Cutis Laxa Panel

Test code: DE0501

Is ideal for patients with a clinical suspicion of cutis laxa.

It has usually autosomal recessive (AR) inheritance although autosomal dominant pattern is observed in *ELN* related cutis laxa and some AR genes (*ALDH18A1* and *FBLN5*) associate also to dominant disease.

About Cutis Laxa

Cutis laxa is a group of connective tissue disorder where loose or lax skin is common feature leading to sagging of the skin and a droopy appearance of the face. Cutis laxa may also affect heart, blood vessels, joints, intestines and lungs. Cardiovascular involvement includes arterial tortuosity, aneurysms and aortic stenosis. Inguinal and umbilical hernias as well as bladder diverticula are relatively common. Some people with cutis laxa develop emphysema during childhood especially when *EFEMP2* or *FBLN5* is defective. In general, the autosomal recessive forms of cutis laxa (ARCL) tend to be more severe than the autosomal dominant form. Aneurysms are more frequent in *EFEMP2* and *SLC2A10* related cutis laxa whereas developmental delay in *ALDH18A1*, *ATP6V0A2* and *PYCR1*. Clinical manifestations associated with *EFEMP2* mutations are highly variable and some patients even die prenatally or shortly after birth due to cardiopulmonary complications. In addition to the features described above, some people with ARCL may lose the ability to walk by adolescence even though the skin condition may improve over time. Wrinkly skin syndrome is an allelic disorder to ARCL but is a relatively mild disorder presenting with reduced skin elasticity, dental abnormalities and delayed closure of the fontanel. Cutis laxa is usually inherited in an autosomal recessive (AR) manner although autosomal dominant inheritance is observed in *ELN* related cutis laxa and some AR genes (*ALDH18A1* and *FBLN5*) associate to both recessive and dominant disease. The X-linked form of cutis laxa, caused by mutations in *ATP7A*, is often called occipital horn syndrome. This form of the disorder is considered a mild type of Menkes syndrome. In addition to characteristic skin changes, occipital horn syndrome presents with wedge-shaped calcium deposits in a bone at the base of the skull, coarse hair and loose joints.

Availability

Results in 3-4 weeks

Gene set description

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated phenotypes</th>
<th>Inheritance</th>
<th>ClinVar</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALDH18A1</td>
<td>Spastic paraplegia, Cutis laxa</td>
<td>AD/AR</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>ATP6V0A2</td>
<td>Cutis laxa, Wrinkly skin syndrome</td>
<td>AR</td>
<td>16</td>
<td>56</td>
</tr>
<tr>
<td>ATP7A</td>
<td>Menkes disease, Occipital horn syndrome, Spinal muscular atrophy, distal, X-linked 3</td>
<td>XL</td>
<td>116</td>
<td>354</td>
</tr>
<tr>
<td>EFEMP2</td>
<td>Cutis laxa</td>
<td>AR</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>ELN</td>
<td>Cutis laxa, Supravalvular aortic stenosis</td>
<td>AD</td>
<td>78</td>
<td>113</td>
</tr>
<tr>
<td>FBLN5</td>
<td>Cutis laxa, Macular degeneration, age-related</td>
<td>AD/AR</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>GORAB</td>
<td>Geroderma osteodysplasticum</td>
<td>AR</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>LTBP4</td>
<td>Cutis laxa with severe pulmonary, gastrointestinal, and urinary abnormalities</td>
<td>AR</td>
<td>10</td>
<td>17</td>
</tr>
</tbody>
</table>
Some regions of the gene are duplicated in the genome leading to limited sensitivity within the regions. Thus, low-quality variants are filtered out from the duplicated regions and only high-quality variants confirmed by other methods are reported out. Read more.

Gene, refers to HGNC approved gene symbol; Inheritance to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL); ClinVar, refers to a number of variants in the gene classified as pathogenic or likely pathogenic in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/); HGMD, refers to a number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/). The list of associated (gene specific) phenotypes are generated from CDG (http://research.nhgri.nih.gov/CGD/) or Orphanet (http://www.orpha.net/) databases.

### Non-coding disease causing variants covered by the panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genomic location HG19</th>
<th>HGVS</th>
<th>RefSeq</th>
<th>RS-number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP7A</td>
<td>ChrX:77279056</td>
<td>c.2916+2480T&gt;G</td>
<td>NM_000052.5</td>
<td></td>
</tr>
<tr>
<td>ATP7A</td>
<td>ChrX:77287843</td>
<td>c.3294+763C&gt;G</td>
<td>NM_000052.5</td>
<td></td>
</tr>
<tr>
<td>ELN</td>
<td>Chr7:73480347</td>
<td>c.2272+20C&gt;G</td>
<td>NM_001278939.1</td>
<td></td>
</tr>
</tbody>
</table>

### Test performance

The Blueprint Genetics cutis laxa panel covers classical genes associated with arterial tortuosity, Wrinkly skin syndrome and cutis laxa. The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sliced from our high-quality whole exome sequencing data. Please see our sequencing and detection performance table for different types of alterations at the whole exome level (Table).

Assays have been validated for different starting materials including EDTA-blood, isolated DNA (no FFPE), saliva and dry blood spots (filter card) and all provide high-quality results. The diagnostic yield varies substantially depending on the assay used, referring healthcare professional, hospital and country. Blueprint Genetics’ Plus Analysis (Seq+Del/Dup) maximizes the chance to find a molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be a cost-effective first line test if your patient's phenotype is suggestive of a specific mutation type.

### Bioinformatics

The target region for each gene includes coding exons and ±20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the "Test limitations" section above. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the-art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases such as, but not limited, to 1000 Genomes Project, gnomAD, ClinVar and HGMD into our clinical interpretation software to make the process effective and efficient. For missense variants, in silico variant prediction tools such as SIFT, PolyPhen, MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, the customer has an access to details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with inadequate coverage if present. This reflects our mission to build fully transparent
diagnostics where customers have easy access to crucial details of the analysis process.

Clinical interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the cornerstone of clinical interpretation and resulting patient management decisions. Our classifications follow the Blueprint Genetics Variant Classification Schemes based on the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis of sequence variants is confirmation of variants classified as pathogenic or likely pathogenic using bi-directional Sanger sequencing. Variant(s) fulfilling the following criteria are not Sanger confirmed: the variant quality score is above the internal threshold for a true positive call, and visual check-up of the variant at IGV is in-line with the variant call. Reported variants of uncertain significance are confirmed with bi-directional Sanger sequencing only if the quality score is below our internally defined quality score for true positive call. Reported copy number variations with a size <10 exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen less than three times at Blueprint Genetics.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, in silico predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene’s variation in population cohorts and detailed information about related phenotypes. We also provide links to the references used, congress abstracts and mutation databases to help our customers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification within the family. In the case of variants of uncertain significance (VUS), we do not recommend family member risk stratification based on the VUS result. Furthermore, in the case of VUS, we do not recommend the use of genetic information in patient management or genetic counseling.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Thus, our database, and our understanding of variants and related phenotypes, is growing by leaps and bounds. Our laboratory is therefore well positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

ICD codes

Commonly used ICD-10 codes when ordering the Cutis Laxa Panel

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q82.8</td>
<td>Cutis laxa</td>
</tr>
</tbody>
</table>
Accepted sample types

- EDTA blood, min. 1 ml
- Purified DNA, min. 3μg*
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient’s name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

Resources

- Cutis Laxa Internationale
- GeneReviews - *ATP6VOA2* related Cutis Laxa
- GeneReviews - *EFEMP2* related Cutis Laxa
- GeneReviews - *FBLN5* related Cutis Laxa
- GeneReviews - *LTBP4* related Cutis Laxa
- NORD - Cutis Laxa
- National Organization for Rare Disorders