Oral Manifestations in the Epidermolysis Bullosa Spectrum

J. Timothy Wright, DDS, MS

KEYWORDS

• Mucosa • Enamel • Odontogenic • Dental caries
• Periodontal • Enamel hypoplasia • Microstomia
• Ankyloglosia

Epidermolysis bullosa (EB) represents a spectrum of conditions characterized by blistering and mechanical fragility of the skin. There is tremendous genetic heterogeneity and marked variation in clinical phenotypes in the multiple EB disorders. The most recent classification recognizes four major EB groupings and more than 30 EB subtypes.[1] The four major EB groups include intraepidermal EB (simplex), junctional EB, dermolytic EB (dystrophic), and mixed EB (Kindler syndrome). The molecular basis is now known for 13 of EB subtypes.[1] Depending on the specific EB type there can be significant morbidity involving the soft and hard tissues of the craniofacial complex (**Table 1**).

Individuals with EB display tremendous diversity in the various tissues and body systems involved and phenotypic severity.[2–4] Similarly, the craniofacial and oral manifestations of the different EB types vary markedly in character and severity depending largely on the EB type.[5,6] The tissues affected and the phenotypes displayed in affected individuals are closely related to the specific abnormal or absent proteins resulting from the causative genetic mutations for these disorders. For example, type VII collagen is critical for maintaining the integrity of the oral mucosa in the same manner it is in skin. It is not essential for normal development in the forming tooth bud. Consequently individuals with type VII collagen mutations typically have a developmentally normal dentition but can have severely affected oral soft tissues. In contrast, laminin 332 is highly expressed during tooth development so individuals with mutations that affect laminin 332 function have defects in the enamel of their teeth.[7–9] In this article, the major oral manifestations are reviewed for different EB subtypes and related to the causative genetic mutations and gene expression.

INTRAEPIDERMAL EPIDERMOLYSIS BULLOSA

The EB simplex subtypes are caused by mutations in the *PKP1*, *DSP*, *KRT5*, *KRT14*, *PLEC1*, and *ITGA6* genes.[1] These genes all cause intraepidermal cleavage in the skin and are all expressed by the oral mucosa which, like skin, is comprised of a stratified epithelium.[10–12] Not surprisingly, individuals with EB simplex also exhibit an increased fragility of the oral mucosa with a high percentage of individuals experiencing blistering and ulceration of the oral mucosa.[5] In most cases, these are localized and occur most often secondary to trauma or tissue manipulation; however, some individuals can experience significant oral blistering and severe mucosal involvement. Typically, oral soft tissue lesions heal without scarring although some severely affected EB simplex subtypes (eg, Dowling-Meara) can display some oral scarring (**Fig. 1**).

Although many of the causative genes for EB simplex are known to be expressed in the odontogenic epithelium of developing teeth, the dentition in EB simplex tends to form normally.[9] These genes are also known to be expressed by the epithelial glands of the salivary tissues. Salivary function seems normal in people with

Department of Pediatric Dentistry, School of Dentistry, Brauer Hall # 7450, The University of North Carolina, Chapel Hill, NC 27599-7450, USA
E-mail address: tim_wright@dentistry.unc.edu

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Table 1
Oral manifestations in common epidermolysis bullosa subtypes

EB Type	OMIM no.	Oral Blistering	Oral Scarring	Microstomia	Enamel Defects
Simplex					
Localized	#131800	+	–	–	–
Generalized	#131900	+	–	–	–
Dowling-Meara	#131760	+	±	–	–
Junctional					
Non-Herlitz	#226650	+	–	–	++
Herlitz	#226700	+	–*	+	++
Dystrophic					
Dominant	#131750	+	±	–	±
Recessive	#226600	++	++	++	–
Kindler					
Kindler Syndrome	#173650	+	+	+	

Abbreviations: OMIM, Online Mendelian Inheritance in Man; +, frequently present; ++, always present; ±, variably present or absent; –, not present.

the EB simplex subtypes who have been tested.[13] The limited intraoral soft tissue morbidity in EB simplex and the normal tooth formation are likely the primary reasons that individuals with these EB subtypes have a prevalence of dental caries similar to unaffected populations.[14]

JUNCTIONAL EPIDERMOLYSIS BULLOSA

The junctional forms of EB are caused by mutations in *LAMA3*, *LAMB3*, *LAMC3*, *COL17A1*, *ITG6A*, and *ITGB4*, which are important in basement membrane–mediated cell adhesion.[1,15,16] The proteins transcribed from these genes are important in epithelial cell adhesion in the oral mucosa and the developing tooth bud.[8,17] The tissue fragility resulting from these mutations is variable but almost all individuals with the junctional forms of EB have an increased fragility of the oral mucosa that is accompanied by blister formation and ulceration.[5,18] In some individuals this can be severe. Despite the high prevalence of oral soft tissue lesions in the different junctional EB subtypes, most affected individuals do not have significant oral scarring. The soft tissue mobility and architecture remain relatively normal. One exception to this is the Herlitz EB subtype that is characterized by exuberant perioral granulation tissue (**Fig. 2**). This frequently results in a reduction in the oral opening (microstomia) and some loss of tissue mobility in the lips and perioral tissues.[5]

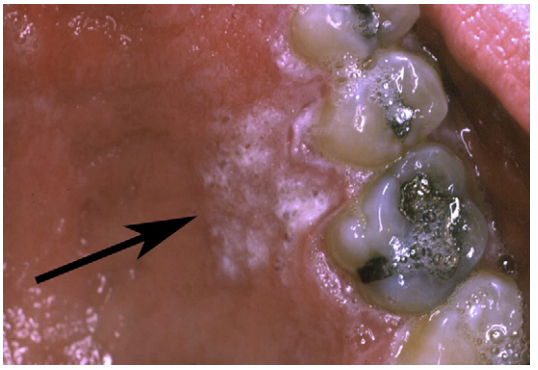

Fig. 1. This adult with EBS Dowling-Meara shows a normal soft tissue palatal architecture and a localized area of gingival hyperkeratosis (*arrow*).

The genes that are causative of the junctional EB subtypes are all critical for normal tooth formation.[8,17] Specifically, these genes produce proteins that are involved in cell adhesion of the odontogenic epithelium, which gives rise to the cells that produce the dental enamel, the ameloblasts. Ameloblasts secrete an extracellular matrix and maintain contact and adhesion to the adjacent ameloblasts and thereby control the microenvironment that is critical for allowing normal mineralization of the enamel. When cell adhesion between ameloblasts is lost, then enamel defects are created. Dysfunctional ameloblast adhesion can result in leaking of serum fluids into the developing enamel, resulting in a retention of albumin and decreased mineralization.[19] In cases of individuals with junctional EB, the enamel lesions can vary from generalized pitting to a generalized hypoplasia, leaving only a very thin layer of enamel on the tooth surface (see **Fig. 2**). Some cases of Herlitz EB subtype also exhibit abnormal tooth