GENEReviews

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Epidermolysis Bullosa with Pyloric Atresia

[*Carmi Syndrome, EB-PA, Junctional Epidermolysis Bullosa with Pyloric Atresia, PA-JEB. Includes: ITGA6-Related Epidermolysis Bullosa with Pyloric Atresia, ITGB4-Related Epidermolysis Bullosa with Pyloric Atresia, PLEC1-Related Epidermolysis Bullosa with Pyloric Atresia*]

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Summary

Disease characteristics. Epidermolysis bullosa with pyloric atresia (EB-PA) is characterized by fragility of the skin and mucous membranes, manifest by blistering with little or no trauma; congenital pyloric atresia; and ureteral and renal anomalies (dysplastic/multicystic kidney, hydronephrosis/hydroureter, ureterocele, duplicated renal collecting system, absent bladder). The course of EB-PA is usually severe and often lethal in the neonatal period. Although most affected children succumb as neonates, those who survive may have severe blistering with formation of granulation tissue on the skin around the mouth, nose, fingers, and toes, and internally around the trachea. However, some affected individuals have little or no blistering later in life. Additional features shared by EB-PA and the other major forms of EB include congenital localized absence of skin (aplasia cutis congenita), milia, nail dystrophy, scarring alopecia, hypotrichosis, and contractures.

Diagnosis/testing. Because the clinical features of all types of epidermolysis bullosa (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. The three genes known to be associated with EB-PA are *ITGB4* (~80% of EB-PA), *ITGA6* (~5%), and *PLEC1* (~15%). Molecular genetic testing is available clinically for *ITGB4* and *ITGA6*.

Management. *Treatment of manifestations:* surgical intervention to correct pyloric atresia. Lance and drain new blisters and dress with three layers (primary: nonadherent; secondary: for stability and protection; third: elastic properties to ensure integrity). protect skin from shearing forces; teach caretakers proper handling of infants and children; psychosocial support, including social services and psychological counseling. *Prevention of secondary complications:* antibiotics and antiseptics to prevent wound infections; attention to fluid and electrolyte balance; 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. *Other:* Consider cesarean section to reduce trauma to the skin of an affected fetus during delivery.

Genetic counseling. EB-PA 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 are possible, 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. 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 epidermolysis bullosa with pyloric atresia (EB-PA) is suspected in newborns with the following:

- 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
- Congenital pyloric atresia with vomiting and abdominal distension resulting from complete obstruction of the gastric outlet. Radiographs reveal that the stomach is distended and filled with air (see Figure 1).
- Ureteral and renal anomalies, including hydronephrosis, ureterocele, absent bladder, dysplastic kidneys, urinary collecting system/kidney duplication, obstructive uropathy, glomerulosclerosis

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 of EB-PA, 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 the diagnosis of EB-PA.

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 in EB-PA include the following:

- Cleavage may be within the lamina lucida or just above the hemidesmosomes in the lowest layer of the basal keratinocytes.
- Hemidesmosomes may be reduced in number or dysmorphic [Kunz et al 2000f, Jonkman et al 2002, Charlesworth et al 2003, Pasmooij et al 2004].

Immunofluorescent antibody/antigen mapping. Findings include the following:

- Abnormal or absent staining with antibodies to α6β4 integrin in EB-PA and other rare forms of junctional epidermolysis bullosa (JEB) as a result of mutations in either *ITGA6* or *ITGB4*
- Abnormal or absent staining with antibodies to plectin in EB-PA as a result of *PLEC1* mutations

Normal staining for other antigens (e.g., collagen VII, laminin 332, keratins 5 and 14) confirms the diagnosis of EB-PA.

Note: Especially in milder forms of EB, indirect immunofluorescent studies are often not sufficient to make the diagnosis because near-normal antigen levels are detected and no cleavage plane is observed. In addition, absence of one hemidesmosomal component (e.g., *ITGA6* or *ITGB4*) may reduce the staining of other hemidesmosomal components as well (e.g., *PLEC1*, COL17). In these cases electron microscopic examination of a skin biopsy must be performed.

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. Three genes are associated with EB-PA [Nakamura et al 2005, Pfendner & Uitto 2005, Pfendner et al 2005, Varki et al 2006, Pfendner et al 2007]:

- *ITGB4* accounts for ~80% of EB-PA
- *ITGA6* accounts for ~5% of EB-PA
- *PLEC1* accounts for ~15% of EB-PA

Clinical testing

- **Sequence analysis**

- ***ITGB4.*** Sequencing of *ITGB4* detects greater than 98% of *ITGB4* mutations.
- ***ITGA6.*** Sequencing of *ITGA6* detects greater than 98% of *ITGA6* mutations overall.

- **Deletion/duplication analysis**
  - ***ITGB4.*** No large deletions or duplications have been reported in *ITGB4*. Based on the high sensitivity of the *ITGB4* sequencing test, a screening test for large deletions/duplications is expected to have a very low yield.
  - ***ITGA6.*** No large insertions or deletions have been reported in *ITGA6*. Based on the high sensitivity of the *ITGA6* sequencing test, a screening test for large deletions/duplications is expected to have a very low yield.

Research testing

- ***PLEC1.*** Sequencing of *PLEC1* detects more than 98% of *PLEC1* mutations.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Epidermolysis Bullosa with Pyloric Atresia

Gene Symbol	Proportion of EB-PA Attributed to Mutations in This Gene [1]	Test Method	Mutation Detection Frequency by Test Method	Test Availability
ITGB4	80%	Sequence analysis	>98% [2]	Clinical Testing
		Deletion/duplication analysis [3]	<1%	
ITGA6	5%	Sequence analysis	>98%	Clinical Testing
		Deletion/duplication analysis [3]	<1%	
PLEC1	15%	Sequence analysis	>98%	Research only

1. Varki et al 2006
2. 50% of persons of Hispanic heritage in the US have the *ITGB4* mutation p.Cys61Tyr [Varki et al 2006].
3. Although no large deletions/duplications have been reported in these genes, such testing would be expected to detect exonic, multiexonic, and whole-gene deletions/duplications.

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

Testing Strategy

Confirmation of the diagnosis in a proband. The skin biopsy should be used to guide the molecular genetic testing strategy:

- If the α6β4 integrin protein is reduced or absent on immunofluorescent antibody/antigen mapping and the cleavage plane on TEM is within the lamina lucida, most often mutations in *ITGB4* are responsible and molecular genetic testing of *ITGB4* should be pursued.
- If no *ITGB4* mutations are identified and the biopsy suggests by immunofluorescent antibody/antigen mapping that the α6β4 integrin protein is affected, molecular genetic testing of *ITGA6* may be pursued.
- In some cases the cleavage plane on TEM may be just above the hemidesmosomes in the lowest keratinocyte layer and plectin staining is reduced or absent on immunofluorescent antibody/antigen mapping [Charlesworth et al 2003, Nakamura et al 2004, Pfendner & Uitto 2005]. In these cases *PLEC1* sequencing should be undertaken before *ITGA6*; however, such testing is currently available on a research basis only.

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 genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

ITGB4. Mutations in *ITGB4* can result in EB-PA, EBS (rare), or JEB (rare) [Inoue et al 2000, Jonkman et al 2000].

ITGA6. EB-PA is the only phenotype associated with mutations in *ITGA6*.

PLEC1. The other phenotypes associated with *PLEC1* mutations:

- **EB with muscular dystrophy (EB-MD)** [OMIM 226670, Charlesworth et al 2003, Koss-Harnes et al 2004, Schara et al 2004, Pfendner et al 2005]. Approximately 50 cases of EB-muscular dystrophy (EB-MD) have been reported worldwide. 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 mRNA [Pfendner et al 2005]. Inheritance is autosomal recessive.
- **EB simplex-Ogna** (see Epidermolysis Bullosa Simplex), observed in one Norwegian and one German family with autosomal dominant inheritance, is a result of the site-specific 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*.

Clinical Description

Natural History

The course of epidermolysis bullosa with pyloric atresia (EB-PA) is usually severe and often lethal in the neonatal period. Infants with extensive aplasia cutis congenita and blistering or erosions may have fatal infections with sepsis and severe electrolyte imbalance in the first weeks to months of life.

Although most affected children succumb as neonates, those who survive may have severe blistering with formation of granulation tissue on the skin around the mouth, nose, fingers, and toes, and internally around the trachea. However, some affected individuals have little or no blistering later in life.

Although mutations in *ITGB4*, *ITGA6*, and plectin usually result in EB-PA, there are also rare reports of *ITGB4* resulting in milder forms of EB described as EBS and JEB [Inoue et al 2000, Jonkman et al 2000]. Although plectin mutations causing EB-PA usually result in severe

blistering associated with PA, other mutations result in milder blistering and the disorders EBS Ogna and EB-MD.

Pyloric atresia may be detected in utero as oligohydramnios. Pyloric atresia is evident at birth and is characterized by vomiting, failure to tolerate any feeding or to pass stool, and a distended abdomen with a large stomach bubble (see Figure 1). Surgical repair of the pyloric atresia is necessary for survival.

Renal and ureteral anomalies can 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, Varki et al 2006, Pfendner et al 2007].

The long-term prognosis of EB-PA depends on the severity of the cutaneous manifestations.

Manifestations that can occur in EB-PA as well as junctional epidermolysis bullosa of the Herlitz (H-JEB) and non-Herlitz (NH-JEB) types, 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

The forms of EB-PA with the severest cutaneous manifestations are caused by mutations that result in premature termination codons on both alleles, although a number of amino acid substitutions also result in a severe phenotype such as the recurrent *ITGB4* mutation p.Cys61Tyr in Hispanic individuals with EB-PA [Varki et al 2006].

Individuals with EB-PA mutations in the genes encoding α6 or β4 integrin may also show renal and ureteral anomalies.

Penetrance

Mutations in *ITGB4*, *ITGA6*, and *PLEC1* are 100% penetrant in individuals who have two mutations on different alleles in the same gene.

Although *PLEC1* mutations may result in several different phenotypes (EB-MD, EBS, and EB-PA) and *ITGB4* mutations may result in EB without pyloric atresia, all individuals with mutations in *ITGB4*, *ITGA6*, and *PLEC1* exhibit skin blisters.

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]. Historically, EB-PA was considered a subclass of JEB; however, EB-PA is rare and its prevalence and incidence have not been determined.

Differential Diagnosis

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

Pyloric atresia. In contrast to pyloric stenosis, which presents insidiously with vomiting, pyloric atresia is present at birth and causes complete obstruction of the gastric outlet. The diagnosis of epidermolysis bullosa with pyloric atresia (EB-PA) should be considered in every neonate with pyloric atresia regardless of the degree of skin blistering.

Epidermolysis bullosa. The four major types of EB, caused by mutations in ten different genes, are EBS, hemidesmosomal EB, JEB, and DEB (see Figure 2).

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 include 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 either DEB or JEB.
- 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).
- Granulation tissue suggests JEB.
- Hyperkeratosis of the palms and soles suggests EBS, especially the Dowling-Meara 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.

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

- **EB with muscular dystrophy (EB-MD).** See Genetically Related Disorders.
- **EB with pyloric atresia (EB-PA)** See Clinical Description.
- **EB-Ogna** See Genetically Related Disorders.

Junctional EB (JEB). Separation occurs above the basement membrane of the dermis, within the lamina lucida of the dermal-epidermal junction, resulting in nonscarring blistering.

Because atrophy may develop over time, in Europe the term "atrophicans" has been applied to individuals with some form of JEB.

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

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

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 epidermolysis bullosa with pyloric atresia (EB-PA), the following evaluations are recommended:

- Evaluation of the sites of blister formation including skin and oral mucosa
- Renal ultrasound examination and tests of renal function
- Delineation of involvement of the upper esophagus by barium swallow or endoscopy as needed

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 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®)

GI tract. Surgical intervention is required to correct pyloric atresia.

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

Other. 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

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.

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 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 possibly 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 may be necessary followed by local excision.

Agents/Circumstances to Avoid

Most persons with EB-PA 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

See Junctional Epidermolysis Bullosa, Management, Therapies Under Investigation.

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

Epidermolysis bullosa with pyloric atresia (EB-PA) is inherited in an autosomal recessive manner.

To date, there is no evidence to indicate that a heterozygous mutation in *ITGB4*, *ITGA6*, or *PLEC1* results in EB-PA.

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 in JEB [Pulkkinen, Bullrich et al 1997; Takizawa et al 2000; Cserhalmi-Friedman et al 2002; Fassihi et al 2005] and could be found in EB-PA, carrier status of parents needs to be confirmed with molecular genetic testing.
- Heterozygotes (carriers) are asymptomatic.

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.

Offspring of a proband. The offspring of an individual with EB-PA 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 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 EB-PA 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 alleles 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.

Ultrasound examination. Occasionally pyloric atresia may be suspected because of oligohydramnios, with or without elevated concentration of alpha-fetoprotein and acetylcholinesterase, and echogenic material in the amniotic fluid [Dolan et al 1993, Azarian et al 2006].

Fetoscopy. Electron microscopic evaluation of fetal skin biopsies obtained by fetoscopy is also diagnostic in EB-PA. Fetoscopy carries a greater risk to pregnancy than CVS or amniocentesis and is performed relatively late (18-20 weeks) in gestation. Prenatal diagnosis for EB-PA 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 Epidermolysis Bullosa with Pyloric Atresia

Gene Symbol	Chromosomal Locus	Protein Name
ITGA6	Chromosome 2	Integrin alpha-6
ITGB4	17q11-qter	Integrin beta-4
PLEC1	8q24	Plectin-1

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 Epidermolysis Bullosa with Pyloric Atresia

147556	INTEGRIN, ALPHA-6; ITGA6
147557	INTEGRIN, BETA-4; ITGB4
226730	EPIDERMOLYSIS BULLOSA WITH PYLORIC ATRESIA
601282	PLECTIN 1; PLEC1

Table C. Genomic Databases for Epidermolysis Bullosa with Pyloric Atresia

Gene Symbol	Entrez Gene	HGMD
ITGA6	3655 (MIM No. 147556)	ITGA6
ITGB4	3691 (MIM No. 147557)	ITGB4
PLEC1	5339 (MIM No. 601282)	PLEC1

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

Note: HGMD requires registration.

ITGB4

Normal allelic variants: The normal full-length cDNA is encoded in 41 exons spanning 36 kb of the genomic DNA. The cDNA comprises 5921 bp with an open reading frame of 5258 nucleotides encoding 1822 amino acids. Two splicing variants express different isoforms of the protein [Pulkkinen, Kurtz et al 1997]. The most common epidermal variant does not express exon 33.

Pathologic allelic variants: Over 100 mutations spanning the entire *ITGB4* gene have been described in EB-PA [Pulkkinen, Kimonis et al 1997; Pulkkinen, Kurtz et al 1997; Pulkkinen, Bruckner-Tuderman et al 1998; Pulkkinen, Rouan et al 1998; Ashton et al 2001; Nakano et al 2001; Iacovacci et al 2003; Varki et al 2006]. Mutations that cause premature termination codons on both alleles result in the most severe phenotypes, which are frequently lethal in the neonatal period. Other types of mutations including amino acid substitutions and splicing mutations may result in a less severe phenotype [Mellerio, Pulkkinen et al 1998; Pulkkinen, Rouan et al 1998]; Chavanas et al 1999; Varki et al 2006]. In a one case severe blistering without pyloric atresia was described from a homozygous missense mutation in *ITGB4* [Inoue et al 2000] and in another a homozygote with missense and PTC *ITGB4* mutations [Inoue et al 2000, Jonkman et al 2000]. Few recurrent mutations have been described; however the mutation p.Cys61Tyr is common in US Hispanic JEB-PA patients [Varki et al 2006]. See Table 2.

Table 2. *ITGB4* Pathologic Allelic Variants Discussed in the *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.182G>A	p.Cys61Tyr	NM_000213.3 NP_000204.3

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

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

ITGA6

Normal allelic variants: Two transcript variants encoding two different isoforms have been found for this gene. The normal cDNA of variant 1 comprises 5680 bp with an open reading frame of 3273 nucleotides encoding 1091 amino acids in 26 exons. Transcript variant 2 contains an alternate coding exon from variant 1 that results in a frameshift and is encoded in a 5810 bp cDNA. The resulting protein isoform b is shorter (1073 amino acids) than isoform a and has a distinct C terminus.

Pathologic allelic variants: Only five individuals with EB-PA as a result of α6 integrin mutations have been described in the literature. Insertion/deletion, splice junction, and amino acid substitution mutations have been described [Ruzzi et al 1997, Gache et al 1998, Lepinard et al 2000, Varki et al 2006].

Normal gene product: Integrins associate in pairs containing one alpha and one beta chain. α6β4 integrin comprises one α6 and one β4 integrin from the integrin family of proteins and is a component of the hemidesmosomes of the epidermis. Integrins are known to participate in cell adhesion as well as cell-surface-mediated signaling.

Abnormal gene product: Null alleles may result in little or no protein seen with staining with anti-α6β4 integrin antibodies.

PLEC1

Normal allelic variants: The normal cDNA of variant 1 is 14755 bp with an open reading frame of 13722 nucleotides encoding 4575 amino acids in 32 exons [McLean et al 1996]. Expression of the different isoforms result from alternative splicing of exon 1 as well as use of different 5' untranslated regions. At least ten other variant transcripts have been described. The expression of different 5' regions affects the subcellular localization of the protein and the resulting attachments to organelles and intermediate filaments [Rezniczek et al 2003]. There is also a rodless form lacking exon 31.

Pathologic allelic variants: The three phenotypes associated with plectin mutations are EB-PA, EB-MD, and EBS-Ogna:

- All types of plectin mutations causing EB-PA and EB-MD have been described: nonsense, missense, insertions, deletions, and splicing mutations [Schara et al 2004, Nakamura et al 2005, Pfendner et al 2005], Uitto et al 2007]. These mutations have an autosomal recessive inheritance pattern and may be found throughout the gene although clustering in the last two large exons has been observed. The mildest phenotypes are usually associated with amino acid substitutions or in-frame insertions or deletions, which do not alter the reading frame of the mRNA [Pfendner et al 2005].
- EBS-Ogna, described in two families, is a result of the autosomal dominant p.Arg2110Trp mutation in the rod domain. See Table 3.

Table 3. *PLEC1* Pathologic Allelic Variants Discussed in the *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.6328C>T	p.Arg2110Trp [1]	Z54367 CAA91196.1

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

1. Koss-Harnes et al 2002

Normal gene product: Plectin is a large cytolinker protein expressed in the epidermis, muscle, and other tissues. Plectin acts in the epidermis to link the intermediate filament network to the hemidesmosome and desmosomes thereby allowing stable attachments between cells and of cells to the underlying basal lamina. In the epidermis, plectin is found as a component of the hemidesmosome and forms attachments toα6β4 integrin. At least 11 different isoforms are produced by alternative splicing and use of different 5' untranslated regions [Rezniczek et al 2003].

Abnormal gene product: Null alleles may result in little or no protein seen with staining with anti-plectin antibodies. In-frame deletions or insertions, splicing mutations, and certain missense mutations may result in some partially functional protein and reduced or patchy staining with anti-plectin antibodies and a milder phenotype.

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
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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.

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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

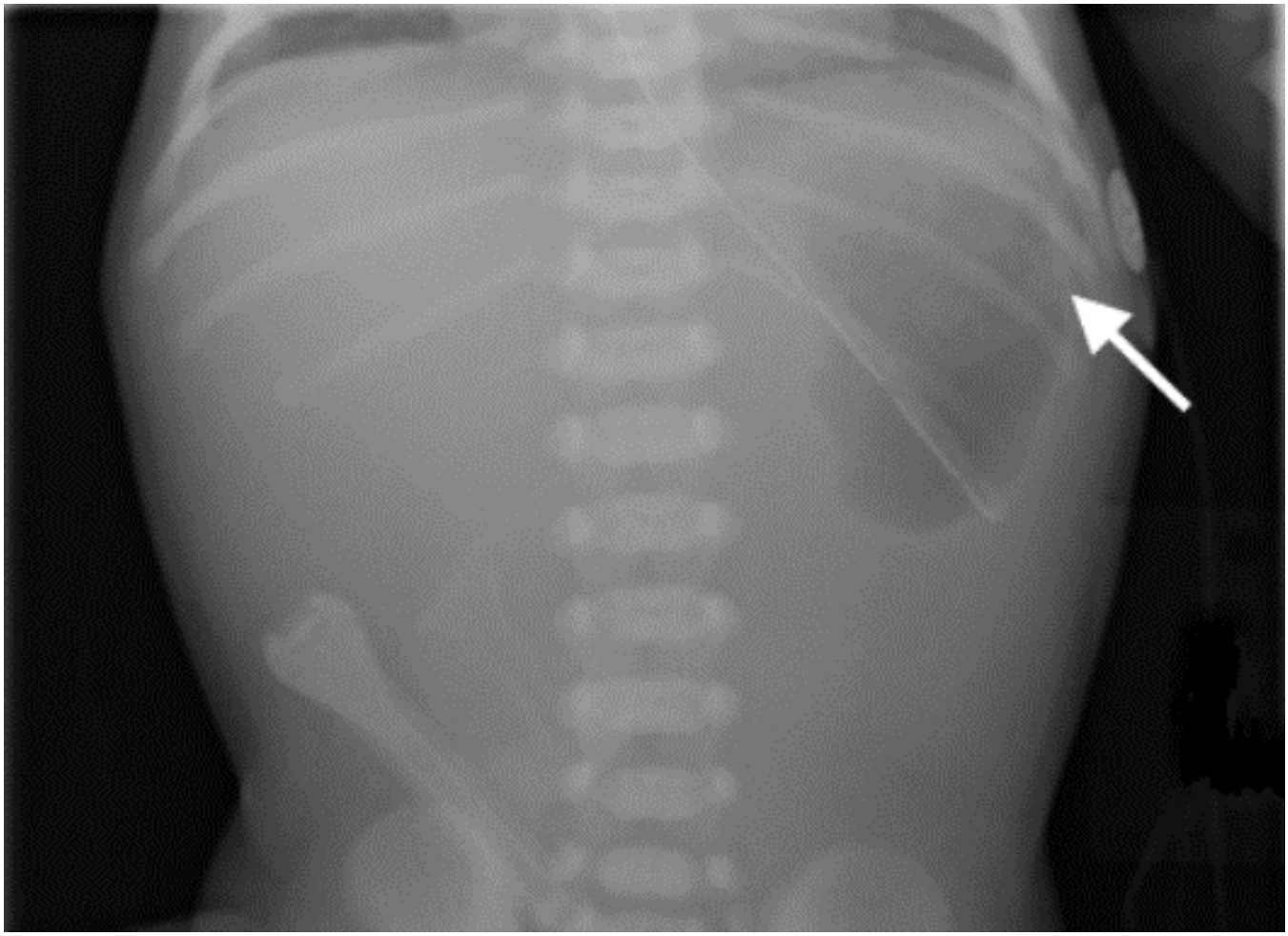

Figure 1. Radiograph of a 36-week gestational-age, one-day-old neonate with EB-PA. Note the single gastric bubble (white arrow).

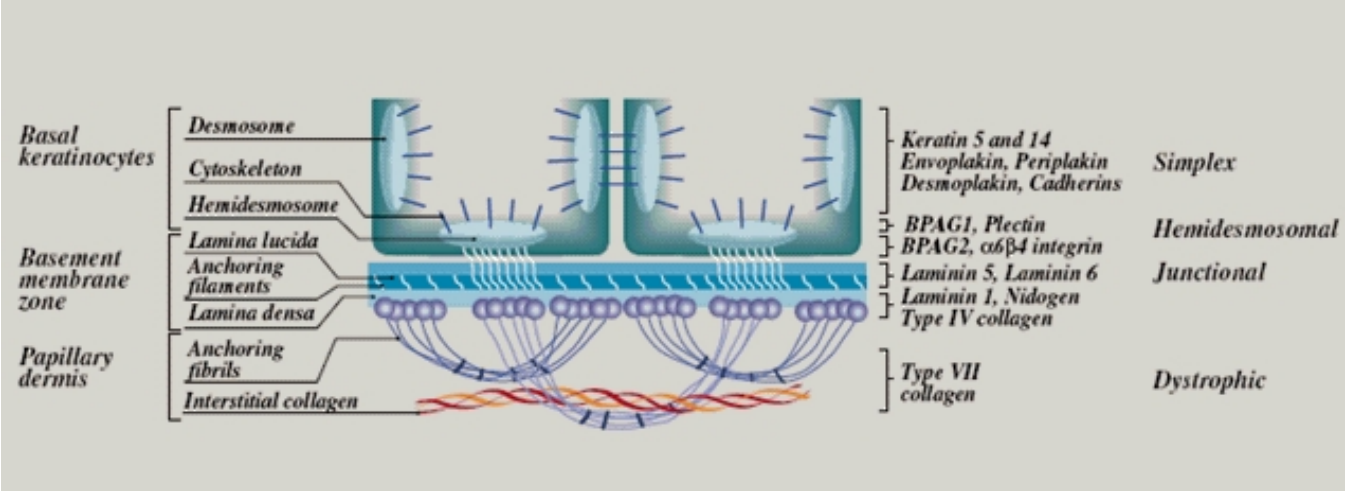

Figure 2. Diagram showing locations affected by mutations causing the four major subtypes of EB syndromes