

## Testing of the Laminin-5 Genes (*LAMA3*, *LAMB3*, and *LAMC2*) in Junctional Epidermolysis Bullosa (JEB)

**Disorders Also Known As:** Herlitz JEB

**Clinical Features:**

Depending on the clinical sub-type, blistering begins in the neonatal period and continues throughout life. Blisters are usually generalized and include oral and esophageal lesions. The Herlitz form is severe and usually results in demise during the first year of life, while the non-Herlitz, mitis and GABEB forms are less severe and affected individuals usually survive to adulthood. The tissue separation (blister) occurs within the lamina lucida of the basement membrane and anchoring filaments may be reduced or absent. Blisters generally heal without scarring.

**Inheritance Pattern/Genetics:**

The junctional EBs are a genetically heterogeneous group of disorders, which generally show autosomal recessive inheritance and high penetrance. One case of autosomal dominant JEB has been reported with a variant in the *COL17A1* gene.<sup>1</sup> The recurrence risk for couples with an affected child with autosomal recessive JEB is 25%. The recurrence risk to extended family members is rare in the absence of consanguinity. Only one *de novo* variant has been reported in the literature.

**Test Methods:**

GeneDx offers a complex approach to JEB variant analysis. First, a variant-specific assay is offered to detect 6 common, recurrent variants. Specifically, bi-directional sequence analysis is used to identify the following hot spot variants: R635X, R42X, Q243X in *LAMB3*, R661X in *LAMA3* and R95X in *LAMC2*. Screening for a 77bp insertion in *LAMB3* (957ins77) is performed by bi-directional sequence analysis. If the analysis of these hot spots yields no variant, sequence analysis of all 3 laminin-5 genes, *LAMB3*, *LAMC2* and *LAMA3* is available, usually recommended in this order. For *LAMB3*, the 22 coding exons and their splice junctions are screened for variant using bi-directional sequence analysis. Similarly, bi-directional sequence analysis is performed to screen the 23 coding exons of the *LAMC2* gene and the 38 coding exons of the *LAMA3* gene for variants. If a sequence change is identified in any of these tests, the variant is confirmed by a second analysis, using sequencing, heteroduplex or restriction fragment analysis.

## Test Sensitivity:

Analysis for the common hot spot variants identifies the underlying genetic cause in 40% of patients with the clinical and histologic features of JEB<sup>2</sup>. Other variants in these or other genes associated with JEB will not be detected through this targeted analysis. Sequencing of the *LAMB3* gene is expected to identify another 30% of patients with clinical and histologic features of JEB. Finally, sequence analysis of the *LAMC2* and *LAMA3* genes identifies another 9% of variant in each gene in biopsy-proven cases of JEB<sup>2</sup>. The underlying genetic cause of JEB in the remaining cases may be due to variants in other EB genes (e.g. *ITGB4* associated with EB with and (rarely) without pyloric atresia<sup>3</sup> and *COL17A1* associated with GABEB, non-Herlitz and Herlitz JEB<sup>2</sup>).

The common hot spot variants in JEB are generally found in individuals with specific ethnic backgrounds. R635X in *LAMB3* is most common in Caucasian and Hispanic populations, Q243X in *LAMB3* in Middle Easterners and Caucasians, and R42X and 957ins77 in *LAMB3* in individuals of African descent, including African Americans.

The R95X variant in *LAMC2* and R661X variant in *LAMA3* are found in patients of European and Pakistani backgrounds, respectively. Including the “hot spot” variant in *LAMB3* noted above, most reported variants in *LAMB3*, *LAMC2* and *LAMA3* are nonsense variants, small insertions or deletions that may affect any exon of the laminin B3, C2 and A3 genes and result in reduced or absent laminin 5 protein complex. Non-Herlitz JEB patients may have missense or splice junction variants on one or both alleles.<sup>2</sup>

## References:

1. Almaani et al., 2008 Br. J Dermatol 160:1094-1097
2. Varki et al., 2006 J Medical Genet 43:641-52
3. Inoue et al., 2000 J Invest Dermatol 114:1061-4