XomeDx® Slice – 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 occur 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. Data are filtered and analyzed to identify sequence variants and most deletions and duplications involving three or more coding exons. 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

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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 *XomeDx*® Slice - EB captures and sequences the whole exome, analysis is targeted to the limited and specific phenotype-driven gene list for epidermolysis bullosa.

TEST SENSITIVITY

The clinical sensitivity of the *XomeDx*® Slice - 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 (e.g., 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
CD151	Nephropathy with pretibial epidermolysis bullosa and deafness	Autosomal Recessive	~1% of autosomal recessive EB[1,2]
CDSN	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[3,4]
CHST8	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[5]
COL17A1	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive / Autosomal Dominant (rare)	12% of JEB[6]
COL7A1	Dystrophic epidermolysis bullosa (DEB)	Autosomal Dominant / Autosomal Recessive	100% of DEB[7]
CSTA	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[8,9]
DSG1	Palmoplantar keratoderma (PPK)	Autosomal Dominant / Autosomal Recessive	Rare[10,11,12]
DSP	Cardiomyopathy with woolly hair and palmoplantar keratoderma	Autosomal Dominant / Autosomal Recessive	Rare[13,14]
DST	Epidermolysis bullosa simplex (EBS)	Autosomal Recessive	Rare[15,16]
EXPH5	Epidermolysis bullosa simplex (EBS)	Autosomal Recessive	~1-2% of EBS[16,17,18]
FERMT1	Kindler syndrome	Autosomal Recessive	~98% of Kindler syndrome[19]
FLG2	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[20,21,22]
ITGA3	Interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa	Autosomal Recessive	Rare[23,24]
ITGA6	Epidermolysis bullosa with pyloric atresia (EBPA)	Autosomal Recessive	5% of EBPA[25]
ITGB4	Epidermolysis bullosa with pyloric atresia (EBPA)	Autosomal Recessive	77% of EBPA[25]

Gene	Disorder	Inheritance	Clinical
JUP	Naxos disease	Autosomal Recessive	Rare[26,27]
KLHL24	Epidermolysis bullosa simplex (EBS) with scarring and hair loss	Autosomal Dominant	~1% of EBS[17]
KRT1	Epidermolytic ichthyosis (EI)	Autosomal Dominant	32% of EI[28]
KRT5	Epidermolysis bullosa simplex (EBS); Dowling Dagos disease	Autosomal Dominant / Autosomal Recessive (rare)	37% of EBS[17]
KRT10	Epidermolytic ichthyosis (EI)	Autosomal Dominant	68% of EI[28]
KRT14	Epidermolysis bullosa simplex (EBS); NaegeliFranceschetti-Jadassohn syndrome	Autosomal Dominant / Autosomal Recessive (rare)	37% of EBS[17]
LAMA3	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive	9% of JEB[6]
LAMB3	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive	70% of JEB[6]
LAMC2	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive	9% of JEB[6]
PKP1	Ectodermal dysplasia-skin fragility syndrome	Autosomal Recessive	Rare[29,30]
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[31]; >97% of EBMD[32]; 18% of EBPA[25]
SERPINB8	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[33]
TGM5	Acral peeling skin syndrome (APSS)	Autosomal Recessive	Rare[34,35]

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