

Leber Congenital Amaurosis and Retinitis Pigmentosa via CRB1 Gene Sequencing--Test #681

Brief Description of Disorders: Leber Congenital Amaurosis (LCA, OMIM 204100) and Retinitis Pigmentosa (RP, OMIM 268000) are inherited degenerative diseases of the retina. LCA is characterized by bilateral congenital blindness. RP is characterized by night blindness, with age of onset varying from childhood to middle age, and progressing to constriction of the peripheral visual field and, eventually, to loss of central vision. Several clinical features of LCA overlap with those of RP. These include attenuated retinal vessels, abnormal electroretinographic (ERG) findings and a variable amount of retinal pigmentation (Perrault et al. Nat Genet 14:461-464, 1996; Daiger et al. Arch Ophthalmol 125:151-158, 2007; Gu et al. J Med Genet 36:705-707, 1999). Both LCA and RP are clinically and genetically heterogeneous. For more information see Weleber et al. GeneReviews, 2006 at www.genetests.org.

Genetics: LCA is inherited as an autosomal recessive trait in the vast majority of patients, while RP is either sporadic or familial with various modes of Mendelian, mitochondrial or digenic inheritance. To date, 14 and 25 genes have been implicated in LCA and autosomal recessive RP (AR-RP), respectively (den Hollander et al. Prog Retin Eye Res 27:391-419, 2008; Daiger et al. Arch Ophthalmol 125:151-158, 2007). The clinical overlap between LCA and RP is illustrated by the involvement of six genes in both conditions. These include the *CRB1* gene. *CRB1* mutations were first identified in patients with a severe form of AR-RP characterized by preservation of the para-arteriolar retinal pigment epithelium (PPRPE) (RP12, OMIM 600105) (den Hollander et al. Nat Genet 23:217-221, 1999). Subsequently *CRB1* mutations were reported in patients with LCA (Lotery et al. Arch Ophthalmol 119: 415-420, 2001). Over 40 and 32 different *CRB1* mutations have been reported in patients with LCA and RP, respectively. These mutations include missense, nonsense, splicing, and small deletions/insertions. In addition to LCA and RP12, *CRB1* mutations were found in rare cases with severe AR-RP without PPRPE (Lotery et al. Ophthalmic Genet 22:163-169, 2001; Booiij et al. J Med Genet 42: e67, 2005) and in one family with a history of autosomal dominant pigmented paravenous chorioretinal atrophy (PPCRA, OMIM 172870) (McKay et al. Invest Ophthalmol Vis Sci 46: 322-328, 2005).

Description of This Particular Test. The CRB1 protein is expressed specifically in human retina and brain. This test involves bidirectional DNA sequencing of all 12 coding exons and splice sites of the *CRB1* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. We will sequence any single or double exons in family members of patients with known mutations or to confirm results.

Reference Sequences: Genomic: **NC_000001.9** mRNA and protein: **CCDS 1390.1**

Indications for Test: All patients with LCA and with early onset RP are candidates.

Sensitivity of Test: *CRB1* mutations account for ~ 15 % of patients with LCA (Yzer et al. Invest Ophthalmol Vis Sci 47:1167-1176, 2006), 6.5 % of patients with AR-RP (Bernal et al. J Med Genet 40:e89, 2003) and up to 50% of patients with AR-RP and PPRPE (den Hollander et al. Hum Mutat 24:355-369, 2004).

Turn Around Time: Maximum of 40 calendar days

Specimen Requirement: See page 4 of the Requisition Form

Price: **Sequencing of all coding exons of the *CRB1* gene:** **\$ 1040**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x20	83898	\$ 320	Sequencing x20	83904	\$ 480
Separation x1	83894	\$ 80	Interpretation/Report x1	83912	\$ 90

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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