**PLEC-related Epidermolysis Bullosa: PLEC Gene Sequencing**

**Condition Description**

Epidermolysis Bullosa with Muscular Dystrophy (EB-MD)

Approximately 50 cases of epidermolysis bullosa-muscular dystrophy (EB-MD) have been reported worldwide. Blistering occurs early and is generally mild. Muscular dystrophy may not appear until later childhood, adolescence, or in some cases adulthood, and can cause immobility and eventually death later in life. Mutations have been described throughout the PLEC (also known as PLEC1) gene (8q24). Inheritance is autosomal recessive.

Epidermolysis Bullosa with Pyloric Atresia (EB-PA)

Epidermolysis bullosa with pyloric atresia (EB-PA) is characterized by fragility of the skin and mucous membranes, manifest by blistering with little or no trauma; congenital pyloric atresia; and ureteral and renal anomalies (dysplastic/multicystic kidney, hydronephrosis/hydroureter, ureterocele, duplicated renal collecting system, absent bladder). The course of EB-PA is usually severe and often lethal in the neonatal period. Although most affected children succumb as neonates, those who survive may have severe blistering with formation of granulation tissue on the skin around the mouth, nose, fingers, and toes, and internally around the trachea. However, some affected individuals have little or no blistering later in life. Additional features shared by EB-PA and the other major forms of EB include congenital localized absence of skin (aplasia cutis congenita), milia, nail dystrophy, scarring alopecia, hypotrichosis, and contractures.

Because the clinical features of all types of epidermolysis bullosa (EB) overlap significantly, examination of a skin biopsy by transmission electron microscopy (TEM) and/or immunofluorescent antibody/antigen mapping is usually required to establish the diagnosis. The three genes known to be associated with EB-PA are ITGB4 (~80% of EB-PA), ITGA6 (~5%), and PLEC (~15%).

EB-PA is inherited in an autosomal recessive manner.

Epidermolysis Bullosa Simplex, Ogna Type

Epidermolysis bullosa simplex, Ogna type has been observed in one Norwegian and one German family with autosomal dominant inheritance. It is a result of the site-specific missense p.Arg2110Trp mutation in PLEC. A single lethal case of autosomal recessive EBS resulting from PLEC mutations has also been described, as has a case of EBS with severe mucous membrane involvement as a result of mutations in PLEC.

For patients with suspected PLEC-related EB, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

References:
- GeneReviews: Epidermolysis Bullosa with Pyloric Atresia
- OMIM #612138: Epidermolysis Bullosa Simplex with Pyloric Atresia
- OMIM #226670: Epidermolysis Bullosa Simplex with Muscular Dystrophy
- OMIM #131950: Epidermolysis Bullosa Simplex, Ogna Type

**Genes**

PLEC, PLEC1

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of PLEC-related epidermolysis bullosa.
- Carrier testing in adults with a family history of PLEC-related epidermolysis bullosa.

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient’s genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown genetic significance.
significance. Variants of unknown significance may require further studies of the patient and/or family members.

### Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%.

### Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml.

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Deletion/duplication analysis of the PLEC gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to adults who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.