Glycine Substitution Mutations in the \textit{COL7A1} Gene: Implications for Inheritance of Dystrophic Epidermolysis Bullosa – Dominant vs. Recessive

Phenotypic Variability of Epidermolysis Bullosa. Epidermolysis bullosa (EB) is a clinically heterogeneous group of disorders characterized by blistering and erosions of the skin and mucous membranes, associated with variable additional clinical manifestations in the nails, teeth and eyes, as well as the gastrointestinal and vesicoureinary tract (1, 2). The most severe forms of the disease are associated with early demise of the affected individuals, and in some patients, mutilating scarring of the hands and feet and aggressively metastasizing squamous cell carcinomas develop. EB is divided into distinct subcategories primarily based on the level of blister formation within the skin, as documented by transmission electron microscopy or immune-epitope mapping. As many as 14 genes are currently known to harbor mutations in different variants of EB, and the spatial expression of these genes within the skin, the types and combinations of mutations and their consequences at mRNA and protein levels, when superimposed on an individual patient’s genetic background and exposure to environmental trauma, all contribute to the tremendous phenotypic variability noted in this group of disorders (3).

Molecular Basis of the Dystrophic Forms of EB. Inheritance of dystrophic EB (DEB) can be either autosomal dominant (DDEB) or autosomal recessive (RDEB). Nevertheless, patients with all variants of DEB demonstrate ultrastructurally a sub-lamina densa plane of tissue separation. Moreover, the fragility of skin can be explained by abnormalities in anchoring fibrils, critical attachment complexes that extend from the lamina densa to the underlying dermis and secure the stable association of the dermal-epidermal junction (Fig. 1). Anchoring fibrils in patients with DEB have been shown to be morphologically altered, reduced in number or completely absent. Patients with DEB, both dominant and recessive, harbor mutations in the \textit{COL7A1} gene which encodes type VII collagen protein, the predominant, if not exclusive, component of the anchoring fibrils (4). \textit{COL7A1} emerged initially as a candidate gene for mutations when immunofluorescence staining of the skin of patients with the most severe forms of RDEB demonstrated lack of type VII collagen epitopes (5).

Cloning of human type VII collagen gene and the corresponding cDNA provided the opportunity to assess the hypothesis that type VII collagen serves as the candidate gene/protein system for this group of blistering disorders. Specifically, genetic linkage studies utilizing informative polymorphic markers in the \textit{COL7A1} gene were consistent with the notion that most, if not all, cases with DEB are the result of mutations in this gene (see 4). Subsequent development of mutation detection strategies has allowed examination of a large number of cases with DEB, and well over 300 distinct mutations in the \textit{COL7A1} gene have now been disclosed in both DDEB and RDEB (6, 7). The types of mutations range from premature termination codon (PTC) causing loss-of-function mutations to more subtle missense mutations. This information has facilitated genotype/phenotype correlations, improved...
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In families with known mutations (9). For example, should heterozygous carriers of a mutation, such as p.Gly1483Asp, which in some cases shows clinical manifestations while in others not, be counseled for being at risk for which DEB phenotype, if any? This question is also directly relevant to prenatal testing that is now in routine use for the most severe forms of EB (10, 11). These and similar questions could be answered by examination of a larger cohort of families with evidence of both dominant and recessive mode of inheritance as a result of the same mutation.

In addition to focusing on the glycine substitution mutations that may be accompanied with both dominant and recessive forms of DEB, the authors report 30 previously unreported glycine substitution mutations that apparently are associated exclusively with either dominant or recessive forms of DEB. These are important additions to the still growing COL7A1 mutation database which serves as a valuable resource for evaluation and management of patients with dystrophic forms of EB, with implications for genetic counseling of families at risk of recurrence. In addition, to tabulating in the paper all known “mixed” glycine substitution mutations that can cause both dominant and recessive forms of DEB, in the Supplementary material to the article, the authors have listed all currently known/published glycine substitution mutations in type VII collagen, dividing these into dominant or recessive. This information provides a useful resource for all clinicians and molecular laboratories involved in classifying DEB and improving diagnostic precision for this group of mechanobullous diseases.

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REFERENCES


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