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Junctional Epidermolysis Bullosa

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Summary

Clinical characteristics

Junctional epidermolysis bullosa (JEB) is characterized by fragility of the skin and mucous membranes, manifest by blistering with little or no trauma. 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. Broad classification of JEB includes JEB generalized severe and JEB generalized intermediate. In JEB generalized severe, blisters are present at birth or become apparent in the neonatal period. Congenital malformations of the urinary tract and bladder may also occur. In JEB generalized intermediate, the phenotype may be mild with blistering localized to hands, feet, knees, and elbows with or without renal or ureteral involvement. Some individuals never blister after the newborn period. Additional features shared by JEB and the other major forms of epidermolysis bullosa (EB) include congenital localized absence of skin (aplasia cutis congenita), milia, nail dystrophy, scarring alopecia, hypotrichosis, pseudosyndactyly, and other contractures.

Diagnosis/testing

The diagnosis of JEB is established in a proband with characteristic clinical findings by molecular genetic testing that identifies biallelic pathogenic variants in one of the genes associated with JEB: *COL17A1*, *ITGB4*, *LAMA3*, *LAMB3*, or *LAMC2*. Skin biopsy using transmission electron microscopy (TEM) and/or immunofluorescent antibody/antigen mapping can be performed but is no longer the preferred method of diagnosis.

Management

Treatment of manifestations: Lance and drain new blisters and dress with three layers (primary: non-adherent; secondary: for stability and protection; third: elastic properties to ensure integrity); protect skin from shearing forces; teach caretakers proper handling of infants and children; treatment of granulation tissue with high-potency topical steroids, silver nitrate, electrocautery, or autologous skin grafts; antibiotics and antiseptics as

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needed for wound care and infection; dilation of esophageal strictures (rare); tracheostomy if appropriate; gastrostomy tube if needed; standard treatment of gastroesophageal disease; appropriate footwear and physical therapy to promote/preserve ambulation; psychosocial support, including social services and psychological counseling; appropriate management of chronic pain; regular dental care; treatment of urologic and renal disease using standard treatments.

Prevention of secondary complications: Attention to fluid and electrolyte balance in severely affected infants (especially sodium levels); nutritional support including feeding gastrostomy when necessary; calcium, vitamin D, zinc, and iron supplements.

Surveillance: Annual screening for iron-deficiency anemia, zinc deficiency, vitamin D deficiency; periodic bone mineral density scanning for osteopenia and/or osteoporosis; periodic echocardiograms to evaluate for dilated cardiomyopathy; in the second decade of life, surveillance for squamous cell carcinoma is appropriate.

Agents/circumstances to avoid: Ordinary medical tape or Band-Aids®, poorly fitting or coarse-textured clothing and footwear, activities that can traumatize the skin (e.g., hiking, mountain biking, contact sports).

Pregnancy management: Consider cesarean section delivery to reduce trauma to the skin of an affected fetus.

Genetic counseling

JEB is inherited in an autosomal recessive manner. The parents of an affected child are usually obligate heterozygotes (i.e., carriers). Because germline mosaicism and uniparental isodisomy have been reported, carrier status of parents needs to be confirmed with molecular genetic testing. At conception, each sib of an affected individual whose parents are both carriers has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. The offspring of an individual with autosomal recessive JEB are obligate heterozygotes (carriers) for a pathogenic variant. Carrier testing for family members at increased risk and prenatal testing for a pregnancy at increased risk are possible if both pathogenic variants have been identified in the family.

Diagnosis

Suggestive Findings

Junctional epidermolysis bullosa (JEB) **should be suspected** in individuals who have fragility of the skin with:

- Blistering with little or no trauma. Blistering may be mild or severe; however, blisters generally heal with no significant scarring.
- Significant oral and mucous membrane involvement

Note: Blistering may be severe and granulation tissue can form on the skin around the oral and nasal cavities, fingers and toes, and internally in and around the upper airway and the trachea (see Figure 1, Figure 2).

Establishing the Diagnosis

The diagnosis of JEB **is established** in a proband with one or both of the following:

- Identification by molecular genetic testing of biallelic pathogenic variants in one of the genes listed in Table 1
- Skin biopsy using transmission electron microscopy (TEM) and/or immunofluorescent antibody/antigen mapping (see Skin Biopsy)

Note: Genetic testing is the preferred diagnostic method. Skin biopsy for diagnostic purposes is no longer routinely performed unless molecular genetic testing is not conclusive.

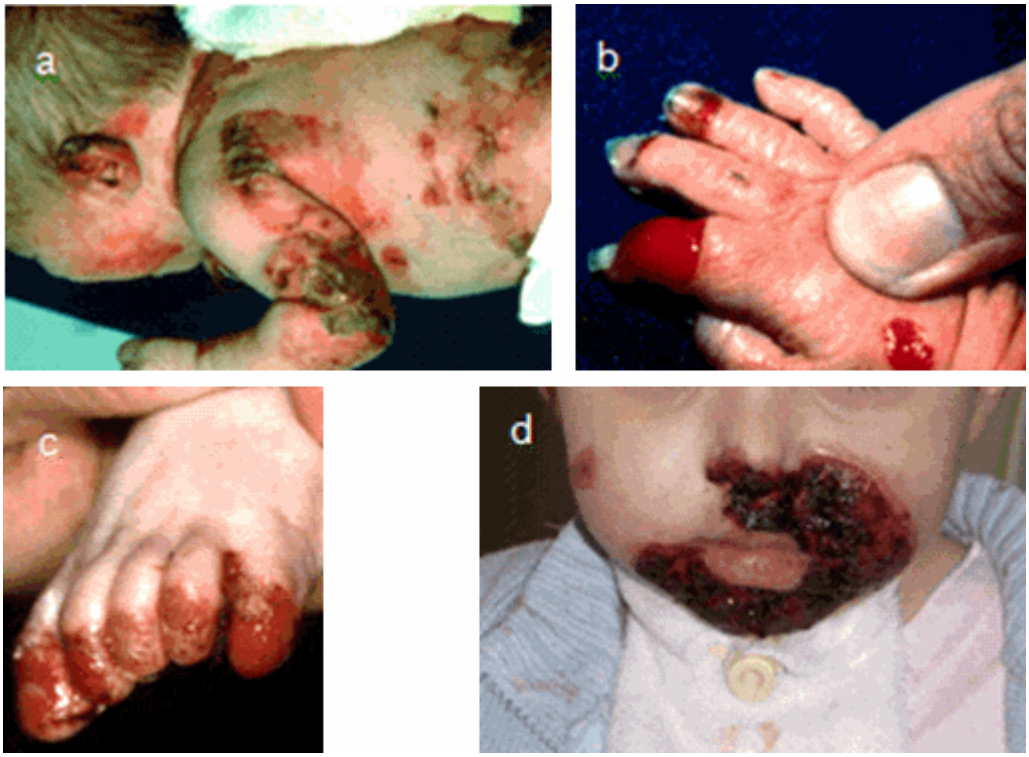

Figure 1. JEB generalized severe

a. Extensive widespread blistering and granulation tissue on ear

b. Hand of a child showing aplasia cutis congenita

c. Foot of an affected child

d. Exuberant perioral granulation tissue and tracheostomy in a child

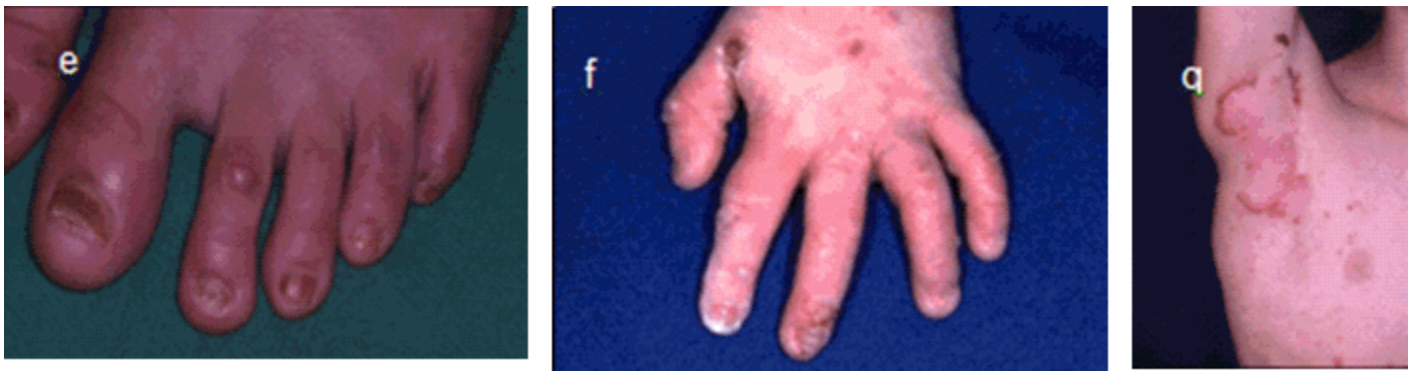

Figure 2. JEB generalized intermediate

e. Minor nail dystrophy in an older child

f. Multiple blisters on the hands of an active toddler

g. Non-scarring superficial axillary erosions

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel, targeted molecular genetic testing) and **comprehensive genomic testing** (exome sequencing, genome sequencing, exome array) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of junctional epidermolysis bullosa is broad, 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 fragile skin and blistering, or presenting in the neonatal period before significant sequelae such as exuberant granulomatous tissue has developed, are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of junctional epidermolysis bullosa, molecular genetic testing approaches can include use of a **multigene panel** or **targeted molecular testing** [Lucky et al 2018].

A junctional epidermolysis bullosa **multigene panel** that includes *COL17A1*, *ITGB4*, *LAMB3*, *LAMA3*, *LAMC2*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory 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) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by skin fragility and blistering, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

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 Junctional Epidermolysis Bullosa

Gene [1, 2]	Proportion of JEB Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
COL17A1	12%	>98%	<2% [6]
ITGB4	<1% [7]	~100%	<1%
LAMA3	9%	>98% [8]	<1% [6]
LAMB3	70%	>98%	<2% [9]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of JEB Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
LAMC2	9%	>98%	<2% [6]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. 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.
5. 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.
6. Pulkkinen et al [1997a], Takizawa et al [2000b], Fassihi et al [2005], Varki et al [2006]
7. Biallelic pathogenic variants in *ITGB4* are a rare cause of JEB [Author, personal communication].
8. Care must be taken to sequence the genomic region of the longest transcript of *LAMA3* (NM_198129.2) rather than one of the shorter transcript variants.
9. Pulkkinen et al [1995], Cserhalmi-Friedman et al [1998], Takizawa et al [2000b], Huber et al [2002], Micheloni et al [2004], Posteraro et al [2004]

Skin Biopsy

Examination of a skin biopsy by (1) transmission electron microscopy (TEM) and/or (2) immunofluorescent antibody/antigen mapping is sometimes performed to establish the diagnosis of JEB.

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.)

Note:

- **For TEM**
  - Specimens must be placed in fixation medium (e.g., gluteraldehyde) as designated by the laboratory performing the test.
  - Formaldehyde-fixed samples cannot be used for electron microscopy.
- **For immunofluorescent antibody/antigen mapping**
  - 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 antigens for the proteins of interest in EB is preferred because both the level of cleavage and the presence or absence of the specific gene products mutated in EB can be assessed.
- **Light microscopy** is inadequate and unacceptable for the accurate diagnosis of any subtypes of EB.

Transmission electron microscopy (TEM) is used to examine the number and morphology of basement membrane zone structures – in particular: the number and morphology of anchoring fibrils; the presence of and morphology of hemidesmosomes, anchoring filaments, and keratin intermediate filaments; and the presence of microvesicles showing the tissue cleavage plane.

Findings on TEM in JEB include the following [Shinkuma et al 2011]:

- **All forms of JEB.** Splitting is seen in the lamina lucida of the basement membrane of the epidermis or just above the basement membrane at the level of the hemidesmosomes in the lowest level of the keratinocytes layer.
- **JEB generalized severe.** Hemidesmosomes are hypoplastic and reduced in number. Anchoring filaments are markedly reduced or absent.
- **JEB generalized intermediate.** Anchoring filaments may be reduced; hemidesmosomes may be reduced or hypoplastic.

Immunofluorescent antibody/antigen mapping. Findings include the following:

- Abnormal or absent staining with antibodies to laminin 332 (aka LAM5) [Aumailley et al 2005] resulting from pathogenic variants in *LAMA3*, *LAMB3*, or *LAMC2* in JEB generalized severe or JEB generalized intermediate
- Abnormal or absent staining with antibodies to collagen XVII in JEB caused by pathogenic variants in *COL17A1*

Normal staining for other antigens (e.g., collagen VII, keratins 5 and 14) confirms the diagnosis of JEB.

Note: Especially in milder forms of EB, indirect immunofluorescent studies are often not sufficient to make the diagnosis because near-normal antigen levels are detected and no cleavage plane is observed. In these cases electron microscopic examination of the skin biopsy must be performed.

Clinical Characteristics

Clinical Description

Junctional epidermolysis bullosa (JEB) is characterized by fragility of the skin and mucous membranes, manifest by blistering with little or no trauma. Broad classification of JEB includes JEB generalized severe and JEB generalized intermediate and is based on severity and survival past the first years of life [Yuen et al 2013, Kelly-Mancuso et al 2014].

JEB generalized severe (previously called JEB Herlitz). Severe blistering is present at birth or becomes apparent in the neonatal period and may lead to large regions of affected skin with significant granulation tissue. Granulation tissue characteristically appears around the nose, mouth, ears, and tips of the fingers and toes as well as in areas subject to friction such as the buttocks and the back of the head. Persistent plaques on the face can be challenging to treat. The granulation tissue manifests as large eroded patches and plaques often with serpiginous or annular borders that are friable and bleed easily and profusely. There can be extensive loss of blood, fluid, and protein. Such erosions are often life threatening because they make these infants susceptible to electrolyte imbalance and infection including sepsis and sudden death. If the infant survives, blistering may continue throughout life, generally without scarring unless there has been severe secondary infection. Scarring pseudosyndactyly of the hands and feet fusing the digits into "mitten" hands and feet with severe loss of function has been seen in some of the individuals with JEB generalized severe who survive [Fine et al 1999]. In one series, 73% of 71 children born in a five-year period died at an average age of five months [Kelly-Mancuso et al 2014].

In addition to cutaneous involvement, mucosal involvement of the mouth, upper respiratory tract, esophagus, bladder, urethra, and corneas can be seen. Amelogenesis imperfecta with pitting of tooth enamel is common. Accumulation of granulation tissue surrounding the airway is usually subglottic and the first manifestation is a weak, hoarse cry. Eventually, compression and obstruction of the airway result in stridor and respiratory distress. Unless tracheostomy is performed, many children succumb from respiratory complications. However, managing a tracheostomy in a child with such fragile skin is difficult [Ida et al 2012].

Bladder and urethral epithelial involvement can cause dysuria, urinary retention, urinary tract infections, and eventual renal compromise. Renal and ureteral anomalies that can be seen include dysplastic/multicystic kidney, hydronephrosis/hydroureter, acute renal tubular necrosis, obstructive uropathy, ureterocele, duplicated renal collecting system, and absent bladder [Puvabanditsin et al 1997, Kambham et al 2000, Nakano et al 2000, Wallerstein et al 2000, Fine et al 2004, Varki et al 2006, Pfendner et al 2007].

Esophageal narrowing has been reported, but is less common than in children with autosomal recessive dystrophic EB.

Secondary complications common in JEB generalized severe include malnutrition and growth retardation, anemia, alopecia, cutaneous infection, sepsis, electrolyte imbalance, osteoporosis [Fewtrell et al 2006], dilated cardiomyopathy, squamous cell carcinoma [Yuen & Jonkman 2011], and dental enamel dysplasia with pitting [Krämer 2010, Stellingsma et al 2011].

Most children with JEB generalized severe do not survive past the first year of life.

JEB generalized intermediate (previously called JEB non-Herlitz) includes a spectrum of less severe clinical phenotypes than JEB generalized severe. The phenotype may be mild with blistering localized to hands, feet, knees, and elbows with or without renal, ureteral, or esophageal involvement; or relatively more widespread including flexural areas and trunk. Some children virtually never blister after the newborn period. The severe granulation tissue and respiratory compromise seen in individuals with JEB generalized severe are rare.

Varying degrees of alopecia and onychodystrophy as well as dental enamel pitting remain hallmarks of this type of JEB.

Additional manifestations of JEB generalized severe and JEB generalized intermediate include:

- Congenital localized absence of skin (aplasia cutis congenita)
- Exuberant granulation tissue
- Nail dystrophy
- Scarring alopecia
- Squamous cell carcinoma in individuals with JEB generalized intermediate [Montaudié et al 2016]
- Pseudosyndactyly and other contractures. Pseudosyndactyly is defined as the partial or complete loss of web spaces between any digits of the hands or feet (rare).
- Milia (rare)
- Scarring (rare)

Genotype-Phenotype Correlations

JEB generalized severe is the result of inactivating pathogenic variants on both alleles, which result in little or no functional protein [Varki et al 2006]. For frameshift variants, the severity may be related to where the stop codon is located and whether any functional (although truncated) protein is formed; the presence of some functional protein appears to be the most important factor in mitigating disease severity [Kiritsi et al 2013].

JEB generalized intermediate generally results from amino acid substitutions and splice-junction variants, although it is difficult to generalize because of the wide phenotypic variability and range of allelic variants that have been identified [Varki et al 2006]. In addition, moderation of phenotypes expected to be severe has occurred through in-frame skipping of exons containing nonsense or frameshift variants [McGrath et al 1999, Kowalewski et al 2016].

Nomenclature

Table 2. Junctional Epidermolysis Bullosa Nomenclature

Current Nomenclature			2008 Nomenclature	2013 "Onion Skin" Nomenclature	Other Specific JEB Designations Used in the Past
JEB Subtype		Abbreviation			
Generalized	JEB, generalized severe	JEB-gen sev	Herlitz JEB (H-JEB)	JEB generalized severe, laminin-332 absent, *LAMA3*, *LAMB3*, or *LAMC2* pathogenic variants (specify type)	• Epidermolysis bullosa letalis • Epidermolysis bullosa junctional Herlitz-Pearson • Junctional epidermolysis bullosa mitis
	JEB, generalized intermediate	JEB-gen intermed	Non-Herlitz JEB (NH-JEB)	JEB generalized intermediate, laminin-332 or collagen XVII reduced staining, *LAMA3*, *LAMB3*, *LAMC2*, or *COL17A1* pathogenic (specify type)	• Epidermolysis bullosa, generalized atrophic benign (GABEB) • Epidermolysis bullosa junctionalis, disentis type • Epidermolysis bullosa junctionalis, progressive • Epidermolysis bullosa junctionalis, severe non-lethal
	JEB with pyloric atresia	JEB-PA			
	JEB-late onset	JEB-LO			
	JEB with respiratory and renal involvement	JEB-RR			
Localized	JEB, localized	JEB-loc			
	JEB, inversa	JEB-inv; JEB-I			
	JEB-LOC syndrome				

Adapted from Fine et al [2014]
JEB = junctional epidermolysis bullosa

Prevalence

According to the National EB Registry, prevalence of all types of JEB is 0.44 per million in the US population [Fine et al 1999]. Recent data estimate the incidence of JEB at between 3.59 and 6.7 per million per year with a 73% mortality rate [Kelly-Mancuso et al 2014, Hammersen et al 2016].

- The prevalence of JEB generalized severe is estimated at 0.4 per million but may be underrepresented. JEB generalized severe incidence is also very low (0.41 per million), but is probably underestimated: many individuals with JEB generalized severe go unreported because infants succumb to the disease in the neonatal period (a mortality rate of 73% in infancy has been reported) [Kelly-Mancuso et al 2014].
- JEB generalized intermediate incidence is 2.0 per million.
- Carrier risk of all forms of JEB in the US population has been calculated as 1:270 [Author, personal communication].
- Carrier risk of JEB generalized severe has been calculated as 1:781 [Nakano et al 2000, Pfendner et al 2001].

Genetically Related (Allelic) Disorders

Allelic disorders with phenotypic characteristics similar to JEB generalized intermediate:

- ***LAMA3.*** A related disorder, laryngoonychocutaneous syndrome (LOCS or Shabbir syndrome; OMIM 245660), is described in Punjabi Indians and individuals of Iranian descent. LOCS has many phenotypic characteristics similar to JEB generalized severe. Skin fragility manifests as mild blistering and erosions of the hands and face that spread to other parts of the body and heal with crusted lesions. Neonates may have a hoarse cry and later laryngeal abnormalities and growths, conjunctival disease, abnormal nails, and hypoplastic dental enamel. Eventually, conjunctival disease may cause blindness and laryngeal disease may cause life-threatening airway obstruction requiring tracheostomy [Cohn & Murrell 2010]. Two *LAMA3* pathogenic variants, c.151dupG and Gln57Ter in exon 39 on one of three *LAMA3* isoforms, have been identified as causative [McLean et al 2003, Barzegar et al 2013]. Inheritance is autosomal recessive.

  Diagnosis of LOCS may be complicated by the lack of a definitive cleavage plane on TEM and reduced but not absent laminin 5 staining by immunofluorescence for the basement membrane proteins. Sequence analysis of all 76 exons of *LAMA3*, which encodes all three isoforms, is necessary to provide a definitive diagnosis, especially in neonates.

- ***ITGB4.*** Biallelic pathogenic variants in *ITGB4* are more commonly associated with epidermolysis bullosa with pyloric atresia (EB-PA). More than 100 pathogenic variants spanning all of *ITGB4* have been described in EB-PA. Pathogenic variants that cause premature termination codons on both alleles result in the most severe phenotypes, which are frequently lethal in the neonatal period. EB-PA is characterized by fragility of the skin and mucous membranes, manifested by blistering with little or no trauma; congenital pyloric atresia; and ureteral and renal anomalies (dysplastic/multicystic kidney, hydronephrosis/hydroureter, ureterocele, duplicated renal collecting system, absent bladder). Biallelic pathogenic variants in *ITGB4* rarely cause **epidermolysis** bullosa simplex (EBS) or pyloric atresia with desquamative enteropathy and no skin disease [Salvestrini et al 2008].

Other allelic disorders (not in the differential diagnosis of JEB):

- ***COL17A1.*** Pathogenic variants in *COL17A1* may also be associated with an epidermal keratinocyte cleavage plane usually associated with epidermolysis bullosa simplex.
- ***LAMB3* and *LAMA3*** pathogenic variants are associated with hypoplastic amelogenesis imperfecta [Yuen et al 2012, Kim et al 2013, Poulter et al 2014, Lee et al 2015, Wang et al 2015, Gostyńska et al 2016, Du et al 2018].

LAMC2. No phenotypes other than JEB are known to be associated with pathogenic variants in *LAMC2*.

Differential Diagnosis

Epidermolysis bullosa (EB). According to the 2014 classification system, the four major types of EB, caused by pathogenic variants in 18 different genes, are EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (KS) [Fine et al 2014]. 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 and supported by molecular diagnosis.

The four major types of EB share easy fragility of the skin (and mucosa in many cases), manifested by blistering with little or no trauma. 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. The ability to induce blisters with friction (although the amount of friction can vary) and to enlarge blisters by applying pressure to the blister edge is common to all; mucosal and nail involvement and the presence or absence of milia may not be helpful discriminators.

Post-inflammatory changes, such as those seen in generalized severe EBS (EBS-gen sev), are often mistaken for scarring or mottled pigmentation. Scarring can occur in EBS and JEB as a result of infection of erosions or scratching, which further damage the exposed surface. Congenital absence of the skin can be seen in any of the four major types of EB and is not a discriminating diagnostic feature.

Corneal erosions, esophageal strictures, and nail involvement may indicate either DEB or JEB. In milder presentations, scarring (especially of the dorsal hands and feet) suggests DEB. Pseudosyndactyly (mitten deformities) resulting from scarring of the hands and feet in older children and adults usually suggests DEB.

Epidermolysis bullosa simplex (EBS) is characterized by fragility of the skin that results in nonscarring blisters caused by little or no trauma. The four most common clinical subtypes of EBS range from relatively mild blistering of the hands and feet to more generalized blistering, which can be fatal. The majority of individuals with EBS have heterozygous (or rarely biallelic) pathogenic variants in *KRT5* or *KRT14*. More recently, variants in *EXPH5*, *TGM5*, *DST*, *ITGA3*, *KLHL24*, and *CD151* have been described.

- In **EBS, localized** (EBS-loc; previously known as Weber-Cockayne type), blisters are rarely present at birth and may occur on the knees and shins with crawling or on the feet at approximately age 18 months; some individuals manifest the disease in adolescence or early adulthood. Blisters are usually confined to the hands and feet, but can occur anywhere if trauma is significant.
- In **EBS, generalized intermediate** (**EBS-gen intermed**; previously known as Koebner type), blisters may be present at birth or develop within the first few months of life. Involvement is more widespread than in EBS-loc, but generally milder than in EBS-gen sev.
- In **EBS with mottled pigmentation type (EBS-MP)**, skin fragility is evident at birth and clinically indistinguishable from EBS-gen sev; over time, progressive brown pigmentation interspersed with depigmented spots develops on the trunk and extremities, the pigmentation disappearing in adult life. Focal palmar and plantar hyperkeratoses may occur.
- In **EBS, generalized severe** (**EBS-gen sev**; previously known as Dowling-Meara type), onset is usually at birth; severity varies greatly, both within and among families. Widespread and severe blistering and/or multiple grouped clumps of small blisters are typical and hemorrhagic blisters are common. Improvement occurs during mid- to late childhood. Progressive hyperkeratosis of the palms and soles begins in childhood and may be the major complaint of affected individuals in adult life. Nail dystrophy and milia are common. Both hyperpigmentation and hypopigmentation can occur. Mucosal involvement in EBS-gen sev may interfere with feeding. Blistering can be severe enough to result in neonatal or infant death.

EB caused by pathogenic variants in *PLEC* (OMIM 601282) can vary from relatively mild, previously known as the Ogna form, to more severe and sometimes lethal. Up to 8% of EBS may be caused by *PLEC* pathogenic variants. In most individuals with *PLEC* pathogenic variants, the associated phenotypes (i.e., EB with muscular dystrophy [EB-MD], EB with pyloric atresia [EB-PA]) are more complex:

- **EB-MD** (OMIM 226670). More than 50 individuals with EB-MD have been reported worldwide. Blistering occurs early and is generally mild. Muscular dystrophy may not appear until later childhood, adolescence, or adulthood, and can cause immobility and eventually death later in life. Pathogenic variants have been described throughout *PLEC* but seem to cluster in the two long open reading frames containing exons in the 3' end of the gene. Nonsense, missense, insertion/deletion, and splice-junction variants have been described. The mildest phenotypes are usually associated with in-frame insertions or deletions, which do not alter the reading frame of the microRNA (mRNA). Inheritance is autosomal recessive.

- **EB-PA.** In several US and Japanese families, EB-PA is associated with premature termination variants in *PLEC*. EB-PA is more commonly associated with *ITGB4* pathogenic variants, and rarely *ITGA6* pathogenic variants. Although disease course is severe and often lethal in the neonatal period, non-lethal forms have been described. Individuals with pathogenic variants in *ITGB4* or *ITGA6* may also have renal and ureteral anomalies, including dysplastic/multicystic kidney, hydronephrosis/hydroureter, acute renal tubular necrosis, obstructive uropathy, ureterocele, duplicated renal collecting system, and absent bladder. Occasionally, pyloric atresia may be suspected during gestation as a result of oligohydramnios, with or without elevated alpha-fetoprotein and acetylcholinesterase levels, and echogenic material in the amniotic fluid.

Dystrophic EB (DEB). The blister forms below the basement membrane, in the superficial dermis. The basement membrane is attached to the blister roof, resulting in scarring when blisters heal. Pathogenic variants in *COL7A1*, the gene encoding type VII collagen, have been demonstrated in all forms of DEB, both dominant and recessive.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with junctional epidermolysis bullosa (JEB), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Evaluation of the sites of blister formation, including mouth, esophagus, and airway in a child with progressive hoarseness or stridor
- Direct examination of the airway by an experienced otolaryngologist with appropriately small and lubricated instruments to determine the extent of airway compromise so that decisions regarding tracheostomy can be discussed with the family
- Evaluation for gastroesophageal reflux disease, which may cause additional trauma to the upper airway [Ida et al 2012]
- Evaluation for existing osteopenia through skeletal radiographs or DXA (dual-energy x-ray absorptiometry) scan
- Evaluation for cardiomyopathy by clinical evaluation and/or echocardiogram [Fine et all 2008]
- Measurements of hemoglobin and electrolytes to evaluate for anemia and electrolyte imbalance
- Skin bacterial cultures and blood cultures in clinically ill infants to decide appropriate antibiotic treatment
- Consultation with a clinical geneticist and/or genetic counselor

Note: Clinical decision making in children who manifest sign and symptoms of severe JEB with a very poor prognosis has been debated and remains difficult [Hammersen et al 2016].

Treatment of Manifestations

Skin. The skin needs to be protected from shearing forces and caretakers need to learn how to handle the child with EB [Denyer 2010, Pope et al 2012].

New blisters should be lanced and drained to prevent further spread from fluid pressure. In most cases, dressings for blisters involve three layers:

- A primary non-adherent dressing that does not strip the top layers of the epidermis. Tolerance to different primary layers varies. Primary layers include the following:
  - Ordinary Band-Aids®

- Dressings impregnated with an emollient such as petrolatum or topical antiseptic (e.g., Vaseline® gauze, Adaptic®, Xeroform®)
- Nonstick products (e.g., Telfa®, N-terface®)
- Silicone-based products without adhesive (e.g., Mepitel®, Mepilex®)

- A secondary layer that provides stability for the primary layer and adds padding to allow more activity. Rolls of gauze (e.g., Conform® , Flexicon®) are commonly used.
- A tertiary layer that usually has some elastic properties and ensures the integrity of the dressing (e.g., Coban® or elasticized tube gauze of varying diameters such as Band Net® or Tubifast®)

Treatment of granulation tissue can be attempted with high-potency topical steroids, silver nitrate, electrocautery, or autologous skin grafts.

Other. The most common secondary complication in individuals with JEB is infection. In addition to wound care, treatment of chronic infection of wounds is a challenge. Many affected individuals become infected with resistant bacteria, most often methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. Both antibiotics and antiseptics need to be employed.

Esophageal strictures and webs can be dilated repeatedly to improve swallowing [Azizkhan et al 2007].

A hoarse cry in an infant should alert to the possibility of airway obstruction with granulation tissue or other upper airway abnormalities. Decisions about tracheostomy should involve the family and take into consideration the medical condition of the infant. Because of the poor prognosis and severe pain and discomfort experienced by these infants, discussions with the family and a hospital ethics committee often help to determine the type of intervention and comfort care to provide [Yan et al 2007, Ida et al 2012].

Gastroesophageal reflux disease, when present, should be treated as in the general population.

Some children have delays or difficulty walking because of blistering and hyperkeratosis. Appropriate footwear and physical therapy are essential to preserve ambulation.

Psychosocial support, including social services and psychological counseling, is essential [Lucky et al 2007].

Pain management becomes an important part of daily care [Goldschneider et al 2014]. In those with difficult-to-control pain, referral to a pain management specialist can be considered.

Dental care is necessary because of inherent enamel abnormalities [Kirkham et al 2000, Krämer et al 2012].

Urologic and renal problems may be serious in this population [Kajbafzadeh et al 2010]. For those affected individuals who survive, referral to a urologist may be considered.

Prevention of Secondary Complications

The following are indicated:

- Management of fluid and electrolyte deficiencies in the neonatal period and in infants with widespread disease
- Nutritional support including a feeding gastrostomy tube for infants and children with inadequate caloric intake and failure to thrive
- Calcium and vitamin D replacement for osteopenia and osteoporosis
- Zinc supplementation for wound healing
- Treatment of iron-deficiency anemia with oral or intravenous iron infusions and red blood cell transfusions

Surveillance

Surveillance includes the following:

- Annual complete blood counts and measurement of serum iron concentration to screen for iron-deficiency anemia
- Annual measurement of serum zinc concentration to screen for zinc deficiency
- Annual measurement of serum vitamin D
- Screening with bone mineral density scanning may detect early osteopenia and/or osteoporosis. No guidelines have been established regarding the age at which this should be initiated.
- Screening for dilated cardiomyopathy with periodic echocardiograms [Lara-Corrales et al 2010]
- Skin examination starting in the second decade of life for wounds that do not heal, have exuberant scar tissue, or otherwise look abnormal to screen for squamous cell carcinoma. Frequent biopsies of suspicious lesions followed by local excision may be necessary.

Agents/Circumstances to Avoid

Most persons with JEB cannot use ordinary medical tape or Band-Aids®. Silicone-based products provide a good substitute for tape.

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

Activities such as hiking, mountain biking, and contact sports traumatize the skin; affected individuals who are determined to participate in such activities should be encouraged to find creative ways to protect their skin.

Evaluation of Relatives at Risk

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

Pregnancy Management

Cesarean section may be recommended to reduce trauma to the skin of an affected fetus during delivery.

Therapies Under Investigation

Several approaches to gene therapy for JEB, focused on retroviral modification of in vitro epidermal cells, have been proposed [Robbins et al 2001, Ortiz-Urda et al 2003]. One successful clinical trial has been conducted using transplantation of sheets of genetically modified epidermal stem cells in one affected individual with biallelic *LAMB3* pathogenic variants [Mavilio et al 2006, Di Nunzio et al 2008, De Rosa et al 2013]. Animal models include intra-amniotic prenatal laminin 332 delivery in mouse [Mühle et al 2006, Endo et al 2012] and a spontaneous form of JEB in dog [Capt et al 2005, Spirito et al 2006].

The use of a variety of viral vectors, including AAV [Melo et al 2014], lentivirus [Endo et al 2012], and retroviruses [Mavilio et al 2006, De Rosa et al 2013], is being explored to correct the pathogenic variants in cells cultured from individuals with JEB in preparation for transplantation back onto severely affected sites, and shows promise for future clinical trials. In an expedited trial in a single individual, retroviral mediated correction of autologous skin keratinocytes transplanted back onto affected sites also led to stem cell correction and the formation of a self-renewing keratinocyte population and replacement of mutated keratinocytes, leading to whole-body correction of the JEB phenotype [Hirsch et al 2017].

Natural gene therapy is being investigated using autologous revertant cells cultured from patches of non-blistering skin [Gostyński et al 2014], and the pluripotent stem cells that can be generated from these revertant cells [Umegaki-Arao et al 2014].

The knockout mouse model for all JEB-related genes should facilitate the development of these therapeutic approaches [Jiang & Uitto 2005, Bubier et al 2010, Hammersen et al 2015]. Large animal models, such as dog and horse, have also been described [Nagata et al 1997, Spirito et al 2002, Capt et al 2005, Spirito et al 2006, Pertica et al 2010]. Animal models that have been used to study EB were reviewed in Natsuga et al [2010].

Induced pleuripotent stem cells (IPS) are being studied in several laboratories around the world to address the treatment of JEB and other types of EB [Osborn et al 2013, Tolar et al 2013].

Protein replacement therapy with LAMB3 has been studied in vitro [Igoucheva et al 2008] with promising results.

The use of gentamicin as a chemical agent to induce read-through of pathogenic premature termination codons in keratinocytes containing expression vectors with various nonsense variants has also been explored and has shown promising results in cell cultures, but has not yet been demonstrated in individuals with JEB [Lincoln et al 2018].

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

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

Junctional epidermolysis bullosa (JEB) is inherited in an autosomal recessive manner.

While there is no evidence to date that a single (i.e., heterozygous) pathogenic variant in *COL17A1*, *LAMA3*, *LAMB3*, or *LAMC2* results in JEB, dental anomalies have been reported in individuals who have a heterozygous *LAMB3*, *LAMA3*, or *COL17A1* variant [McGrath et al 1996, Almaani et al 2009, Yuen et al 2012, Kim et al 2013, Poulter et al 2014, Lee et al 2015, Wang et al 2015, Gostyńska et al 2016, Du et al 2018].

Risk to Family Members

Parents of a proband

- The parents of an affected child are usually obligate heterozygotes (i.e., carriers of one *COL17A1*, *ITGB4*, *LAMA3*, *LAMB3*, or *LAMC2* pathogenic variant).
- Because germline mosaicism and uniparental isodisomy have been reported [Pulkkinen et al 1997a, Takizawa et al 2000b, Cserhalmi-Friedman et al 2002, Fassihi et al 2005], carrier status of parents needs to be confirmed with molecular genetic testing.
- Heterozygotes (carriers) are asymptomatic except in a few rare instances where carriers of a *COL17A1*, *LAMA3*, or *LAMB3* pathogenic variant have been reported to have dental enamel hypoplasia and/or pitting with resulting caries [Nakamura et al 2006, Murrell et al 2007, Yuen et al 2012, Kim et al 2013, Poulter et al 2014, Lee et al 2015, Wang et al 2015, Gostyńska et al 2016, Du et al 2018].

Sibs of a proband

- At conception, each sib of an affected individual whose parents are both carriers has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.

- Heterozygotes (carriers) are asymptomatic except in the case of *COL17A1* or *LAMB3* pathogenic variants, where carriers may exhibit dental enamel hypoplasia and/or pitting and caries [Nakamura et al 2006, Murrell et al 2007, Kim et al 2013, Poulter et al 2014].

Offspring of a proband. The offspring of an individual with autosomal recessive JEB are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members. Each sib of the proband's carrier parents is at a 50% risk of being a carrier of a *COL17A1*, *ITGB4*, *LAMA3*, *LAMB3*, or *LAMC2* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk family members is possible if the pathogenic variants in the family have been identified.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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, are carriers, or are at risk of being carriers.

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

Molecular genetic testing. Once the *COL17A1*, *ITGB4*, *LAMA3*, *LAMB3*, or *LAMC2* pathogenic variants have been identified in an affected family member, prenatal testing and preimplantation genetic testing for JEB are possible.

Fetoscopy. Electron microscopic evaluation of fetal skin biopsies obtained by fetoscopy is also diagnostic in JEB. Fetoscopy carries a greater risk to pregnancy than CVS or amniocentesis and is performed relatively late (18-20 weeks) in gestation. Prenatal testing for JEB using fetoscopy is not currently available in the US, but may be available in Europe.

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
- **Epidermolysis Bullosa Medical Research Foundation**
  Phone: 310-205-5119
  Email: a.pett@bep-la.com
  EBMRF
- **Medline Plus**
  Epidermolysis bullosa
- **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. Junctional Epidermolysis Bullosa: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COL17A1	10q25.1	Collagen alpha-1(XVII) chain	COL17A1 @ LOVD	COL17A1	COL17A1
ITGB4	17q25.1	Integrin beta-4	ITGB4 database	ITGB4	ITGB4
LAMA3	18q11.2	Laminin subunit alpha-3	LAMA3 database	LAMA3	LAMA3
LAMB3	1q32.2	Laminin subunit beta-3	LAMB3 database	LAMB3	LAMB3
LAMC2	1q25.3	Laminin subunit gamma-2	LAMC2 database	LAMC2	LAMC2

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 Junctional Epidermolysis Bullosa (View All in OMIM)

113811	COLLAGEN, TYPE XVII, ALPHA-1; COL17A1
147557	INTEGRIN, BETA-4; ITGB4
150292	LAMININ, GAMMA-2; LAMC2
150310	LAMININ, BETA-3; LAMB3
226650	EPIDERMOLYSIS BULLOSA, JUNCTIONAL 1A, INTERMEDIATE; JEB1A
226700	EPIDERMOLYSIS BULLOSA, JUNCTIONAL 1B, SEVERE; JEB1B
226730	EPIDERMOLYSIS BULLOSA, JUNCTIONAL 5B, WITH PYLORIC ATRESIA; JEB5B
600805	LAMININ, ALPHA-3; LAMA3

Molecular Pathogenesis

The proteins encoded by *LAMA3*, *LAMB3*, and *LAMC2* assemble into the laminin 332 heterotrimer (aka LAM5 [Aumailley et al 2005]). A pathogenic variant in these genes can lead to reduced resistance to minor trauma and the resulting mucocutaneous blistering that is the hallmark of junctional epidermolysis bullosa (JEB) (reviewed by Kiritsi et al [2013]). The type of variant, the biochemical properties of the substituted amino acid, if present, and its location determine the severity of the blistering phenotype (see Genotype-Phenotype Correlations). Pathogenic nonsense variants predominate in the severe forms of JEB and result in the absence of one of the three proteins that assemble into laminin 332. Pathogenic missense variants in key positions of the protein subunits affect the ability of the laminin α3, β3, and γ2 polypeptides to assemble into a trimeric molecule, its secondary structure, and its ability to form the intracellular anchoring fibrils of the lamina densa.

Collagen XVII forms an integral part of the hemidesmosome and has an intracellular as well as extracellular component. There is evidence that it interacts with alpha-6 integrin within the hemidesmosome. The hemidesmosomes – structures made up of several protein components including COLXVII, alpha-6 beta-4 integrin, BPAG1, and plectin – anchor the epidermal cells to the underlying dermis. The type and position of variants in *COL17A1* determine whether some partially functional protein is made and also affect the level of the cleavage plane of the skin. In some cases, variants affecting the intracellular domain result in a cleavage plane within the lowest level of the basal keratinocytes usually associated with epidermolysis bullosa simplex (EBS) [Charlesworth et al 2003].

Integrins associate in pairs containing one alpha and one beta chain. α6β4 integrin comprises one α6 and one β4 integrin from the integrin family of proteins and is a component of the hemidesmosomes of the epidermis. Integrins are known to participate in cell adhesion as well as cell-surface-mediated signaling. Insertion/deletion, splice junction, and amino acid substitution variants in both α6 and β4 integrin have been described and would result in EB-PA [Ruzzi et al 1997, Gache et al 1998, Lépinard et al 2000, Varki et al 2006, Masunaga et al 2015, Mencía et al 2016, Masunaga et al 2017].

COL17A1

Gene structure. The cDNA NM_000494.3 encodes 1,497 amino acids in 56 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. There is one alternatively spliced mRNA variant [Ruzzi et al 2001].

Pathogenic variants. Pathogenic variants in *COL17A1*, which encodes the collagen XVII protein, a component of the hemidesmosome, typically result in JEB generalized intermediate [Gatalica et al 1997, Pulkkinen et al 1999, Takizawa et al 2000a, van Leusden et al 2001, Pasmooij et al 2004], although a few individuals with lethal JEB resulting from *COL17A1* pathogenic variants have been described [Varki et al 2006, Murrell et al 2007]. All types of variants (including premature termination codon, nonsense, insertion/deletion, splice junction, and missense variants) distributed throughout the gene have been described. The type and location of the variants and the response of the cells to the variants determines the phenotype, which can range from mild to severe and in some cases lethal. Reversion to a normal phenotype has been described [Pasmooij et al 2005, Pasmooij et al 2012].

Normal gene product. Collagen XVII, NP_000485.3, (also known as BP180) has 1,497 amino acids and is composed of intracellular and extracellular domains separated by a transmembrane domain that distinguishes collagen XVII from other collagen family members. The intracellular domain is localized within the basal keratinocyte; the ectodomain is localized outside the cell and serves as an association point with other components of the basement membrane zone. The carboxy-terminal half of collagen XVII, a stretch of 916 amino acids, consists of 15 collagen domains of variable length (15 to 242 amino acids) that are separated by

short stretches of non-collagen sequences. The collagenous domains associate to form a homotrimeric triple helical segment of the molecule characteristic of all collagen family members.

Abnormal gene product. Premature termination codon pathogenic variants that result in a null allele cause skin fragility, dental abnormalities, and alopecia usually found in individuals with JEB generalized intermediate. Other pathogenic variants may result in varying phenotypic severity. Although *COL17A1* variants do not usually result in lethality, several cases of a neonatal lethal phenotype were described [Varki et al 2006, Murrell et al 2007]. Pathogenic variants that affect the intracellular domain may result in a cleavage plane more consistent with EBS and be misleading in terms of diagnosis based on electron microscopy biopsy results. Pathogenic variants that affect the transmembrane domain may result in intracellular accumulation of collagen XVII protein. Although glycine substitutions in *COL17A1* have been described, no autosomal dominant variants resulting in skin fragility have been identified. Heterozygous carriers of a glycine substitution [Nakamura et al 2006] or other *COL17A1* variants [Murrell et al 2007] may exhibit dental enamel pitting and this characteristic may be diagnostic for *COL17A1* pathogenic variants in a family with an affected child [Murrell et al 2007].

ITGB4

Gene structure. The normal full-length cDNA is encoded in 41 exons spanning 36 kb of the genomic DNA. The cDNA comprises 6,033 bp with an open reading frame of 5,469 nucleotides encoding 1,822 amino acids. Two splicing variants express different isoforms of the protein [Pulkkinen et al 1997c]. The most common epidermal variant does not express exon 33. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 100 pathogenic variants spanning all of *ITGB4* have been described in individuals with EB-PA [Pulkkinen et al 1997b, Pulkkinen et al 1997c, Pulkkinen et al 1998a, Pulkkinen et al 1998b, Ashton et al 2001, Nakano et al 2001, Iacovacci et al 2003, Varki et al 2006, Masunaga et al 2015]. Pathogenic variants that cause premature termination codons on both alleles result in the most severe phenotypes, which are frequently lethal in the neonatal period. Other types of variants including amino acid substitutions and splicing variants may result in a less severe phenotype [Mellerio et al 1998, Pulkkinen et al 1998b, Chavanas et al 1999, Varki et al 2006]. In one individual severe blistering without pyloric atresia was described from a homozygous missense variant in *ITGB4* [Inoue et al 2000] and in another a homozygote with missense and PTC *ITGB4* variants [Inoue et al 2000, Jonkman et al 2000]. Few recurrent pathogenic variants have been described; however, the variant p.Cys61Tyr is common in individuals of Hispanic ancestry with JEB-PA in the US [Varki et al 2006]. See Table 3.

Table 3. *ITGB4* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.182G>A	p.Cys61Tyr	NM_000213.4 NP_000204.3

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.

Normal gene product. Integrins associate in pairs containing one alpha and one beta chain. α6β4 integrin comprises one α6 and one β4 integrin protein from the integrin family of proteins and is a component of the hemidesmosomes of the epidermis. Within the hemidesmosome, α6β4 integrin forms attachments with collagen XVII to fulfill its role in the network of protein giving the epidermal strength and integrity and anchoring the epidermal cells to the underlying dermis through adhesion of the hemidesmosomes to the basement membrane. α6β4 integrin has also been shown to be involved in cell signaling and may play a role in carcinogenesis [Chung et al 2004, Guo et al 2006, Yoon et al 2006, Folgiero et al 2007].

Abnormal gene product. Null alleles may result in little or no protein seen with staining with anti-α6β4 integrin antibodies. Reduced staining was seen in some milder cases resulting from amino acid substitutions or splice junction variants.

LAMA3

Gene structure. All of *LAMA3* is encoded in 76 exons spanning 318 kb on chromosome 18q11.2. Transcript variants are produced by alternative splicing (see Table 4 and McLean et al [2003]). For a detailed summary of gene information along with additional transcripts and protein isoforms, see Table A, **Gene**.

Pathogenic variants. Nonsense, missense, splicing, and insertion/deletion variants have been reported [Nakano et al 2002a, Varki et al 2006]. Premature termination codon pathogenic variants on both alleles result in JEB generalized severe in most instances. A few mildly affected individuals with JEB with premature termination codon variants have been reported [Nakano et al 2002a]. Amino acid substitutions and splicing variants may result in a milder phenotype [Posteraro et al 1998, Nakano et al 2002a]. Overlapping phenotypes in which pathogenic variants in *LAMA3* result in skin fragility with eye and laryngeal involvement may exist [Varki et al 2006, Figueira et al 2007].

Table 4. *LAMA3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.151dupG [1]	p.Val51GlyfsTer4	NM_000227.4 NP_000218.3
c.1981C>T [2]	p.Arg661Ter	

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. See Genetically Related Disorders.
2. Cited by McGrath et al [1996] as c.1948C>T (p.Arg650Ter) without a reference sequence. Coordinates here from citation in OMIM 600805, allelic variant 0.0002 with dbSNP identification of rs17852757, which gives the above HGVS coordinates for the reference sequence in this table.

Table 5. *LAMA3* Transcript Variants and Protein Isoforms Discussed in This *GeneReview*

Transcript Variants				Protein Isoforms			
Name(s)	Accession #	Length (nt)	Total # Exons	Name(s)	Accession #	Amino Acids (#)	Encoded by Exon #s [1]
2, 3a	NM_000227.4	5,623	38	α3a, 2, LAMA3a	NP_000218.3	1,724	39-76
1, 3b1	NM_198129.2 [2]	10,666	75	α3b1, 1, LAM3b1	NP_937762.2	3,333	1-38 & 40-76
3, 3b2	NM_001127717.2	10,498	74	α3b2, 3, LAM3b2	NP_001121189.2	3,277	1-9, 11-38, & 40-76

See *LAMA3*, genomic sequence NC_000018.10
1. Exon numbers based on McLean et al [2003]
2. Longest transcript; the genomic sequence of *LAMA3* should be sequenced for diagnostic purposes (Table 1, footnote 8).

Normal gene product. There are three isoforms (α3a, α3b1, α3b2) produced by alternative splicing (Table 4). Note that the shorter α3b2 isoform of 1,724 amino acids is encoded in 38 exons (exons 39-76 of *LAMA3*) and is unique in that exon 39 is expressed.

The laminin A3 protein associates with laminin B3 and C2 proteins to form the laminin 332 heterotrimer that comprises the anchoring fibrils in the epidermis. The anchoring fibrils hold the layers of the basal lamina together and form associations with collagen VII on the dermal side and plectin and α6β4 integrin in the

hemidesmosomes on the epidermal side. This interaction allows the formation of the protein network of the epidermis, which results in a flexible and resilient barrier to resist trauma.

Abnormal gene product. See Molecular Pathogenesis. In all three genes (*LAMB3*, *LAMC2*, and *LAMA3*), amino acid substitutions, splicing variants, and in-frame deletions and insertions may result in the formation of some partially functional protein that results in a milder phenotype. Specific amino acid substitutions, such as replacement of cysteine residues, inhibit the formation of disulfide bonds, result in altered laminin 332 intra- and intermolecular associations, and may result in a more severe phenotype. On a skin biopsy studied with immunofluorescence, if synthesis of one of the proteins is disrupted, the staining for the other two proteins will usually also be affected.

LAMB3

Gene structure. The normal *LAMB3* cDNA has an open reading frame of 3,516 nucleotides in 23 exons spanning 29 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Nonsense, missense, splicing, and insertion/deletion variants have been reported [Nakano et al 2002b, Varki et al 2006]. A few mildly affected persons with premature termination codon variants have been reported [Pulkkinen et al 1998a, Nakano et al 2002a]. Amino acid substitutions and splicing variants may result in a milder phenotype [Mellerio et al 1998, Posteraro et al 1998, Nakano et al 2002a]. The following *LAMB3* pathogenic variants, p.Arg635Ter, p.Gln243Ter, c.957ins77, p.Arg42Ter are present in approximately 45% of individuals with H-JEB in the US [Varki et al 2006]. These pathogenic variants invariably result in premature termination codons and when found on both alleles result in JEB generalized severe.

Table 6. *LAMB3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.124C>T	p.Arg42Ter	NM_000228.2 NP_000219.2
c.727C>T	p.Gln243Ter	
c.957ins77	p.Glu320Ter	
c.1903C>T	p.Arg635Ter	

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.

Normal gene product. The laminin B3 protein has 1,172 amino acids. It associates with laminin A3 and C2 proteins to form the laminin 332 heterotrimer that comprises the anchoring fibrils in the epidermis.

Abnormal gene product. See Molecular Pathogenesis. In all three genes (*LAMB3*, *LAMC2*, and *LAMA3*), amino acid substitutions, splicing variants, and in-frame deletions and insertions may result in the formation of some partially functional protein that results in a milder phenotype. Specific amino acid substitutions, such as replacement of cysteine residues, inhibit the formation of disulfide bonds, result in altered laminin 332 intra- and intermolecular associations, and may result in a more severe phenotype. On a skin biopsy studied with immunofluorescence, if synthesis of one of the proteins is disrupted, the staining for the other two proteins will usually also be affected. Reversion by *LAMB3* mosaicism to a normal phenotype has been described and has implications for treatment [Pasmooij et al 2007].

LAMC2

Gene structure. Two *LAMC2* transcript variants result from alternative splicing. The longer *LAMC2* cDNA transcript NM_005562.2 is expressed in the epidermis and encodes 1,193 amino acids in 23 exons spanning 55 kb. The shorter transcript variant, NM_018891.2, is expressed in the cerebral cortex, lung, and distal tubules of the kidney. For a detailed summary of gene, transcript, and protein information, see Table A, **Gene**.

Pathogenic variants. Nonsense, missense, splicing, and insertion/deletion variants have been reported [Castiglia et al 2001, Nakano et al 2002b, Varki et al 2006]. Amino acid substitutions and splicing variants may result in a milder phenotype [Posteraro et al 1998, Castiglia et al 2001, Nakano et al 2002a].

Table 7. *LAMC2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.283C>T	p.Arg95Ter	NM_005562.2 NP_005553.2

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.

Normal gene product. The laminin C2 protein associates with laminins A3 and C2 to form the laminin 332 heterotrimer that makes up the anchoring fibrils in the epidermis.

Abnormal gene product. See Molecular Pathogenesis. In all three genes (*LAMB3*, *LAMC2*, and *LAMA3*), amino acid substitutions, splicing variants, and in-frame deletions and insertions may result in the formation of some partially functional protein that results in a milder phenotype. Specific amino acid substitutions, such as replacement of cysteine residues, inhibit the formation of disulfide bonds, result in altered laminin 332 intra- and intermolecular associations, and may result in a more severe phenotype. On a skin biopsy studied with immunofluorescence, if synthesis of one of the proteins is disrupted, the staining for the other two proteins will usually also be affected.

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Chapter Notes

Author Notes

GeneDx website

Cincinnati Children's Epidermolysis Bullosa Center website

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- 20 December 2018 (sw) Comprehensive update posted live
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