COL7A1 Gene Analysis in Dystrophic Epidermolysis Bullosa (DEB)

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/Genetics:
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 (Pfendner 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 Methods:
Sequencing of the COL7A1 genes is offered. Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region and splice junctions of the COL7A1 gene (118 coding exons) is analyzed where over 90% of pathogenic variants have been identified in DEB patients with clinically and histologically confirmed disease. Variant found in the first person of a family to be tested is confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. Sequencing of

specific exons may be recommended for specific ethnic groups or phenotypes, especially in confirmed or suspected dominant dystrophic EB, after consultation with the EB specialist at GeneDx (Ellen@genedx.com, 610,-574-3479). Deletion of specific exons has been reported rarely. Testing for deletions is available after full COL7A1 gene screening at GeneDx, where one or both variants are not detected and biopsy confirming the diagnosis of DEB has been performed.

Test Sensitivity:

Sequencing of the COL7A1 gene is expected to identify pathogenic variants in greater than 90% 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.

References:

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