XomeDxSlice – Epidermolysis Bullosa (EB)

Panel Gene List:
CD151, CDSN, CHST8, COL17A1, COL7A1, CSTA, DSG1, DSP, DST, EXPH5, FERMT1, FLG2, ITGA3, ITGA6, ITGB4, JUP, KLHL24, KRT1, KRT5, KRT10, KRT14, LAMA3, LAMB3, LAMC2, PKP1, PLEC, SERPINB8, TGM5

Clinical Features and Genetics:
Epidermolysis bullosa (EB) is an inherited skin and connective tissue disease that causes skin fragility and bullae (blisters) with mild trauma. The disorder follows an autosomal dominant (i.e. KRT5, KRT14) or an autosomal recessive inheritance pattern (i.e. EXPH5, TGM5, FERMT1). The severity of the disorder depends on the layer of skin where the tissue separation occurs. In EB simplex (EBS) the blisters occur in the basal layer of the epidermis and do not leave scars. Most cases are caused by a pathogenic variant in either KRT5, KRT14, TGM5, KLHL24, 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 type VII collagen anchoring fibrils that attach the epidermis to the underlying dermis. Dystrophic EB due to pathogenic variants in the COL7A1 gene may be inherited as an autosomal dominant (DDEB) or recessive (RDEB) trait, and blisters often heal with scars. Junctional EB (JEB) is a heterogeneous disorder in which the blisters occurr within or just above the lamina lucida (between the dermis and epidermis), but these blisters typically do not result in scarring. JEB can be mild or severe and even lethal in the neonatal period; however, blistering in surviving individuals may improve with age. Pathogenic variants in several different genes can result in autosomal recessive JEB, including COL17A1, LAMA3, LAMB3, LAMC2, ITGA6, and ITGB4. Variant forms of EB with other phenotypic features also exist, including EB with pyloric atresia (EBPA) caused by pathogenic variants in the ITGA6, ITGB4, or PLEC1 gene; EB with muscular dystrophy (EB-MD) caused by pathogenic variants 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 pathogenic variants causing EB without pyloric atresia but with associated urinary and gastrointestinal tract abnormalities. Peeling skin syndrome (PSS) is a rare autosomal recessive genodermatosis characterized by spontaneous peeling of the epidermis, which can be localized or generalized, pruritic or nonpruritic, noninflammatory (type A) or inflammatory (type B), and may include erythema. Presentation of PSS varies from congenital through adult onset and can be caused by multiple genes including CDSN, TGM5 (acral PSS), CHST8, CSTA, SERPINB8, and FLG2. The variety of genes and their relative complex phenotypes may sometimes complicate interpretation of genetic test results. In such instances, a skin biopsy studied with antibodies to the various skin proteins by indirect immunofluorescence may help to clarify the type of EB.

Test Methods:

Genomic DNA from the submitted specimen is enriched for the complete coding regions and splice site junctions for most genes of the human genome using a proprietary capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. Using a custom-developed analysis tool (XomeAnalyzer), data is filtered and analyzed to identify sequence variants and most deletions and duplications involving three or more coding exons in the selected genes or regions of interest.[1] Smaller deletions or duplications may not be reliably identified. Reported clinically significant variants are confirmed by an appropriate orthogonal method. For the FLG2 gene, only loss-of-function variants are reported. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported. Please note that while XomeDxSlice - EB captures and sequences the whole exome, analysis is targeted to the limited and specific phenotype-driven gene list for epidermolysis bullosa.

Special Case of EB Simplex and KRT5/KRT14 Testing:

While XomeDxSlice - EB is appropriate for most cases of EB, it may be more cost-effective to perform KRT5/KRT14 Hot Spot analysis first for individuals 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 layers of the epidermis. If the KRT5/14 Hot Spot test is negative, reflex to this XomeDxSlice - EB test is available.

Test Sensitivity:

The clinical sensitivity of the XomeDxSlice - EB test depends in part on the patient's clinical phenotype. Specific information about the diagnostic yield for each gene in selected populations is summarized in the table below. All genes have 99-100% coverage with a depth of 10 or more reads. Note that small sections of a few individual genes (eg., keratin genes and FLG2) have inherent sequence properties that yield suboptimal data and variants in those regions may not be identified reliably.

Gene	Disorder	Inheritance	Clinical sensitivity
CD151	Nephropathy with pretibial epidermolysis bullosa and deafness	Autosomal Recessive	~1% of autosomal recessive EB[2,3]
CDSN	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[4,5]
CHST8	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[6]
COL17A1	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive / Autosomal Dominant (rare)	12% of JEB[7]
COL7A1	Dystrophic epidermolysis bullosa (DEB)	Autosomal Dominant / Autosomal Recessive	100% of DEB[8]
CSTA	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[9,10]

DSG1	Palmoplantar keratoderma (PPK)	Autosomal Dominant / Autosomal Recessive	Rare[11,12,13]
DSP	Cardiomyopathy with woolly hair and palmoplantar keratoderma	Autosomal Dominant / Autosomal Recessive	Rare[14,15]
DST	Epidermolysis bullosa simplex (EBS)	Autosomal Recessive	Rare[16,17]
EXPH5	Epidermolysis bullosa simplex (EBS)	Autosomal Recessive	~1-2% of EBS[17,18,19]
FERMT1	Kindler syndrome	Autosomal Recessive	~98% of Kindler syndrome[20]
FLG2	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[21,22,23]
ITGA3	Interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa	Autosomal Recessive	Rare[24,25]
ITGA6	Epidermolysis bullosa with pyloric atresia (EBPA)	Autosomal Recessive	5% of EBPA[26]
ITGB4	Epidermolysis bullosa with pyloric atresia (EBPA)	Autosomal Recessive	77% of EBPA[26]
JUP	Naxos disease	Autosomal Recessive	Rare[27,28]
KLHL24	Epidermolysis bullosa simplex (EBS) with scarring and hair loss	Autosomal Dominant	~1% of EBS[18]
KRT1	Epidermolytic ichthyosis (EI)	Autosomal Dominant	32% of EI[29]
KRT5	Epidermolysis bullosa simplex (EBS); Dowling Dagos disease	Autosomal Dominant / Autosomal Recessive (rare)	37% of EBS[18]
KRT10	Epidermolytic ichthyosis (EI)	Autosomal Dominant	68% of EI[29]
KRT14	Epidermolysis bullosa simplex (EBS); Naegeli-Franceschetti-Jadassohn syndrome	Autosomal Dominant / Autosomal Recessive (rare)	37% of EBS[18]
LAMA3	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive	9% of JEB[7]
LAMB3	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive	70% of JEB[7]
LAMC2	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive	9% of JEB[7]
PKP1	Ectodermal dysplasia-skin fragility syndrome	Autosomal Recessive	Rare[30,31]
PLEC	Epidermolysis bullosa simplex (EBS); epidermolysis bullosa with muscular dystrophy (EBMD); epidermolysis bullosa with pyloric atresia (EBPA)	Autosomal Recessive/ Autosomal Dominant (rare)	8% of EBS[32]; >97% of EBMD[33]; 18% of EBPA[26]
SERPINB8	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[34]
TGM5	Acral peeling skin syndrome (APSS)	Autosomal Recessive	Rare[35,36]

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