XomeDxSlice – Epidermolysis Bullosa (EB)

Panel Gene List:
CD151, CDSN, CHST8, COL17A1, COL7A1, CSTA, DSG1, DSG2, DSG3, DSG4, DSP, DST, EXPH5, FERMT1, GRIP1, ITGA3, ITGA6, ITGB4, KLHL24, KRT1, KRT10, KRT14, KRT5, LAMA3, LAMB3, LAMC2, MMP1, NID1, PKP1, PLEC, TGM5

Clinical Features:
Epidermolysis bullosa (EB) is an inherited skin and connective tissue disease that causes bullae (blisters) with mild trauma. The severity of the disorder depends on the layer of skin where the tissue separation occurs. In EB Simplex the blisters occur in the basal layer of the epidermis and do not leave scars. Most cases are caused by a mutation or mutations in either KRT5, KRT14, TGM5 or EXPH5. Dystrophic EB (DEB) is a disorder with a range of severity from very severe to relatively mild. The blisters are caused by abnormalities of the anchoring fibrils, which are made up of type VII collagen, that attach the epidermis to the underlying dermis. Mutations in the COL7A1 gene can be autosomal dominant or recessive, and the blisters leave scars. Junctional EB is a heterogeneous disorder with the blisters occurring within or just above the lamina lucida (between the dermis and epidermis). In most cases, the blisters do not result in scarring. Junctional EB can be mild or severe and even lethal in the neonatal period; however surviving patients may improve with age. Mutations in several different genes can result in Junctional EB (virtually all recessive), including LAMA3, LAMB3, LAMC2, ITGA6, ITGB4, and COL17A1. There are also variant forms of EB in which other phenotypic features are found, including EB with pyloric atresia caused by mutations in the ITGA6, ITGB4 or PLEC1 gene, EB with muscular dystrophy (EB-MD) caused by mutations in the PLEC1 gene and variant forms of DEB in which only nails are affected (COL7A1). Additionally, there is considerable overlap in some features such as ITGB4 mutations causing EB without pyloric atresia but with associated urinary and gastrointestinal tract abnormalities. The variety of genes, and their relative complexity makes genetic testing challenging and a skin biopsy studied with antibodies to the various skin proteins by indirect immunofluorescence can help elucidate the type of EB and to inform the testing and mutation/gene assignment to be identified by XomeDxSlice - EB testing.

Genetics:
The disorder follows an autosomal dominant inheritance pattern (i.e. KRT5, KRT14), or autosomal recessive inheritance pattern (i.e. EXPH5,TGM5 FERMT1).

Test Methods:
Using genomic DNA from the submitted specimen(s), the exonic regions and flanking splice junctions of the genome are sequenced by massively parallel (NextGen) sequencing on an

Illumina sequencing system with 100bp or greater paired-end reads. Reads are aligned to human genome build GRCh37/UCSC hg19, and analyzed for sequence variants using a custom-developed analysis tool (Xome Analyzer). Capillary sequencing or another appropriate method is used to confirm all potentially pathogenic variants identified. Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Please note that while XomeDxSlice captures and sequences the whole exome, analysis is targeted to the limited and specific phenotype-driven gene list for epidermolysis bullosa (31 genes).

Test Sensitivity:

Approximately 99% of patients with biopsy proven EB will have mutation(s) in one of the ten definite EB genes. XomeDxSlice-EB testing covers all of these EB genes known to be associated with the EB phenotype. All genes have 97-100% coverage with a depth of 10 or more reads. This indicates that most single nucleotide changes and small insertions and deletions will be identified by the XomeDxSlice – EB analysis. Large insertions and deletions encompassing more than 100 base pairs, although rare in this set of genes, may not be identified. If an affected individual is found by XomeDxSlice-EB to have only a single mutation in a gene with recessive inheritance, deletion/duplication analysis of that gene may be performed at no additional cost.

Special Case of EB Simplex and KRT5/14 Testing:

While XomeDxSlice-EB is appropriate for most cases of EB, it may be more cost-effective to perform KRT5/14 Hot Spot analysis first for patients with a clinical diagnosis of Dowling-Meara, Koebner, Weber-Cockayne or other suspected forms of EB Simplex, where the blister has been shown to occur above the basal layer of the epidermis. If this test is negative, reflex to XomeDxSlice-EB is available.

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