GENEReviews

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Junctional Epidermolysis Bullosa

[*Includes: COL17A1-Related Junctional Epidermolysis Bullosa; LAMA3-Related Junctional Epidermolysis Bullosa; LAMB3-Related Junctional Epidermolysis Bullosa; LAMC2-Related Junctional Epidermolysis Bullosa*]

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Summary

Disease 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 trachea. Blisters generally heal with no significant scarring. Broad classification of JEB includes Herlitz JEB (aka lethal) and non-Herlitz JEB (aka nonlethal). In Herlitz JEB, the classic severe form of JEB, blisters are present at birth or become apparent in the neonatal period. Congenital malformations of the urinary tract and bladder may also occur. In non-Herlitz JEB, 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. Because the clinical features of all types of EB overlap significantly, examination of a skin biopsy by transmission electron microscopy (TEM) and/ or immunofluorescent antibody/antigen mapping is usually required to establish the diagnosis of JEB, especially in infants. The four genes known to be associated with JEB are *LAMB3* (70% of all JEB), *COL17A1* (12%), *LAMC2* (9%), and *LAMA3* (9%). Molecular genetic testing is available clinically for all four genes.

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; tracheostomy if appropriate; routine dental care; appropriate footwear and physical therapy to promote/preserve ambulation; psychosocial support, including social services and psychological counseling. *Prevention of secondary complications:* antiseptics to treat wound infections; attention to fluid and electrolyte balance in severely affected infants; additional nutritional support including a feeding gastrostomy when necessary; calcium, vitamin D, zinc, and iron supplements. *Surveillance:* routine screening for iron-deficiency anemia, zinc deficiency, osteopenia and/or osteoporosis. *Agents/circumstances to avoid:* ordinary medical tape or Band-Aids®, poorly fitting or coarse-textured clothing and footwear, activities that in general traumatize the skin (e.g., hiking, mountain biking, contact sports).

Other: Consider cesarean section to reduce trauma to the skin of an affected fetus during delivery.

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 disease-causing mutation. Carrier testing for family members at increased risk and prenatal diagnosis for pregnancies at increased risk are possible if both disease-causing mutations have been identified in the family.

Diagnosis

Clinical Diagnosis

The diagnosis of junctional epidermolysis bullosa (JEB) is suspected in individuals with 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

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

Because the clinical features of all types of epidermolysis bullosa (EB) overlap significantly (see Differential Diagnosis), clinical diagnosis is unreliable and examination of a skin biopsy is usually required to establish the diagnosis, especially in infants.

Testing

Skin biopsy. Examination of a skin biopsy by transmission electron microscopy (TEM) and/or immunofluorescent antibody/antigen mapping is the best way to reliably establish 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) or mechanically induced blister and should include some normal adjacent skin. (Older blisters undergo change that may obscure the diagnostic morphology.)

Note:

(1) **For TEM**
(a) Specimens must be placed in fixation medium (such as gluteraldehyde) as designated by the laboratory performing the test.
(b) Formaldehyde-fixed samples cannot be used for electron microscopy

(2) **For immunofluorescent antibody/antigen mapping**
(a) Specimens should be sent in sterile carrying medium (such as Michel's of Zeus) as specified by the laboratory performing the test.
(b) Some laboratories prefer flash-frozen tissue.
(c) 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 the

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.

(3) Light microscopy is inadequate and unacceptable for the accurate diagnosis of EB.

Transmission electron microscopy (TEM) is used to examine the number and morphology of the 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 as well as the presence of micro-vessicles showing the tissue cleavage plane.

Findings on TEM include the following [Kunz et al 2000; Jonkman et al 2002; Charlesworth et al 2003; Pasmooij, van der Steege et al 2004]:

- **In all forms of JEB.** Splitting 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.
- **In Herlitz JEB (H-JEB).** Hemidesmosomes are reduced in number and hypoplastic. Anchoring filaments are markedly reduced or absent.
- **In non-Herlitz JEB (NH-JEB).** 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 mutations in *LAMA3*, *LAMB3*, or *LAMC2* in Herlitz or non-Herlitz forms of JEB
- Abnormal or absent staining with antibodies to collagen XVII in JEB caused by mutations 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 may not be 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. Alternatively, rebiopsy allowing more time (several hours) between rubbing the skin or the patient performing an activity that induces fresh blistering and blister formation prior to biopsy for IFM or EM may be required.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. Four genes are commonly associated with the two major phenotypes of JEB, Herlitz and non-Herlitz JEB [Fine et al 1999, Anton-Lamprecht & Gedde-Dahl 2002]:

- *LAMB3* accounts for 70% of all JEB.
- *COL17A1* accounts for 12% of all JEB.

- *LAMC2* accounts for 9% of all JEB.
- *LAMA3* accounts for 9% of all JEB.

Clinical testing

- **Sequence analysis**

LAMB3. Sequencing of *LAMB3* detects more than 98% of *LAMB3* mutations overall. Large deletions (i.e., exonic and whole-gene deletions) have been identified in *LAMB3* in fewer than 1% of cases [Pulkkinen et al 1995; Cserhalmi-Friedman et al 1998; Takizawa, Pulkkinen et al 2000; Huber et al 2002; Micheloni et al 2004; Posteraro et al 2004].

COL17A1. Sequencing of *COL17A1* detects more than 98% of *COL17A1* mutations overall.

LAMC2. Sequencing of *LAMC2* detects more than 98% of *LAMC2* mutations overall.

LAMA3. Sequencing of *LAMA3* detects more than 98% of *LAMA3* mutations overall.

Note: Care must be taken to sequence the entire *LAMA3* gene rather than one of the shorter isoforms.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Junctional Epidermolysis Bullosa

Gene Symbol	Proportion of JEB Attributed to Mutations in This Gene [1]	Test Method	Mutation Detection Frequency by Test Method [2]	Test Availability
LAMB3	70%	Sequence analysis	>98% [3]	Clinical Testing
		Deletion analysis	<1% [4]	
		Targeted mutation analysis	See footnote [5]	
COL17A1	12%	Sequence analysis	>98%	Clinical Testing
		Deletion analysis	<1% [4]	
LAMC2	9%	Sequence analysis	>98%	Clinical Testing
		Deletion analysis	<1% [4]	
		Targeted mutation analysis	See footnote [5]	
LAMA3	9%	Sequence analysis	>98% [6]	Clinical Testing
		Deletion analysis	<1% [4]	
		Targeted mutation analysis	See footnote [5]	

1. Varki et al 2006
2. Sequencing of all four genes results in a mutation detection frequency of 98%. Large deletions and intronic variations that alter splicing are thought to be responsible for the other 2%; however, rare mutations in *ITGB4* and *PLEC1* have also resulted in a JEB-like phenotype (see EB-PA) and must be taken into consideration when no mutations are identified in either of the four genes included in Table 1 [Inoue et al 2000, Kunz et al 2000, Charlesworth et al 2003].
3. Rarely, large deletions have been identified in *LAMB3* which may result in a lower detection frequency [Pulkkinen et al 1995; Cserhalmi-Friedman et al 1998; Takizawa, Pulkkinen et al 2000; Huber et al 2002; Micheloni et al 2004; Posteraro et al 2004].
4. Pulkkinen et al 1997; Takizawa, Pulkkinen et al 2000; Fassihi et al 2005; Varki et al 2006
5. One laboratory offers targeted mutation analysis for p.Arg42X, p.Gln243X, p.Arg635X, and p.957ins77 in *LAMB3*; p.R95X mutation in *LAMC2*; and p.Arg650X in *LAMA3* with a 45% mutation detection frequency in Caucasians.
6. Care must be taken to sequence the entire *LAMA3* gene rather than one of the shorter isoforms.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Establishing the diagnosis in a proband

- **Skin biopsy.** Especially in newborns, a skin biopsy from a newly induced blister should be performed as soon as possible after initial evaluation. The skin biopsy should be studied with electron microscopy and/or indirect immunofluorescence for the basement membrane proteins to identify the affected proteins and suggest the appropriate genes to be tested.

  Note: Lethal forms of JEB resulting from *COL17A1* mutations were recently described [Varki et al 2006, Murrell et al 2007] so the strict criteria of a lethal versus nonlethal form of JEB are not sufficient to define the order of molecular genetic testing.

- **Molecular genetic testing.** When any form of JEB is suspected, targeted mutation analysis should be the first step for individuals of the following ethnic groups:
  - Caucasian: *LAMB3* (p.Arg635X, p.Gln243X)
  - Hispanic and African American: *LAMB3* (c.957ins77, p.Arg42X)
  - Pakistani: *LAMA3* (p.Arg650X) [McGrath et al 1996]
  - Italian: *LAMC2* (p.Arg95X) [Posteraro et al 2004]

These mutations may account for up to 45% of JEB-causing mutations.

If neither or only one mutation is identified in an individual with biopsy-proven **Herlitz JEB** following targeted mutation analysis, sequence analysis of the four known genes has the following mutation detection frequencies [Varki et al 2006]:

- *LAMB3*: 25%
- *LAMC2*: 9%
- *LAMA3*: 10%
- *COL17A1*: 8%

If neither or only one mutation is identified in an individual with biopsy-proven **non-Herlitz JEB** following targeted mutation analysis, sequence analysis of the four known genes has the following mutation detection frequencies [Varki et al 2006]:

- *LAMB3*: 25%
- *COL17A1*: 25%
- *LAMC2*: 3%
- *LAMA3*: 8%

Carrier testing for at-risk relatives (in families with autosomal recessive inheritance) requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation(s) in the family.

Genetically Related (Allelic) Disorders

***LAMB3* and *LAMC2*.** No phenotypes other than JEB are associated with mutations in *LAMB3* and *LAMC2*.

***LAMA3*.** A related disorder, laryngo-onycho-cutaneous (LOC or Shabbir) syndrome, or LOCS [OMIM 245660] is described in Punjabi Indians. LOCS has many phenotypic characteristics similar to NH-JEB [Figueira et al 2007, Pfendner et al 2007]. Skin fragility manifests as mild blistering and erosions of the hands and face that spreads to other parts of the body and heals 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 tracheotomy.

The *LAMA3* mutation c.151insG in exon 39, one of three *LAMA3* isoforms, is causative [McLean et al 2003]. 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 the *LAMA3* gene, which encodes all three isoforms, is necessary to provide definitive diagnosis, especially in neonates.

***COL17A1*.** Mutations in *COL17A1* may also be associated with an epidermal keratinocyte cleavage plane usually associated with epidermolysis bullosa simplex (EBS) [Pasmooij, van der Steege et al 2004].

Clinical Description

Natural History

Before the molecular basis of junctional epidermolysis bullosa (JEB) was understood, subtypes were identified (see Nomenclature) based primarily on clinical features, mode of inheritance, and the presence or absence of laminin 5 and anchoring filaments on skin biopsy. Broad classification of JEB includes H-JEB (aka lethal) and NH-JEB (aka nonlethal) and is based on severity and survival past the first years of life [Fine et al 1999, Pulkkinen & Uitto 1999, Irvine & McLean 2003, Uitto & Richard 2005].

Herlitz JEB (H-JEB). In this classic severe form of JEB, blisters are present at birth or become apparent in the neonatal period.

Blistering is very severe 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 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 a few individuals with H-JEB who survive [Fine et al 1999].

In addition to cutaneous involvement, mucosal involvement of the mouth, upper respiratory tract, esophagus, bladder, urethra, and corneas can be seen. 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.

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 recessive dystrophic EB (RDEB).

Secondary complications common in H-JEB include the following:

- Growth retardation from malnutrition as a result of poor intake and an increased nutritional demand for tissue healing
- Anemia
- Alopecia
- Cutaneous infection
- Sepsis
- Electrolyte imbalance
- Osteoporosis [Fewtrell et al 2006]
- Squamous cell carcinoma [Mallipeddi et al 2004]
- Enamel dysplasia with pitting of the teeth [Kirkham et al 2000, Nakamura et al 2006]

Most children with H-JEB do not survive past the first year of life.

Non-Herlitz JEB (NH-JEB). A spectrum of JEB clinical phenotypes, all of which are less severe than classic H-JEB, comprises NH-JEB. 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 of H-JEB are rare.

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

Manifestations that can occur in H-JEB, NH-JEB, and EB with pyloric atresia (EB-PA) as well as dystrophic epidermolysis bullosa (DEB) and epidermolysis bullosa simplex (EBS). The following manifestations are now recognized to be found in the major EB types as described in the findings of the National EB Registry [Fine et al 1999]:

- **Congenital localized absence of skin (aplasia cutis congenita)** can be seen in any of the major types of EB and is not a discriminating diagnostic feature of any of these

types of EB in general or any subtype of JEB. Congenital absence of skin on the extremities had been classified as Bart syndrome [OMIM 132000] but currently is considered a manifestation of all types of EB.

- **Milia** are small white-topped papules; they are often confused with epidermal cysts and are not confined to any type of EB, although they are most common in individuals with DEB.
- **Nail dystrophy** is defined as changes in size, color, shape, or texture of nails and is not confined to any one form of EB.
- **Scarring alopecia** is defined as complete loss of scalp hair follicles as a result of scarring and loss of hair follicles. Scarring alopecia is more prevalent in JEB and DEB but is not confined solely to any one form of EB.
- **Hypotrichosis** is defined as reduction in the number of hair follicles in a given area compared to the number of hair follicles in the same area of a normal individual of the same gender. Hypotrichosis is not confined to any one form of EB.
- **Pseudosyndactyly and other contractures.** Pseudosyndactyly is defined as the partial or complete loss of web spaces between any digits of the hands or feet. "Other contractures" refers to loss of mobility of any other joints as a result of fibrous tissue scars. Although these changes are more prevalent in DEB, they have also been observed occasionally in the other forms of EB.
- **Scarring** is not confined to any form of EB and has been observed in 30% of those with EBS, 76% of those with JEB, and up to 98% of those with DEB.
- **Exuberant granulation tissue.** Although exuberant granulation tissue was previously thought to be confined to those with JEB (23%), it has also been observed in a small percentage of those with DEB (≤12%) and EBS (0.7%). This finding is misleading because it does not usually appear until the affected child is a few years old and most children with H-JEB do not survive that long.

Genotype-Phenotype Correlations

H-JEB. The severest forms of H-JEB are a result of inactivating mutations on both alleles, which result in little or no functional protein [Varki et al 2006]. For frameshift mutations, the severity may be related to the position of the stop codon; however, the presence of some functional protein seems to be the most important factor in ameliorating disease severity.

Less severe forms of H-JEB generally result from other amino acid substitutions and splice-junction mutations, although it is difficult to generalize because of the wide phenotypic variability and range of mutations that has 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 mutations [McGrath et al 1999].

Penetrance

Mutations in *LAMB3*, *LAMA3*, *LAMC2*, and *COL17A1* are 100% penetrant in individuals who have two mutations on different alleles in the same gene.

Nomenclature

The following hierarchy includes as synonyms specific designations for JEB that have been used in the past. Designations in current use are in **boldface**:

- **Junctional epidermolysis bullosa, Herlitz** (synonyms: epidermolysis bullosa letalis; epidermolysis bullosa junctional Herlitz-Pearson; junctional epidermolysis bullosa, mitis)

In descending order of frequency:

- ***LAMB3*-related junctional epidermolysis bullosa**
- ***LAMC2*-related junctional epidermolysis bullosa**
- ***LAMA3*-related junctional epidermolysis bullosa**
- ***COL17A1*-related junctional epidermolysis bullosa**

In descending order of frequency:

- ***LAMB3*-related junctional epidermolysis bullosa**
- ***COL17A1*-related junctional epidermolysis bullosa**
- ***LAMC2*-related junctional epidermolysis bullosa**
- ***LAMA3*-related junctional epidermolysis bullosa**

Generalized atrophic benign EB (GABEB), originally described as a separate clinical entity caused by mutations in *COL17A1*, is now included within the NH-JEB category because of significant phenotypic overlap.

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].

- H-JEB prevalence is estimated at 0.37 per million but may be underrepresented. JEB incidence is also very low (0.41 per million), but is probably underestimated: many Herlitz cases go unreported because infants succumb to the disease in the neonatal period.
- NH-JEB incidence is 0.07 per million.

Carrier risk of all forms of JEB in the US population has been calculated as 1:350.

- Carrier risk of H-JEB has been calculated as 1:781 [Nakano et al 2000, Pfendner et al 2001].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The four major types of EB, caused by mutations in ten different genes, are EBS, hemidesmosomal EB, junctional epidermolysis bullosa (JEB), and DEB (Figure 3). Although agreement exists as to diagnostic criteria for some types of EB, the validity of rarer subtypes and their diagnostic criteria are disputed. Excellent clinical reviews are the chapter on EB in Principles and Practice of Medical Genetics [Anton-Lamprecht & Gedde-Dahl 2002] and Fine's Revised Classification System [Fine et al 1999,Fine et al 2000].

The four major types of EB share fragility of the skin, manifested by blistering with little or no trauma. A positive Nikolsky sign (blistering of uninvolved skin after rubbing) is common to all types of EB. No clinical findings are specific to a given type; thus, establishing the type of EB type requires a fresh skin biopsy from a newly induced blister that is stained by indirect immunofluorescence for critical basement membrane protein components. The diagnosis is

established by determining the cleavage plane on TEM and the presence/absence of these protein components by immunofluorescent antibody/antigen mapping and their distribution. Electron microscopy is also diagnostic and often more useful in milder forms of EB.

Clinical examination is useful in determining the extent of blistering, the presence of oral and other mucous membrane lesions, and the presence and extent of scarring.

Limitations of the clinical findings in establishing the type of EB include the following:

- In young children and neonates the extent and severity of blistering and scarring may not be established or significant enough to allow identification of EB type.
- Mucosal and nail involvement and the presence or absence of milia may not be helpful discriminators (see Clinical Description).
- Post-inflammatory changes such as those seen in EBS, Dowling-Meara type (EBS-DM) 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 damages the exposed surface.
- Congenital absence of the skin can be seen in any of the three major types of EB (i.e., EBS, JEB, DEB) and is not a discriminating diagnostic feature (see Clinical Description).

Clinical findings that tend to be characteristic for a specific type of EB include the following:

- Corneal erosions, esophageal strictures, and nail involvement may indicate DEB.
- Scarring limited to the hands and feet in milder cases suggests autosomal dominant DEB (DDEB).
- Pseudosyndactyly (mitten deformities) and contractures in older children and adults usually suggests autosomal recessive DEB (RDEB).
- Hoarseness and respiratory distress suggest H-JEB.
- Granulation tissue suggests JEB.
- Hyperkeratosis of the palms and soles suggests EBS, especially the DM type.

Epidermolysis bullosa simplex (EBS) is characterized by fragility of the skin that results in nonscarring blisters caused by little or no trauma. Four clinical subtypes of EBS range from relatively mild blistering of the hands and feet to more generalized blistering, which can be fatal.

- In **EBS, Weber-Cockayne type (EBS-WC)**, 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, Koebner type (EBS-K)**, blisters may be present at birth or develop within the first few months of life. Involvement is more widespread than in EBS-WC, but generally milder than in EBS-DM.
- In **EBS with mottled pigmentation type (EBS-MP)**, skin fragility is evident at birth and clinically indistinguishable from EBS-DM; 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, Dowling-Meara type (EBS-DM)**, 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. EBS-DM appears to improve with warmth in some individuals. 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-DM may interfere with feeding. Blistering can be severe enough to result in neonatal or infant death.

Hemidesmosomal EB. Pulkkinen & Uitto (1999) proposed that EB with muscular dystrophy (EB-MD) and EB with pyloric atresia (EB-PA) be considered "hemidesmosomal JEB" because the involved proteins are located in the hemidesmosomes. Within basal keratinocytes, plectin is localized to the inner plaques of the hemidesmosomes, which are hypoplastic and show poor association with keratin filaments. Electron microscopy of skin biopsies reveals a plane of cleavage (level of separation) within the bottom layer of the basal keratinocytes, just above the hemidesmosomes. (See EB-PA.)

Note: "Hemidesmosomal epidermolysis bullosa" is not a universally accepted designation; the following three types typically have been included either with EBS or JEB.

- **EB-MD** [OMIM 226670]. Approximately 50 cases of EB-MD have been reported worldwide. Some persons with EB as a result of *PLEC1* mutations develop muscular dystrophy [Smith et al 1996, Charlesworth et al 2003, Koss-Harnes et al 2004, Schara et al 2004, Pfendner et al 2005]. Blistering occurs early and is generally mild. Muscular dystrophy may not appear until later childhood, adolescence, or in some cases adulthood, and can cause immobility and eventually death later in life. Mutations have been described throughout *PLEC1* 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 mutations 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) [Pfendner et al 2005]. Inheritance is autosomal recessive.

  A single lethal case of autosomal recessive EBS as a result of *PLEC1* mutations has also been described [Charlesworth et al 2003]. Kunz et al (2000) also described a case of EBS with severe mucous membrane involvement as a result of mutations in *PLEC1*.

- **EB-PA**. In several US and Japanese families, EB with pyloric atresia is associated with premature termination mutations in *PLEC1* [Nakamura et al 2005, Pfendner & Uitto 2005], and more commonly, the gene encoding β4 integrin *(ITGB4*). Rare cases of EB-PA are associated with mutations in the α6 integrin gene *(ITGA6*). Although disease course is severe and often lethal in the neonatal period, nonlethal forms have been described. Individuals with mutations in the genes encodingα6 or β4 integrin may also show renal and ureteral anomalies, including 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, Varki et al 2006, Pfendner et al 2007]. 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 [Dolan et al 1993, Azarian et al 2006].

- **EB-Ogna** [OMIM 131950], observed in one Norwegian and one German family, is a result of the site-specific autosomal dominant missense p.Arg2110Trp mutation within the rod domain of *PLEC1* [Koss-Harnes et al 2002]. A single lethal case of autosomal recessive EBS resulting from *PLEC1* mutations has also been described [Charlesworth et al 2003]. Kunz et al (2000) also described a case of EBS with severe mucous membrane involvement as a result of mutations in *PLEC1*.

Dystrophic EB (DEB). The blister forms below the basement membrane, and the basement membrane is attached to the blister roof, resulting in scarring when blisters heal. Mutations in *COL7A1*, the gene encoding type VII collagen, have been demonstrated in all forms of DEB, both dominant and recessive [Varki et al 2007].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with junctional epidermolysis bullosa (JEB), the following evaluations 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
- 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

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.

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 nonadherent 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., Kerlix®) 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®)

Other. The most common secondary complication 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. 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, a discussion with the family and hospital ethics committee often helps to determine the type of intervention and comfort care to provide [Yan et al 2007].

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].

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

Prevention of Secondary Complications

Fluid and electrolyte problems, which can be significant and even life-threatening in the neonatal period and in infants with widespread disease, require careful management.

In infants and children with JEB with more severe involvement, failure to thrive may be a problem, requiring additional nutritional support including a feeding gastrostomy when necessary to assure adequate caloric intake [Haynes et al 2006].

In children who survive the newborn period, nutritional deficiencies must also be addressed when they are identified:

- Calcium and vitamin D replacement for osteopenia and osteoporosis
- Zinc supplementation for wound healing [Mellerio et al 2007]

Iron-deficiency anemia, a chronic problem, can be treated with oral or intravenous iron infusions and red blood cell transfusions.

Surveillance

Screening for iron-deficiency anemia should be routine with complete blood counts and measurement of serum iron concentration to provide iron supplementation when necessary.

Screening for zinc deficiency by measuring serum zinc concentration should be routine to provide zinc supplementation when necessary to enhance wound healing.

Screening with bone mineral density scanning may pick up early osteopenia and/ or osteoporosis. No guidelines have been established regarding the age at which this should begin.

Because of the risk for squamous cell carcinoma, surveillance in the second decade of life for wounds that do not heal, have exuberant scar tissue, or otherwise look abnormal is essential. 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®.

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

Activities that, in general, traumatize the skin (e.g., hiking, mountain biking, contact sports) should be avoided; affected individuals who are determined to participate in such activities should be encouraged to find creative ways to protect their skin.

Testing of Relatives at Risk

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

Therapies Under Investigation

Several approaches to gene therapy for JEB have been proposed focused on retroviral modification of in vitro epidermal cells [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 a patient with *LAMB3* mutations [Mavilio et al 2006]. Animal models include intra-amniotic prenatal laminin 332 delivery in the mouse [Muhle et al 2006] and a spontaneous form of JEB in the dog [Capt et al 2005, Spirito et al 2006].

The knockout mouse model for all JEB genes should facilitate the development of these therapeutic approaches [Jiang & Uitto 2005].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Cesarean section is often recommended to reduce trauma to the skin of an affected fetus during delivery.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

There is no evidence to date that a single (i.e., heterozygous) mutation in *LAMA3*, *LAMB3*, *LAMC2*, or *COL17A1* results in JEB.

Risk to Family Members

Parents of a proband

- The parents of an affected child are usually obligate heterozygotes and therefore each parent carries one mutant allele. Because germline mosaicism and uniparental isodisomy have been reported [Pulkkinen et al 1997; Takizawa, Pulkkinen et al 2000; 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 cases of carriers of *COL17A1* mutations where dental enamel hypoplasia and resulting caries have been reported [Nakamura et al 2006, Murrell et al 2007].

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 an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic except in the case of *COL17A1* mutations where carriers may exhibit dental enamel pitting and caries [Nakamura et al 2006, Murrell et al 2007].

Offspring of a proband. The offspring of an individual with autosomal recessive JEB are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members of a proband. Each sib of the proband's carrier parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the family.

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 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 carriers.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing. Prenatal testing for pregnancies at increased risk for JEB is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at

approximately ten to 12 weeks' gestation. The disease-causing allele(s) must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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 diagnosis for JEB using fetoscopy is not currently available in the US, but may be available in Europe.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Junctional Epidermolysis Bullosa

Gene Symbol	Chromosomal Locus	Protein Name
COL17A1	10q24.3	Collagen alpha-1(XVII) chain
LAMA3	18q11.2	Laminin subunit alpha-3
LAMB3	1q32	Laminin subunit beta-3
LAMC2	1q25-q31	Laminin subunit gamma-2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Junctional Epidermolysis Bullosa

113811	COLLAGEN, TYPE XVII, ALPHA-1; COL17A1
150292	LAMININ, GAMMA-2; LAMC2
150310	LAMININ, BETA-3; LAMB3
226650	EPIDERMOLYSIS BULLOSA, GENERALIZED ATROPHIC BENIGN; GABEB
226700	EPIDERMOLYSIS BULLOSA LETALIS
600805	LAMININ, ALPHA-3; LAMA3

Table C. Genomic Databases for Junctional Epidermolysis Bullosa

Gene Symbol	Entrez Gene	HGMD
COL17A1	1308 (MIM No. 113811)	COL17A1
LAMA3	3909 (MIM No. 600805)	LAMA3
LAMB3	3914 (MIM No. 150310)	LAMB3
LAMC2	3918 (MIM No. 150292)	LAMC2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The proteins encoded by *LAMA3*, *LAMB3*, and *LAMC2* assemble into the laminin 332 heterotrimer (aka LAM5 [Aumailley et al 2005]). A mutation in these genes can lead to reduced resistance to minor trauma and the resulting muco-cutaneous blistering that is the hallmark of junctional epidermolysis bullosa (JEB). The type of mutation, the biochemical properties of the substituted amino acid, if present, and its location determine the severity of the blistering phenotype (see Genotype-Phenotype Correlations). Nonsense mutations predominate in the severe forms of JEB and result in the absence of one of the three proteins that assemble into laminin 332. Missense mutations in key positions of the protein subunits affect the ability of the lamininα3 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 mutations 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, mutations affecting the intracellular domain result in a cleavage plane within the lowest level of the basal keratinocytes usually associated with EBS [Charlesworth et al 2003].

LAMA3

Normal allelic variants: The entire *LAMA3* gene is encoded in 76 exons spanning 318 kb on chromosome 18q11.2. There are three isoforms *(LAMA3*a, *LAMA3*b1, and *LAMA3*b2) produced by alternative splicing (see Normal gene product).

Pathologic allelic variants: Nonsense, missense, splicing, and insertion deletion mutations have been reported [Varki et al 2006; Nakano, Chao et al 2002]. Premature termination codon mutations on both alleles result in the severe (Herlitz) form of JEB in most instances. A few mildly affected individuals with JEB with premature termination codon mutations have been reported [Nakano, Chao et al et al 2002]. Amino acid substitutions and splicing mutations may result in a milder phenotype [Posteraro et al 1998; Nakano, Chao et al 2002]. The common hot spot mutations are reportedly present in approximately 45% of H-JEB cases in the US (see Testing Strategy). These mutations invariably result in premature termination codons and when found on both alleles result in H-JEB. Overlapping phenotypes may exist in which mutations in *LAMA3* result in skin fragility with eye and laryngeal involvement [Varki et al 2006, Figueira et al 2007].

Table 2. *LAMA3* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.151insG	p.Val51GlyfsX3	AY327114.1 AAQ72569.1
c.1948A>T	p.Arg650X	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product: There are three isoforms *(LAMA3*a, *LAMA3*b1, and *LAMA3*b2) produced by alternative splicing. Of the two *LAMA3*b isoforms, *LAMA3*b1 encodes a longer protein of 3,333 amino acids in 75 exons (exons 1-38 and 40-76 of the gene); the shorter isoform *LAMA3*b2 encodes a protein of 3289 amino acids in 74 exons (exons 1-9, 11-38, and 40-76 of the gene) and differs from *LAMA3*b1 in that exon 10 is removed by alternative splicing. The

shorter *LAMA3*a isoform of 1724 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 andα6 β4 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 Genetic Pathogenesis. In all three genes *(LAMB3*, *LAMC2*, and *LAMA3*), amino acid substitutions, splicing mutations, 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. Usually, on a skin biopsy studied with immunofluorescence, if synthesis of one of the proteins is disrupted, the staining for the other two proteins will also be affected.

LAMB3

Normal allelic variants: The normal *LAMB3* cDNA has an open reading frame of 3516 nucleotides in 23 exons spanning 29 kb.

Pathologic allelic variants: Nonsense, missense, splicing, and insertion deletion mutations have been reported [Nakano, Lestringant et al 2002; Varki et al 2006]. A few cases of mildly affected JEB patients with premature termination codon mutations have been reported [Pulkkinen et al 1998; Nakano, Chao et al 2002]. Amino acid substitutions and splicing mutations may result in a milder phenotype [Mellerio et al 1998; Posteraro et al 1998; Nakano, Chao et al 2002].

Table 3. *LAMB3* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.124C>T	p.Arg42X	NM_000228.2 NP_000219.2
c.727C>T	p.Gln243X	
c.957ins77	p.Glu320X	
c.1903C>T	p.Arg635X	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

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 Genetic Pathogenesis. In all three genes *(LAMB3*, *LAMC2*, and *LAMA3*), amino acid substitutions, splicing mutations, 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. Usually, on a skin biopsy studied with immunofluorescence, if synthesis of one of the proteins is disrupted, the staining for the

other two proteins will also be affected. Reversion by *LAMB3* mosaicism to a normal phenotype has been described and has implications for treatment [Pasmooij et al 2007].

LAMC2

Normal allelic variants: Two protein isoforms are encoded by *LAMC2*. The longest is encoded in 23 exons and is expressed in the epidermis. The shorter isoform produced by alternative splicing ends two codons past exon 22 and is expressed in the cerebral cortex, lung, and distal tubules of the kidney. The epidermal *LAMC2* cDNA has an open reading frame of 3573 nucleotides encoding 1191 amino acids in 23 exons spanning 55 kb.

Pathologic allelic variants: Nonsense, missense, splicing, and insertion deletion mutations have been reported [Castiglia et al 2001; Nakano, Lestringant et al 2002; Varki et al 2006]. Amino acid substitutions and splicing mutations may result in a milder phenotype [Posteraro et al 1998; Castiglia et al 2001; Nakano, Chao et al 2002].

Table 4. *LAMC2* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.283C>T	p.Arg95X	NM_005562.2 NP_005553.2

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

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 Genetic Pathogenesis. In all three genes *(LAMB3*, *LAMC2*, and *LAMA3*), amino acid substitutions, splicing mutations, 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. Usually, on a skin biopsy studied with immunofluorescence, if synthesis of one of the proteins is disrupted, the staining for the other two proteins will also be affected.

COL17A1

Normal allelic variants: The cDNA has an open reading frame of 5610 nucleotides encoding 1497 amino acids in 56 exons. There is one alternatively spliced mRNA variant [Ruzzi et al 2001].

Pathologic allelic variants: Mutations in *COL17A1*, which encodes the collagen XVII protein, a component of the hemidesmosome, result in typically less severe forms of JEB (non-Herlitz) [Gatalica et al 1997; Pulkkinen et al 1999; Takizawa, Hiraoka et al 2000; van Leusden et al 2001; Pasmooij, van Zalen et al 2004], although a few cases of lethal JEB resulting from *COL17A1* mutations have been reported [Varki et al 2006, Murrell et al 2007]. All types of mutations, including premature termination codon, nonsense, insertion/deletion, splice junction, and missense, distributed throughout the gene have been described. The type and location of the mutations and the response of the cells to the mutations 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].

Normal gene product: Collagen XVII (also known as BP180) 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 mutations that result in a null allele cause skin fragility, dental abnormalities, and alopecia usually found in patients with NH-JEB. Other mutations may result in varying phenotypic severity. Although *COL17A1* mutations do not usually result in lethality, several cases of a neonatal lethal phenotype were recently described [Varki et al 2006, Murrell et al 2007]. Mutations 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. Mutations 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 mutations resulting in skin fragility have been identified. Heterozygote carriers of a glycine substitution [Nakamura et al 2006] or other *COL17A1* mutations [Murrell et al 2007] may exhibit dental enamel pitting and this characteristic may be diagnostic for *COL17A1* mutations in a family with an affected child [Murrell et al 2007].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

DEBRA International
www.debra-international.org

DEBRA of America
(Dystrophic Epidermolysis Bullosa Research Association of America)
5 West 36th Street Room 404
New York NY 10018
Phone: 866-DEBRA76 (866-332-7276); 212-868-1573
Fax: 212-868-9296
Email: staff@debra.org
www.debra.org

DEBRA-UK
DebRA House
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Email: DebRA@DebRA.org.uk
www.debra.org.uk

Medline Plus
Epidermolysis bullosa

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Anton-Lamprecht I, Gedde-Dahl T. Epidermolysis bullosa. In: Rimoin DL, Connor MJ, Pyeritz RE, Korf BR, Emery AEH (eds) Principles and Practice of Medical Genetics, 4th edition. Churchill Livingstone Publishers, NY. 2002

Aumailley M, Bruckner-Tuderman L, Carter WG, Deutzmann R, Edgar D, Ekblom P, Engel J, Engvall E, Hohenester E, Jones JC, Kleinman HK, Marinkovich MP, Martin GR, Mayer U, Meneguzzi G, Miner JH, Miyazaki K, Patarroyo M, Paulsson M, Quaranta V, Sanes JR, Sasaki T, Sekiguchi K, Sorokin LM, Talts JF, Tryggvason K, Uitto J, Virtanen I, von der Mark K, Wewer UM, Yamada Y, Yurchenco PD. A simplified laminin nomenclature. Matrix Biol. 2005;24:326–32. [PubMed: 15979864]

Azarian M, Dreux S, Vuillard E, Meneguzzi G, Haber S, Guimiot F, Muller F. Prenatal diagnosis of inherited epidermolysis bullosa in a patient with no family history: a case report and literature review. Prenat Diagn. 2006;26:57–9. [PubMed: 16378325]

Azizkhan RG, Denyer JE, Mellerio JE, Gonzalez R, Bacigalupo M, Kantor A, Passalacqua G, Palisson F, Lucky AW. Surgical management of epidermolysis bullosa: Proceedings of the IInd International Symposium on Epidermolysis Bullosa, Santiago, Chile, 2005. Int J Dermatol. 2007;46:801–8. [PubMed: 17651160]

Capt A, Spirito F, Guaguere E, Spadafora A, Ortonne JP, Meneguzzi G. Inherited junctional epidermolysis bullosa in the German Pointer: establishment of a large animal model. J Invest Dermatol. 2005;124:530–5. [PubMed: 15737193]

Castiglia D, Posteraro P, Spirito F, Pinola M, Angelo C, Puddu P, Meneguzzi G, Zambruno G. Novel mutations in the LAMC2 gene in non-Herlitz junctional epidermolysis bullosa: effects on laminin-5 assembly, secretion, and deposition. J Invest Dermatol. 2001;117:731–9. [PubMed: 11564184]

Charlesworth A, Gagnoux-Palacios L, Bonduelle M, Ortonne JP, De Raeve L, Meneguzzi G. Identification of a lethal form of epidermolysis bullosa simplex associated with a homozygous genetic mutation in plectin. J Invest Dermatol. 2003;121:1344–8. [PubMed: 14675180]

Cserhalmi-Friedman PB, Anyane-Yeboa K, Christiano AM. Paternal germline mosaicism in Herlitz junctional epidermolysis bullosa. Exp Dermatol. 2002;11:468–70. [PubMed: 12366701]

Cserhalmi-Friedman PB, Baden H, Burgeson RE, Christiano AM. Molecular basis of non-lethal junctional epidermolysis bullosa: identification of a 38 basepair insertion and a splice site mutation in exon 14 of the LAMB3 gene. Exp Dermatol. 1998;7:105–11. [PubMed: 9583749]

Dolan CR, Smith LT, Sybert VP. Prenatal detection of epidermolysis bullosa letalis with pyloric atresia in a fetus by abnormal ultrasound and elevated alpha-fetoprotein. Am J Med Genet. 1993;47:395–400. [PubMed: 7510931]

Fassihi H, Wessagowit V, Ashton GH, Moss C, Ward R, Denyer J, Mellerio JE, McGrath JA. Complete paternal uniparental isodisomy of chromosome 1 resulting in Herlitz junctional epidermolysis bullosa. Clin Exp Dermatol. 2005;30:71–4. [PubMed: 15663509]

Fewtrell MS, Allgrove J, Gordon I, Brain C, Atherton D, Harper J, Mellerio JE, Martinez AE. Bone mineralization in children with epidermolysis bullosa. Br J Dermatol. 2006;154:959–62. [PubMed: 16634901]

Figueira EC, Crotty A, Challinor CJ, Coroneo MT, Murrell DF. Granulation tissue in the eyelid margin and conjunctiva in junctional epidermolysis bullosa with features of laryngo-onycho-cutaneous syndrome. Clin Experiment Ophthalmol. 2007;35:163–6. [PubMed: 17362460]

Fine JD, Bauer EA, McGuire J Moshell A. (1999) Epidermolysis Bullosa; Clinical epidemiologic, and laboratory advances and the findings of the National Epidermolysis Bullosa Registry. Johns Hopkins University Press, Baltimore. eds

Fine JD, Eady RA, Bauer EA, Briggaman RA, Bruckner-Tuderman L, Christiano A, Heagerty A, Hintner H, Jonkman MF, McGrath J, McGuire J, Moshell A, Shimizu H, Tadini G, Uitto J. Revised classification system for inherited epidermolysis bullosa: Report of the Second International Consensus Meeting on diagnosis and classification of epidermolysis bullosa. J Am Acad Dermatol. 2000;42:1051–66. [PubMed: 10827412]

Fine JD, Johnson LB, Weiner M, Stein A, Cash S, DeLeoz J, Devries DT, Suchindran C, National Epidermolysis Bullosa Registry. Inherited epidermolysis bullosa and the risk of death from renal disease: experience of the National Epidermolysis Bullosa Registry. Am J Kidney Dis. 2004;44:651–60. [PubMed: 15384016]

Gatalica B, Pulkkinen L, Li K, Kuokkanen K, Ryynanen M, McGrath JA, Uitto J. Cloning of the human type XVII collagen gene (COL17A1), and detection of novel mutations in generalized atrophic benign epidermolysis bullosa. Am J Hum Genet. 1997;60:352–65. [PubMed: 9012408]

Haynes L. Nutritional support for children with epidermolysis bullosa. Br J Nurs. 2006;15:1097–101. [PubMed: 17170656]

Huber M, Floeth M, Borradori L, Schacke H, Rugg EL, Lane EB, Frenk E, Hohl D, Bruckner-Tuderman L. Deletion of the cytoplasmatic domain of BP180/collagen XVII causes a phenotype with predominant features of epidermolysis bullosa simplex. J Invest Dermatol. 2002;118:185–92. [PubMed: 11851893]

Inoue M, Tamai K, Shimizu H, Owaribe K, Nakama T, Hashimoto T, McGrath JA. A homozygous missense mutation in the cytoplasmic tail of beta4 integrin, G931D, that disrupts hemidesmosome assembly and underlies Non-Herlitz junctional epidermolysis bullosa without pyloric atresia? J Invest Dermatol. 2000;114:1061–4. [PubMed: 10792571]

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

Jiang QJ, Uitto J. Animal models of epidermolysis bullosa--targets for gene therapy. J Invest Dermatol. 2005;124:xi–xiii. [PubMed: 15812910]

Jonkman MF, Pas HH, Nijenhuis M, Kloosterhuis G, Steege G. Deletion of a cytoplasmic domain of integrin beta4 causes epidermolysis bullosa simplex. J Invest Dermatol. 2002;119:1275–81. [PubMed: 12485428]

Kambham N, Tanji N, Seigle RL, Markowitz GS, Pulkkinen L, Uitto J, D'Agati VD. Congenital focal segmental glomerulosclerosis associated with beta4 integrin mutation and epidermolysis bullosa. Am J Kidney Dis. 2000;36:190–6. [PubMed: 10873890]

Kirkham J, Robinson C, Strafford SM, Shore RC, Bonass WA, Brookes SJ, Wright JT. The chemical composition of tooth enamel in junctional epidermolysis bullosa. Arch Oral Biol. 2000;45:377–86. [PubMed: 10739859]

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

Koss-Harnes D, Hoyheim B, Jonkman MF, de Groot WP, de Weerdt CJ, Nikolic B, Wiche G, Gedde-Dahl T Jr. Life-long course and molecular characterization of the original Dutch family with epidermolysis bullosa simplex with muscular dystrophy due to a homozygous novel plectin point mutation. Acta Derm Venereol. 2004;84:124–31. [PubMed: 15206692]

Kunz M, Rouan F, Pulkkinen L, Hamm H, Jeschke R, Bruckner-Tuderman L, Brocker EB, Wiche G, Uitto J, Zillikens D. Mutation reports: epidermolysis bullosa simplex associated with severe mucous membrane involvement and novel mutations in the plectin gene. J Invest Dermatol. 2000;114:376–80. [PubMed: 10652001]

Lucky AW, Pfendner E, Pillay E, Paskel J, Weiner M, Palisson F. Psychosocial aspects of epidermolysis bullosa: Proceedings of the IInd International Symposium on Epidermolysis Bullosa, Santiago, Chile, 2005. Int J Dermatol. 2007;46:809–14. [PubMed: 17651161]

Mallipeddi R, Keane FM, McGrath JA, Mayou BJ, Eady RA. Increased risk of squamous cell carcinoma in junctional epidermolysis bullosa. J Eur Acad Dermatol Venereol. 2004;18:521–6. [PubMed: 15324385]

Mavilio F, Pellegrini G, Ferrari S, Di Nunzio F, Di Iorio E, Recchia A, Maruggi G, Ferrari G, Provasi E, Bonini C, Capurro S, Conti A, Magnoni C, Giannetti A, De Luca M. Correction of junctional epidermolysis bullosa by transplantation of genetically modified epidermal stem cells. Nat Med. 2006;12:1397–402. [PubMed: 17115047]

McGrath JA, Ashton GH, Mellerio JE, Salas-Alanis JC, Swensson O, McMillan JR, Eady RA. Moderation of phenotypic severity in dystrophic and junctional forms of epidermolysis bullosa through in-frame skipping of exons containing non-sense or frameshift mutations. J Invest Dermatol. 1999;113:314–21. [PubMed: 10469327]

McGrath JA, Kivirikko S, Ciatti S, Moss C, Christiano AM, Uitto J. A recurrent homozygous nonsense mutation within the LAMA3 gene as a cause of Herlitz junctional epidermolysis bullosa in patients of Pakistani ancestry: evidence for a founder effect. J Invest Dermatol. 1996;106:781–4. [PubMed: 8618022]

McLean WH, Irvine AD, Hamill KJ, Whittock NV, Coleman-Campbell CM, Mellerio JE, Ashton GS, Dopping-Hepenstal PJ, Eady RA, Jamil T, Phillips RJ, Shabbir SG, Haroon TS, Khurshid K, Moore JE, Page B, Darling J, Atherton DJ, Van Steensel MA, Munro CS, Smith FJ, McGrath JA. An unusual N-terminal deletion of the laminin alpha3a isoform leads to the chronic granulation tissue disorder laryngo-onycho-cutaneous syndrome. Hum Mol Genet. 2003;12:2395–409. [PubMed: 12915477]

Mellerio JE, Eady RA, Atherton DJ, Lake BD, McGrath JA. E210K mutation in the gene encoding the beta3 chain of laminin-5 (LAMB3) is predictive of a phenotype of generalized atrophic benign epidermolysis bullosa. Br J Dermatol. 1998;139:325–31. [PubMed: 9767254]

Mellerio JE, Weiner M, Denyer JE, Pillay EI, Lucky AW, Bruckner A, Palisson F. Medical management of epidermolysis bullosa: Proceedings of the IInd International Symposium on Epidermolysis Bullosa, Santiago, Chile, 2005. Int J Dermatol. 2007;46:795–800. [PubMed: 17651159]

Micheloni A, De Luca N, Tadini G, Zambruno G, D'Alessio M. Intracellular degradation of beta4 integrin in lethal junctional epidermolysis bullosa with pyloric atresia. Br J Dermatol. 2004;151:796–802. [PubMed: 15491419]

Muhle C, Neuner A, Park J, Pacho F, Jiang Q, Waddington SN, Schneider H. Evaluation of prenatal intra-amniotic LAMB3 gene delivery in a mouse model of Herlitz disease. Gene Ther. 2006;13:1665–76. [PubMed: 16871230]

Murrell DF, Pasmooij AM, Pas HH, Marr P, Klingberg S, Pfendner E, Uitto J, Sadowski S, Collins F, Widmer R, Jonkman MF. Retrospective diagnosis of fatal BP180-deficient non-Herlitz junctional epidermolysis bullosa suggested by immunofluorescence (IF) antigen-mapping of parental carriers bearing enamel defects. J Invest Dermatol. 2007;127:1772–5. [PubMed: 17344927]

Nakamura H, Sawamura D, Goto M, Nakamura H, McMillan JR, Park S, Kono S, Hasegawa S, Paku S, Nakamura T, Ogiso Y, Shimizu H. Epidermolysis bullosa simplex associated with pyloric atresia is a novel clinical subtype caused by mutations in the plectin gene (PLEC1). J Mol Diagn. 2005;7:28–35. [PubMed: 15681471]

Nakamura H, Sawamura D, Goto M, Nakamura H, Kida M, Ariga T, Sakiyama Y, Tomizawa K, Mitsui H, Tamaki K, Shimizu H. Analysis of the COL17A1 in non-Herlitz junctional epidermolysis bullosa and amelogenesis imperfecta. Int J Mol Med. 2006;18:333–7. [PubMed: 16820943]

Nakano A, Chao SC, Pulkkinen L, Murrell D, Bruckner-Tuderman L, Pfendner E, Uitto J. Laminin 5 mutations in junctional epidermolysis bullosa: molecular basis of Herlitz vs. non-Herlitz phenotypes. Hum Genet. 2002;110:41–51. [PubMed: 11810295]

Nakano A, Lestringant GG, Paperna T, Bergman R, Gershoni R, Frossard P, Kanaan M, Meneguzzi G, Richard G, Pfendner E, Uitto J, Pulkkinen L, Sprecher E. Junctional epidermolysis bullosa in the Middle East: clinical and genetic studies in a series of consanguineous families. J Am Acad Dermatol. 2002;46:510–6. [PubMed: 11907499]

Nakano A, Pfendner E, Hashimoto I, Uitto J. Herlitz junctional epidermolysis bullosa: novel and recurrent mutations in the LAMB3 gene and the population carrier frequency. J Invest Dermatol. 2000;115:493–8. [PubMed: 11023379]

Ortiz-Urda S, Lin Q, Yant SR, Keene D, Kay MA, Khavari PA. Sustainable correction of junctional epidermolysis bullosa via transposon-mediated nonviral gene transfer. Gene Ther. 2003;10:1099–104. [PubMed: 12808440]

Pasmooij AM, Pas HH, Bolling MC, Jonkman MF. Revertant mosaicism in junctional epidermolysis bullosa due to multiple correcting second-site mutations in LAMB3. J Clin Invest. 2007;117:1240–8. [PubMed: 17476356]

Pasmooij AM, Pas HH, Deviaene FC, Nijenhuis M, Jonkman MF. Multiple correcting COL17A1 mutations in patients with revertant mosaicism of epidermolysis bullosa. Am J Hum Genet. 2005;77:727–40. [PubMed: 16252234]

Pasmooij AM, van der Steege G, Pas HH, Smitt JH, Nijenhuis AM, Zuiderveen J, Jonkman MF. Features of epidermolysis bullosa simplex due to mutations in the ectodomain of type XVII collagen. Br J Dermatol. 2004;151:669–74. [PubMed: 15377356]

Pasmooij AM, van Zalen S, Nijenhuis AM, Kloosterhuis AJ, Zuiderveen J, Jonkman MF, Pas HH. A very mild form of non-Herlitz junctional epidermolysis bullosa: BP180 rescue by outsplicing of mutated exon 30 coding for the COL15 domain. Exp Dermatol. 2004;13:125–8. [PubMed: 15009107]

Pfendner E, Uitto J. Plectin gene mutations can cause epidermolysis bullosa with pyloric atresia. J Invest Dermatol. 2005;124:111–5. [PubMed: 15654962]

Pfendner E, Rouan F, Uitto J. Progress in epidermolysis bullosa: the phenotypic spectrum of plectin mutations. Exp Dermatol. 2005;14:241–9. [PubMed: 15810881]

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

Pfendner EG, Bruckner A, Conget P, Mellerio J, Palisson F, Lucky AW. Basic science of epidermolysis bullosa and diagnostic and molecular characterization: Proceedings of the IInd International Symposium on Epidermolysis Bullosa, Santiago, Chile, 2005. Int J Dermatol. 2007;46:781–94. [PubMed: 17651158]

Posteraro P, De Luca N, Meneguzzi G, El Hachem M, Angelo C, Gobello T, Tadini G, Zambruno G, Castiglia D. Laminin-5 mutational analysis in an Italian cohort of patients with junctional epidermolysis bullosa. J Invest Dermatol. 2004;123:639–48. [PubMed: 15373767]

Posteraro P, Sorvillo S, Gagnoux-Palacios L, Angelo C, Paradisi M, Meneguzzi G, Castiglia D, Zambruno G. Compound heterozygosity for an out-of-frame deletion and a splice site mutation in the LAMB3 gene causes nonlethal junctional epidermolysis bullosa. Biochem Biophys Res Commun. 1998;243:758–64. [PubMed: 9501007]

Pulkkinen L, Uitto J. Mutation analysis and molecular genetics of epidermolysis bullosa. Matrix Biol. 1999;18:29–42. [PubMed: 10367729]

Pulkkinen L, Bruckner-Tuderman L, August C, Uitto J. Compound heterozygosity for missense (L156P) and nonsense (R554X) mutations in the beta4 integrin gene (ITGB4) underlies mild, nonlethal phenotype of epidermolysis bullosa with pyloric atresia. Am J Pathol. 1998;152:935–41. [PubMed: 9546354]

Pulkkinen L, Bullrich F, Czarnecki P, Weiss L, Uitto J. Maternal uniparental disomy of chromosome 1 with reduction to homozygosity of the LAMB3 locus in a patient with Herlitz junctional epidermolysis bullosa. Am J Hum Genet. 1997;61:611–9. [PubMed: 9326326]

Pulkkinen L, Marinkovich MP, Tran HT, Lin L, Herron GS, Uitto J. Compound heterozygosity for novel splice site mutations in the BPAG2/COL17A1 gene underlies generalized atrophic benign epidermolysis bullosa. J Invest Dermatol. 1999;113:1114–8. [PubMed: 10636730]

Pulkkinen L, McGrath JA, Christiano AM, Uitto J. Detection of sequence variants in the gene encoding the beta 3 chain of laminin 5 (LAMB3). Hum Mutat. 1995;6:77–84. [PubMed: 7550237]

Puvabanditsin S, Garrow E, Samransamraujkit R, Lopez LA, Lambert WC. Epidermolysis bullosa associated with congenital localized absence of skin, fetal abdominal mass, and pyloric atresia. Pediatr Dermatol. 1997;14:359–62. [PubMed: 9336805]

Robbins PB, Lin Q, Goodnough JB, Tian H, Chen X, Khavari PA. In vivo restoration of laminin 5 beta 3 expression and function in junctional epidermolysis bullosa. Proc Natl Acad Sci U S A. 2001;98:5193–8. [PubMed: 11296269]

Ruzzi L, Pas H, Posteraro P, Mazzanti C, Didona B, Owaribe K, Meneguzzi G, Zambruno G, Castiglia D, D'Alessio M. A homozygous nonsense mutation in type XVII collagen gene (COL17A1) uncovers an alternatively spliced mRNA accounting for an unusually mild form of non-Herlitz junctional epidermolysis bullosa. J Invest Dermatol. 2001;116:182–7. [PubMed: 11168815]

Schara U, Tucke J, Mortier W, Nusslein T, Rouan F, Pfendner E, Zillikens D, Bruckner-Tuderman L, Uitto J, Wiche G, Schroder 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: 14963703]

Smith FJ, Eady RA, Leigh IM, McMillan JR, Rugg EL, Kelsell DP, Bryant SP, Spurr NK, Geddes JF, Kirtschig G, Milana G, de Bono AG, Owaribe K, Wiche G, Pulkkinen L, Uitto J, McLean WH, Lane EB. Plectin deficiency results in muscular dystrophy with epidermolysis bullosa. Nat Genet. 1996;13:450–7. [PubMed: 8696340]

Spirito F, Capt A, Del Rio M, Larcher F, Guaguere E, Danos O, Meneguzzi G. Sustained phenotypic reversion of junctional epidermolysis bullosa dog keratinocytes: Establishment of an immunocompetent animal model for cutaneous gene therapy. Biochem Biophys Res Commun. 2006;339:769–78. [PubMed: 16316622]

Takizawa Y, Hiraoka Y, Takahashi H, Ishiko A, Yasuraoka I, Hashimoto I, Aiso S, Nishikawa T, Shimizu H. Compound heterozygosity for a point mutation and a deletion located at splice acceptor sites in the LAMB3 gene leads to generalized atrophic benign epidermolysis bullosa. J Invest Dermatol. 2000;115:312–6. [PubMed: 10951252]

Takizawa Y, Pulkkinen L, Chao SC, Nakajima H, Nakano Y, Shimizu H, Uitto J. Mutation report: complete paternal uniparental isodisomy of chromosome 1: a novel mechanism for Herlitz junctional epidermolysis bullosa. J Invest Dermatol. 2000;115:307–11. [PubMed: 10951251]

Uitto J, Richard G. Progress in epidermolysis bullosa: from eponyms to molecular genetic classification. Clin Dermatol. 2005;23:33–40. [PubMed: 15708287]

van Leusden MR, Pas HH, Gedde-Dahl T Jr, Sonnenberg A, Jonkman MF. Truncated typeXVII collagen expression in a patient with non-herlitz junctional epidermolysis bullosa caused by a homozygous splice-site mutation. Lab Invest. 2001;81:887–94. [PubMed: 11406649]

Varki R, Sadowski S, Pfendner E, Uitto J. Epidermolysis bullosa. I. Molecular genetics of the junctional and hemidesmosomal variants. J Med Genet. 2006;43:641–52. [PubMed: 16473856]

Varki R, Sadowski S, Uitto J, Pfendner E. Epidermolysis bullosa. II. Type VII collagen mutations and phenotype-genotype correlations in the dystrophic subtypes. J Med Genet. 2007;44:181–92. [PubMed: 16971478]

Wallerstein R, Klein ML, Genieser N, Pulkkinen L, Uitto J. Epidermolysis bullosa, pyloric atresia, and obstructive uropathy: a report of two case reports with molecular correlation and clinical management. Pediatr Dermatol. 2000;17:286–9. [PubMed: 10990577]

Yan EG, Paris JJ, Ahluwalia J, Lane AT, Bruckner AL. Treatment decision-making for patients with the Herlitz subtype of junctional epidermolysis bullosa. J Perinatol. 2007;27:307–11. [PubMed: 17363907]

Suggested Readings

Uitto J and Pulkkinen L. Epidermolysis bullosa: the disease of the cutaneous basement membrane zone. In: Scriver CR. Beaudet AL, Sly WS, Valle D, Vogelstein B. The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 222. Available at www.ommbid.com. Accessed 2-13-08. eds

Chapter Notes

Author Notes

Web: www.genedx.com

Web: www.cincinnatichildrens.org/eb-center

Revision History

- 22 February 2008 (me) Review posted to live Web site
- 10 May 2007 (egp) Original submission

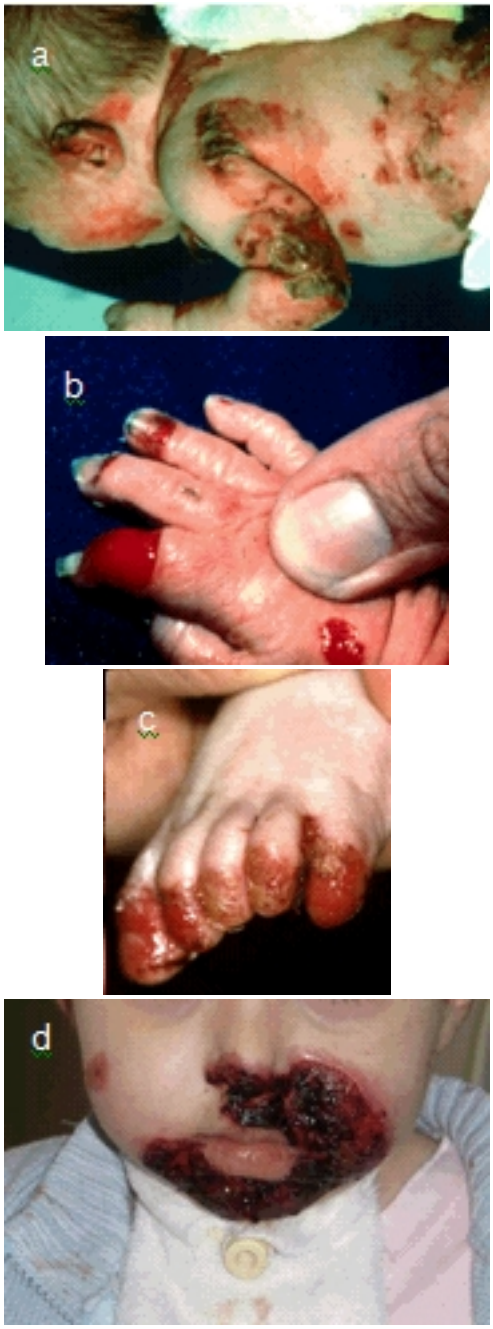

Figure 1. Herlitz JEB
a. Extensive widespread blistering and granulation tissue on ear
b. Hand of a child showing aplasia cutis congenital
c. Foot of an affected child
d. Exuberant perioral granulation tissue and tracheostomy in a child

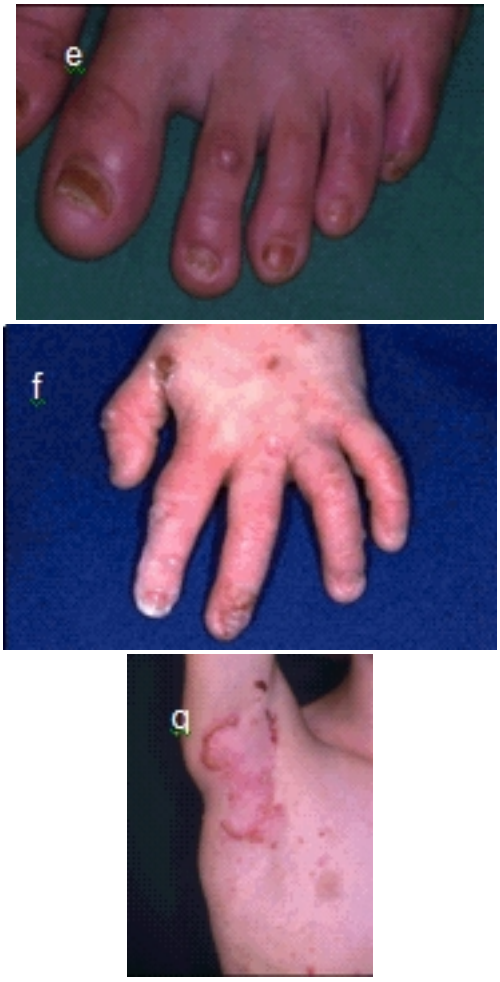

Figure 2. Non-Herlitz JEB
e. Minor nail dystrophy in an older child
f. Multiple blisters on the hands of an active toddler
g. Non-scarring superficial axillary erosions

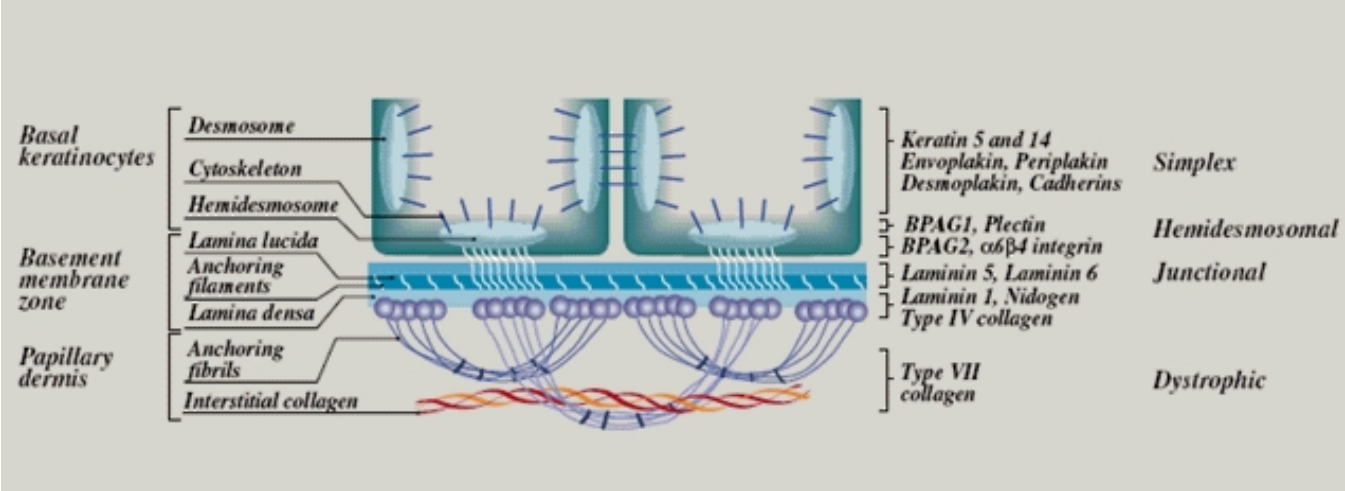

Figure 3. Diagram showing locations affected by mutations causing the four major subtypes of EB syndromes