

XomeDx® Slice – Epidermolysis Bullosa (EB)

PANEL GENE LIST

CDI51, 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 in the selected genes or regions of interest. Smaller deletions or duplications may not be reliably identified. Reported variants are confirmed, if necessary, by an appropriate orthogonal method in the proband and, if submitted, in selected relatives. Sequence variants

are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported. For the *FLG2* gene, only loss-of-function variants are reported. Available evidence for variant classification may change over time and reported variant(s) may be reclassified according to the ACMG/AMP Standards and Guidelines (PMID: 25741868), which may lead to issuing a revised report. 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
<i>CDI51</i>	Nephropathy with pretibial epidermolysis bullosa and deafness	Autosomal Recessive	~1% of autosomal recessive EB (PMID: 15265795, 29138120)
<i>CDSN</i>	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare (PMID: 20691404, 25473393)
<i>CHST8</i>	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare (PMID: 22289416)
<i>COL17A1</i>	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive / Autosomal Dominant (rare)	12% of JEB (PMID: 20301304)
<i>COL7A1</i>	Dystrophic epidermolysis bullosa (DEB)	Autosomal Dominant / Autosomal Recessive	100% of DEB (PMID: 20301481)
<i>CSTA</i>	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare (PMID: 21944047, 23534700)
<i>DSG1</i>	Palmoplantar keratoderma (PPK)	Autosomal Dominant / Autosomal Recessive	Rare (PMID: 19157795, 27534273, 29489036)
<i>DSP</i>	Cardiomyopathy with woolly hair and palmoplantar keratoderma	Autosomal Dominant / Autosomal Recessive	Rare (PMID: 20738328, 26604139)
<i>DST</i>	Epidermolysis bullosa simplex (EBS)	Autosomal Recessive	Rare (PMID: 20164846, 26719633)
<i>EXPH5</i>	Epidermolysis bullosa simplex (EBS)	Autosomal Recessive	~1-2% of EBS (PMID: 26719633, 20301543, 23176819)
<i>FERMT1</i>	Kindler syndrome	Autosomal Recessive	~98% of Kindler syndrome (PMID: 26937547)
<i>FLG2</i>	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare (PMID: 28884927, 29505760, 29758285)

Gene	Disorder	Inheritance	Clinical
<i>ITGA3</i>	Interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa	Autosomal Recessive	Rare (PMID: 22512483, 27717396)
<i>ITGA6</i>	Epidermolysis bullosa with pyloric atresia (EBPA)	Autosomal Recessive	5% of EBPA (PMID: 16473856)
<i>ITGB4</i>	Epidermolysis bullosa with pyloric atresia (EBPA)	Autosomal Recessive	77% of EBPA (PMID: 16473856)
<i>JUP</i>	Naxos disease	Autosomal Recessive	Rare (PMID: 10902626, 21668431)
<i>KLHL24</i>	Epidermolysis bullosa simplex (EBS) with scarring and hair loss	Autosomal Dominant	~1% of EBS (PMID: 20301543)
<i>KRT1</i>	Epidermolytic ichthyosis (EI)	Autosomal Dominant	32% of EI (PMID: 21271994)
<i>KRT5</i>	Epidermolysis bullosa simplex (EBS); Dowling Dajos disease	Autosomal Dominant / Autosomal Recessive (rare)	37% of EBS (PMID: 20301543)
<i>KRT10</i>	Epidermolytic ichthyosis (EI)	Autosomal Dominant	68% of EI (PMID: 21271994)
<i>KRT14</i>	Epidermolysis bullosa simplex (EBS); NaegeliFranceschetti-Jadassohn syndrome	Autosomal Dominant / Autosomal Recessive (rare)	37% of EBS (PMID: 20301543)
<i>LAMA3</i>	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive	9% of JEB (PMID: 20301304)
<i>LAMB3</i>	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive	70% of JEB (PMID: 20301304)
<i>LAMC2</i>	Junctional epidermolysis bullosa (JEB)	Autosomal Recessive	9% of JEB (PMID: 20301304)
<i>PKP1</i>	Ectodermal dysplasia-skin fragility syndrome	Autosomal Recessive	Rare (PMID: 9326952, 22309335)
<i>PLEC</i>	Epidermolysis bullosa simplex (EBS); epidermolysis bullosa with muscular dystrophy (EBMD); epidermolysis bullosa with pyloric atresia (EBPA)	Autosomal Recessive/ Autosomal Dominant (rare)	8% of EBS (PMID: 23774525); >97% of EBMD (PMID: 28400893); 18% of EBPA (PMID: 16473856)
<i>SERPINB8</i>	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare (PMID: 27476651)
<i>TGM5</i>	Acral peeling skin syndrome (APSS)	Autosomal Recessive	Rare (PMID: 16380904, 22622422)