

CEP290 Hotspot Gene Analysis in Leber Congenital Amaurosis

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.¹⁻⁵ Clinical findings include severe and early vision loss, sensory nystagmus, amaurotic pupils, and the electroretinogram (ERG) shows severely reduced scotopic and photopic responses.¹⁻⁵ A normal ERG excludes a diagnosis of LCA.¹⁻⁵ 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:

Autosomal recessive

Test Sensitivity:

Variants in the CEP290 gene are the most frequent cause of LCA, accounting for 21-30% of all arLCA⁵⁻⁶ with the IVS26+1655 A>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%).⁶ Variants in the CEP290 gene have also been reported in Joubert syndrome, Meckel syndrome, Senior-Loken syndrome and Bardet-Biedl syndrome.

Test Methods:

Using genomic DNA from the submitted specimen, the relevant portion of CEP290 containing the IVS26+1655 A>G variant is 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. Reported clinically significant variants are confirmed by an appropriate method. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. 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. Stone (2007) Am J Ophthalmol 144(6):791-811 (PMID: 17964524)
6. den Hollander (2006) Am J Hum Genet 79(3):556-61 (PMID: 16909394)