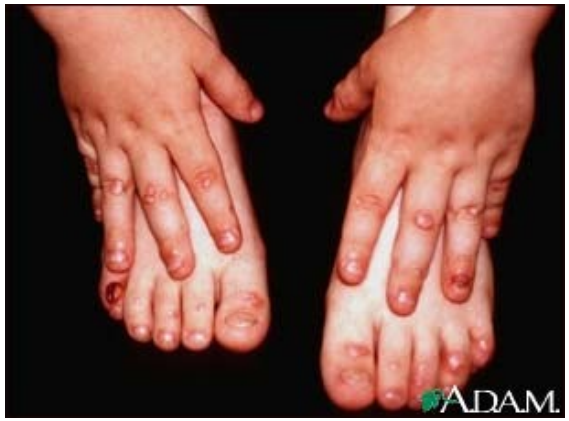
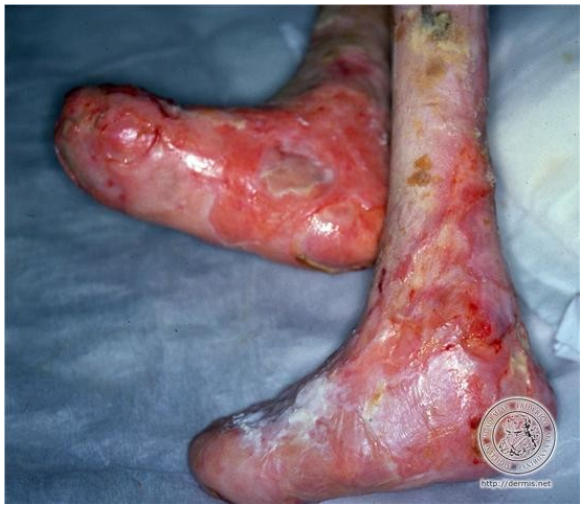
Genodermatózy – kožní choroby podmíněné mutací/mutacemi v určitém genu

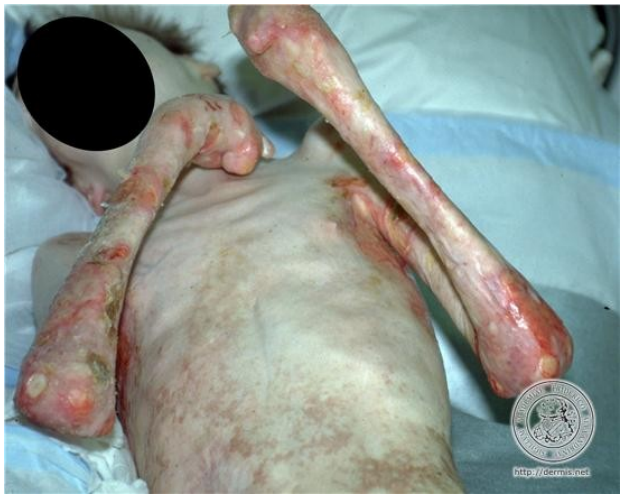
Disease	Type	OMIM number	Pattern of inheritance	Causal protein/gene
Epidermolysis bullosa				
EB simplex	Dowling-Meara type	131760	AD	Keratin (K), K14
	Köbner type	131900	AD	K5, K14
	Weber-Cockayne type	131800	AD	K5, K14
	EBS associated with muscular dystrophy	226670	AR	Plectin
Junctional EB	Herlitz type	226700	AR	Laminin 332 (laminin 5)
	Non-Herlitz type	226650	AR	Laminin 332, type XVII collagen
	JEB associated with pyloric atresia	226730	AR	Integrin α 6, β 4
Dystrophic EB	Autosomal dominant dystrophic type	131750, 131850	AD	Type VII collagen
	Hallopeau-Siemens recessive type	226600	AR	Type VII collagen
	Non-Hallopeau-Siemens recessive type	132200	AR	Type VII collagen
Keratotic disorders				
Ichthyoses	Ichthyosis vulgaris	146700	SD	Filaggrin
	X-linked ichthyosis	308100	XR	Steroid sulfatase
	Lamellar ichthyosis	242100	AR	Transglutaminase I
	Bullous congenital ichthyosiform erythroderma	113800	AD	K1, K10
	Ichthyosis bullosa of Siemens	146800	AD	K2e
	Harlequin ichthyosis	242500	AR	ABCA12
	Cyclic ichthyosis with epidermolytic hyperkeratosis	604602	AD	K1, K10
	Curth-Macklin-type ichthyosis	146590, 146600	AD	K1, K10
	Netherton syndrome	256500	AD	SPINK5
	KID syndrome	242150	AD	Connexin26
	Sjögren-Larsson syndrome	270200	AR	ALDA3A2
	Chanarin-Dorfman syndrome	275630	AR	CGI-58
Palmoplantar keratoses	Vörner syndrome	144200	AD	K9
	Non-epidermolytic palmoplantar keratoderma	144200	AD	K1
	Vohwinkel syndrome (classical type)	124500	AD	Connexin26
	Vohwinkel syndrome (ichthyotic type)	604117	AD	Loricrin
	Keratosis palmoplantaris linearis	148700	AD	K1, Desmoplakin, Desmoglein
	Pachyonychia congenita type I	167200	AD	K6A, K16
	Pachyonychia congenita type II	167210	AD	K6B, K17
	Papillon-Lefévre syndrome	245000	AR	Cathepsin C
Keratosis pilaris	Darier's disease	124200	AD	SERCA2
	Hailey-Hailey disease	169600	AD	ATP2C1
Erythrokeratodermias	Erythrokeratoderma variabilis	133200	AD	Connexin31
	Progressive symmetrical erythrokeratodermia	602036	AD	Loricrin
Disorder of skin color				
Oculocutaneous albinism	Type IA	203100	AR	Tyrosinase
	Type IB	606952	AR	Tyrosinase
	Type II	203200	AR	P Protein
	Type III	203290	AR	TYRP
	Type IV	606574	AR	MATP
Chédiak-Higashi syndrome		214500	AR	CHS
Hermansky-Pudlak syndrome	Type I	203300	AR	HPS1
	Type II	203300	AR	AP3B1
	Type III	203300	AR	HPS3
	Type IV	203300	AR	HPS4
Peutz-Jeghers syndrome		175200	AD	STK11/LKB1
Piebaldism		172800	AD	KIT
Incontinentia pigmenti		308310	XR	NEMO
Syndromes in which a tumor occurs				
Neurofibromatosis	Type I	162200	AD	NF1
	Type II	101000	AD	NF2
Basal-cell nevus syndrome		109400	AD	PTCH
Tuberous sclerosis		191100	AD	TSC1-4
Xeroderma pigmentosum	Group A	278700	AR	XPA
	Group B	133510	AR	XPB/ERCC3
	Group C	278720	AR	XPC
	Group D	278730	AR	XPD/ERCC2
	Group E	278740	AR	DDB2
	Group F	278760	AR	ERCC4
	Group G	278780	AR	ERCC5
	Variant	278750	AR	POLH
Cowden's syndrome		158350	AD	PTEN
Gardner's syndrome		175100	AD	APC
Dyskeratosis congenita (X-linked recessive)		305000	XR	DKC1
Dyskeratosis congenita (dominant)		127500	AD	TERC
Genodermatoses originating from ectoderm				
Ectodermal dysplasia		305100	XR	ED1
		129500	AD	GJB6
Ectodermal dysplasia/skin fragility syndrome		604536	AR	PKP1
Nail patella syndrome		161200	AD	LMX1B
Genodermatoses associated with connective tissue				
Ehlers-Danlos syndrome	Type I	130000	AD	Type V collagen
	Type II	130010	AD	Type V collagen
	Type IV	130050	AD	Type III collagen
	Type VI	225400	AR	Procollagen lysine hydroxylase
	Type VIIa, VIIb	130060	AD	Type I collagen
	Type VIIc	225410	AR	ADAMTS2
Ehlers-Danlos progeroid form		130700	AD	XGPT1
Ehlers-Danlos-like syndrome from tenascin X deficiency		606408	AR	tenascin X
Marfan's syndrome		154700	AD	Fibrillin-1
Pseudoxanthoma elasticum		264800	AR	MRP6
Cutis laxa		123700	AD	ELN
Vascular genodermatoses				
Osler's disease	Type I	187300	AD	ENG
	Type II	600376	AD	ACVRLK1
Porphyrias				
Congenital erythropoietic porphyria		263700	AR	UROS
Erythropoietic protoporphyria		177000	AD	FECH
Hepatoerythropoietic porphyria		176100	AD	UROD
Porphyria cutanea tarda		176100	AD	UROD, HFE
Variegate porphyria		176200	AD	PPOX
Other genodermatoses				
Werner's syndrome		277700	AR	WRN
Bloom's syndrome		210900	AR	BLM
Rothmund-Thomson syndrome		268400	AR	RECQL4
Cockayne syndrome	Type I	216400	AR	CKN1
	Type B	133540	AR	CSB
Familial cylindromatosis		132700	AD	CYLD1
Lipoid proteinosis		247100	AR	ECM1
Fabry's disease		301500	XR	α-galactosidase A
Kanzaki disease		104170	AR	NAGA
(Hereditary) acrodermatitis enteropathica		201100	AR	ZIP4
von Hippel-Lindau syndrome		193300	AD	VHL
Ataxia telangiectasia		208900	AR	ATM
(Hereditary) angioedema		106100	AD	C1NH
Progeria		176670	AR	LMNA

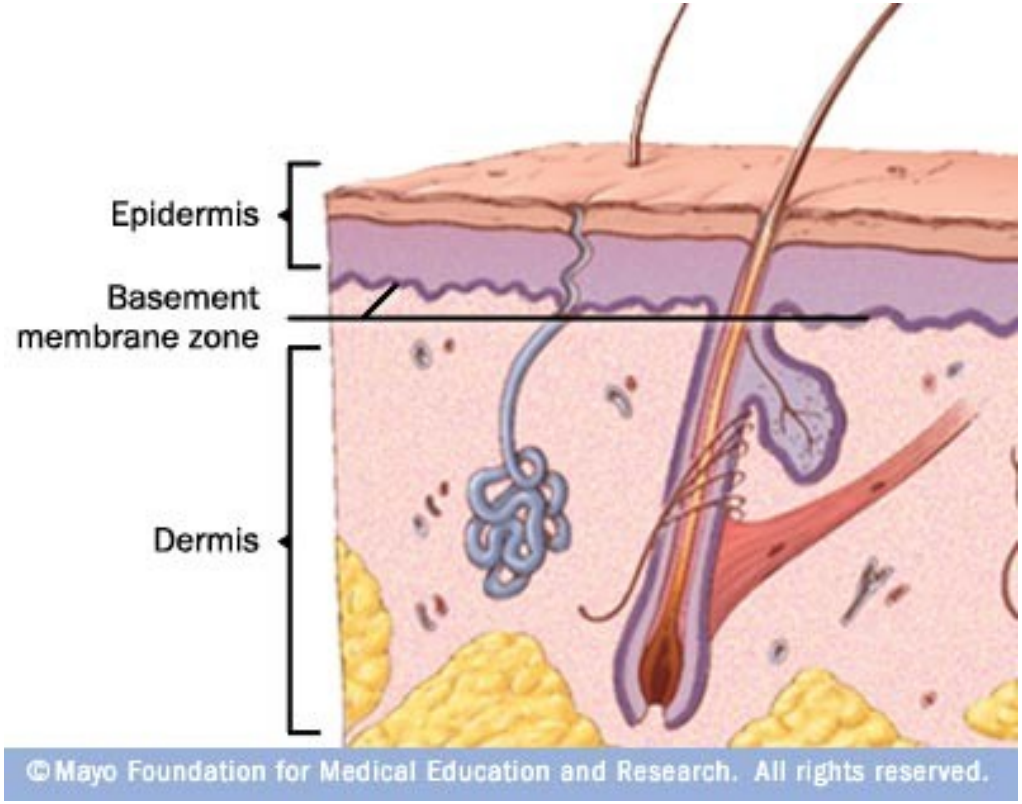
Epidermolysis bullosa (EB) - a group of diseases sharing two common characteristic features - **fragility of the skin** and **blistering.**

The clinical features of EB have a broad range of severity from isolated nail dystrophy through relatively mild, localized blistering of the extremities to generalized blistering and mutilation; adding to the cutaneous complexity is the finding of extracutaneous manifestations. → **30 different subtypes of EB**.





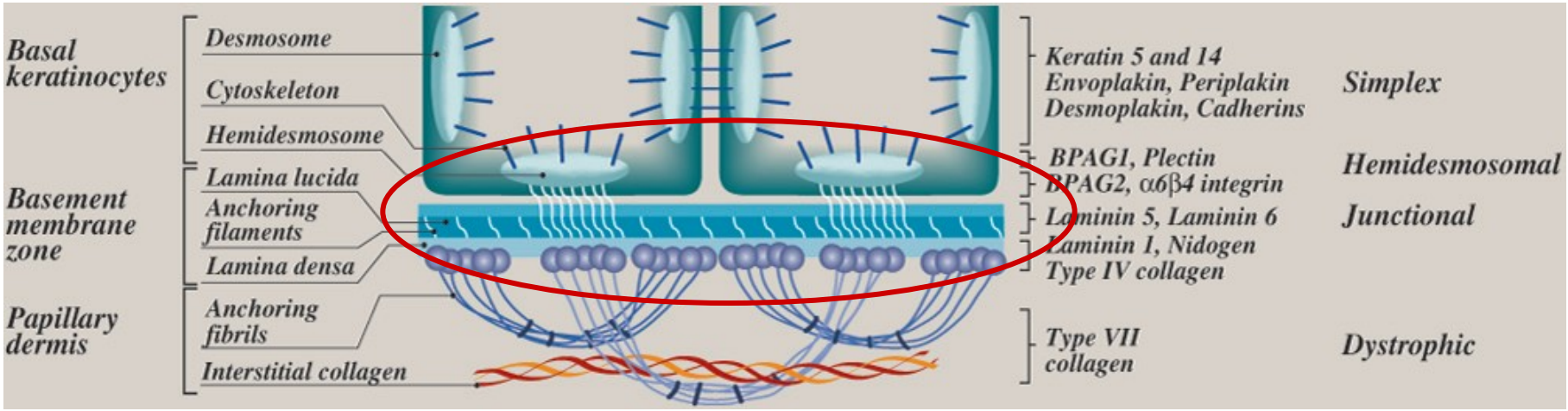




Three major forms of EB have been defined depending on the level of blister formation:

- **The simplex form of EB** - blisters occur in the top layer of skin (epidermis).
- **The junctional form of EB** - blisters occur in basement membrane zone.
- **The dystrophic form of EB** - blisters occur in the bottom layer of skin (dermis)

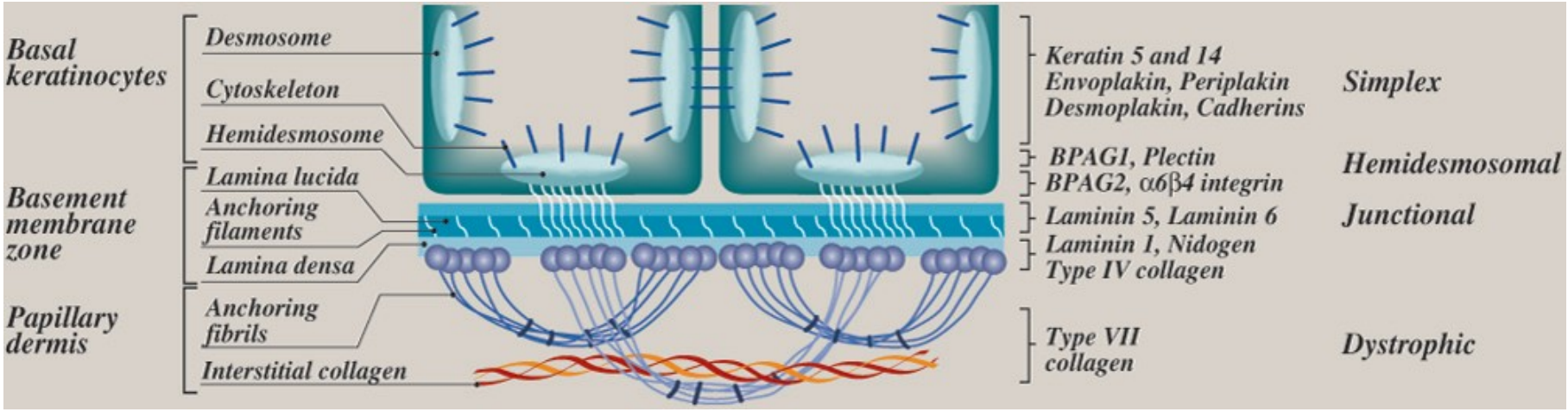
Pathophysiology of EB - ultrastructural recognition of distinct complexes within epidermis-basement membrane zone-dermis; these include **hemidesmosomes**, which extend from the intracellular milieu of basal keratinocytes to the extracellular space, **anchoring filaments** that traverse the lamina lucida, and the **anchoring fibrils**, which extend from the lower part of the cutaneous basement membrane to the underlying dermis. **These structures form a contiguous network necessary for stabilization of the basal keratinocytes to the underlying basement membrane and its attachment to the papillary dermis.**



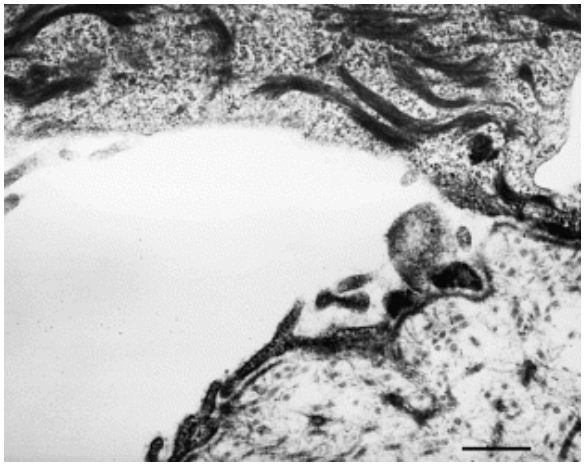
Acta Derm Venereol 2009; 89: 228–235

• In **simplex forms of EB**, tissue separation occurs within the basal keratinocytes, which lyse as a result of minor trauma.
• In **junctional forms of EB**, tissue separation occurs within the lamina lucida.
• In **dystrophic of EB**, tissue separation occurs below the lamina densa, within the upper papillary dermis at the level of anchoring fibrils.

• EB is inherited either in **an autosomal dominant or autosomal recessive mode (DDEB and RDEB, respectively)**.
• In some cases, **mutations in the same gene can cause either autosomal dominant or autosomal recessive form of the disease.**

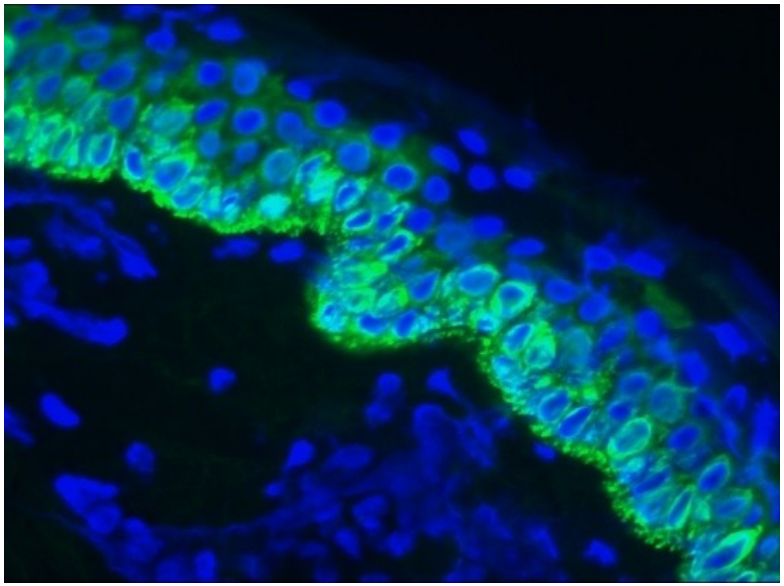


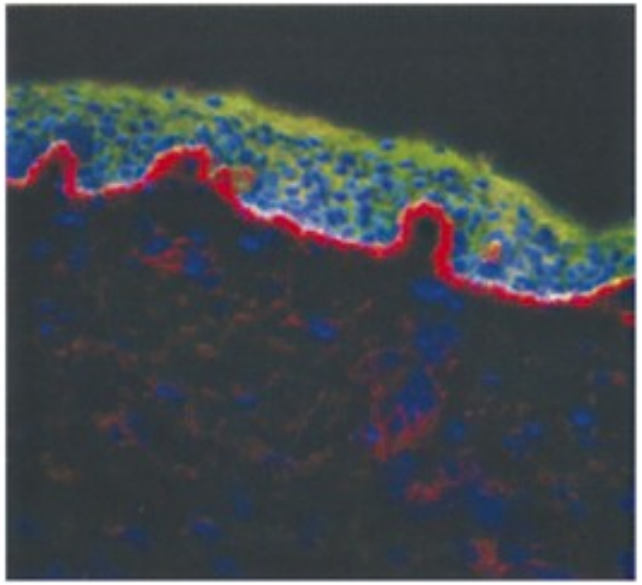
EB diagnostics

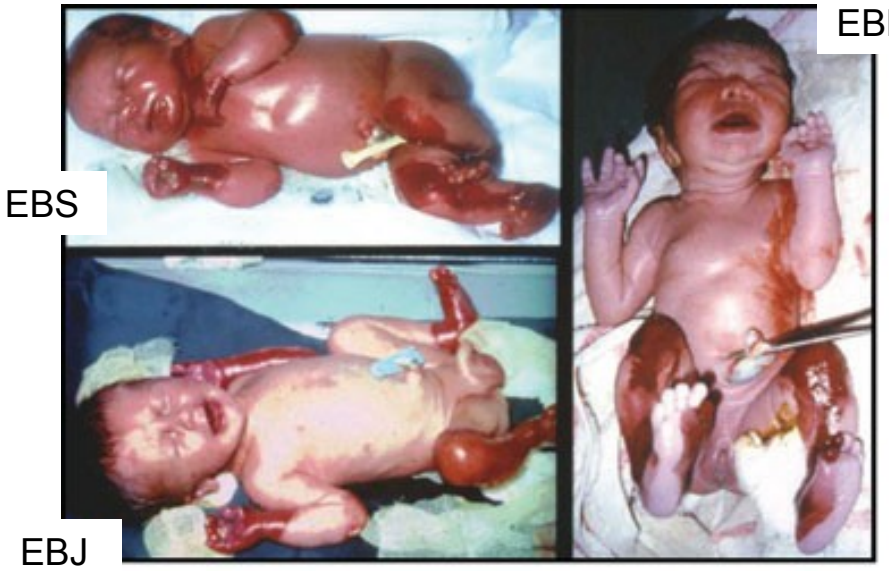


• In the 1960s, **transmission electron microscopy (TEM)** was first applied to establish and subdivide EB into three main categories.

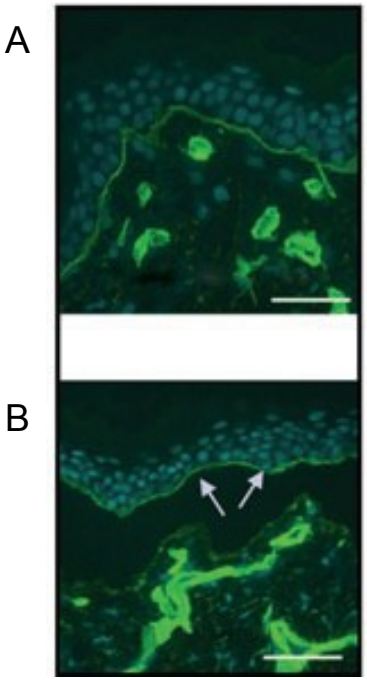
• In the 1980s, the discovery and development of **monoclonal and polyclonal antibodies** to different skin proteins permitted further insight into the pathophysiology of EB by **immunofluorescence mapping of protein**.

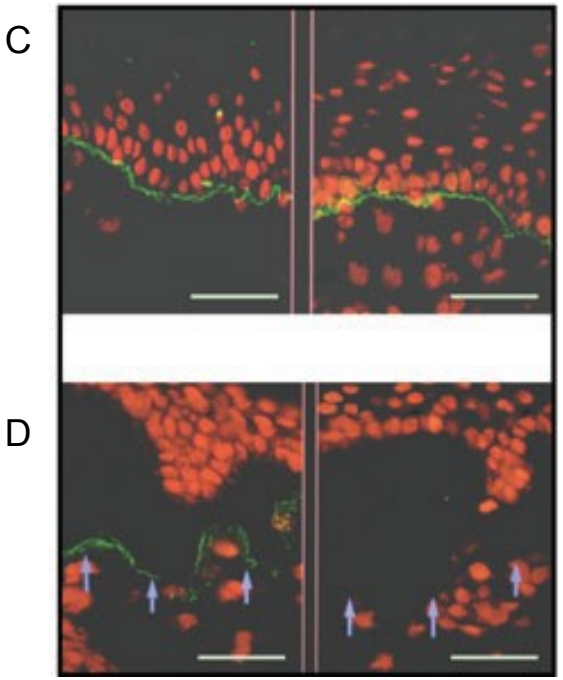


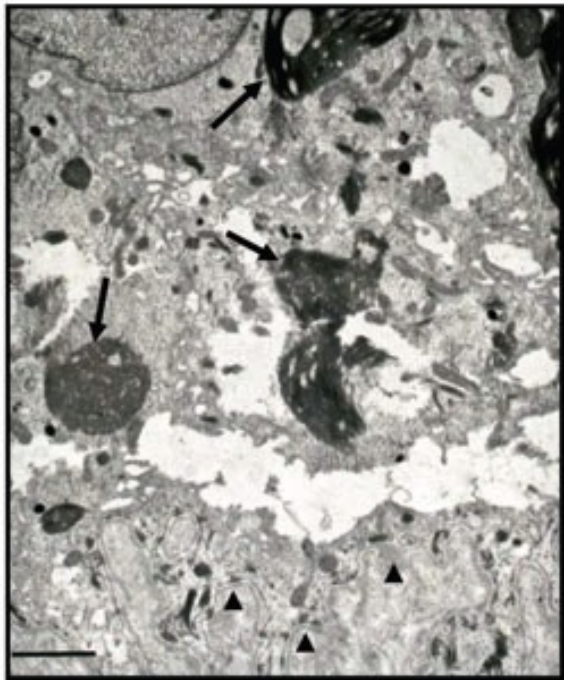




A) normal skin, antibody to type IV collagen, linear staining at the dermal–epidermal junction. B) a patient, naturally occurring blister (*) and the dermal–epidermal junction labelling maps to the roof of the split (arrows), indicating a sublamina densa plane of cleavage → EBD. C) normal skin, antibodies to laminin, linear immunoreactivity at the dermal–epidermal junction. D) a patient, there is a blister (*). Laminin labelling is present but maps to the base of the split →EBJ. G) Diagnosis of Dowling–Meara EB simplex by transmission electron microscopy.







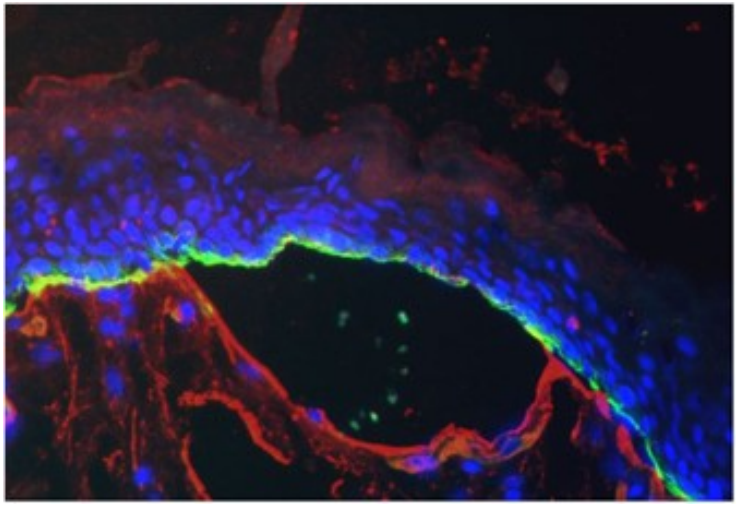
Histopathology 2010, 56, 91–99.

Dermatopathology provides new insight into the disease pathophysiology of inherited blistering skin diseases. A, Clinical appearances of neonates with different inherited forms of EB (top left, Dowling–Meara EB simplex; bottom left, Herlitz junctional EB; right, severe, generalized recessive dystrophic EB). Clinical distinction between the different subtypes can be very difficult and skin biopsy is necessary to establish a diagnosis and to facilitate molecular gene screening. B, Diagnosis of dystrophic EB by antigen mapping. Labelling of normal skin (top figure) with an antibody to type IV collagen shows linear staining at the dermal–epidermal junction and immunoreactivity around dermal blood vessels and adnexae. In the lower panel from a patient with EB, there is a naturally occurring blister (*) and the dermal–epidermal junction labelling maps to the roof of the split (arrows), indicating a sublamina densa plane of cleavage and giving a rapid diagnosis of dystrophic EB (bar = 50 lm). C, Diagnosis of non-Herlitz junctional EB by specific antibody probes. In normal skin (upper panels), immunolabelling with antibodies to laminin-332 (left) and type XVII collagen (180-kDa bullous pemphigoid antigen, right) shows linear immunoreactivity at the dermal–epidermal junction. In the patient skin (lower panels), there is a blister (*). Laminin-332 labelling is present but maps to the base of the split (left), whereas there is complete absence of type XVII collagen immunoreactivity. These findings give a rapid diagnosis of non-Herlitz junctional EB and exclude a diagnosis of the more clinically severe Herlitz disease (bar = 50 lm). D, Diagnosis of Dowling–Meara EB simplex by transmission electron microscopy. Dominant forms of EB may require ultrastructural examination of a skin biopsy specimen to establish the diagnosis. In this electron micrograph there is blister formation (cytolysis) within the basal keratinocyte (*) just above the dermal–epidermal junction (arrowheads). Within the basal keratinocyte, there are ball-like aggregates of keratin filaments (arrows). Identification of this skin biopsy feature provides a rationale for molecular screening of the genes encoding keratins 5 and 14, the principal keratins expressed in basal keratinocytes (bar = 0.5 lm). *Histopathology 2010, 56, 91–99.*

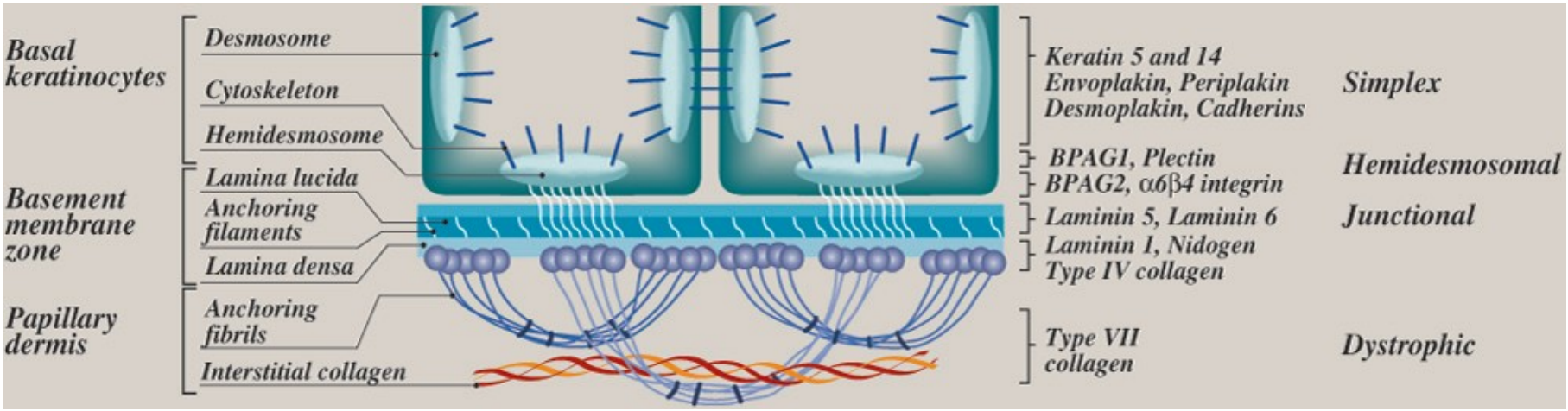
• **Mapping of type IV collagen** (which labels the lamina densa) **to the roof of a blister** in an EB patient's skin, provided a rapid diagnosis of **dystrophic EB**.

• **Mapping of type IV collagen to the floor of blister** in an EB patient s skin, provided diagnosis of **EB simplex or junctional EB**.

• Absent type VII collagen immunolabelling is found in severe generalized recessive dystrophic EB.

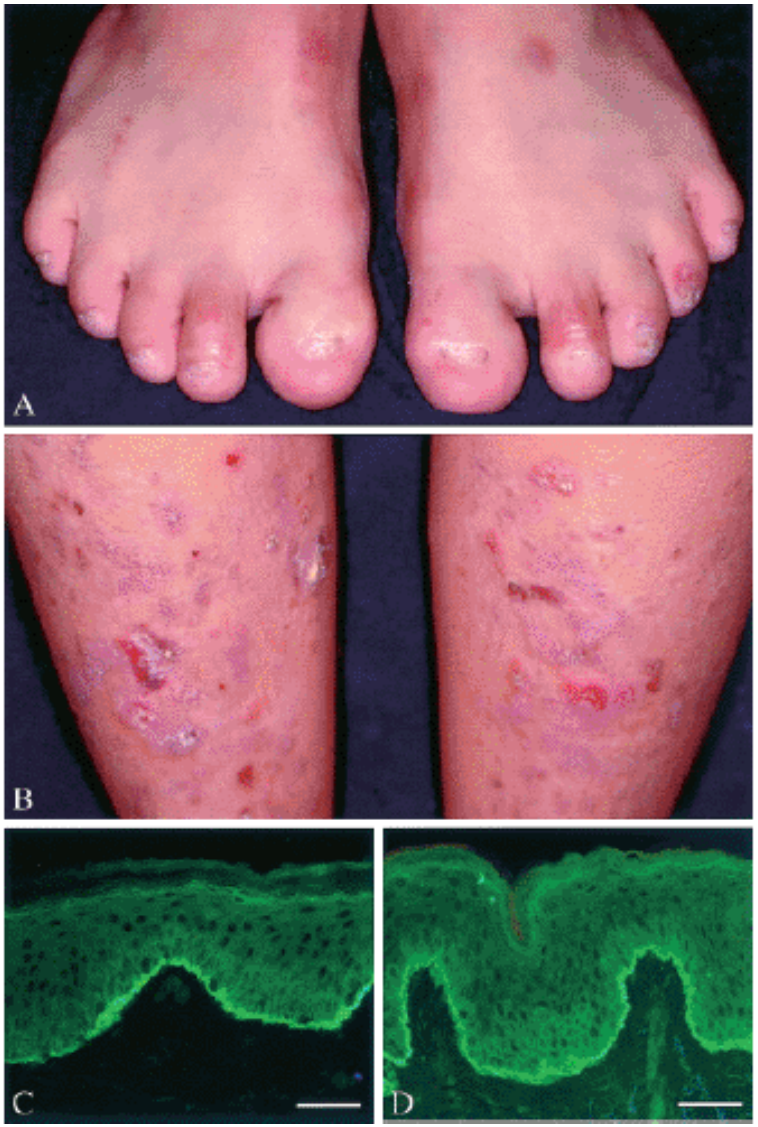


Focal separation within the epidermal basement membrane delineated by type IV collagen (stained red) and bullous pemphigoid antigen 2 (stained green). Nuclei (counterstained blue) outline the overlying epidermis as well as selected cells in the dermis.



• Skin biopsy for immunohistochemical analysis is an important and relevant diagnostic test for all **recessive forms of EB** since these disease are typically associated with alterations in protein expression.

• In the most common form of **EB simplex (localized hands and feet) and dominant dystrophic EB**, skin immunohistochemistry typically shows no major differences from normal skin. Moreover, the ultrastructural changes observed by TEM may be too subtle to be diagnostic. In such cases, it is probably more appropriate to move straight to molecular biology screening of the *KRT5* and *KRT14* genes in EB simplex, and the *COL7A1* gene in dominant dystrophic EB.



Clinicopathological assessment is consistent with dominant dystrophic epidermolysis bullosa. *The clinical features include (A) dystrophic or rudimentary toenails and (B) blisters, erosions, and inflammatory papules on the shins. Indirect immunofluorescent staining with monoclonal antibody (NC-1 domain of type VII collagen) shows bright linear labeling at the dermal–epidermal junction in the patient's skin (C) of intensity and distribution similar to normal control skin (D). Scale bar=40 μm. Journal of Investigative Dermatology (2005) 124, 863–866*

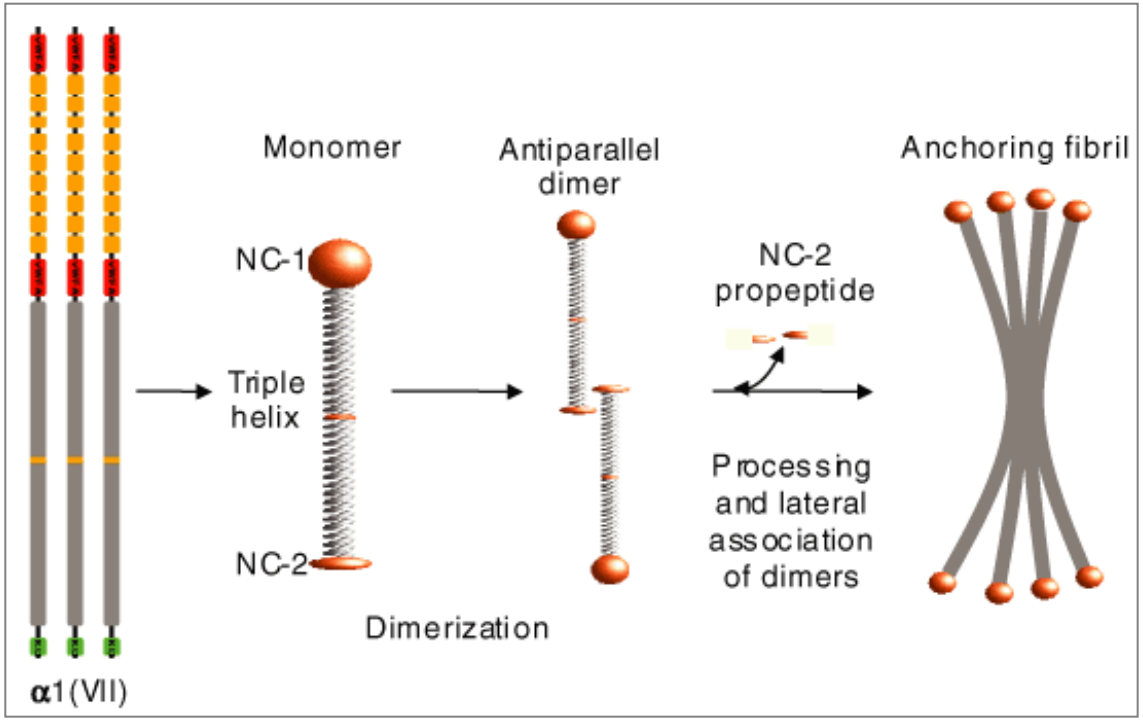
Dystrophic epidermolysis bullosa (DEB) is an inherited skin fragility disorder in which blistering occurs below sublamina densa zone at the level of anchoring fibrils.

• Associated with mutations in the ***COL7A1*** gene (3p21, 32 kb, 118 exons).

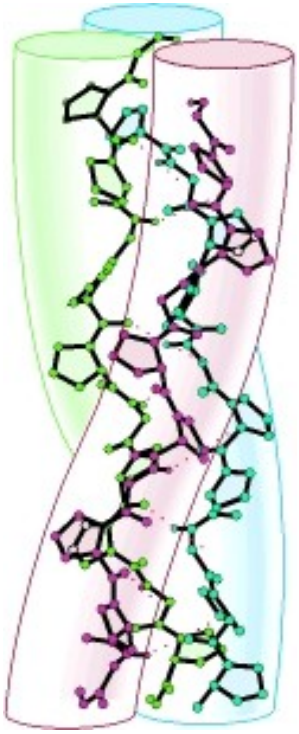
• *COL7A1* encodes **procollagen VII alpha chain**. Each proa1(VII) chain contains a central triple helical collagenous domain flanked by both a large amino-terminal non-collagenous (NC-1) domain and a small carboxyl-terminal non-collagenous (NC-2) domain..

• The triple helical domain consists of a repeating **Gly-X-Y** sequence that is disrupted 19 times by non-collagenous regions.

Three proa1(VII) chains folded into procollagen monomer. Two monomers form an antiparallel dimer, from which the NC-2 propeptides are removed proteolytically. Finally, the mature dimers laterally aggregate into anchoring fibrils.

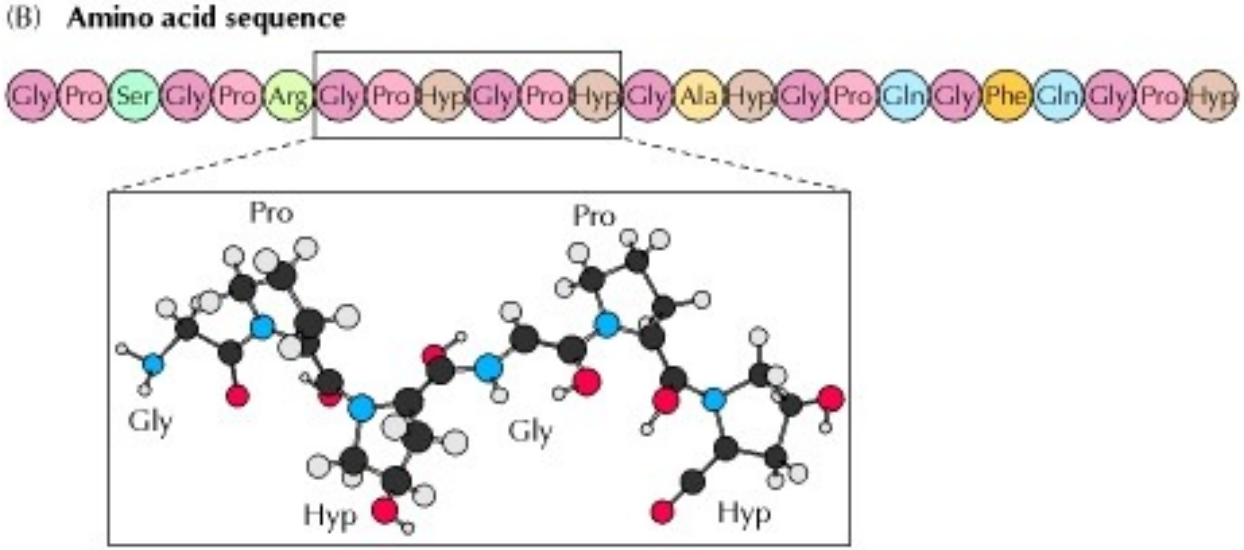


(A)



Structure of collagen

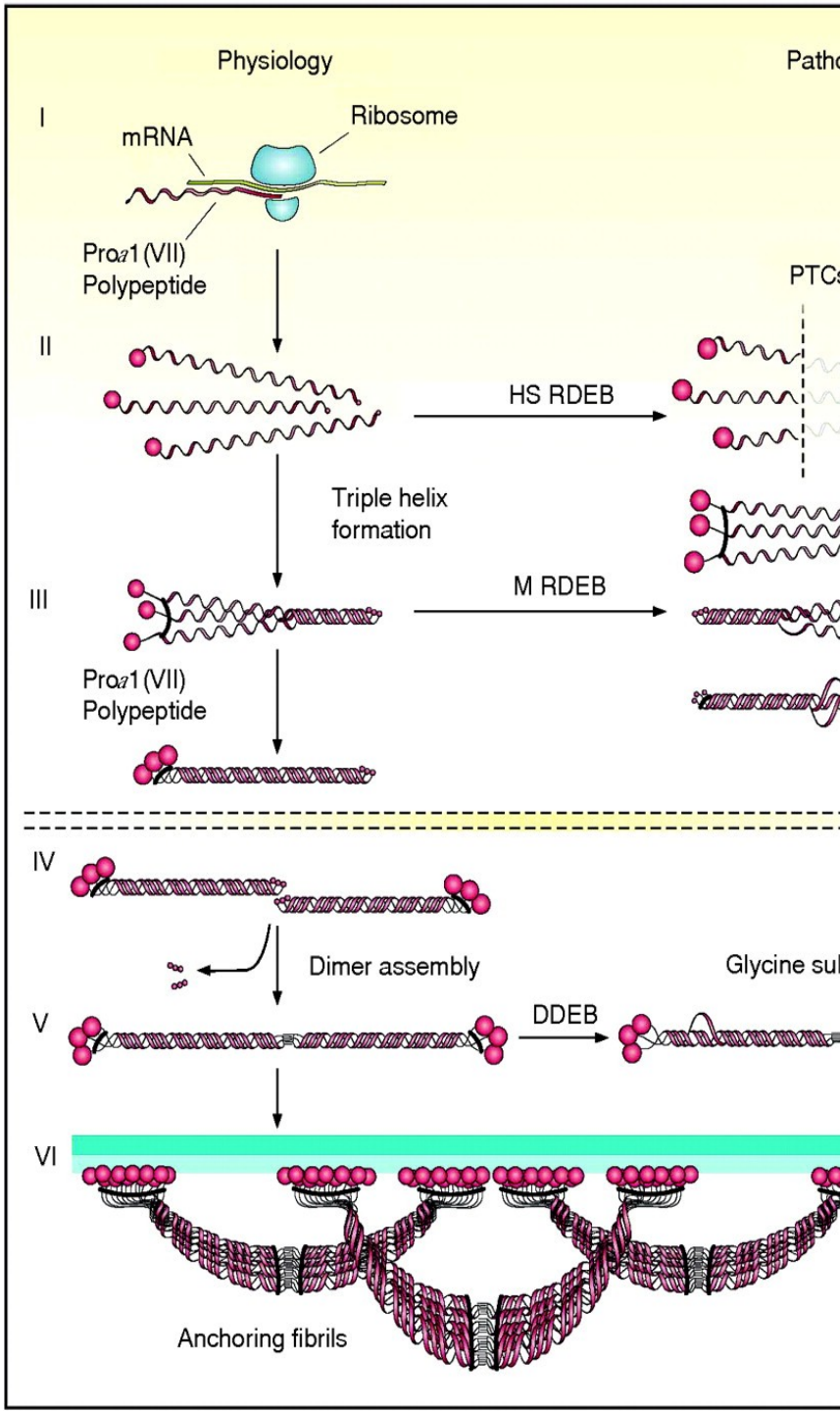
(A) Three procollagen VII alpha chains coil around one another in a characteristic triple helix structure. (B) The amino acid sequence of a collagen triple helix domain consists of **Gly-X-Y repeats**. **Gly-X-Y repeat is prerequisite for the formation of collagen triple helix** which is stabilised by tle presence of hydroxyproline and hydroxylysine.



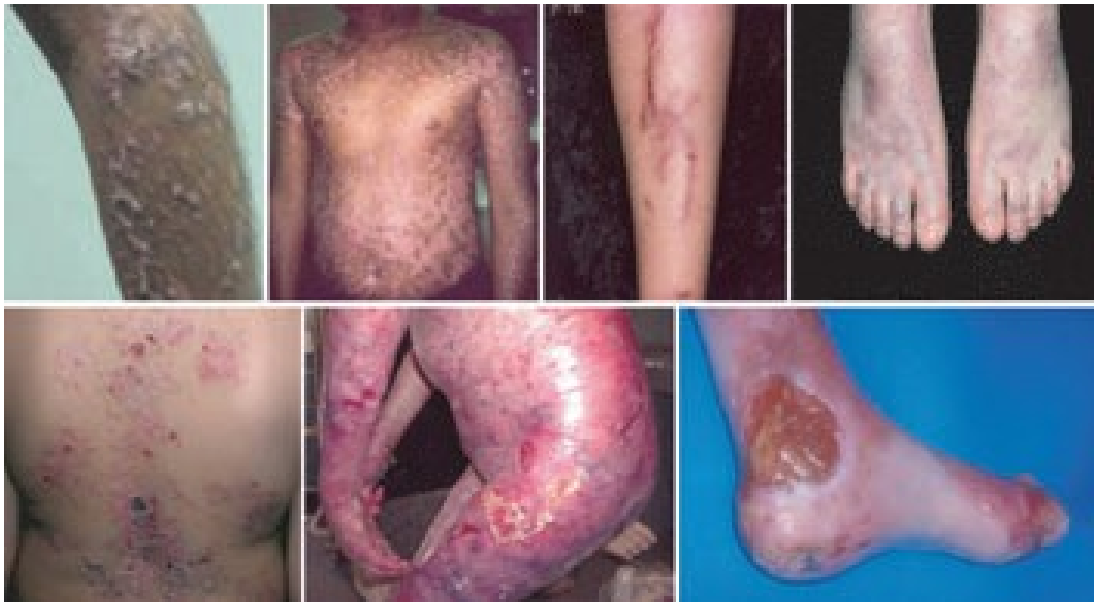
Anchoring fibril assembly. The left side shows the physiology of type VII collagen and the right side shows the pathology.

- I: proa1(VII) polypeptides are synthesized.
- II: Three of these chains assemble into a triple helical type VII collagen molecule.
- At stages III & IV, two homotrimers form antiparallel tail-to-tail dimers with a central carboxy-terminal overlap and with the amino-termini outwards, a portion of the NC-2 domain is removed, and the association of the monomers in stabilized by intermolecular disulphide bonds.
- Stages V & VI: a large number of dimer molecules assemble into anchoring fibrils and the complete NC-1 domain keeps the adhesive property at both ends.

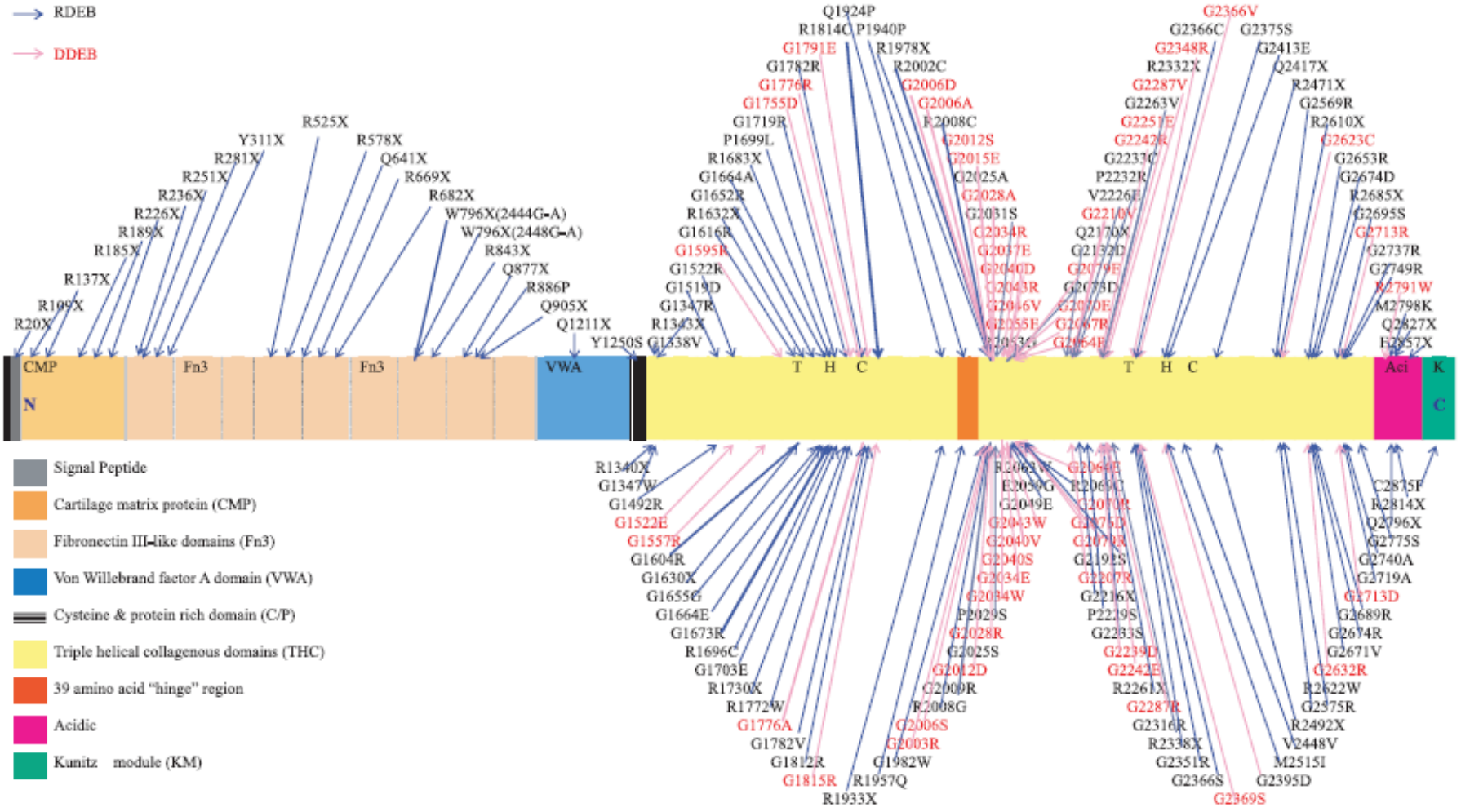
Premature termination codon mutations (PTC) decrease the amount of the mutated transcripts and result in truncated non-functional polypeptides which are unable to assemble into anchoring fibrils, then causing RDEB-HS. Missense mutations alter homotrimer formation and/or subsequent stabilization of the dimer molecules by disulphide bonds result in decreased stability and/or alter function of VII collagen known as milder type of RDEB-nHS. Glycine substitutions often happen in triple helix region of COL7A1 affecting the correct folding and the secretion of type VII collagen.



• Dystrophic epidermolysis bullosa (DEB) is inherited in both **an autosomal dominant (DDEB) and an autosomal recessive manner (RDEB).**
• The clinical features of DEB have a broad range of severity from isolated nail dystrophy through relatively mild, localized blistering of the extremities to generalized blistering and mutilation.
• **The severe Hallopeau-Siemens RDEB (RDEB-HS)** is associated with premature termination codon (PTC) mutations (nonsense, frameshift or splice-site mutations) on both COL7A1 alleles which result in either nonsense-mediated decay of the mRNA or truncated polypeptides that are unable to assemble into functional AFs.
• **The milder, non-Hallopeau- Siemens RDEB (RDEB-nHS)** is often caused by compound heterozygous mutations: one PTC mutation and one missense mutation. Full-length type VII collagen polypeptides can be synthesized, but they have a different conformation and affect the stabilization of the AF.
• **DDEB usually involves glycine substitutions** within the triple helix of COL7A1.

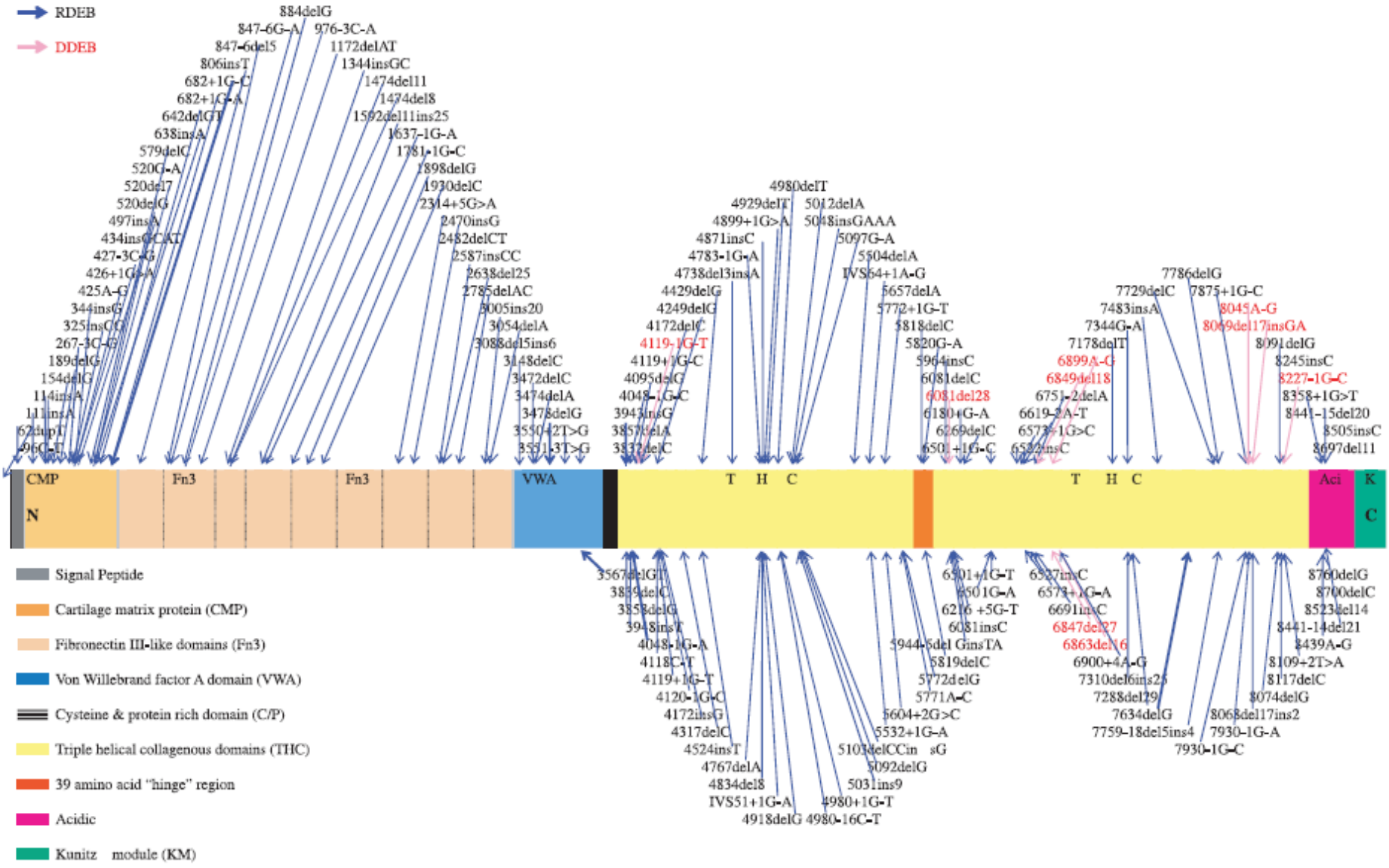


Clinical presentation of DEB patients. Pruriginosa (a) and albopapuloid (b) lesions on the arm and 90% of body surface covered with lesions in DDEB; severe phenotype. (c) and (d) Mild healed erosions on leg and severely dystrophic toenails in DDEB. (e) Localized atrophic scarring and erosions on the trunk in non-Hallopeau-Siemens recessive dystrophic epidermolysis bullosa (RDEB-nHS). (f) and (g) Widespread blisters, erosions, scars and atrophy and significant nail dystrophy and syndactyly of the feet in RDEB-HS.



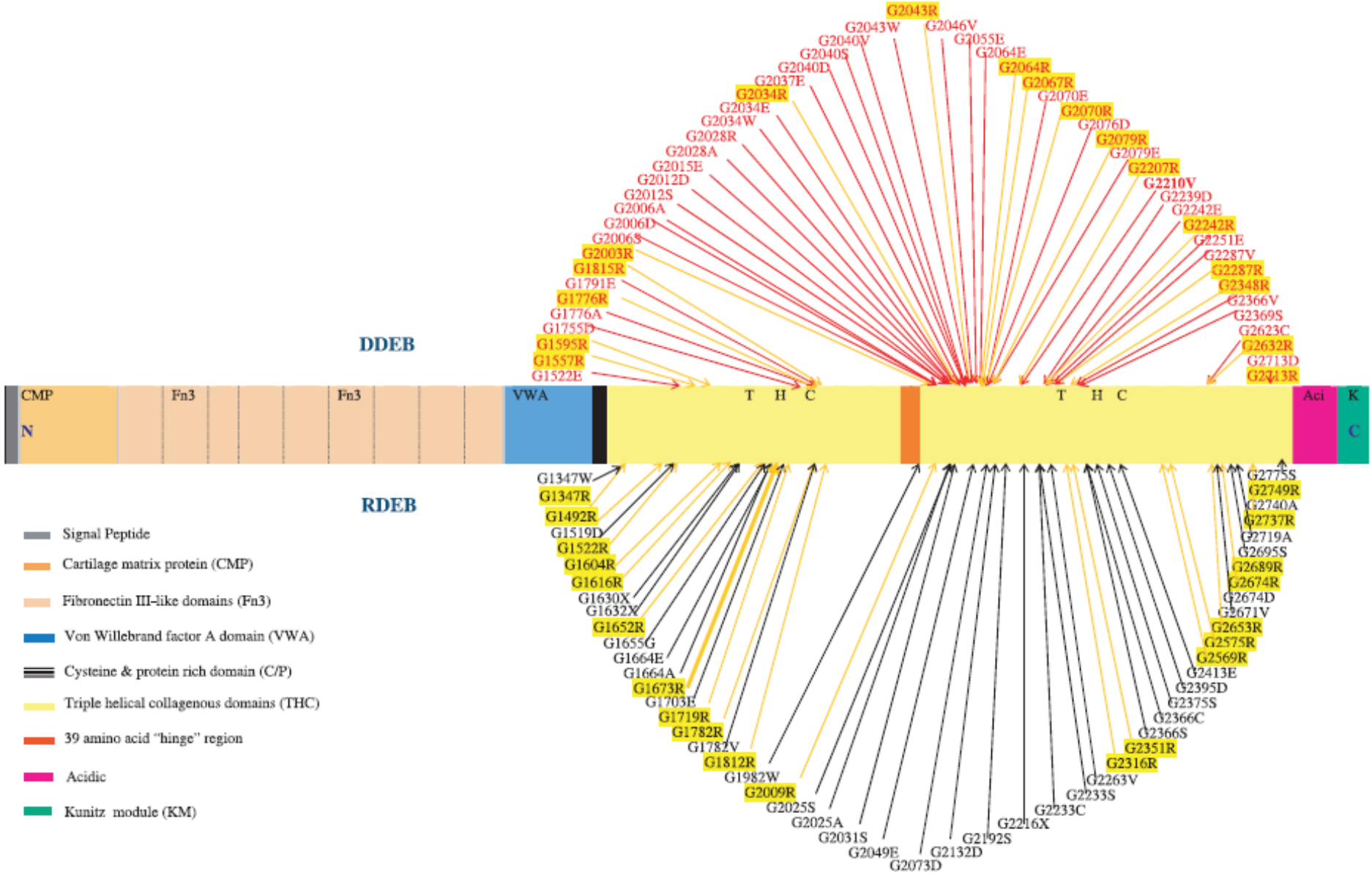
Experimental Dermatology, 17, 553–568

COL7A1 missense and nonsense mutations in DEB patients. The red lettering signifies dominant and the black signifies recessive



Experimental Dermatology, 17, 553–568

COL7A1 deletions, insertions, splice mutations in DEB patients.

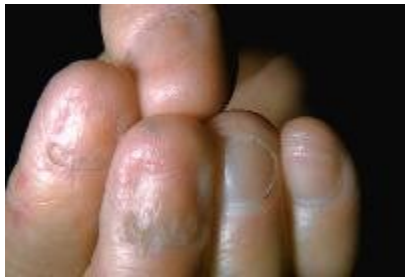


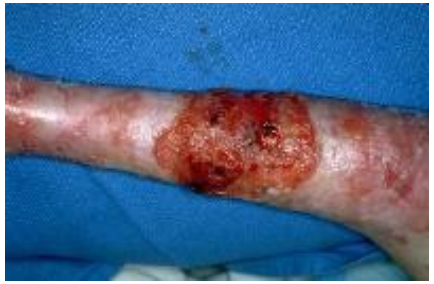
Experimental Dermatology, 17, 553–568

Glycine substitutions in DEB. The ones above represent DDEB, whereas the ones below RDEB.

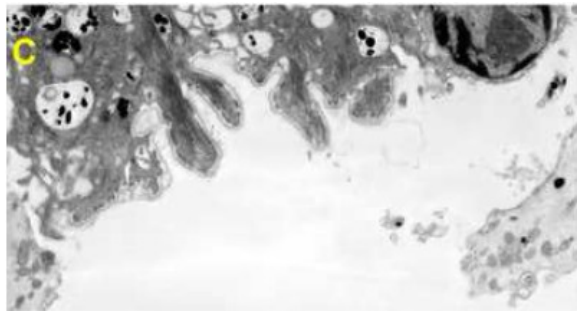
Diagnostika DEB:

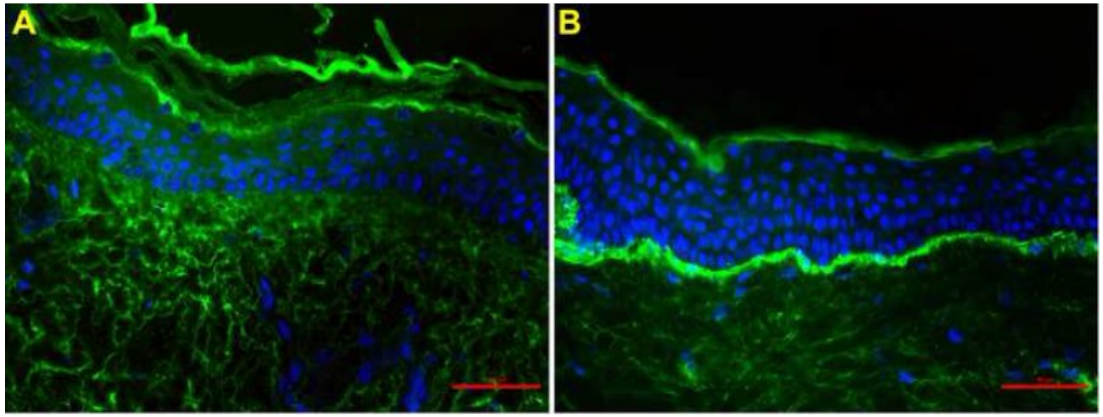
1. Klinické příznaky





2. Transmisní elektronová mikroskopie

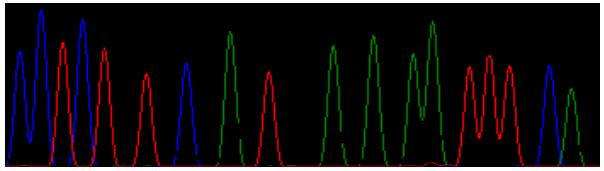




3. Imunofluorescenční antigenní mapování

Immunofluorescence microscopy findings at the dermo-epidermal junction zone using tle monoclonal antibody to colagen VII: the patient with absence of the signal (A), bar indicates 100 μm; positive control (B), bar indicates 50 μm. (C) Electron microscopy findings in tle skin of patient with lumen of blister at the bottom and clearly visible lamina densa at the blister roof, indicating a subepidermal cleavage plane. Original magnification x 6000.

4. DNA nalýza (PCR-sekvenční analýza)



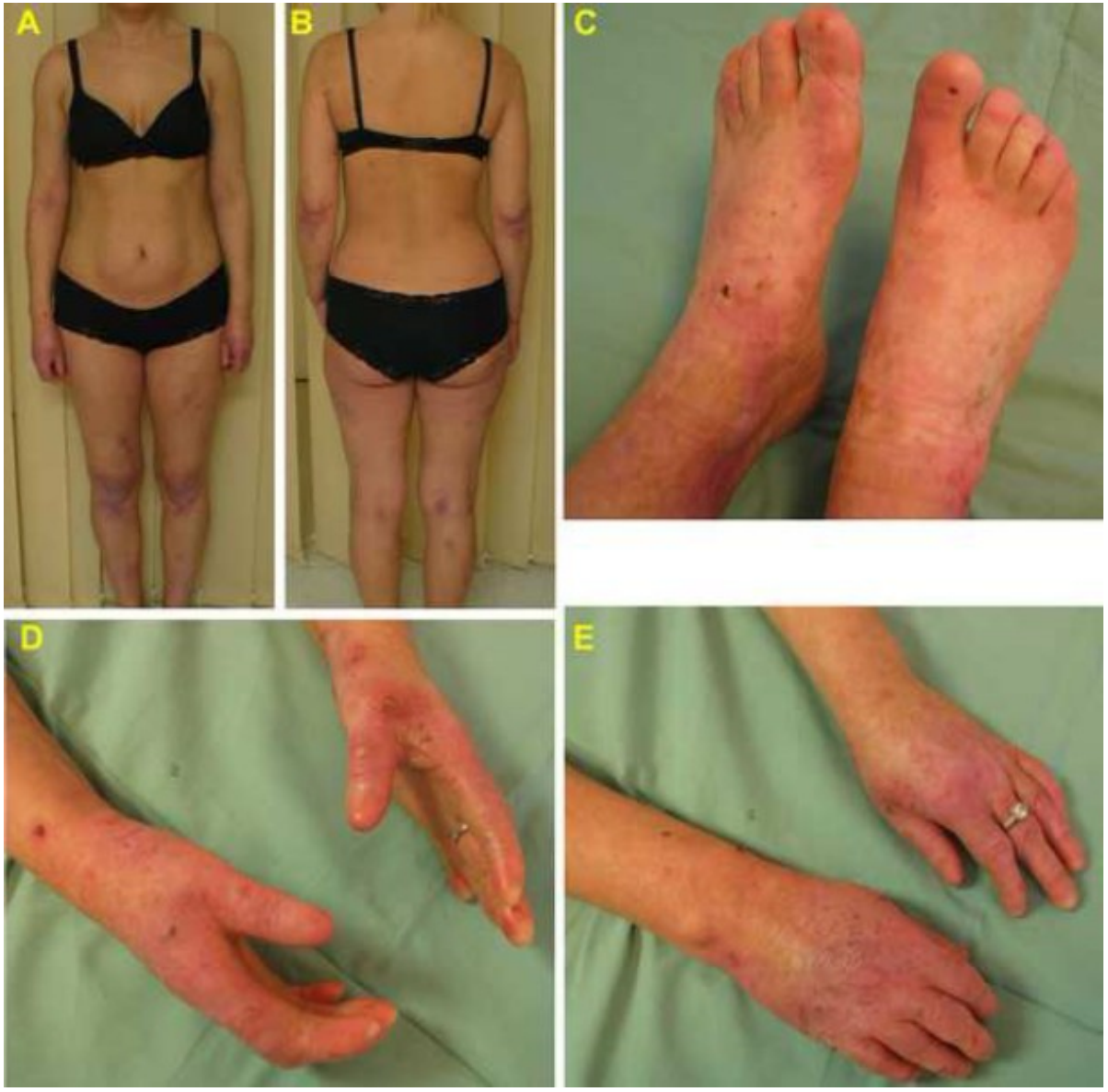
DNA diagnostics of DEB

- The promoter region and 118 exons of the *COL7A1* gene, as well as adjacent intron regions, were amplified and sequenced.
- Mutation/mutations were detected in 9 DDEB and 29 RDEB probands.
- **34 different sequence variants were found, 14 of which have not been reported previously.**

DEB with a new mutation

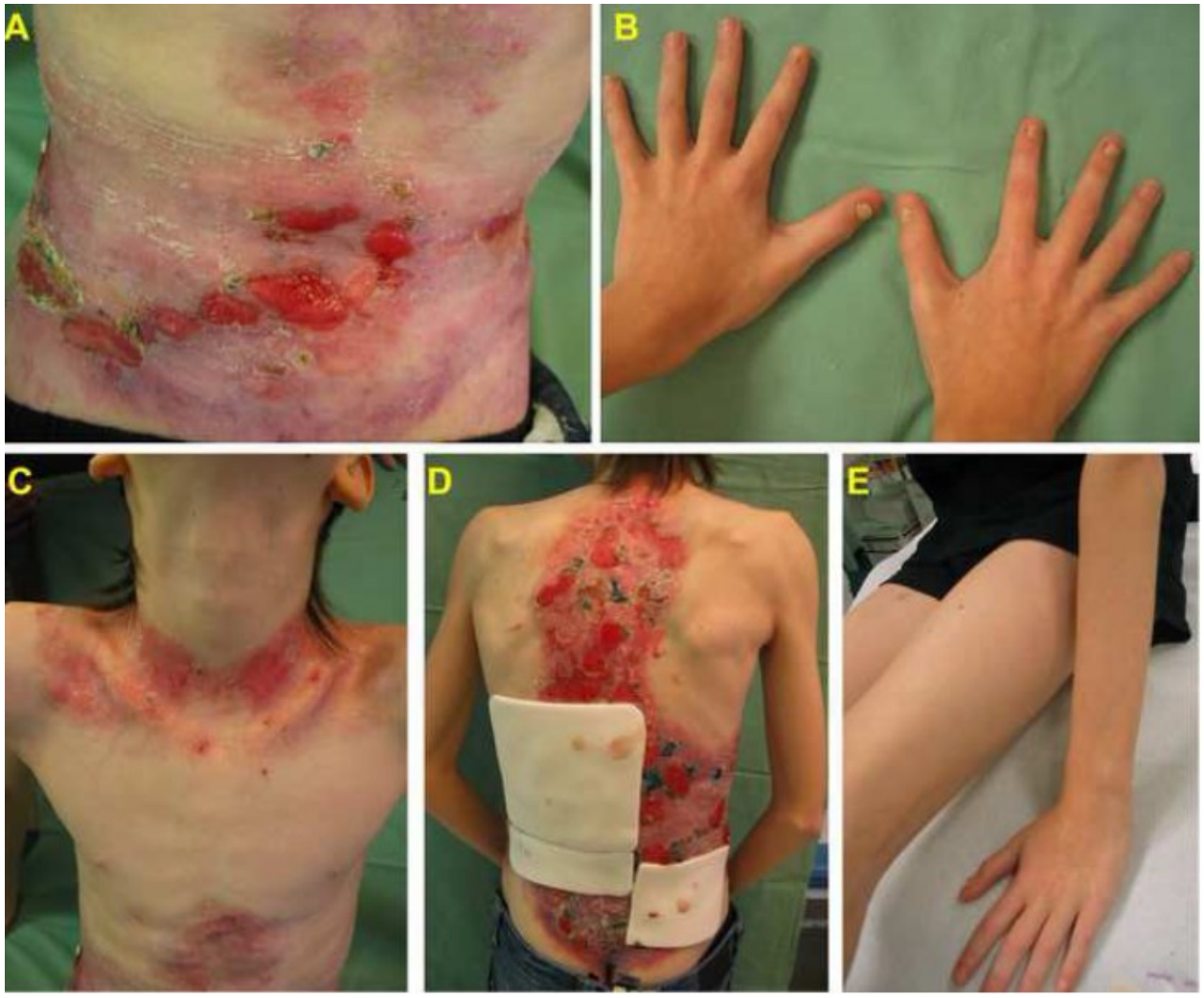
RDEB-sev gen	22	c.4027C>T	p.Arg1343X	**c.7669G>A**	**p.Gly2557Arg**	Aplasia cutis, generalised blistering, pseudosyndactyly, loss of nails	Extracutaneous involvement, corneal dystrophy
RDEB-sev gen	18	c.6081insC	PTC	**c.4556delG**	**PTC**	Generalised blistering, atrophic scarring, skin contractures, pseudosyndactyly, defluvium, loss of nails	Ankyloglossia, oral cavity erosions, corneal erosion, dysphagia
RDEB-sev gen	21	c.6146G>A	p.Gly2049Glu	**c.5644insA**	**PTC**	Aplasia cutis, generalised blistering, atrophic scarring, skin contractures, partial pseudosyndactyly, pruritus, defluvium, loss of nails	Microstomia, ankyloglossia, oral cavity erosions, oesophageal stenosis
RDEB-sev gen	34	c.6146G>A	p.Gly2049Glu	**c.5856+1G>A**	**Splice site**	Generalised blistering, atrophic scarring, skin contractures, pruritus, defluvium, loss of nails, spinocellular carcinoma	Ankyloglossia, oral cavity erosions, oesophageal stenosis, corneal erosion
RDEB-sev gen	34	c.6146G>A	p.Gly2049Glu	**c.6751-2delAG**	**Splice site**	Generalised blistering, atrophic scarring, skin contractures, pseudosyndactyly, loss of nails	Ankyloglossia, oral cavity erosions, oesophageal stenosis
RDEB-sev gen	6	**c.6751-2delAG**	**Splice site**	**c.6751-2delAG**	**Splice site**	Aplasia cutis, generalised blistering, atrophic scarring, skin contractures, partial pseudosyndactyly, pruritus, loss of nails	Ankyloglossia, oral cavity erosions

RDEB-I	57	c.6205C>T	p.Arg2069Cys	**c.3894+1G>A**	**Splice site**	Predominant blistering in intertriginous, lumbosacral, and axial distribution; atrophic scarring; defluvium, onychodystrophy; basocellular carcinoma	Ankyloglossia, oral cavity erosions, oesophageal stenosis, corneal erosions
RDEB-O	25	c.425A>G	Splice site	**c.5533G>A**	**p.Gly1845Arg**	Mild generalised blistering, atrophic scarring, onychodystrophy	Ankyloglossia, oral cavity erosions, oesophageal stenosis, corneal erosions
RDEB-ac	36	c.497insA	PTC	**c.5942A>G**	**p.Lys1981Arg**	Mild generalised blistering predominant in acral and knee distribution; atrophic scarring; partial pseudosyndactyly; defluvium; loss of nails	Oral cavity erosions, dysphagia
RDEB-O	15	c.1573C>T	p.Arg525X	**c.6887G>A**	**p.Gly2296Glu**	Aplasia cutis, generalised blistering, atrophic scarring,pruritus, onychodystrophy	Microstomia, ankyloglossia, oral cavity erosions, dysphagia, corneal erosions



(A),(B) Atrophic skin in acral areas and knees. (C) Loss of toe-nails, hypopigmentation, small hemorrhagic crusts. (D),(E) Loss of finger-nails, semiflectional position of fingers, partial pseudosyndactyly (the right hand is more afflicted), sporadically small erosions and crusts.

RDEB-ac	36	c.497insA	PTC	**c.5942A>G**	**p.Lys1981 Arg**	Mild generalised blistering predominant in acral and knee distribution; atrophic scarring; partial pseudosyndactyly; defluvium; loss of nails	Oral cavity erosions, dysphagia

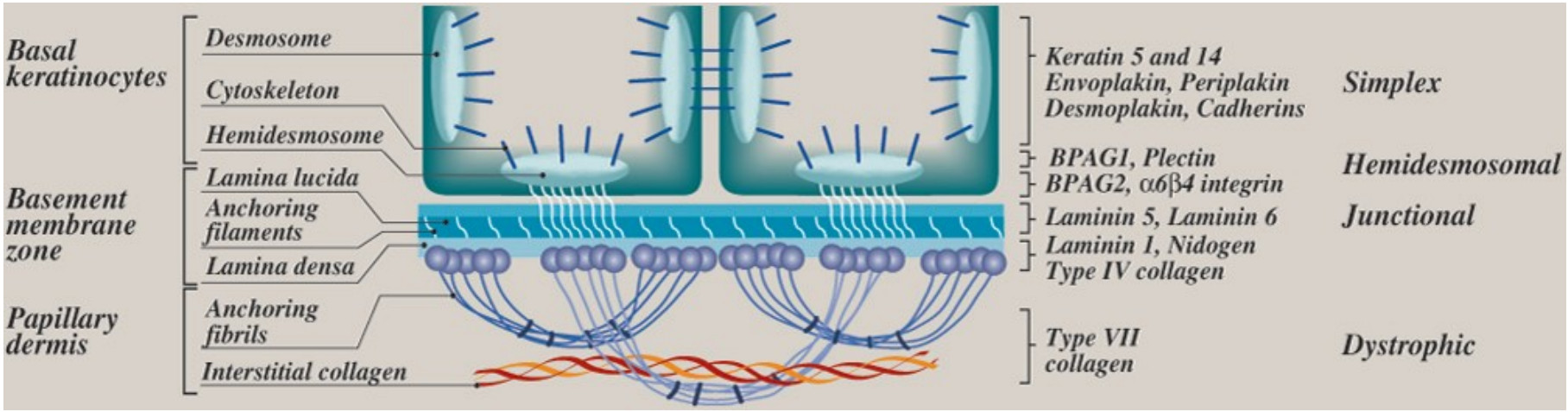


(A) Atrophic skin on abdomen, hypergranulating tissue in lesions. (B) Onychodystrophy, hands without signes of pseudosyndactyly and semiflectional position of fingers. (C) Atrophic skin on neck and below sternum. (D) Extensive defects on back area. (D) Limbs without skin defects.

RDEB-O	15	c.1573C>T	p.Arg525X	**c.6887G>A**	**p.Gly2296 Glu**	Aplasia cutis, generalised blistering, atrophic scarring,pruritus, onychodystrophy	Microstomia, ankyloglossia, oral cavity erosions, dysphagia, corneal erosions

Epidermolysis bullosa simplex

• characterized by separation of the skin above the basement membrane due to cytolysis of basal keratinocytes.

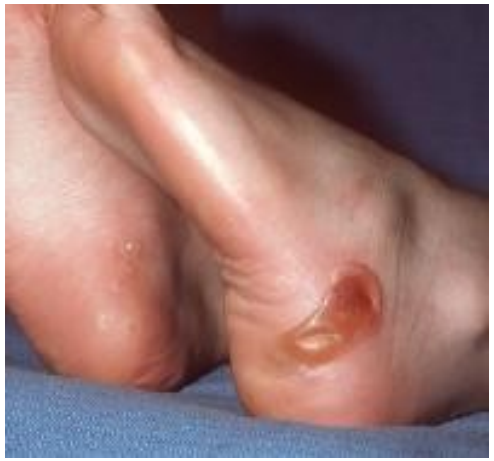


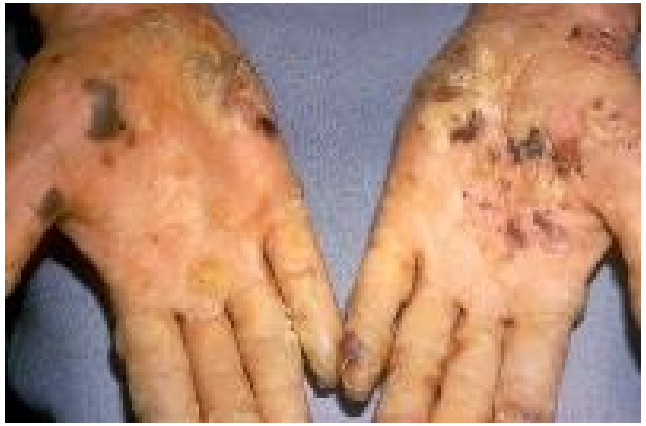
Epidermolysis bullosa simplex

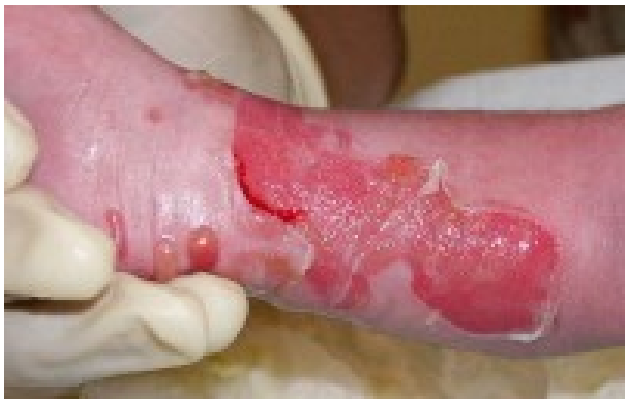
Three main autosomal dominant subtypes of EBS are distinguished based on the severity of blistering:

- **EBS localized (EBS-loc)** - blistering is usually limited to the hands and feet.
- **EBS another generalized (EBS-gen non-Dowling–Meara)** more widespread blistering is observed but it is usually milder than in the most severe variant.
- **EBS Dowling-Meara (EBS-DM)** – the most severe variant, characterized by generalized herpetiform blistering especially in the neonatal and infant periods.

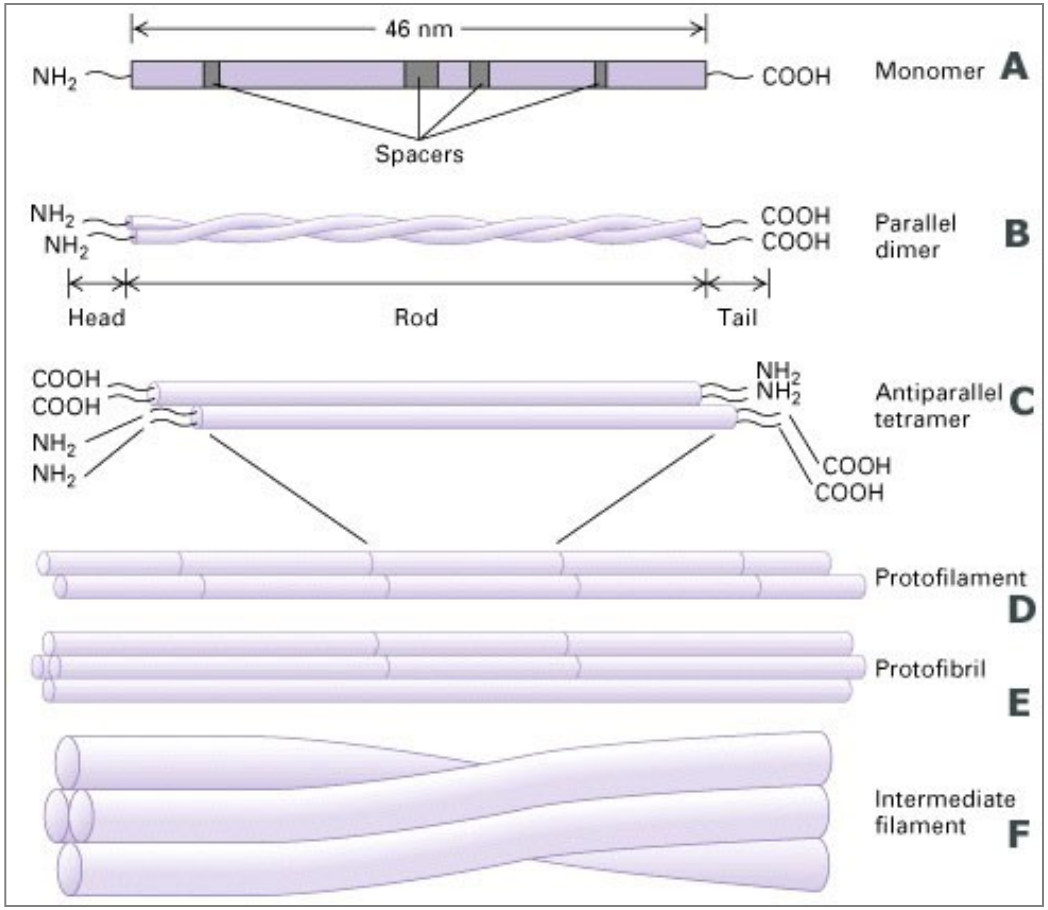
- These subtypes of EBS are caused by mutations in either the **keratin 5** (*KRT5*) or the **keratin 14** (*KRT14*) genes. **Most keratin mutations are inherited in an autosomal dominant manner.**



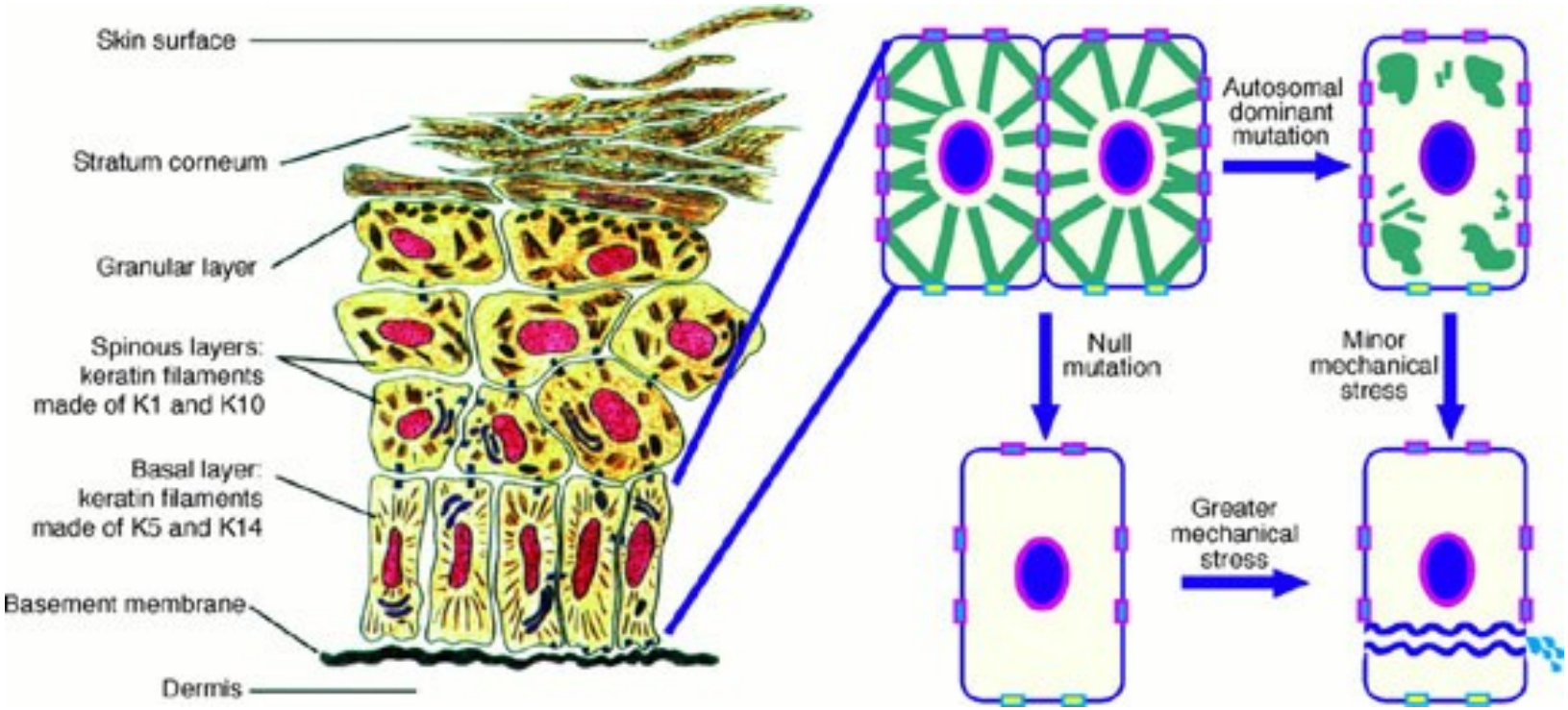




• Keratins are a group of structural proteins that polymerize to form **keratin intermediate filaments.**
• A characteristic feature of all intermediate filament proteins is the central alpha-helical rod domain, which is divided into four helices (1A, 1B, 2A and 2B) by three short nonhelical linker domains and terminated by globular head domains.



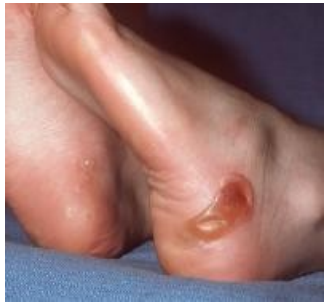
• Keratins are divided into type I (KRT9–KRT24) or type II (KRT1–KRT8) proteins according to their physical and chemical properties, and the basic structural unit of intermediate filaments is a heterodimer of one type I keratin and its corresponding type II partner.
• **Keratins 5 and 14 are natural partners that dimerize by coiled-coil interactions.**

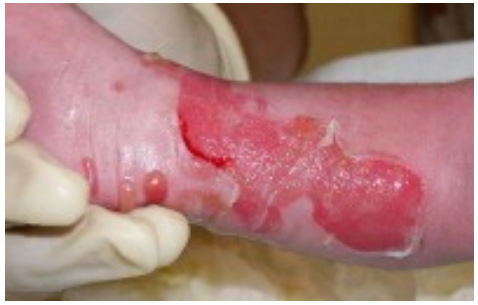


The following image illustrates the cell in EBS patients. It displays what a normal cell cytoskeleton ought to look like and what happens in EB disease states.

Diagnostika EBS:

1. Klinické příznaky





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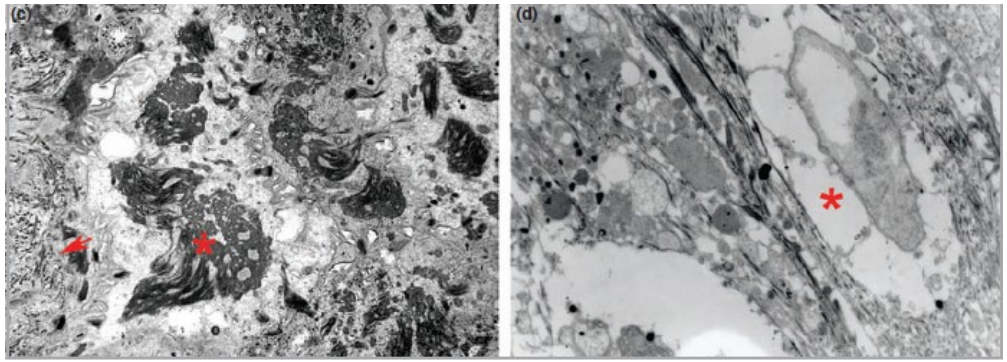
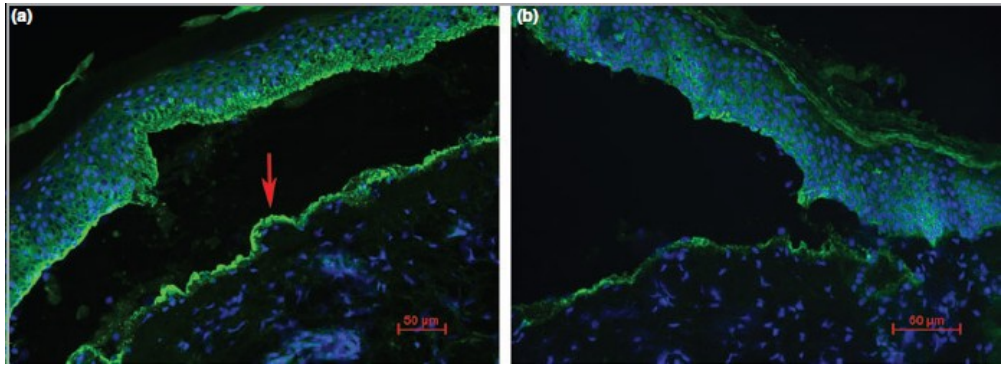


3. Imunofluorescenční antigenní mapování



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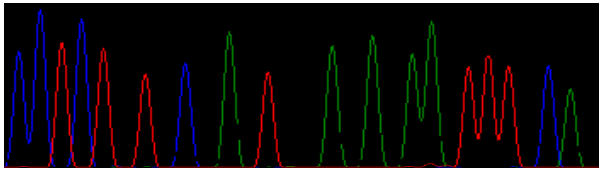
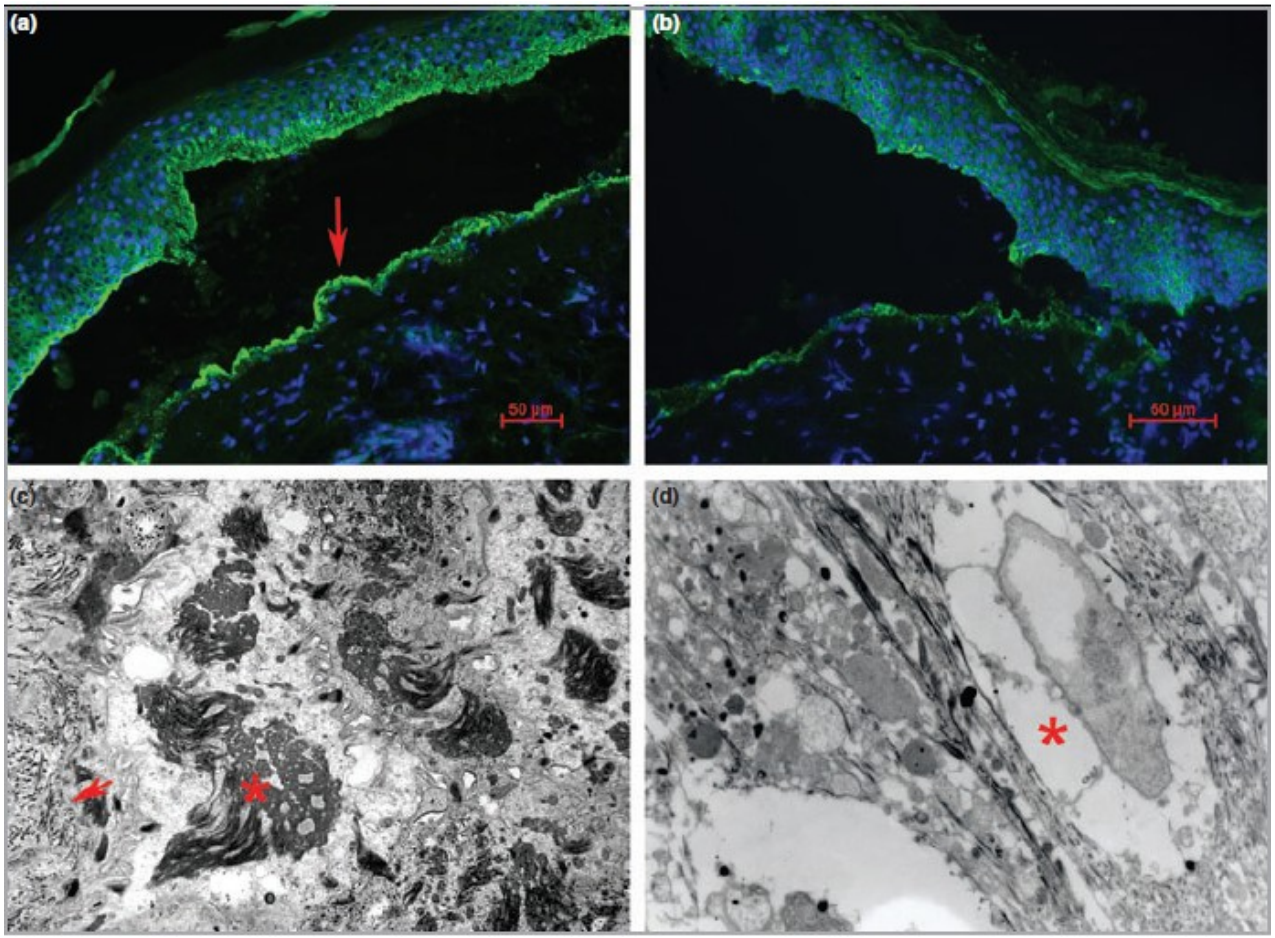




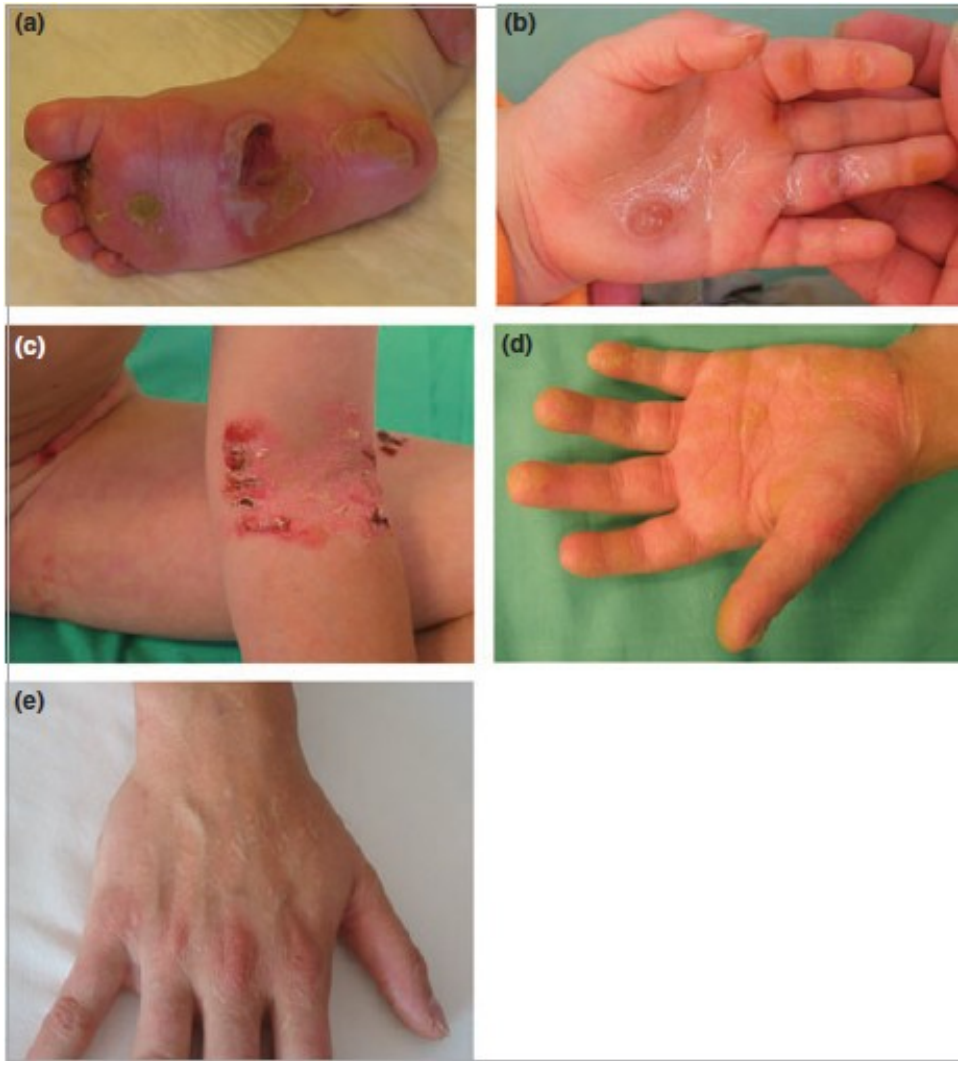
(a) Immunofluorescence microscopy findings in the skin of the patient with epidermolysis bullosa simplex (EBS) with the mutation KRT14-p.Gln374_Leu387dup(14) using monoclonal antibody to keratin 14, with positive staining of basal and suprabasal keratinocytes including the blister floor (arrow). (b) Immunofluorescence labelling of a skin biopsy from the same patient using monoclonal antibody to keratin 5 with a distribution pattern similar to (a). (c) Electron microscopy findings in the skin of the patient with EB with mutation KRT14-p.Ser128Pro. Ultrastructural changes are pronounced clumping of curled tonofilaments (*) in basal and suprabasal keratinocytes above the dermoepidermal junction (arrow) characteristic of EBS-Dowling Meara. Some subtle cytolysis is also present. Original magnification 6000. (d) Electron microscopy findings in the skin of the patient with EB with mutation KRT14-p.Val143Ala. Ultrastructurally, advanced cytolysis of keratinocytes with vacuolization of cytoplasm (*) is seen. Original magnification 6000.

DNA diagnostics

• PCR-sequencing analysis of all exons and adjacent intron regions of the **keratin 5** (*KRT5,*12q13, **9 exons**) and **keratin 14** (*KRT14,* 17q12, **8 exons**) genes.

• Our results - a causative mutation was detected in 21 probands

• **15 different sequence variants were found, 6 of which have not been reported previously.**



(a) Partly haemorrhagic blisters, with erosions on the inflammatory skin on the sole and haemorrhagic crust under the fingers, in **a 2-year-old patient with EBS-DM with the mutation KRT14-p.Ser128Pro**. (b) Fresh and several older clear blisters on the palm and fingers in the same patient at age 4 years. (c) Partly haemorrhagic blisters in a herpetiform distribution with inflammatory surrounding in cubital localization in a **6-year-old patient with EBS-DM with the mutation KRT14-p.Glu374_Leu387dup(14)**. (d) Extensive hyperkeratosis in the palm of the same patient. (e) Multiple tiny linear white scars on the dorsum of the hand in **a 30-year-old patient with EBS with the KRT14-p.Leu136Pro mutation.**