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Dystrophic Epidermolysis Bullosa

[*Epidermolysis Bullosa Dystrophica. Includes: Dystrophic Epidermolysis Bullosa, Autosomal Dominant; Dystrophic Epidermolysis Bullosa, Autosomal Recessive (Hallopeau-Siemens Type and non-Hallopeau-Siemens Type)*]

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Summary

Disease characteristics. Dystrophic epidermolysis bullosa (DEB) includes three subtypes: recessive DEB, Hallopeau-Siemens type (RDEB-HS); recessive DEB, non-Hallopeau-Siemens type (non-HS RDEB); and dominant DEB (DDEB). In RDEB-HS, the classic severe form of DEB, blisters affecting the whole body are present in the neonatal period. Oral involvement may lead to fusion of the tongue to the floor of the mouth and progressive diminution of the size of the oral cavity. Esophageal erosions can lead to webs and strictures that can cause severe dysphagia. Corneal erosions can lead to scarring and loss of vision. Blistering of the hands and feet followed by scarring fuses the digits into "mitten" hands and feet, a hallmark of this disorder. The lifetime risk of aggressive squamous cell carcinoma is over 90%. In contrast, the blistering in non-HS RDEB is localized to hands, feet, knees, and elbows with or without involvement of flexural areas and the trunk, and without the severe, mutilating scarring seen in classic RDEB-HS. In DDEB, blistering is often mild and limited to hands, feet, knees, and elbows, but nonetheless heals with scarring. Dystrophic nails, especially toenails, are common and may be the only manifestation of DDEB.

Diagnosis/testing. Examination of a skin biopsy by transmission electron microscopy (EM) or immunofluorescent (IF) antibody/antigen mapping is the best way to reliably establish the diagnosis. The only gene known to be associated with DEB is *COL7A1*. Sequencing of exons 73, 74, and 75 of *COL7A1* detects mutations in 75% of families with DDEB; sequencing of all coding exons detects mutations in about 95% of individuals with either DDEB or RDEB.

Management. New blisters should be lanced, drained, and in most cases dressed with a non-adherent material, padding for stability and protection, and an elastic wrap for integrity. Infants and children with severe RDEB and failure to thrive require attention to fluid and electrolyte balance and may require nutritional support, including feeding gastrostomy. Anemia is treated with oral iron supplements and transfusions as needed. Other nutritional supplements may include calcium, vitamin D, selenium, carnitine, and zinc. Occupational therapy may help prevent hand contractures. Surgical release of fingers often needs to be repeated. Surveillance includes biopsy of abnormal-appearing wounds that do not heal or have exuberant scar tissue for evidence of squamous cell carcinoma beginning in the second decade; and screening for

deficiency of iron, zinc, selenium, and carnitine. In general, activities that traumatize the skin should be avoided.

Genetic counseling. Dystrophic epidermolysis bullosa (DEB) is inherited in either an autosomal dominant or autosomal recessive manner. Molecular characterization of pathogenic mutations is the only accurate method to determine mode of inheritance and recurrence risk; phenotype severity and EM/IF findings alone are not sufficient. About 70% of individuals diagnosed with autosomal dominant DEB are reported to have an affected parent. If a parent of a proband with autosomal dominant DEB is affected, the risk to the sibs is 50%. Each child of an individual with autosomal dominant DEB has a 50% chance of inheriting the mutation. For autosomal recessive DEB, each sib of an affected individual whose parents are both carriers has at conception 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. Prenatal testing for pregnancies at increased risk for DEB is possible if the disease-causing allele(s) of an affected family member is (are) known.

Diagnosis

Clinical Diagnosis

The diagnosis of dystrophic epidermolysis bullosa (DEB) is suspected in individuals with fragility of the skin, manifest by blistering with little or no trauma. Blisters heal with milia and scarring that in the severest forms of DEB can result in mutilating pseudosyndactyly of the hands and feet.

Because the clinical features of all types of EB overlap significantly, clinical diagnosis is unreliable and examination of a skin biopsy is usually required to establish the diagnosis, especially in infants (see Figure 1).

Testing

Skin biopsy. Examination of a skin biopsy by transmission electron microscopy or immunofluorescent antibody/antigen mapping is the best way to reliably establish the diagnosis of DEB. However, sometimes, especially in milder forms of EB, indirect immunofluorescent studies are not sufficient to make the diagnosis because near-normal antigen levels are detected and no cleavage plane is observed. In such cases, electron microscopic examination of the skin biopsy must be carried out to examine the number and morphology of the basement membrane zone structures — in particular, the number and morphology of anchoring fibrils and the presence and morphology of hemidesmosomes, anchoring filaments, and keratin intermediate filaments.

In DEB, the blister forms below the basement membrane, which becomes attached to the blister roof, thus resulting in scarring when the blister heals.

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

The biopsy should be taken from the leading edge of a fresh (less than 12 hours old) or mechanically induced blister and should include some normal adjacent skin; older blisters undergo change that may obscure the diagnostic morphology. Elliptical or shave excisions are often used. Although a punch biopsy can introduce confusing artifact, careful use of the punch can avoid loss of the epidermis.

Findings on transmission electron microscopy (TEM)

- All DEB. Splitting is observed below the lamina densa of the basement membrane of the epidermis.

- Autosomal recessive DEB (RDEB), Hallopeau-Siemens type. Anchoring fibrils are markedly reduced or absent.
- Autosomal dominant DEB (DDEB)
  - Anchoring fibrils may appear reduced in number and show altered morphology.
  - Intracellular retention of collagen VII can be observed in some individuals.
  - In some individuals who have transient blistering in the newborn period, collagen VII may be retained intracellularly within the basal keratinocytes instead of being transported to the basement membrane zone.

Findings on immunofluorescent antibody/antigen mapping

- Staining of collagen VII using antibodies is abnormal or absent. (In mild DEB, staining for collagen VII may appear normal, but cleavage planes in the form of vesicles or microvesicles can be observed below the lamina densa and below the collagen VII staining.)
- Normal staining for other antigens (e.g., laminin 5, collagen XVII, plectin, α6β4 integrin, and keratins 5 and 14) confirms the diagnosis of DEB.

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—Gene. The only gene known to be associated with dystrophic EB is *COL7A1*.

Clinical uses

- Confirmatory diagnostic testing
- Carrier testing (in families with autosomal recessive inheritance)
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Clinical testing

- **Sequence analysis**

DDEB. When DDEB is suspected, sequence analysis of exons 73, 74, and 75 of *COL7A1*, which detects approximately 75% of the dominant dystrophic EB mutations, is performed first. *De novo* and recurrent mutations, especially p.Gly2043Arg and p.Gly2034Arg in exon 73, have been described.

If no mutation is identified in exons 73-75, sequencing of the remaining coding exons is performed. Mutation detection rate in individuals with biopsy-diagnosed DEB is 95% [Kern et al 2006; Pfendner, unpublished observation].

RDEB. Sequencing of the entire coding region is usually necessary to identify both mutations in individuals with RDEB. Mutations may be nonsense, missense, splicing, or small insertions and deletions. Detection rate for sequencing of the entire *COL7A1* gene is greater than 95%.

Note: Although sequencing of exons in which founder mutations are identified in individuals of certain ethnic backgrounds has been described in European populations, such an approach has not been fruitful in the US population, in which mutations can be found in any of the 118 exons of *COL7A1*.

- **Deletion/duplication analysis.** Using methods such as quantitative real-time PCR, deletions/duplications in *COL7A1* may be detected.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Dystrophic Epidermolysis Bullosa

Dystrophic EB Type	Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Autosomal dominant DEB	Sequencing of exons 73, 74, 75 of *COL7A1*	*COL7A1* sequence variants	75%	Clinical Testing
Autosomal dominant DEB	Sequencing of all *COL7A1* coding exons		95%	
Autosomal recessive DEB				
Autosomal dominant DEB	Deletion/duplication analysis	*COL7A1* deletions/ duplications	Unknown	
Autosomal recessive DEB				

1. Proportion of individuals with biopsy-diagnosed DEB who have a mutation(s) as classified by DEB type and test method

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

Testing Strategy

Especially in newborns, a skin biopsy should be performed as soon as possible after initial evaluation.

Genetically Related (Allelic) Disorders

No phenotypes other than DEB are associated with mutations in *COL7A1*.

Clinical Description

Natural History

Before the molecular basis of dystrophic epidermolysis bullosa (DEB) was understood, subtypes were identified (see Nomenclature) based primarily on clinical features, mode of inheritance, and the presence or absence of collagen VII and anchoring fibrils detected on skin biopsy. The current classification system includes the following three subtypes which are discussed below: recessive DEB, Hallopeau-Siemens type; recessive DEB, non-Hallopeau-Siemens type; and dominant DEB [Fine et al 1999, Pulkkinen & Uitto 1999, Irvine & McLean 2003, Uitto & Richard 2005].

Autosomal recessive DEB (RDEB)

- **RDEB Hallopeau-Siemens (RDEB-HS).** In this classic severe form of DEB, blisters are present at birth or become apparent in the neonatal period.

  As early as the newborn period, blisters affect the whole body including the oral mucosa, the esophageal mucosa, and the cornea. Oral involvement may lead to fusion of the tongue to the floor of the mouth (ankyloglossia) and progressive diminution of the size of the oral cavity and mouth opening (microstomia) which, along with poor

dental hygiene and caries, impairs food intake [Serrano-Martinez et al 2003, De Benedittis et al 2004]. Esophageal erosions and esophageal webs and strictures can cause severe dysphagia with resultant poor nutrition [Castillo et al 2002]. Rarely, affected individuals can have esophageal disease with few or no skin manifestations [Zimmer et al 2002]. Anal erosions can cause severe constipation.

Corneal erosions can lead to scarring and loss of vision [Matsumoto et al 2005].

Blistering continues throughout life with scarring that may lead to disfigurement. Scarring pseudosyndactyly of the hands and feet, a hallmark of this disorder, fuses the digits into "mitten" hands and feet with severe loss of function.

The lifetime risk of aggressive squamous cell carcinoma (SCC) is greater than 90% with significant metastatic potential [Fine et al 1999]. SCC usually appears in the third decade but can appear as early as the second decade [Ayman et al 2002]. Affected individuals usually succumb to aggressive metastatic SCC.

Many individuals develop large, irregular, brown patches that histologically comprise collections of nevus cells [Gallardo et al 2005, Natsuga et al 2005].

Secondary complications that may be found in RDEB-HS include the following:

- Growth retardation from malnutrition caused by poor intake and an increased nutritional demand for tissue healing
- Anemia
- Osteoporosis [Kawaguchi et al 1999]
- Renal amyloidosis [Kaneko et al 2000]
- Pulmonary amyloidosis [Csikos et al 2003]
- Dilated cardiomyopathy [Cunnington & Addison 2002]

- **Non-Hallopeau-Siemans RDEB (Non-HS RDEB).** Many clinical variants make up the spectrum of non-HS RDEB; all are less severe than classic RDEB-HS [Hovnanian et al 1997; Jarvikallio et al 1997; Ashton et al 1999; Mellerio, Salas-Alanis et al 1999; Whittock et al 1999; Gardella, Castiglia et al 2002; Murata et al 2004; Sawamura et al 2005]. The phenotype may be mild, with mild blistering localized to hands, feet, knees, and elbows and dystrophic nails, or relatively more widespread including flexural areas and trunk, but without the severe, mutilating scarring seen in HS-RDEB.

  In the variant known as DEB inversa, blistering and skin atrophy occurs on the trunk, neck, thighs, and legs while no changes are observed on the hands, feet, elbows, or knees. Otherwise, the phenotype resembles DEB types with blistering and resulting scarring. Blisters of the hands and feet may be present in infancy.

Autosomal dominant DEB (DDEB). In this milder form of DEB, blistering is often limited to the hands, feet, knees, and elbows. Blistering may be relatively benign but nonetheless heals with scarring. Dystrophic nails, especially toenails, are common and loss of nails may occur. In the mildest forms, dystrophic nails may be the only characteristic noted [Dharma et al 2001, Sato-Matsumura et al 2002, Tosti et al 2003]. Blistering in DDEB often improves somewhat with age, possibly as a result of reduced physical activity.

Manifestations that can occur in both RDEB and DDEB. Although previously thought to be separate subtypes of DEB, the following manifestations are now recognized to be common to the three major subtypes as discussed in this entry:

- **Congenital localized absence of skin (previously called DEB, Bart type).** Congenital absence of the skin can be seen in any of the three major types of EB (i.e., epidermolysis bullosa simplex, or EBS; junctional epidermolysis simplex, or JEB; and DEB) and is not a discriminating diagnostic feature of any EB type or DEB subtype.
- **Transient bullous dermolysis of the newborn.** Mild to moderate skin fragility at birth diminishes with age but may not entirely disappear [Christiano, Fine et al 1997; Hammami-Hauasli, Raghunath et al 1998; Fassihi et al 2005].
- **DEB, pretibial with lichenoid features.** Pretibial blisters develop into prurigo-like hyperkeratotic lesions. The lesions occur predominantly on the pretibial areas, sparing the knees and other parts of the skin. Other findings include nail dystrophy, albopapuloid skin lesions, and hypertrophic scars without pretibial predominance.

Genotype-Phenotype Correlations

Autosomal recessive DEB (RDEB)

- **The severest forms** are caused by mutations on both alleles that result in either null alleles or out-of-frame mutations from insertions/deletions, single base changes, and splice junction [Christiano, Amano et al 1997; Mellerio et al 1997; Cserhalmi-Friedman et al 1998; Mellerio, Ashton et al 1999; Gardella, Castiglia et al 2002; Gardella, Zoppi et al 2002; Mallipeddi et al 2003]. The severity may be related to the position of the stop codon [Tamai et al 1999]; however, the presence of some functional protein seems to be the most important factor in ameliorating the disease severity.
- **Moderately severe forms** result from glycine substitutions on one allele and a stop codon-forming mutation on the other allele, which result in the formation of only a small amount of partially functional protein [Murata et al 2000; Dharma et al 2001; Pfendner, unpublished observation.
- **Less severe forms** 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 (over 500 reported in the literature) that have been identified [Hovnanian et al 1997; Jarvikallio et al 1997; Ashton et al 1999; Mellerio, Salas-Alanis et al 1999; Whittock et al 1999; Gardella, Castiglia et al 2002; Murata et al 2004; Sawamura et al 2005].

Autosomal dominant DEB (DDEB). Most DDEB results from dominant-negative amino acid substitutions involving glycine substitution mutations in the collagenous triple helical domain of collagen VII, although a few splice junction and other amino acid substitution mutations have been reported. Phenotypes may show intra- and interfamilial variability with the same mutation [Kon, McGrath et al 1997; Hammami-Hauasli, Schumann et al 1998; Murata et al 2000; Vaccaro et al 2000; Mallipeddi et al 2003; Nakamura et al 2004; Wessagowit et al 2005].

Penetrance

Until recently, mutations in *COL7A1* were considered to be 100% penetrant when family members were evaluated for mild features of the disease. However, in two instances, an individual with DDEB with an identified *COL7A1* mutation had no signs of the disease. Penetrance therefore appears to be less than 100%, at least in DDEB [Pfendner, unpublished observation].

Anticipation

Anticipation is not a feature of DEB.

Nomenclature

The following hierarchy includes specific designations for dystrophic EB that were used in the past before its molecular basis was known (designations in current use are in **boldface**):

- **Autosomal recessive dystrophic EB (RDEB)**
  - **Hallopeau-Siemens type, RDEB**
  - **Non-Hallopeau-Siemens type, RDEB**
    - Dystrophic EB, Pasini type
    - Dystrophic EB, Cockayne-Touraine type
  - Inversa type, RDEB
  - Mitis type, RDEB
- **Autosomal recessive dystrophic EB (RDEB)**
  - Dystrophic EB, Bart
  - Dystrophic EB, pruriginosa
  - Transient bullous dermolysis of the newborn
  - Dystrophic EB, pretibial
  - Dystrophic EB, pretibial with lichenoid features
  - Toenal dystrophy, isolated *

* This relatively newly described entity may not be considered DDEB.

Prevalence

According to the National EB Registry, the incidence of all types of DEB is 6.5 per million live births in the US population.

- Mild forms of DDEB are estimated at 2.9 per million but may be under-represented.
- RDEB incidence is 0.4-0.6 per million live births.

The carrier frequency of RDEB in the US population has been calculated as one in 370 [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 epidermolysis bullosa syndrome, caused by mutations in ten different genes, are EB simplex (EBS), hemidesmosomal EB, junctional EB (JEB), and dystrophic EB (DEB) (Figure 2). While agreement exists as to diagnostic criteria for some types of epidermolysis bullosa, the validity of rarer subtypes and their diagnostic criteria are disputed. Excellent clinical reviews are the chapter on epidermolysis bullosa 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 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 and the presence/absence and distribution of these protein components. 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.
- 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 EB simplex and junctional EB 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.

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

- Corneal erosions, esophageal strictures, nail involvement, and tooth enamel involvement may indicate either DEB or JEB.
- Scarring of the hands and feet in milder cases suggests DEB.
- Pseudosyndactyly (mitten deformities) caused by scarring of the hands and feet in older children and adults usually suggests DEB.

EB simplex. Epidermolysis bullosa simplex (EBS) is characterized by fragility of the skin that results in non-scarring 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, potentially fatal blistering.

- 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 about 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, Dowling-Meara type (EBS-DM).
- In EBS with mottled pigmentation (**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, with pigmentation disappearing in adult life. Focal palmar and plantar hyperkeratoses may occur.

- In EBS, Dowling-Meara type (**EBS-DM**), onset is usually at birth; great intra- and interfamilial variation in severity is observed. Widespread and severe blistering and/or multiple grouped clumps of small blisters are typical; hemorrhagic blisters are common. Improvement occurs in 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 and EB with pyloric atresia 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.

- **EB with muscular dystrophy** [OMIM 226670]. Some individuals with EB caused by *PLEC1* mutations develop muscular dystrophy either in childhood or later in life [Smith et al 1996, Charlesworth et al 2003, Koss-Harnes et al 2004, Schara et al 2004, Pfendner et al 2005]. Inheritance is autosomal recessive.
- **EB with pyloric atresia (EB-PA).** In several US and Japanese families, EB-PA is associated with premature termination mutations in *PLEC1* and the genes encoding α6 integrin *(ITGA6)* and β4 integrin *(ITGB4)* [Nakamura et al 2004, Pfendner & Uitto 2005]. Although disease course is severe and often lethal in the neonatal period, non-lethal forms have been described. Individuals with EB-PA-causing mutations in *ITGA6* or *ITGB4* may also show urologic abnormalities.
- **EBS, Ogna type** [OMIM 131950], observed in one Norwegian and one German family, is caused by a site-specific missense mutation within the rod domain of *PLEC1* [Koss-Harnes et al 2002]. Inheritance is autosomal dominant.

Junctional EB (JEB). Separation occurs above the basement membrane of the dermis, within the lamina lucida of the dermal-epidermal junction, resulting in non-scarring blistering. Because atrophy may develop over time, the term "atrophicans" has been applied by the Europeans to individuals with some form of junctional EB.

Broad classification of JEB includes lethal JEB (aka Herlitz) and non-lethal JEB (aka non-Herlitz), based on severity and survival past the first years of life. GABEB (generalized atrophic benign epidermolysis bullosa) historically has been ascribed to *COL17A1* mutations, but the phenotype overlaps significantly with non-Herlitz JEB.

Mutations in the genes that encode the subunits of laminin 5 *(LAMA3*, *LAMC2*, *LAMB3*) and the gene that encodes type 17 collagen *(COL17A1*) are causative. JEB with pyloric atresia has been associated with α6β4 integrin and plectin mutations (see EB with pyloric atresia).

Management

Evaluations Following Initial Diagnosis

Evaluation of the sites of blister formation including oral and esophageal blisters and erosions may indicate the severity of the disease.

Treatment of Manifestations

Skin. 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 may include any the following:
  - Ordinary Band-Aids®
  - Dressings impregnated with an emollient such as petrolatum or topical antiseptic (e.g., Vaseline® gauze, Adaptic®, Xeroform®)
  - Non-stick products (e.g., Telfa® or N-terface®)
  - Silicone-based products without adhesive (e.g., Mepitel® or Mepilex®)
- A secondary layer providing stability for the primary layer and adding padding to allow more activity. Rolls of gauze (e.g., Kerlix®) are commonly used.
- A tertiary layer (usually with some elastic properties) that ensures the integrity of the dressing (e.g., Coban® or elasticized tube-gauze of varying diameters such as Band Net®)

In infants and children with RDEB 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 1996]. Esophageal strictures and webs can be dilated repeatedly to improve swallowing [Castillo et al 2002, Kay & Wyllie 2002, Azizkhan et al 2006].

Other. 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.

Anemia is a chronic problem with RDEB and can be treated with oral or intravenous iron infusions and red blood cell transfusions.

Other nutritional deficiencies must also be addressed:

- Calcium and vitamin D supplementation for osteopenia and osteoporosis
- Selenium and carnitine replacement to help prevent dilated cardiomyopathy
- Zinc replacement to enhance wound healing

Dental care is necessary to ensure adequate caloric intake [Harris et al 2001].

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

Occupational therapy may be helpful in preventing progressive hand contractures. Splinting of the hands can be problematic because of skin fragility. Surgical release of fingers by several methods has been described; it often needs to be performed repeatedly [Marin-Bertolin et al 1999, Glicenstein et al 2000].

Psychosocial support including social services and psychological counseling is essential.

Prevention of Primary Manifestations

Age-appropriate play involving activities that cause minimal trauma to the skin is encouraged.

Dressings and padding are needed to protect bony prominences from blister-inducing impact.

If a fetus is known to be affected with any form of DEB, cesarean delivery may reduce trauma to the skin during delivery.

Prevention of Secondary Complications

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.

Surveillance

Because the lifetime risk of metastatic squamous cell carcinoma is greater than 90% in RDEB, 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 may be necessary followed by local excision.

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

Screening for zinc deficiency by measurement of serum zinc concentration should be routine in order to provide zinc supplementation when necessary to enhance wound healing.

Screening for predisposition to dilated cardiomyopathy secondary to selenium deficiency and carnitine deficiency is possible by measurement of serum concentrations of selenium and carnitine. Screening for dilated cardiomyopathy by transthoracic echocardiogram is also useful [Sidwell et al 2000]. No guidelines regarding the age at which such screening should begin have been established.

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.

Agents/Circumstances to Avoid

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

In general, activities that 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 devise ways of protecting the skin.

Most persons with DEB cannot use ordinary medical tape or Band-Aids®.

Testing of Relatives at Risk

Evaluating an at-risk newborn for evidence of blistering is appropriate so that trauma to the skin can be avoided as much as possible.

Cesarean section is often recommended to avoid vaginal delivery in a fetus at risk.

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

Therapies Under Investigation

Although several approaches to gene therapy for DEB have been proposed, no clinical trials have been conducted. The knockout mouse model for DEB should facilitate the development of the following therapeutic approaches [Heinonen et al 1999]:

- Use of viral and nonviral vectors for transfer of recombinant *COL7A1* [Mecklenbeck et al 2002; Baldeschi et al 2003; Woodley, Keene, Atha, Huang, Ram et al 2004]
- Introduction directly into the skin of *COL7A1* genes [Chen et al 2002, Ortiz-Urda et al 2002], protein [Woodley, Keene, Atha, Huang, Lipman et al 2004], and gene corrected fibroblasts [Woodley et al 2003]
- Introduction of a compensating mutation [McGrath et al 1999]
- Anti-type VII collagen NC1 antibody therapy: theoretically effective in preventing tumorogenesis, based on animal models and the observation that type VII collagen is necessary for tumorogenesis [Ortiz-Urda et al 2005].

Medical treatment of lesions suspicious for squamous cell carcinoma with agents such as topical imiquimod needs to be studied further.

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

Other

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

Dystrophic epidermolysis bullosa (DEB) is inherited in an autosomal dominant or autosomal recessive manner.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- About 70% of individuals diagnosed with autosomal dominant DEB (DDEB) are reported to have an affected parent and about 30% of probands may have the disorder as the result of a *de novo* dominant gene mutation [Wessagowit et al 2001; Pfendner,

unpublished observation]; however, these numbers may not reflect the true proportion of *de novo* mutations because of bias of ascertainment.

- Maternal germline mosaicism has been reported [Cserhalmi-Friedman et al 2001].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include molecular genetic testing for the mutation found in the proband.

Note: (1) Although 70% of individuals diagnosed with DDEB have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. (2) If the parent is the individual in whom the mutation first occurred, s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low (~1 in 10^6) but greater than that of the general population because germline mosaicism has been reported [Rouan et al 1998, Cserhalmi-Friedman et al 1999, Cserhalmi-Friedman et al 2001].

Offspring of a proband. Each child of an individual with DDEB has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of a child with autosomal recessive dystrophic epidermolysis bullosa (RDEB) are obligate heterozygotes and therefore each parent carries one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an individual with RDEB 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.

Offspring of a proband. The offspring of an individual with RDEB 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 a proband with RDEB.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Determining the mode of inheritance in a simplex case (i.e., a single occurrence in a family). Molecular characterization of pathogenetic mutations is the only accurate method of determining mode of inheritance and recurrence risk. Seven individuals with a combination of a recessive mutation on one allele and a dominantly inherited amino acid substitution on the other allele have been reported, suggesting caution when predicting recurrence risk based on parental phenotype alone (i.e., without molecular genetic testing) [Pfendner, unpublished observation].

Phenotype severity and EM/IF findings alone are not sufficient to determine mode of inheritance and recurrence risk, as phenotypic variability is extreme in recessive DEB [Kon, McGrath et al 1997; Rouan et al 1998; Hashimoto et al 1999; Vaccaro et al 2000; Mallipeddi et al 2003]. An individual with a mild phenotype and no family history may have either autosomal dominant or autosomal recessive DEB; numerous descriptions of the spectrum of phenotypes in RDEB document that some are very mild and mimic DDEB [Kon, McGrath et al 1997; Rouan et al 1998; Hashimoto et al 1999; Vaccaro et al 2000; Mallipeddi et al 2003].

Family planning. The optimal time for determination of genetic risk, clarification of carrier status (for RDEB), and discussion of the availability of prenatal testing is before pregnancy.

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 in situations in which the sensitivity of currently available testing is less than 100%. See 

for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing. Prenatal testing for pregnancies at increased risk for DEB is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele(s) of an affected family member 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 DEB. Fetoscopy carries a greater risk to pregnancy than CVS or amniocentesis and is performed relatively late (18-20 weeks) in gestation. Prenatal diagnosis for DEB 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 mutation(s) has/have been identified in an affected family member. 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 Dystrophic Epidermolysis Bullosa

Gene Symbol	Chromosomal Locus	Protein Name
COL7A1	3p21.3	Collagen alpha-1(VII) chain

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 Dystrophic Epidermolysis Bullosa

120120	COLLAGEN, TYPE VII, ALPHA-1; COL7A1
131705	TRANSIENT BULLOUS DERMOLYSIS OF THE NEWBORN; TBDN
131750	EPIDERMOLYSIS BULLOSA DYSTROPHICA, PASINI TYPE
132000	EPIDERMOLYSIS BULLOSA WITH CONGENITAL LOCALIZED ABSENCE OF SKIN AND DEFORMITY OF NAILS
226450	EPIDERMOLYSIS BULLOSA INVERSA DYSTROPHICA
226600	EPIDERMOLYSIS BULLOSA DYSTROPHICA, HALLOPEAU-SIEMENS TYPE; EBR1

Table C. Genomic Databases for Dystrophic Epidermolysis Bullosa

Gene Symbol	Entrez Gene	HGMD
COL7A1	1294 (MIM No. 120120)	COL7A1

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

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The *COL7A1* gene is expressed in the keratinocytes including the basal keratinocytes of the epidermis where the protein products are assembled into homotrimeric molecules with a helical triple collagen domain. These molecules then assemble into homodimers and are found in the extracellular matrix below the lamina densa and form the anchoring fibrils that anchor the basement membrane to the underlying dermis (Figure 2). The anchoring fibrils are linked to the basement membrane through attachment to laminin 5 and the keratinocyte hemidesmosomes directly above. The intracellular keratin intermediate filament network is linked directly to the hemidesmosomes that anchor the keratinocytes to the basal lamina and to the desmosomes that lead to strong attachment of the keratinocytes to one another. These associations along with the network itself supply stability and resistance to stress that enable the keratinocytes to maintain their structural integrity during minor trauma and remain anchored to the basement membrane and dermis [Bruckner-Tuderman 1999].

Mutations in the *COL7A1* gene can lead to reduced resistance to minor trauma and the resulting blistering that is the hallmark of DEB. The type of mutation, the biochemical properties of the substituted amino acid, and its location determine the severity of the blistering phenotype (see Genotype-Phenotype Correlations) and inheritance pattern. Missense mutations predominate in autosomal dominant forms of DEB and may affect the ability of the collagen VII to assemble into a triple helix (its secondary structure) and to form the intracellular network. Null mutations

predominate in autosomal recessive forms of DEB and the absence of functional collagen VII and resulting absence of anchoring fibrils lead to the most severe forms of DEB. Intrafamilial phenotypic variability in dominant DEB suggests that other factors can affect the resistance of the cells to friction [Anton-Lamprecht & Gedde-Dahl 2002, Ortiz-Urda et al 2005].

Individuals with HS-RDEB have a greater than 90% lifetime risk of aggressive metastasizing squamous cell carcinoma. The reason for the elevated risk has not been clear until recently: Ortiz-Urda et al (2005) examined Ras-driven tumorigenesis in RDEB keratinocytes and found that cells lacking collagen VII did not form tumors in mice, whereas those retaining a specific collagen VII fragment (the amino-terminal noncollagenous domain NC1) were tumorigenic. Restoring NC1 expression restored tumorigenicity in collagen VII-deficient cells. They conclude that tumor-stroma interactions mediated by collagen VII promote neoplasia, and retention of NC1 sequences in a subset of individuals with RDEB may be a factor in their increased susceptibility to squamous cell carcinoma.

Normal allelic variants: The normal cDNA comprises 9.2 kbp with an open reading frame of 8,833 nucleotides encoding 2944 amino acids in 118 exons spanning 32 kb.

Pathologic allelic variants: Glycine substitution mutations in the triple helical domain (especially in exons 73, 74, and 75) predominate (>75%) in DDEB. Mutations p.Gly2034Arg and p.Gly2043Arg are the most common DDEB-causing mutations, making up 50% of the dominant mutations reported in the largest US cohort [Pfendner, unpublished observation]. Glycine substitutions as well as other amino acid substitutions and splice junction mutations outside of this region may also be found in dominant DEB; often, however, inheritance pattern cannot be predicted without determination of parental phenotype and corresponding genotype.

More than 400 recessive DEB-causing mutations spanning the entire gene have been described for both HS and non-HS [Hovnanian et al 1997; Jarvikallio et al 1997; Ashton et al 1999; Mellerio, Salas-Alanis et al 1999; Whittock et al 1999; Gardella, Castiglia et al 2002; Murata et al 2004; Sawamura et al 2005; Pfendner, unpublished observation]. Common mutations have been described in certain ethnic backgrounds — including 497insA [Ashton et al 1999; Gardella, Castiglia et al 2002], 2470insG [Mellerio, Salas-Alanis et al 1999], p.Arg587X [Whittock et al 1999], 3840delC [Whittock et al 1999], and 4919delG [Whittock et al 1999] — and are recurrent in the US population. Each mutation, however, accounts for no more than 1%-2% of the total number of mutations described. Null mutations predominate in RDEB, though glycine substitutions and other amino acid substitutions have been described. Milder forms of RDEB are often caused by splice junction mutations or other missense mutations.

Normal gene product: Collagen VII is a monomer of 2944 amino acids that associates into a homotrimer with a triple helical collagenous domain. The homotrimers then associate via disulfide bonds into homodimeric structures that form the anchoring fibrils.

Abnormal gene product: In dominant DEB, collagen VII with a glycine substitution in the collagenous domain may result in abnormal triple helical coiling and a partially nonfunctional protein product. These proteins may exhibit altered morphology on electron microscopy while immunofluorescent staining may be normal or slightly reduced in intensity, making diagnosis by immunofluorescent staining of a skin biopsy difficult unless a cleavage plane is present. In addition, in-frame exon skipping may serve to modulate disease severity in recessive disease and generate a partially functional gene product [Cserhalmi-Friedman et al 1998, McGrath et al 1999].

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.

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www.debra.org.uk

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, 4 ed. Churchill Livingstone Publishers, NY. 2002

Ashton GH, Mellerio JE, Dunnill MG, Milana G, Mayou BJ, Carrera J, McGrath JA, Eady RA. Recurrent molecular abnormalities in type VII collagen in Southern Italian patients with recessive dystrophic epidermolysis bullosa. Clin Exp Dermatol. 1999;24:232–5. [PubMed: 10354186]

Ayman T, Yerebakan O, Ciftcioglu MA, Alpsoy E. A 13-year-old girl with recessive dystrophic epidermolysis bullosa presenting with squamous cell carcinoma. Pediatr Dermatol. 2002;19:436–8. [PubMed: 12383103]

Azizkhan RG, Stehr W, Cohen AP, Wittkugel E, Farrell MK, Lucky AW, Hammelman BD, Johnson ND, Racadio JM. Esophageal strictures in children with recessive dystrophic Epidermolysis bullosa: an 11-year experience with fluoroscopically guided balloon dilatation. J Pediatr Surg. 2006;41:55–60. [PubMed: 16410108]

Baldeschi C, Gache Y, Rattenholl A, Bouille P, Danos O, Ortonne JP, Bruckner-Tuderman L, Meneguzzi G. Genetic correction of canine dystrophic epidermolysis bullosa mediated by retroviral vectors. Hum Mol Genet. 2003;12:1897–905. [PubMed: 12874109]

Bruckner-Tuderman L. Hereditary skin diseases of anchoring fibrils. J Dermatol Sci. 1999;20:122–33. [PubMed: 10379704]

Castillo RO, Davies YK, Lin YC, Garcia M, Young H. Management of esophageal strictures in children with recessive dystrophic epidermolysis bullosa. J Pediatr Gastroenterol Nutr. 2002;34:535–41. [PubMed: 12050581]

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]

Chen M, Kasahara N, Keene DR, Chan L, Hoeffler WK, Finlay D, Barcova M, Cannon PM, Mazurek C, Woodley DT. Restoration of type VII collagen expression and function in dystrophic epidermolysis bullosa. Nat Genet. 2002;32:670–5. [PubMed: 12426566]

Christiano AM, Amano S, Eichenfield LF, Burgeson RE, Uitto J. Premature termination codon mutations in the type VII collagen gene in recessive dystrophic epidermolysis bullosa result in nonsense-mediated mRNA decay and absence of functional protein. J Invest Dermatol. 1997;109:390–4. [PubMed: 9284110]

Christiano AM, Fine JD, Uitto J. Genetic basis of dominantly inherited transient bullous dermolysis of the newborn: a splice site mutation in the type VII collagen gene. J Invest Dermatol. 1997;109:811–4. [PubMed: 9406826]

Cserhalmi-Friedman PB, Garzon MC, Guzman E, Martinez-Mir A, Chung WK, Anyane-Yeboa K, Christiano AM. Maternal germline mosaicism in dominant dystrophic epidermolysis bullosa. J Invest Dermatol. 2001;117:1327–8. [PubMed: 11710955]

Cserhalmi-Friedman PB, Grossman J, Karpati S, Ahmad W, Horvath A, Christiano AM. Identification of a de novo glycine substitution in the type VII collagen gene in a proband with mild dystrophic epidermolysis bullosa. Exp Dermatol. 1999;8:143–5. [PubMed: 10232407]

Cserhalmi-Friedman PB, McGrath JA, Mellerio JE, Romero R, Salas-Alanis JC, Paller AS, Dietz HC, Christiano AM. Restoration of open reading frame resulting from skipping of an exon with an internal deletion in the COL7A1 gene. Lab Invest. 1998;78:1483–92. [PubMed: 9881948]

Csikos M, Orosz Z, Bottlik G, Szocs H, Szalai Z, Rozgonyi Z, Harsing J, Torok E, Bruckner-Tuderman L, Horvath A, Karpati S. Dystrophic epidermolysis bullosa complicated by cutaneous squamous cell carcinoma and pulmonary and renal amyloidosis. Clin Exp Dermatol. 2003;28:163–6. [PubMed: 12653705]

Cunnington PM, Addison R. Dilated cardiomyopathy in dystrophic epidermolysis bullosa: a lethal complication of epidermolysis bullosa. Eur J Anaesthesiol. 2002;19:689–90. [PubMed: 12243296]

De Benedittis M, Petruzzi M, Favia G, Serpico R. Oro-dental manifestations in Hallopeau-Siemens-type recessive dystrophic epidermolysis bullosa. Clin Exp Dermatol. 2004;29:128–32. [PubMed: 14987265]

Dharma B, Moss C, McGrath JA, Mellerio JE, Ilchyshyn A. Dominant dystrophic epidermolysis bullosa presenting as familial nail dystrophy. Clin Exp Dermatol. 2001;26:93–6. [PubMed: 11260188]

Fassihi H, Diba VC, Wessagowit V, Dopping-Hepenstal PJ, Jones CA, Burrows NP, McGrath JA. Transient bullous dermolysis of the newborn in three generations. Br J Dermatol. 2005;153:1058–63. [PubMed: 16225626]

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

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]

Gallardo F, Toll A, Malvehy J, Mascaro-Galy JM, Lloreta J, Barranco C, Pujol RM. Large atypical melanocytic nevi in recessive dystrophic epidermolysis bullosa: clinicopathological, ultrastructural, and dermoscopic study. Pediatr Dermatol. 2005;22:338–43. [PubMed: 16060872]

Gardella R, Castiglia D, Posteraro P, Bernardini S, Zoppi N, Paradisi M, Tadini G, Barlati S, McGrath JA, Zambruno G, Colombi M. Genotype-phenotype correlation in italian patients with dystrophic epidermolysis bullosa. J Invest Dermatol. 2002;119:1456–62. [PubMed: 12485454]

Gardella R, Zoppi N, Zambruno G, Barlati S, Colombi M. Different phenotypes in recessive dystrophic epidermolysis bullosa patients sharing the same mutation in compound heterozygosity with two novel mutations in the type VII collagen gene. Br J Dermatol. 2002;147:450–7. [PubMed: 12207583]

Glicenstein J, Mariani D, Haddad R. The hand in recessive dystrophic epidermolysis bullosa. Hand Clin. 2000;16:637–45. [PubMed: 11117053]

Hammami-Hauasli N, Raghunath M, Kuster W, Bruckner-Tuderman L. Transient bullous dermolysis of the newborn associated with compound heterozygosity for recessive and dominant COL7A1 mutations. J Invest Dermatol. 1998;111:1214–9. [PubMed: 9856844]

Hammami-Hauasli N, Schumann H, Raghunath M, Kilgus O, Luthi U, Luger T, Bruckner-Tuderman L. Some, but not all, glycine substitution mutations in COL7A1 result in intracellular accumulation of collagen VII, loss of anchoring fibrils, and skin blistering. J Biol Chem. 1998;273:19228–34. [PubMed: 9668111]

Harris JC, Bryan RA, Lucas VS, Roberts GJ. Dental disease and caries related microflora in children with dystrophic epidermolysis bullosa. Pediatr Dent. 2001;23:438–43. [PubMed: 11699172]

Hashimoto I, Kon A, Tamai K, Uitto J. Diagnostic dilemma of "sporadic" cases of dystrophic epidermolysis bullosa: a new dominant or mitis recessive mutation? Exp Dermatol. 1999;8:140–2. [PubMed: 10232406]

Haynes L, Atherton DJ, Ade-Ajayi N, Wheeler R, Kiely EM. Gastrostomy and growth in dystrophic epidermolysis bullosa. Br J Dermatol. 1996;134:872–9. [PubMed: 8736328]

Heinonen S, Mannikko M, Klement JF, Whitaker-Menezes D, Murphy GF, Uitto J. Targeted inactivation of the type VII collagen gene (Col7a1) in mice results in severe blistering phenotype: a model for recessive dystrophic epidermolysis bullosa. J Cell Sci 112 (Pt. 1999;21):3641–8. [PubMed: 10523500]

Hovnanian A, Rochat A, Bodemer C, Petit E, Rivers CA, Prost C, Fraitag S, Christiano AM, Uitto J, Lathrop M, Barrandon Y, de Prost Y. Characterization of 18 new mutations in COL7A1 in recessive dystrophic epidermolysis bullosa provides evidence for distinct molecular mechanisms underlying defective anchoring fibril formation. Am J Hum Genet. 1997;61:599–610. [PubMed: 9326325]

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]

Jarvikallio A, Pulkkinen L, Uitto J. Molecular basis of dystrophic epidermolysis bullosa: mutations in the type VII collagen gene (COL7A1). Hum Mutat. 1997;10:338–47. [PubMed: 9375848]

Kaneko K, Kakuta M, Ohtomo Y, Shimizu T, Yamashiro Y, Ogawa H, Manabe M. Renal amyloidosis in recessive dystrophic epidermolysis bullosa. Dermatology. 2000;200:209–12. [PubMed: 10828628]

Kawaguchi M, Mitsuhashi Y, Kondo S. Osteoporosis in a patient with recessive dystrophic epidermolysis bullosa. Br J Dermatol. 1999;141:934–5. [PubMed: 10583187]

Kay M, Wyllie R. Endoscopic dilatation of esophageal strictures in recessive dystrophic epidermolysis bullosa: new equipment, new techniques. J Pediatr Gastroenterol Nutr. 2002;34:515–8. [PubMed: 12050577]

Kern JS, Kohlhase J, Bruckner-Tuderman L, Has C. Expanding the COL7A1 mutation database: novel and recurrent mutations and unusual genotype-phenotype constellations in 41 patients with dystrophic epidermolysis bullosa. J Invest Dermatol. 2006;126:1006–12. [PubMed: 16484981]

Kon A, McGrath JA, Pulkkinen L, Nomura K, Nakamura T, Maekawa Y, Christiano AM, Hashimoto I, Uitto J. Glycine substitution mutations in the type VII collagen gene (COL7A1) in dystrophic epidermolysis bullosa: implications for genetic counseling. J Invest Dermatol. 1997;108:224–8. [PubMed: 9008239]

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]

Mallipeddi R, Bleck O, Mellerio JE, Ashton GH, Eady RA, McGrath JA. Dilemmas in distinguishing between dominant and recessive forms of dystrophic epidermolysis bullosa. Br J Dermatol. 2003;149:810–8. [PubMed: 14616374]

Marin-Bertolin S, Amaya Valero JV, Neira Gimenez C, Marquina Vila P, Amorrortu-Velayos J. Surgical management of hand contractures and pseudosyndactyly in dystrophic epidermolysis bullosa. Ann Plast Surg. 1999;43:555–9. [PubMed: 10560876]

Matsumoto Y, Dogru M, Tsubota K. Ocular surface findings in Hallopeau-Siemens subtype of dystrophic epidermolysis bullosa: report of a case and literature review. Cornea. 2005;24:474–9. [PubMed: 15829808]

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]

Mecklenbeck S, Compton SH, Mejia JE, Cervini R, Hovnanian A, Bruckner-Tuderman L, Barrandon Y. A microinjected COL7A1-PAC vector restores synthesis of intact procollagen VII in a dystrophic epidermolysis bullosa keratinocyte cell line. Hum Gene Ther. 2002;13:1655–62. [PubMed: 12228020]

Mellerio JE, Ashton GH, Mohammedi R, Lyon CC, Kirby B, Harman KE, Salas-Alanis JC, Atherton DJ, Harrison PV, Griffiths WA, Black MM, Eady RA, McGrath JA. Allelic heterogeneity of dominant and recessive COL7A1 mutations underlying epidermolysis bullosa pruriginosa. J Invest Dermatol. 1999;112:984–7. [PubMed: 10383749]

Mellerio JE, Dunnill MG, Allison W, Ashton GH, Christiano AM, Uitto J, Eady RA, McGrath JA. Recurrent mutations in the type VII collagen gene (COL7A1) in patients with recessive dystrophic epidermolysis bullosa. J Invest Dermatol. 1997;109:246–9. [PubMed: 9242516]

Mellerio JE, Salas-Alanis JC, Amaya-Guerra M, Tamez E, Ashton GH, Mohammedi R, Eady RA, McGrath JA. A recurrent frameshift mutation in exon 19 of the type VII collagen gene (COL7A1) in Mexican patients with recessive dystrophic epidermolysis bullosa. Exp Dermatol. 1999;8:22–9. [PubMed: 10206718]

Murata T, Masunaga T, Ishiko A, Shimizu H, Nishikawa T. Differences in recurrent COL7A1 mutations in dystrophic epidermolysis bullosa: ethnic-specific and worldwide recurrent mutations. Arch Dermatol Res. 2004;295:442–7. [PubMed: 14727126]

Murata T, Masunaga T, Shimizu H, Takizawa Y, Ishiko A, Hatta N, Nishikawa T. Glycine substitution mutations by different amino acids in the same codon of COL7A1 lead to heterogeneous clinical phenotypes of dominant dystrophic epidermolysis bullosa. Arch Dermatol Res. 2000;292:477–81. [PubMed: 11142768]

Nakamura H, Sawamura D, Goto M, Sato-Matsumura KC, LaDuca J, Lee JY, Masunaga T, Shimizu H. The G2028R glycine substitution mutation in COL7A1 leads to marked inter-familiar clinical heterogeneity in dominant dystrophic epidermolysis bullosa. J Dermatol Sci. 2004;34:195–200. [PubMed: 15113589]

Natsuga K, Akiyama M, Sato-Matsumura KC, Tsuchiya K, Shimizu H. Two cases of atypical melanocytic lesions in recessive dystrophic epidermolysis bullosa infants. Clin Exp Dermatol. 2005;30:636–9. [PubMed: 16197375]

Ortiz-Urda S, Garcia J, Green CL, Chen L, Lin Q, Veitch DP, Sakai LY, Lee H, Marinkovich MP, Khavari PA. Type VII collagen is required for Ras-driven human epidermal tumorigenesis. Science. 2005;307:1773–6. [PubMed: 15774758]

Ortiz-Urda S, Thyagarajan B, Keene DR, Lin Q, Fang M, Calos MP, Khavari PA. Stable nonviral genetic correction of inherited human skin disease. Nat Med. 2002;8:1166–70. [PubMed: 12244305]

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]

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

Rouan F, Pulkkinen L, Jonkman MF, Bauer JW, Cserhalmi-Friedman PB, Christiano AM, Uitto J. Novel and de novo glycine substitution mutations in the type VII collagen gene (COL7A1) in dystrophic epidermolysis bullosa: implications for genetic counseling. J Invest Dermatol. 1998;111:1210–3. [PubMed: 9856843]

Sato-Matsumura KC, Yasukawa K, Tomita Y, Shimizu H. Toenail dystrophy with COL7A1 glycine substitution mutations segregates as an autosomal dominant trait in 2 families with dystrophic epidermolysis bullosa. Arch Dermatol. 2002;138:269–71. [PubMed: 11843659]

Sawamura D, Goto M, Yasukawa K, Sato-Matsumura K, Nakamura H, Ito K, Nakamura H, Tomita Y, Shimizu H. Genetic studies of 20 Japanese families of dystrophic epidermolysis bullosa. J Hum Genet. 2005;50:543–6. [PubMed: 16189623]

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]

Serrano-Martinez MC, Bagan JV, Silvestre FJ, Viguer MT. Oral lesions in recessive dystrophic epidermolysis bullosa. Oral Dis. 2003;9:264–8. [PubMed: 14628894]

Sidwell RU, Yates R, Atherton D. Dilated cardiomyopathy in dystrophic epidermolysis bullosa. Arch Dis Child. 2000;83:59–63. [PubMed: 10869001]

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]

Tamai K, Murai T, Mayama M, Kon A, Nomura K, Sawamura D, Hanada K, Hashimoto I, Shimizu H, Masunaga T, Nishikawa T, Mitsuhashi Y, Ishida-Yamamoto A, Ikeda S, Ogawa H, McGrath JA, Pulkkinen L, Uitto J. Recurrent COL7A1 mutations in Japanese patients with dystrophic epidermolysis bullosa: positional effects of premature termination codon mutations on clinical severity. Japanese Collaborative Study Group on Epidermolysis Bullosa. J Invest Dermatol. 1999;112:991–3. [PubMed: 10383751]

Tosti A, Piraccini BM, Scher RK. Isolated nail dystrophy suggestive of dominant dystrophic epidermolysis bullosa. Pediatr Dermatol. 2003;20:456–7. [PubMed: 14521572]

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

Vaccaro M, Moretti G, Guarneri F, Cannavo S, Magaudda L. "Sporadic" dystrophic epidermolysis bullosa: a new dominant or mitis recessive mutation? Eur J Dermatol. 2000;10:436–8. [PubMed: 10980463]

Wessagowit V, Ashton GH, Mohammedi R, Salas-Alanis JC, Denyer JE, Mellerio JE, Eady RA, McGrath JA. Three cases of de novo dominant dystrophic epidermolysis bullosa associated with the mutation G2043R in COL7A1. Clin Exp Dermatol. 2001;26:97–9. [PubMed: 11260189]

Wessagowit V, Kim SC, Woong Oh S, McGrath JA. Genotype-phenotype correlation in recessive dystrophic epidermolysis bullosa: when missense doesn't make sense. J Invest Dermatol. 2005;124:863–6. [PubMed: 15816848]

Whittock NV, Ashton GH, Mohammedi R, Mellerio JE, Mathew CG, Abbs SJ, Eady RA, McGrath JA. Comparative mutation detection screening of the type VII collagen gene (COL7A1) using the protein truncation test, fluorescent chemical cleavage of mismatch, and conformation sensitive gel electrophoresis. J Invest Dermatol. 1999;113:673–86. [PubMed: 10504458]

Woodley DT, Keene DR, Atha T, Huang Y, Lipman K, Li W, Chen M. Injection of recombinant human type VII collagen restores collagen function in dystrophic epidermolysis bullosa. Nat Med. 2004;10:693–5. [PubMed: 15195089]

Woodley DT, Keene DR, Atha T, Huang Y, Ram R, Kasahara N, Chen M. Intradermal injection of lentiviral vectors corrects regenerated human dystrophic epidermolysis bullosa skin tissue in vivo. Mol Ther. 2004;10:318–26. [PubMed: 15294178]

Woodley DT, Krueger GG, Jorgensen CM, Fairley JA, Atha T, Huang Y, Chan L, Keene DR, Chen M. Normal and gene-corrected dystrophic epidermolysis bullosa fibroblasts alone can produce type VII collagen at the basement membrane zone. J Invest Dermatol. 2003;121:1021–8. [PubMed: 14708601]

Zimmer KP, Schumann H, Mecklenbeck S, Bruckner-Tuderman L. Esophageal stenosis in childhood: dystrophic epidermolysis bullosa without skin blistering due to collagen VII mutations. Gastroenterology. 2002;122:220–5. [PubMed: 11781296]

Suggested Readings

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

Chapter Notes

Author Notes

www.genedx.com

www.cincinnatichildrens.org/eb-center

Revision History

- 4 October 2007 (cd) Revision: deletion/duplication analysis available on a clinical basis
- 21 September 2007 (cd) Revision: deletion/duplication analysis no longer available on a clinical basis
- 17 October 2006 (cd) Revision: deletion/duplication analysis available on a clinical basis
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- 27 December 2005 (ep) Original submission

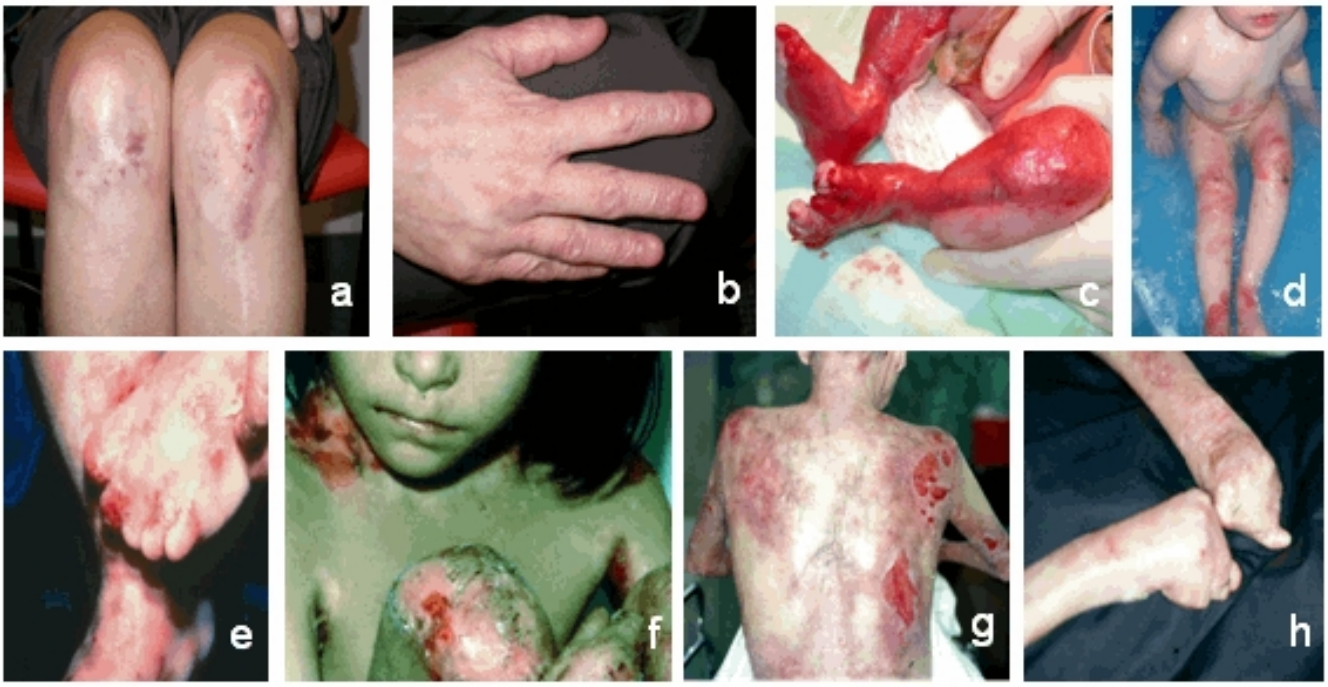

Figure 1. Common findings of dystrophic epidermolysis bullosa:
a,b: Scarring on knees and hands and dystrophic nails found in dominant DEB in an adult
c: Aplasia cutis congenita in a newborn with recessive DEB
d: Generalized blistering in a child with recessive DEB
e: Scarring of feet with pseudosyndactyly of toes caused by scarring in Hallopeau-Siemen recessive DEB
f: Severe generalized blistering in recessive DEB in an adult
g: Severe generalized scarring in a young adult with recessived DEB
h: Pseudosyndactyly caused by scarring in recessive DEB in an adult

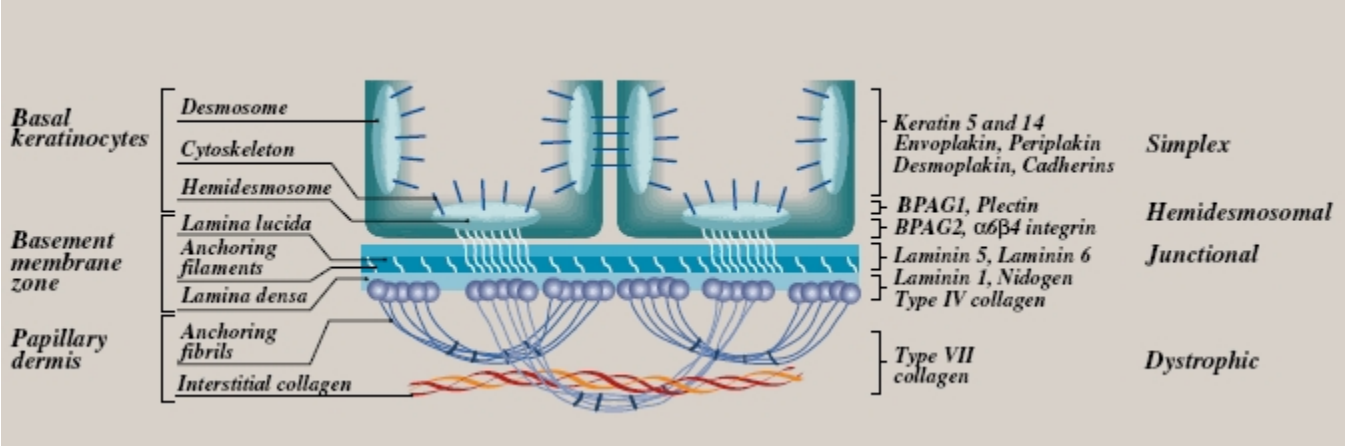

Figure 2. Locations affected by mutations causing the four major subtypes of epidermolysis bullosa syndromes