Leber Congenital Amaurosis Panel

Test code: OP1701

Is ideal for patients with a clinical suspicion / diagnosis of Leber congenital amaurosis.

The panel covers genes associated with autosomal recessive and dominant Leber congenital amaurosis (LCA) and is estimated to provide molecular diagnosis for 70% of patients with LCA. This panel is included in the Retinal Dystrophy Panel.

About Leber Congenital Amaurosis

Leber congenital amaurosis (LCA) is a severe retinal dystrophy causing blindness or severe visual impairment before the age of 1 year. It accounts for 10-18% of congenital blindness and 5% of all retinal dystrophies. LCA is clinically characterized by poor visual function often accompanied by nystagmus, abnormal pupillary responses, photophobia, high hyperopia, markedly diminished electroretinogram, and keratoconus. A characteristic finding is Franceschetti’s oculo-digital sign, comprising eye poking, pressing, and rubbing. LCA is a genetically heterogeneous disorder and is typically inherited in an autosomal recessive manner. Rare dominant cases have been reported. Recent clinical trials with \textit{RPE65} replacement therapy have been shown to be promising in improving vision in patients with \textit{RPE65}-associated LCA (PMID: 23341635). The prevalence of LCA is 1:50,000 to 1:33,000.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Leber Congenital Amaurosis Panel and their clinical significance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated phenotypes</th>
<th>Inheritance</th>
<th>ClinVar</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIPL1</td>
<td>Retinitis pigmentosa, Cone rod dystrophy, Leber congenital amaurosis</td>
<td>AD/AR</td>
<td>10</td>
<td>79</td>
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<tr>
<td>ALMS1*</td>
<td>Alström syndrome</td>
<td>AR</td>
<td>197</td>
<td>302</td>
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<tr>
<td>BBS4</td>
<td>Bardet-Biedl syndrome</td>
<td>AR</td>
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<td>53</td>
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<tr>
<td>CABP4</td>
<td>Night blindness, congenital stationary</td>
<td>AR</td>
<td>6</td>
<td>11</td>
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<tr>
<td>CEP290*</td>
<td>Bardet-Biedl syndrome, Leber congenital amaurosis, Joubert syndrome, Senior-Loken syndrome, Meckel syndrome</td>
<td>AR</td>
<td>130</td>
<td>289</td>
</tr>
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<td>CNGA3</td>
<td>Leber congenital amaurosis, Achromatopsia</td>
<td>AR</td>
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<td>149</td>
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<td>CRB1</td>
<td>Retinitis pigmentosa, Pigmented paravenous chorioretinal atrophy, Leber congenital amaurosis</td>
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<td>CRX</td>
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<tr>
<td>CWC27</td>
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<tr>
<td>GUCY2D</td>
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<td>AD/AR</td>
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<td>IDH3A</td>
<td>Leber congenital amaurosis</td>
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<tr>
<td>Gene</td>
<td>Genomic location HG19</td>
<td>HGVS</td>
<td>RefSeq</td>
<td>RS-number</td>
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<td>--------</td>
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<tr>
<td>BBS4</td>
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<td>c.77-216delA</td>
<td>NM_033028.4</td>
<td>rs113994189</td>
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<tr>
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<tr>
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<td>c.103-18_103-13delGCTTTT</td>
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</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/clnvar/); 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.
CNGA3 Chr2:98986401 c.-37-1G>C NM_001298.2
GUCY2D Chr17:7906220 c.-9-137T>C NM_000180.3
LRAT Chr4:155670121 c.541-15T>G NM_004744.3 rs779487944
MYO7A Chr11:76839534 c.-48A>G NM_000260.3
MYO7A Chr11:76893448 c.3109-21G>A NM_000260.3
MYO7A Chr11:76915107 c.5327-14T>G NM_000260.3
MYO7A Chr11:76915110 c.5327-11A>G NM_000260.3 rs397516316
MYO7A Chr11:76919448 c.5857-27_5857-26insTTGAG NM_000260.3
NMNAT1 Chr1:10003560 c.-70A>T NM_022787.3
NMNAT1 Chr1:10003561 c.-69C>T NM_022787.3
NMNAT1 Chr1:10003580 c.-57+7T>G NM_022787.3
RDH5 Chr12:56114302 c.33+2dupT NM_002905.3
RPE65 Chr1:68910577 c.246-11A>G NM_000329.2
RPGRIP1 Chr14:21789155 c.1468-263G>C NM_020366.3
RPGRIP1 Chr14:21789588 c.1611+27G>A NM_020366.3
RPGRIP1 Chr14:21793563 c.2367+23delG NM_020366.3 rs781728563
RPGRIP1 Chr14:21795769 c.2711-13G>T NM_020366.3 rs369991630

Test performance

The Blueprint Genetics Leber congenital amaurosis panel covers classical genes associated with Leber congenital amaurosis. 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 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 corner stone 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, zyosity, 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 Leber Congenital Amaurosis Panel

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
</tr>
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</table>

https://blueprintgenetics.com/
H35.50 Leber congenital amaurosis

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

- American Association for Pediatric Ophthalmology and Strabismus - Leber Congenital Amaurosis
- Fighting Blindness - Leber Congenital Amaurosis
- Foundation Fighting Blindness
- GeneReviews
- GeneReviews - Leber Congenital Amaurosis
- National Organization for rare disorders - Leber Congenital Amaurosis
- Retina International