Genotyping of unusual phenotypes of epidermolysis bullosa
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Chapter 8

General discussion and future perspectives

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Mosaic Phenotypes

Before 2005, only one type of reversion event was thought to occur in mosaic individuals. Last year, however, we published two mosaic COL17A1 patients with multiple reversion events (chapter 2). In the same year also other reports appeared that described various in vivo reversions within one patient in the hereditary disorders tyrosinemia type I [MIM 276700] and Omenn syndrome [MIM 603554] [1,2]. It seems thus that, like we predicted in chapter 2, multiple reversion mechanisms are found in other genetic diseases as well.

We believe that the prevalence of revertant mosaicism might be underestimated. There are several observations that underscore this hypothesis. First, there is the presence of revertant cells in both affected and unaffected skin. If we would not have studied all skin biopsies of the upper arm of patient EB 093-01, the presence of the revertant cells in one of the three biopsy specimens would have stayed unnoticed. Likewise, the unforeseen small amount of about 25 revertant cells in the upper arm biopsy of patient EB 078-01 also demonstrates in vivo reversion in affected skin. Because of these observations, we now routinely ask patients that consult our multidisciplinary EB polyclinic if they have any unaffected skin areas. In the beginning of 2006, we asked this question to a 63-yr-old male patient EB 029-01 with junctional epidermolysis bullosa (JEB) due to LAMB3 mutations. He confirmed that he had three patches that remained free of blisters and these were located on his upper arm and back. We took a biopsy of the upper arm area and performed molecular analysis. Immunofluorescence staining was reduced in the affected skin area, whereas this upper arm biopsy revealed bright staining for laminin-332 (LM-332) along the epidermal-dermal junction. Hence, another mosaic patient was identified by this rather simple approach (chapter 3). Second, in 2002 a patient with recessive EB simplex (EBS) caused by homozygosity for a splice-site mutation in KRT14 was described by our group [3]. She had a mosaic pattern in her skin, but no clinically healthy skin areas. No additional DNA changes were detected, therefore RNA editing was held responsible for the partial reversion. Interestingly, this mosaic pattern was also observed in her brother, and in two other unrelated patients with the same mutations. Accordingly, we believe that if more attention is paid to possible mosaicism we will ‘see’ this more often in the future.

In vivo reversion – random or directed?
An interesting question is if these in vivo reversions result from a random or a directed process. There is no clear answer to this question yet, although the presence of
different second-site mutations correcting the same 628G→A LAMB3 mutation argue against a directed process. In case of a specific mechanism, one would expect the same correcting second-site mutation instead of different substitutions. A similar view was expressed by the group of McLean in their article on a patient with dominant EBS, where they stated that such mutations occur in everyone’s epidermis [4]. If that would be the case, then most of us would be mosaics, and revertant mosaicism would not be such an unusual phenotype after all. On the other hand, in revertant mosaic cases in the genetic disorders Fanconi anemia [MIM 227650] and Wiskott-Aldrich syndrome [MIM 301000] the same correcting mutation was identified between family members [5-7]. DNA polymerase slippage [6,7] and methylation-mediated transversion [5] were suggested to have influenced the reversions. In addition, in our female patient EB 026-01 it seems that the rate of gene conversion is higher around the exon 18 maternal mutation, perhaps due to the stretch of GT repeats. These GT repeats have been implicated in leading to a higher rate of recombination frequency [8]. Even more, Hamanoue et al [9] suggested that the Poly(T) sequence surrounding 2546C in the FANCA gene was likely to be susceptible to both forward and reverse mutations, explaining the recurrence of reversion at this site in different individuals.

For some genes it is known that their mutation rate is higher. Mutations in the NF1 gene on chromosome 17 result in the autosomal dominantly inherited disorder neurofibromatosis type 1 [MIM 162200] with a population frequency of ~1/2,500 individuals [10]. The NF1 gene has one of the highest mutation rates described for any human disorder (~ 1 x 10^{-4}/gamete/generation), with the result that ~30-50% of neurofibromatosis type 1 cases represent new mutations [10]. The contribution of interchromosomal gene conversion to the high mutation rate in neurofibromatosis type 1 is limited, whereas the susceptibility for C to T transitions was substantial [11]. Another example of a higher gene mutation rate with more chance on reversion is Bloom syndrome [MIM 210900] in which somatic intragenetic recombinations may occur in the causative RECQL3 helicase gene (also known as BML gene) due to increased non-specific chromosomal breaks [12]. Thus, although it seems that there is not a specific directed process, surrounding DNA sequences can certainly increase the chance on a certain in vivo reversion event or mutation.

Expansion of revertant skin

Another fascinating issue is if the expansion rate of the LM-332 revertant skin in EB 078-01 was continuous or is subject to phases in life. Unfortunately it is not possible anymore to check the revertant skin of patient EB 078-01. However, our
understanding of this phenomenon will increase if we carefully monitor the unaffected LM-332 revertant skin areas of patient EB 029-01 in time. Moreover, patient EB 029-01 has a sister with the same disease. She too has to be investigated for having unaffected skin areas. The potential expansion of LM-332 revertant skin would be a major benefit to cell and gene therapy (see below), as the successfulness of such therapies increases with a growth advantage of revertant stem cells compared to their deficient counterparts.

The fact that the reverted skin patches in the COL17A1 mosaic patients do not change size shows that in vitro experiments cannot simply be extrapolated to the in vivo situation. In in vitro wound healing assays, keratinocytes lacking type XVII collagen repopulated the wound faster than normal human keratinocytes [13]. If this would be also the case in vivo, the healthy skin area in patients EB 026-01 and EB 093-01 would have decreased over time. Photographs taken over ten years nevertheless showed that the skin patches remained the same size.

Using revertant mosaicism in cell therapy
As suggested in chapter 3 as a treatment for EB patients with revertant mosaicism one might think of culturing keratinocytes from a healthy skin biopsy to obtain graftable epithelia for transplantation on affected areas. Over the past 25 years such autologous cultured epithelium transplantation has successfully been applied for extensive third degree burn wounds. The generated epidermis self-renews for years [14,15]. In short, human epidermal cells are isolated from a small skin biopsy and plated onto a feeder layer of lethally irradiated 3T3 cells, which supports optimal keratinocyte growth. An initial population of colony-forming clonogenic keratinocytes is amplified by subculturing [16], and eventually the transplantable matrix with keratinocytes can be transferred onto a suitably prepared wound bed. An advantage of such a therapy is the fact that the patient’s own keratinocytes are used to develop the graft and probable immune responses are overcome. A major drawback could lie in the way the epidermis is removed from the affected area to be covered by the transplant. If tape is applied to remove the upper epidermal layers leaving the basement membrane and dermis intact, deficient stem cells residing in the hair follicle and the sebaceous glands would be left behind. These deficient stem cell populations might interfere with the reverted cells of the graft. The follicular stem cells are spatially distinct from the epidermal stem cell population [17]. In intact tissue the stem cells resident in the follicular bulge will not give rise to formation of the epidermis nor being the source of the stem cells of the interfollicular epidermis [18]. Their major contribution is instead to the hair follicle
Discussion and perspectives

[19]. The intact epidermis contains its own dedicated stem cells resident in the interfollicular epidermis. In response to trauma, however, the long-term multipotent follicular stem cells temporarily contribute to the epidermis [20,21]. This contribution can be a disadvantage for the successfulness of the transplantation therapy in mosaic patients as deficient stem cells are present in the remaining hair follicle bulges of the deficient skin. Recently however, both Claudinot et al [22] and Ito et al [23] independently showed that although the bulge-derived cells can acquire an epidermal phenotype, most are eliminated from the epidermis over several weeks, because the epidermal cells possess a survival advantage over bulge-derived cells. Seemingly, the bulge stem cells respond rapidly to epidermal injury by generating short-lived transit-amplifying cells that migrate to the epidermis after excisional wounding as well as superficial wounding [23]. During superficial wounding, as in removal of the upper epidermal layers by tape, the bulge-derived cells migrated to the superficial epidermis, while after excisional wounding migration was to the basal layer. The findings of short-lived bulge-derived migrating cells indicate that perhaps the remaining deficient stem cells in the hair follicle are less disadvantageous as seemed initially.

Another issue that has to be considered in the transplantation of mosaic patients is the display of a mosaic pattern on a microscopic level in the unaffected skin [24]. A risk is that the biopsy specimen used to grow the keratinocytes for the graft is consisting not only of revertant keratinocytes but also of deficient keratinocytes. These different cell populations can have a different response to environmental conditions, for example dispase treatment to loosen them from the culturing area or to culturing growth conditions. Of course for a successful graft one wants to stimulate the growth of the revertant keratinocytes. Future research into the different characteristics between revertant keratinocytes and deficient keratinocytes will benefit not only cell transplantation but also gene therapy.

Transplantation studies have already been performed in other EB patients as in restricted JEB [25]. This proband, who had since birth recurrent blistering on the pretibial regions of both shins, was treated with normal-appearing skin of his thigh. Although transient blistering lasting up to 10 months was induced on the donor sites of the thighs, the therapy was successful, since the shins were almost completely free of blistering and erosions after five years of follow-up. Notably, the Phase-I clinical trial by Mavilio et al [26] offers good prospects using revertant mosaicism in cell therapy of LM-332 deficient patients. In their study the patient’s own genetically corrected epidermal stem cells were used to grow epidermal sheets. These grafts were transplanted on both legs of the patient affected by non-lethal JEB due to LAMB3 mutations. The transplanted skin remained stable in the absence of
blistering or inflammation for the duration of the follow-up, i.e. 4 months at the time of writing [26]. Thus, in principle culturing of ‘naturally corrected’ keratinocytes of patient EB 029-01 and transplanting them to affected skin area should result in skin with absence of blister formation as well. We are intending to investigate the possibilities of using revertant mosaicism in cell therapy in the future.

**Unexpected Mild Phenotypes**

Our findings in chapters 4, 5 and 6 show that a generalized phenotype (GABEB) can be differentiated from a localized (LABEB) phenotype on basis of immuno-fluorescence microscopy. The blistering in our patients with a localized phenotype was confined to hands, lower legs and face. Väisänen et al [27] observed a milder phenotype in their type XVII collagen-deficient patients with mutations in the fifteenth collagenous domain (COL15). Three of their patients had localized blistering mainly to acral body parts, as was the case in our patients. Alopecia was observed, but to a lesser extent than the GABEB phenotype. The phenotype of their patients can be classified as LABEB. Similarly, the patients with a localized phenotype described by Ruzzi et al [28] and Mazzanti et al [29], and the patient homozygous for the 4013G→A mutation described by Schumann et al [30] may be classified as LABEB.

Both patients in chapters 4 and 5 had a small deletion in the COL15 domain, respectively of exon 30 and of exon 22. These deletions were in-frame and did not disturb the Gly-X-Y motif [31]. Another proband has been described with a small deletion in the same COL15 domain, but of exon 32. This proband did not express type XVII collagen and consequently had the more severe GABEB phenotype [32]. Exon 32 consists of three Gly-X-Y amino acid triplets and therefore does not influence the collagenous amino acid repeat. The absence of type XVII collagen protein was suggested to be caused by an alteration of the protein due to loss of possible proline hydroxylation sites. Recently, Väisänen et al [27] investigated mutant recombinant collagens and their results contradict the proposed hypothesis of structural de-stability. Several mutations were introduced into recombinant collagen XVII and the thermal stability was studied, among these was a deletion of the amino acids 779-787, comparable with the deletion of exon 32. Although all introduced glycine substitution mutations influenced the thermal stability, the removal of 779-787 had no overall effect on the stability. Like suggested in chapter 4, this specific region might be important in the ligand binding of other hemidesmosome components or in signal transduction, and therefore result in the more severe GABEB phenotype.

We also investigated the genomic DNA of the healthy parents of the 36-yr-old male...
LABEB patient (EB 098-01) described in **chapter 4**. Mutation analysis disclosed the heterozygous presence of $COL17A1$ mutations: the father carried the deletion 3432delT in exon 48 and the mother the nonsense mutation 2356C→T in exon 30. Besides, the mother had an additional substitution in intron 30, 2367+13T→G, on the mutated allele. In the skin of the mother most likely two different type XVII collagen proteins will be present, the wild-type protein of the normal allele and the slightly smaller protein with a deletion in COL15 due to the nonsense mutation 2356C→T. This smaller protein has a deletion of 12 amino acids in COL15, which has been implicated to be important in the formation of the trimeric structure. We are curious if mixed trimeric structures of wild-type protein and exon-30 skipped protein are formed in this female’s skin, or if only homotrimers build from a single form of type XVII collagen molecules are found. The participation of the exon 30-skipped transcript in the final production of type XVII collagen protein is probably rather small. Studies upon the amount of produced $COL17A1$ mRNA transcript in patients with type XVII collagen deficiency have shown that these mRNA levels are significantly lower than in healthy control keratinocytes [33]. Precisely, the relative expression level of $COL17A1$ mRNA in patient EB 098-01 was only 8%, where hypothetically a level of 50% could be expected.

Proof of aberrant molecule synthesis in healthy keratinocytes was found in the parents of the child with acantholytic EB (AEB) in **chapter 7**. As above, we again are interested if this shortened desmoplakin missing the C-terminal tail influences desmoplakin dimerization, and thereby desmosome formation.

**PTC-induced exon skipping therapy**

Most mutations in the dystrophin gene are null mutations that result in the total absence of the dystrophin protein, thereby affecting the whole musculature and leading to Duchenne Muscular Dystrophy (DMD). However, if there is some residual synthesis of a complete or partial protein, than the milder Becker Muscular Dystrophy (BMD) phenotype is observed. Consequently, the outcome of a deletion (approximately 60% of all mutations) in the dystrophin gene depends on the phasing of translational frames between the bordering exons. Dystrophin has an actin-binding domain at the N terminus, a central rod domain that contains 24 spectrin-like repeats and four hinge segments, and a C-terminal domain. Dystrophin that still functioned but missed some of the spectrin-like repeats of the central rod domain has been observed [34]. Similarly, in the patients described in **chapters 4** and **5** exon skipping of a part of the type XVII collagen protein resulted in a partly functional protein. At present, for the dystrophin gene, several research groups are working...
on an exon-skip gene therapy for DMD. This approach is based upon restoration of the reading frame. One possible option is to use oligonucleotides [35]. These small molecule drugs could restore the disrupted reading frame of DMD transcripts by inducing specific exon skipping as has been shown already in mice [36]. Only eight different oligonucleotides can cover 65% of the patients with deletion mutations. In cooperation with the company Prosensa in Leiden two oligonucleotides are manufactured -PR0046 and PR0051- to skip mutations surrounding respectively exons 46 and exon 51 [37]. A start has been made with intramuscular injection. Investigations on intravenous injection will commence if positive results are obtained in this initial study. Another approach, based on the same mechanism, is the rescue of dystrophin through U7 snRNA-mediated exon skipping [38]. In mice a single administration of an AAV vector expressing antisense sequences linked to a modified U7 small nuclear RNA resulted in persistent exon skipping removing the mutated exon. In principle, an exon-skipping approach would also be feasible in COL17A1. The PTC-induced exon skipping observed in patient EB 098-01 in fact is a kind of exon-skip therapy. There is only one major difference: cells lacking dystrophin have a leaky membrane and therefore such cells easily take up oligonucleotides. In type XVII collagen-deficient keratinocytes a transporter would be necessary to get the oligonucleotides into the cell.

**Nucleotide numbering**

The COL17A1 mutations, as can be seen in figure 4 of chapter 1, are found throughout the gene. Missense mutations in COL17A1 are rarely reported. All known glycine substitutions affect sequences coding for COL15, except for one mutation in exon 18, G539E [39]. The triple helix folding supposedly occurs in an N- to C-terminal directionality, which is the opposite of the classic fibril-forming of pro-collagens [40]. It might therefore be that substitutions in the COL15 domain, which is the first actual domain to wind, have a more profound effect on the trimerization. Possibly glycine substitutions in later domains will go unnoticed if such substitutions have a less profound effect on secondary structure.

When preparing the overview of all the COL17A1 mutations in chapter 6 we noticed that there is no consensus about nucleotide numbering of COL17A1 mRNA. Two different numberings exist at the same time. Giudice et al [41] numbers the first nucleotide of the start codon as 106, based on the original cloned sequence, while others number this first nucleotide as 1. This is no problem if the sequence itself is depicted in articles in question as it is easy to delineate the chosen numbering from the surrounding base pairs. However, if sequences are not present, it is sometimes
difficult to find out which numbering is used. Therefore we would like to state here
that it is in everyone’s interest to use one and the same numbering. Otherwise
mistakes will be made with same mutations getting different names and vice versa,
leading to erroneous functional interpretations and consequently false genotype-
phenotype correlations.

Proposal for a New EB Classification

EB is traditionally divided on basis of the level of tissue separation in three broad
categories: the simplex, junctional and dystrophic forms (table 1) [42,43].

Table 1 Revised classification of inherited EB, based on clinical phenotype and genotype, for the most
commonly observed and well-characterized variants or subtypes of this disease [43]

<table>
<thead>
<tr>
<th>Major EB type</th>
<th>Minor EB subtype</th>
<th>Protein/gene systems involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBS (“epidermolytic EB”)</td>
<td>EBS-WC</td>
<td>K5, K14</td>
</tr>
<tr>
<td></td>
<td>EBS-K</td>
<td>K5, K14</td>
</tr>
<tr>
<td></td>
<td>EBS-DM</td>
<td>K5, K14</td>
</tr>
<tr>
<td></td>
<td>EBS-MD</td>
<td>Plectin</td>
</tr>
<tr>
<td>JEB</td>
<td>JEB-H</td>
<td>Laminin-332</td>
</tr>
<tr>
<td></td>
<td>JEB-nH</td>
<td>Laminin-332; type XVII collagen</td>
</tr>
<tr>
<td></td>
<td>JEB-PA†</td>
<td>Integrin α6β4</td>
</tr>
<tr>
<td>DEB (“dermolytic EB”)</td>
<td>DDEB</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td></td>
<td>RDEB-HS</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td></td>
<td>RDEB-nHS</td>
<td>Type VII collagen</td>
</tr>
</tbody>
</table>

* DDEB, Dominant dystrophic EB; EBS-DM, EBS, Dowling-Meara; EBS-K, EBS, Koebner; EBS-MD, EBS
  with muscular dystrophy; EBS-WC, EBS, Weber-Cockayne; JEB-H, JEB, Herlitz; JEB-nH, JEB, non-Her-
  litz; JEB-PA, JEB with pyloric atresia; RDEB-HS, recessive dystrophic EB, Hallopeau-Siemens; RDEB-
  nHS, RDEB, non-Hallopeau-Siemens.
* †Some cases of EB associated with pyloric atresia may have intraepidermal cleavage or both intra-
  lamina lucida and intraepidermal clefts.

In 1998 Pulkkinen and Uitto proposed the addition of a fourth main category,
hemidesmosomal EB (HEB), in which blister formation takes place at the basal cell-
lamina lucida interface at the level of the hemidesmosomes [44,45]. These authors
divided the JEB category as described in the consensus classification system in two
EB variants into the hemidesmosomal variant and the junctional variant. Furthermore,
they also included the EB phenotype caused by plectin mutations with muscular
dystrophy, EB-MD, in the hemidesmosomal category instead of being part of the
simplex group (table 2). Since plectin is a hemidesmosomal protein, including EB-
MD in the hemidesmosomal category seems logical. Collectively, HEB is caused by
mutations in one of the genes encoding the hemidesmosomal plaque proteins, type
XVII collagen (COL17A1) [46,47], integrin α6β4 (ITGA6, ITGB4) [48,49] or plectin
In contrast, the mutations that are underlying JEB are located in one of the genes encoding LM-332 (*LAMA3, LAMB3, LAMC2*). Pulkkinnen and Uitto [44] also reintroduced the subcategory GABEB, caused by either type XVII collagen or LM-332 deficiency [46,47,51] in their classification.

**Table 2** Classification described by Uitto and Pulkkinen [45]

<table>
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<td>Plectin</td>
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</tr>
<tr>
<td>JEB</td>
<td>JEB-Herlitz</td>
<td>Laminin-332</td>
</tr>
<tr>
<td></td>
<td>JEB non-lethal</td>
<td>Laminin-332</td>
</tr>
<tr>
<td>DEB</td>
<td></td>
<td>Type VII collagen</td>
</tr>
</tbody>
</table>

*EB-MD indicates EB with late-onset muscular dystrophy; GABEB, generalized atrophic benign EB; and EB-PA, EB with congenital pyloric atresia.*

Although the Second International Consensus Meeting did not adopt the term HEB in its classification system, we agree with Pulkkinen and Uitto [44] that the addition of this broad category would be useful in determining mutation detection strategies. The 2000 classification is mainly based upon the ultrastructural analysis of the skin and data obtained by immunofluorescence microscopy are not incorporated. With immuno-epitope mapping data it becomes feasible to differentiate between a cleavage high in the lamina lucida and a cleavage low in the lamina lucida, which cannot be made by electron microscopy [52]. The high lamina lucida split is seen in patients with absence of type XVII collagen, in which LM-332 will locate to the blister floor. In the lower lamina lucida split, such as seen in GABEB patients with mutations in LM-332, the reduced staining of LM-332 will be located to the blister floor and roof. Using the lamina lucida cleavage level information from immunofluorescence microscopy, allows for a more direct mutation identification strategy and faster identification.

Besides the addition of this fourth HEB category we also propose here to add a fifth main category to the consensus classification system, acantholytic EB. Chapter 7 describes a child born with epidermolysis that progressed from 30% to 70% within the first day and to 90% by the fifth day. Ultrastructural analysis revealed disconnection of KIF from desmosomes. Accordingly, the disease-causing mutations were found in the *DSP* gene encoding the desmosomal protein desmoplakin. We named this phenotype ‘lethal acantholytic epidermolysis bullosa’. Blister formation in AEB starts in the suprabasal layers of the epidermis with separation of the epidermal cells (acantholysis) (fig. 1).
Figure 1 Level of blister formation in different categories of EB. The highest blister formation occurs in AEB, with acantholysis of the suprabasal cells in the epidermis. In EBS the plane of cleavage is through the basal cells, whereas in HEB blister formation takes place at the basal cell-lamina lucida interface at the level of the hemidesmosome. In JEB blister formation is seen at the level of the lamina lucida. Separation in DEB takes place beneath the lamina densa, in the dermis.

Not only the child described in chapter 7 can be appointed as having a form of AEB, but also other previously reported patients [53-55]. For instance, patients with skin fragility/woolly hair syndrome [MIM 607655] [55], caused by heterozygosity for nonsense and missense mutations in the \( DSP \) gene, showed also ultrastructurally dysadhesion between keratinocytes of the suprabasal layers. Mutations in the plakophilin 1 gene (\( PKP1 \)) can also result in widening of keratinocyte intercellular spaces and perturbed desmosome/KIF interactions [54], which makes that skin fragility-ectodermal dysplasia syndrome [MIM 604536] can also be classified as a form of AEB. Also the acral acantholytic EB variant described by Hoffman et al [53], for which the disease-causing gene is yet unknown, should be added to this list. Together with the genes \( DSP \) and \( PKP1 \) a total of 12 genes are now known that can result in EB.

We deliberately separate the hereditary poikilodermas accompanied by blistering from EB. In this group there exist several entities such as hereditary bullous poikiloderma of Kindler [MIM 173650] caused by mutations in \( KIND1 \) [56], congenital poikiloderma of Rothmund-Thompson [MIM 268400] and ataxia telangiectasia
syndrome [MIM 208900], which may be bullous and are caused by recessive mutations in the *RECQL4* [57] and *ATS* [58] genes, respectively, and hereditary macular type of bullous dystrophy of Mendes da Costa [MIM 302000] for which the gene has not been identified yet. We also separate from EB the peeling skin syndromes, such as acral peeling skin syndrome [MIM 609796] caused by dominant mutations in *TGM5* [59], and keratolytic winter erythema or Oudtshoorn disease [MIM 148370], as well as the bullous forms of ichthyosis, such as bullous congenital ichthyosiform erythroderma of Brocq [MIM 113800] caused by mutations in *KRT1* and *KRT10* [60], and bullous ichthyosis of Siemens [MIM 146800] caused by mutations in *KRT2E* [61]. Nor do we include epidermolytic palmoplantar keratoderma of Vörner [MIM 144200] caused by mutations in *KRT9* [62] or the unilateral palmoplantar verrucous nevus caused by mutations in *KRT16* [63] in the classification of EB.

In figure 2 this above mentioned proposal for a new classification is depicted, with its classification into five major categories and further subdivision into different EB subtypes.

References

Figure 2 Proposal for a new classification for epidermolysis bullosa.

SF-EDS, skin fragility - ectodermal dysplasia syndrome; SF-WHS, skin fragility - woolly hair syndrome; LAEB, lethal acantholytic epidermolysis bullosa; AAEB, acral acantholytic EB; AR, autosomal recessive; AD, autosomal dominant; EBS-K, EB simplex, Koebner; EBS-WC, EBS, Weber-Cockayne; EBS-DM, EBS, Dowling-Meara; EBS-MP, EBS with mottled pigmentation; EB-PA, EB with muscular dystrophy; EB-PA, EB with pyloric atresia; LABEB, localized atrophic benign EB; GABEB, generalized atrophic benign EB; JEB-loc, junctional EB, non-Herlitz; JEB-loc, JEB, localized; JEB-lo, JEB, late-onset; JEB-H, JEB, Herlitz; DDEB, dominant dystrophic EB; DDEB-Pt, DDEB, pretibial; DDEB-TBDN, DDEB, transient bullous dermolysis of the newborn; RDEB-loc, recessive dystrophic EB, localized; RDEB-I, RDEB, inversa; RDEB-HS-nm, RDEB, Hallopeau-Siemens, non-mutilans; RDEB-HS-m, RDEB, Hallopeau-Siemens, mutilans.
Chapter 8


