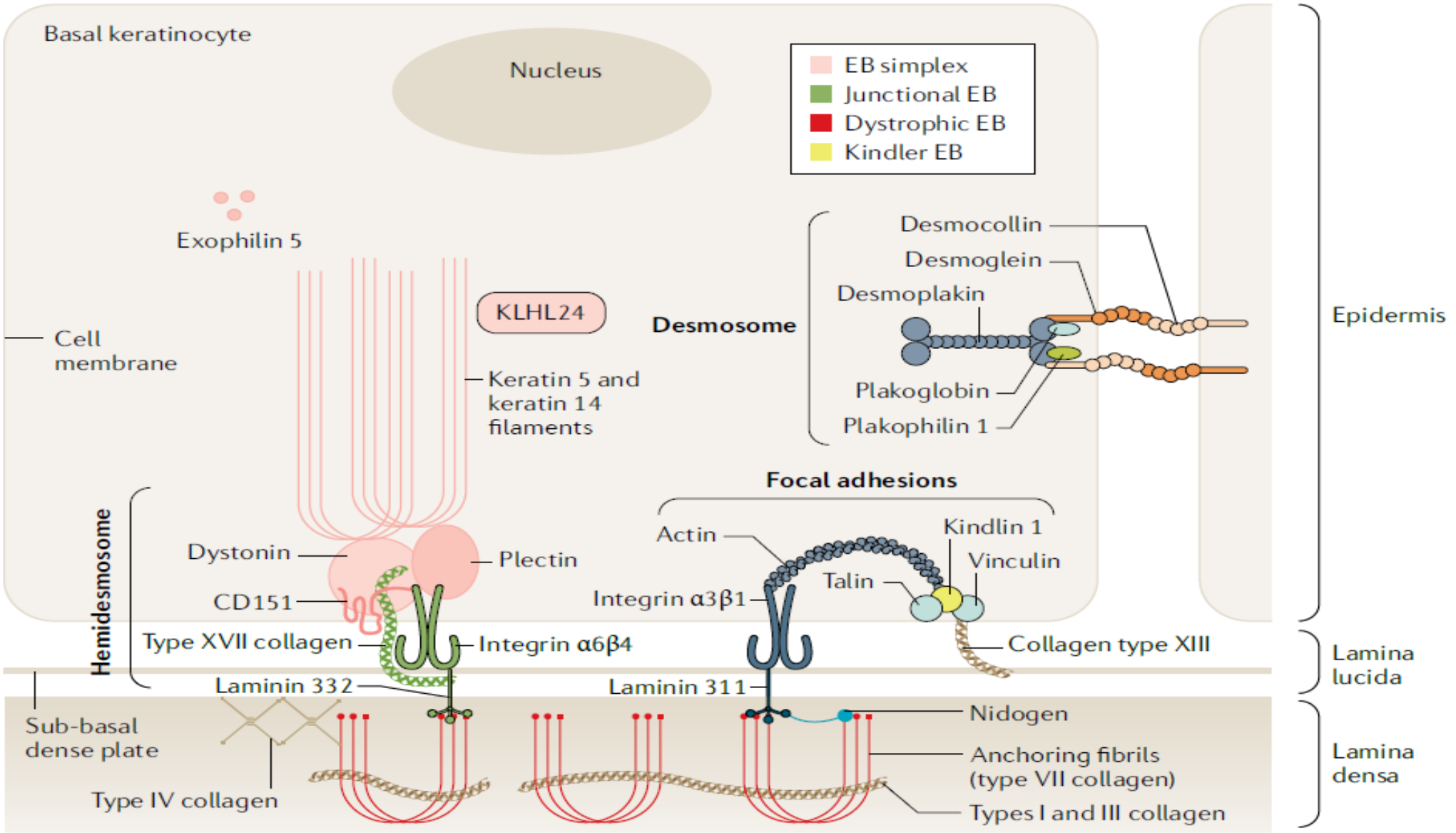
- Rare
  - *Childhood*: Blisters, *photosensitivity,* mucosal fragility palmoplantar keratoderma
  - *Later*: poikiloderma (dorsum hands / neck), erythema, hyper/hypopigmentation, skin atrophy, mucocutaneous scarring, palmoplantar hyperkeratosis. +/- *colitis, esophageal narrowing*
  - Epithelial cancers and non-melanoma skin cancer (SCC)
  - Ectopic hair follicle development
  - Splits at different levels: scars and fibrosis



Has et al, 2020 Br J Dermatology

Kindler EB

- Kindlin-1 (*FERMT1*)
  - Integrin activator: effect on cellular adhesion, migration, proliferation, surivival and proliferation, and ECM assembly.
  - Wide tissue distribution
  - TGFβ and WNT – β-catenin signaling (avβ6-mediated)
  - UVB radiation induces pro-inflammatory cytokines (IL6, TNF) → apoptosis anti-oxidant therapy?



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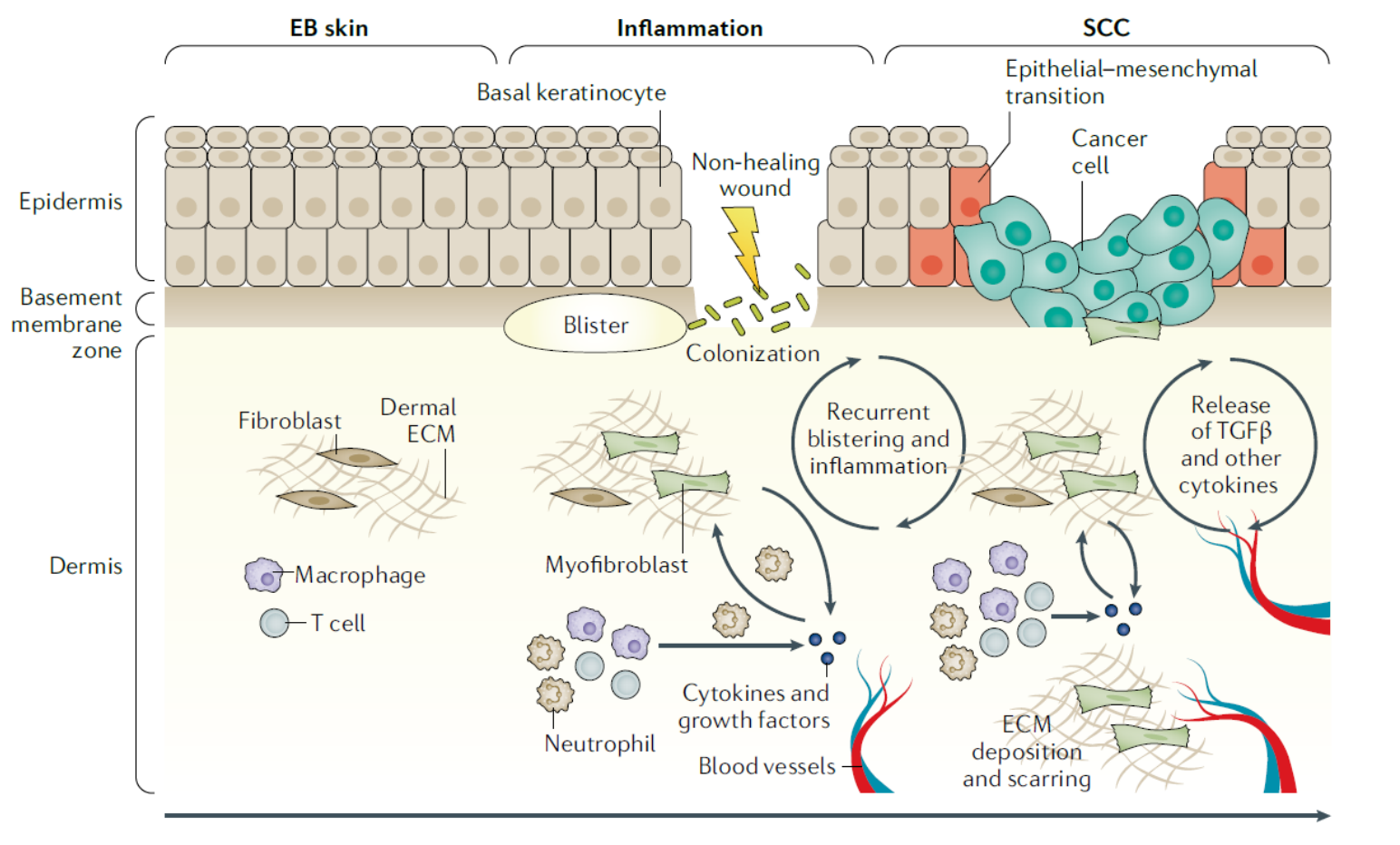
Cancer risk

- Skin/mucosal squamous cell carcinoma (>>RDEB), ↑ above 20y
  - 40% ✝ 35
  - 80% ✝ 55Y
  - Mean survival 5 years following first SCC diagnosis

- Basal cell carcinoma (UV-exposed)

Cancer risk



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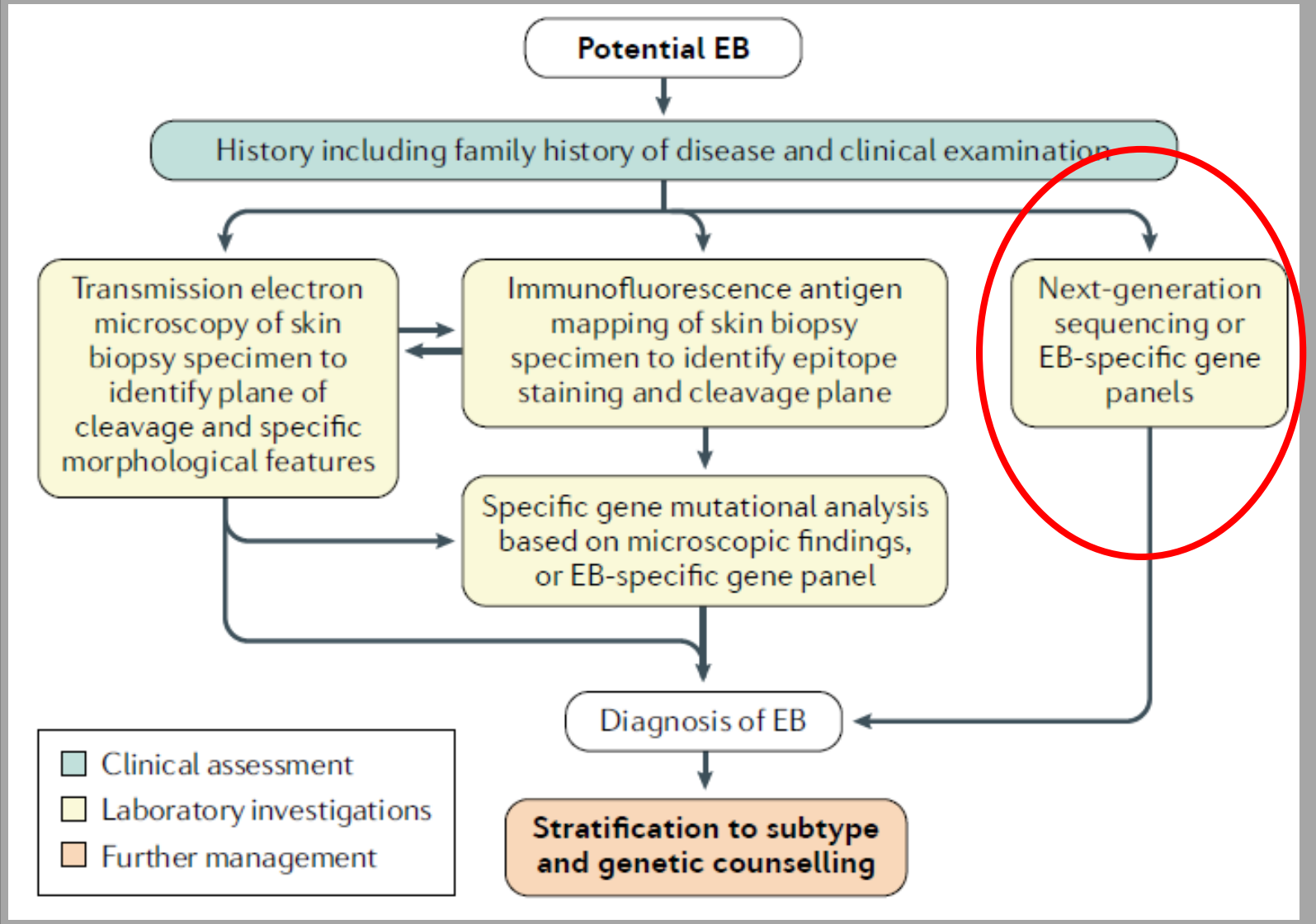
Diagnosis

- Clinical diagnosis (and prognosis): often difficult at birth – onset
- Later onset: diaper – crawling

- *Specific* clinical signs:
  - blisters and keratoderma: localized EBS
  - Confluent PPK and herpetiform blisters: severe EBS
  - Microstomia, mitten deformity, contractures, milia: dystrophic EB
  - Photosenstivity Kindler EB
  - Erosions + neonatal pyoric stenosis: JEB (α6β4 integrin)
  - NS (ITGA3, JEB)



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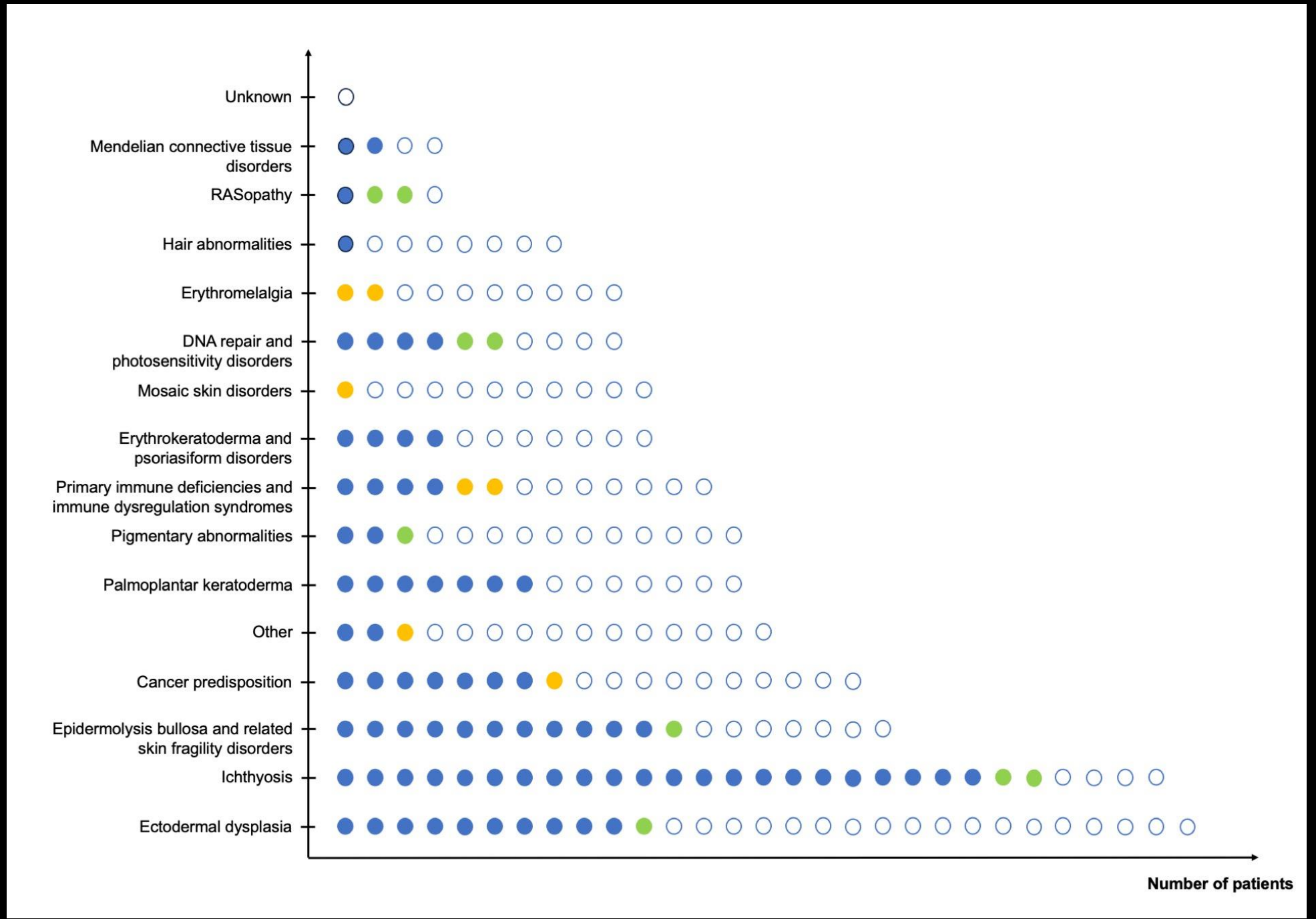
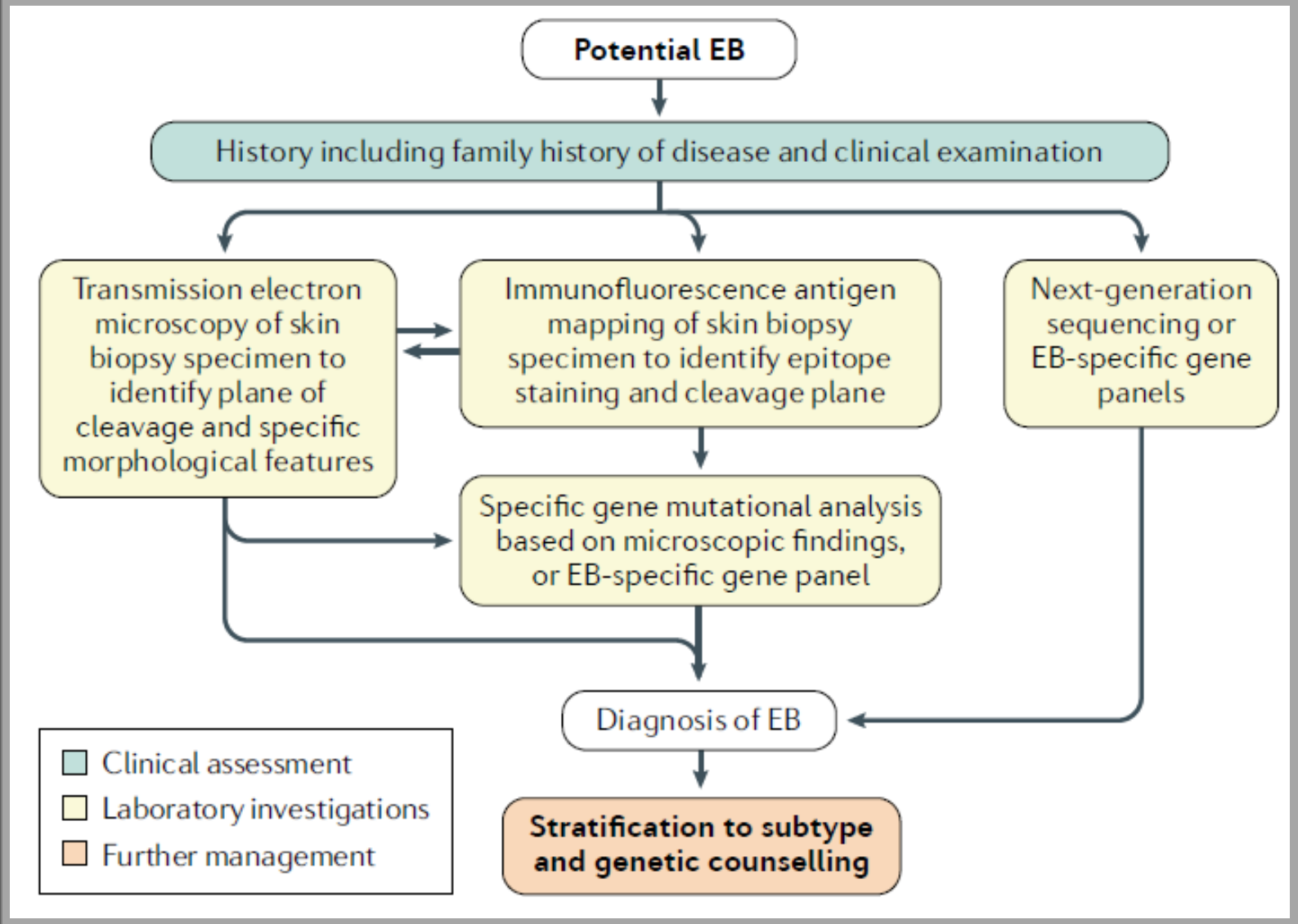

Unknown
Mendelian connective tissue disorders
RASopathy
Hair abnormalities
Erythromelalgia
DNA repair and photosensitivity disorders
Mosaic skin disorders
Erythrokeratoderma and psoriasiform disorders
Primary immune deficiencies and immune dysregulation syndromes
Pigmentary abnormalities
Palmoplantar keratoderma
Other
Cancer predisposition
Epidermolysis bullosa and related skin fragility disorders
Ichthyosis
Ectodermal dysplasia
Number of patients

Diagnosis

- Prognosis – management - therapy
- Prenatal diagnosis
- Preïmplantation diagnosis



Bardhan et al, 2020
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Differential diagnosis

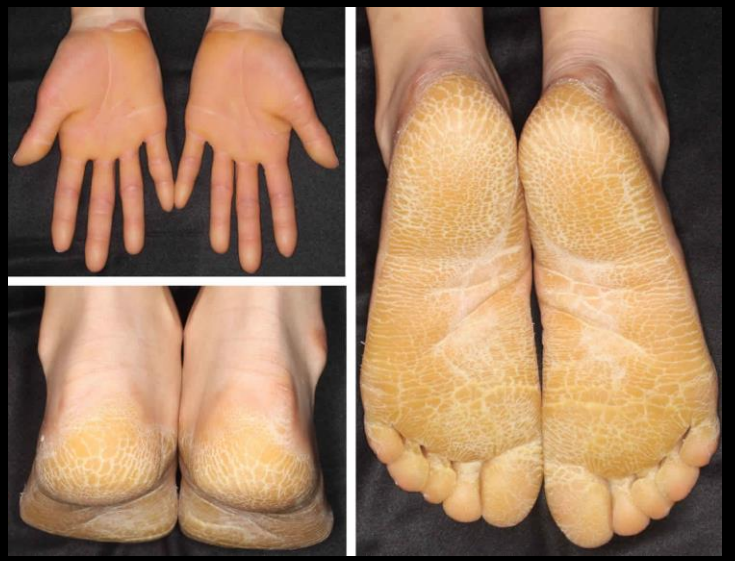
- Skin fragility disorders (AR)
  - *DSP* (*JUP*): generalized skin and mucosal erosions, absent nails and hair: lethal
  - *PKP1*: ectodermal dsyplasia – skin fragility
  - *DSC3*: recurrent skin vesicles, hypotrichosis (crown and facial hair)

- Peeling skin (AR)
  - *TGM5*: palms and soles
  - *CSTA*: palmoplantar peeling – widespread exfoliative ichthyosis
  - *CSTB*: seasonal PPK - peeling
  - *CDSN*, *SERPINB8*, *FLG2*: inflammatory ichthyosiform erythroderma
  - *SPINK5*: Netherton sy
  - *CAST*: Plack syndrome: leukonychia, acral punctate keratoses, hypotrichosis, knuckle pads
  - *DSG1*, *DSP*: *PPK*, hypotrichosis, hyper-IgE, erosions, scaling

- Hyperkeratotic disorders (> AD)
  - *KRT1*, *2*, *10*: erythroderma – blistering – scaling (flexural areas) +/- PPK
  - *KRT6A*, *6B*, *6C*, *16*, *17*: painful PPK + blistering, hyperkeratotic nail dystrophy

- CTD: *PLOD3*: bone fragility – aneurysms – contractures- blistering

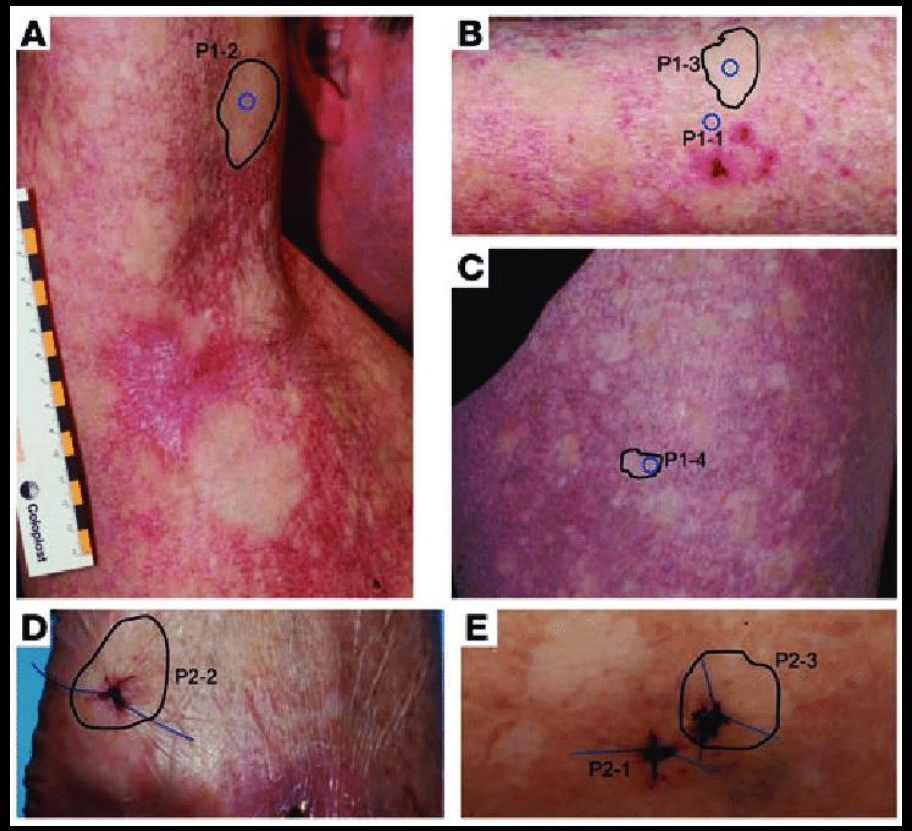
Peeling skin

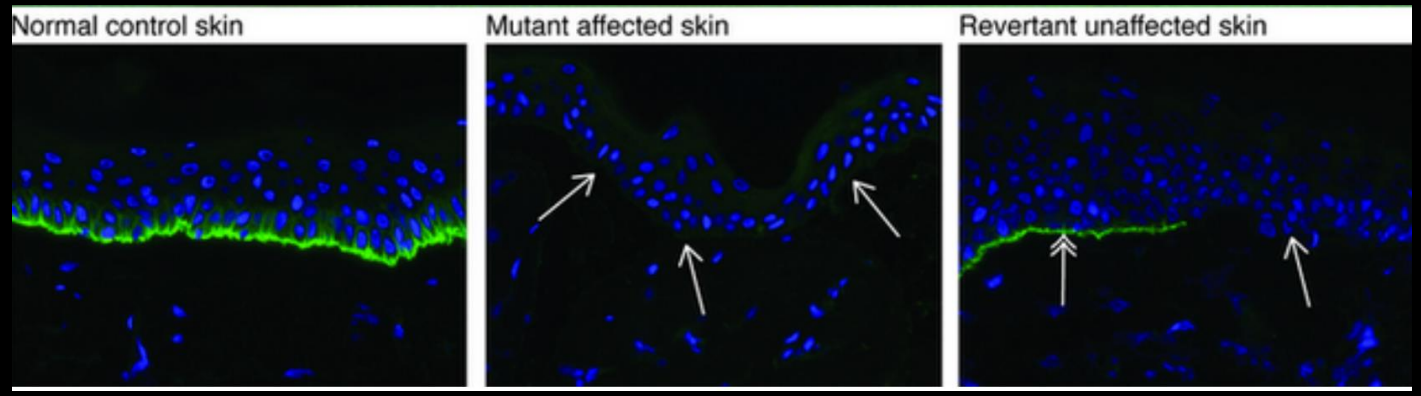


PPK

Revertant mozaicism

- Jonkman et al. Cell. 1997 Feb 21;88(4):543-51: atrophic epidermolysis bullosa
  COL17A1: c.1706delA; c.C3676T ➔ reverted mozaicism of c.1706delA in keratinocytes





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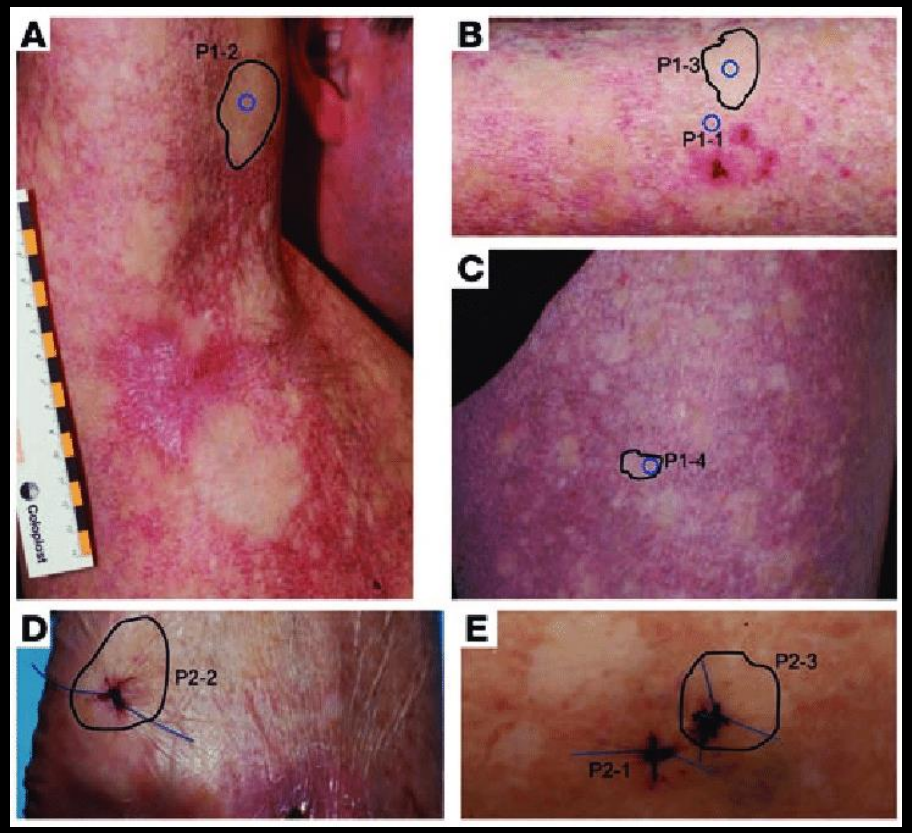
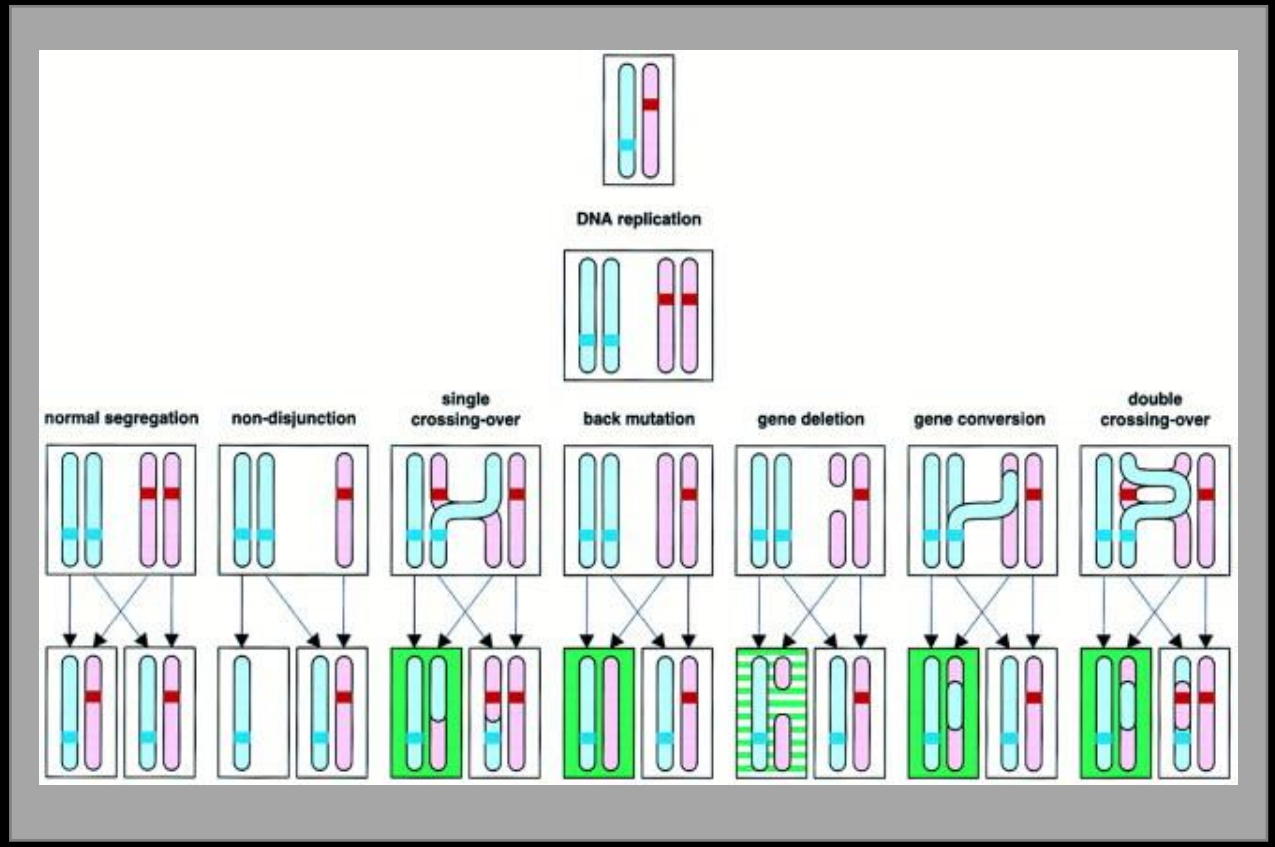
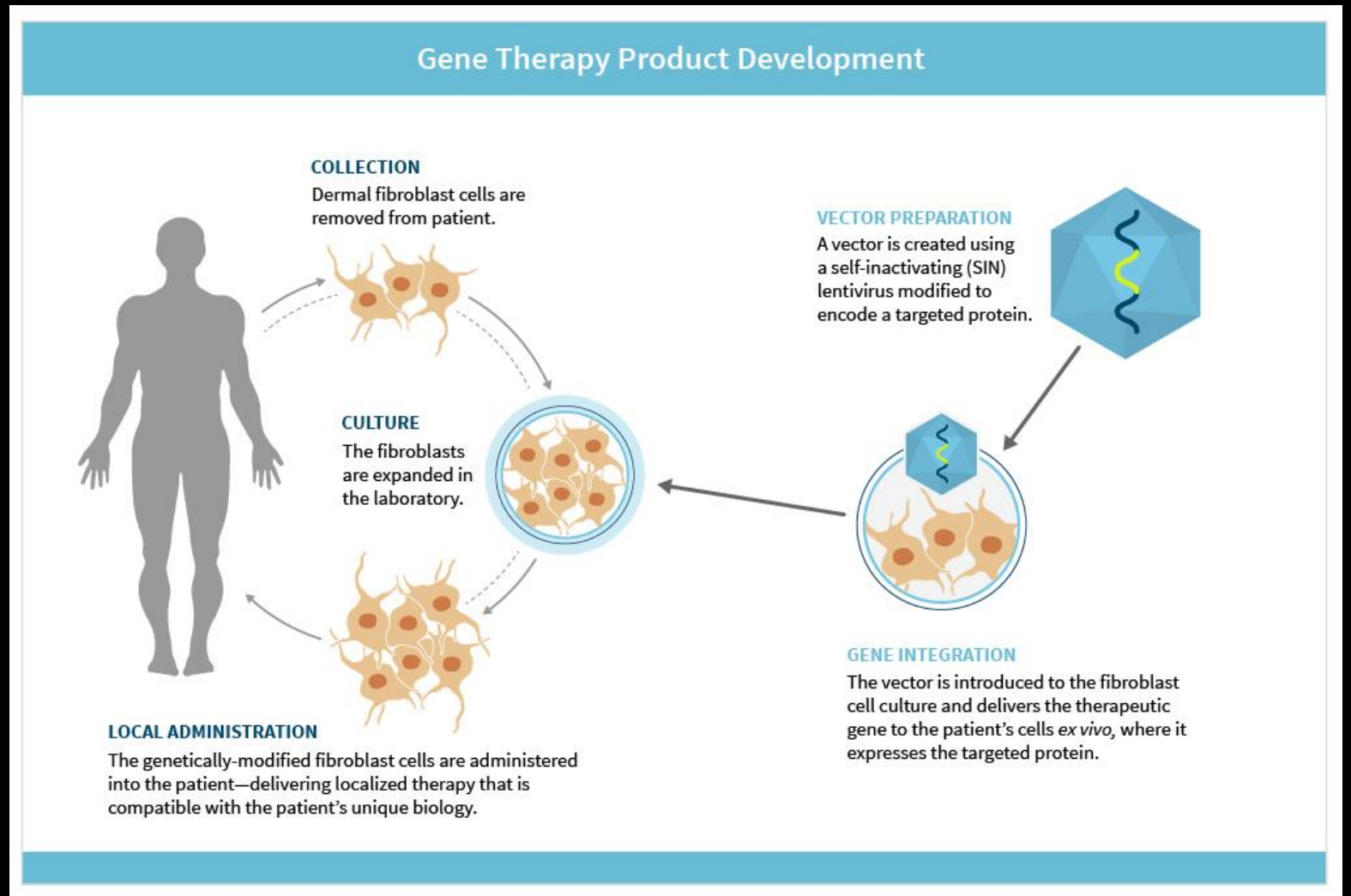
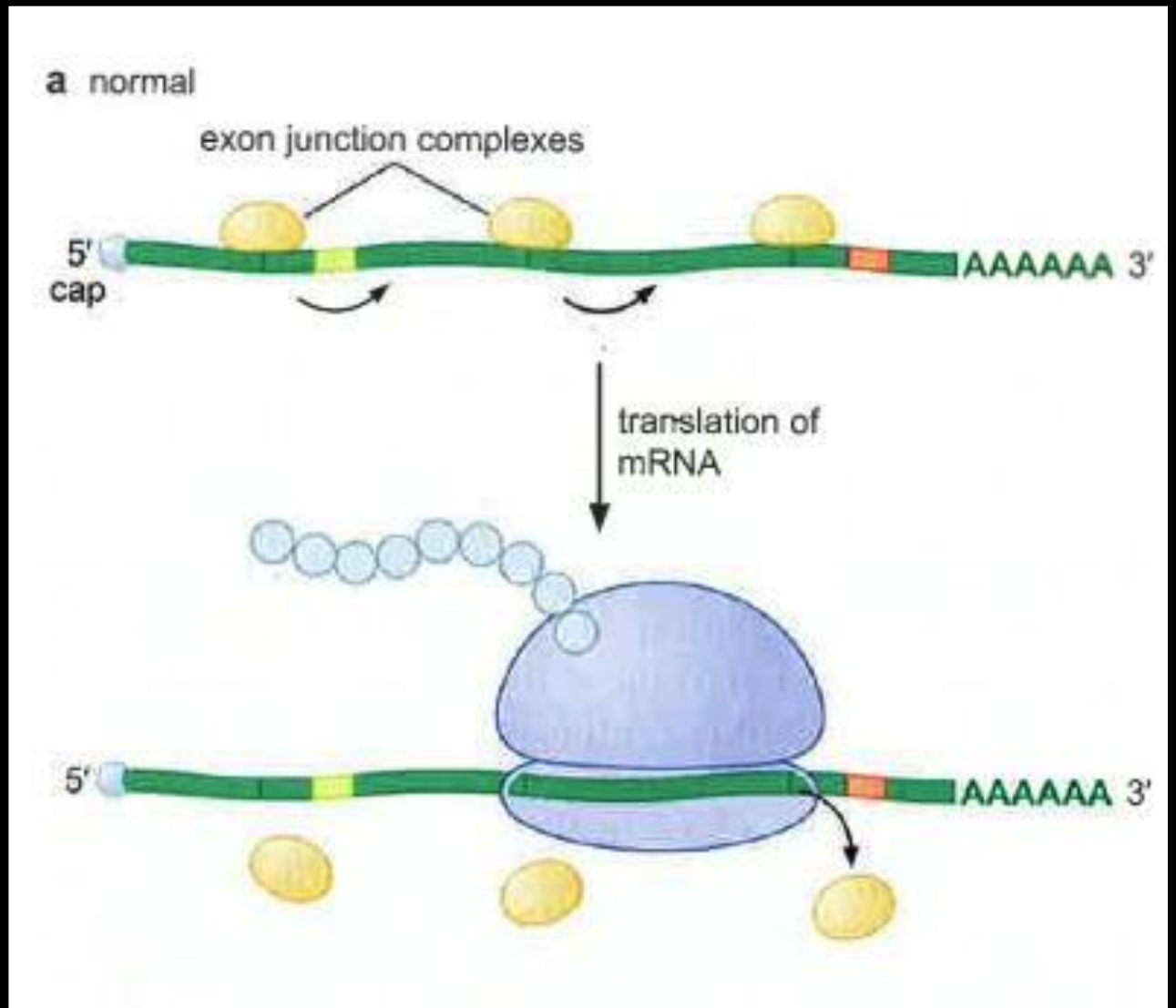


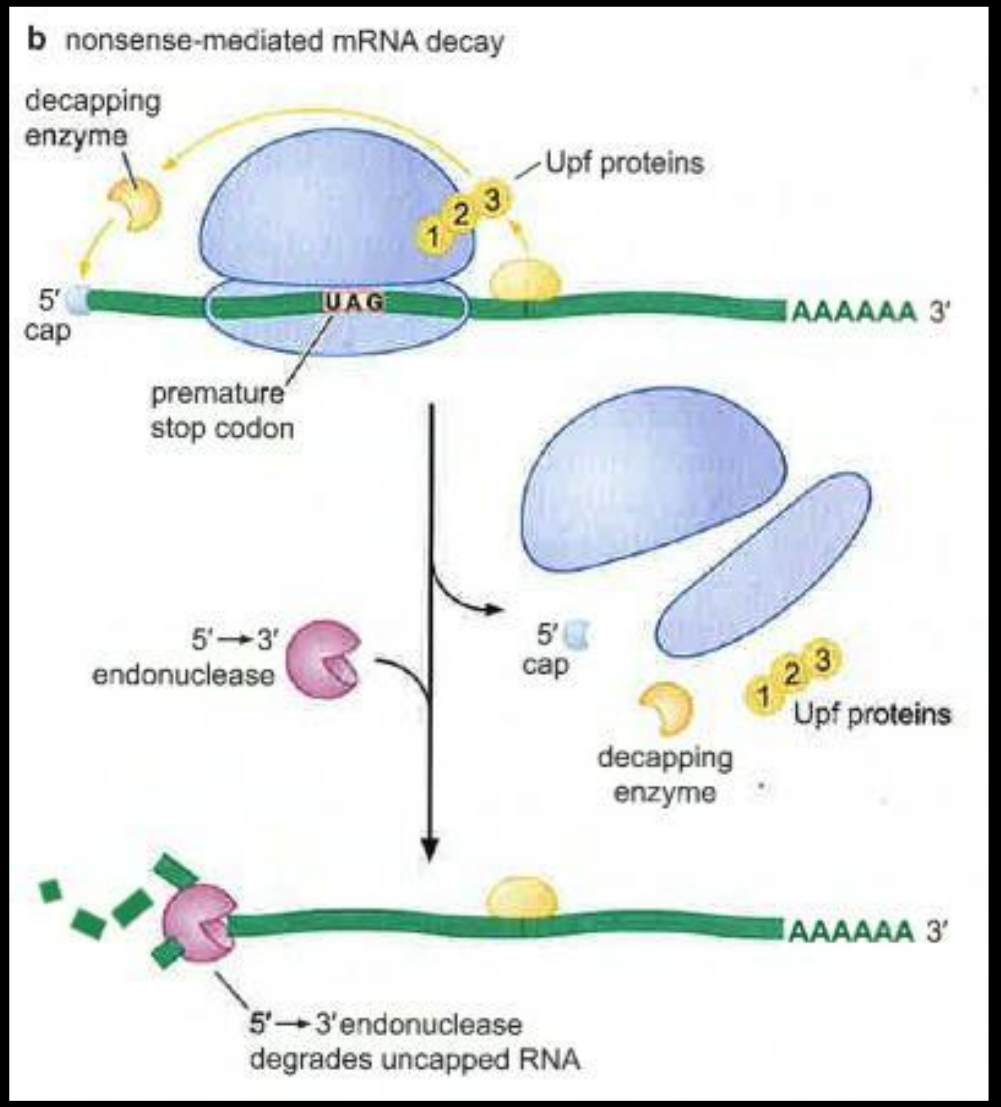


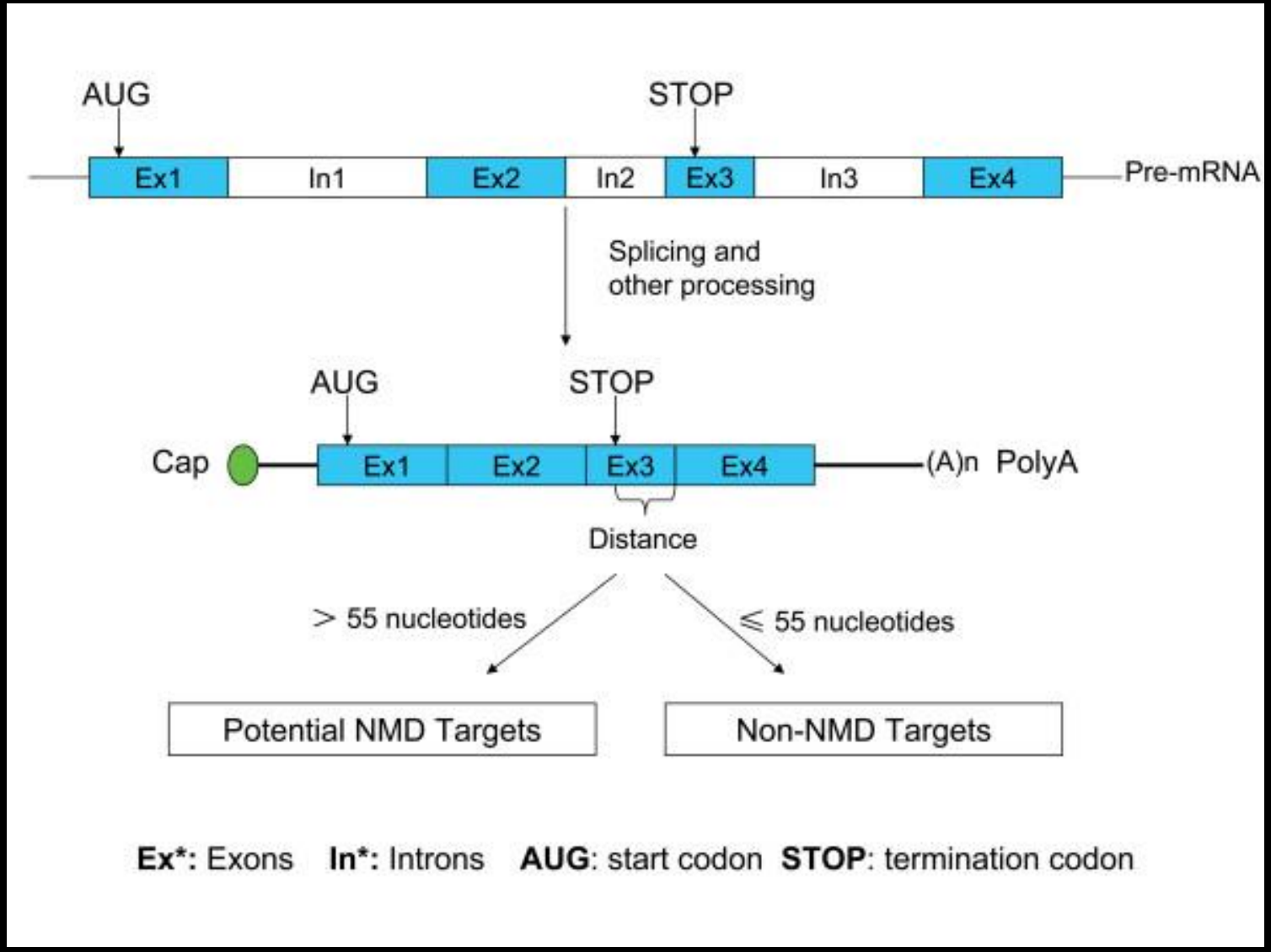
Revertant mozaicism → Gene therapy



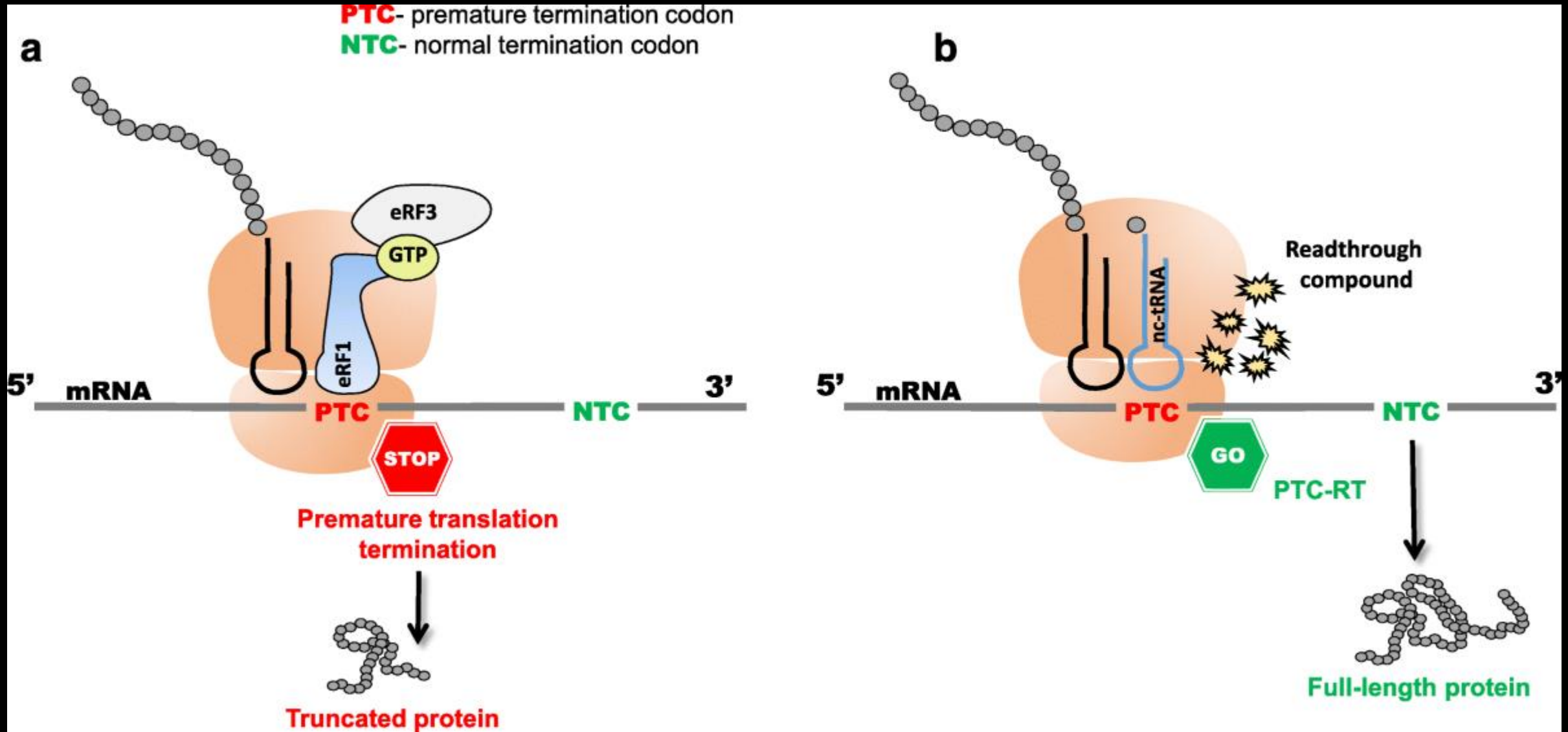
Nonsense mediated decay

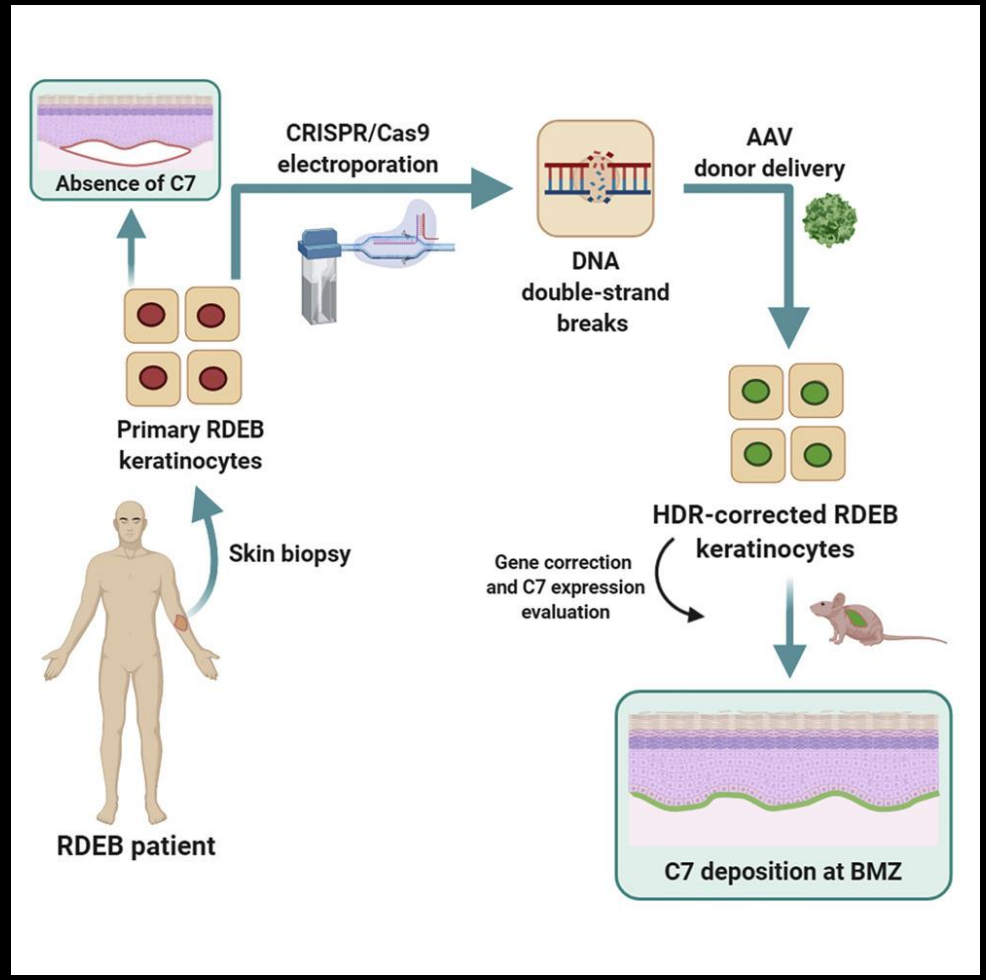


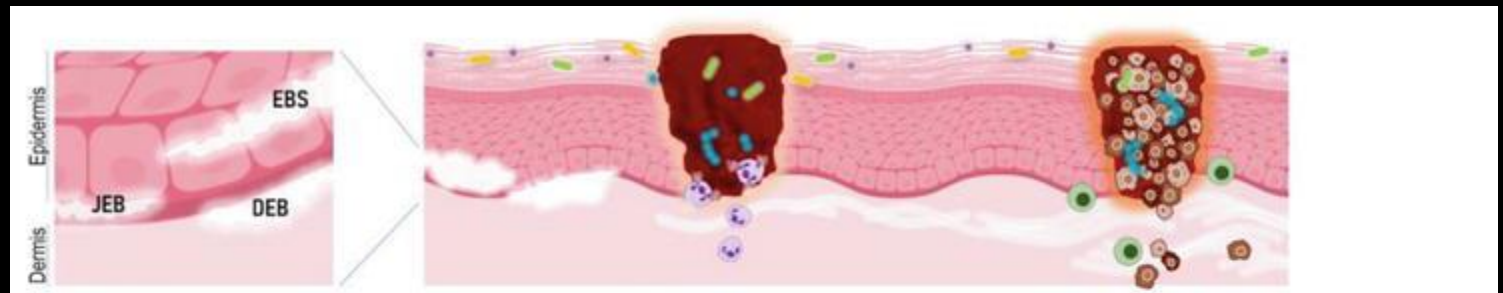



AUG
STOP
Ex1
In1
Ex2
In2
Ex3
In3
Ex4
Pre-mRNA
Splicing and
other processing
AUG
STOP
Cap
Ex1
Ex2
Ex3
Ex4
(A)n PolyA
Distance
> 55 nucleotides
⩽ 55 nucleotides
Potential NMD Targets
Non-NMD Targets
Ex*: Exons In*: Introns AUG: start codon STOP: termination codon

Read-through drug: e.g. gentamycin, AON




Absence of C7
CRISPR/Cas9
electroporation
DNA
double-strand
breaks
AAV
donor delivery
Primary RDEB
keratinocytes
Skin biopsy
RDEB patient
HDR-corrected RDEB
keratinocytes
Gene correction
and C7 expression
evaluation
C7 deposition at BMZ



Skin fragility

- Causal mutations
  - Gene editing
  - cDNA replacement
- Missing/dysfunctional protein
  - AON-therapy
  - Protein/cell replacement
  - PTC read-through strategies

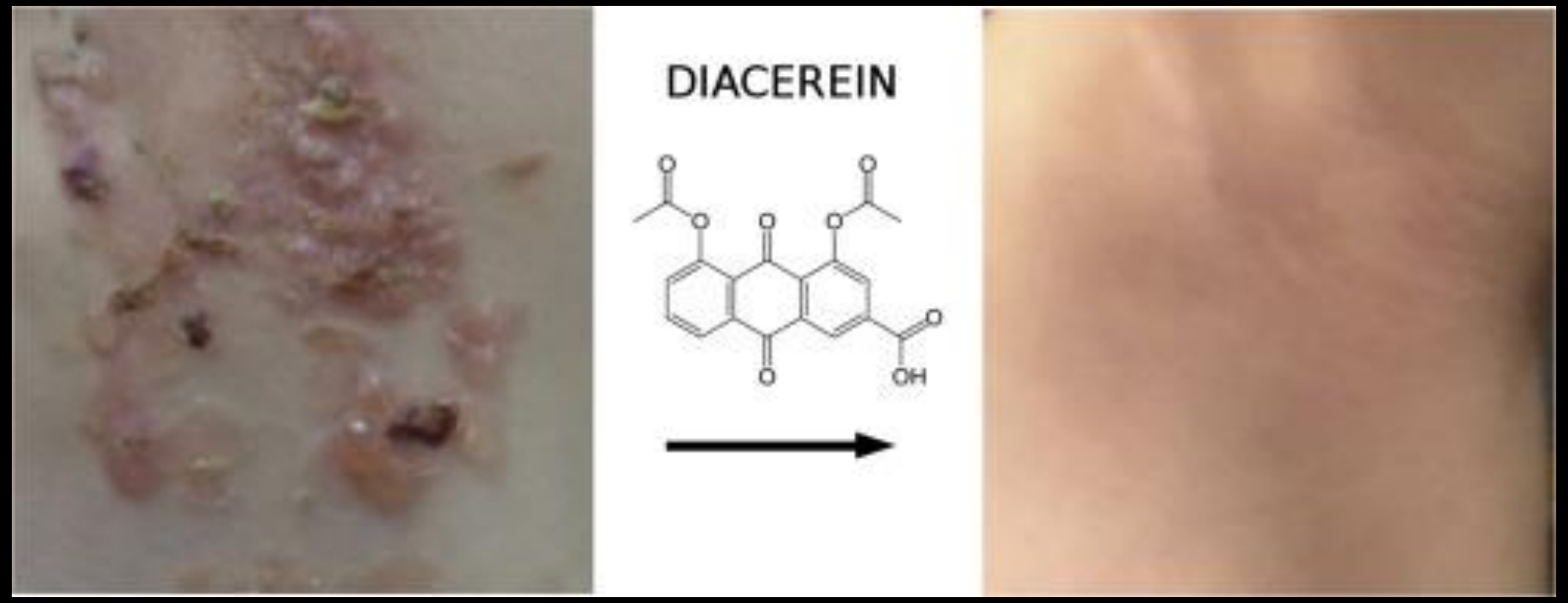
Blisters / Wounds

- Infection/Inflammation
  - Filzuvez
  - Gentamicin
  - Diacerein
- Itch
  - Serlopitant
  - Dupilumab
  - Calcipotriol
- Fibrosis
  - Losartan

Skin tumor

- Tumor cell pathways
  - Cetuximab
  - Ruxolitinib
  - Rigosertib
- Tumor microenvironment
  - Immune checkpoint blockade

- Keratin aggregates → autocrine IL1β signaling → stress → cytolysis

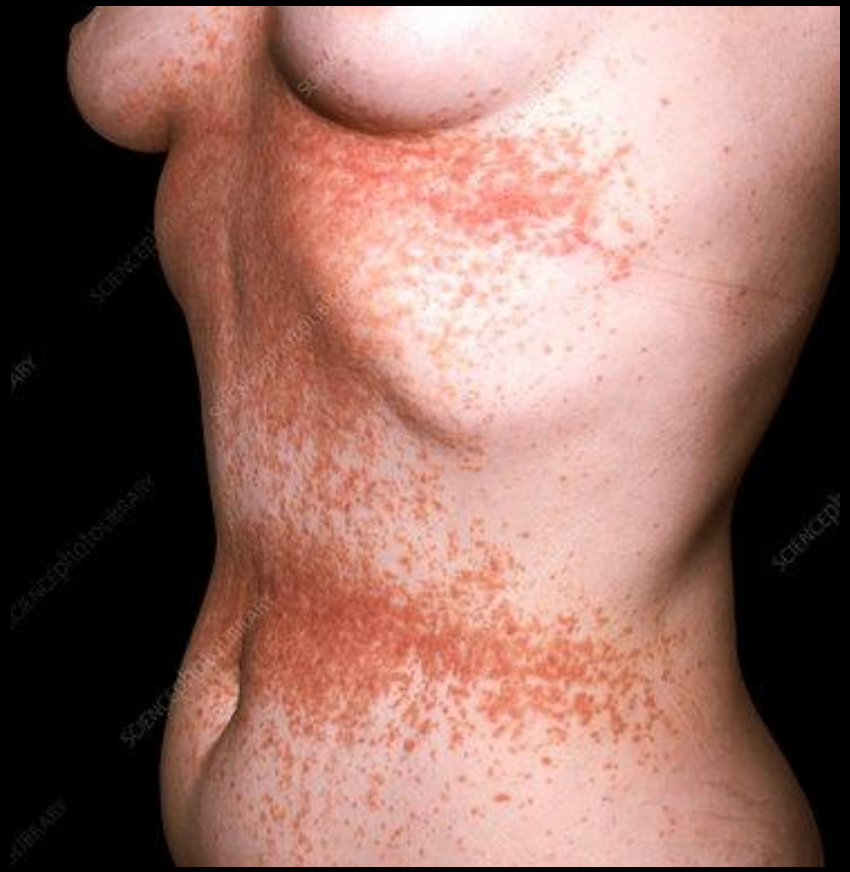


IL1β ↓

Wally et al, 2018, JAAD

Darier disease

- Autosomal dominant
- Multiple red or brown papules with hyperkeratosis (rough – wart-like)
  “keratosis follicularis”
  > chest, back, scalp, and forehead
- nail abnormalities (eg, longitudinal erythronychia)
- mucosal involvement
- Usually starts around puberty
- Exacerbations throughout the lifespan



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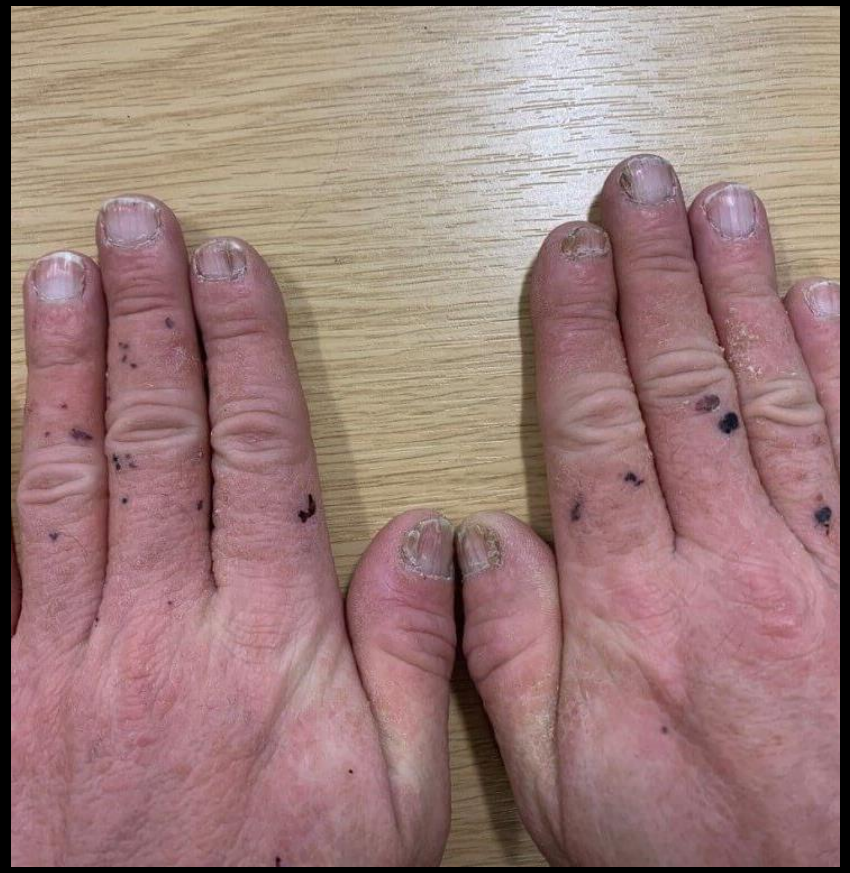
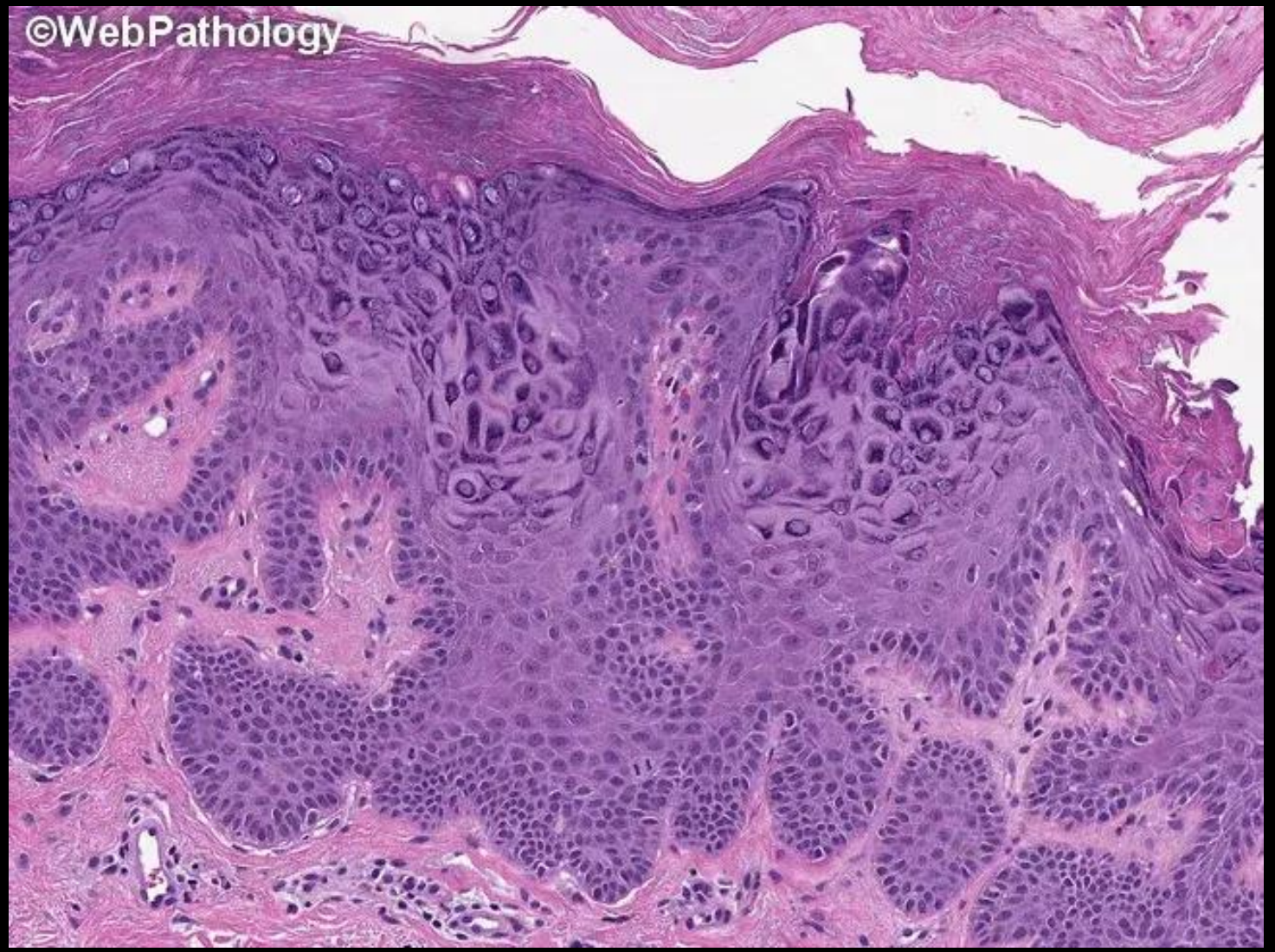


Darier disease

- Exacerbations
  - sunlight
  - Heat and humidity
  - Friction
  - Stress
  - Medications

Darier disease

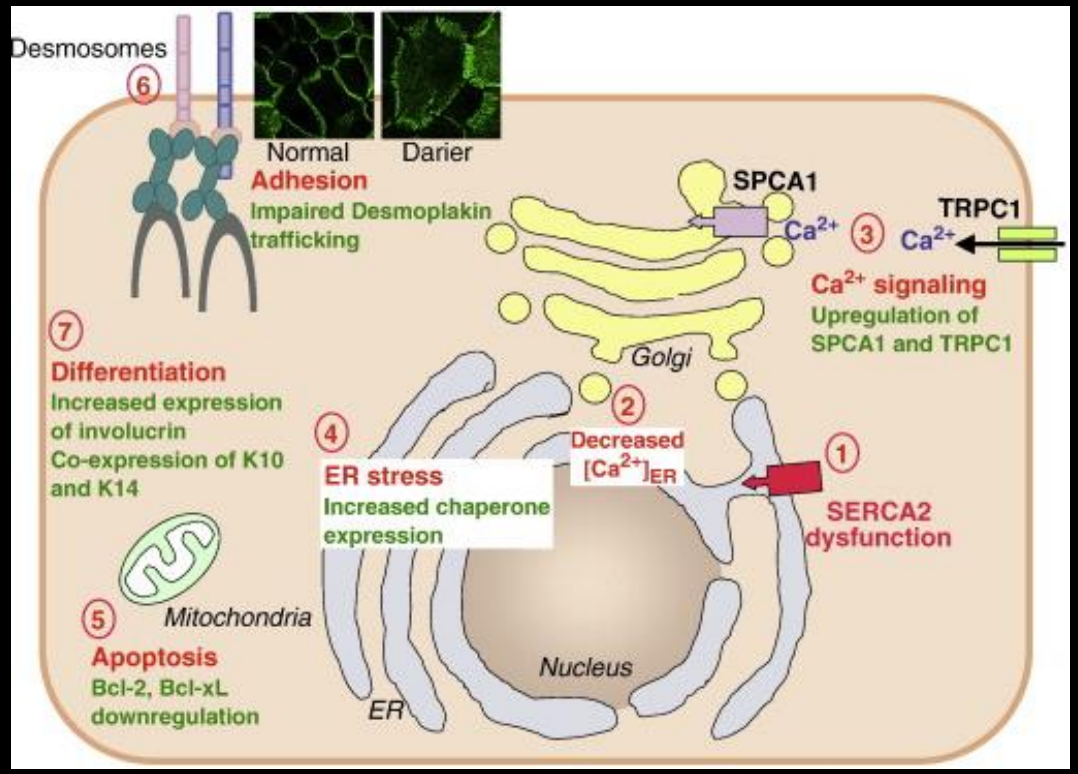
- Diagnosis
  - Clinical
  - Skin biopsy
  - Genetics: *ATP2A2* (AD)



Darier disease

- Diagnosis
  - Clinical
  - Skin biopsy
  - Genetics: *ATP2A2*

- Therapy
  - Retinoids, corticosteroids, and moisturizers.
  - Oral retinoids (e.g., Acitretin or Isotretinoin) for severe cases.
  - Antibiotics for secondary infections.
  - Lifestyle modifications to reduce triggers.

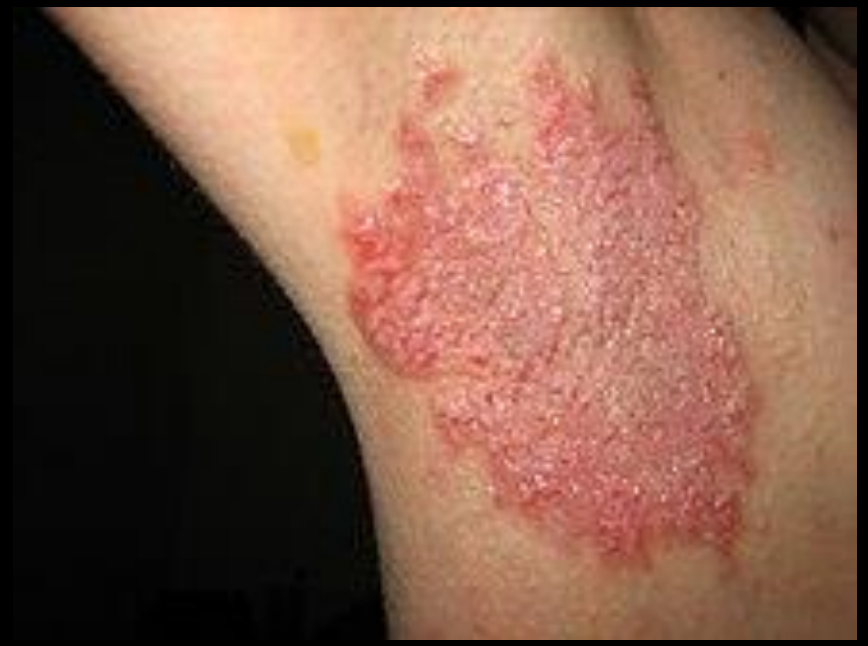


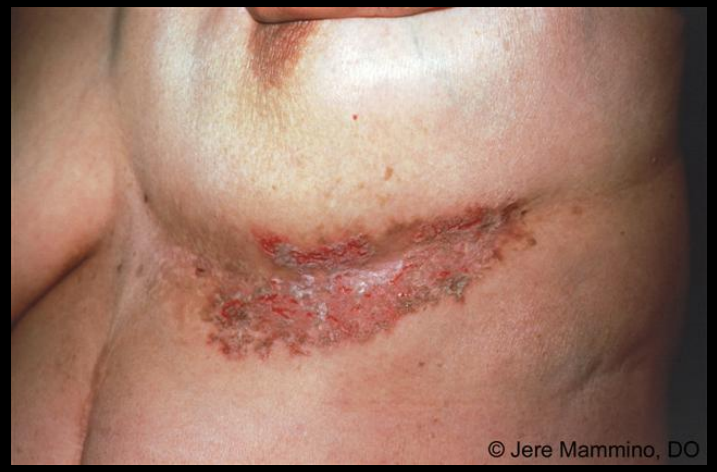
Savignac et al, 2011, BAA

Hailey – Hailey disease

- Autosomal dominant
- red, raw, and blistered areas of skin that occur most often in skin folds, such as the groin, armpits, neck, and under the breasts.

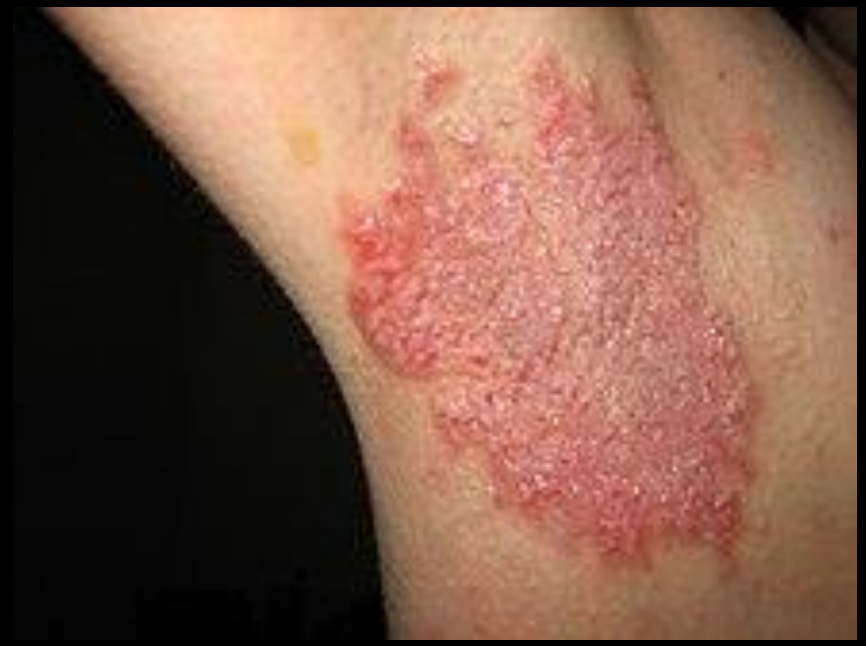
  Crusty scaly → itchy/burny
- "Benign chronic pemphigus"
- Squamous cell carcinoma
- Early adulthood
- Exacerbations throughout the life span

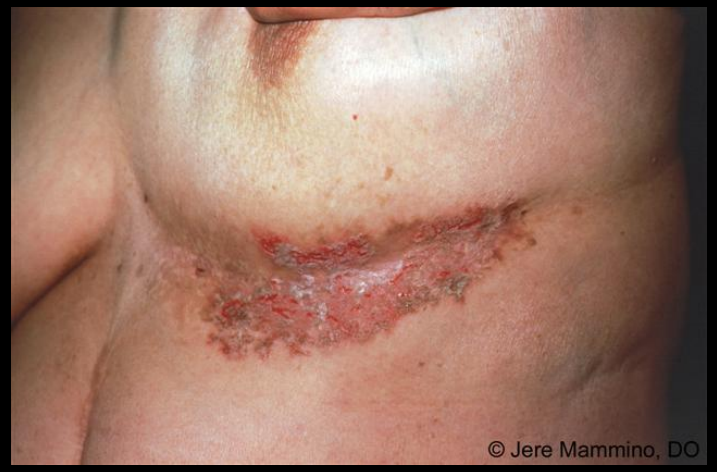




Hailey – Hailey disease

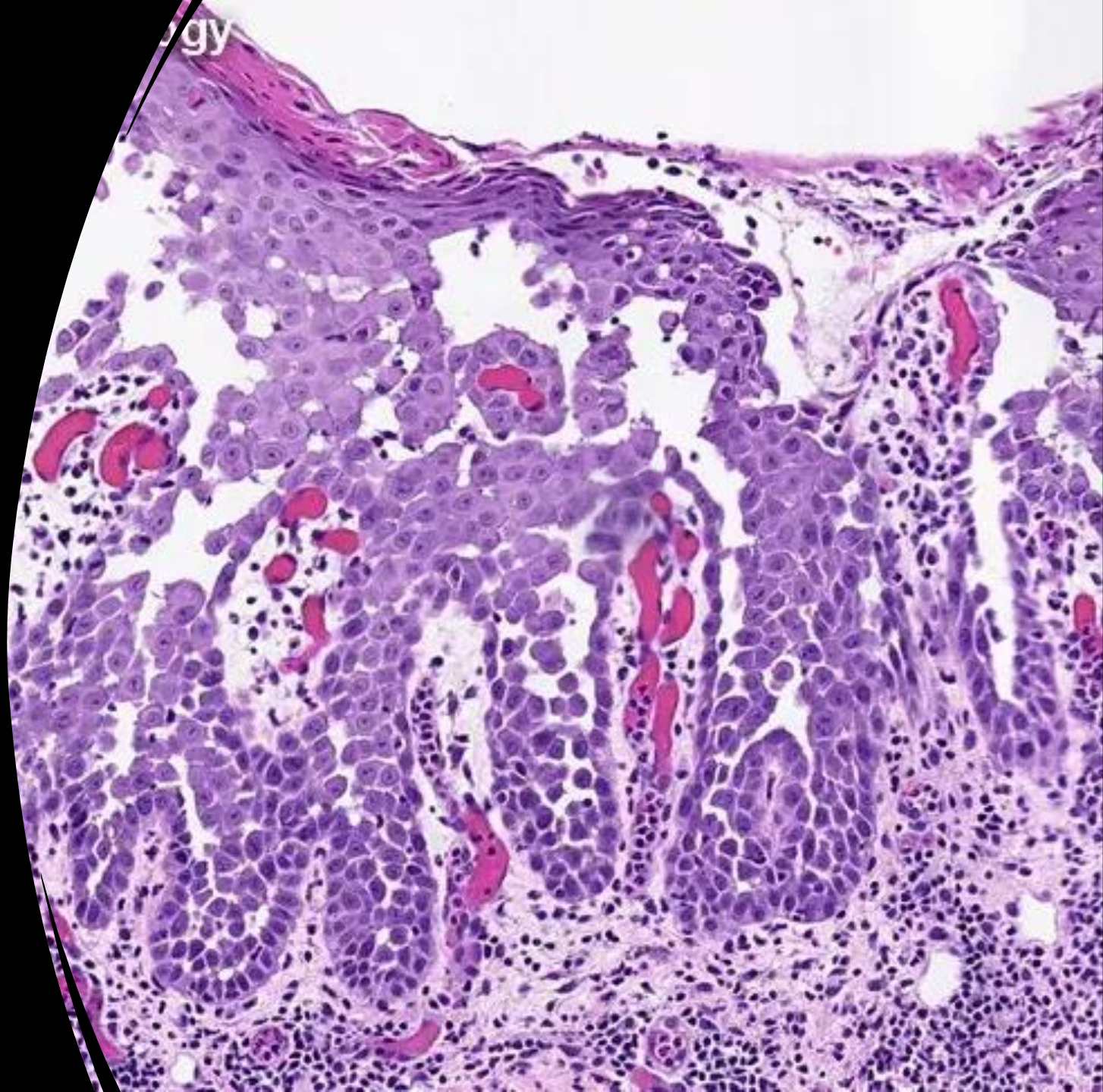
- Exacerbations
  - Moisture (such as sweat)
  - Friction
  - weather



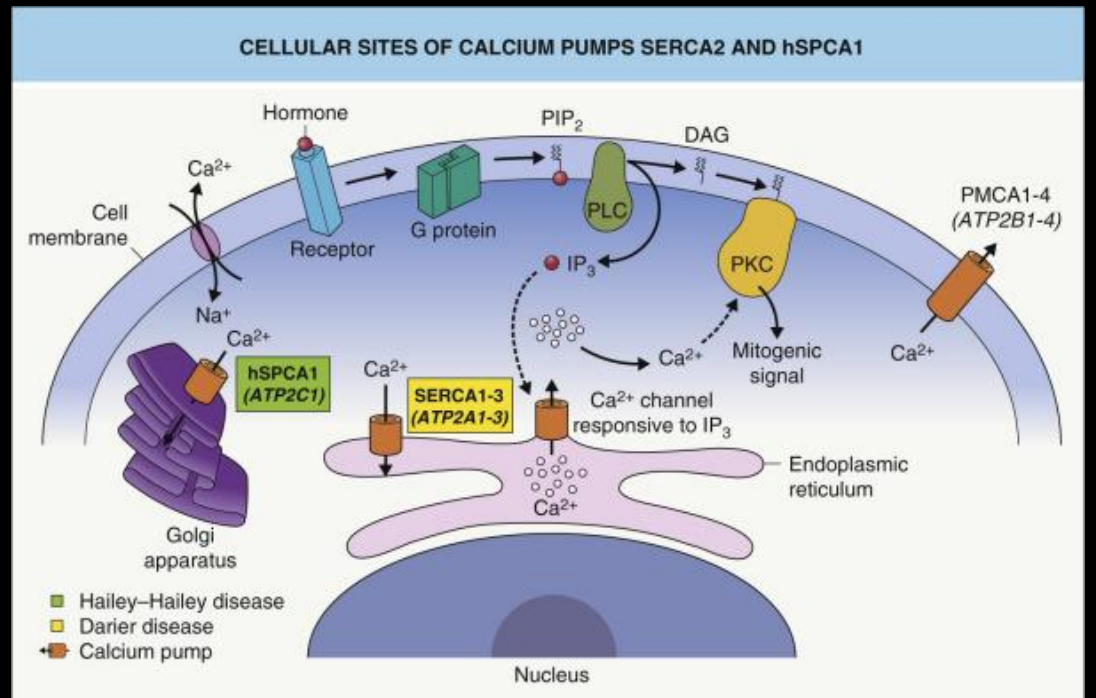


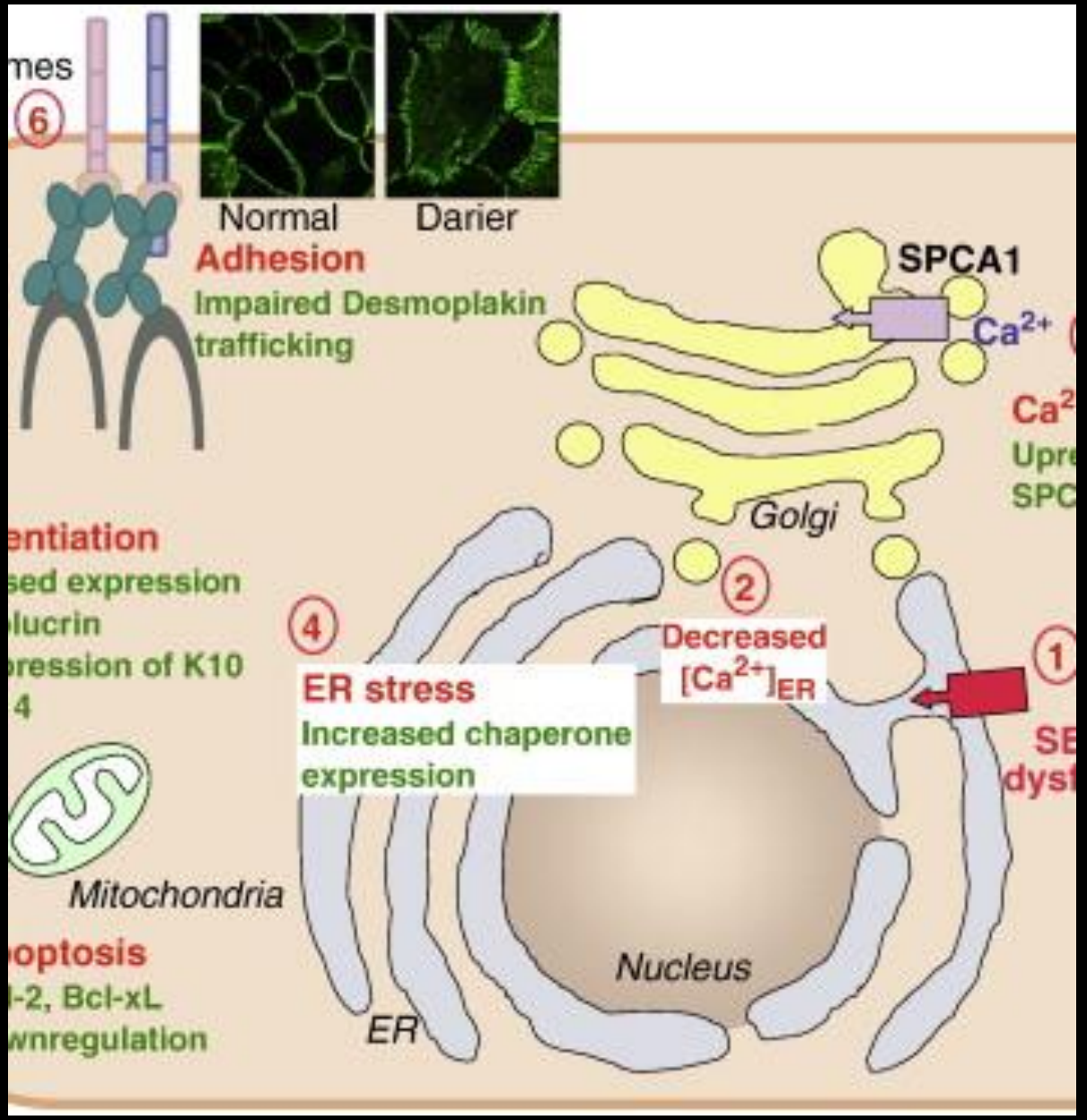
Hailey – Hailey disease

- Suprabasal clefting
  - Vesicles and bullae
  - Papillae extend into bullae
  - Individual and groups of cells in bullae
- Loss of intercellular bridges
  - Loose cell connections
  - ‘brick wall’ appearance



- Hailey Hailey disease *ATPC1A2*
- Darrier disease: *ATP2A2*





Thank you for your attention !

Bullous disease

- Classification EB ~ level of split
- Multisystemic disorder
- Clinical diagnosis / prognosis is difficult

  ➔ NGS
- Promising therapy (gene addition / knock down)