

RPE65 Gene Analysis in Leber Congenital Amaurosis (LCA)

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 year¹⁻⁶. Clinical findings include severe and early vision loss, sensory nystagmus, amaurotic pupils, and the electroretinogram (ERG) shows severely reduced scotopic and photopic responses¹⁻⁶. A normal ERG excludes a diagnosis of LCA¹⁻⁶. 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 recessive

Test Sensitivity:

RPE65 variants contribute to 8%-16% of LCA and 2% of arRP worldwide.^{2,5}

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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.

References:

1. Booiij (2005) J Med Genet 42:67-75 (PMID: 16272259)
2. den Hollander (2008) Prog Retin Eye Res 27:391-419 (PMID: 18632300)
3. Hanein (2004) Hum Mutat 23:306-317 (PMID: 15024725)

4. Koenekoop (2007) Clin Exp Ophthalmol 35:473-485 (PMID: 17651254)
5. Morimura (1998) Proc Natl Acad Sci 95:3088–3093 (PMID: 9501220)
6. Stone (2007) Am J Ophthalmol 144(6):791-811 (PMID: 17964524)