HETEROGENEOUS MUTATIONS OF THE TYPE VII COLLAGEN GENE (COL7A1) IN DYSTROPHIC EPIDERMOLYSIS BULLOSA

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Dystrophic epidermolysis bullosa (DEB) is an inherited disease characterised by blistering at the cutaneous basement membrane zone and abnormal anchoring fibril morphology. The major component of anchoring fibrils is type VII collagen, and recently, over 70 different mutations in the gene encoding this protein, COL7A1, have been shown to underlie both autosomal dominant and recessive DEB. Almost all cases of dominant disease result from glycine substitution mutations in the collagenous triple helix of type VII collagen. In contrast, mutations in recessive DEB are more diverse in nature with the majority resulting in premature termination codons. We have performed mutation analysis of 57 patients from 51 families with dominant (n=13) or recessive (n=40) DEB using PCR, heteroduplex analysis and direct nucleotide sequencing of exons displaying bandshifts. Of the 13 families with dominant DEB, 11 had glycine substitution mutations which are predicted to cause dominant-negative interference between mutant and wild-type proteins. In the other 2 families, mutation analysis demonstrated a 16 basepair deletion in one and a splice site mutation in the other, which both resulted in in-frame exon skipping. In both families, there was also coexistence with recessive DEB in individuals who had inherited the dominant mutation in addition to a splice site or nonsense mutation on the second COL7A1 allele. Of the remaining families with recessive disease, mutation analysis revealed 9 nonsense mutations, 26 insertion or deletion mutations, 12 splice site mutations, 4 silent glycine substitutions and 1 missense mutation. In all, this study demonstrated the presence of 42 different mutations. These results provide insight into the nature of mutations in DEB and confirm the allelic heterogeneity of this disease. Elucidation of specific mutations in patients with DEB has consequences for genetic counselling, enables first trimester DNA-based prenatal diagnosis in pregnancies at risk for recurrence of severe recessive disease, and paves the way for new treatment strategies, including gene therapy.