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Epidermolysis Bullosa Simplex

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Summary

Clinical characteristics

Epidermolysis bullosa simplex (EBS) is characterized by fragility of the skin (and mucosal epithelia in some instances) that results in non-scarring blisters and erosions caused by minor mechanical trauma. EBS is distinguished from other types of epidermolysis bullosa (EB) or non-EB skin fragility syndromes by the location of the blistering in relation to the dermal-epidermal junction. In EBS, blistering occurs within basal keratinocytes. The severity of blistering ranges from limited to hands and feet to widespread involvement. Additional features can include hyperkeratosis of the palms and soles (keratoderma), nail dystrophy, milia, and hyper- and/or hypopigmentation. Rare EBS subtypes have been associated with additional clinical features including pyloric atresia, muscular dystrophy, cardiomyopathy, and/or nephropathy.

Diagnosis/testing

The diagnosis of EBS is established in a proband by: the identification of a heterozygous dominant-negative variant or biallelic loss-of-function variants in *KRT5*, *KRT14*, or *PLEC*; a heterozygous pathogenic variant in *KLHL24*; or biallelic pathogenic variants in *CD151*, *DST*, or *EXPH5*; and/or presence of characteristic findings on examination of a skin biopsy using transmission electron microscopy and/or immunofluorescent mapping.

Management

Treatment of manifestations: Supportive care to protect the skin from blistering; use of dressings that will protect the skin and promote healing of wounds. Encourage activities that minimize trauma to the skin; appropriate footwear and physical therapy to preserve ambulation; lance and drain without unroofing new blisters. Dressings consist of three layers: a primary nonadherent contact layer; a secondary layer that provides stability, adds padding, and absorbs drainage; and a tertiary layer with elastic properties. Aluminum chloride (20%) applied to palms and soles can reduce sweating and therefore minimize blister formation in some individuals with EBS. In addition, botulinum toxin, cyproheptadine (Periactin®), tetracycline, erythromycin, diacerein, sirolimus, apremilast, cannabidiol oil, and gentamicin have all been reported to be beneficial. Keratolytic agents for palmar

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and plantar hyperkeratosis may reduce skin thickening and cracking. Topical and/or systemic antibiotics or silver-impregnated dressings or gels can be used to treat skin infection or reduce bacteria colonization, thereby promoting wound healing. Identification and management of specific causes of pain and itching; management with a pain specialist as needed. Management of fluid and electrolyte imbalance in severely affected infants may be critical during the postnatal period. Nutritional support including vitamin and mineral supplementation, feeding via gastrostomy tube, guided feeding therapy, and Haberman feeder may be necessary for infants and children with oral manifestations of EBS. Iron supplementation for those with anemia as a result of chronic inflammation from blistering and wounding. Weight management and treatment of obesity in older individuals. Standard treatment for basal cell carcinomas in individuals with severe EBS. Psychosocial support when needed. Standard treatments for additional features reported in rare subtypes including pyloric atresia, muscular dystrophy, cardiomyopathy, and nephropathy.

Surveillance: Dermatologic assessment for blisters, oral disease, hyperkeratosis, hyperhidrosis, signs and symptoms of wound infection, as well as pruritus and pain. At each visit, assessment of hydration status, growth, nutrition, weight, motor development and mobility, and psychosocial well-being. Consider serum B-type natriuretic peptide (BNP) and creatinine kinase in those with EBS, intermediate with cardiomyopathy; serum renal function studies and urinalysis for those with nephropathy; and neurologic assessment for those with muscular dystrophy as needed.

Agents/circumstances to avoid: Excessive heat exposure may exacerbate blistering and infection. Avoid poorly fitting or coarse-textured clothing/footwear and activities that traumatize the skin. Avoid adhesives from regular medical tapes or Band-Aids®.

Genetic counseling

EBS is typically inherited in an autosomal recessive or an autosomal dominant manner. Autosomal recessive EBS is associated with either biallelic loss-of-function variants in *KRT5*, *KRT14*, or *PLEC* or biallelic pathogenic variants in *CD151*, *DST*, or *EXPH5*. Autosomal dominant EBS is associated with either a heterozygous dominant-negative variant in *KRT5*, *KRT14*, or *PLEC* or a heterozygous pathogenic variant in *KLHL24.* In rare instances, EBS is caused by the presence of heterozygous pathogenic variants in both *KRT5* and *KRT14* and is inherited in a digenic manner.

- **Autosomal recessive EBS.** If both parents are known to be heterozygous for an EBS-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- **Autosomal dominant EBS.** In families with autosomal dominant inheritance, each child of an affected individual has a 50% chance of inheriting the pathogenic variant and (most likely) being affected with EBS (penetrance appears to be <100% for known heterozygous dominant-negative *KRT5* and *KRT14* variants).

Once the EBS-related pathogenic variant(s) have been identified in an affected family member, molecular genetic testing for at-risk family members and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

Table. Epidermolysis Bullosa Simplex (EBS): Included Phenotypes

Most Common EBS Subtypes	Rare EBS Subtypes
• Localized EBS • Intermediate EBS • Severe EBS • EBS with mottled pigmentation	• EBS, intermediate with *PLEC* pathogenic variants • EBS, intermediate with muscular dystrophy • EBS, severe with pyloric atresia • EBS with migratory circinate erythema • EBS, intermediate with cardiomyopathy • EBS, localized or intermediate with BP230 deficiency • EBS, localized or intermediate with exophilin 5 deficiency • EBS, localized with nephropathy with CD151 deficiency

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

Epidermolysis bullosa simplex (EBS) **should be suspected** in individuals with the following clinical findings:

- Fragility of the skin manifested by blistering with little or no trauma, which typically heals without scarring
- Blistering that:
  - May be present in the neonatal period
  - Primarily affects the hands and feet but can affect the whole body
  - Occurs in annular or curvilinear groups or clusters
  - Can lead to progressive hyperpigmentation interspersed with hypopigmented spots on the trunk and extremities that frequently disappears in adult life
  - Is associated with palmar and plantar hyperkeratosis that may be severe
- Nail dystrophy
- Milia
- Natal teeth

Establishing the Diagnosis

The diagnosis of EBS is **established** in a proband with one or both of the following [Has et al 2020b]:

- Identification of a heterozygous dominant-negative or biallelic loss-of-function pathogenic (or likely pathogenic) variants in *KRT5*, *KRT14*, or *PLEC*; a heterozygous pathogenic (or likely pathogenic) variant involving *KLHL24*; or biallelic pathogenic (or likely pathogenic) variants involving *CD151*, *DST*, or *EXPH5* by molecular genetic testing (See Table 1.)
- Characteristic findings on skin biopsy examined via immunofluorescent mapping (IFM) and/or transmission electron microscopy (TEM) (See Skin Biopsy.)

Note: (1) Both genetic testing and skin biopsy for IFM are often recommended to improve the sensitivity of the diagnostic tests. TEM may also be performed to assess for ultrastructural abnormalities in individuals with inconclusive genetic testing and IFM. (2) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (3) Identification of a variant(s) of uncertain significance does not establish or rule out the diagnosis of EBS.

Molecular testing approaches can include **use of a multigene panel**, **single-gene testing**, or **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype. Therefore, genetics consultation prior to testing is recommended.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with epidermolysis bullosa are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A multigene panel that includes some or all of the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of EBS while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Multigene panels can be particularly useful for the diagnosis of infants or children, as features of skin fragility may not be characteristic, and some clinical features specific to certain subtypes (e.g., progressive muscle weakness in EBS, intermediate with muscular dystrophy) may not be present in young individuals.

Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratories conducting the tests and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Tests conducted in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Single-gene testing may be considered if findings on skin biopsy or additional phenotypic features (see Phenotype Correlations by Gene) suggest a pathogenic variant(s) in a specific EBS-related gene. Sequence analysis is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, typically the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications. To date, large intragenic deletions and duplications have not been reported in individuals with *CD1515*-, *DST*-, *EXPH5*-, or *KLHL24*-related EBS.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Epidermolysis Bullosa Simplex

Gene [1, 2]	Proportion of EBS Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method [5]	
		Sequence analysis [3, 6]	Gene-targeted deletion/duplication analysis [3, 7]
CD151	<1%	100%	None reported
DST	<1%	100%	None reported

Table 1. continued from previous page.

Gene [1, 2]	Proportion of EBS Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method [5]	
		Sequence analysis [3, 6]	Gene-targeted deletion/ duplication analysis [3, 7]
EXPH5	<2%	100%	None reported
KLHL24	<1%	100%	None reported
KRT5	>40%	~98%	~2%
KRT14	>30%	~97%	~3%
PLEC	~8 [8]	~93% [8]	~7%
Unknown [9]	<17%	NA	NA

NA = not applicable
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
4. See Molecular Genetics for information on variants detected in this gene.
5. In individuals with EBS diagnosed by findings on skin biopsy.
6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
8. Bolling et al [2014]
9. Cincinnati Children's – EBSeq (pdf).

Skin Biopsy

Examination of a skin biopsy by (1) immunofluorescent mapping (IFM) and/or (2) transmission electron microscopy (TEM) may be performed to establish the diagnosis of EBS. IFM is generally preferred as it can yield results rapidly. Moreover, IFM is less expensive and is therefore more widely performed; it may also be used in prognostication and assessment of disease severity [Has & He 2016, Has et al 2020b]. TEM may be performed if results from genetic testing and IFM are inconclusive.

A punch biopsy that includes the full basement membrane zone is preferred. The biopsy should be taken from the leading edge of a fresh (<12 hours old) blister or from a mechanically induced blister and should include some normal adjacent skin. (Older blisters undergo change that may obscure the diagnostic morphology and can be misleading.)

- **Immunofluorescent mapping (IFM).** Specimens should be sent in sterile carrying medium (e.g., Michel's or Zeus's) as specified by the laboratory performing the test. Some laboratories prefer flash-frozen tissue. In some laboratories the mapping only designates the level of the cleavage by using various marker antibodies of different layers of the basement membrane. A laboratory that has antibodies for the proteins of interest is preferred because both the level of cleavage and the presence or absence of the protein can be assessed.
- **Transmission electron microscopy (TEM).** Specimens must be placed in fixation medium (e.g., glutaraldehyde) as designated by the laboratory performing the test. Formaldehyde-fixed samples cannot be used for electron microscopy.

  Note: Light microscopy is inadequate and unacceptable for the accurate diagnosis of any subtypes of EB.

IFM findings

- Normal staining with antibodies to keratin 5, keratin 14, or plectin resulting from heterozygous pathogenic variants in *KRT5*, *KRT14*, *PLEC*, or *KLHL24*
- Abnormal or absent staining with antibodies to keratin 5, keratin 14, plectin, BP230 (i.e., BPAG1, BPAG1-e), exophilin 5, and CD151 resulting from biallelic pathogenic variants in *KRT5*, *KRT14*, *PLEC*, *DST*, *EXPH5*, and *CD151*, respectively

TEM findings

- Keratin intermediate filaments (i.e., tonofilaments) may be clumped in severe EBS [Bergman et al 2007] and EBS with mottled pigmentation [Irvine et al 2001] or EBS, localized or intermediate with exophilin 5 deficiency [Diociaiuti et al 2020]. While this finding is not specific to severe EBS, it is only seen using TEM, making this study useful when the diagnosis of severe EBS is suspected or when it is necessary to distinguish between severe EBS and other forms of inherited EB, such as severe recessive dystrophic EB or severe junctional EB [Has et al 2020b].
- The absence of keratin intermediate filaments is a distinguishing feature of *KRT14*-related autosomal recessive EBS.
- In EBS caused by biallelic pathogenic variants in *EXPH5*, widened space between keratinocytes, aggregation of keratin filaments, and vesicles near the plasma membrane and nucleus have been reported [McGrath et al 2012].

Clinical Characteristics

Clinical Description

In contrast to prior classification schemes, the most recent 2020 reclassification system distinguishes between EBS, defined by blistering *within* the basal keratinocytes, and other disorders with skin fragility that lack significant blistering as a result of superficial skin cleavage *above* the basal keratinocytes [Has et al 2020a].

The most common forms of EBS – localized EBS, intermediate EBS, severe EBS, and EBS with mottled pigmentation – are distinguished primarily on dermatologic, genetic, and histopathologic findings. The clinical features of these disorders are summarized in Table 2. Rare subtypes including several distinct syndromes have also been identified.

Table 2. Select Features of the Four Most Common EBS Subtypes

Clinical Features	EBS Subtype			
	Localized	Intermediate	Severe	W/mottled pigmentation
Age of onset	Infancy, usually by 12-18 mos	Birth/infancy	Birth	Birth/infancy
Blisters	• Blisters usually limited to hands, feet; can occur at sites of repeated trauma • Rare mucosal blisters	• Generalized • Occasional mucosal blisters	• Generalized • Grouped (herpetiform) blisters • Mucosal blisters	• Generalized • ± grouped (herpetiform) blisters • ± mucosal blisters
Hyperkeratosis of palms & soles (keratoderma)	Occasionally	Occasionally	Common, progressive, & diffuse	Common, focal
Nail involvement	Occasionally	Occasionally	Common	Occasionally
Milia	Rare	Occasionally	Common	Unknown

Table 2. continued from previous page.

Clinical Features	EBS Subtype			
	Localized	Intermediate	Severe	W/mottled pigmentation
Hyper-/ hypopigmentation	No	Can occur	Common	Always

Localized EBS

Localized EBS, the most common EBS subtype, occurs in approximately 60% of individuals with EBS. Blisters begin in infancy and can present at birth; severity is usually mild. The first episodes may occur on the knees and shins with crawling or on the feet at approximately age 12-18 months, after walking is firmly established. Some affected individuals do not manifest the disease until adolescence or early adult life. Although blisters are usually confined to the hands and feet, they can occur anywhere given adequate trauma; for example, blisters can develop on the buttocks after horseback riding or around the waist after wearing a tight belt.

Symptoms can be seasonal, worsening with warm weather and sweating. The palms and soles are usually more involved than the backs of the hands and the tops of the feet, and lesions may be associated with pain and pruritus resulting in reduced mobility during active disease flares. Affected individuals may additionally develop hyperhidrosis of the palms and soles, which in turn can further worsen blistering. Mucosal involvement is rare. Focal hyperkeratosis of the palms and soles at sites of repeated mechanical friction and trauma can develop beginning in late childhood and early adulthood and can cause significant pain and reduced mobility. Occasionally, a large blister in a nail bed may result in shedding of the nail.

Intermediate EBS

Intermediate EBS occurs in 15% of individuals with EBS. Blisters can be present at birth or develop within the first few months of life. Blistering and wounding may be severe and life-threatening in neonates and infants, but typically improves as individuals approach late childhood and early adulthood. In general, intermediate EBS is milder than severe EBS, but clinical overlap is high. Similarly, mild intermediate EBS can be indistinguishable from localized EBS. Intermediate EBS is distinguished from localized EBS by its more widespread involvement, and from severe EBS by the absence of clumped keratin intermediate filaments (tonofilaments) in basal keratinocytes on electron microscopy (see Establishing the Diagnosis, Skin Biopsy). Branches of one large pedigree were reported separately as EBS-Koebner (now intermediate EBS) and EBS-Weber Cockayne (now localized EBS), reflecting the variability in severity even within families.

Severe EBS

Severe EBS occurs in approximately 25% of individuals with EBS. Onset is usually at birth and severity varies greatly both between and within families. Blisters may be large, hemorrhagic, and severe, particularly within the neonatal period. In newborns, there may be significant overlap in clinical presentation with other forms of inherited EB, including dystrophic EB and junctional EB. Widespread and severe blistering and/or multiple grouped clumps of small blisters are typical. Hemorrhagic blisters are common. Mucosal involvement such as oral and esophageal blisters and erosions can occur and may interfere with feeding, particularly during infancy and early childhood; this usually improves with age. Laryngeal involvement including laryngeal stenoses or strictures may manifest as hoarseness but is not life threatening. Decreased frequency of blistering occurs during mid- to late childhood and blistering may be a minimal component of the disorder in adult life. Dysphagia and constipation are uncommon but can develop in a subset of individuals; other gastrointestinal involvement more frequently identified in other forms of inherited EB (e.g., esophageal strictures) are not observed in EBS. Progressive hyperkeratosis (focal or diffuse) of the palms and soles begins in childhood and may be the major feature in affected adults. Nail dystrophy (thickened, deformed nails) is common. Both hyper- and hypopigmentation can occur, typically in areas of blistering. Increased cumulative risk of basal cell carcinomas

have been identified in individuals with severe EBS; however, increased development of basal cell carcinomas has not been observed in localized EBS or intermediate EBS [Fine et al 2009].

EBS with Mottled Pigmentation

EBS with mottled pigmentation is rare and occurs in fewer than 1% of individuals with EBS. Skin fragility is evident at birth and is clinically indistinguishable from that seen in generalized forms of EBS, including severe EBS. The defining characteristic is the development of small hyperpigmented macules that begin to appear in early childhood, progress over time, and coalesce to a reticulate pattern. Hypopigmented macules may be interspersed. These changes tend to develop on the trunk (particularly in flexural areas; e.g., the neck, groin, and axillae) and then on the extremities (particularly the arms). This pigmentation is not preceded by blistering, which distinguishes it from post-inflammatory hyperpigmentation and hypopigmentation, and often disappears during adulthood. Focal palmar and plantar hyperkeratoses may occur.

Additional Rare Forms of EBS

Recessive EBS, intermediate or severe with *KRT14* or *KRT5* pathogenic variants. Individuals with biallelic loss-of-function variants in *KRT14* or *KRT5* generally present with severe, generalized blistering at birth (which may not improve with age, in contrast to EBS caused by heterozygous dominant-negative variants in *KRT14* or *KRT5*) and may develop keratoderma, nail dystrophy, oral and genital erosions, anemia, and post-inflammatory hyperpigmentation at the site of prior lesions [Yiasemides et al 2008, García et al 2011, Diociaiuti et al 2018, Tryon et al 2019, Vahidnezhad et al 2019a].

EBS associated with *PLEC* pathogenic variants ranges widely in presentation, from limited cutaneous blistering and scarring without systemic involvement (e.g., EBS, intermediate with *PLEC* pathogenic variants), to generalized blistering with muscular dystrophy and cardiomyopathy (e.g., EBS, intermediate with muscular dystrophy), to life-threatening generalized blistering with pyloric atresia and early death (e.g., EBS, severe with pyloric atresia). Phenotypes vary based on the type of *PLEC* variant and the presence of a heterozygous or biallelic variant(s) [Kiritsi et al 2021].

- **EBS, intermediate with *PLEC* pathogenic variants** are most often associated with heterozygous *PLEC* pathogenic variants; however, biallelic *PLEC* pathogenic variants have been reported in rare cases [Gostyńska et al 2015, Khan et al 2021]. The heterozygous pathogenic missense variant (c.5998C>T; p.Arg2000Trp) within the rod domain of *PLEC* [Koss-Harnes et al 2002, Kiritsi et al 2013] causes the subtype formerly known as EBS-Ogna. Clinical features include limited, relatively mild blistering following trauma with bruising, hypopigmentation following blister formation, nail dystrophy, and no internal involvement. Transmission electron microscopy (TEM) of a skin biopsy identified the cleavage plane to be just above the inner plates of the hemidesmosomes in the deep basal cell cytoplasm; immunofluorescent mapping showed reduced and/or patchy plectin staining.
- **EBS, intermediate with muscular dystrophy** is associated with biallelic pathogenic variants in *PLEC*. Cutaneous findings include intermediate, generalized blistering and nail dystrophy or loss; severe-to-life-threatening involvement of the oral, laryngeal, and urethral mucosa can also occur [Schara et al 2004, Prodinger et al 2017, Bourhis et al 2019]. Onset of muscular dystrophy ranges from infancy to adulthood [Kyrova et al 2016, Winter et al 2016], and progressive muscle weakness can result in death for affected individuals by the third or fourth decade of life. Other clinical manifestations include myasthenic symptoms [Forrest et al 2010] and cardiomyopathy, which may be life threatening [Bolling et al 2010, Villa et al 2015]. Pyloric atresia is rare [Natsuga et al 2010]. TEM reveals a plane of cleavage (level of separation) within the bottom layer of the basal keratinocytes, just above the hemidesmosomes.
- **EBS, severe with pyloric atresia** is associated with biallelic premature termination variants in *PLEC*. Disease course is severe and usually lethal in neonates, although rare survival past the neonatal period has been reported [Charlesworth et al 2013, Walker et al 2017]. Clinical features include pyloric atresia,

anemia, ear anomalies, growth deficiency, and joint contractures. Extensive, generalized congenital absence of the skin (congenital aplasia cutis) may also be present [Mariath et al 2021] and is also a significant cause of early mortality.

EBS with migratory circinate erythema is caused by heterozygous pathogenic variants in *KRT5* and is associated with the development of small, often intensely pruritic blisters, frequently on the extremities or following trauma, against a background of migratory and circinate erythema and brown post-inflammatory hyperpigmentation from healing lesions [Castiglia et al 2014, Yalici-Armagan et al 2020]. Blistering may improve with age, and nail dystrophy may be present.

EBS, intermediate with cardiomyopathy is associated with heterozygous pathogenic variants within the initiation codon of *KLHL24*. Blistering can be severe and generalized at birth but improve with age. Cutaneous manifestations also include whorled hyper- or hypopigmentation, palmoplantar keratoderma, nail dystrophy and thickening, and hair loss. Congenital aplasia cutis may be present [Mariath et al 2021]. Importantly, individuals may develop early-onset progressive dilated cardiomyopathy that can lead to premature death [He et al 2016, Lee et al 2017, Alkhalifah et al 2018, Yenamandra et al 2018, Grilletta 2019, Schwieger-Briel et al 2019].

EBS, localized or intermediate with BP230 deficiency is caused by reduced or absent expression of BP230 (i.e., epithelial BPAG1, BPAG1-e) due to biallelic loss-of-function variants in *DST*. Clinical manifestations include relatively mild blistering (primarily localized to acral surfaces) and keratoderma [Groves et al 2010, Liu et al 2012, Takeichi et al 2015, Ganani et al 2021].

EBS, localized or intermediate with exophilin 5 deficiency is associated with biallelic *EXPH5* pathogenic variants resulting in absent exophilin 5. This subtype is characterized by generally mild blistering (particularly in an acral distribution) that improves with age, easy bleeding, and mild, generalized mottled reticulated hyperpigmentation [Liu et al 2014, Turcan et al 2016, Diociaiuti et al 2020].

EBS, localized with nephropathy with CD151 deficiency. Affected individuals have biallelic loss-of-function variants in *CD151*. Mucocutaneous symptoms include blistering that may be widespread or primarily on the shins, poikiloderma, nail dystrophy, acrogeria, alopecia, mucosal erosions, and esophageal strictures; systemic manifestations are notable for nephropathy resulting in proteinuria [Vahidnezhad et al 2018]. Epilepsy has also been reported in association with this rare EBS subtype [Dunn et al 2022].

Secondary Complications

Infection is a common secondary complication in EBS, particularly among individuals with extensive body surface area involvement or chronic wounds, and may range from wound colonization (bacteria are present that can impede wound healing) to overt infection with clinical signs of infection such as purulence, drainage, erythema, and pain. Complications of infections include deep tissue involvement (cellulitis), bone involvement (osteomyelitis), or systemic disease (sepsis) if not treated.

Infections may be associated with significant morbidity and mortality, particularly among neonates and infants with severe EBS who are at increased risk of death due to sepsis [Fine et al 2008b]. Infected or colonized wounds may also be painful or pruritic, and resultant chronic inflammation from longstanding non-healing wounds may contribute to anemia or nutritional deficiencies. Bacterial species commonly identified within wounds include *Staphylococcus aureus*, *Streptococci*, and *Pseudomonas aeruginosa* [Brandling-Bennett & Morel 2010, Levin et al 2021]. Antibiotic resistance resulting from repeated infections is common.

Pain and itch are extremely common and can be severe and debilitating, even in individuals with localized EBS [Brun et al 2017, Bruckner et al 2020, So et al 2022]. Pain and itch are associated with repeated cycles of wounding and healing and are often worsened during active disease flares. These symptoms may significantly impact quality of life, psychosocial well-being, and ability to participate in school and work.

Fluid and electrolyte disturbances range widely in neonates with EBS, and causes are multifactorial. Rapid demise in neonates and infants can occur with extensive skin involvement and severe skin fragility (e.g., as in newborns presenting with congenital aplasia cutis) as a result of significant transepidermal water loss, electrolyte abnormalities, systemic inflammation, and hypermetabolic state. Nutritional support and close monitoring may be crucial for infants and children with severe EBS or intermediate EBS who have more generalized involvement. Infants with significant oral disease may develop an aversion to feeding that persists even after oral disease improves. Dehydration and electrolyte imbalances may exacerbate the disease secondary to impeded wound healing, growth, and development. Chronic anemia may develop during both childhood and adulthood as a result of chronic inflammation from ongoing blistering and wounding.

Keratoderma (thickened skin on the hands and feet) is common in all EBS subtypes, with approximately 76% of individuals developing plantar keratoderma over their lifetime in one recent study [Reimer-Taschenbrecker et al 2021]. Plantar keratoderma is a painful and often debilitating secondary complication of EBS, and can contribute to disease-related obesity, impaired mobility, and loss of bone density due insufficient weight bearing. Focal plantar keratoderma at sites of mechanical trauma and pressure on the feet may be present in all EBS subtypes, including localized EBS; however, diffuse plantar keratoderma is observed primarily among individuals with intermediate EBS and severe EBS.

Impaired mobility, obesity, and metabolic disease. Children with EBS may have delay in walking. Individuals with all EBS subtypes may experience difficulties walking because of painful blisters, erosions, and keratoses on the feet. Adolescents and adults with both mild and severe forms EBS are at increased risk of becoming overweight or obese [So et al 2022], a clinical feature distinct from other forms of inherited EB. Causes for excess weight gain include a sedentary lifestyle due to reduced mobility and ability to participate in physical activities as a result of painful blisters and keratoderma on the feet, and decreased oral involvement with age [Haynes 2010, Yerlett 2020, Reimer-Taschenbrecker et al 2021]. However, medical complications associated with obesity such as type 2 diabetes, cardiovascular disease, and/or stroke have not yet been characterized specifically among individuals with EBS.

Quality of life and psychosocial considerations. Individuals may experience reduced quality of life and significant psychosocial and economic challenges as a result of EBS, including feelings of anxiety, frustration, and depression, strained interpersonal relationships with family, financial burden due to the cost of wound dressing supplies and medications, and reduced employment opportunities [Tabolli et al 2009, Williams et al 2011, Brun et al 2017, Bruckner et al 2020, So et al 2022]. Individuals may also miss school or work, particularly during active disease flares.

Cancer risk. Squamous cell carcinoma is not usually associated with EBS. Individuals with severe EBS are at increased risk for basal cell carcinoma; however, this heightened risk has not been observed in other EBS subtypes [Fine et al 2009].

Phenotype Correlations by Gene

Table 3. Epidermolysis Bullosa Simplex Phenotype Correlations by Gene

Gene	MOI	Reported Phenotypes				
		Localized EBS	Intermediate EBS	EBS w/mottled pigmentation	Severe EBS	Other EBS subtypes
CD151	AR					EBS, localized w/nephropathy w/CD151 deficiency
DST	AR	●	●			EBS, localized or intermediate w/BP230 deficiency
EXPH5	AR	●	●	●		EBS, localized or intermediate w/exophilin 5 deficiency
KLHL24	AD					EBS, intermediate w/cardiomyopathy

Table 3. continued from previous page.

Gene	MOI	Reported Phenotypes				
		Localized EBS	Intermediate EBS	EBS w/mottled pigmentation	Severe EBS	Other EBS subtypes
KRT5	AD [1]	●	●	●	●	EBS w/migratory circinate erythema
	AR		●		●	Recessive EBS, intermediate or severe w/*KRT5* pathogenic variants
KRT14	AD [1]	●	●	●	●	
	AR		●		●	Recessive EBS, intermediate or severe w/*KRT14* pathogenic variants
PLEC	AD		●			EBS, intermediate w/*PLEC* pathogenic variants [2]
	AR		●			• EBS, intermediate w/*PLEC* pathogenic variants • EBS, intermediate w/muscular dystrophy • EBS, severe w/pyloric atresia

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. Pathogenic variants associated with autosomal dominant inheritance act in a dominant-negative manner.

2. The heterozygous pathogenic *PLEC* variant c.5998C>T causes the autosomal dominant subtype formerly known as EBS-Ogna.

Genotype-Phenotype Correlations

Limited genotype-phenotype correlations have been reported. Digenic inheritance adds further complexity to genotype-phenotype associations observed in EBS [Padalon-Brauch et al 2012, Kim et al 2017, Yu et al 2020].

***KRT5* and *KRT14*.** A moderate correlation exists between the EBS phenotype and the functional domain of either *KRT5* or *KRT14* in which the pathogenic variant is located [Irvine & McLean 2003, Müller et al 2006, Coulombe et al 2009, Arin et al 2010]. Phenotypic expression can be highly variable; localized EBS, intermediate EBS, and severe EBS phenotypes have been reported in affected individuals from the same family [Deng et al 2011].

- Heterozygous pathogenic variants in the nonhelical head and linker segments (L1 and L2), and in the 1A segment of the rod domain are associated with localized EBS.
- Heterozygous pathogenic variants in the 1A or 2B segments of the rod domain of *KRT5* and *KRT14* are common for intermediate EBS.
- Heterozygous pathogenic variants in the beginning of the 1A or the end of the 2B segments of the rod domain of *KRT5* and beginning of the 1A or 2B segments of the rod domain of *KRT5* and *KRT14* are typical in severe EBS. These domains are highly conserved and are thought to be critical to filament assembly.
- Heterozygous *KRT5* variants p.Pro25Leu and c.1649delG and *KRT14* variants p.Met119Thr and c.1117_1158dup are associated with EBS with mottled pigmentation [Harel et al 2006, Pascucci et al 2006, Shurman et al 2006, Arin et al 2010].
- In rare consanguineous families, biallelic *KRT14* and *KRT5* loss-of-function variants are associated with autosomal recessive inheritance of intermediate or severe EBS.

***PLEC*.** Biallelic pathogenic variants within exon 31 of *PLEC* (which encodes for the rod domain of plectin) are associated with EBS, intermediate with muscular dystrophy, while biallelic pathogenic variants outside of exon 31 are associated with EBS, severe with pyloric atresia [Natsuga 2015].

Penetrance

Penetrance is 100% for biallelic *KRT5* and *KRT14* loss-of-function variants but appears to be less than 100% for heterozygous dominant-negative variants, as rare heterozygotes for dominant-negative variants are asymptomatic [Wertheim-Tysarowska et al 2016]. Heterozygous pathogenic variants in *PLEC* and *KLHL24* and biallelic pathogenic variants in *CD151*, *DST*, *EXPH5*, and *PLEC* are presumed to be fully penetrant as asymptomatic individuals have not been reported to date.

Nomenclature

In 1886, Koebner coined the term epidermolysis bullosa hereditaria. In the late nineteenth and early twentieth centuries, Brocq and Hallopeau coined the terms traumatic pemphigus, congenital traumatic blistering, and acantholysis bullosa; these terms are no longer in use [Fine et al 1999].

The nomenclature for EBS has changed five times in the last 20 years. The eponyms EBS-Weber-Cockayne and EBS-Koebner were changed to EBS, localized and EBS, other generalized in the 2008 classification system [Fine et al 2008a]. A new classification system was developed in 2014, referred to as the "onion skin" terminology, which considers the level of blistering, phenotypic characteristics including distribution and severity of cutaneous blisters and wounding, and associated gene [Fine et al 2014].

In February 2020, the most recent reclassification system for EB and other skin fragility disorders was published following the 2019 international consensus meeting [Has et al 2020a]. This 2020 consensus reclassification system incorporates genotype-phenotype associations and novel pathogenic variants identified in affected individuals (see Table 4).

Table 4. Comparison of 2008 Epidermolysis Bullosa Simplex Nomenclature with 2020 Nomenclature

2008 Nomenclature [1]	2020 Nomenclature [2]
EBS, localized	Localized EBS, normal keratin 5 & 14 staining, *KRT5* or *KRT14* pathogenic variant (specify type)
EBS, generalized other	Intermediate EBS, normal keratin 5 & 14 staining, *KRT5* or *KRT14* pathogenic variant (specify type)
EBS-MP	EBS w/mottled pigmentation, normal keratin 5 staining, *KRT5* pathogenic variant (specify type)
EBS, Dowling-Meara	Severe EBS, normal keratin 5 & 14 staining, *KRT5* or *KRT14* pathogenic variant (specify type)

EBS = epidermolysis bullosa simplex; MP = mottled pigmentation
1. Representative examples
2. Has et al [2020a]

Prevalence

The prevalence of EBS is uncertain; estimates from different countries range from 6:1,000,000 to 28.6:1,000,000 live births and vary by geographic location [Horn et al 1997, Pfendner et al 2001, Kho et al 2010, Petrof et al 2022]. One recent study among Dutch individuals estimated a prevalence of 11.9:1,000,000 [Baardman et al 2021]. Localized EBS is most common and the prevalence of localized EBS may be underestimated, as it does not cause significant morbidity and mortality, even in newborns, and many individuals may not be reported. Intermediate and severe EBS are rare, and EBS with mottled pigmentation is even rarer. The experience of the National Epidermolysis Bullosa Registry (NEBR) suggests that ascertainment is highly biased and incomplete, and that EBS likely remains underdiagnosed, particularly among individuals with mild clinical presentations [Has 2018a].

Genetically Related (Allelic) Disorders

Table 5. Genetically Related Disorders

Gene	Disorder
CD151	No phenotypes other than those discussed in this *GeneReview*
DST	Biallelic *DST* pathogenic variants cause hereditary sensory & autonomic neuropathy VI (HSAN-VI), which manifests as severe psychomotor and cognitive delay, encephalopathy, myopathy, dysautonomia, & potential early death (see Charcot-Marie-Tooth Hereditary Neuropathy Overview).
EXPH5	No phenotypes other than those discussed in this *GeneReview*
KLHL24	No phenotypes other than those discussed in this *GeneReview*
KRT5	Dowling-Degos disease (DDD), characterized by progressive & disfiguring reticulate hyperpigmentation of flexures, is caused by heterozygous *KRT5* loss-of-function variants (OMIM 179850). Galli-Galli disease, a variant of DDD that exhibits the same hyperpigmentation pattern accompanied by acantholytic lesions, is also caused by heterozygous *KRT5* loss-of-function variants (OMIM 179850).
KRT14	Naegeli-Franceschetti-Jadassohn syndrome (OMIM 161000) & dermatopathia pigmentosa reticularis (OMIM 125595) are phenotypically similar ectodermal dysplasia syndromes characterized by complete absence of dermatoglyphics (fingerprint lines), a reticulate pattern of skin hyperpigmentation, thickening of palms & soles (palmoplantar keratoderma), abnormal sweating, & other subtle developmental anomalies of teeth, hair, & skin. Inheritance is autosomal dominant.
PLEC	Autosomal recessive limb-girdle muscular dystrophy 17 (OMIM 613723) is caused by homozygosity for a 9-bp deletion & characterized by progressive muscle weakness w/o cutaneous findings [Gundesli et al 2010].

Differential Diagnosis

The 2020 classification system [Has et al 2020a] names four major types of epidermolysis bullosa (EB):

- EB simplex (EBS)
- Junctional EB (JEB)
- Dystrophic EB (DEB)
- Kindler syndrome

All forms of EB are characterized by increased skin fragility (and often mucosa) and blistering with little or no trauma. Classification into major type is based on the location of blistering in relation to the dermal-epidermal junction of skin. Subtypes are predominantly determined by clinical features (see Table 6) and supported by molecular diagnosis (see Table 7).

Table 6. Clinical Features Observed in the Four Major Types of Epidermolysis Bullosa

Feature	Comment
Easy fragility of skin (& often mucosa) manifested by blistering w/little or no trauma	Shared by 4 major EB types
Blisters can be induced w/friction (amount of friction can vary) & enlarged by applying pressure to blister edge.	Shared by 4 major EB types
Mucosal & nail involvement	May not be helpful discriminators
Presence or absence of milia	May not be helpful discriminators
Scarring [1]	Can occur in EBS & JEB as a result of infection of erosions or scratching, which further damages exposed surface. In milder presentations, scarring (esp of dorsal hands & feet) suggests DEB.
Congenital absence of skin (congenital aplasia cutis)	Can be seen in all forms of EB & may not be distinguishing feature of any particular form of EB

Table 6. continued from previous page.

Feature	Comment
Corneal erosions	May indicate either DEB or JEB
Esophageal strictures	May indicate either DEB or JEB
Nail & tooth enamel involvement	Generally indicates either DEB or JEB; in rare cases can be seen in EBS (e.g., in EBS, intermediate w/muscular dystrophy)
Pseudosyndactyly (mitten deformities) [2]	Usually suggests DEB

DEB = dystrophic epidermolysis bullosa; EB = epidermolysis bullosa; EBS = epidermolysis bullosa simplex; JEB = junctional epidermolysis bullosa

1. Post-inflammatory changes, such as those seen in severe EBS, are often mistaken for scarring or mottled pigmentation.

2. Results from extensive scarring of the hands and feet in older children and adults

Although clinical examination is useful in determining the extent of blistering and the presence of oral and other mucous membrane lesions, defining characteristics such as the presence and extent of scarring – especially in young children and neonates – may not be established or significant enough to allow identification of EB type; thus, molecular genetic testing (or less commonly skin biopsy) is usually required to establish the most precise diagnosis.

Table 7. Genes of Interest in the Differential Diagnosis of Epidermolysis Bullosa Simplex

	Level of Skin Cleavage	Gene	MOI	Phenotype(s) / Comment
Epidermolysis bullosa (EB)	**Junctional**	*COL17A1*	AR	JEB
		ITGA3	AR	JEB
		ITGA6	AR	JEB; JEB-PA
		ITGB4	AR	JEB; JEB-PA
		LAMA3	AR	JEB
		LAMB3	AR	JEB
		LAMC2	AR	JEB
	Dermal	*COL7A1*	AD, AR	DEB
	Mixed	*FERMT1*	AR	Kindler syndrome
Other disorders w/skin fragility	**Intra-epidermal**	*CAST*	AR	PLACK syndrome
		CDSN	AR	Generalized inflammatory skin peeling syndrome
		CSTA	AR	Acral peeling skin disease
		CTSB	AD	Keratolytic winter erythema
		DSC3	AR	Hypotrichosis w/recurrent skin vesicles
		DSG1	AR	SAM syndrome
		DSG3	AR	Acantholytic blisters in oral & laryngeal mucosa
		DSP	AR	Acantholytic erosive disorder
			AD	SAM syndrome
			AR	Skin fragility-woolly hair syndrome

Table 7. continued from previous page.

	Level of Skin Cleavage	Gene	MOI	Phenotype(s) / Comment
		FLG2	AR	Generalized peeling skin syndrome (noninflammatory)
		JUP	AR	Acantholytic erosive disorder; skin fragility-woolly hair syndrome
		KRT1	AD, AR	Epidermolytic ichthyosis
			AD	Annular epidermolytic ichthyosis
		KRT10	AD, AR	Epidermolytic ichthyosis
			AD	Annular epidermolytic ichthyosis
		KRT16	AD	Pachyonychia congenita-K16
		KRT17	AD	Pachyonychia congenita-K17
		KRT2	AD	Superficial epidermolytic ichthyosis
		KRT6A	AD	Pachyonychia congenita-6A
		KRT6B	AD	Pachyonychia congenita-6B
		KRT6C	AD	Pachyonychia congenita-6C
		PKP1	AR	Ectodermal dysplasia-skin fragility syndrome
		SERPINB8	AR	Exfoliative ichthyosis
		SPINK5	AR	Netherton syndrome
		TGM5	AR	Acral peeling skin disease
	Dermal	*PLOD3*	AR	Connective tissue disorder w/skin fragility

Adapted from Tables 1 and 2 in Has et al [2020a]
AD = autosomal dominant; AR = autosomal recessive; DEB = dystrophic epidermolysis bullosa; EB = epidermolysis bullosa; JEB-PA = junctional epidermolysis bullosa with pyloric atresia; MOI = mode of inheritance

Junctional EB (JEB) Blistering may be severe and granulation tissue can form on the skin around the oral and nasal cavities, fingers, and toes, and internally around the upper airway. Blisters generally heal with no significant scarring. Additional features shared by JEB and the other major forms of epidermolysis bullosa include congenital localized absence of skin (congenital aplasia cutis), milia, nail dystrophy, scarring alopecia, hypotrichosis, and joint contractures. Additional features reported in some JEB subtypes include congenital malformations of the urinary tract and bladder, pyloric atresia, and respiratory and renal involvement.

Dystrophic EB (DEB). In DEB, the blister forms below the basement membrane, in the superficial dermis. The basement membrane is attached to the blister roof, resulting in scarring and milia when blisters heal. DEB may be caused by heterozygous or biallelic *COL7A1* pathogenic variants. Autosomal recessive DEB (referred to as RDEB) presents with fragile skin and severe, devastating blistering and wounding at birth with extensive scarring, nail dystrophy and loss, alopecia, pseudosyndactyly (mitten deformity) of the hands and feet, and increased risk for aggressive squamous cell carcinomas and early death; extracutaneous manifestations include joint contractures, gastrointestinal strictures, treatment-resistant anemia, and severe malnutrition. The clinical presentation of autosomal dominant DEB (referred to as DDEB) is generally milder than RDEB, with limited blistering and scarring, and nail dystrophy.

Kindler syndrome is characterized by skin fragility and acral blister formation beginning at birth, diffuse cutaneous atrophy, photosensitivity (most prominent during childhood), poikiloderma, diffuse palmoplantar hyperkeratosis, and pseudosyndactyly. Mucosal manifestations are also common and include hemorrhagic mucositis and gingivitis, periodontal disease, premature loss of teeth, and labial leukokeratosis. Other mucosal findings can include ectropion, urethral stenosis, and severe phimosis.

Non-EB skin fragility disorders. Skin fragility disorders arising from suprabasilar cleavage (e.g., cleavage above the basal keratinocyte plane) or dermal cleavage are considered distinct from EBS and other inherited forms of EB as these disorders do not present with significant blistering. These non-EB skin fragility disorders include erosive disorders, peeling skin disorders, hyperkeratotic disorders, and connective tissue disorders.

- **EBS superficialis** is no longer considered a distinct subtype of EBS and has been removed from the 2020 consensus reclassification system [Has et al 2020a], as it remains a poorly defined clinical entity and the underlying pathogenesis is unknown.
- **Erosive disorders with skin fragility** range in severity, and include the following:
  - **Acantholytic erosive disorder** (previously EBS-acantholytic) is caused by biallelic pathogenic variants in *DSP* or *JUP* [Jonkman et al 2005, Pigors et al 2011, Rotemberg et al 2017]. Affected neonates present with progressive erosions without blistering, alopecia, neonatal teeth, respiratory involvement, or loss of nails. Death within the first days after birth secondary to profound fluid and electrolyte imbalance is common.
  - **Ectodermal dysplasia skin-fragility syndrome** (previously EBS-plakophilin) is characterized by mild skin fragility associated with perioral cracking and cheilitis, hypotrichosis or alopecia, and a painful and fissured palmoplantar keratoderma; it is caused by biallelic loss-of-function variants in *PKP1* [McGrath et al 1997, McGrath & Mellerio 2010].
  - **Skin fragility-wooly hair syndrome** is associated with biallelic variants in *DSP* or *JUP*. Affected individuals present with superficial erosions without blisters, woolly hair, cardiomyopathy, and hyperkeratosis.
- **Peeling skin disorders with skin fragility** include acral peeling skin disease (caused by biallelic pathogenic variants in *TGM5* or *CSTA*), exfoliative ichthyosis (caused by biallelic pathogenic variants in *SERPINB8*), and Netherton syndrome (caused by biallelic pathogenic variants in *SPINK5*). Peeling skin disorders are characterized by spontaneous superficial peeling. Peeling may be inflammatory or noninflammatory, localized (e.g., to acral surfaces) or diffuse. In syndromic forms, individuals may also present with growth deficiency, hair abnormalities, and atopy [Has 2018b].
- **Hyperkeratotic skin disorders with skin fragility** include pachyonychia congenita and epidermolytic ichthyosis.
  - **Pachyonychia congenita** is caused by heterozygous pathogenic variants in *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, and *KRT17*, and is characterized by focal palmoplantar keratoderma and blistering, and nail dystrophy.
  - **Epidermolytic ichthyosis** is caused by heterozygous or biallelic *KRT1* pathogenic variants. Individuals with epidermolytic ichthyosis present with erythema, hyperkeratosis, ichthyosiform lesions, and superficial blisters following trauma.
- **Connective tissue disorder with skin fragility** is caused by biallelic pathogenic variants in *PLOD3*, which encodes for lysyl hydroxylase 3 and results in intradermal blistering. Affected individuals develop blisters with trauma from birth and have developmental delay and widespread connective tissue abnormalities including joint contractures and scoliosis [Vahidnezhad et al 2019b].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with epidermolysis bullosa simplex (EBS), the evaluations summarized in Table 8 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 8. Recommended Evaluations Following Initial Diagnosis in Individuals with Epidermolysis Bullosa Simplex

System/Concern	Evaluation	Comment
Skin	• Consultation w/dermatologist to evaluate sites of blister formation • Assess for signs/symptoms of wound infection.	
	Assess for dehydration (fluid & electrolyte disturbances) as needed.	Fluid & electrolyte disturbances can be life threatening in neonatal period & in infants w/widespread disease.
Oral mucosa	• Assess for involvement of oral mucosa. • Assess feeding & growth in those w/oral disease. • Refer to feeding therapist or consider nutritional interventions incl feeding supplementation & gastrostomy tube placement if indicated.	Dental caries are common. Early referral for eval by experienced pediatric dentist may be helpful.
Nutrition & growth	• Assess need for vitamin & mineral supplementation incl assessment for anemia. • Assess weight gain.	
Physical activity & mobility	• Assess footwear & for mobility issues. • Referral to PT as needed	
Other	Referral to neurologist, cardiologist, &/or nephrologist as needed for rare manifestations of EBS	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of EBS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

EBS = epidermolysis bullosa simplex; MOI = mode of inheritance; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to protect the skin from blistering, appropriate dressings that will not further damage the skin and will promote healing of open wounds, and prevention and treatment of secondary infection are the mainstays of treatment.

Blistering. Encourage children to tailor physical activities to minimize trauma to the skin while staying active and engaging with peers in age-appropriate learning and social activities.

Lance and drain new blisters (without unroofing the blisters) to prevent further spread from fluid pressure.

Dressings usually involve three layers:

- A primary nonadherent dressing that will adhere to the top layers of the epidermis must be used. There is wide variability in tolerance to different primary layers; some individuals with EBS can use ordinary bandages. Some dressings are impregnated with an emollient such as petrolatum or topical antiseptic (e.g., Vaseline® Gauze, Adaptic®, Xeroform®). Nonstick products (e.g., Telfa™ or N-Terface®) or silicone-based products without adhesive (e.g., Mepitel® or Mepilex®) are also popular. In noninfected wounds, a thin layer of simple, nonirritating moisturizer such as petrolatum may be applied either directly to the skin or to the primary nonadherent dressing prior to wound dressing. Topical antibiotics (e.g., gentamicin or mupirocin ointment) may also be applied as indicated.
- A secondary layer absorbs drainage, provides stability for the primary layer, and adds padding to allow more activity. Foam dressings and/or rolls of gauze (e.g., Kerlix®) are commonly used.
- A tertiary layer, usually with some elastic properties, ensures the integrity of the dressing (e.g., Coban™ or elasticized tube gauze of varying diameters such as BandNet®).

Note: Many individuals with EBS, in contrast to those with junctional EB and dystrophic EB, find that excessive bandaging may actually lead to more blistering, presumably as a result of increased heat and sweating. Such individuals may benefit from dusting the affected areas with cornstarch or Zeasorb® to help absorb moisture and reduce friction on the skin, followed by a simple (i.e., one-layer) dressing [Lara-Corrales et al 2010, El Hachem et al 2014].

Newer generations of antimicrobial dressing with impregnated silver, iodine, gentian violet blue, or medical-grade honey may be used to reduce bacterial colonization and promote wound healing. However, these dressings are usually much more costly.

In the following studies, small sample sizes limit the statistical validity and generalizability of the results; however, given the lack of effective treatments for EBS, these potentially helpful treatments should be considered:

- In some individuals with EBS, 20% aluminum chloride applied to palms and soles can reduce blister formation, presumably by decreasing sweating.
- Case reports and small studies suggest that injection of botulinum toxin into the feet is effective in reducing blistering and associated pain. The mechanism of action is unclear, but likely relates to reduction of sweating and subsequent maceration of the skin [Abitbol & Zhou 2009, Swartling et al 2010, Holahan et al 2016].
- In one study of a limited number of individuals with severe EBS, cyproheptadine (Periactin®) reduced blistering. This may result from the anti-pruritic effect of the medication; the true mechanism is not clear [Neufeld-Kaiser & Sybert 1997].
- In another study, tetracycline reduced blister counts in two thirds of persons with localized EBS [Weiner et al 2004]. One study evaluated three months of oral erythromycin therapy in six children ages one to eight years with severe EBS, and showed that the medication was well tolerated and improved blistering in three children [Chiaverini et al 2015]. An anti-inflammatory mechanism, rather than an antimicrobial mechanism, is proposed for the effect of antibiotics in the treatment of EBS.
- In a clinical trial, topical diacerein cream reduced blister counts in 60% of individuals with severe EBS [Wally et al 2018]. In 17 children ages four to 12 years with severe EBS, 1% diacerein cream was applied once daily to skin areas with blisters and resulted in reduced blistering within treated areas. In vitro studies suggest that diacerein applied topically may reduce blister formation by downregulating the pro-inflammatory interleukin 1β pathway to subsequently stabilize keratin intermediate filament networks within basal keratinocytes.
- One pilot study of two individuals suggested that topical application of sirolimus, an mTOR inhibitor, may reduce plantar blistering and keratoderma and improve ambulation [Lee et al 2022]. These observed

improvements may arise from regulation of key cytokines and pathways implicated in blister formation and inflammation.
- In a small pilot study of individuals with severe EBS, treatment with apremilast resulted in decreased blistering, potentially through the downregulation of Th17-associated inflammation [Castela et al 2019].
- A small case series noted anecdotal reductions in blistering and pain with walking, and increased speed of wound healing following treatment of affected areas with topical cannabidiol oil [Chelliah et al 2018]. These effects may be due to both the analgesic and anti-inflammatory effects of cannabinoids.
- A case report suggested that treatment with intravenous gentamicin may improve translational readthrough and increase plectin expression in individuals with EBS, intermediate with muscular dystrophy caused by *PLEC* truncating variants. Treatment with gentamicin resulted in increased plectin expression for several months, improvements in clinical outcomes including reduced mucosal erosions and blisters, and improved neuromuscular and respiratory functionality [Martínez-Santamaría et al 2022].

Hyperkeratosis. Use of moisturizers, keratolytics, and softening agents containing petrolatum, alpha hydroxy acid, and urea are often recommended for palmar and plantar hyperkeratoses to prevent skin thickening and cracking. In addition, soaking the hands and feet in saltwater helps soften hyperkeratosis, ease debridement of the thick skin, and promote penetration of skin emollients.

Infection. Treatment with topical and/or systemic antibiotics or silver-impregnated dressings or gels can be helpful. Saltwater baths with and without acetic acid added may also reduce infections [Petersen et al 2015]. Diluted bleach water soak has become a common practice to reduce both colonization with *Staphylococcus aureus* and skin inflammation [Pope et al 2012].

Pain and itch. Effective management of pain and itch requires identifying and eliminating a specific cause, where possible (e.g., administration of antibiotics for pain or itch caused by an acute skin infection), as well as an overarching multimodal strategy that includes pharmacologic, physical, and psychosocial interventions to maintain daily function and quality of life [Goldschneider et al 2014, Bruckner et al 2015, Cohn & Teng 2016]. For individuals who require prescription analgesics, early referral to pain specialists for management including biofeedback therapy can be beneficial. Neurokinin-1 receptor antagonists are being studied for the treatment of itch in all types of EB (NCT03836001), as systemic antihistamines have not been shown to be effective.

Nutrition, dehydration, and electrolyte disturbances

- Management of dehydration and electrolyte disturbances
- Nutritional support including age-appropriate vitamin and mineral supplementation, and dietary modifications with nutrient-rich feeds. Gastrostomy tubes may be required to ensure adequate intake and to treat or prevent failure to thrive in neonates, infants, and children with intermediate EBS or severe EBS [Haynes 2010, Haynes et al 2012, Salera et al 2020, Marro et al 2021].
- Feeding modifications such as Haberman feeders to reduce trauma to the oral mucosa during breastfeeding, soft or pureed foods, and early involvement with a feeding therapist in those with oral aversion as a result of severe oral disease [Salera et al 2020]
- Iron supplementation should be considered in those with anemia due to chronic inflammation from ongoing blistering and wounding.

Excess weight gain and obesity in adolescents and adults with EBS. Weight management beginning in preadolescence is recommended to reduce the risk of obesity and associated conditions [Yerlett 2020].

Physical activity and mobility. Appropriate footwear is essential to preserve ambulation and mobility, including socks to wick moisture and reduce friction, orthotics and insoles, and supportive shoes [Khan et al 2020]. Tailored interventions including physical therapy and debridement of plantar keratoderma should also be considered.

Basal cell carcinoma in individuals with severe EBS is treated in the standard manner.

Decreased quality of life and other psychosocial considerations. Psychosocial support should be provided for reduced quality of life and significant psychosocial and economic challenges resulting from EBS, including feelings of anxiety, frustration, and depression, strained interpersonal relationships with family, financial burden due to the cost of wound dressing supplies and medications, reduced employment opportunities, and missed work days [Tabolli et al 2009, Williams et al 2011, Brun et al 2017, Martin et al 2019, Bruckner et al 2020, So et al 2022].

Standard treatment is indicated for other manifestations reported, including **muscular dystrophy**, **pyloric atresia**, **cardiomyopathy**, and **nephropathy**.

Surveillance

Table 9. Recommended Surveillance for Individuals with Epidermolysis Bullosa Simplex

System/Concern	Evaluation	Frequency
Skin	• Dermatologic assessment for blisters, oral disease, hyperkeratosis, hyperhidrosis, signs/symptoms of wound infection, pain, & itching • Assess hydration status.	At each visit
Growth, weight, & nutrition	Assess growth & nutritional status, incl poor or excess weight gain, feeding issues, & signs/symptoms of anemia & dietary deficiencies.	
Motor development & mobility	Assess effect of skin disease on motor skills & functional mobility, incl walking.	
Psychosocial well-being	Assess psychosocial well-being & quality of life.	
Cardiac	**In persons w/EBS, intermediate w/cardiomyopathy:** consider serum BNP & creatinine kinase due to ↑ risk for early-onset dilated cardiomyopathy. [1]	As needed &/or as recommended by cardiologist
Other	• Neurologic assessment for those w/muscular dystrophy • Nephrology assessment for those w/nephropathy	As needed &/or as recommended by relevant specialist

BNP = B-type natriuretic peptide
1. Grilletta [2019], Schwieger-Briel et al [2019], Has et al [2020a]

Agents/Circumstances to Avoid

Excessive heat and sweating may exacerbate blistering, wounding, and infection in EBS.

Poorly fitting or coarse-textured clothing and footwear can cause trauma and should be avoided.

Avoiding activities that traumatize the skin (e.g., hiking, mountain biking, contact sports) can reduce skin damage; however, affected individuals who are determined to find ways to participate in these endeavors should be encouraged.

Many individuals with EBS cannot use medical tape or Band-Aids® with adhesives.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

If a fetus is known to be affected with any form of EBS, cæsarean delivery may reduce the trauma to the skin during delivery. Vigorous rubbing of the infant after delivery should be avoided to reduce skin trauma. In

pregnant mothers with EBS, vaginal delivery is not strictly contraindicated; early discussion of individual preferences and planning with a multidisciplinary care team including obstetricians, anesthesiologists, and neonatologists is recommended to ensure the safety and well-being of both the mother and baby [Greenblatt et al 2022].

Therapies Under Investigation

Proposed approaches for gene therapy in EBS include the use of CRISPR/Cas9-mediated DNA repair [Kocher et al 2017], TALEN-mediated DNA repair [Aushev et al 2017], viral vectors carrying corrected gene products to transduce keratinocytes [Petek et al 2010], RNA trans-splicing repair [Wally et al 2008, Peking et al 2019], addition of other functional proteins [D'Alessandro et al 2004], induction of a compensating pathogenic variant via revertant mosaicism [Smith et al 2004], and pathogenic variant-specific siRNAs [Atkinson et al 2011]. Systemic gentamicin may also induce *PLEC* readthrough and increase plectin expression in individuals with EBS, intermediate with muscular dystrophy caused by pathogenic nonsense variants (see Treatment of Manifestations) [Martínez-Santamaría et al 2022]. To date, however, no clinical trials of gene therapy for EBS have been completed. The recent development of a human induced pluripotent stem cell-derived keratinocyte model for EBS should facilitate further exploration of these therapeutic approaches [Coutier et al 2022].

Several clinical trials investigating new or repurposed therapeutics to reduce blistering, pain, and itch in EBS are ongoing, and novel computational methods leveraging transcriptome analysis may facilitate further identification of potential drug candidates for repurposing [Lee et al 2022]. Active clinical trials include investigations of topical TolaSure™ gel (NCT05062070) and Oleogel-S10 (NCT03068780), a birch bark extract, to improve wound healing; botulinum toxin injections to reduce sweating and improve clinical disease (NCT03453632); and oral serlopitant (NCT03836001), a neurokinin-1 inhibitor, to reduce itch.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

The use of vitamin E in treating EBS has been reported anecdotally [Sehgal & Sanyal 1972]. Topical steroids are often used for symptomatic relief as pruritus is common during wound healing. Poorly controlled excoriation may cause secondary trauma and repeated blistering. However, no rigorous clinical trials have been undertaken for these topical treatments.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Epidermolysis bullosa simplex (EBS) is typically inherited in an autosomal recessive or an autosomal dominant manner. Genetic counseling regarding risk to family members depends on accurate molecular diagnosis (i.e., identification of the causative pathogenic variant[s] in an affected family member) and confirmation of the mode of inheritance in each family.

Autosomal recessive EBS is associated with:

- Biallelic loss-of-function variants in *KRT5*, *KRT14*, or *PLEC*; and
- Biallelic pathogenic variants in *CD151*, *DST*, or *EXPH5*.

Autosomal dominant EBS is associated with:

- Heterozygous dominant-negative variants in *KRT5*, *KRT14*, or *PLEC*; and
- Heterozygous pathogenic variants in *KLHL24*.

In rare instances, EBS is caused by the presence of heterozygous pathogenic variants in both *KRT5* and *KRT14* and is inherited in a digenic manner (i.e., the presence of both the *KRT5* and the *KRT14* pathogenic variant is required for expression of the EBS phenotype) [Kim et al 2017, Yu et al 2020].

Note: Skin biopsy findings cannot be used to assess inheritance pattern.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an EBS-related pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an EBS-related pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Typically, heterozygous parents of a child with autosomal recessive EBS are unaffected. (*KRT5* and *KRT14* pathogenic variants that cause autosomal recessive EBS are not currently known to be associated with the autosomal dominant disorders Dowling-Degos disease, Naegeli-Franceschetti-Jadassohn syndrome, and dermatopathia pigmentosa reticularis; see Genetically Related Disorders.)

Sibs of a proband

- If both parents are known to be heterozygous for an EBS-related pathogenic variant, each sib of an affected individual has at conception 25% chance of inheriting biallelic pathogenic variants being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Typically, heterozygous sibs of a proband with autosomal recessive EBS are unaffected. (*KRT5* and *KRT14* pathogenic variants that cause autosomal recessive EBS are not currently known to be associated with the autosomal dominant disorders Dowling-Degos disease, Naegeli-Franceschetti-Jadassohn syndrome, and dermatopathia pigmentosa reticularis; see Genetically Related Disorders.)

Offspring of a proband. The offspring of an individual with autosomal recessive EBS are obligate heterozygotes for an EBS-related pathogenic variant.

Other family members. Each sib of a proband's parents is at a 50% risk of being having an EBS-related pathogenic variant.

Heterozygote Detection

Heterozygote testing for at-risk relatives requires prior identification of the EBS-related pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Individuals diagnosed with EBS caused by a heterozygous dominant-negative *KRT5*, *KRT14,* or *PLEC* variant or a heterozygous *KLHL24* pathogenic variant may have an affected parent from whom they inherited a pathogenic variant.
- Some individuals diagnosed with autosomal dominant EBS have the disorder as the result of a *de novo* pathogenic variant. Individuals with severe forms of autosomal dominant EBS usually have a *de novo* pathogenic variant.
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Nagao-Watanabe et al 2004, Chen et al 2022]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure to recognize the syndrome and/or a milder phenotypic presentation in affected family members. Many families include individuals with a history of "blistering" but are unaware that these individuals have EBS. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
  - Penetrance appears to be less than 100% for known heterozygous dominant-negative *KRT5* and *KRT14* variants (see Penetrance). Phenotypic expression can be highly variable; localized EBS, intermediate EBS, and severe EBS phenotypes have been reported in affected individuals from the same family (see Genotype-Phenotype Correlations).
  - Heterozygous dominant-negative variants in *PLEC* and heterozygous pathogenic variants in *KLHL24* are presumed to be fully penetrant, as asymptomatic heterozygous individuals have not been reported to date.
- If the EBS-related pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Nagao-Watanabe et al 2004, Chen et al 2022].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of parental germline mosaicism.

Offspring of a proband

- Each child of an individual with autosomal dominant EBS has a 50% chance of inheriting the EBS-related pathogenic variant.
- In the rare situation in which both parents have an autosomal dominant pathogenic variant in the same gene (e.g., in consanguineous unions), each child has a 75% chance of having at least one pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being heterozygous for an EBS-related pathogenic variant.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the EBS-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **DEBRA**
  United Kingdom
  Phone: 01344 771961
  Email: debra@debra.org.uk
  debra.org.uk
- **DEBRA International**
  debra-international.org
- **debra of America**
  Phone: 833-debraUS
  Email: staff@debra.org
  debra.org

- **EB Research Partnership (EBRP)**
  Phone: 646-844-0902
  Email: info@ebresearch.org
  www.ebresearch.org
- **Epidermolysis Bullosa Medical Research Foundation**
  Phone: 310-205-5119
  Email: a.pett@bep-la.com
  EBMRF
- **MedlinePlus**
  Epidermolysis bullosa simplex
- **EBCare Registry**
  Email: connect@invitae.com
  ebcare.patientcrossroads.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Epidermolysis Bullosa Simplex: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CD151	11p15.5	CD151 antigen	CD151 database Blood Group Antigen Gene Mutation Database (CD151)	CD151	CD151
DST	6p12.1	Dystonin		DST	DST
EXPH5	11q22.3	Exophilin-5		EXPH5	EXPH5
KLHL24	3q27.1	Kelch-like protein 24		KLHL24	KLHL24
KRT5	12q13.13	Keratin, type II cytoskeletal 5	Human Intermediate Filament Database KRT5 KRT5 database	KRT5	KRT5
KRT14	17q21.2	Keratin, type I cytoskeletal 14	Human Intermediate Filament Database KRT14 KRT14 database	KRT14	KRT14
PLEC	8q24.3	Plectin	PLEC homepage - Leiden Muscular Dystrophy pages	PLEC	PLEC

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Epidermolysis Bullosa Simplex (View All in OMIM)

113810	DYSTONIN; DST
131760	EPIDERMOLYSIS BULLOSA SIMPLEX 1A, GENERALIZED SEVERE; EBS1A
131800	EPIDERMOLYSIS BULLOSA SIMPLEX 1C, LOCALIZED; EBS1C
131900	EPIDERMOLYSIS BULLOSA SIMPLEX 1B, GENERALIZED INTERMEDIATE; EBS1B
131960	EPIDERMOLYSIS BULLOSA SIMPLEX 2F, WITH MOTTLED PIGMENTATION; EBS2F
148040	KERATIN 5, TYPE II; KRT5

Table B. continued from previous page.

148066	KERATIN 14, TYPE I; KRT14
226670	EPIDERMOLYSIS BULLOSA SIMPLEX 5B, WITH MUSCULAR DYSTROPHY; EBS5B
601001	EPIDERMOLYSIS BULLOSA SIMPLEX 1D, GENERALIZED, INTERMEDIATE OR SEVERE, AUTOSOMAL RECESSIVE; EBS1D
601282	PLECTIN; PLEC
602243	CD151 ANTIGEN; CD151
609057	EPIDERMOLYSIS BULLOSA SIMPLEX 7, WITH NEPHROPATHY AND DEAFNESS; EBS7
609352	EPIDERMOLYSIS BULLOSA SIMPLEX 2E, WITH MIGRATORY CIRCINATE ERYTHEMA; EBS2E
611295	KELCH-LIKE 24; KLHL24
612878	EXOPHILIN 5; EXPH5
615028	EPIDERMOLYSIS BULLOSA SIMPLEX 4, LOCALIZED OR GENERALIZED INTERMEDIATE, AUTOSOMAL RECESSIVE; EBS4
615425	EPIDERMOLYSIS BULLOSA SIMPLEX 3, LOCALIZED OR GENERALIZED INTERMEDIATE, WITH BP230 DEFICIENCY; EBS3
617294	EPIDERMOLYSIS BULLOSA SIMPLEX 6, GENERALIZED INTERMEDIATE, WITH OR WITHOUT CARDIOMYOPATHY; EBS6
619555	EPIDERMOLYSIS BULLOSA SIMPLEX 2A, GENERALIZED SEVERE; EBS2A
619594	EPIDERMOLYSIS BULLOSA SIMPLEX 2C, LOCALIZED; EBS2C
619599	EPIDERMOLYSIS BULLOSA SIMPLEX 2D, GENERALIZED, INTERMEDIATE OR SEVERE, AUTOSOMAL RECESSIVE; EBS2D

Molecular Pathogenesis

KRT5 and *KRT14* are expressed in the basal keratinocytes of the epidermis (the innermost layer), where their protein products form heterodimeric molecules that assemble into the intracellular keratin intermediate filament network. This network is linked directly to the hemidesmosomes that anchor the keratinocytes to the basal lamina and to the desmosomes, leading to strong attachment of the keratinocytes to one another. These associations along with the network itself supply stability and resistance to stress, enabling the keratinocytes to maintain their structural integrity during minor trauma.

DST encodes the epidermal plakin protein BP230 (i.e., epithelial BPAG1, BPAG1-e), which facilitates dermal-epidermal adhesion through linkage of keratin intermediate filament networks and hemidesmosomes (for review, see Bouameur et al [2014]).

PLEC is widely expressed across a range of tissues including muscle, brain, cardiac, and stratified epithelium. Within the skin, three plectin isoforms are expressed to maintain mechanical integrity by linking keratin intermediate filament networks to intracellular desmosomes and hemidesmosomes. Plectin is highly versatile, and also binds to intermediate filaments within muscle and neural tissues, which may underlie the wide range of clinical phenotypes observed in *PLEC*-associated epidermolysis bullosa simplex (EBS) [Charlesworth et al 2013, Bouameur et al 2014, Kiritsi et al 2021].

Within the epidermis, *CD151* expression is localized to hemidesmosomes and is thought to be critical for hemidesmosome formation and cell adhesion and signaling (for review, see [Vahidnezhad et al 2019c]. CD151 is also necessary for appropriate assembly of renal basement membranes, which may contribute to the syndromic presentation including protein-wasting nephropathy observed in individuals with *CD151*-associated EBS [Karamatic Crew et al 2004, Vahidnezhad et al 2018].

EBS may also be caused by pathogenic variants in nonstructural proteins. *KLHL24* encodes for Kelch-like protein 24 (KLHL24), which is the receptor for a cullin-RING E3 ubiquitin ligase complex that regulates intermediate filament stability through turnover of keratin 14 (for review, see Has [2017] and Bolling & Jonkman [2019]). Pathogenic variants may cause skin fragility through increased ubiquitination and degradation of keratin 14 [Lin et al 2016], or impaired ability to promote keratin 14 degradation resulting in disorganized and fragmented intermediate filaments [He et al 2016].

EXPH5 encodes a RAB27b GTPase effector protein, exophilin-5, which plays a role in cell membrane trafficking and vesicle formation.

Dominant-negative missense variants in *KRT5* and *KRT14* predominate and often affect the ability of the keratin to associate with its keratin partner, its secondary structure, and its ability to form the intracellular network. Intrafamilial phenotypic variability exists, suggesting that other factors can affect the resistance of the cells to friction [Rugg & Leigh 2004, Smith et al 2004, Werner et al 2004, Deng et al 2011].

Mechanism of disease causation. Pathogenic variants in genes encoding structural proteins (e.g., *KRT5*, *KRT14*, *PLEC*) are associated with dominant-negative or loss-of-function mechanisms. Pathogenic variants in nonstructural proteins may exhibit gain of function (e.g., *KLHL24*) or loss of function (e.g., *EXPH5*).

Table 10. Epidermolysis Bullosa Simplex: Mechanism of Disease Causation

Gene [1]	Special Consideration
CD151	Loss-of-function variants assoc w/AR inheritance
DST	
EXPH5	
KLHL24	Gain-of-function & dominant-negative variants assoc w/AD inheritance.
KRT5	• Dominant-negative missense variants assoc w/AD inheritance. The mechanism of disease is dependent on the variant, but often results in protein that prevents proper assoc w/the protein partner (e.g., keratin 5, keratin 14) & assembly of those assoc dimers into bundles & fibers. • Loss-of-function (typically functionally null alleles) variants assoc w/AR inheritance
KRT14	• Dominant-negative missense variants assoc w/AD inheritance • Loss-of-function (typically functionally null alleles) variants that have been assoc w/AR inheritance
PLEC	• The missense variant c.5998C>T identified in the AD subtype previously known as EBS-Ogna is presumed to be dominant negative [Koss-Harnes et al 2002]. • Loss-of-function variants assoc w/AR subtypes incl EBS, intermediate w/PLEC pathogenic variants; EBS, intermediate w/muscular dystrophy; & EBS, severe w/ pyloric atresia

AD = autosomal dominant; AR = autosomal recessive; EBS = epidermolysis bullosa simplex
1. Genes from Table 1 in alphabetic order

Table 11. Epidermolysis Bullosa Simplex: Gene-Specific Laboratory Considerations

Gene	Special Consideration
DST	*DST* comprises 107 exons w/3 major alternative spliced isoforms, incl BP230 (i.e., epithelial BPAG1, BPAG1-e).
PLEC	*PLEC* comprises 33 exons w/12 distinct isoforms following alternative splicing. 3 isoforms (plectins 1, 1a, & 1c) are expressed w/in the epidermis.

Table 12. Epidermolysis Bullosa Simplex: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
KRT5	NM_000424.4 NP_000415.2	c.74C>T	p.Pro25Leu	Accounts for 90%-95% of identified pathogenic variants in persons w/EBS w/mottled pigmentation [Moog et al 1999]
		c.1649delG	p.Gly550AlafsTer77	Assoc w/EBS w/mottled pigmentation [Horiguchi et al 2005]
KRT14	NM_000526.5 NP_000517.3	c.356T>C	p.Met119Thr	Assoc w/EBS w/mottled pigmentation [Harel et al 2006]
		c.368A>G	p.Asn123Ser	Account for ~70% of persons w/severe EBS [Stephens et al 1997, Pfendner et al 2005]
		c.373C>T	p.Arg125Cys	
		c.374G>A	p.Arg125His	
	NG_008624.1	c.1117_1158dup42		Assoc w/EBS w/mottled pigmentation [Arin et al 2010]
PLEC	NM_000445.5 NP_000436.2	c.5998C>T	p.Arg2000Trp	Assoc w/AD EBS, intermediate w/*PLEC* pathogenic variants (previously called EBS-Ogna) [Koss-Harnes et al 2002, Kiritsi et al 2013]

AD = autosomal dominant; EBS = epidermolysis bullosa simplex
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes from Table 1 in alphabetic order

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References

Literature Cited

Abitbol RJ, Zhou LH. Treatment of epidermolysis bullosa simplex, Weber-Cockayne type, with botulinum toxin type A. Arch Dermatol. 2009;145:13–5. PubMed PMID: 19153338.

Alkhalifah A, Chiaverini C, Charlesworth A, Has C, Lacour JP. Burnlike scars: a sign suggestive of KLHL24-related epidermolysis bullosa simplex. Pediatr Dermatol. 2018;35:e193–5. PubMed PMID: 29574966.

Arin MJ, Grimberg G, Schumann H, De Almeida H, Chang YR, Tadini G, Kohlhase J, Krieg T, Bruckner-Tuderman L, Has C. 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. PubMed PMID: 20199538.

Atkinson SD, McGilligan VE, Liao H, Szeverenyi I, Smith FJD, Moore CBT, McLean WHI. Development of allele-specific therapeutic siRNA for keratin 5 mutations in epidermolysis bullosa simplex. J Invest Dermatol. 2011;131:2079–86. PubMed PMID: 21716320.

Aushev M, Koller U, Mussolino C, Cathomen T, Reichelt J. Traceless targeting and isolation of gene-edited immortalized keratinocytes from epidermolysis bullosa simplex patients. Mol Ther Methods Clin Dev. 2017;6:112–23. PubMed PMID: 28765827.

Baardman R, Yenamandra VK, Duipmans JC, Pasmooij AMG, Jonkman MF, van den Akker PC, Bolling MC. Novel insights into the epidemiology of epidermolysis bullosa (EB) from the Dutch EB Registry: EB more common than previously assumed? J Eur Acad Dermatol Venereol. 2021;35:995–1006. PubMed PMID: 33095945.

Bergman R, Harel A, Sprecher E. Dyskeratosis as a histologic feature in epidermolysis bullosa simplex-Dowling Meara. J Am Acad Dermatol. 2007;57:463–6. PubMed PMID: 17707151.

Bolling MC, Jonkman MF. KLHL24: beyond skin fragility. J Invest Dermatol. 2019;139:22–4. PubMed PMID: 30579426.

Bolling MC, Pas HH, De Visser M, Aronica E, Pfendner EG, Van Den Berg MP, Diercks GFH, Suurmeijer AJH, Jonkman MF. PLEC1 mutations underlie adult-onset dilated cardiomyopathy in epidermolysis bullosa simplex with muscular dystrophy. J Invest Dermatol. 2010;130:1178–81. PubMed PMID: 20016501.

Bolling MC, Jongbloed JDH, Boven LG, Diercks GFH, Smith FJD, McLean WHI, Jonkman MF. Plectin mutations underlie epidermolysis bullosa simplex in 8% of patients. J Invest Dermatol. 2014;134:273–6. PubMed PMID: 23774525.

Bouameur JE, Favre B, Borradori L. Plakins, a versatile family of cytolinkers: roles in skin integrity and in human diseases. J Invest Dermatol. 2014;134:885–94. PubMed PMID: 24352042.

Bourhis T, Buche S, Fraitag S, Fayoux P. Laryngeal lesion associated with epidermolysis bullosa secondary to congenital plectin deficiency. Eur Ann Otorhinolaryngol Head Neck Dis. 2019;136:203–5. PubMed PMID: 30880037.

Brandling-Bennett HA, Morel KD. Common wound colonizers in patients with epidermolysis bullosa. Pediatr Dermatol. 2010;27:25–8. PubMed PMID: 20199405.

Bruckner AL, Losow M, Wisk J, Patel N, Reha A, Lagast H, Gault J, Gershkowitz J, Kopelan B, Hund M, Murrell DF. The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. Orphanet J Rare Dis. 2020;15:1–14. PubMed PMID: 31900176.

Bruckner AL, Pope E, Mellerio JE, Bodemer C, Colomb V, Diem A, Murrell DF. *Supportive Care: Bathing, Wound Care, Nutrition, Pain and Itch Management, Psychosocial Support, Palliation*. Berlin: Springer; 2015.

Brun J, Chiaverini C, Devos C, Leclerc-Mercier S, Mazereeuw J, Bourrat E, Maruani A, Mallet S, Abasq C, Phan A, Vabres P, Martin L, Bodemer C, Lagrange S, Lacour JP. Pain and quality of life evaluation in patients with localized epidermolysis bullosa simplex. Orphanet J Rare Dis. 2017;12:119. PubMed PMID: 28659151.

Castela E, Tulic MK, Rozières A, Bourrat E, Nicolas JF, Kanitakis J, Vabres P, Bessis D, Mazereeuw J, Morice-Picard F, Baty D, Berard F, Lacour JP, Passeron T, Chiaverini C. Epidermolysis bullosa simplex generalized severe induces a T helper 17 response and is improved by apremilast treatment. Br J Dermatol. 2019;180:357–64. PubMed PMID: 29932457.

Castiglia D, El Hachem M, Diociaiuti A, Carbone T, De Luca N, Pascucci M, Zambruno G, Cavani A. T-lymphocytes are directly involved in the clinical expression of migratory circinate erythema in epidermolysis bullosa simplex patients. Acta Derm Venereol. 2014;94:307–11. PubMed PMID: 24104543.

Charlesworth A, Chiaverini C, Chevrant-Breton J, Delrio M, Diociaiuti A, Dupuis RP, El Hachem M, Le Fiblec B, Sankari-Ho AM, Valhquist A, Wierzbicka E, Lacour JP, Meneguzzi G. Epidermolysis bullosa simplex with PLEC mutations: new phenotypes and new mutations. Br J Dermatol. 2013;168:808–14. PubMed PMID: 23289980.

Chelliah MP, Zinn Z, Khuu P, Teng JMC. Self-initiated use of topical cannabidiol oil for epidermolysis bullosa. Pediatr Dermatol. 2018;35:e224–7. PubMed PMID: 29786144.

Chen F, Deng D, Pan C, Yao Z, Gu Y, Li M. Detection and characterization of low-level mosaicism among clinically unaffected parents of "sporadic" epidermolysis bullosa simplex cases. Br J Dermatol. 2022. Epub ahead of print. PubMed PMID: 35191026.

Chiaverini C, Fontas E, Vabres P, Bessis D, Mazereeuw J, Charlesworth A, Meneguzzi G, Lacour JP. Oral erythromycin therapy in epidermolysis bullosa simplex generalized severe. Br J Dermatol. 2015;173:563–4. PubMed PMID: 25601422.

Cohn HI, Teng JMC. Advancement in management of epidermolysis bullosa. Curr Opin Pediatr. 2016;28:507–16. PubMed PMID: 27386970.

Coulombe PA, Kerns ML, Fuchs E. Epidermolysis bullosa simplex: a paradigm for disorders of tissue fragility. J Clin Invest. 2009;119:1784–93. PubMed PMID: 19587453.

Coutier J, Bonnette M, Martineau S, Mercadier A, Domingues S, Saidani M, Jarrige M, Polveche H, Darle A, Holic N, Hadj-Rabia S, Bodemer C, Lemaitre G, Martinat C, Baldeschi C. Human-induced pluripotent stem cell–derived keratinocytes, a useful model to identify and explore the pathological phenotype of epidermolysis bullosa simplex. J Invest Dermatol. 2022. Epub ahead of print. PubMed PMID: 35490743.

D'Alessandro M, Morley SM, Ogden PH, Liovic M, Porter RM, Lane EB. Functional improvement of mutant keratin cells on addition of desmin: an alternative approach to gene therapy for dominant diseases. Gene Ther. 2004;11:1290–5. PubMed PMID: 15215887.

Deng W, Yuan P, Lai W, Chen M, Wang Y, Dai S. A novel KRT5 mutation, p.Lys199Asn, is associated with three subtypes of epidermolysis bullosa simplex phenotypes in a single Chinese family. J Dermatol Sci. 2011;64:241–3. PubMed PMID: 22005030.

Diociaiuti A, Castiglia D, Naim M, Condorelli AG, Zambruno G, El Hachem M. Autosomal recessive epidermolysis bullosa simplex due to KRT14 mutation: two large Palestinian families and literature review. J Eur Acad Dermatol Venereol. 2018;32:e149–51. PubMed PMID: 29024068.

Diociaiuti A, Pisaneschi E, Rossi S, Condorelli AG, Carnevale C, Zambruno G, El Hachem M. Autosomal recessive epidermolysis bullosa simplex due to EXPH5 mutation: neonatal diagnosis of the first Italian case and literature review. J Eur Acad Dermatol Venereol. 2020;34:e694–7. PubMed PMID: 32176379.

Dunn C, Ambur A, Foss M, Nathoo R. Expanding the spectrum of epidermolysis bullosa simplex: Syndromic epidermolysis bullosa simplex with nephropathy and epilepsy secondary to CD151 tetraspanin defect—a case report and review of the literature. JAAD Case Reports. 2022;23:136–40. PubMed PMID: 35519797.

Fine JD, Bauer EA, McGuire J, Moshell A. *Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances and the Findings of the National Epidermolysis Bullosa Registry*. 1st ed. Baltimore: Johns Hopkins University Press; 1999.

Fine JD, Bruckner-Tuderman L, Eady RAJ, Bauer EA, Bauer JW, Has C, Heagerty A, Hintner H, Hovnanian A, Jonkman MF, Leigh I, Marinkovich MP, Martinez AE, McGrath JA, Mellerio JE, Moss C, Murrell DF, Shimizu H, Uitto J, Woodley D, Zambruno G. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. J Am Acad Dermatol. 2014;70:1103–26. PubMed PMID: 24690439.

Fine JD, Eady RAJ, Bauer EA, Bauer JW, Bruckner-Tuderman L, Heagerty A, Hintner H, Hovnanian A, Jonkman MF, Leigh I, McGrath JA, Mellerio JE, Murrell DF, Shimizu H, Uitto J, Vahlquist A, Woodley D, Zambruno G. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol. 2008a;58:931–50. PubMed PMID: 18374450.

Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006. J Am Acad Dermatol. 2009;60:203–11. PubMed PMID: 19026465.

Fine JD, Johnson LB, Weiner M, Suchindran C. Cause-specific risks of childhood death in inherited epidermolysis bullosa. J Pediatr. 2008b;152:276–80. PubMed PMID: 18206702.

Forrest K, Mellerio JE, Robb S, Dopping-Hepenstal PJC, Mcgrath JA, Liu L, Buk SJA, Al-Sarraj S, Wraige E, Jungbluth H. Congenital muscular dystrophy, myasthenic symptoms and epidermolysis bullosa simplex (EBS) associated with mutations in the PLEC1 gene encoding plectin. Neuromuscul Disord. 2010;20:709–11. PubMed PMID: 20624679.

Ganani D, Malovitski K, Sarig O, Gat A, Sprecher E, Samuelov L. Epidermolysis bullosa simplex due to bi-allelic DST mutations: case series and review of the literature. Pediatr Dermatol. 2021;38:436–41. PubMed PMID: 33471381.

García M, Santiago JL, Terrõn A, Hernández-Martín A, Vicente A, Fortuny C, De Lucas R, Lõpez JC, Cuadrado-Corrales N, Holguín A, Illera N, Duarte B, Sánchez-Jimeno C, Llames S, García E, Ayuso C, Martínez-Santamaría L, Castiglia D, De Luca N, Torrelo A, Mechan D, Baty D, Zambruno G, Escámez MJ, Del Río M. Two novel recessive mutations in KRT14 identified in a cohort of 21 Spanish families with epidermolysis bullosa simplex. Br J Dermatol. 2011;165:683–92. PubMed PMID: 21623745.

Goldschneider KR, Good J, Harrop E, Liossi C, Lynch-Jordan A, Martinez AE, Maxwell LG, Stanko-Lopp D. Pain care for patients with epidermolysis bullosa: best care practice guidelines. BMC Med. 2014;12:178. PubMed PMID: 25603875.

Gostyńska KB, Nijenhuis M, Lemmink H, Pas HH, Pasmooij AMG, Lang KK, Castañón MJ, Wiche G, Jonkman MF. 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. PubMed PMID: 25712130.

Greenblatt DT, Pillay E, Snelson K, Saad R, Torres Pradilla M, Widhiati S, Diem A, Knight C, Thompson K, Azzopardi N, Werkentoft M, Moore Z, Patton D, Mayre-Chilton KM, Murrell DF, Mellerio JE. Recommendations on pregnancy, childbirth and aftercare in epidermolysis bullosa: a consensus-based guideline. Br J Dermatol. 2022;186:620–32. PubMed PMID: 34687549.

Grilletta EA. Cardiac transplant for epidermolysis bullosa simplex with KLHL24 mutation-associated cardiomyopathy. JAAD Case Reports. 2019;5:912–4. PubMed PMID: 31649980.

Groves RW, Liu L, Dopping-Hepenstal PJ, Markus HS, Lovell PA, Ozoemena L, Lai-Cheong JE, Gawler J, Owaribe K, Hashimoto T, Mellerio JE, Mee JB, McGrath JA. 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. PubMed PMID: 20164846.

Gundesli H, Talim B, Korkusuz P, Balci-Hayta B, Cirak S, Akarsu NA, Topaloglu H, Dincer P. Mutation in exon 1f of PLEC, leading to disruption of plectin isoform 1f, causes autosomal-recessive limb-girdle muscular dystrophy. Am J Hum Genet. 2010;87:834–41. PubMed PMID: 21109228.

El Hachem M, Zambruno G, Bourdon-Lanoy E, Ciasulli A, Buisson C, Hadj-Rabia S, Diociaiuti A, Gouveia CF, Hernández-Martín A, De Lucas Laguna R, Dolenc-Voljč M, Tadini G, Salvatori G, De Ranieri C, Leclerc-Mercier S, Bodemer C. Multicentre consensus recommendations for skin care in inherited epidermolysis bullosa. Orphanet J Rare Dis. 2014;9:76. PubMed PMID: 24884811.

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. [3]. PubMed PMID: 16601668.

Has C, Bauer JW, Bodemer C, Bolling MC, Bruckner-Tuderman L, Diem A, Fine JD, Heagerty A, Hovnanian A, Marinkovich MP, Martinez AE, McGrath JA, Moss C, Murrell DF, Palisson F, Schwieger-Briel A, Sprecher E, Tamai K, Uitto J, Woodley DT, Zambruno G, Mellerio JE. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. Br J Dermatol. 2020a;183:614–27. PubMed PMID: 32017015.

Has C, Liu L, Bolling MC, Charlesworth A V., El Hachem M, Escámez MJ, Fuentes I, Büchel S, Hiremagalore R, Pohla-Gubo G, van den Akker PC, Wertheim-Tysarowska K, Zambruno G. Clinical practice guidelines for laboratory diagnosis of epidermolysis bullosa. Br J Dermatol. 2020b;182:574–92. PubMed PMID: 31090061.

Has C. Advances in understanding the molecular basis of skin fragility. F1000Research. 2018a;7:279. PubMed PMID: 29568501.

Has C. Peeling skin disorders: a paradigm for skin desquamation. J Invest Dermatol. 2018b;138:1689–91. PubMed PMID: 30032785.

Has C. The "Kelch" surprise: KLHL24, a new player in the pathogenesis of skin fragility. J Invest Dermatol. 2017;137:1211–2. PubMed PMID: 28532758.

Has C, He Y. Research techniques made simple: immunofluorescence antigen mapping in epidermolysis bullosa. J Invest Dermatol. 2016;136:e65–71. PubMed PMID: 27342035.

Haynes L. Nutrition for children with epidermolysis bullosa. Dermatol Clin. 2010;28:289–301. PubMed PMID: 20447494.

Haynes L, Mellerio JE, Martinez AE. Gastrostomy tube feeding in children with epidermolysis bullosa: consideration of key issues. Pediatr Dermatol. 2012;29:277–84. PubMed PMID: 22288644.

He Y, Maier K, Leppert J, Hausser I, Schwieger-Briel A, Weibel L, Theiler M, Kiritsi D, Busch H, Boerries M, Hannula-Jouppi K, Heikkilä H, Tasanen K, Castiglia D, Zambruno G, Has C. monoallelic mutations in the translation initiation codon of KLHL24 cause skin fragility. Am J Hum Genet. 2016;99:1395–404. PubMed PMID: 27889062.

Holahan HM, Farah RS, Ferguson NN, Paller AS, Legler AA. Treatment of symptomatic epidermolysis bullosa simplex with botulinum toxin in a pediatric patient. JAAD Case Reports. 2016;2:259–60. PubMed PMID: 27486588.

Horiguchi Y, Sawamura D, Mori R, Nakamura H, Takahashi K, Shimizu H. Clinical heterogeneity of 1649delG mutation in the tail domain of keratin 5: a Japanese family with epidermolysis bullosa simplex with mottled pigmentation. J Invest Dermatol. 2005;125:83–5. PubMed PMID: 15982306.

Horn HM, Priestley GC, Eady RAJ, Tidman MJ. The prevalence of epidermolysis bullosa in Scotland. Br J Dermatol. 1997;136:560–4. PubMed PMID: 9155958.

Irvine AD, McLean WHI. The molecular genetics of the genodermatoses: progress to date and future directions. Br J Dermatol. 2003;148:1–13. PubMed PMID: 12534588.

Irvine AD, Rugg EL, Lane EB, Hoare S, Peret C, Hughes AE, Heagerty AH. Molecular confirmation of the unique phenotype of epidermolysis bullosa simplex with mottled pigmentation. Br J Dermatol. 2001;144:40–5. PubMed PMID: 11167681.

Jonkman MF, Pasmooij AMG, Pasmans SGMA, Van Den Berg MP, Ter Horst HJ, Timmer A, Pas HH. Loss of desmoplakin tail causes lethal acantholytic epidermolysis bullosa. Am J Hum Genet. 2005;77:653–60. PubMed PMID: 16175511.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Karamatic Crew V, Burton N, Kagan A, Green CA, Levene C, Flinter F, Brady RL, Daniels G, Anstee DJ. 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. PubMed PMID: 15265795.

Khan FF, Khan N, Rehman S, Ejaz A, Ali U, Erfan M, Ahmed ZM, Naeem M. Identification and computational analysis of novel pathogenic variants in pakistani families with diverse epidermolysis bullosa phenotypes. Biomolecules. 2021;11:620. PubMed PMID: 33921969.

Khan MT, O'Sullivan M, Faitli B, Mellerio JE, Fawkes R, Wood M, Hubbard LD, Harris AG, Iacobaccio L, Vlahovic T, James L, Brains L, Fitzpatrick M, Mayre-Chilton K. Foot care in epidermolysis bullosa: evidence-based guideline. Br J Dermatol. 2020;182:593–604. PubMed PMID: 31397882.

Kho YC, Rhodes LM, Robertson SJ, Su J, Varigos G, Robertson I, Hogan P, Orchard D, Murrell DF. 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. PubMed PMID: 20566927.

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. PubMed PMID: 27611893.

Kiritsi D, Pigors M, Tantcheva-Poor I, Wessel C, Arin MJ, Kohlhase J, Bruckner-Tuderman L, Has C. Epidermolysis bullosa simplex ogna revisited. J Invest Dermatol. 2013;133:270–3. PubMed PMID: 22854623.

Kiritsi D, Tsakiris L, Schauer F. Plectin in skin fragility disorders. Cells. 2021;10:2738. PubMed PMID: 34685719.

Kocher T, Peking P, Klausegger A, Murauer EM, Hofbauer JP, Wally V, Lettner T, Hainzl S, Ablinger M, Bauer JW, Reichelt J, Koller U. Cut and paste: efficient homology-directed repair of a dominant negative KRT14 mutation via CRISPR/Cas9 nickases. Mol Ther. 2017;25:2585–98. PubMed PMID: 28888469.

Koss-Harnes D, Høyheim B, Anton-Lamprecht I, Gjesti A, Jørgensen RS, Jahnsen FL, Olaisen B, Wiche G, Gedde-Dahl T. A site-specific plectin mutation causes dominant epidermolysis bullosa simplex Ogna: two identical de novo mutations. J Invest Dermatol. 2002;118:87–93. PubMed PMID: 11851880.

Kyrova J, Kopeckova L, Buckova H, Mrazova L, Vesely K, Hermanova M, Oslejskova H, Fajkusova L. Epidermolysis bullosa simplex with muscular dystrophy. Review of the literature and a case report. J Dermatol Case Rep. 2016;10:39–48. PubMed PMID: 28400893.

Lara-Corrales I, Arbuckle A, Zarinehbaf S, Pope E. Principles of wound care in patients with epidermolysis bullosa. Pediatr Dermatol. 2010;27:229–37. PubMed PMID: 20403117.

Lee GH, Lekwuttikarn R, Tafoya E, Martin M, Sarin KY, Teng JM. Transcriptomic repositioning analysis identifies mTOR inhibitor as potential therapy for epidermolysis bullosa simplex. J Invest Dermatol. 2022;142:382–9. PubMed PMID: 34536484.

Lee JYW, Liu L, Hsu CK, Aristodemou S, Ozoemena L, Ogboli M, Moss C, Martinez AE, Mellerio JE, McGrath JA. Mutations in KLHL24 add to the molecular heterogeneity of epidermolysis bullosa simplex. J Invest Dermatol. 2017;137:1378–80. PubMed PMID: 28111128.

Levin LE, Shayegan LH, Lucky AW, Hook KP, Bruckner AL, Feinstein JA, Whittier S, Lauren CT, Pope E, Lara-Corrales I, Wiss K, McCuaig CC, Powell J, Eichenfield LF, Levy ML, Diaz L, Glick SA, Paller AS, Price HN, Browning JC, Morel KD. Characterization of wound microbes in epidermolysis bullosa: results from the epidermolysis bullosa clinical characterization and outcomes database. Pediatr Dermatol. 2021;38:119–24. PubMed PMID: 33247481.

Lin Z, Li S, Feng C, Yang S, Wang H, Ma D, Jing Zhang, Gou M, Bu D, Zhang T, Kong X, Wang X, Sarig O, Ren Y, Dai L, Liu H, Zhang Jianguo, Li F, Hu Y, Padalon-Brauch G, Vodo D, Zhou F, Chen T, Deng H, Sprecher E, Yang Y, Tan X. Stabilizing mutations of KLHL24 ubiquitin ligase cause loss of keratin 14 and human skin fragility. Nat Genet. 2016;48:1508–16. PubMed PMID: 27798626.

Liu L, Mellerio JE, Martinez AE, McMillan JR, Aristodemou S, Parsons M, McGrath JA. Mutations in EXPH5 result in autosomal recessive inherited skin fragility. Br J Dermatol. 2014;170:196–9. PubMed PMID: 24443915.

Liu L, Dopping-Hepenstal PJ, Lovell PA, Michael M, Horn H, Fong K, Lai-Cheong JE, Mellerio JE, Parsons M, McGrath JA. Autosomal recessive epidermolysis bullosa simplex due to loss of BPAG1-e expression. J Invest Dermatol. 2012;132:742–4. PubMed PMID: 22113475.

Mariath LM, Santin JT, Frantz JA, Doriqui MJR, Schuler-Faccini L, Kiszewski AE. Genotype-phenotype correlations on epidermolysis bullosa with congenital absence of skin: a comprehensive review. Clin Genet. 2021;99:29–41. PubMed PMID: 32506467.

Marro M, De Smet S, Caldari D, Lambe C, Leclerc-Mercier S, Chiaverini C. Gastrostomy for infants with severe epidermolysis bullosa simplex in neonatal intensive care. Orphanet J Rare Dis. 2021;16:271. PubMed PMID: 34116697.

Martin K, Geuens S, Asche JK, Bodan R, Browne F, Downe A, García García N, Jaega G, Kennedy B, Mauritz PJ, Pérez F, Soon K, Zmazek V, Mayre-Chilton KM. Psychosocial recommendations for the care of children and adults with epidermolysis bullosa and their family: evidence based guidelines. Orphanet J Rare Dis. 2019;14:133. PubMed PMID: 31186066.

Martínez-Santamaría L, Maseda R, De Arriba MDC, Membrilla JA, Sigüenza AI, Mascías J, García M, Quintana L, Esteban-Rodríguez I, Hernández-Fernández CP, Illera N, Duarte B, Guerrero-Aspizúa S, Woodley DT, Del Río M, De Lucas R, Larcher F, Escámez MJ. Evaluation of systemic gentamicin as translational readthrough therapy for a patient with epidermolysis bullosa simplex with muscular dystrophy owing to PLEC1 pathogenic nonsense variants. JAMA Dermatol. 2022;158:439–43. PubMed PMID: 35234827.

McGrath JA, McMillan JR, Shemanko CS, Runswick SK, Leigh IM, Lane EB, Garrod DR, Eady RAJ. Mutations in the plakophilin 1 gene result in ectodermal dysplasia/skin fragility syndrome. Nat Genet. 1997;17:240. PubMed PMID: 9326952.

McGrath JA, Mellerio JE. Ectodermal dysplasia-skin fragility syndrome. Dermatol Clin. 2010;28:125–9. PubMed PMID: 19945625.

McGrath JA, Stone KL, Begum R, Simpson MA, Dopping-Hepenstal PJ, Liu L, McMillan JR, South AP, Pourreyron C, McLean WHI, Martinez AE, Mellerio JE, Parsons M. Germline mutation in EXPH5 implicates the Rab27B effector protein Slac2-b in inherited skin fragility. Am J Hum Genet. 2012;91:1115–21. PubMed PMID: 23176819.

Moog U, De Die-Smulders CEM, Scheffer H, Van Der Vlies P, Henquet CJM, Jonkman MF. Epidermolysis bullosa simplex with mottled pigmentation: Clinical aspects and confirmation of the P24L mutation in the KRT5 gene in further patients. Am J Med Genet. 1999;86:376–9. PubMed PMID: 10494094.

Müller FB, Küster W, Wodecki K, Almeida H, Bruckner-Tuderman L, Krieg T, Korge BP, Arin MJ. Novel and recurrent mutations in keratin KRT5 and KRT14 genes in epidermolysis bullosa simplex: implications for disease phenotype and keratin filament assembly. Hum Mutat. 2006;27:719–20. PubMed PMID: 16786515.

Nagao-Watanabe M, Fukao T, Matsui E, Kaneko H, Inoue R, Kawatomo N, Kasahara K, Nagai M, Ichiki Y, Kitajima Y, Kondo N. Identification of somatic and germline mosaicism for a keratin 5 mutation in epidermolysis bullosa simplex in a family of which the proband was previously regarded as a sporadic case. Clin Genet. 2004;66:236–8. PubMed PMID: 15324323.

Natsuga K. Plectin-related skin diseases. J Dermatol Sci. 2015;77:139–45. PubMed PMID: 25530118.

Natsuga K, Nishie W, Shinkuma S, Arita K, Nakamura H, Ohyama M, Osaka H, Kambara T, Hirako Y, Shimizu H. Plectin deficiency leads to both muscular dystrophy and pyloric atresia in epidermolysis bullosa simplex. Hum Mutat. 2010;31:E1687–98. PubMed PMID: 20665883.

Neufeld-Kaiser W, Sybert VP. In cyproheptadine effective in the treatment of subjects with epidermolysis bullosa simplex-Dowling-Meara? Arch Dermatol. 1997;133:251–2. PubMed PMID: 9041851.

Padalon-Brauch G, Amitai D, Ben, Vodo D, Harel A, Sarig O, Sprecher E, Mashiah J. Digenic inheritance in epidermolysis bullosa simplex. J Invest Dermatol. 2012;132:2852–4. PubMed PMID: 22832485.

Pascucci M, Posteraro P, Pedicelli C, Provini A, Auricchio L, Paradisi M, Castiglia D. Epidermolysis bullosa simplex with mottled pigmentation due to de novo P25L mutation in keratin 5 in an Italian patient. Eur J Dermatol. 2006;16:620–2. PubMed PMID: 17229601.

Peking P, Breitenbach JS, Ablinger M, Muss WH, Poetschke FJ, Kocher T, Koller U, Hainzl S, Kitzmueller S, Bauer JW, Reichelt J, Lettner T, Wally V. An ex vivo RNA trans-splicing strategy to correct human generalized severe epidermolysis bullosa simplex. Br J Dermatol. 2019;180:141–8. PubMed PMID: 30099737.

Petek LM, Fleckman P, Miller DG. Efficient KRT14 targeting and functional characterization of transplanted human keratinocytes for the treatment of epidermolysis bullosa simplex. Mol Ther. 2010;18:1624–32. PubMed PMID: 20571545.

Petersen BW, Arbuckle HA, Berman S. Effectiveness of saltwater baths in the treatment of epidermolysis bullosa. Pediatr Dermatol. 2015;32:60–3. PubMed PMID: 25644039.

Petrof G, Papanikolaou M, Martinez AE, Mellerio JE, McGrath JA, Bardhan A, Harper N, Heagerty A, Ogboli M, Chiswell C, Moss C. The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. Br J Dermatol. 2022;186:843–8. PubMed PMID: 34927719.

Pfendner EG, Sadowski SG, Uitto J. Epidermolysis bullosa simplex: Recurrent and de novo mutations in the KRT5 and KRT14 genes, phenotype/genotype correlations, and implications for genetic counseling and prenatal diagnosis. J Invest Dermatol. 2005;125:239–43. PubMed PMID: 16098032.

Pfendner E, Uitto J, Fine JD. Epidermolysis bullosa carrier frequencies in the US population. J Invest Dermatol. 2001;116:483–4. PubMed PMID: 11231335.

Pigors M, Kiritsi D, Krümpelmann S, Wagner N, He Y, Podda M, Kohlhase J, Hausser I, Bruckner-Tuderman L, Has C. Lack of plakoglobin leads to lethal congenital epidermolysis bullosa: A novel clinico-genetic entity. Hum Mol Genet. 2011;20:1811–9. PubMed PMID: 21320868.

Pope E, Lara-Corrales I, Mellerio J, Martinez A, Schultz G, Burrell R, Goodman L, Coutts P, Wagner J, Allen U, Sibbald G. A consensus approach to wound care in epidermolysis bullosa. J Am Acad Dermatol. 2012;67:904–17. PubMed PMID: 22387035.

Prodinger C, Klausegger A, Diem A, Bauer JW, Laimer M. Laryngo-onycho-cutaneous (-like) syndrome due to mutated Plectin. J Eur Acad Dermatol Venereol. 2017;31:e373–4. PubMed PMID: 28213897.

Reimer-Taschenbrecker A, Hess M, Hotz A, Fischer J, Bruckner-Tuderman L, Has C. Plantar involvement correlates with obesity, pain and impaired mobility in epidermolysis bullosa simplex: a retrospective cohort study. J Eur Acad Dermatol Venereol. 2021;35:2097–104. PubMed PMID: 33960018.

Rotemberg V, Garzon M, Lauren C, Iglesias A, Brachio SS, Aggarwal V, Stong N, Goldstein DB, Diacovo T. A novel mutation in junctional plakoglobin causing lethal congenital epidermolysis bullosa. J Pediatr. 2017;191:266–269.e1. PubMed PMID: 29173316.

Rugg EL, Leigh IM. The keratins and their disorders. Am J Med Genet C Semin Med Genet. 2004;131:4–11. PubMed PMID: 15452838.

Salera S, Tadini G, Rossetti D, Grassi FS, Marchisio P, Agostoni C, Giavoli C, Rodari G, Guez S. A nutrition-based approach to epidermolysis bullosa: causes, assessments, requirements and management. Clin Nutr. 2020;39:343–52. PubMed PMID: 30857908.

Schara U, Tücke J, Mortier W, Nüßlein T, Rouan F, Pfendner E, Zillikens D, Bruckner-Tuderman L, Uitto J, Wiche G, Schröder R. Severe mucous membrane involvement in epidermolysis bullosa simplex with muscular dystrophy due to a novel plectin gene mutation. Eur J Pediatr. 2004;163:218–22. PubMed PMID: 14963703.

Schwieger-Briel A, Fuentes I, Castiglia D, Barbato A, Greutmann M, Leppert J, Duchatelet S, Hovnanian A, Burattini S, Yubero MJ, Ibañez-Arenas R, Rebolledo-Jaramillo B, Gräni C, Ott H, Theiler M, Weibel L, Paller AS, Zambruno G, Fischer J, Palisson F, Has C. Epidermolysis bullosa simplex with KLHL24 mutations is associated with dilated cardiomyopathy. J Invest Dermatol. 2019;139:244–9. PubMed PMID: 30120936.

Sehgal VN, Sanyal RK. Vitamin E therapy in dystrophic epidermolysis bullosa. Arch Dermatol. 1972;105:460. PubMed PMID: 5012154.

Shurman D, Losi-Sasaki J, Grimwood R, Kivirikko S, Tichy E, Uitto J, Richard G. Epidermolysis bullosa simplex with mottled pigmentation: mutation analysis in the first reported Hispanic pedigree with the largest single generation of affected individuals to date. Eur J Dermatol. 2006;16:132–5. PubMed PMID: 16581562.

Smith FJD, Morley SM, McLean WHI. Novel mechanism of revertant mosaicism in Dowling - Meara epidermolysis bullosa simplex. J Invest Dermatol. 2004;122:73–7. PubMed PMID: 14962092.

So JY, Fulchand S, Wong CY, Li S, Nazaroff J, Gorell ES, de Souza MP, Murrell D, Teng JM, Chiou AS, Tang JY. A global, cross-sectional survey of patient-reported outcomes, disease burden, and quality of life in epidermolysis bullosa simplex. Orphanet J Rare Dis. 2022;17:270. PubMed PMID: 35841105.

Stenson PD, Mort M, Ball E V., Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Stephens K, Ehrlich P, Weaver M, Le R, Spencer A, Sybert VP. Primers for exon-specific amplification of the KRT5 gene: Identification of novel and recurrent mutations in epidermolysis bullosa simplex patients. J Invest Dermatol. 1997;108:349–53. PubMed PMID: 9036937.

Swartling C, Karlqvist M, Hymnelius K, Weis J, Vahlquist A. Botulinum toxin in the treatment of sweat-worsened foot problems in patients with epidermolysis bullosa simplex and pachyonychia congenita. Br J Dermatol. 2010;163:1072–6. PubMed PMID: 20618323.

Tabolli S, Sampogna F, Di Pietro C, Paradisi A, Uras C, Zotti P, Castiglia D, Zambruno G, Abeni D. Quality of life in patients with epidermolysis bullosa. Br J Dermatol. 2009;161:869–77. PubMed PMID: 19624546.

Takeichi T, Nanda A, Liu L, Aristodemou S, McMillan JR, Sugiura K, Akiyama M, Al-Ajmi H, Simpson MA, McGrath JA. Founder mutation in dystonin-e underlying autosomal recessive epidermolysis bullosa simplex in Kuwait. Br J Dermatol. 2015;172:527–31. PubMed PMID: 25059916.

Tryon RK, Tolar J, Preusser SM, Riddle MJ, Keene DR, Bower M, Thyagarajan B, Ebens CL. A homozygous frameshift variant in the KRT5 gene is compatible with life and results in severe recessive epidermolysis bullosa simplex. JAAD Case Reports. 2019;5:576–9. PubMed PMID: 31312705.

Turcan I, Pasmooij AMG, Van Den Akker PC, Lemmink H, Sinke RJ, Jonkman MF. Association of epidermolysis bullosa simplex with mottled pigmentation and EXPH5 mutations. JAMA Dermatol. 2016;152:1137–41. PubMed PMID: 27384765.

Vahidnezhad H, Youssefian L, Daneshpazhooh M, Mahmoudi H, Kariminejad A, Fischer J, Christiansen J, Schneider H, Guy A, Liu L, McGrath JA, Has C, Uitto J. Biallelic KRT5 mutations in autosomal recessive epidermolysis bullosa simplex, including a complete human keratin 5 "knock-out.". Matrix Biol. 2019a;83:48–59. PubMed PMID: 31302245.

Vahidnezhad H, Youssefian L, Saeidian AH, Mahmoudi H, Touati A, Abiri M, Kajbafzadeh AM, Aristodemou S, Liu L, McGrath JA, Ertel A, Londin E, Kariminejad A, Zeinali S, Fortina P, Uitto J. Recessive mutation in tetraspanin CD151 causes Kindler syndrome-like epidermolysis bullosa with multi-systemic manifestations including nephropathy. Matrix Biol. 2018;66:22–33. PubMed PMID: 29138120.

Vahidnezhad H, Youssefian L, Saeidian AH, Touati A, Pajouhanfar S, Baghdadi T, Shadmehri AA, Giunta C, Kraenzlin M, Syx D, Malfait F, Has C, Lwin SM, Karamzadeh R, Liu L, Guy A, Hamid M, Kariminejad A, Zeinali S, McGrath JA, Uitto J. Mutations in PLOD3, encoding lysyl hydroxylase 3, cause a complex connective tissue disorder including recessive dystrophic epidermolysis bullosa-like blistering phenotype with abnormal anchoring fibrils and type VII collagen deficiency. Matrix Biol. 2019b;81:91–106. PubMed PMID: 30463024.

Vahidnezhad H, Youssefian L, Saeidian AH, Uitto J. Phenotypic spectrum of epidermolysis bullosa: the paradigm of syndromic versus non-syndromic skin fragility disorders. J Invest Dermatol. 2019c;139:522–7. PubMed PMID: 30393082.

Villa CR, Ryan TD, Collins JJ, Taylor MD, Lucky AW, Jefferies JL. Left ventricular non-compaction cardiomyopathy associated with epidermolysis bullosa simplex with muscular dystrophy and PLEC1 mutation. Neuromuscul Disord. 2015;25:165–8. PubMed PMID: 25454730.

Walker GD, Woody M, Orrin E, Mellerio JE, Levy ML. Epidermolysis bullosa with pyloric atresia and significant urologic involvement. Pediatr Dermatol. 2017;34:e61–4. PubMed PMID: 27813154.

Wally V, Hovnanian A, Ly J, Buckova H, Brunner V, Lettner T, Ablinger M, Felder TK, Hofbauer P, Wolkersdorfer M, Lagler FB, Hitzl W, Laimer M, Kitzmüller S, Diem A, Bauer JW. Diacerein orphan drug development for epidermolysis bullosa simplex: a phase 2/3 randomized, placebo-controlled, double-blind clinical trial. J Am Acad Dermatol. 2018;78:892–901.e7. PubMed PMID: 29410318.

Wally V, Klausegger A, Koller U, Lochmüller H, Krause S, Wiche G, Mitchell LG, Hintner H, Bauer JW. 5′ trans-splicing repair of the PLEC1 gene. J Invest Dermatol. 2008;128:568–74. PubMed PMID: 17989727.

Weiner M, Stein A, Cash S, De Leoz J, Fine JD. Tetracycline and epidermolysis bullosa simplex: A double-blind, placebo-controlled, crossover randomized clinical trial. Br J Dermatol. 2004;150:613–4. PubMed PMID: 15030362.

Werner NS, Windoffer R, Strnad P, Grund C, Leube RE, Magin TM. epidermolysis bullosa simplex-type mutations alter the dynamics of the keratin cytoskeleton and reveal a contribution of actin to the transport of keratin subunits. Mol Biol Cell. 2004;15:990–1002. PubMed PMID: 14668478.

Wertheim-Tysarowska K, Ołdak M, Giza A, Kutkowska-Kaźmierczak A, Sota J, Przybylska D, Woźniak K, Śniegórska D, Niepokój K, Sobczyńska-Tomaszewska A, Rygiel AM, Płoski R, Bal J, Kowalewski C. 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. PubMed PMID: 26432462.

Williams EF, Gannon K, Soon K. The experiences of young people with epidermolysis bullosa simplex: a qualitative study. J Health Psychol. 2011;16:701–10. PubMed PMID: 21441362.

Winter L, Türk M, Harter PN, Mittelbronn M, Kornblum C, Norwood F, Jungbluth H, Thiel CT, Schlötzer-Schrehardt U, Schröder R. Downstream effects of plectin mutations in epidermolysis bullosa simplex with muscular dystrophy. Acta Neuropathol Commun. 2016;4:44. PubMed PMID: 27121971.

Yalici-Armagan B, Kabacam S, Taskiran ZE, Gököz Ö, Utine GE, Ersoy-Evans S. A novel mutation of keratin 5 in epidermolysis bullosa simplex with migratory circinate erythema. Pediatr Dermatol. 2020;37:358–61. PubMed PMID: 31965605.

Yenamandra VK, van den Akker PC, Lemmink HH, Jan SZ, Diercks GFH, Vermeer M, van den Berg MP, van der Meer P, Pasmooij AMG, Sinke RJ, Jonkman MF, Bolling MC. Cardiomyopathy in patients with epidermolysis bullosa simplex with mutations in KLHL24. Br J Dermatol. 2018;179:1181–3. PubMed PMID: 29779254.

Yerlett N. Epidermolysis bullosa and rare skin disorders. In: Shaw V, ed. *Clinical Paediatric Dietetics*. 5th ed. Oxford: Wiley-Blackwell; 2020:438-55.

Yiasemides E, Trisnowati N, Su J, Dang N, Klingberg S, Marr P, Melbourne W, Tran K, Chow CW, Orchard D, Varigos G, Murrell DF. Clinical heterogeneity in recessive epidermolysis bullosa due to mutations in the keratin 14 gene, KRT14. Clin Exp Dermatol. 2008;33:689–97. PubMed PMID: 18713255.

Yu Y, Mi Z, Fu X, Wang Z, Sun L, Liu H, Zhang F. Digenic inheritance of KRT5 and KRT14 mutations in a family with epidermolysis bullosa simplex. Australas J Dermatol. 2020;61:e267–9. PubMed PMID: 31919841.

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