

Leber Congenital Amaurosis (LCA) Panel

Panel Gene List: AIPL1, CEP290, CRB1, CRX, GUCY2D, IMPDH1, RPE65 and RPGRIP1

Clinical Features:

Leber Congenital Amaurosis (LCA) is a group of congenital inherited diseases of the retina that lead to severe early infantile blindness before the age of 1 year^{2,9,10,13,18}. Clinical findings include severe and early vision loss, sensory nystagmus, amaurotic pupils, and the electroretinogram (ERG) shows severely reduced scotopic and photopic responses^{2,9,10,13,18}. A normal ERG excludes a diagnosis of LCA^{2,9,10,13,18}. Visual function and acuity in LCA patients varies widely. LCA patients often have high refractive errors as well as photoaversion (photophobia) and night blindness. Other ocular findings may include cataract and keratoconus, which is a degenerative non-inflammatory disorder of the cornea. Patients with LCA may also experience olfactory dysfunction. The ocular disorders whose phenotype overlaps with LCA include complete and incomplete achromatopsia, complete and incomplete congenital stationary night blindness, albinism, and optic nerve hypoplasia.

Inheritance Pattern/Genetics:

Autosomal dominant or autosomal recessive

Test Methods:

The coding regions and splice junctions of the 8 genes of this panel are enriched using a proprietary targeted capture system developed by GeneDx. The targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequence is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 19 reads are achieved by NextGen sequencing.

Test Sensitivity:

Autosomal Dominant

CRX gene: Cone-rod homeobox

Variants in CRX contribute to 2%-3% of autosomal dominant LCA and rare cases of autosomal recessive LCA and less than 1% of adRP¹⁴. Variants in CRX are the most common cause for adCORD, with variants accounting for 5%-12% of all cases.

IMPDH1 gene: Inosine monophosphate dehydrogenase 1

De novo variants in IMPDH1 have been identified in 2 out of 24 LCA simplex patients (8%). Additionally, variants in IMPDH1 account for approximately 2% of families with adRP³.

Autosomal Recessive

AIPL1 gene: Aryl hydrocarbon receptor interacting protein-like 1

Variants in the AIPL1 gene have been reported in ~5% of arLCA patients^{9,18}. Additionally, in-frame deletions located in the C-terminus of the AIPL1 protein appear to be associated with adCORD and juvenile retinitis pigmentosa (RP)¹⁷.

CEP290 gene: Centrosomal protein 290kDa

Variants in the CEP290 gene are the most frequent cause of LCA, accounting for 21-30% of all arLCA^{8,18} with the IVS26+1655A>G (p.Cys998Stop or C998X) variant being the most common LCA disease causing variant in North America and North Western-Europe as it was identified in 16 out of 76 unrelated LCA patients (21%)⁸. Variants in the CEP290 gene have also been reported in Joubert syndrome, Meckel syndrome, Senior-Loken syndrome and Bardet-Biedl syndrome.

CRB1 gene: Crumbs homologue 1

Variants in the CRB1 gene have been reported in patients with a variety of autosomal recessive retinal dystrophies. The CRB1 gene has been implicated in 10%-13% of LCA patients. In addition, in one study, 6 of 92 arRP families (6%) were found to have variants in CRB1⁶. In another study CRB1 variants were identified in 1% of families with Juvenile arRP and 22% of patients with isolated juvenile RP (2 out of 9)⁸. Finally, CRB1 variants have been found in 67%-83% of the patients with RP and preserved para-arteriolar retinal pigment epithelium and in 29%-56% of RP patients who had developed Coats-like exudative vasculopathy, a relatively rare complication of RP characterized by vascular abnormalities, yellow extravascular lipid depositions, and severe cases retinal detachment⁵⁻⁷.

GUCY2D gene: Guanylate cyclase 2D, membrane

This gene accounts for 6%-12% of arLCA patients^{9, 18}. Variants in GUCY2D also cause autosomal dominant cone-rod dystrophy (adCORD) (up to 30% in a study of Japanese patients¹¹ with adCORD, and most often variants occur in codon Arg838 in exon 13).

RPE65 gene: Retinal pigment epithelium-specific protein 65kDa

RPE65 variants contribute to 8%-16% of LCA and 2% of arRP worldwide^{9, 15}

RPGRIP1 gene: Retinitis pigmentosa GTPase regulator-interacting protein

Variants in the RPGRIP1 gene have been reported in ~5-6% of arLCA patients¹².

Gene	Protein	Inheritance	Disease Associations
<i>AIPL1</i>	Aryl hydrocarbon receptor interacting protein-like 1	AR	Leber congenital amaurosis 4; cone-rod dystrophy; retinitis pigmentosa, juvenile
<i>CEP290</i>	Centrosomal protein 290kDa	AR	Leber congenital amaurosis 10; Bardet-Biedel syndrome 14; Joubert syndrome 5; Meckel syndrome 4; Senior-Loken

			syndrome 6
<i>CRB1</i>	Crumbs homologue 1	AR	Leber congenital amaurosis 8; pigmented paravenous chorioretinal atrophy; retinitis pigmentosa-12, autosomal recessive
<i>CRX</i>	Cone-rod homeobox	AD	Leber congenital amaurosis 7; cone-rod retinal dystrophy-2
<i>GUCY2D</i>	Guanylate cyclase 2D, membrane	AR	Leber congenital amaurosis 1; cone-rod dystrophy 6
<i>IMPDH1</i>	Inosine monophosphate dehydrogenase 1	AD	Leber congenital amaurosis 11; retinitis pigmentosa 10
<i>RPE65</i>	Retinal pigment epithelium-specific protein 65kDa	AR	Leber congenital amaurosis 2; retinitis pigmentosa 20
<i>RPGRIP1</i>	Retinitis pigmentosa GTPase regulator-interacting protein	AR	Leber congenital amaurosis 6; cone-rod dystrophy13

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