# Supporting information

# Appendix S1. Clinical manifestations and genetics of classical epidermolysis bullosa

The main clinical features and genetics of classical types of EB are summarized below. For detailed descriptions we refer to the original articles and to Fine et al 2014.1

**Epidermolysis bullosa simplex**

**Common EBS subtypes**

The common EBS subtypes comprise: localized (previously known as Weber-Cockayne), intermediate (previously known as EBS generalized intermediate, EBS Köbner) and severe (previously known as EBS generalized severe, EBS Dowling-Meara) EBS.

*Main cutaneous manifestations*

* Skin blistering begins at birth in severe and intermediate EBS, and at birth or in early infancy in localized EBS. The intra-epidermal blistering is superficial, leading to erosions and crusts, and is enhanced by heat, humidity and sweating. The tendency to blistering diminishes in adolescence, when it may become localized to hands and feet. Blisters may heal with hyperpigmentation.
* In severe EBS, skin fragility is very prominent at birth, and congenital ulcerated areas on hands and feet as well as nail involvement are common (Figure 1a). In the neonatal period, large tense blisters can occur after minimal mechanical trauma or spontaneously. The condition may be life threatening in the first year of life. This subtype has been defined by the herpetiform (arciform) pattern of the blisters, a crusting-necrotic aspect of the lesions that are often associated or preceded by inflammatory plaques (Figure 1b), and by clumping of keratin intermediate filaments as shown by transmission electron microscopy.
* Blistering is generalized, but less severe in intermediate EBS.
* Blisters are mainly restricted to hands and feet in localized EBS (Figure 1c).
* Plantar keratoderma occurs in all three common EBS subtypes. It develops gradually, is painful, may reduce mobility, and may strongly impair quality of life (Figure 1d). Confluent palmoplantar keratoderma is mostly seen in severe EBS.
* Milia may occur in the first weeks of life.
* EB naevi are common (Table S2 and Figure S2a).

*Mucosal membranes*

* The oral mucosa is usually involved in infants with severe EBS.

*Nails, hair*

* Nails may be thick and dystrophic (Figure 1e).
* Hair is not affected.

*Extracutaneous involvement*

* Specific pathogenic variants causing severe EBS have been associated with neonatal complications and a lethal outcome attributed to infection, malnutrition and respiratory failure.2 It remains unclear what makes infants so susceptible.
* Gastro-oesophageal reflux may occur in infancy in severe EBS, often needing aggressive medical treatment.
* Growth retardation is common in infants with severe EBS.
* There is no primary involvement of extracutaneous organs.

*Genetics*

* Autosomal dominant inheritance.
* Monoallelic missense, nonsense, frameshift or splice site pathogenic variants, or in frame deletions in *KRT5* or in *KRT14* (www.interfil.org/)3.
* High rate (about 30%) of *de novo* mutations.
* Semidominant inheritance and variable penetrance of pathogenic variants has been reported.4,5
* Digenic occurrence of pathogenic variants in both, *KRT5* and *KRT14* has been reported.6–8

*Genotype-phenotype correlations*

* Pathogenic variants located in the keratin 5 or 14 genes with variable locations outside the helix initiation and termination regions lead to localized EBS, while those located in the helix initiation or termination motifs lead to severe EBS (www.interfil.org).3,9
* Keratin 14 pathogenic variants affecting codon 125 (p.R125C, p.R125L or p.R125H) are common “hot spot mutations”, and are associated with severe EBS.9
* The keratin 5 amino acid substitution, p.E477K has been associated with a very severe course, even a lethal outcome in the neonatal period.10,11 Some pathogenic variants in keratin 14, such as p.M119T and c.1246del have also been correlated with a very severe clinical course.12

**Rare EBS subtypes**

**EBS, with mottled pigmentation**

*Main clinical manifestations*

* Skin blistering starts at birth and is generalized, of intermediate severity.
* Mottled or reticulate pigmentation develops gradually (Figure 1f)
* Focal keratoses of the palms and soles, and dystrophic, thickened nails occur over time.

*Genetics*

* Autosomal dominant inheritance.
* The keratin 5 monoallelic pathogenic variant c.74C>T, p.P25L typically causes this phenotype,13 but cases with other variants in *KRT5,* *KRT14* or *EXPH5* have been reported.14–16

**EBS, migratory circinate erythema**

*Main clinical manifestations*

* Multiple vesicles are present from birth onwards and acquire over time a typical circinate migratory pattern on an erythematous background; post-inflammatory hyperpigmentation develops gradually and may have a mottled pattern.
* Nails may be dystrophic.

*Genetics*

* Autosomal dominant inheritance.
* Monoallelic pathogenic variants in *KRT5* which affect the variable 2 domain and result in frameshift and elongated keratin 5 polypeptide cause this phenotype.17

**EBS, intermediate with cardiomyopathy**

*Main clinical manifestations*

* Extensive skin defects on the extremities are present at birth and heal with hypo- and hyperpigmentation and skin atrophy, initially resembling burn-like scars (Figure 1g).18 Skin blistering diminishes in adulthood, but fragility persists, with erosions occurring after minimal mechanical trauma.
* Diffuse or focal plantar keratoderma.
* Nail thickening and onychogryphosis (Figure 1g).
* Diffuse alopecia has been reported in some adult patients.19
* Dilated cardiomyopathy has been reported in young adulthood.20,21 Laboratory screening (pro-BNP, creatine kinase, creatine kinase MB) should be started as early as the age of 2 years, with yearly follow-ups. If pathologic values are found, cardiologic examination, ECG and cardiac ultrasound should be performed.

*Genetics*

* Autosomal dominant inheritance.
* Monoallelic pathogenic variants in the translation initiation codon of *KLHL24,* coding for the kelch-like member24 cause this disorder.19,22,23
* High rate (50%) of *de novo* mutations.19

**Recessive EBS, intermediate or severe with keratin 14 or 5 pathogenic variants**

*Main clinical manifestations*

* Skin blistering starts at birth and is generalized and severe in most cases. No improvement of cutaneous fragility is expected with age. Healing of lesions leads to post-inflammatory hyperpigmentation.
* Absence of keratin 5 leads to widespread blisters and erosions and early lethality.24,25

*Genetics*

* Autosomal recessive inheritance.
* Biallelic nonsense, missense or frameshift *KRT14* pathogenic variants.26,27
* Biallelic loss-of-function or missense *KRT5* pathogenic variants.24,25

**EBS, localized or intermediate with BP230 deficiency**

*Main clinical manifestations*

* Skin blistering starts at birth or in childhood, and is mostly localized to acral extremities.
* Plantar keratoderma.
* Nail dystrophy.

*Genetics*

* Autosomal recessive inheritance.
* Biallelic loss-of-function pathogenic variants in *DST* lead to absence of BP230 and cause this subtype.28

**EBS, localized or intermediate with exophilin 5 deficiency**

*Main clinical manifestations*

* Generalized skin blistering starts at birth or in infancy. Blistering tendency may diminish with age, while crusts and scabs reflect the fragility of the skin.
* Mild mottled pigmentary changes may develop.16

*Genetics*

* Autosomal recessive inheritance.
* Biallelic loss-of-function pathogenic variants in *EXPH5* lead to absence of exophilin 5 and cause this subtype.29

**EBS, intermediate with *PLEC* pathogenic variants**

*Main clinical manifestations*

* Skin blistering starts at birth, is mainly acral but may be widespread. The autosomal dominant subtype is characterized by a mild course, mainly acral erosions and postlesional violaceous and hypopigmented macules.30 Only three cases with the autosomal recessive subtype have been published yet, all of intermediate severity.31,32
* Plantar keratoderma.
* Dystrophic thickened nails, sometimes onychogryphosis.
* No muscular dystrophy.

*Genetics*

* Autosomal dominant or recessive inheritance.
* The monoallelic *PLEC* pathogenic variant, c.5998C>T, p.R2000W causes the autosomal dominant subtype previously known as EBS Ogna.30
* Biallelic pathogenic variants in the exon 1a of the *PLEC1a* isoform (expressed in skin, but not in muscles), in particular, c.46C>T, p.R16\*, cause the autosomal recessive subtype.31

**EBS, intermediate with muscular dystrophy**

*Main clinical manifestations*

* Generalized skin blistering starts at birth and is of intermediate severity. Blistering tendency diminishes with age.
* Focal plantar keratoderma.
* Nail dystrophy and loss.
* Mucosal involvement including oral, ocular and urethral mucosae is common.
* Dental anomalies.
* Muscular dystrophy starts at a variable age, ranging from infancy to adulthood.33
* Cardiomyopathy may be associated.34
* Granulation tissue and stenosis of the upper respiratory tract and hoarseness may occur.30,31,35
* Muscular dystrophy is usually life-limiting in childhood or early adulthood.
* Pyloric atresia may be associated in rare cases.36

*Genetics*

* Autosomal recessive inheritance.
* Biallelic loss-of-function pathogenic variants in *PLEC* coding for plectin cause this phenotype. They result in lack of immunoreactivity for plectin and a plane of cleavage deep within the basal pole of the basal keratinocytes.37

**EBS, severe with pyloric atresia**

*Main clinical manifestations*

* Widespread full-thickness congenital absence of skin.
* Pyloric atresia.
* Involvement of the oral mucosa.
* Anaemia and growth retardation.
* Neonatal lethal course.

*Genetics*

* Autosomal recessive inheritance.
* Biallelic loss-of-function pathogenic variants in *PLEC* cause this phenotype.38

**EBS, localized with nephropathy with CD151 deficiency**

*Main clinical manifestations*

* Only a few individuals with this subtype have been reported so far in the literature.39,40
* Skin blistering starts at birth and is widespread primarily in the pretibial area but also scattered on other parts of the body, particularly those exposed to trauma.39,40
* Facial freckling, poikiloderma and atrophy of the skin, and acrogeria of the backs of the hands on the sun-exposed areas reported in one case.39
* Erosions of the oral mucous membranes.
* Nail dystrophy.
* Early-onset alopecia.
* Nasolacrimal duct stenosis.
* Oesophageal webbing and strictures.
* Nephropathy manifesting with proteinuria. The scarcity of reported cases precludes firm screening recommendations but annual urinalysis and urea and electrolytes should probably be undertaken following diagnosis.

*Genetics*

* Autosomal recessive inheritance.
* Biallelic loss-of-function pathogenic variants in *CD151*, coding for the CD151 antigencause this EBS subtype.39,40

**Junctional epidermolysis bullosa**

**Common JEB subtypes**

The two major subtypes of JEB are severe JEB (previously known as JEB generalized severe, Herlitz JEB) and intermediate JEB (previously known as JEB generalized intermediate, non-Herlitz JEB).

*Main cutaneous manifestations*

In both major forms of JEB, blistering begins at birth or shortly afterwards. Blisters tend to rupture leaving erosions, which can become extensive. Areas of ulcerated skin may be present at birth, most commonly on the lower limbs or dorsa of the feet and ankles. Blisters and ulcers may heal with atrophic scarring and variable hypo- or hyperpigmentation.

* In severe JEB, blisters may be few the first couple weeks of life and tend to occur on the buttocks, elbows, and around the nails; however, despite an initially mild clinical picture, JEB severe must be suspected. From a few weeks to months of age, wounds may become chronic with a bed of friable granulation tissue. This commonly affects the face, ears and distal digits (see below) (Figure 2a). Persistent large gluteal wounds are common.
* Blistering is generalized but less severe in intermediate JEB, usually without the tendency for developing chronic granulation tissue (Figure 2b) although this can occur in chronic wounds (Figure 2c).
* Development of cutaneous squamous cell carcinoma (SCC) can occur in adulthood in intermediate JEB.41
* EB naevi may occur in patients with intermediate JEB (Figure S2b).

*Mucous membranes*

* Involvement of the oral mucosa occurs in both severe and intermediate JEB.
* Severe JEB is typically associated with laryngeal mucosal involvement with blistering, erosions, granulation tissue and scarring giving rise to hoarseness, stridor and potentially life-threatening airway obstruction.42
* Ocular involvement with corneal blistering and erosions is common in both intermediate and severe JEB. Pannus formation, scarring and symblepharon may follow episodes of blistering.43
* Involvement of the genitourinary tract can occur in either form but most commonly presents in older individuals with intermediate JEB with urethral stricture disease.44

*Nails, hair*

* In intermediate JEB, nails are usually lost or dystrophic with atrophy, thickening or ridging of the nail plate (Figure 2d).
* Severe JEB is characterized by the loss of all nails in the first few months of life with the development of friable granulation tissue and soft tissue swelling of the distal digits (Figure 2a).
* Both forms of JEB can be associated with scarring or non-scarring alopecia and diffuse hair loss (Figure 2e).

*Extracutaneous involvement*

* Infants with severe JEB usually develop profound failure to thrive despite adequate nutritional intake.
* Anaemia is common in severe JEB and, to a lesser extent, in intermediate JEB with widespread cutaneous involvement.45
* Severe JEB usually results in death in the first 24 months due to failure to thrive, airway involvement or sepsis.46–48
* Dental enamel defects occur in all individuals with JEB (Figure 2f). Monoallelic pathogenic variants in *COL17A1, LAMA3* or *LAMB3* can cause dominant hypoplastic amelogenesis imperfecta.49–52

*Genetics*

* Autosomal recessive inheritance.
* In severe JEB: biallelic nonsense, frameshift or splice site pathogenic variants in *LAMA3*, *LAMB3* or *LAMC2.*53
* The most common pathogenic variant causing severe JEB is located in the *LAMB3* gene, and leads to a PTC, p.R635\*47,54,55; in addition, there are some recurrent population–specific *LAMB*3 variants, such as c.3228+1G>A56, c.1133-22G>A57.
* In intermediate JEB: biallelic missense, nonsense, frameshift or splice site pathogenic variants in *LAMA3*, *LAMB3* or *LAMC2*; or biallelic missense, nonsense, frameshift or splice site pathogenic variants in *COL17A1.*53,58
* Revertant mosaicism is relatively frequent in intermediate JEB, particularly those with *COL17A1* mutations.59–62

*Genotype-phenotype correlations*

* Biallelic loss-of-function pathogenic variants in *LAMA3*, *LAMB3* or *LAMC2* result in severe JEB, while absence of type XVII collagen results in intermediate JEB.
* The presence of a non-loss-of-function pathogenic variant on one or both alleles of these genes results in intermediate or localized JEB.63,64

**Other JEB subtypes**

**JEB with pyloric atresia**

*Main clinical manifestations*

* Full thickness skin loss over extensive areas of the head, trunk and limbs at birth.
* Subsequent severe skin fragility.
* Skin loss can cause deformity of structures such as the ears and nose. Severe phenotypes can present with rudimentary ears.
* Nail dystrophy and loss.
* Pyloric atresia is usually evident within the first days-week of life.
* May have atresia at other gastrointestinal sites e.g. duodenal or anal.
* Usually lethal within the first few weeks of life despite surgical correction of pyloric atresia.
* Milder, non-lethal forms have less severe skin and nail involvement but with frequent genitourinary tract involvement.65,66

*Genetics*

* Biallelic loss-of-function, splice site or missense pathogenic variants in *ITGA6* result in a severe and rapidly lethal phenotype.53,65,67,68
* Biallelic loss-of-function or splice site pathogenic variants in *ITGB4* that result in loss of 4 integrin result in a severe and rapidly lethal phenotype.53,66,69,70
* Biallelic loss-of-function, missense, splice site or in-frame deletion mutations in *ITGB4* which result in reduced 4 integrin expression result in a milder form of JEB with pyloric atresia.66,69,71,72
* Biallelic mutations in *ITGB4* may result in JEB without pyloric atresia.65,66,72

**JEB localized**

*Main clinical manifestations*

* Limited cutaneous fragility and blistering, often only acral.
* Variable nail dystrophy and mucosal involvement.
* Variable dental enamel defects.
* Normal hair.

*Genetics*

* Autosomal recessive inheritance.
* Homozygous or compound heterozygous pathogenic variants in *COL17A1*, *LAMA3*, *LAMB3*, *LAMC2*, *ITGB4*, *ITGA3.*63,64,73–76

**JEB inversa**

*Main clinical manifestations*

* Onset of blistering from birth in flexural sites.
* Atrophic scarring.
* Dental enamel abnormalities.
* Variable nail loss.

*Genetics*

* Pathogenic variants associated with residual expression of laminin 332.77

**JEB late onset**

*Main clinical manifestations*

* Onset of skin fragility in childhood often starting acrally.
* Progressive fragility with age.
* Healing with skin atrophy and loss of dermatoglyphs.
* Scarring leading to flexion contractures of the fingers and reduction of mouth opening may occur with age.
* Variable dental enamel and nail involvement.

*Genetics*

* Autosomal recessive inheritance.
* Biallelic pathogenic variants in *COL17A1,* specifically the missense variant c.3908G>A, p.R1303Q, cause this phenotype.78,79

**JEB-laryngo-onycho-cutaneous (LOC) syndrome**

Syn. Shabbir syndrome.

*Main clinical manifestations*

* Onset of skin fragility from birth with blistered areas leaving erosions and granulation tissue (much more than JEB severe) (Figure S3a).
* Predilection for the face and neck.
* Nail dystrophy and loss with granulation tissue of the nail beds (Figure S3b).
* Conjunctival and eyelid granulation tissue leading to symblepharon, scarring and impaired vision (Figure S3a).80
* Laryngeal granulation tissue leading to respiratory obstruction which can be lethal (Figure S3a).
* Profound Anaemia is a major feature due to bleeding from over granulating wounds.

*Genetics*

* Autosomal recessive inheritance.
* Most cases in Punjabi Muslim individuals with a homozygous founder single nucleotide insertion mutation in exon 39 of *LAMA3* which is specific to the *LAMA3A* isoform.81
* Compound heterozygosity for mutations in *LAMA3A* and *LAMA3* result in a similar JEB-LOC phenotype.80

**JEB with interstitial lung disease and nephrotic syndrome (syn. ILNEB, interstitial lung disease, nephrotic syndrome and epidermolysis bullosa)**

Syn. ILNEB, interstitial lung disease, nephrotic syndrome and epidermolysis bullosa.

*Main clinical manifestations*

* Variable cutaneous features with absence or presence of skin fragility from infancy.
* Nails may be dystrophic and hair may be sparse.
* Interstitial lung disease and nephrotic syndrome predominate the phenotype, and can be diagnosed soon after birth.
* Death in infancy or early childhood is the norm.

*Genetics*

* Most reported cases result from homozygous loss-of-function pathogenic variants in *ITGA3.*75,82,83
* Missense *ITGA3* mutations reported in milder cases surviving to later childhood.84,85

**Dystrophic epidermolysis bullosa**

**Common DEB subtypes**

Major subtypes of DEB include localized DDEB (previously encompassing nails only, pretibial and acral DDEB), intermediate DDEB (previously known as generalized DDEB), intermediate RDEB (previously known as RDEB generalized intermediate, non-Hallopeau-Siemens RDEB) and severe RDEB (previously RDEB generalized severe, Hallopeau-Siemens RDEB).

*Main cutaneous manifestations*

* In localized DDEB, the onset of skin fragility is usually from birth or early childhood and is limited in anatomical extent (Figure 3a). This may be predominantly acral in distribution or just affect the nails with progressive dystrophy and loss, mainly of the toenails. Some individuals have a predominantly pretibial distribution of blistering and scarring; in this form symptoms may not develop until later childhood or adulthood.
* Intermediate DDEB and intermediate RDEB manifest with more generalized skin fragility, scarring and milia from birth or early childhood, with a predilection for bony prominences including the elbows, knees, ankles and dorsa of the hands and feet (Figure 3a). Although severity tends to be greater in the recessive form, there is considerable phenotypic overlap and it is often not possible to distinguish these types on clinical grounds. Mild flexion contractures or a striate-pattern of keratoderma of the fingers and limited digital fusion in the proximal digital web spaces may occur, particularly in intermediate RDEB.
* Skin blistering in severe RDEB is widespread and manifests from birth with significant fragility from minor skin trauma (Figure 4a). From infancy, blistering is more marked over bony prominences and causes extensive scarring which can lead to flexion contractures of the large joints (Figure 4b). Progressive pseudosyndactyly (digital fusion), flexion contractures and distal resorption of the digits lead to mitten deformities of the hands and feet (Figure 4c). Chronic wounds are frequent at sites of repeated blistering (Figure 4b).
* Congenital skin ulceration is a common presenting feature in neonates with severe RDEB but can also occur in other forms of DEB, JEB or EBS. It may be uni- or bilateral and most commonly affects the dorsomedial foot and ankle, and the medial lower leg.
* The development of aggressive cutaneous SCC is very common and a frequent cause of death in severe RDEB increasing in incidence from the teen years onwards, arising in areas of repeated trauma, wounds and scarring (Figure 4d).41 The risk of developing SCC is also increased in intermediate DDEB, RDEB and, to a lesser extent, localized DDEB, but is less common than in severe RDEB and occurs later in adulthood.
* EB naevi may occur (Table S2 and Figure S2c).

*Mucosal membranes*

* The oral mucosa may be involved in all forms of DEB with blistering, erosions and scarring but changes are most extensive and marked in severe RDEB (Figure 4e).
* In severe RDEB, progressive scarring leads to microstomia and ankyloglossia, which can result in dental overcrowding and malalignment, and the development of secondary caries (Figure 4e).
* Oesophageal blistering and scarring are common in severe and intermediate forms of DEB. Left untreated, progressive strictures can significantly limit oral nutritional intake.86
* Recurrent blistering and fissuring around the anal margin are common in all forms of DEB, particularly the more severe types, and may exacerbate constipation.86
* Involvement of the conjunctiva and cornea in severe and intermediate DEB is common, leading to corneal erosions, scarring, pannus, symblepharon formation and reduced visual acuity (Figure 4f).43
* Urethral strictures may occur in more severe forms of DEB, particularly severe RDEB.44

*Nails, hair*

* Localized DDEB may present solely with loss or dystrophy of the nails, most commonly the toenails (Figure 3b).
* Nail dystrophy and loss secondary to trauma are common in all forms of DEB. In severe RDEB, nails are usually lost progressively during the first several years of life.
* Scarring alopecia and crusting are common with increasing age in severe RDEB.

*Extracutaneous involvement*

* Nutritional impairment is common in severe RDEB and may also occur in intermediate forms of DEB; it results from reduced intake due to factors such as microstomia, dental caries and oesophageal stricture disease, in combination with increased metabolic demands due to chronic wounds, infection and inflammation.
* Constipation is common in DEB due to pain on defection resulting from anal fissuring and blistering, exacerbated by poor intake of fibre-rich foods when intake is compromised.86
* A mixed picture of Anaemia due to iron deficiency and inflammation is common in severe RDEB.45,87
* Osteopenia, osteoporosis and vertebral fractures are common in severe RDEB and may be due to reduced mobility, chronic inflammation, vitamin D and calcium deficiency, and pubertal delay.88,89
* Renal impairment and failure may occur in severe RDEB as a result of acute kidney injury, post-streptococcal glomerulonephritis, renal amyloid or IgA nephropathy.44
* Cardiomyopathy may rarely arise in severe RDEB; aetiology is probably multifactorial including micronutrient deficiency, iron overload, drugs and viral causes.90

*Genetics*

* DDEB: autosomal dominant inheritance. Monoallelic missense, splice site or deletion mutations in *COL7A1.*91,92
* Intermediate RDEB: autosomal recessive inheritance. Biallelic missense, nonsense, deletion, insertion, small insertion/deletion or splice site mutations.91,92
* Severe RDEB: autosomal recessive inheritance. Biallelic nonsense, splice site, deletion, insertion, small insertion/deletion or missense mutations. Mutations usually result in null alleles.91,92
* The most common recurrent “hot spot” *COL7A1* mutation is c.425A>G at the donor splice site of exon 3. Other frequently encountered or population specific RDEB mutations are c.6527dup, c.497dup, p.R2069C, c.682+1G>A, p.R578\*, p.R2063W, p.R185\*, p.R1933\*, c.6269\_6270delC, c.4233delT (databases.lovd.nl).93–96
* Revertant mosaicism has been described in RDEB through a variety of mechanisms including *COL7A1* somatic mutation and intragenic crossover.97–99
* Forward non-revertant mosaicism has been demonstrated in RDEB with a germline *COL7A1* frameshift mutation and a somatic splice site mutation.100
* Somatic mosaicism for a dominant glycine substitution mutation in *COL7A1* has been identified in the parent of an individual with DDEB.101

*Genotype-phenotype correlations*

* DDEB is most commonly caused by missense mutations resulting in a glycine substitution around the hinge region of the collagenous triple helix of *COL7A1*. Less commonly, glycine substitution mutations are recessive only giving rise to an RDEB disease phenotype when inherited *in trans* with a second *COL7A1* mutation.91,92
* Compound heterozygosity for a loss-of-function mutation on one *COL7A1* allele and a non-loss-of-function mutation on the second allele usually results in an intermediate RDEB phenotype.91,92
* Homozygosity or compound heterozygosity for truncating *COL7A1* mutations usually results in severe RDEB.91,92

**Rare DEB subtypes**

**DDEB, pruriginosa and RDEB, pruriginosa**

*Main clinical manifestations*

* Usually presents initially as localized or intermediate DDEB or RDEB in childhood and early adulthood.
* Characterized by intensely pruritic, excoriated violaceous papules or linear plaques and scars particularly on the lower legs, thighs and arms which can become more progressive from adolescence through adulthood (Figure 3c).
* Nail dystrophy and milia are common.
* May co-exist with non-pruriginosa DEB within families.

*Genetics*

* Autosomal dominant or autosomal recessive inheritance.
* Monoallelic or biallelic mutations in *COL7A1* similar to those identified in non-pruriginosa DDEB or RDEB without identification of a specific genotype-phenotype correlation for the pruriginosa phenotype.102–104

**DDEB, self-improving and RDEB, self-improving (syn. bullous dermolysis of the newborn)**

*Main clinical manifestations*

* Skin blistering presents at or shortly after birth, usually on the extremities.
* Aplasia cutis of the lower limbs may be present.
* Scarring and milia occur at sites of blistering.
* Skin fragility improves spontaneously and may resolve completely over the first year or two of life although nail dystrophy, particularly of the toenails, may persist throughout life.

*Genetics*

* Autosomal dominant or autosomal recessive.
* *COL7A1* missense mutations, especially glycine substitutions, are most commonly associated but in-frame deletion, premature termination codon and alternative splicing mutations also described.105–107
* Characteristic intra-epidermal retention of type VII collagen on immunohistochemistry and stellate bodies in dilated rough endoplasmic reticulum on transmission electron microscopy.108 These changes tend to improve in parallel with phenotypic improvement.

**RDEB, inversa**

*Main clinical manifestations*

* In the neonatal period and childhood skin blistering is usually generalized and of intermediate severity.
* From adolescence to early adulthood, a predilection for flexural sites develops, specifically in the axillae, groins, perianal area and natal cleft. In women, there may be marked vulvovaginal and inframammary skin blistering (Figure S4a).
* Mucosal disease with blistering and scarring in the mouth and oesophagus is characteristic (Figure S4b).
* Involvement of the external auditory canal may lead to narrowing or complete occlusion (Figure S4c).
* Nail involvement is common.

*Genetics*

* Autosomal recessive inheritance.
* Usually results from compound heterozygosity for a loss-of-function *COL7A1* mutation in combination with a missense mutation; specific glycine and arginine substitutions have been suggested as causative for this specific phenotype.109

**RDEB, localized**

*Main clinical manifestations*

* Skin fragility usually presents at or shortly after birth but may rarely be of late onset in adulthood.
* Blistering is limited in extent; it may affect predominantly the hands and feet, but in others may be restricted to the pretibial area.
* Nail dystrophy and loss are common.
* Oral and esophageal mucosal involvement are usually mild or absent.

*Genetics*

* Autosomal recessive inheritance.
* Compound heterozygosity for *COL7A1* missense, splice site and frameshift mutations described.91,92

**Dominant and recessive compound heterozygous DEB**

*Main clinical manifestations*

* Severe skin and mucosal fragility presenting from birth indistinguishable from severe RDEB.
* May have a family history of DDEB in family members.

*Genetics*

* Compound heterozygosity for a dominant *COL7A1* glycine substitution mutation and a recessive mutation on the second allele.110–112

**Kindler epidermolysis bullosa**

*Cutaneous manifestations*

* Skin blistering begins at birth and is generalized with predilection for the extremities. The tendency to blistering decreases with age.
* Skin atrophy and poikiloderma start on the dorsal aspects of the hands and on the neck during childhood and extend to the entire integument (Figure 5a).
* Diffuse palmoplantar keratoderma and loss of dermatoglyphs (Figure 5a).
* Photosensitivity is of variable severity.
* SCC on extremities, lips or oral cavity develop in young adulthood, have a severe course and cause premature death related to the disease.113,114

*Mucosal membranes*

* Gingivitis with tooth loss, gingival hyperplasia, oesophageal strictures and colitis in a few cases (Figure 5b).115
* Urogenital strictures.
* Ectropion, corneal erosions (Figure 5c).

*Nails, hair*

* Nail dystrophy.
* No abnormalities of scalp hair.

*Genetics*

* Autosomal recessive inheritance.
* Biallelic *FERMT1* pathogenic variants (nonsense, frame shift, splicing, large deletions, in regulatory regions, missense), mostly leading to absence of kindlin-1.115–117
* Some *FERMT1* pathogenic variants are recurrent or population specific.118,119
* Revertant mosaicism has been reported mainly in patients with particular frameshift mutations within nucleotide repeats.120,121

*Genotype-phenotype correlations*

* Absence of kindlin-1 is associated with variable disease severity that is determined by additional factors. An in frame deletion of one amino acid, p.R100del leading to residual kindlin-1 expression and function lead to a mild Kindler EB phenotype.122

## References

1 Fine J-D, Bruckner-Tuderman L, Eady RAJ, *et al.* Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. *J Am Acad Dermatol* 2014; **70**:1103–26.

2 Fine JD, Johnson LB, Weiner M, Suchindran C. Cause-specific risks of childhood death in inherited epidermolysis bullosa. *J Pediatr* 2008; **152**:276–80.

3 Szeverenyi I, Cassidy AJ, Chung CW, *et al.* The Human Intermediate Filament Database: comprehensive information on a gene family involved in many human diseases. *Hum Mutat* 2008; **29**:351–60.

4 Vahidnezhad H, Youssefian L, Saeidian AH, *et al.* KRT5 and KRT14 Mutations in Epidermolysis Bullosa Simplex with Phenotypic Heterogeneity, and Evidence of Semidominant Inheritance in a Multiplex Family. *J Invest Dermatol* 2016; **136**:1897–901.

5 Wertheim-Tysarowska K, Ołdak M, Giza A, *et al.* Novel sporadic and recurrent mutations in KRT5 and KRT14 genes in Polish epidermolysis bullosa simplex patients: further insights into epidemiology and genotype-phenotype correlation. *J Appl Genet* 2016; **57**:175–81.

6 Kim E, Harris A, Hyland V, Murrell DF. Digenic inheritance in epidermolysis bullosa simplex involving two novel mutations in KRT5 and KRT14. *Br J Dermatol* 2017; **177**:262–4.

7 Wertheim-Tysarowska K, Sota J, Kutkowska-Kazmierczak A, *et al.* Coexistence of KRT14 and KRT5 mutations in a Polish patient with epidermolysis bullosa simplex. *Br J Dermatol* 2014; **170**:468–9.

8 Padalon-Brauch G, Ben Amitai D, Vodo D, *et al.* Digenic inheritance in epidermolysis bullosa simplex. *J Invest Dermatol* 2012; **132**:2852–4.

9 Coulombe PA, Lee C-H. Defining keratin protein function in skin epithelia: epidermolysis bullosa simplex and its aftermath. *J Invest Dermatol* 2012; **132**:763–75.

10 Sathishkumar D, Orrin E, Terron-Kwiatkowski A, *et al.* The p.Glu477Lys Mutation in Keratin 5 Is Strongly Associated with Mortality in Generalized Severe Epidermolysis Bullosa Simplex. *J Invest Dermatol* 2016; **136**:719–21.

11 Lalor L, Titeux M, Palisson F, *et al.* Epidermolysis bullosa simplex-generalized severe type due to keratin 5 p.Glu477Lys mutation: Genotype-phenotype correlation and in silico modeling analysis. *Pediatr Dermatol* 2019; **36**:132–8.

12 Titeux M, Mazereeuw-Hautier J, Hadj-Rabia S, *et al.* Three severe cases of EBS Dowling-Meara caused by missense and frameshift mutations in the keratin 14 gene. *J Invest Dermatol* 2006; **126**:773–6.

13 Irvine AD, Rugg EL, Lane EB, *et al.* Molecular confirmation of the unique phenotype of epidermolysis bullosa simplex with mottled pigmentation. *Br J Dermatol* 2001; **144**:40–5.

14 Arin MJ, Grimberg G, Schumann H, *et al.* Identification of novel and known KRT5 and KRT14 mutations in 53 patients with epidermolysis bullosa simplex: correlation between genotype and phenotype. *Br J Dermatol* 2010; **162**:1365–9.

15 Harel A, Bergman R, Indelman M, Sprecher E. Epidermolysis bullosa simplex with mottled pigmentation resulting from a recurrent mutation in KRT14. *J Invest Dermatol* 2006; **126**:1654–7.

16 Turcan I, Pasmooij AMG, Van den Akker PC, *et al.* Association of Epidermolysis Bullosa Simplex With Mottled Pigmentation and EXPH5 Mutations. *JAMA Dermatol* 2016; **152**:1137–41.

17 Gu LH, Kim SC, Ichiki Y, *et al.* A usual frameshift and delayed termination codon mutation in keratin 5 causes a novel type of epidermolysis bullosa simplex with migratory circinate erythema. *J Invest Dermatol* 2003; **121**:482–5.

18 Alkhalifah A, Chiaverini C, Charlesworth A, *et al.* Burnlike scars: A sign suggestive of KLHL24-related epidermolysis bullosa simplex. *Pediatr Dermatol* 2018; **35**:e193–5.

19 He Y, Maier K, Leppert J, *et al.* Monoallelic Mutations in the Translation Initiation Codon of KLHL24 Cause Skin Fragility. *Am J Hum Genet* 2016; **99**:1395–404.

20 Yenamandra VK, van den Akker PC, Lemmink HH, *et al.* Cardiomyopathy in patients with epidermolysis bullosa simplex with mutations in KLHL24. *Br J Dermatol* 2018; **179**:1181–3.

21 Schwieger-Briel A, Fuentes I, Castiglia D, *et al.* Epidermolysis Bullosa Simplex with KLHL24 Mutations Is Associated with Dilated Cardiomyopathy. *J Invest Dermatol* 2019; **139**:244–9.

22 Lin Z, Li S, Feng C, *et al.* Stabilizing mutations of KLHL24 ubiquitin ligase cause loss of keratin 14 and human skin fragility. *Nat Genet* 2016; **48**:1508–16.

23 Lee JYW, Liu L, Hsu C-K, *et al.* Mutations in KLHL24 Add to the Molecular Heterogeneity of Epidermolysis Bullosa Simplex. *J Invest Dermatol* 2017; **137**:1378–80.

24 Vahidnezhad H, Youssefian L, Daneshpazhooh M, *et al.* Biallelic KRT5 mutations in autosomal recessive epidermolysis bullosa simplex, including a complete human keratin 5 ‘knock-out’. *Matrix Biol* 2019; **83**:48–59.

25 Tryon RK, Tolar J, Preusser SM, *et al.* A homozygous frameshift variant in the KRT5 gene is compatible with life and results in severe recessive epidermolysis bullosa simplex. *JAAD Case Rep* 2019; **5**:576–9.

26 Jonkman MF, Heeres K, Pas HH, *et al.* Effects of keratin 14 ablation on the clinical and cellular phenotype in a kindred with recessive epidermolysis bullosa simplex. *J Invest Dermatol* 1996; **107**:764–9.

27 Hovnanian A, Pollack E, Hilal L, *et al.* A missense mutation in the rod domain of keratin 14 associated with recessive epidermolysis bullosa simplex. *Nat Genet* 1993; **3**:327–32.

28 Groves RW, Liu L, Dopping-Hepenstal PJ, *et al.* A homozygous nonsense mutation within the dystonin gene coding for the coiled-coil domain of the epithelial isoform of BPAG1 underlies a new subtype of autosomal recessive epidermolysis bullosa simplex. *J Invest Dermatol* 2010; **130**:1551–7.

29 McGrath JA, Stone KL, Begum R, *et al.* Germline Mutation in EXPH5 Implicates the Rab27B Effector Protein Slac2-b in Inherited Skin Fragility. *Am J Hum Genet* 2012; **91**:1115–21.

30 Koss-Harnes D, Hoyheim B, Anton-Lamprecht I, *et al.* A site-specific plectin mutation causes dominant epidermolysis bullosa simplex Ogna: two identical de novo mutations. *J Invest Dermatol* 2002; **118**:87–93.

31 Gostynska KB, Nijenhuis M, Lemmink H, *et al.* Mutation in exon 1a of PLEC, leading to disruption of plectin isoform 1a, causes autosomal-recessive skin-only epidermolysis bullosa simplex. *Hum Mol Genet* 2015; **24**:3155–62.

32 Has C, Küsel J, Reimer A, *et al.* The Position of Targeted Next-generation Sequencing in Epidermolysis Bullosa Diagnosis. *Acta Derm Venereol* 2018; **98**:437–40.

33 Kyrova J, Kopeckova L, Buckova H, *et al.* Epidermolysis bullosa simplex with muscular dystrophy. Review of the literature and a case report. *J Dermatol Case Rep* 2016; **10**:39–48.

34 Bolling MC, Pas HH, de Visser M, *et al.* PLEC1 mutations underlie adult-onset dilated cardiomyopathy in epidermolysis bullosa simplex with muscular dystrophy. *J Invest Dermatol* 2010; **130**:1178–81.

35 Prodinger C, Klausegger A, Diem A, *et al.* Laryngo-onycho-cutaneous (-like) syndrome due to mutated Plectin. *J Eur Acad Dermatol Venereol* 2017; **31**:e373–4.

36 Natsuga K, Nishie W, Shinkuma S, *et al.* Plectin deficiency leads to both muscular dystrophy and pyloric atresia in epidermolysis bullosa simplex. *Hum Mutat* 2010; **31**:E1687-98.

37 Smith FJ, Eady RA, Leigh IM, *et al.* Plectin deficiency results in muscular dystrophy with epidermolysis bullosa. *Nat Genet* 1996; **13**:450–7.

38 Pfendner E, Uitto J. Plectin gene mutations can cause epidermolysis bullosa with pyloric atresia. *J Invest Dermatol* 2005; **124**:111–5.

39 Vahidnezhad H, Youssefian L, Saeidian AH, *et al.* Recessive mutation in tetraspanin CD151 causes Kindler syndrome-like epidermolysis bullosa with multi-systemic manifestations including nephropathy. *Matrix Biol* 2018; **66**:22–33.

40 Karamatic Crew V, Burton N, Kagan A, *et al.* CD151, the first member of the tetraspanin (TM4) superfamily detected on erythrocytes, is essential for the correct assembly of human basement membranes in kidney and skin. *Blood* 2004; **104**:2217–23.

41 Fine JD, Johnson LB, Weiner M, *et al.* Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006. *J Am Acad Dermatol* 2009; **60**:203–11.

42 Fine JD, Johnson LB, Weiner M, Suchindran C. Tracheolaryngeal complications of inherited epidermolysis bullosa: cumulative experience of the national epidermolysis bullosa registry. *Laryngoscope* 2007; **117**:1652–60.

43 Fine JD, Johnson LB, Weiner M, *et al.* Eye involvement in inherited epidermolysis bullosa: experience of the National Epidermolysis Bullosa Registry. *Am J Ophthalmol* 2004; **138**:254–62.

44 Fine JD, Johnson LB, Weiner M, *et al.* Genitourinary complications of inherited epidermolysis bullosa: experience of the national epidermylosis bullosa registry and review of the literature. *J Urol* 2004; **172**:2040–4.

45 Hwang SJE, Daniel BS, Fergie B, *et al.* Prevalence of anemia in patients with epidermolysis bullosa registered in Australia. *Int J Womens Dermatol* 2015; **1**:37–40.

46 Yuen WY, Duipmans JC, Molenbuur B, *et al.* Long-term follow-up of patients with Herlitz-type junctional epidermolysis bullosa. *Br J Dermatol* 2012; **167**:374–82.

47 Hammersen J, Has C, Naumann-Bartsch N, *et al.* Genotype, Clinical Course, and Therapeutic Decision Making in 76 Infants with Severe Generalized Junctional Epidermolysis Bullosa. *J Invest Dermatol* 2016; **136**:2150–7.

48 Kho YC, Rhodes LM, Robertson SJ, *et al.* Epidemiology of epidermolysis bullosa in the antipodes: the Australasian Epidermolysis Bullosa Registry with a focus on Herlitz junctional epidermolysis bullosa. *Arch Dermatol* 2010; **146**:635–40.

49 Poulter JA, El-Sayed W, Shore RC, *et al.* Whole-exome sequencing, without prior linkage, identifies a mutation in LAMB3 as a cause of dominant hypoplastic amelogenesis imperfecta. *Eur J Hum Genet* 2014; **22**:132–5.

50 Smith CEL, Poulter JA, Brookes SJ, *et al.* Phenotype and Variant Spectrum in the LAMB3 Form of Amelogenesis Imperfecta. *J Dent Res* 2019; **98**:698–704.

51 McGrath JA, Gatalica B, Li K, *et al.* Compound heterozygosity for a dominant glycine substitution and a recessive internal duplication mutation in the type XVII collagen gene results in junctional epidermolysis bullosa and abnormal dentition. *Am J Pathol* 1996; **148**:1787–96.

52 Yuen WY, Pasmooij AM, Stellingsma C, Jonkman MF. Enamel Defects in Carriers of a Novel LAMA3 Mutation Underlying Epidermolysis Bullosa. *Acta Derm Venereol* 2012; **92**:695–6.

53 Varki R, Sadowski S, Pfendner E, Uitto J. Epidermolysis bullosa. I. Molecular genetics of the junctional and hemidesmosomal variants. *J Med Genet* 2006; **43**:641–52.

54 Yuen WY, Lemmink HH, van Dijk-Bos KK, *et al.* Herlitz junctional epidermolysis bullosa: diagnostic features, mutational profile, incidence and population carrier frequency in the Netherlands. *Br J Dermatol* 2011; **165**:1314–22.

55 Kivirikko S, McGrath JA, Pulkkinen L, *et al.* Mutational hotspots in the LAMB3 gene in the lethal (Herlitz) type of junctional epidermolysis bullosa. *Hum Mol Genet* 1996; **5**:231–7.

56 Fuentes I, Campos M, Repetto G, *et al.* Molecular epidemiology of junctional epidermolysis bullosa: discovery of novel and frequent LAMB3 mutations in Chilean patients with diagnostic significance. *Br J Dermatol* 2017; **176**:1090–2.

57 Mayer B, Silló P, Mazán M, *et al.* A unique LAMB3 splice-site mutation with founder effect from the Balkans causes lethal epidermolysis bullosa in several European countries. *Br J Dermatol* 2016; **175**:721–7.

58 Kiritsi D, Kern JS, Schumann H, *et al.* Molecular mechanisms of phenotypic variability in junctional epidermolysis bullosa. *J Med Genet* 2011; **48**:450–7.

59 Jonkman MF, Scheffer H, Stulp R, *et al.* Revertant mosaicism in epidermolysis bullosa caused by mitotic gene conversion. *Cell* 1997; **88**:543–51.

60 Pasmooij AM, Pas HH, Bolling MC, Jonkman MF. Revertant mosaicism in junctional epidermolysis bullosa due to multiple correcting second-site mutations in LAMB3. *J Clin Invest* 2007; **117**:1240–8.

61 Pasmooij AM, Nijenhuis M, Brander R, Jonkman MF. Natural gene therapy may occur in all patients with generalized non-Herlitz junctional epidermolysis bullosa with COL17A1 mutations. *J Invest Dermatol* 2012; **132**:1374–83.

62 Darling TN, Yee C, Bauer JW, *et al.* Revertant mosaicism: partial correction of a germ-line mutation in COL17A1 by a frame-restoring mutation. *J Clin Invest* 1999; **103**:1371–7.

63 Hoffmann J, Casetti F, Reimer A, *et al.* A Silent COL17A1 Variant Alters Splicing and Causes Junctional Epidermolysis Bullosa. *Acta Derm Venereol* 2019; **99**:460–1.

64 Kiritsi D, Huilaja L, Franzke C-W, *et al.* Junctional epidermolysis bullosa with LAMB3 splice-site mutations. *Acta Derm Venereol* 2015; **95**:849–51.

65 Schumann H, Kiritsi D, Pigors M, *et al.* Phenotypic spectrum of epidermolysis bullosa associated with alpha6beta4 integrin mutations. *Br J Dermatol* 2013; **169**:115–24.

66 Dang N, Klingberg S, Rubin AI, *et al.* Differential expression of pyloric atresia in junctional epidermolysis bullosa with ITGB4 mutations suggests that pyloric atresia is due to factors other than the mutations and not predictive of a poor outcome: three novel mutations and a review of the literature. *Acta Derm Venereol* 2008; **88**:438–48.

67 Allegra M, Gagnoux-Palacios L, Gache Y, *et al.* Rapid decay of alpha6 integrin caused by a mis-sense mutation in the propeller domain results in severe junctional epidermolysis bullosa with pyloric atresia. *J Invest Dermatol* 2003; **121**:1336–43.

68 Masunaga T, Ogawa J, Akiyama M, *et al.* Compound heterozygosity for novel splice site mutations of ITGA6 in lethal junctional epidermolysis bullosa with pyloric atresia. *J Dermatol* 2017; **44**:160–6.

69 Pulkkinen L, Kim DU, Uitto J. Epidermolysis bullosa with pyloric atresia: novel mutations in the beta4 integrin gene (ITGB4). *Am J Pathol* 1998; **152**:157–66.

70 Ashton GH, Sorelli P, Mellerio JE, *et al.* Alpha 6 beta 4 integrin abnormalities in junctional epidermolysis bullosa with pyloric atresia. *Br J Dermatol* 2001; **144**:408–14.

71 Mellerio JE, Pulkkinen L, McMillan JR, *et al.* Pyloric atresia-junctional epidermolysis bullosa syndrome: mutations in the integrin beta4 gene (ITGB4) in two unrelated patients with mild disease. *Br J Dermatol* 1998; **139**:862–71.

72 Inoue M, Tamai K, Shimizu H, *et al.* A homozygous missense mutation in the cytoplasmic tail of beta4 integrin, G931D, that disrupts hemidesmosome assembly and underlies Non-Herlitz junctional epidermolysis bullosa without pyloric atresia? *J Invest Dermatol* 2000; **114**:1061–4.

73 Ruzzi L, Pas H, Posteraro P, *et al.* A homozygous nonsense mutation in type XVII collagen gene (COL17A1) uncovers an alternatively spliced mRNA accounting for an unusually mild form of non-Herlitz junctional epidermolysis bullosa. *J Invest Dermatol* 2001; **116**:182–7.

74 Huber M, Floeth M, Borradori L, *et al.* Deletion of the cytoplasmatic domain of BP180/collagen XVII causes a phenotype with predominant features of epidermolysis bullosa simplex. *J Invest Dermatol* 2002; **118**:185–92.

75 Has C, Spartà G, Kiritsi D, *et al.* Integrin α3 mutations with kidney, lung, and skin disease. *N Engl J Med* 2012; **366**:1508–14.

76 Condrat I, He Y, Cosgarea R, Has C. Junctional Epidermolysis Bullosa: Allelic Heterogeneity and Mutation Stratification for Precision Medicine. *Front Med* 2018; **5**:363.

77 Reimer A, Schwieger-Briel A, He Y, *et al.* Natural history and clinical outcome of junctional epidermolysis bullosa generalized intermediate due to a LAMA3 mutation. *Br J Dermatol* 2018; **178**:973–5.

78 Yuen WY, Pas HH, Sinke RJ, Jonkman MF. Junctional epidermolysis bullosa of late onset explained by mutations in COL17A1. *Br J Dermatol* 2011; **164**:1280–4.

79 Has C, Kiritsi D, Mellerio JE, *et al.* The missense mutation p.R1303Q in type XVII collagen underlies junctional epidermolysis bullosa resembling Kindler syndrome. *J Invest Dermatol* 2014; **134**:845–9.

80 Figueira EC, Crotty A, Challinor CJ, *et al.* Granulation tissue in the eyelid margin and conjunctiva in junctional epidermolysis bullosa with features of laryngo-onycho-cutaneous syndrome. *Clin Exp Ophthalmol* 2007; **35**:163–6.

81 McLean WH, Irvine AD, Hamill KJ, *et al.* An unusual N-terminal deletion of the laminin alpha3a isoform leads to the chronic granulation tissue disorder laryngo-onycho-cutaneous syndrome. *Hum Mol Genet* 2003; **12**:2395–409.

82 Yalcin EG, He Y, Orhan D, *et al.* Crucial role of posttranslational modifications of integrin α3 in interstitial lung disease and nephrotic syndrome. *Hum Mol Genet* 2015; **24**:3679–88.

83 Nicolaou N, Margadant C, Kevelam SH, *et al.* Gain of glycosylation in integrin alpha3 causes lung disease and nephrotic syndrome. *J Clin Invest* 2012; **122**:4375–87.

84 Colombo EA, Spaccini L, Volpi L, *et al.* Viable phenotype of ILNEB syndrome without nephrotic impairment in siblings heterozygous for unreported integrin alpha3 mutations. *Orphanet J Rare Dis* 2016; **11**:136.

85 Cohen-Barak E, Danial-Farran N, Khayat M, *et al.* A Nonjunctional, Nonsyndromic Case of Junctional Epidermolysis Bullosa With Renal and Respiratory Involvement. *JAMA Dermatol* 2019; **155**:498–500.

86 Fine JD, Johnson LB, Weiner M, Suchindran C. Gastrointestinal complications of inherited epidermolysis bullosa: cumulative experience of the National Epidermolysis Bullosa Registry. *J Pediatr Gastroenterol Nutr* 2008; **46**:147–58.

87 Reimer A, Hess M, Schwieger-Briel A, *et al.* Natural history of growth and anaemia in children with epidermolysis bullosa: A retrospective cohort study. *Br J Dermatol* 2019. doi:10.1111/bjd.18475.

88 Fewtrell MS, Allgrove J, Gordon I, *et al.* Bone mineralization in children with epidermolysis bullosa. *Br J Dermatol* 2006; **154**:959–62.

89 Hubbard LD, Mayre-Chilton K. Retrospective longitudinal study of osteoporosis in adults with recessive dystrophic epidermolysis bullosa. *Clin Case Rep* 2019; **7**:58–63.

90 Lara-Corrales I, Mellerio JE, Martinez AE, *et al.* Dilated cardiomyopathy in epidermolysis bullosa: a retrospective, multicenter study. *Pediatr Dermatol* 2010; **27**:238–43.

91 van den Akker PC, Jonkman MF, Rengaw T, *et al.* The international dystrophic epidermolysis bullosa patient registry: an online database of dystrophic epidermolysis bullosa patients and their COL7A1 mutations. *Hum Mutat* 2011; **32**:1100–7.

92 Wertheim-Tysarowska K, Sobczynska-Tomaszewska A, Kowalewski C, *et al.* The COL7A1 mutation database. *Hum Mutat* 2012; **33**:327–31.

93 Almaani N, Liu L, Dopping-Hepenstal PJC, *et al.* Identical glycine substitution mutations in type VII collagen may underlie both dominant and recessive forms of dystrophic epidermolysis bullosa. *Acta Derm Venereol* 2011; **91**:262–6.

94 Vahidnezhad H, Youssefian L, Zeinali S, *et al.* Dystrophic Epidermolysis Bullosa: COL7A1 Mutation Landscape in a Multi-Ethnic Cohort of 152 Extended Families with High Degree of Customary Consanguineous Marriages. *J Invest Dermatol* 2017; **137**:660–9.

95 Kern JS, Kohlhase J, Bruckner-Tuderman L, Has C. Expanding the COL7A1 mutation database: novel and recurrent mutations and unusual genotype-phenotype constellations in 41 patients with dystrophic epidermolysis bullosa. *J Invest Dermatol* 2006; **126**:1006–12.

96 Escamez MJ, Garcia M, Cuadrado-Corrales N, *et al.* The first COL7A1 mutation survey in a large Spanish dystrophic epidermolysis bullosa cohort: c.6527insC disclosed as an unusually recurrent mutation. *Br J Dermatol* 2010; **163**:155–61.

97 Pasmooij AM, Garcia M, Escamez MJ, *et al.* Revertant mosaicism due to a second-site mutation in COL7A1 in a patient with recessive dystrophic epidermolysis bullosa. *J Invest Dermatol* 2010; **130**:2407–11.

98 Almaani N, Nagy N, Liu L, *et al.* Revertant mosaicism in recessive dystrophic epidermolysis bullosa. *J Invest Dermatol* 2010; **130**:1937–40.

99 Tolar J, McGrath JA, Xia L, *et al.* Patient-specific naturally gene-reverted induced pluripotent stem cells in recessive dystrophic epidermolysis bullosa. *J Invest Dermatol* 2014; **134**:1246–54.

100 Shipman AR, Liu L, Lai-Cheong JE, *et al.* Somatic forward (nonrevertant) mosaicism in recessive dystrophic epidermolysis bullosa. *JAMA Dermatol* 2014; **150**:1025–7.

101 van den Akker PC, Pasmooij AM, Meijer R, *et al.* Somatic mosaicism for the COL7A1 mutation p.Gly2034Arg in the unaffected mother of a patient with dystrophic epidermolysis bullosa pruriginosa. *Br J Dermatol* 2015; **172**:778–81.

102 Mellerio JE, Ashton GH, Mohammedi R, *et al.* Allelic heterogeneity of dominant and recessive COL7A1 mutations underlying epidermolysis bullosa pruriginosa. *J Invest Dermatol* 1999; **112**:984–7.

103 Almaani N, Liu L, Harrison N, *et al.* New glycine substitution mutations in type VII collagen underlying epidermolysis bullosa pruriginosa but the phenotype is not explained by a common polymorphism in the matrix metalloproteinase-1 gene promoter. *Acta Derm Venereol* 2009; **89**:6–11.

104 Jiang W, Sun T, Lei P, Zhu X. Genotype-phenotype correlation in Chinese patients with dystrophic epidermolysis bullosa pruriginosa. *Acta Derm Venereol* 2012; **92**:50–3.

105 Christiano AM, Fine JD, Uitto J. Genetic basis of dominantly inherited transient bullous dermolysis of the newborn: a splice site mutation in the type VII collagen gene. *J Invest Dermatol* 1997; **109**:811–4.

106 Fassihi H, Diba VC, Wessagowit V, *et al.* Transient bullous dermolysis of the newborn in three generations. *Br J Dermatol* 2005; **153**:1058–63.

107 Boccaletti V, Zambruno G, Castiglia D, *et al.* Recessive bullous dermolysis of the newborn in preterm siblings with a missense mutation in type VII collagen. *Pediatr Dermatol* 2015; **32**:e42-47.

108 Fine JD, Horiguchi Y, Stein DH, *et al.* Intraepidermal type VII collagen. Evidence for abnormal intracytoplasmic processing of a major basement membrane protein in rare patients with dominant and possibly localized recessive forms of dystrophic epidermolysis bullosa. *J Am Acad Dermatol* 1990; **22**:188–95.

109 van den Akker PC, Mellerio JE, Martinez AE, *et al.* The inversa type of recessive dystrophic epidermolysis bullosa is caused by specific arginine and glycine substitutions in type VII collagen. *J Med Genet* 2011; **48**:160–7.

110 Christiano AM, Anton-Lamprecht I, Amano S, *et al.* Compound heterozygosity for COL7A1 mutations in twins with dystrophic epidermolysis bullosa: a recessive paternal deletion/insertion mutation and a dominant negative maternal glycine substitution result in a severe phenotype. *Am J Hum Genet* 1996; **58**:682–93.

111 Winberg JO, Hammami-Hauasli N, Nilssen O, *et al.* Modulation of disease severity of dystrophic epidermolysis bullosa by a splice site mutation in combination with a missense mutation in the COL7A1 gene. *Hum Mol Genet* 1997; **6**:1125–35.

112 Watson KD, Schoch JJ, Beek GJ, Hand JL. Compound Heterozygosity of Dominant and Recessive COL7A Alleles in a Severely Affected Patient with a Family History of Dystrophic Epidermolysis Bullosa: Clinical Findings, Genetic Testing, and Treatment Implications. *Pediatr Dermatol* 2017; **34**:166–71.

113 Saleva M, Has C, He Y, *et al.* Natural history of Kindler syndrome and propensity for skin cancer - case report and literature review. *J Dtsch Dermatol Ges* 2018; **16**:338–41.

114 Guerrero-Aspizua S, Conti CJ, Escamez MJ, *et al.* Assessment of the risk and characterization of non-melanoma skin cancer in Kindler syndrome: study of a series of 91 patients. *Orphanet J Rare Dis* 2019; **14**:183.

115 Has C, Castiglia D, del Rio M, *et al.* Kindler syndrome: extension of FERMT1 mutational spectrum and natural history. *Hum Mutat* 2011; **32**:1204–12.

116 Jobard F, Bouadjar B, Caux F, *et al.* Identification of mutations in a new gene encoding a FERM family protein with a pleckstrin homology domain in Kindler syndrome. *Hum Mol Genet* 2003; **12**:925–35.

117 Siegel DH, Ashton GH, Penagos HG, *et al.* Loss of kindlin-1, a human homolog of the Caenorhabditis elegans actin-extracellular-matrix linker protein UNC-112, causes Kindler syndrome. *Am J Hum Genet* 2003; **73**:174–87.

118 Youssefian L, Vahidnezhad H, Barzegar M, *et al.* The Kindler Syndrome: A Spectrum of FERMT1 Mutations in Iranian Families. *J Invest Dermatol* 2015; **135**:1447–50.

119 Penagos H, Jaen M, Sancho MT, *et al.* Kindler syndrome in native Americans from Panama: report of 26 cases. *Arch Dermatol* 2004; **140**:939–44.

120 Lai-Cheong JE, Moss C, Parsons M, *et al.* Revertant mosaicism in Kindler syndrome. *J Invest Dermatol* 2012; **132**:730–2.

121 Kiritsi D, He Y, Pasmooij AMG, *et al.* Revertant mosaicism in a human skin fragility disorder results from slipped mispairing and mitotic recombination. *J Clin Invest* 2012; **122**:1742–6.

122 Maier K, He Y, Esser PR, *et al.* Single Amino Acid Deletion in Kindlin-1 Results in Partial Protein Degradation Which Can Be Rescued by Chaperone Treatment. *J Invest Dermatol* 2016; **136**:920–9.

123 Fiete D, Mi Y, Beranek M, *et al.* The glycan-specific sulfotransferase (R77W)GalNAc-4-ST1 putatively responsible for peeling skin syndrome has normal properties consistent with a simple sequence polymorphisim. *Glycobiology* 2017; **27**:450–6.

124 Oji V, Tadini G, Akiyama M, *et al.* Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Soreze 2009. *J Am Acad Dermatol* 2010; **63**:607–41.

125 Samuelov L, Sprecher E. Peeling off the genetics of atopic dermatitis-like congenital disorders. *J Allergy Clin Immunol* 2014; **134**:808–15.

126 Has C. Peeling Skin Disorders: A Paradigm for Skin Desquamation. *J Invest Dermatol* 2018; **138**:1689–91.

127 Pigors M, Kiritsi D, Krumpelmann S, *et al.* Lack of plakoglobin leads to lethal congenital epidermolysis bullosa: a novel clinico-genetic entity. *Hum Mol Genet* 2011; **20**:1811–9.

128 Jonkman MF, Pasmooij AM, Pasmans SG, *et al.* Loss of desmoplakin tail causes lethal acantholytic epidermolysis bullosa. *Am J Hum Genet* 2005; **77**:653–60.

129 McGrath JA, McMillan JR, Shemanko CS, *et al.* Mutations in the plakophilin 1 gene result in ectodermal dysplasia/skin fragility syndrome. *Nat Genet* 1997; **17**:240–4.

130 Ayub M, Basit S, Jelani M, *et al.* A homozygous nonsense mutation in the human desmocollin-3 (DSC3) gene underlies hereditary hypotrichosis and recurrent skin vesicles. *Am J Hum Genet* 2009; **85**:515–20.

131 Kim JH, Kim S-E, Park HS, *et al.* A Homozygous Nonsense Mutation in the DSG3 Gene Causes Acantholytic Blisters in the Oral and Laryngeal Mucosa. *J Invest Dermatol* 2019; **139**:1187–90.

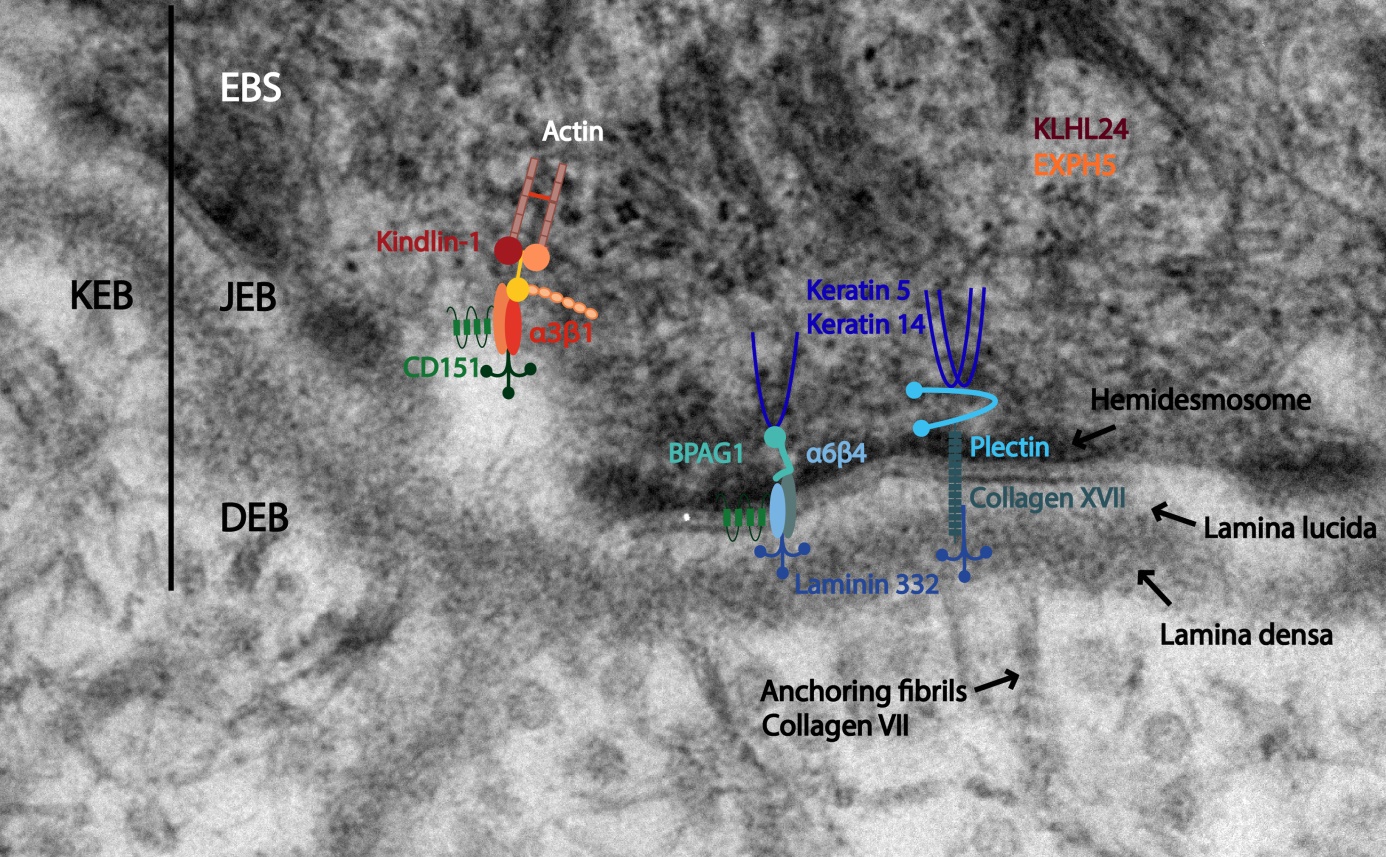
132 Samuelov L, Sprecher E. Inherited desmosomal disorders. *Cell Tissue Res* 2015; **360**:457–75.

133 Whittock NV, Wan H, Morley SM, *et al.* Compound heterozygosity for non-sense and mis-sense mutations in desmoplakin underlies skin fragility/woolly hair syndrome. *J Invest Dermatol* 2002; **118**:232–8.

134 Smith FJ, Wilson NJ, Moss C, *et al.* Compound heterozygous mutations in desmoplakin cause skin fragility and woolly hair. *Br J Dermatol* 2012; **166**:894–6.

135 Knöbel M, O’Toole EA, Smith FJD. Keratins and skin disease. *Cell Tissue Res* 2015; **360**:583–9.

# Supplementary Figures



**Figure S1**. Levels of skin cleavage and proteins involved in classical epidermolysis bullosa. Transmission electron micrograph of the dermo-epidermal junction with schematic representation of the proteins involved in classical EB and the levels of skin cleavage.

**D:\cris 09_2015\EB Classification 2018-2019\paper 2019\BJD\Figure 3.tif**

**Figure S2.** Epidermolysis bullosa (EB) naevi in (a) severe EB simplex; (b) intermediate junctional EB; (c) recessive dystrophic EB.

**D:\cris 09_2015\EB Classification 2018-2019\paper 2019\BJD\Figure 5.tif**

**Figure S3.** Junctional epidermolysis bullosa with laryngo–onycho–cutaneous syndrome (JEB–LOC). (a) Granulation tissue on the cheek and ear. Conjunctival and eyelid granulation tissue with symblepharon formation and conjunctival scarring. Laryngeal involvement may nay necessitate tracheotomy. (b) Nail loss and subungual granulation tissue.

**D:\cris 09_2015\EB Classification 2018-2019\paper 2019\BJD\Figure 8.tif**

**Figure S4.** Recessive dystrophic epidermolysis bullosa (RDEB) inversa. Blistering, ulceration and scarring at predominantly flexural sites. Oral involvement can lead to microstomia. External ear involvement is common.

# Supplementary Tables

# Table S1. Syndromic skin fragility disorders and affected genes

|  |  |  |
| --- | --- | --- |
| Syndromic skin fragility disorder | Extracutaneous manifestations | Affected genes |
| EBS with cardiomyopathy | Cardiomyopathy | *KLHL24* |
| EBS with muscular dystrophy or/and with pyloric atresia | Muscular dystrophy  Cardiomyopathy  Pyloric atresia | *PLEC* |
| EBS with nephropathy | Nephrotic syndrome | *CD151* |
| JEB with interstitial lung disease and nephrotic syndrome | Interstitial lung disease  Nephrotic syndrome, CAKUT | *ITGA3* |
| JEB with pyloric atresia | Pyloric atresia  Urinary tract involvement | *ITGB4, ITGA6* |
| Erosive skin fragility disorder | Cardiomyopathy | *DSP, JUP* |
| Connective tissue disease with skin fragility | Skeletal abnormalities, vascular aneurysms, sensorineural hearing, flexion contractions | *PLOD3* |

Legend: CAKUT, Congenital Anomaly of Kidney and Urinary Tract

**Table S2.** Characteristics of epidermolysis bullosa naevi

* EB naevi may occur in all EB types
* They display variable intralesional pigmentation and irregular borders, but do not evolve to malignancy
* The mechanism is represented by activation of melanocytes due to tissue damage
* Management: they do not require excision

**Table S3.** Peeling skin disorders

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Disease | Cutaneous features | Associated features | Inheritance | Affected gene / protein |
| Localized peeling skin | | | | |
| Acral peeling skin disease  (PPS2, MIM 609796) | Acral superficial blisters in childhood and peeling | None | AR | *TGM5* / Transglutaminase 5 |
| Acral peeling skin disease  (PPS4, MIM 607936) | Acral peeling | None | AR | *CSTA* / Cystatin A |
| Keratolytic winter erythema (MIM 148370) | Acral peeling | None | AD | *CTSB* / Cathepsin B |
| Generalized non-inflammatory peeling skin (A) | | | | |
| Exfoliative ichthyosis  (PSS5, MIM 616265) | Generalized peeling skin | None | AR | *SERPIN8* / Serpin protease inhibitor |
| Generalized peeling skin (PSS6, MIM 618084) | Generalized peeling skin | None | AR | *FLG2* / Filaggrin 2 |
| PLACK syndrome  (MIM 616295) | Generalized peeling skin | Leukonychia, acral punctate keratoses, cheilitis, and knuckle pads. | AR | *CAST* / calpastatin |
| Generalized inflammatory peeling skin (B) | | | | |
| Generalized inflammatory skin peeling  (PSS1, MIM 270300) | Generalized peeling | High IgE, multiple allergies | AR | *CDSN* / Corneodesmosin |
| SAM syndrome spectrum  (MIM 615508) | Dermatitis, palmoplantar keratoderma, | High IgE, multiple allergies, growth retardation (inconstant) | AR  AD | *DSG1* / Desmoglein 1  *DSP* / Desmoplakin |
| Netherton syndrome  (MIM 256500) | Erythroderma, ichthyosis linearis circumflexa | High IgE, multiple allergies, growth retardation, bamboo hair | AR | *SPINK5* / LEKTI |

Notes: The pathogenicity of the *CHST8* variant reported in patients with generalized peeling skin was not proven.123; Superficial epidermolytic ichthyosis should be considered in the differential diagnosis of peeling skin disorders;For detailed description of these disorders we refer to the original articles and to reviews124–126. AD, autosomal dominant; AR, autosomal recessive.

**Table S4.** Erosive disorders

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Disease | Cutaneous features | Associated features | Inheritance | Affected gene / protein |
| Acantholytic erosive disorder  (MIM 609638) | Generalized erosions | Transcutaneous fluid loss, multiorgan failure and neonatal death | AR | *DSP* / Desmoplakin  *JUP* / Plakoglobin |
| Skin fragility-woolly hair syndrome  (MIM 607655) | Skin fragility, palmoplantar keratoderma | Woolly hair, hypotrichosis,  cardiomyopathy,  enamel anomalies | AR | *DSP* / Desmoplakin  *JUP* / Plakoglobin |
| Ectodermal dysplasia-skin fragility syndrome  (MIM 604536) | Erosions,  palmoplantar keratoderma | Woolly hair, hypotrichosis, nail dystrophy, hypohidrosis | AR | *PKP1* / Plakophilin 1 |
| Hypotrichosis with recurrent skin vesicles (MIM 613102) | Recurrent skin vesicles | Hypotrichosis | AR | *DSC3* / Desmocollin 3 |
| Acantholytic blisters in the oral and laryngeal mucosa | None | Oral and laryngeal blisters | AR | *DSG3* / Desmoglein 3 |

Note: For detailed description of these disorders we refer to the original articles127–134; AD, autosomal dominant; AR, autosomal recessive.

**Table S5.** Hyperkeratotic disorders with skin fragility

|  |  |
| --- | --- |
| Hyperkeratotic fragility subtype | Targeted protein(s) |
| Autosomal dominant | |
| Epidermolytic ichthyosis | Keratin 1, 10 |
| Superficial epidermolytic ichthyosis | Keratin 2 |
| Annular epidermolytic ichthyosis | Keratin 1, 10 |
| Pachyonychia congenita *KRT6A* | Keratin 6A |
| Pachyonychia congenita *KRT6B* | Keratin 6B |
| Pachyonychia congenita *KRT6C* | Keratin 6C |
| Pachyonychia congenita *KRT16* | Keratin 16 |
| Pachyonychia congenita *KRT17* | Keratin 17 |
| Autosomal recessive | |
| Epidermolytic ichthyosis | Keratin 1, 10 |

Notes: bold, common types; for detailed description of these disorders we refer to the original articles and to reviews135.