Test Information Sheet

Cutis Laxa Panel

Panel Gene List: *ALDH18A1, ATP6V0A2, ATP6V1E1, ATP7A, EFEMP2, ELN, FBLN5, LTBP4, PYCR1, RIN2, SLC2A10*

Clinical Features:
Cutis Laxa is a heritable disorder of connective tissue characterized by redundant, inelastic, and wrinkled skin. Other organ systems may be variably involved and the spectrum of clinical severity ranges from relatively mild to lethal in early childhood. Additional features may include joint hypermobility, pulmonary emphysema, cardiovascular abnormalities, hernias and gastrointestinal diverticuli[1-4]. Physical and neurological development may be delayed or abnormal, and some individuals may have dysmorphic features, skeletal abnormalities, or congenital brain malformations[1,3,4]. Skin characteristics similar to those seen in cutis laxa may also be present in arterial tortuosity syndrome[5] or occipital horn syndrome[6].

For more in-depth information about Cutis Laxa, please refer to OMIM or GeneReviews, or to the references cited above.

Inheritance Pattern/Genetics: Autosomal Recessive, Autosomal Dominant, X-Linked

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted 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. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reported clinically significant variants are confirmed by an appropriate orthogonal method. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the Cutis Laxa Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined Cutis Laxa phenotype and a family history of disease. The technical sensitivity of the sequencing test is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. This test may not reliably detect copy number variants of less than 500 base pairs or low level mosaicism and cannot

identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Gene	Protein	Inheritance	Disease Association(s)
ALDH18A1	ALDEHYDE DEHYDROGENASE 18 FAMILY, MEMBER A1	AD, AR	Cutis laxa
ATP6V0A2	ATPase H+ TRANSPORTING LYSOSOMAL V0 SUBUNIT A2	AR	Cutis laxa
ATP6V1E1	ATPASE H+ TRANSPORTING V1 SUBUNIT E	AR	Cutis laxa
ATP7A	ATPASE CU(2+)-TRANSPORTING, ALPHA POLYPEPETIDE	XL	Menkes, OHS
EFEMP2	EGF-CONTAINING FIBULIN-LIKE EXTRACELLULAR MATRIX PROTEIN2	AR	Cutis laxa
ELN	ELASTIN	AD	Cutis laxa, Supravalvar Aortic Stenosis
FBLN5	FIBULIN 5	AD, AR	Cutis laxa
LTBP4	LATENT TRANSFORMING GROWTH FACTOR-BETA-BINDING PROTEIN 4	AR	Cutis laxa
PYCR1	PYRROLINE-5-CARBOXYLATE REDUCTASE 1	AR	Cutis laxa
RIN2	RAS and RAB INTERACTOR 2	AR	MACS
SLC2A10	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBRANE 10	AR	Arterial tortuosity syndrome

Abbreviations: AD – autosomal dominant; AR – autosomal recessive; MACS - Macrocephaly, alopecia, cutis laxa, and scoliosis; OHS – occipital horn syndrome; XL – X-linked

References:

1. Morava E et al. (2009) Eur J Hum Genet 17(9):1099-110 (PMID 19401719).
2. Callewaert B et al. (2011) New insights into the pathogenesis of autosomal dominant cutis laxa with report of five ELN mutations. Hum Mutat 32(4):445-55. (PMID 21309044)
3. Mohamed M et al. Metabolic cutis laxa syndromes. J Inherit Metab Dis 2011 34(4): 907-916. (PMID 21431621)
4. Kariminejad A et al. Discriminative Features in Three Autosomal Recessive Cutis Laxa Syndromes: Cutis Laxa IIA, Cutis Laxa IIB, and Geroderma Osteoplastica. Int J Mol Sci 2017 18(3):E635. (PMID 28294978
5. Callewaert B et al. Arterial Tortuosity Syndrome. 2014 Nov 13. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
6. Kaler S. ATP7A-Related Copper Transport Disorders. 2003 May 9 [updated 2016 Aug 18]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.