

Dystrophic Epidermolysis Bullosa (DEB) (COL7A1)

Disorders Included: Hallopeau Siemens form of DEB, Pasini form of DEB, pretibial form of DEB, pruriginosa form, epidermolysis bullosa with congenital absence of skin and deformity of nails, transient bullous dermolysis of the newborn

Clinical Features:

In this clinical type of EB, blistering usually begins in the neonatal period and may continue throughout life or may be transient (transient bullous dermolysis of the newborn). Blisters may be generalized and include oral and esophageal lesions in the severest form (Hallopeau-Siemens) or may be localized to the elbows and knees, and/or hands and feet in the milder forms. In addition, dystrophic nails are also often present. Dystrophic EB is not usually lethal but in the severest cases infants may succumb to infection or other complications. The lifetime risk of squamous cell carcinoma in patients with the Hallopeau-Siemens form is over 90%. In affected individuals the tissue separation (blister) occurs below the lamina densa. Anchoring fibrils may be reduced or absent. Collagen VII staining may be reduced or absent in the more severe forms or may appear relatively normal in the milder forms.

Inheritance Pattern:

Dystrophic EB is due to pathogenic variants in only the COL7A1 gene, although there is significant variability in the severity of the phenotype in different individuals. DEB may have either an autosomal recessive or autosomal dominant inheritance pattern, depending upon the variant and its location. The recurrence risk for couples with a child affected with the recessive form is 25%. In the dominant forms recurrence risk is 50% to offspring of an affected parent, although rarely unaffected carrier individuals have been observed (Pfundner personal communication). The recurrence risk to unaffected extended family members is low in the absence of consanguinity. Many *de novo* dominant variant have been reported and the determination of recurrence risk is dependent upon identification of the variant(s) and inheritance pattern. Risk of recurrence in subsequent pregnancies after a child is born with a *de novo* dominant variant is 2-5%.

Test Sensitivity:

Sequencing of the COL7A1 gene is expected to identify pathogenic variants in greater than 95% of patients with clinical and histologic features of DEB. The underlying genetic cause of DEB in the remaining cases may be due to variants in the promoter, deep into introns, or large deletions not identifiable by our methods. A skin biopsy studied with appropriate collagen VII antibodies and/or electron microscopy to confirm the diagnosis of DEB is strongly recommended prior to pursuing genetic analysis.

All types of pathogenic variants have been reported in the COL7A1 gene and result in reduced or absent collagen VII protein. Generally, the severest forms of the disease are the result of nonsense variants or out of frame insertions or deletions on both alleles while milder forms may be due to splicing variants or missense variants on one or both alleles. However, numerous exceptions have been reported.

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

References:

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2. Rouan F, et al., 1998 J Invest Dermatol 111:1210.
3. Fine J-D et al., 2000 J Am Acad Dermatol 42:1051-106
4. Anton-Lamprecht & Gedde-Dahl, 2002. Epidermolysis bullosa. In: Rimoin DL, Connor JM, Pyeritz RE, Korf BR, eds. Principles and Practice of Medical Genetics. 4th ed. London: Churchill-Livingston 2002, 3810-3897.
5. Varki et al., 2007 J Med Genet 44: 181-192.