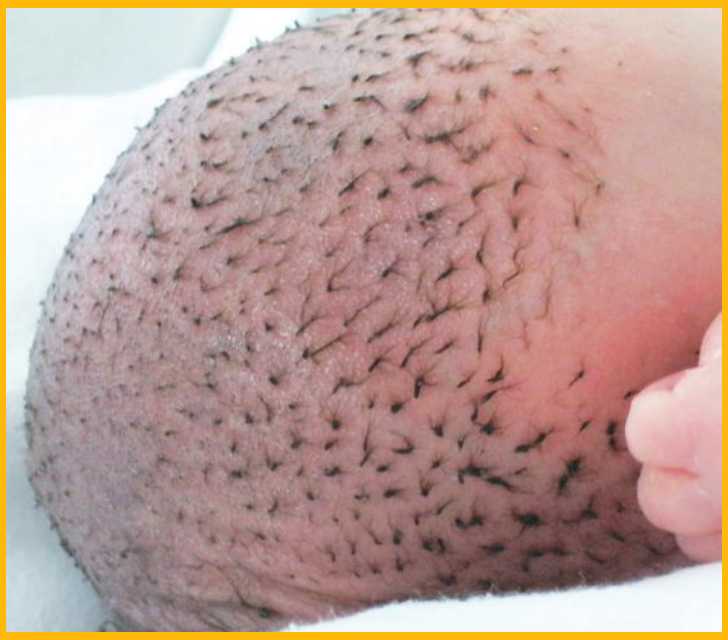
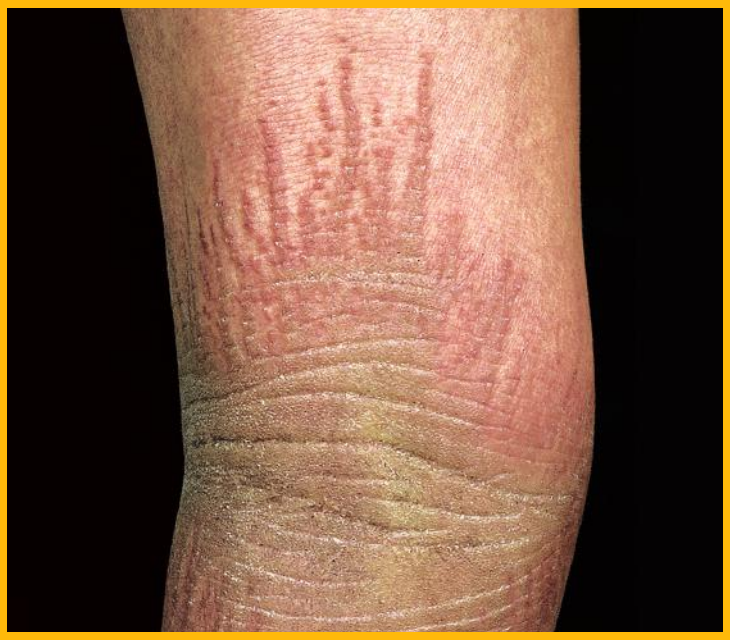
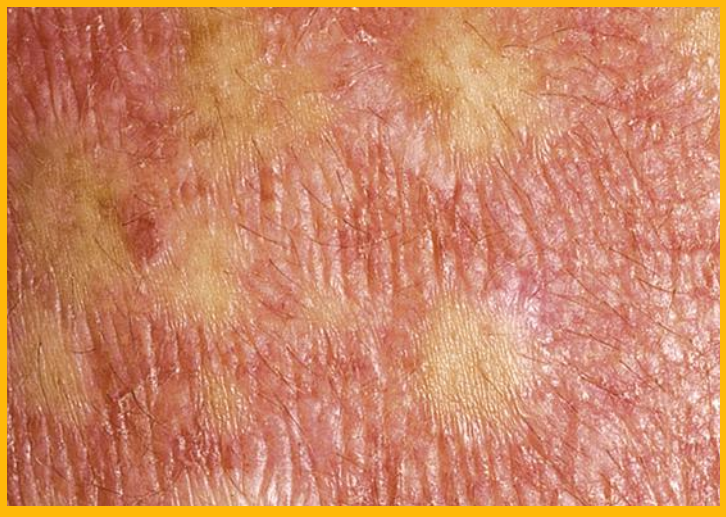




ATLAS OF GENODERMATOSES

SECOND EDITION

Gianluca Tadini
Michela Brena • Carlo Gelmetti • Lidia Pezzani



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Foreword

Recent years have witnessed dramatic advances in our understanding of the biological foundations of inherited skin diseases. These new data are not only profoundly changing the way we diagnose, classify and manage genodermatoses, they are also raising many questions regarding the best way to teach regarding these complex disorders. In a time when genes and genetic mechanisms are playing an increasingly more prominent role in the definition of clinical entities and in their treatment (as they often predict therapeutic responses), clinical aspects of the medical evaluation process should not be overlooked. In fact, the modern diagnostic process very often requires the physician to be able to form links between clinical data and molecular features.

This is why we should applaud and congratulate Prof. Gianluca Tadini for bringing to us, experts and trainees alike, a new edition of the legendary *Atlas of Genodermatoses*. This comprehensive and, at the same time, very focused book is likely to become, like its predecessor, a prerequisite for anyone struggling with a difficult case or wishing to expand his or her knowledge in genodermatology.

Making a diagnosis of a genetic skin disease is always a very challenging moment and a sometimes difficult task for a dermatologist. Genodermatoses are mostly rare diseases, and consequently, most professionals have little experience with these diseases. This unique collection of cases assembled patiently, over the course of years, by the late Ruggero Caputo and by Gianluca Tadini provides an unsurpassed overview of the major genodermatoses encountered in our daily practice, even if only on rare occasions. The new edition of the *Atlas of Genodermatoses* will remain, as in the past, a unique and unmatchable adjunct diagnostic tool in dermatology and related medical disciplines.

Eli Sprecher
Tel Aviv, Israel

Preface

After 10 years, a second edition of our atlas is born!

The heritage of Ruggero Caputo is still alive in our hearts and we dedicate our three-years' efforts to his memory.

Many changes in clinical pattern, classification and genetics have occurred during this time.

However, the general layout of the atlas remains the same—brief captions, a concise text accompanied by relevant bibliographic references, and brief notes on management are the key core.

Many new classifications, accepted worldwide, have been included together with pathway schemes in order to better understand the pathogenic mechanisms of the diseases.

We have featured the works of contributors from all over the world who enriched this atlas with figures of best cases that we were not able to see in our department. This means that this second edition must be considered a *consortium* of authors.

The picture contributions are specifically acknowledged in the *Photographic References* section. Unfortunately, for few diseases and for different reasons, we were not able to collect figures and, for them, the reader will find a concise text with bibliographic references.

We hope that our work may help students, trainees, and colleagues show interest in genodermatology.

Genetic data of each represented patient are available upon request at: gtadinicmce@unimi.it

Acknowledgments

First of all, we dedicate the atlas to the patients and their families.

We are grateful to our colleague Federica Dassoni for the outstanding pictures.

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We also wish to thank all the colleagues from the Department of Dermatology of Milan with whom we shared expertise and constructive discussions and the entire staff of the Center for Inherited Cutaneous Diseases of the University of Milan: Elisa Faure, Luisa C. Rossi, Francesca Santagada, and Elena Colombo.

Finally, we extend a very special thanks to Francesca Besagni from Parma, Italy and Maria Pia Boldrini from Cordoba, Argentina, who, with their grace and brightness, supported us during these years.

Gianluca Tadini
Michela Brena
Carlo Gelmetti
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CHAPTER 1

Epidermolysis bullosa

DEFINITION

Epidermolysis bullosa (EB) consists of a heterogeneous group of mechanobullous diseases due to mutations on at least 17 different genes.

Table 1.1 gives a classification of hereditary epidermolysis bullosa, based on the last contribution of J.D. Fine and Coworkers.

As can be seen in the literature, the denominations *simplex* and *dystrophic* are commonly used, but we prefer to define EB regarding simply the site of the cleavage, abandoning the denomination of *simplex* and *dystrophic* that are, in our opinion, aspecific; i.e., we refuse to call *simplex* a group of

Table 1.1 Classification of hereditary epidermolysis bullosa (EB)

Type	*Subtype*	*Mutated protein*	*Gene defect*
EEB	EEB-generalized	Keratin 5, keratin 14	KRT5, KRT14
	EBS-MP	Keratin 5	p.P25L mutation (KRT 5)
	EBS-MCE	Keratin 5	c.1649delG mutation (K5)
	EEB-MD	Plectin	PLEC1
	EEB-Ogna subtype	Plectin	PLEC1
	EEB-PA	Plectin	PLEC1
	EEB-exophilin 5	Exophilin-5	EXPH5
	EEB-BP230 related	Dystonin	DST
	EEB-lethal acantholytic	Desmoplakin, plakophilin	DSP, PKP1
	APSS	Transglutaminase 5	TGM5
JEB	JEB-severe generalized	Laminin 5[a]	LAMA3, LAMB3, LAMC2
	JEB-generalized intermediate	Laminin 5, collagen type XVII (BPAG2)	LAMA3, LAMB3, LAMC2, COL17A1
	JEB-PA[b]	Integrin α6–β4[c]	ITGA6, ITGB4
	LOC	Laminin α3 gene[d]	LAMA3A
	JEB-RR	Integrin α3	ITGA3
DEB	DDEB	Collagen type VII	COL7A1
	RDEB	Collagen type VII	COL7A1
KINDLER		Kindlin-1	KIND1 (FERMT1)

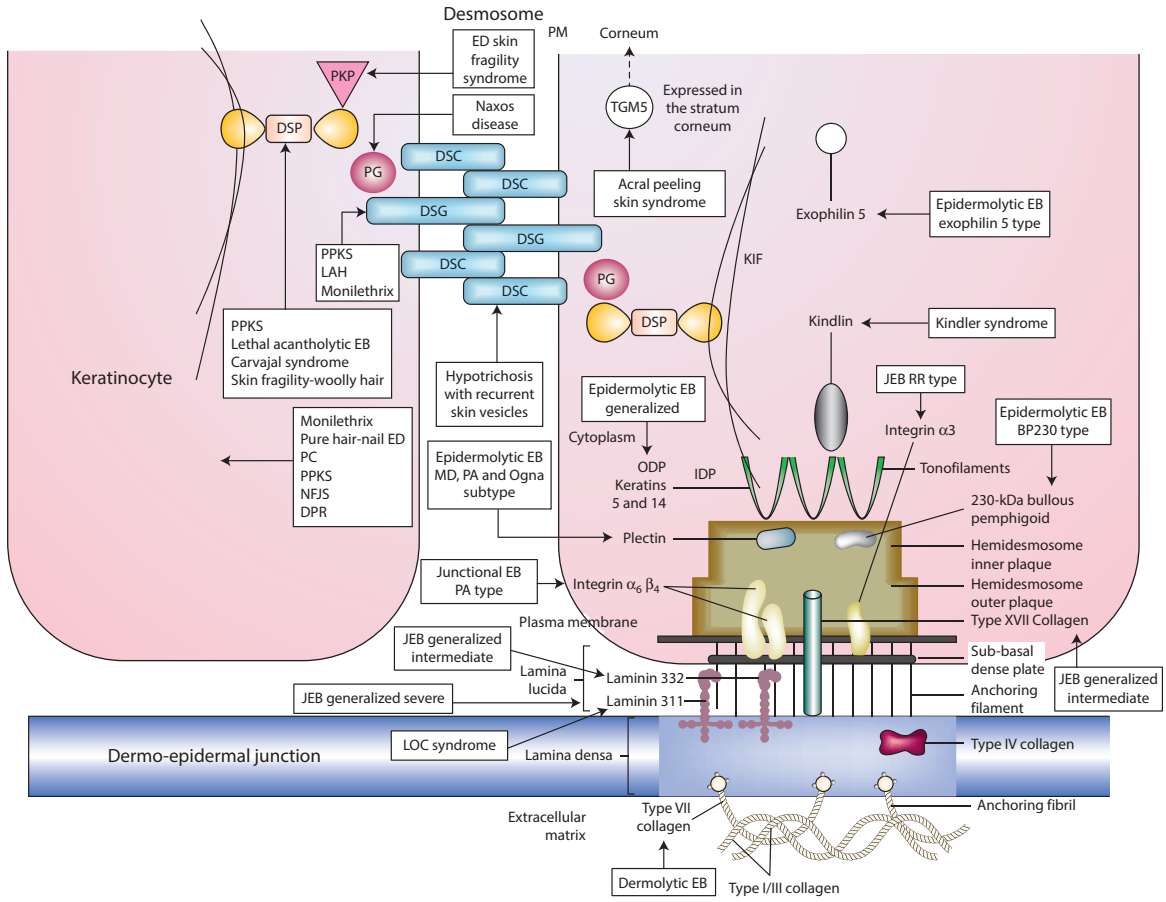
EEB, epidermolytic EB; JEB, junctional EB; DEB, dermolytic EB; DDEB, dominant dermolytic EB; EBS-MP, EBS with mottled pigmentation; EBS-MCE, EBS with migratory mircinate erythema; EEB-MD, EEB with muscular dystrophy; EEB-PA, EEB with pyloric atresia; APSS, acral peeling skin syndrome; JEB-PA, JEB with pyloric atresia; LOC, Laryngo–onycho–cutaneous syndrome; JEB-RR, JEB with respiratory and renal involvement; DDEB, dominant dermolytic EB; RDEB, recessive dermolytic EB.

[a] Laminin 5 is a macromolecule composed of three distinct (α3, β3, γ2) laminin chains; mutations in any of the encoding genes result in a JEB phenotype.

[b] Some cases of EB associated with pyloric atresia may have intraepidermal cleavage or both intralamina lucida and intraepidermal clefts.

[c] α6–β4 integrin is a heterodimeric protein; mutations in either gene have been associated with JEB-PA syndrome.

[d] LAMA3 encodes three different isoforms, called α3a, α3b1, and α3b2; LOC is due to mutations in the α3a protein.



Schematic drawing 1.1 Molecular basis of the different types of EB.

disorders in which there are potentially lethal variants. If the term *epidermolytic* does not fit to all subtypes of EB in which the site of cleavage is intraepithelial (basal or suprabasal), we prefere this term just in order to clearly underline the localization of blisters.

In analogy, we believe that in 2014 the term *dystrophic* is meaningless: we failed to find an exact definition of *dystrophy* that could fit with the subtypes of EB due to a genetic defect in COL7A1 gene.

Simplex and dystrophic are claimed to be maintained in order to avoid confusion in changing a well-established terminology, in other terms, they are used as *eponyms*. Curiously, in the last classification *eponyms* are waived and we agree totally on that.

Schematic drawing 1.1 shows the molecular basis of the different types of EB.

EPIDEMIOLOGY

In Italy there are more than 1000 EB patients among 60,000,000 inhabitants. Epidemiological data from the U.S. National Registry are superimposable.

EPIDERMOLYTIC (INTRAEPIDERMAL, INTRAEPITHELIAL, *SIMPLEX*) EPIDERMOLYSIS BULLOSA (EEB)

Genetics and pathogenesis

This group of EB is, in the vast majority, transmitted as an autosomal dominant trait, and encompasses about 40% of total EB patients. Fewer than 1% of cases are inherited recessively.

The site of cleavage is intraepidermal, with *basal* (cleavage within the basal layer) or *suprabasal* (cleavage in the upper layers).

Nine genes are involved in the pathogenesis of the disease, encoding, respectively, keratin 5 (K5), keratin 14 (K14), plectin (PLEC1), EXPH5 (Slac2b protein) and DST (*coiled-coil* domain of BP230), TGM5 (transglutaminase 5), DSP (desmoplakin), PKP1 (plakophilin), and JUP (plakoglobin).

Clinical cutaneous and extracutaneous findings

Localized, generalized, generalized severe, recessive (genes: K5, K14)

Bullae mainly involve palmoplantar sites (*localized*) (Figures 1.1 and 1.2) or be more widely distributed

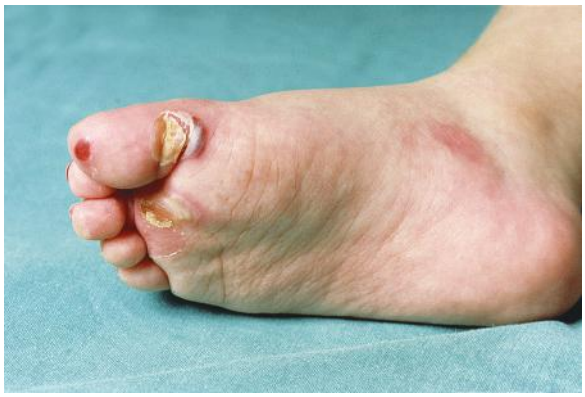


Figure 1.1 Localized epidermolytic epidermolysis bullosa (EEB).

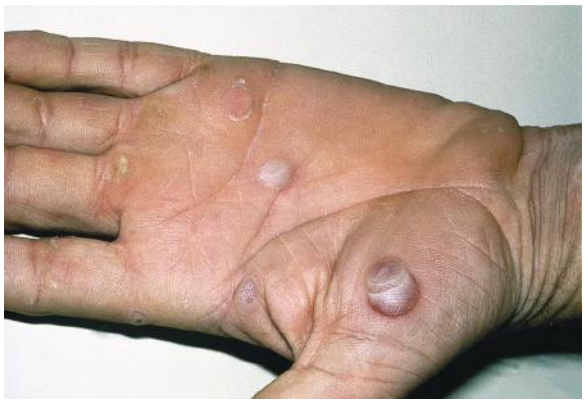


Figure 1.2 Localized epidermolytic epidermolysis bullosa (EEB).

in the napkin areas, face or folds (*generalized*) (Figures 1.3 and 1.4). Normally, the disease is not severe, except in some cases with a herpetiform jewel-like distribution and hemorrhagic bullae (*generalized severe*) (Figures 1.5 and 1.6). In these cases, blisters invariably also involve palmoplantar areas and are rapidly recurrent, causing palmoplantar keratodermas (Figures 1.7 and 1.8). A few fatal cases have been reported in the perinatal period due to the extreme severity of the disease. These

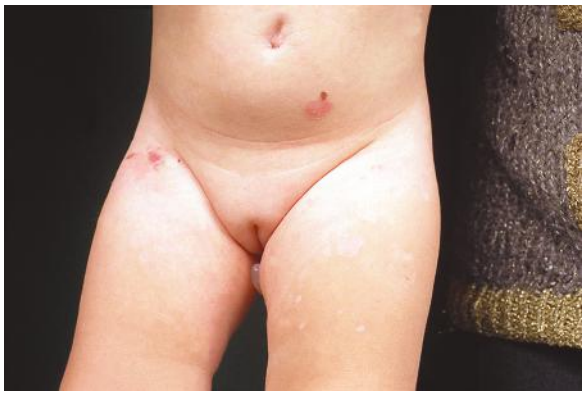


Figure 1.3 Generalized epidermolytic epidermolysis bullosa (EEB).

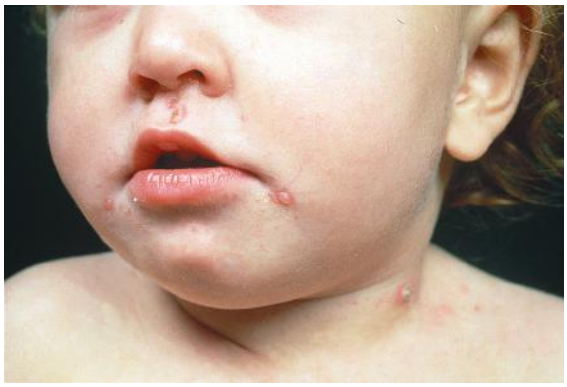


Figure 1.4 Generalized epidermolytic epidermolysis bullosa (EEB).

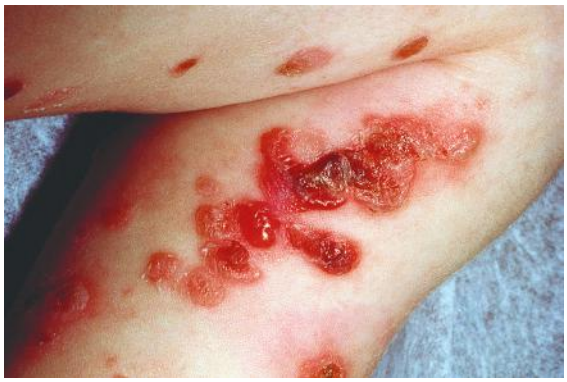


Figure 1.5 Generalized severe epidermolytic epidermolysis bullosa (EEB).

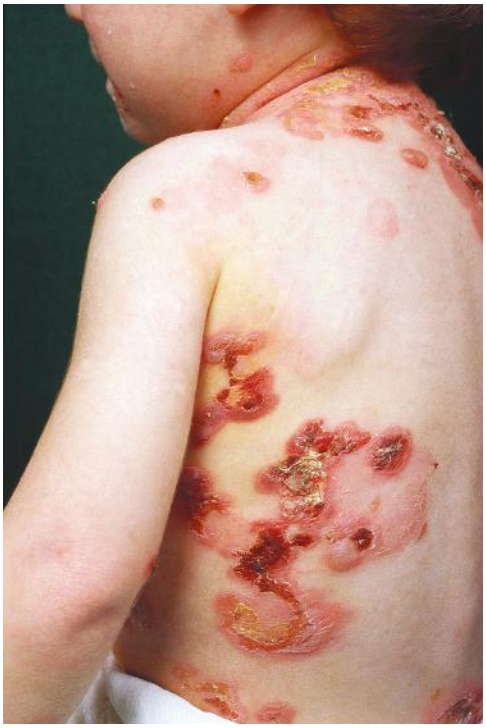


Figure 1.6 Generalized severe epidermolytic epidermolysis bullosa (EEB).

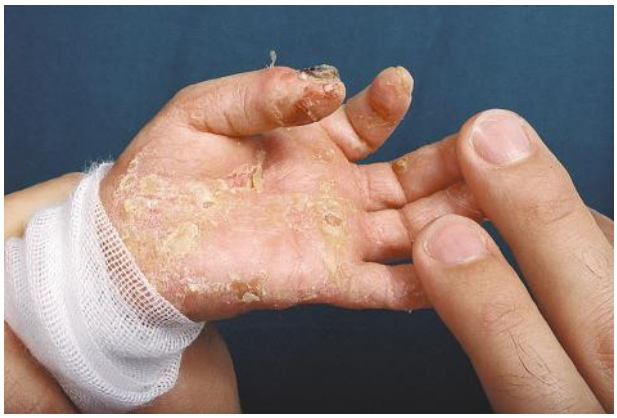


Figure 1.7 Generalized severe epidermolytic epidermolysis bullosa (EEB).

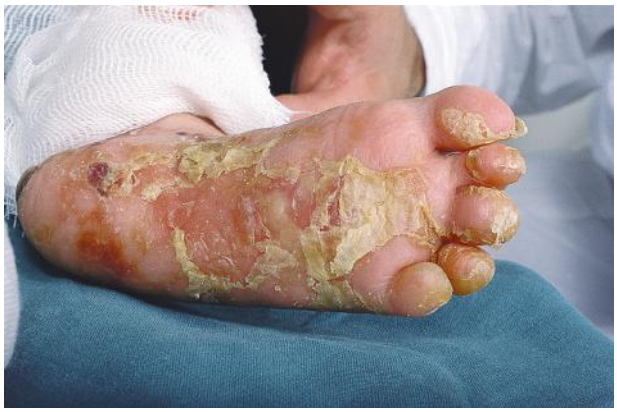


Figure 1.8 Generalized severe epidermolytic epidermolysis bullosa (EEB).

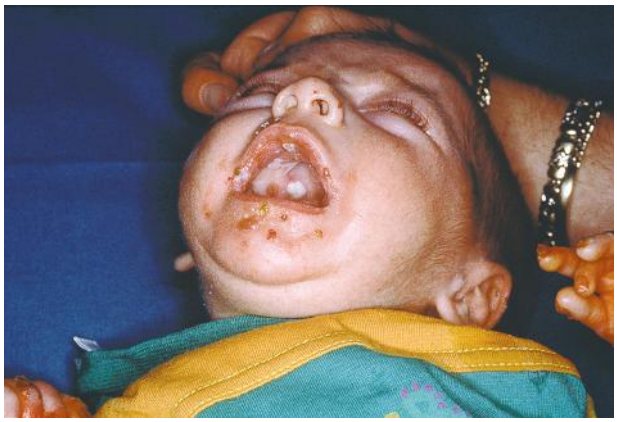


Figure 1.9 Generalized severe epidermolytic epidermolysis bullosa (EEB).

children reach milestones of physical development later, such as the ability to walk and run (and hence attend school), partly because of the palmoplantar lesions and partly because of the frequent oral lesions (Figure 1.9) that impair food consumption and may lead to anemia.

In these patients, nails are frequently absent (Figure 1.10) and alopecic areas may be detected as well as milia on the dorsa of the hands.

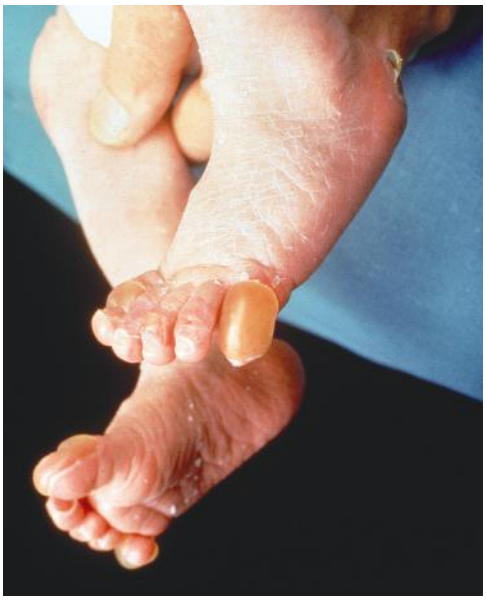


Figure 1.10 Generalized severe epidermolytic epidermolysis bullosa (EEB).

At around 8–10 years of age, the situation tends to improve, and in adulthood, EEB is restricted to occasional mechanically involved sites, such as the feet, elbows and knees.

Symptoms in all of the epidermolytic subtypes tend to worsen during the summer and in hot and humid weather.

In the few described EEB families with the *recessive mode of inheritance of K14 mutations* (1%), lesions are in general more severe (Figures 1.11 and 1.12) than in families with dominant inheritance. They may show severe anogenital lesions, post lesional nevi, ichthyotic plaques and focal palmo-plantar keratoderma.

Mottled pigmentation and migratory circinate erythema subtypes

Mottled pigmentation subtype (EBS-MP) (K5 gene): This subtype, due to a particular K5 gene mutation

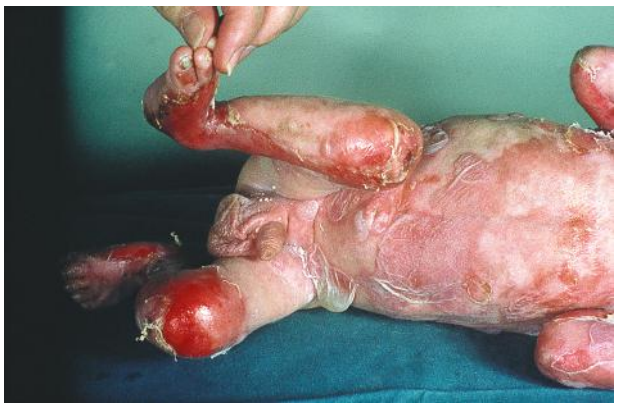


Figure 1.11 Recessive epidermolytic epidermolysis bullosa (EEB).

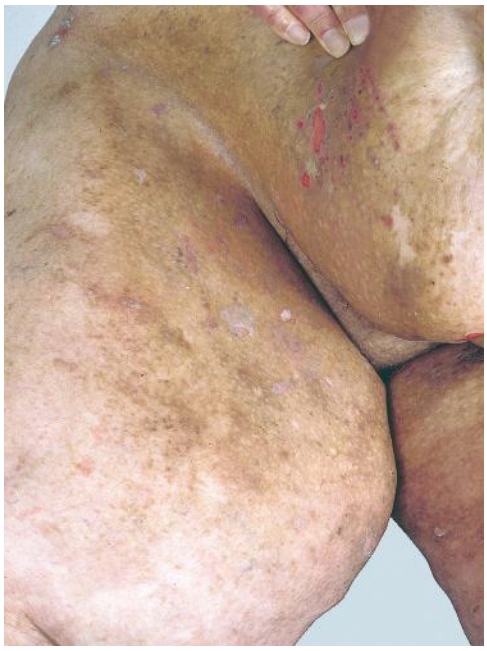


Figure 1.12 Recessive epidermolytic epidermolysis bullosa (EEB).

(p.P25L), is characterized by a generalized clinical pattern with mottled and/or reticulate hyperpigmentation (Figure 1.13).

Migratory circinate erythema subtype (EBS-MCE) (K5 gene) shares hyperpigmented postinflammatory lesions and generalized pattern with the former subtype. The peculiarity resides in slowly enlarging erythema and erosions with centrifugal course. This subtype is caused by a mutation c.1649delG in K5 gene (Figure 1.14).

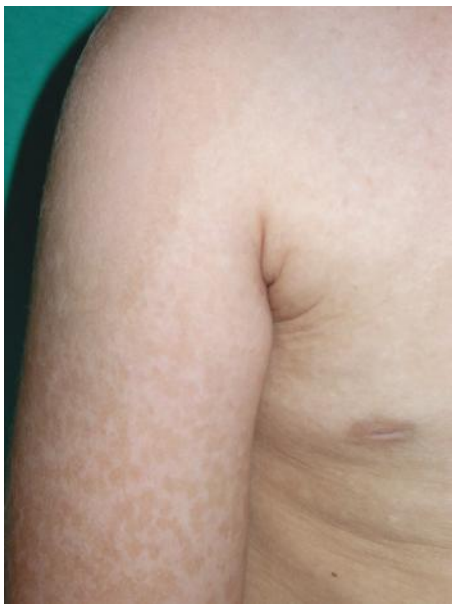


Figure 1.13 Epidermolytic epidermolysis bullosa (EEB) mottled pigmentation subtype.

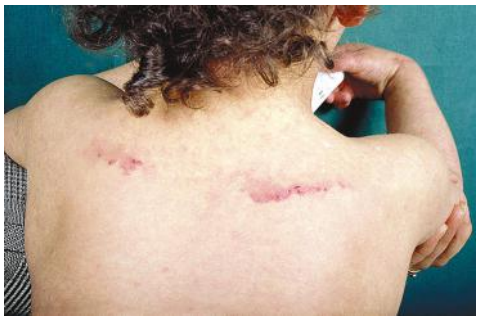


Figure 1.14 Epidermolytic epidermolysis bullosa (EEB) migratory circinate erythema subtype.

Plectin-related subtypes

EEB-muscular dystrophy: This is characterized by a clinical picture of generalized EB inherited recessively, with onset at birth and accompanied by a late-onset progressive muscular weakness (7–10 years) (Figure 1.15). Mucosal manifestations are clinically relevant, with different degrees of severity and with upper respiratory tract involvement with recurrent pneumonitis. In two cases, visceral involvement (esophagus, bladder) has been reported. Obviously, muscular dystrophy tends to overwhelm skin lesions regarding the course and prognosis of the disease.

EEB-ogna: In Norway, mutations of plectin gene have been found in a large group of families with dominant inherited generalized epidermolytic EB without signs of muscular involvement. These patients show mainly acral distribution of lesions and onychogryphosis.

EEB-pyloric atresia: Finally, plectin gene mutations cause in few pedigrees severe epidermolytic EB and concomitant pyloric atresia, heralded by polyhidramnios and premature delivery. Skin signs at birth are very severe with bullous lesions, aplasia-cutis-like areas and early fatal outcome. Only in one case skin signs improved with age but a single case of severe visceral involvement (trachea, esophagus,

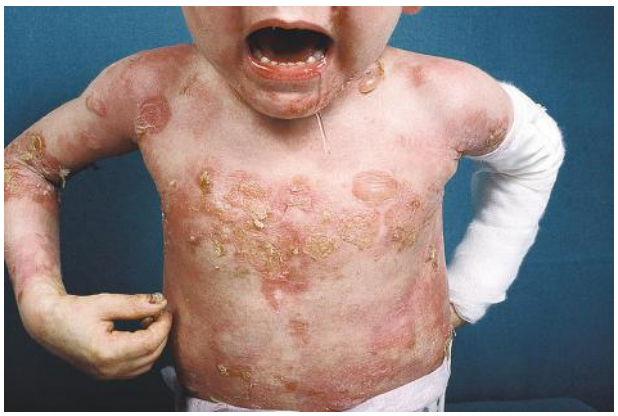


Figure 1.15 EEB-muscular dystrophy.

urethral, and megacolon) have been reported. Nails and teeth may be involved. Malformed pinnae and nasal alae, joint contractures and cryptorchidism have been reported.

It must be remembered that a very similar clinical picture of severe epidermolytic EB associated with pyloric atresia is due to mutations of the genes encoding for the two subunits of integrin α6-β4, causing the variant of junctional EB with pyloric atresia.

Early detection of pyloric defect and surgical treatment are mandatory as early as possible.

EXPH5-related epidermolytic EB

Four cases are described, three from the same Iraqi family and one from Germany.

The disease is inherited in an autosomal recessive pattern. The EXPH5 gene encodes Slac2b–exophilin-5 protein that is involved in intracellular protein transport and exosome secretion. The site of cleavage is within the basal keratinocyte layer.

The onset is characterized by extensive erosions on the arms, legs and thorax (Figures 1.16 and 1.17). Initial lesions are not followed by atrophy and scarring. Pigmentary changes may be visible. Adnexa are spared.

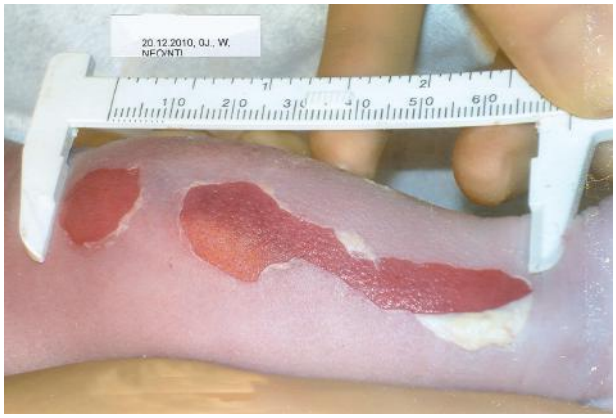


Figure 1.16 EXPH5-related epidermolytic EB.

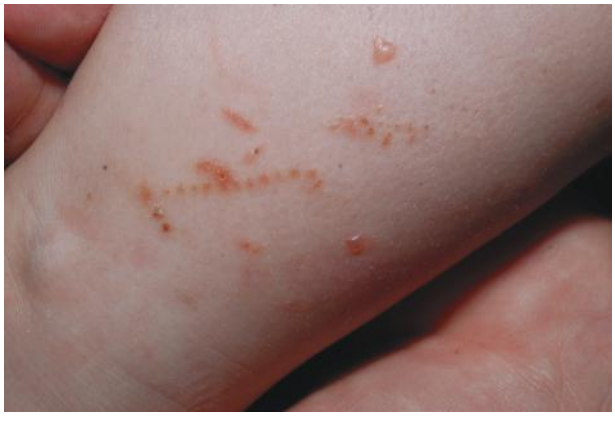


Figure 1.17 EXPH5-related epidermolytic EB.

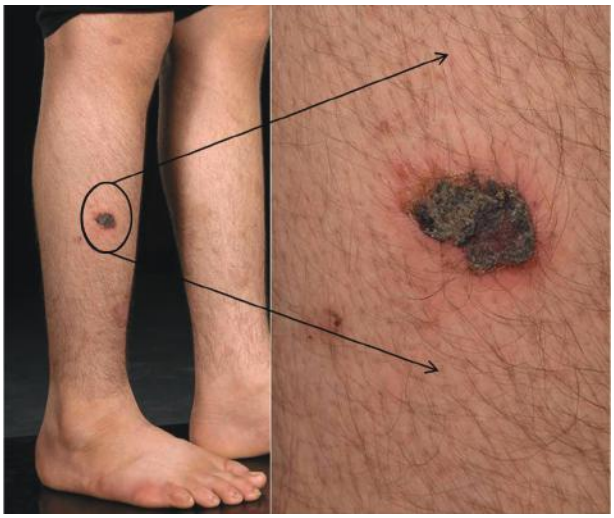


Figure 1.18 EXPH5-related epidermolytic EB.

The course is benign with trauma-induced small blisters–erosions with residual crusting at the extremities (Figure 1.18).

BP230-related EEB

Few cases are signaled in the literature.

BP230 or BPAG1-e is also known as the epithelial isoform of bullous pemphigoid antigen 1 and is one of the components of hemidesmosomes. The DST (dystonin) gene encodes the coiled-coil domain of BP230: Mutations of this gene have been found to cause a subset of EEB, leading to the loss of hemidesmosomal inner plaques and skin fragility.

The disease is transmitted as an autosomal recessive trait.

Onset is at birth, with lifelong, diffuse, spontaneous and trauma-induced blisters and erosions, mainly located at the ankles (Figure 1.19). Nails may be involved.

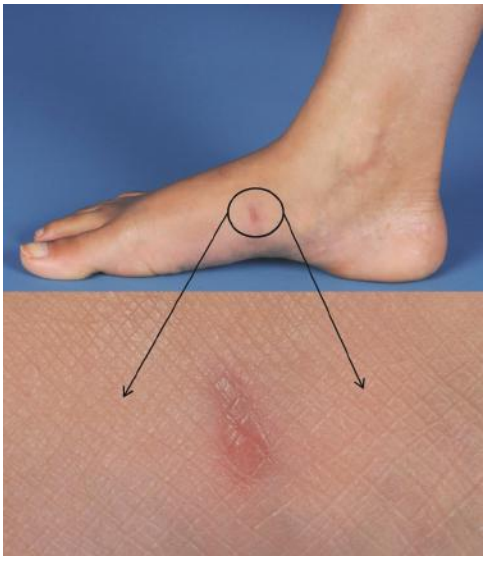


Figure 1.19 BP230-related EEB.

(Lethal) acantholytic EB

This form is characterized by extensive shedding of the epidermis at birth or shortly thereafter (Figure 1.20). Few pedigrees have been described, all invariably with fatal outcome. Total alopecia, nails and external ears malformation and associated cardiomyopathy were observed. This variant is due to mutations in DSP (desmoplakin) and PKP1 (plakophilin) genes. Desmoplakin, is the *leader* in the constitution of desmosomal structures in epithelia and heart. Desmoplakin *anchors* plakoglobin and plakophilin to form the desmosomal plaque. Ultrastructural analysis shows suprabasal cleavage with abnormal tonofilament insertion and rudimentary or absent desmosomal inner plaques.

A further subtype of EEB is denominated as *skin fragility syndromes* (SFS) and includes:

- Desmoplakin-deficiency: SFS-desmoplakin-SFS with wooly hair.
- Plakoglobin-deficiency: SFS-plakoglobin deficiency.
- Plakophilin-deficiency: SFS-ectodermal dysplasia syndrome (see Chapter 13).
- All three subtypes have generalized pattern, with erosions, crusts, and few blisters, involvement of nails bed, may have scalp abnormalities (hypotrichosis and wooly hair) and different degree of palmo-plantar keratoderma (focal, punctuate, or striate). Cardiomyopathy may also be present (see also Chapter 4).

Of note, *acral peeling skin syndrome*-transglutaminase 5-related is included, in the last classification, as a rare variant of suprabasal EB (see Chapter 3).

Finally, a further pedigree defined as *epidermolysis bullosa superficialis* is included in the last classification. Patients are described to be characterized by superficial erosions without blisters but with possible postinflammatory hypopigmentation.

Noteworthy, first described cases with this name turned to be a variant of dominant dermolytic EB (!). The causative gene of the recent proposed cases is unknown.

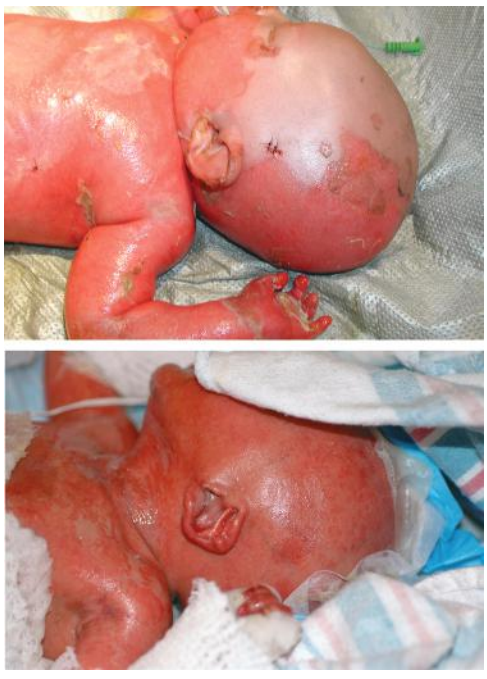


Figure 1.20 EEB acantholytic subtype.

Laboratory findings

- Skin biopsies, taken at the peribullous areas, are necessary to perform immunofluorescence and/or immunohistochemistry that may reveal defect of expression of the different components.
- The second step is electron microscopy (EM) that demonstrates intraepidermal cleavage with cytolysis and clumping of tonofilaments in the basal layers. Based on the EM and DIF results, the further step is represented by molecular studies that are performed with blood samples or cultured keratinocytes, in order to detect mutations in the K5–K14 genes for major forms or the plectin gene for EEB with muscular dystrophy and the Ogna subtypes, plectin or α6-β4 mutations for epidermolytic EB with pyloric atresia, *DSP* and PKP1 genes for acantholytic subtype; DSP, PKP1, and JUP genes for skin fragility syndromes.

Follow-up and therapy

- Fortunately, for the majority of patients, EEB does not represent an obstacle to a normal life. In contrast, the more severe patients (severe generalized subtype) have to be frequently checked during preschool age in order to maintain normal food intake and growth centiles.
- Antibiotic therapy and special dressing are required.
- Orthopedic advice is mandatory to assess devices and physiotherapy for normal walking and development.
- Acantholytic subtype may be lethal in the neonatal period. These patients require hospitalization in neonatal intensive care unit.

JUNCTIONAL EPIDERMOLYSIS BULLOSA (JEB)

Genetics and pathogenesis

Cleavage of JEB is intra-lamina lucida.

JEB is a heterogeneous subgroup of EB due to mutations in several genes encoding the major constituents of the hemidesmosomes, and represents usually fewer than 10% of EB patients.

The involved genes are the following:

- LAMA3, LAMB3, and LAMC2 genes (laminin 332 protein) for generalized severe (former Herlitz subtype), generalized intermediate and for the rare subtypes called *localized* and *inversa*
- LAMA3A (isoform alpha 3 chain) for LOC syndrome
- COL17A1 gene (collagen XVII protein) for generalized intermediate, localized, and *late onset* subtypes
- ITGA6 and ITGB4 genes (integrin α6-β4 protein) for JEB with pyloric atresia (lethal and non-lethal cases)
- ITGB4 is also involved in rare cases of localized subtype
- ITGA3 gene (integrin α3 subunit) for JEB with renal and respiratory involvement

Revertant mosaicism may be visible in JEB (Figure 1.21)

Clinical cutaneous and extracutaneous findings

Severe generalized (former Herlitz) JEB

The extreme severity of this disease is already noticeable at birth (Figure 1.22).

Bullae present spontaneously even with a gentle touch. After the eruption, blisters lose their roof and remain visible as erosions that do not heal (Figure 1.23). In particular, granulomatous and easily bleeding lesions (Figure 1.24) arise on such eroded epithelium.

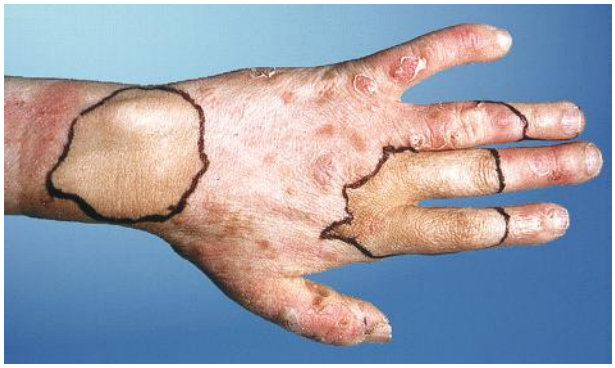


Figure 1.21 Junctional epidermolysis bullosa (JEB).

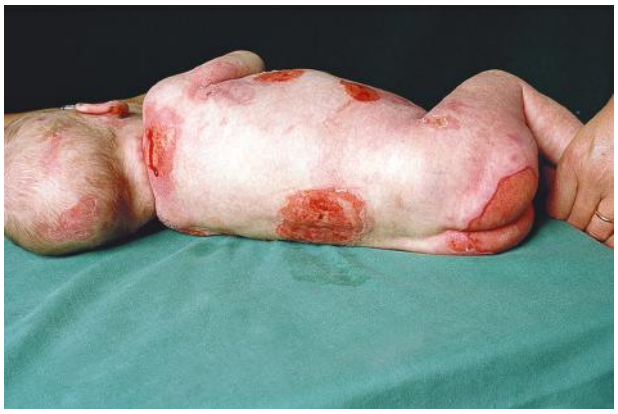


Figure 1.22 Severe generalized JEB.

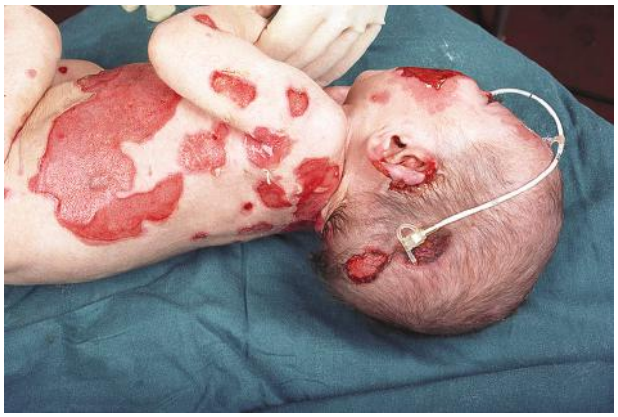


Figure 1.23 Severe generalized JEB.

The general condition is very poor, with characteristic laryngeal stridor and crying.

Pulmonary involvement is frequent, and recurrent, very severe episodes with bronchiolitis and pneumonia are detected and require permanent hospitalization in a neonatal pathology unit.

The oral mucosa is heavily involved as well as the mucosa of the upper respiratory tract. In contrast, the esophageal epithelium is less involved.

Nails are involved and are often absent. Enamel defects are present as well as the high risk to develop caries.

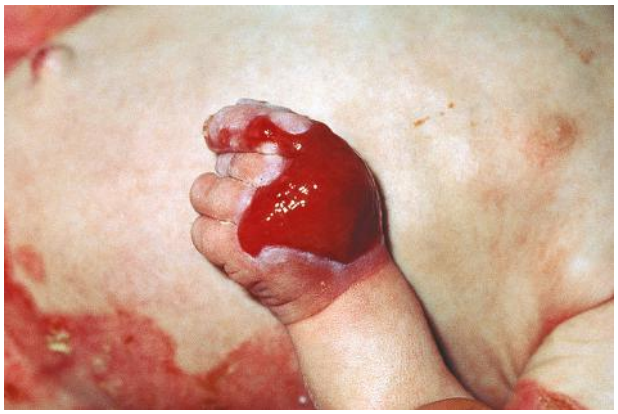


Figure 1.24 Severe generalized JEB.

Figure 1.25 Severe generalized JEB.

Characteristically, eroded lesions begin at the face, in the zygomatic areas (Figure 1.25) and can progressively reach large dimensions (Figures 1.26 and 1.27). Usually these patients die within the first two years of life (due to sepsis or upper respiratory tract occlusion) but some, rare, patients with generalized cutaneous and internal disease reach the age of 10–15 years.

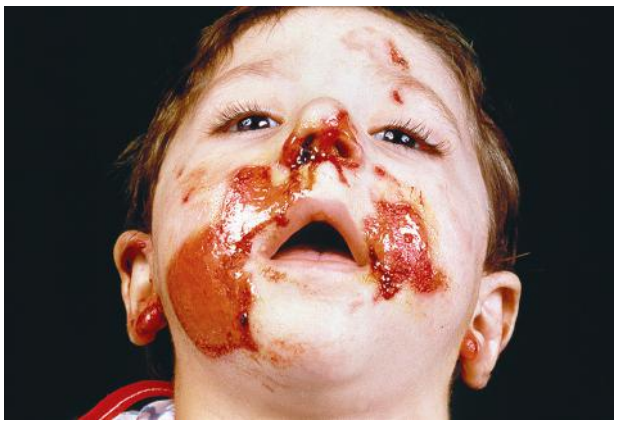


Figure 1.26 Severe generalized JEB.

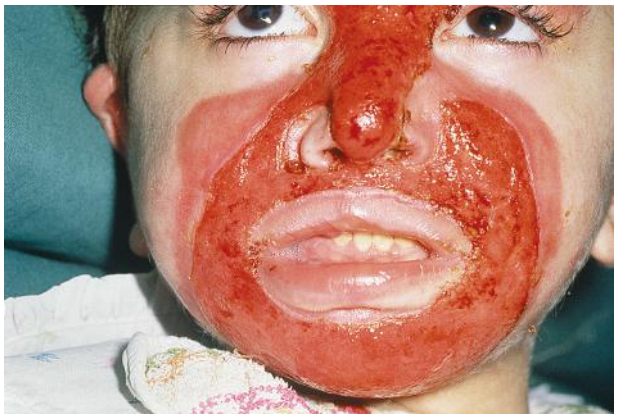


Figure 1.27 Severe generalized JEB.

Generalized intermediate JEB (former non-Herlitz subtypes)

This subgroup is composed of two distinct clinical pictures that diverge in terms of some particular aspects.

The first (related to a laminin 332 deficiency) has generalized involvement, and the bullae are smaller and tend to heal within days (Figures 1.28 and 1.29). Atrophic residual scarring is the rule. The nails are always involved and dystrophic. Oral mucosa is involved and there is a high proneness to caries. In particular, patients develop large ulcerated lesions on pretibial areas, due to the continuous recurrence of the bullae (Figures 1.30 and 1.31). There is a high risk of cancer in these areas (Figure 1.31). Sudden eruptions of small follicular blisters

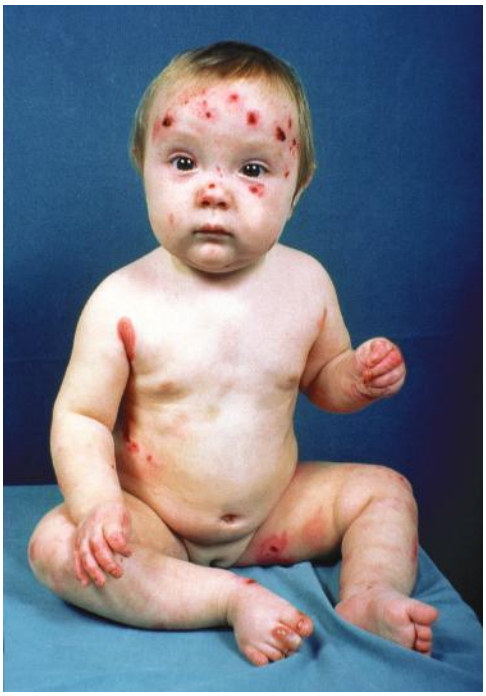


Figure 1.28 Generalized intermediate JEB (laminin 332 deficiency).

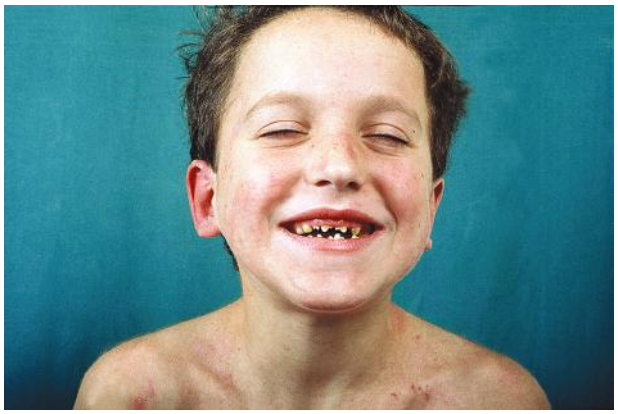


Figure 1.29 Generalized intermediate JEB (laminin 332 deficiency).

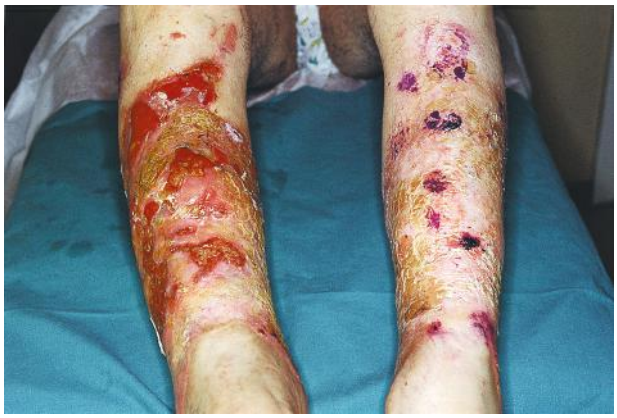


Figure 1.30 Generalized intermediate JEB (laminin 332 deficiency).

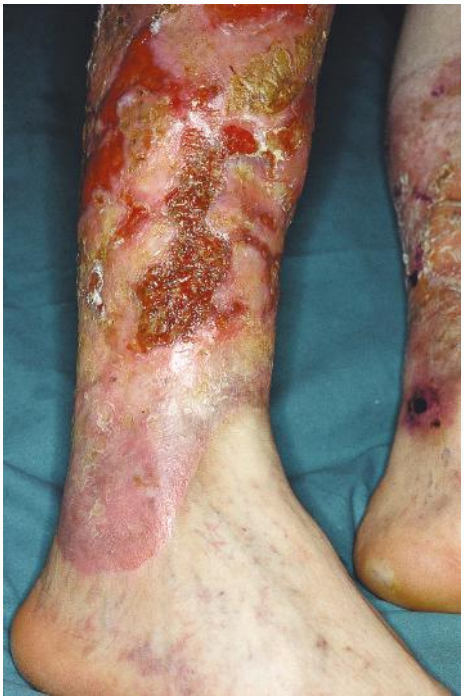


Figure 1.31 Generalized intermediate JEB (laminin 332 deficiency).

are possible during adolescence (Figure 1.32), as well as the development of pigmented post-bullous lesions that, at the epidiascopic examination, are diagnosed as true melanocytic nevi (Figures 1.33 and 1.34). Life expectancy is reduced.

The second group (related to mutations on the COL17A1 gene) is characterized by generalized and severe involvement (Figures 1.35 through 1.37) with oral mucosa and very severe dental anomalies (Figure 1.37), and especially by male pattern-like alopecia that is visible in both sexes (Figure 1.38). The hands and feet are thin and long, with dystrophic or absent nails (Figure 1.39). Atrophic residual scarring is visible.

Despite the risk of squamous cell carcinomas (25%), in these patients the disease allows an almost normal life span.

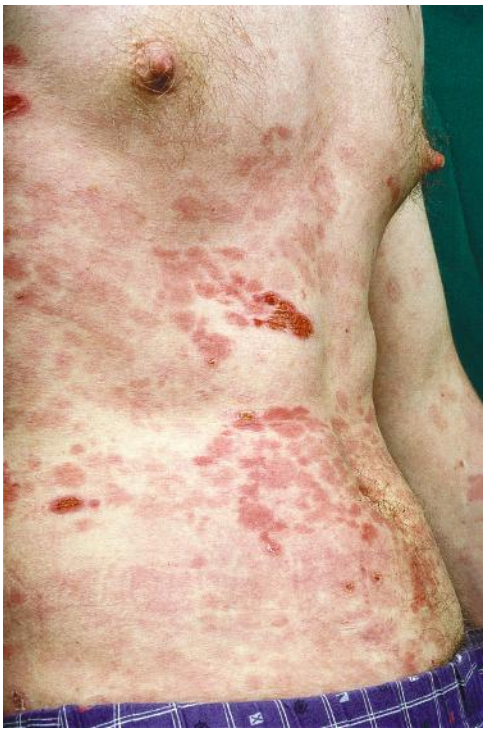


Figure 1.32 Generalized intermediate JEB (laminin 332 deficiency).

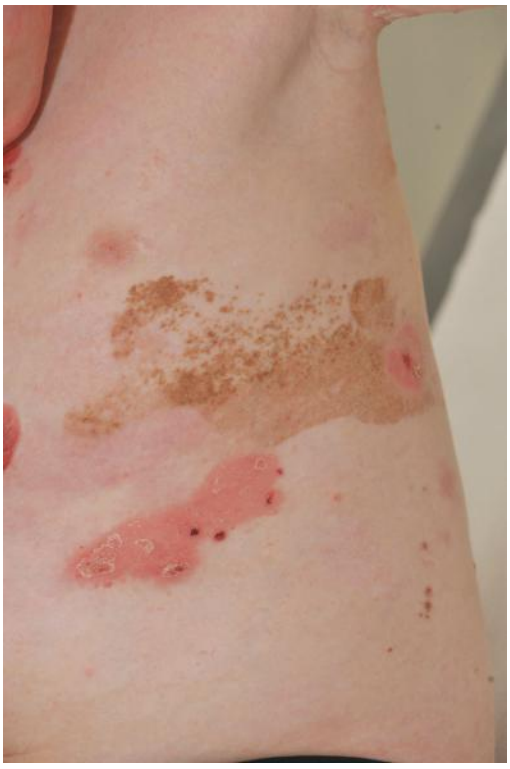


Figure 1.33 Generalized intermediate JEB (laminin 332 deficiency).

JEB with pyloric atresia

Pregnancy may be complicated by polyhydramnios.

Patients are severely involved at birth (Figure 1.40) as in generalized severe JEB, and suddenly develop gastrointestinal symptoms such as intractable

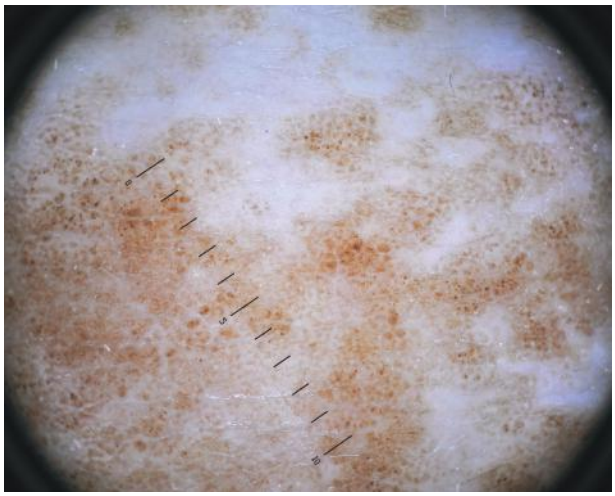


Figure 1.34 Generalized intermediate JEB (laminin 332 deficiency).

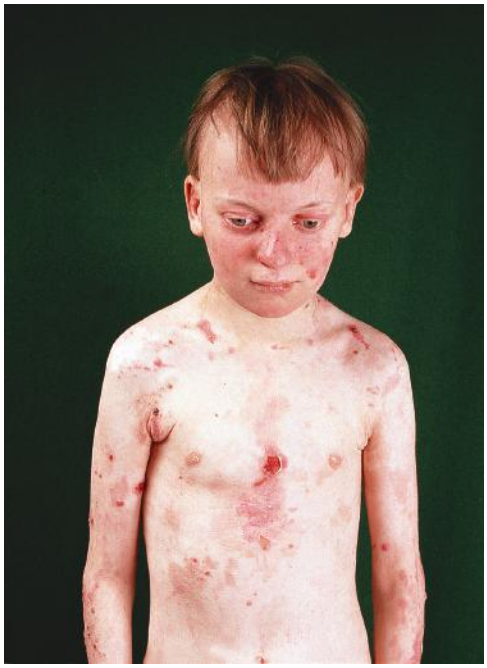


Figure 1.35 Generalized intermediate JEB (COL17A1 mutations).

vomiting. X-rays without contrast demonstrate enlargement of the stomach (Figure 1.41). Duodenal or anal atresia, as well as genitourinary tract malformations, has been reported. Pyloric reconstruction is mandatory in the first days of life. In some patients, cutaneous involvement is not so deep, allowing the recanalized patient to reach a normal life span, but usually these babies die within the first months of life.

JEB-LOC subtype

Laryngo–onycho–cutaneous syndrome (LOC) is an autosomal recessive disease characterized by cutaneous erosions, severe nail involvement and exuberant formation of granulation tissue in the skin, larynx, and conjunctiva (Figures 1.42 through 1.44).

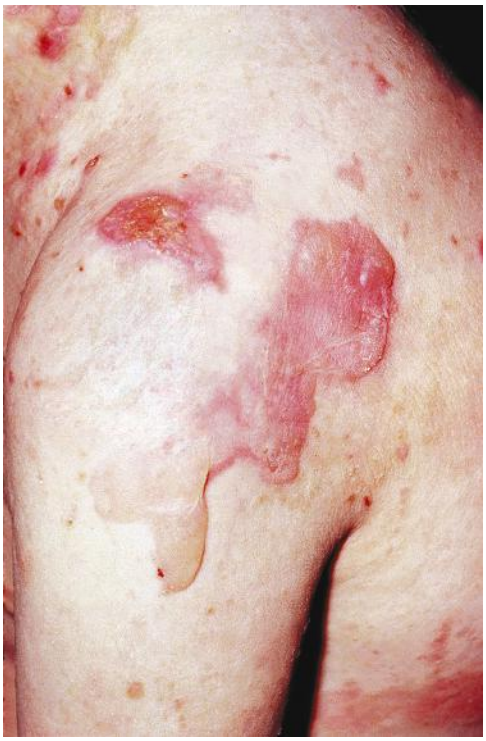


Figure 1.36 Generalized intermediate JEB (COL17A1 mutations).

This disorder is due to mutations in the laminin α3 gene (LAMA3) in which premature stop codon mutations cause the lethal (Herlitz) variant of JEB.

The same gene LAMA3 encodes three different isoforms, called α3a, α3b1, and α3b2.

LOC is due to mutations in the α3a protein that is secreted exclusively by the basal cells of stratified epithelia.

JEB late-onset is included as a further rare subtype of JEB in the last classification of 2014. The onset may be during adulthood or later with diffuse lesions with milia, onicodystrophy, hyperhidrosis, and absent dermatoglyphs. Mucosal lesions and enamel defects may be present. This subtype is due to peculiar COL17A1 mutations.

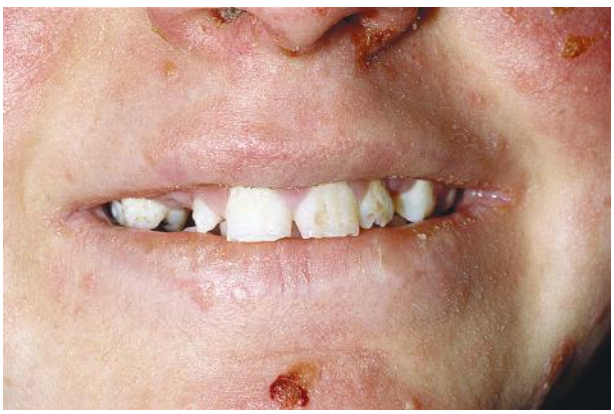


Figure 1.37 Generalized intermediate JEB (COL17A1 mutations).

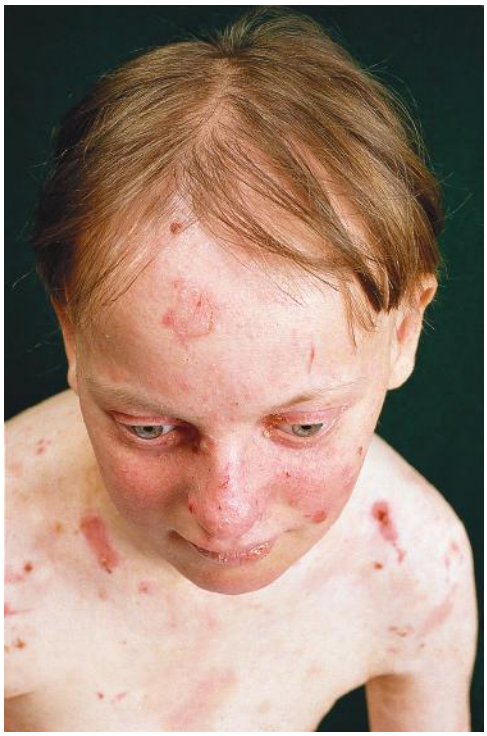


Figure 1.38 Generalized intermediate JEB (COL17A1 mutations).

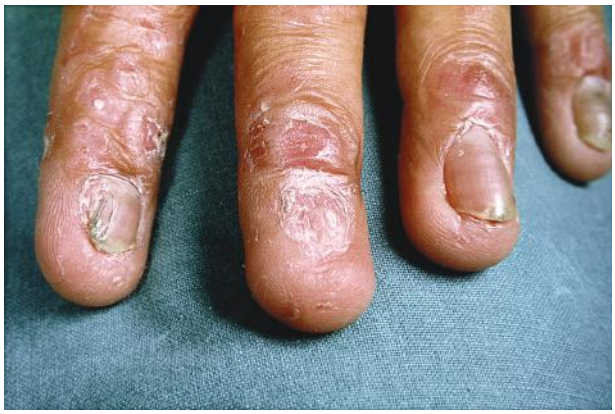


Figure 1.39 Generalized intermediate JEB (COL17A1 mutations).

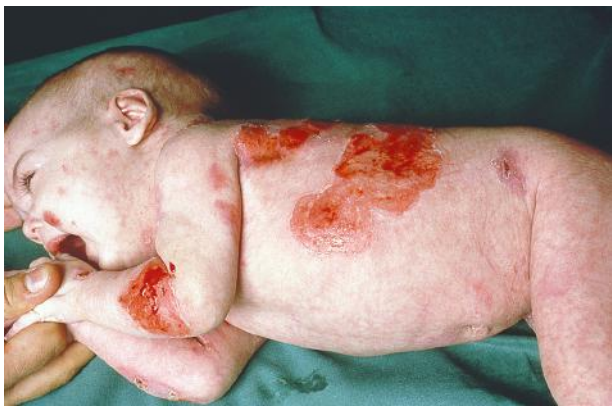


Figure 1.40 JEB with pyloric atresia.

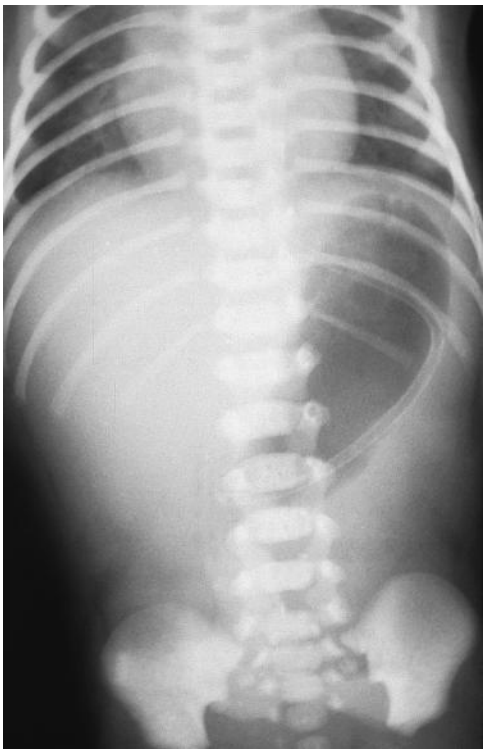


Figure 1.41 JEB with pyloric atresia.

JEB inversa is characterized mainly by the intertriginous distribution of skin lesions (Laminin 332 defect).

JEB localized is characterized by recurrence of blisters and erosion in localized areas of the skin (Laminin 332 defect).

JEB with respiratory and renal involvement is due to mutations (gain of glycosylation) of the ITGA3 gene, coding for alpha 3 integrin. In this rare

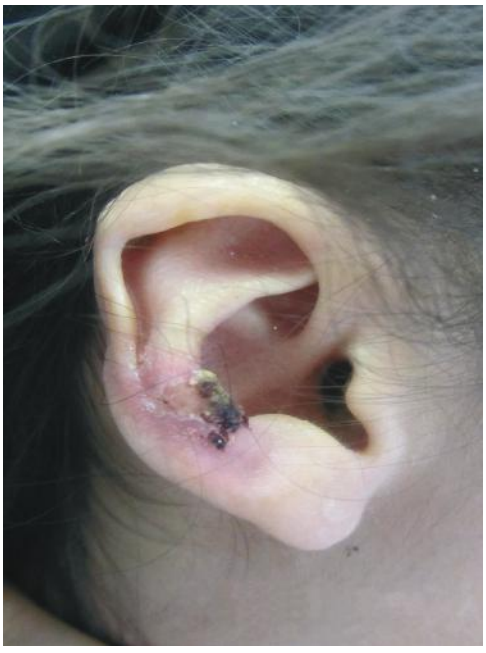


Figure 1.42 JEB-LOC subtype.

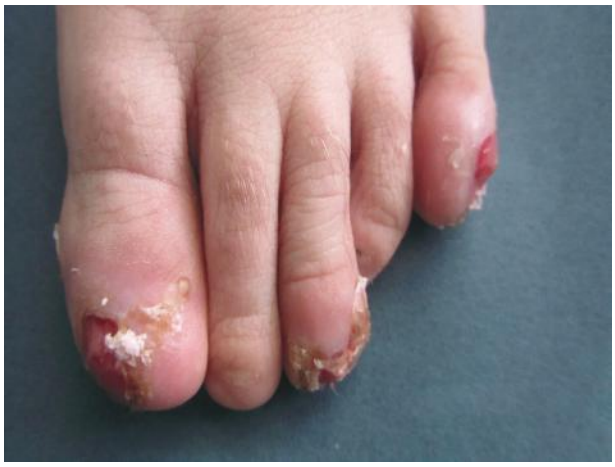


Figure 1.43 JEB-LOC subtype.

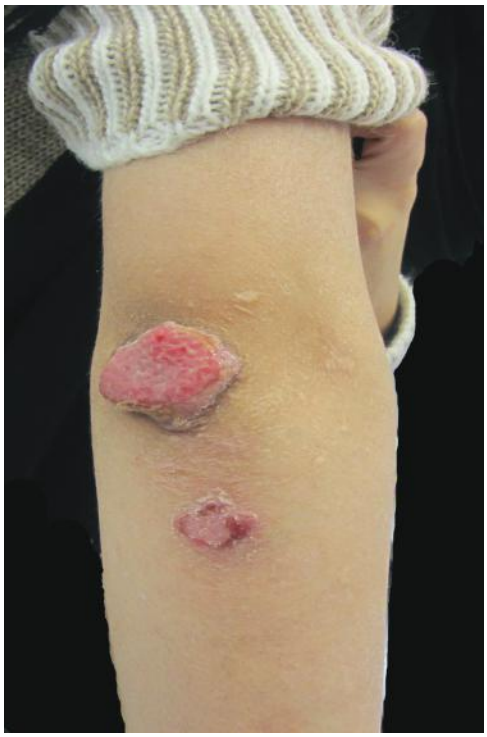


Figure 1.44 JEB-LOC subtype.

subtype, congenital nephrotic syndrome and severe respiratory distress with interstitial pneumopathy are associated to blisters and erosions, mainly located on buttocks and legs. Death is the rule within the first months of life due to the severe and untreatable kidney and pulmonary involvement.

Laboratory findings

- Direct immunofluorescence and electron microscopy to detect expression of targeted proteins and site of cleavage
- Molecular investigation to reveal mutations in the involved genes

Follow-up and therapy

- Neonatal pathology units for severely affected patients
- Antibiotics for pulmonary infections
- Local antisepsis for slowly healing lesions and advanced dressing for the medication of ulcers
- Specific dressing
- Periodic (3–6 months) day-hospital for general examination, especially for neoplastic transformation
- Psychological support for patients and families
- Surgery for pyloric obstruction

DERMOLYTIC (*DYSTROPHIC*) EPIDERMOLYSIS BULLOSA

Genetics and pathogenesis

Cleavage of blisters is below the lamina densa, in the uppermost dermis.

Dermolytic EB can be inherited in both dominant and recessive fashion and account for more than a half of EB patients.

The underlying molecular defect is unique and is related to the COL7A1 gene, encoding for collagen type VII, the major constituent of the anchoring fibers. The wide spectrum of severity in dermolytic EB is determined by the type of mutation in the COL7A1 gene. Noteworthy, revertant mosaicism is visible in these patients (see Figure 1.65 below).

Clinical findings

Dominant inherited subtypes

Lesions are visible at birth and are related to friction areas, especially on the hands and feet, where fingers and nails are always involved.

Blisters invariably cause scars and milia (Figures 1.45 and 1.46). During infancy and childhood, blisters are visible on the extensor surface of the hands, elbows, knees, and shoulders, where they heal and assume an onion-like appearance (Figure 1.47). Nails are seldom healthy and mucosae can be heavily affected, especially in the esophageal tract, where severe strictures are possible, often in sharp contrast with the scarce cutaneous involvement. Usually, fingers and toes are not affected by major cicatricial retractions (Figure 1.48). The former albopapuloid Pasini–Pierini variant defines only a particular healing pattern of these patients (Figure 1.49).

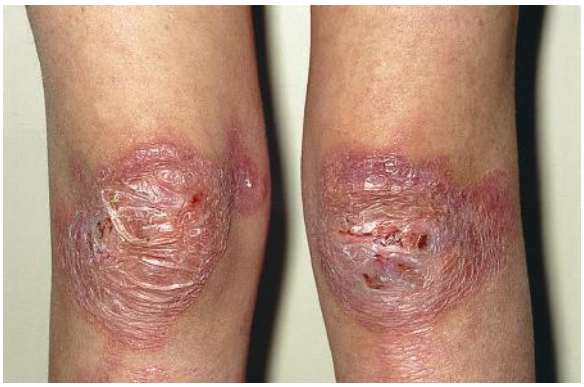


Figure 1.47 Dominant dermolytic epidermolysis bullosa.

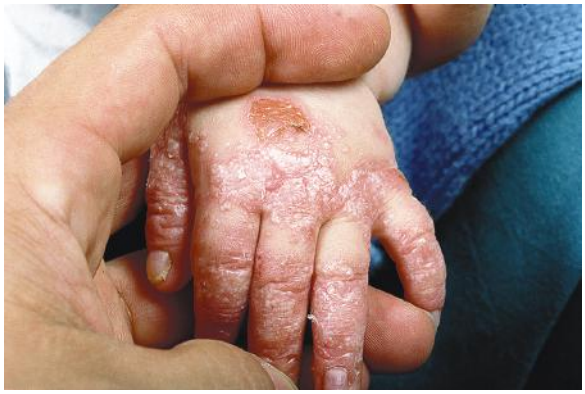


Figure 1.45 Dominant dermolytic epidermolysis bullosa.

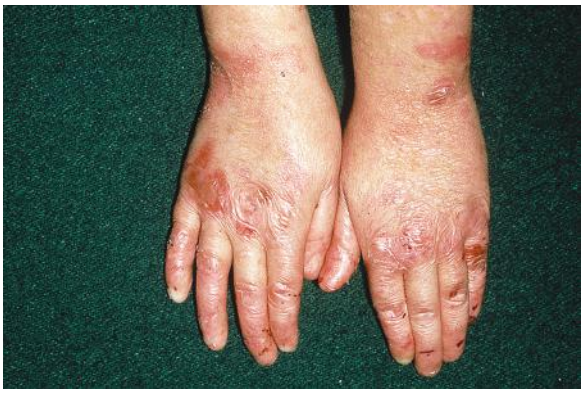


Figure 1.48 Dominant dermolytic epidermolysis bullosa.

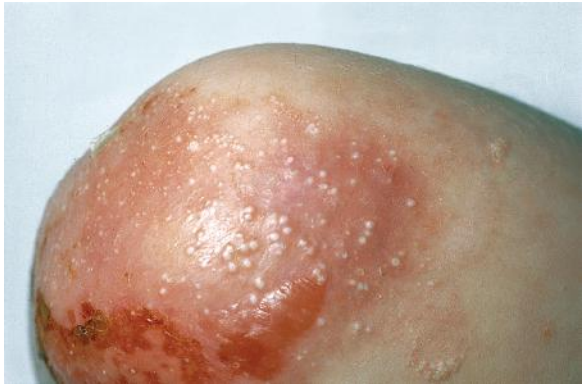


Figure 1.46 Dominant dermolytic epidermolysis bullosa.

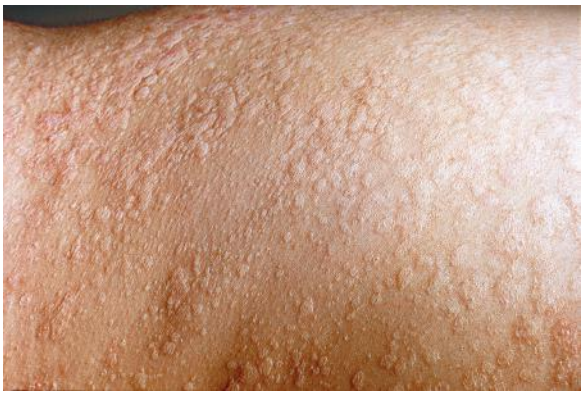


Figure 1.49 Dominant dermolytic epidermolysis bullosa.

To be defined as dominant, each dermolytic EB patient must have confirmation in the pedigree, in order to avoid the false parallelism *mild case = dominant*, *severe case = recessive* that, in the past, led to wrong genetic counseling.

Of note, in the last classification, *acral*, *localized*, *pretibial* and *nails only* subtypes are included as further dominant inherited variants.

Recessive inherited subtypes

In the current classification, two major forms are described as *severe–generalized* and *generalized*.

As previously described, the underlying different genetic defect in COL7A1 defines the clinical picture of the single patient, and theoretically these two types of recessive dermolytic EB may be considered to be a unique group of patients with a wide spectrum of phenotypes (Figures 1.50 through 1.58).

The 'generalized intermediate' subtype is defined by some related mutations leading to a *milder* phenotype, with generalized cutaneous involvement and esophageal strictures with or without cicatricial pseudosyndactyly of the hands and feet (Figures 1.50 and 1.51). Cutaneous-mucosal involvement and esophageal lesions allow the patients to grow following the lower centiles, with minor food intake problems (Figure 1.52). A certain degree of ocular involvement may be visible.

The *generalized severe* subtype defines patients that are often linked to homozygous premature stop codon mutations, leading to a phenotype characterized by generalized cutaneous blisters and erosions that, during early infancy, lead to retractive scars of the hands and feet (pseudosyndactyly), and, later, to retractions of the major joints of the arms and legs that cause, in adolescence, an almost complete inability to stand up correctly (Figures 1.53 through 1.57). The hands are deeply affected, and in extreme cases resemble a bag or a pouch (Figure 1.58).

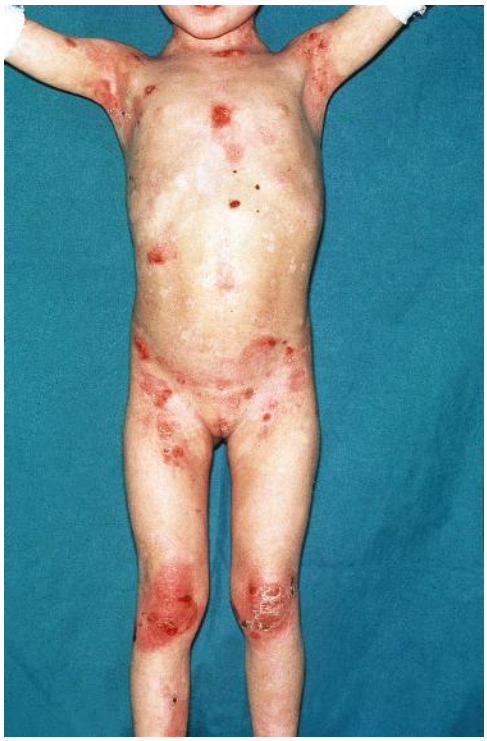


Figure 1.50 Recessive dermolytic epidermolysis bullosa, generalized-intermediate subtype.

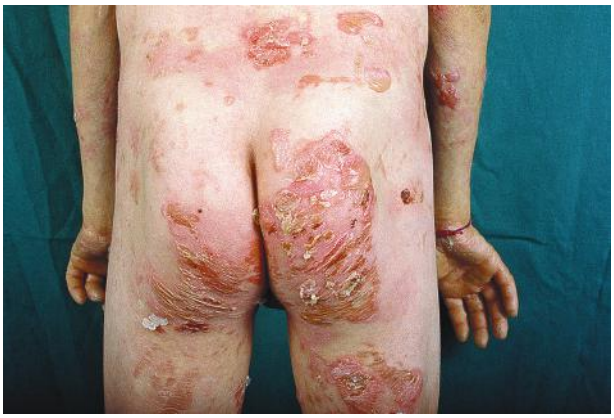


Figure 1.51 Recessive dermolytic epidermolysis bullosa, generalized-intermediate subtype.

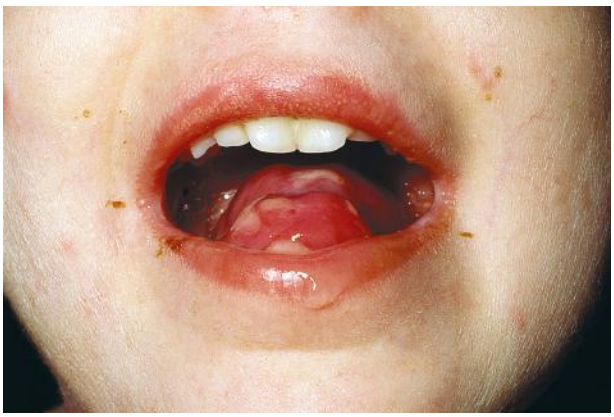


Figure 1.52 Recessive dermolytic epidermolysis bullosa, generalized-intermediate subtype.

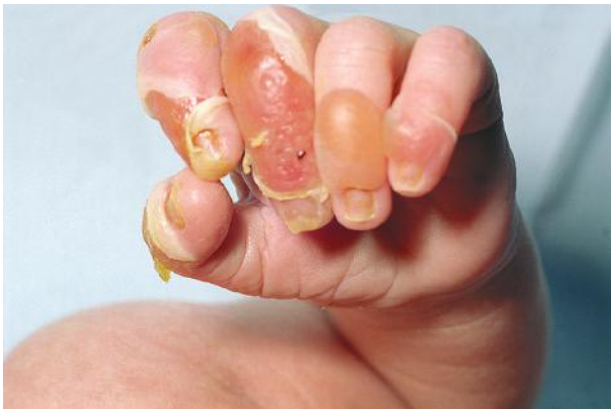


Figure 1.53 Recessive dermolytic epidermolysis bullosa, generalized severe subtype.