**PLEC1 Gene Analysis in Epidermolysis Bullosa with Pyloric Atresia, Epidermolysis Bullosa with Muscular Dystrophy and Epidermolysis Bullosa Simplex**

**Disorders Also Known As:** Epidermolysis Bullosa with pyloric atresia: EB-PA or Carmi Syndrome; Epidermolysis Bullosa with Muscular Dystrophy: EB-MD; Epidermolysis Bullosa Simplex Ogna: EBS-Ogna

**Clinical Features:**
There are three variant phenotypic forms of EB due to plectin variants; EB with pyloric atresia or pyloric stenosis (EB-PA), EB with muscular dystrophy (EB-MD), and a mild autosomal dominant EBS form known as EBS-Ogna\(^1\). In all three forms, blistering begins in the neonatal period and continues throughout life. Blisters are usually generalized and may range from mild to severe. However, aside from blistering, the forms diverge based on the extracutaneous findings. EB-PA is often lethal in the newborn period; however surviving patients may show less severe blistering as they age\(^2\)-\(^4\). In these children pyloric atresia requires surgical intervention in the neonatal period. In EB-MD blistering is usually milder, and muscular dystrophy may appear in late childhood to adulthood\(^2\),\(^5\)-\(^18\). EBS-Ogna is a rare autosomal dominant variant of EB in which variants on one allele have been described in extended family members\(^19\)-\(^20\). In all three of these variants that are caused by plectin variants the tissue separation (blister) occurs just above the lamina lucida at the level of the hemidesmosome. Plectin staining of a skin biopsy may be reduced or absent consistent with plectin variants. Muscle biopsies may also be stained for plectin in cases where MD is suspected and will show reduced or absent plectin staining. In rare cases, EB-PA was identified based on ultrasound abnormalities in fetuses of families with no family history. Subsequent molecular testing revealed the presence of ITGB4 or ITGA6 variants\(^21\)-\(^24\), although this has not been described in EB cases with plectin defects.

**Inheritance Pattern/Genetics:**
EB due to plectin variants is a genetically heterogeneous group of disorders, showing either autosomal recessive (EB-PA and EB-MD) or autosomal dominant (EBS-Ogna) inheritance. Penetration of PLEC1 variants is high. The recurrence risk for couples with an affected child is 25% (EB-PA and EB-MD) or 50% (EBS-Ogna). The recurrence risk to extended family members is rare in the absence of consanguinity. No *de novo* variants have been reported to date.

**Test Methods:**
Using genomic DNA obtained from the submitted biological material, sequencing of the coding region and splice sites of the PLEC1 gene is offered in two tiers. Tier 1 comprises the two main
exons 31 and 32, while Tier 2 includes bi-directional sequence analysis of the remaining 30 exons. Note, numerous alternatively spliced variants of PLEC1 exists but only exon 1 of the longest isoform, which predominates in skin, is performed. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
About 15% of patients who have EB-PA have variants in the PLEC1 gene, the remaining patients have variants in ITGA6 (5%) or ITGB4 (75%) 1. The remaining 5% of patients will have no detectable variants in any of these three genes. ITGB4 and ITGA6 gene analysis for EB-PA are available as separate tests. Approximately 90% of individuals with biopsy proven (skin and muscle biopsy) plectin deficiency and muscular dystrophy have detectable plectin variants 1. EBS-Ogna has been described in a limited number of families; however other forms of EBS due to KRT5 and KRT14 variants have been described. KRT5 and KRT14 analysis is offered as a separate test at GeneDx. The sensitivity of PLEC1 testing in patients with EBS has not been well established since the number of cases described is small19-20.

About 35 cases with autosomal recessive EB with plectin variants have been reported in the literature (9 cases of EB-PA2-4, 16 cases with EB-MD2,5-18, and 10 with AR disease and no reported PA or MD 1,27-30). An additional two families with AD EBS with PLEC1 variants have also been reported 19-20. The variant spectrum includes missense, nonsense, splicing, insertion and deletion variants.

References: