

Leber Congenital Amaurosis, Type VII via CRX Gene Sequencing Test #665

Brief Description of Disorder: Nonsyndromic Leber Congenital Amaurosis (LCA, OMIM 204000) is a group of severe retinal dystrophies with early onset. The clinical hallmarks are bilateral congenital blindness, a diminished or absent electroretinogram and high hyperopia. Additional symptoms include nystagmus, photophobia, eye poking and sluggish pupils (Cremers et al. Hum Mol Genet 11:1169-1176, 2002). LCA affects 3 per 100,000 newborn babies worldwide and has been described in various ethnic groups. Patients with LCA represent ~ 5 % of all retinal dystrophies (Perrault et al. Mol Gen Metabol 68:200-208, 1999). Genetic abnormalities are the primary cause of LCA. See also the Foundation Fighting Blindness (www.ffb.ca).

Genetics: LCA represents the most common genetic cause of congenital visual impairments in infants and adolescents. It is usually inherited in an autosomal recessive manner, although in several families LCA is transmitted as an autosomal dominant trait (Rivolta et al. Hum Mut 18:488-498, 2001). Sporadic patients with LCA were also reported (Hanein et al. Hum Mut 23:306-317, 2004). LCA is genetically and clinically heterogeneous. Currently, mutations in fourteen (14) genes account for ~70% of all cases (den Hollander et al. Prog Retin Eye Res 27:391-419, 2008). These include the CRX gene. About thirteen different CRX mutations, distributed along the entire coding sequence, have been implicated in LCA. All causative CRX mutations were heterozygous and detected in patients with autosomal dominant or sporadic LCA, except for the R90W substitution. This mutation was reported in one patient from a consanguineous Indian family and showed a classical autosomal recessive pattern (Swaroop et al. Hum Mol Genet 8:299-305, 1999). In addition to LCA, CRX mutations were found in patients with autosomal dominant cone-rod dystrophy (AD-CRD, OMIM 120970); and one novel mutation (c.458delC) was reported in an Italian family with autosomal dominant Retinitis Pigmentosa (AD-RP, OMIM 268000) (Ziviello et al. J Med Genet 42:e47, 2005).

Description of This Particular Test. The CRX protein is a photoreceptor-specific transcription factor involved in the regulation of several photoreceptor specific genes. This test involves bidirectional DNA sequencing of all 3 coding exons and splice sites of the CRX gene. The full coding sequence of each exon plus ~ 50 bp of flanking-coding DNA on either side are sequenced. We will sequence any single exon in family members of patients with known mutation.

Reference Sequences: Genomic: **NC_000019.8** mRNA and protein: **CCDS 12706.1**

Indications for Test: Familial cases with symptoms suggestive of LCA and autosomal dominant inheritance, patients with LCA from consanguineous Indian families and isolated cases of LCA. The CRX gene is also a candidate for patients with AD-CRD and patients with AD-RP.

Sensitivity of Test: This test allows the detection of mutations in approximately 2% of patients with LCA (Dharmaraj et al. Ophthalmic Genet 21:135-150, 2000). Except for the R90W mutation, all CRX mutations are completely penetrant and cause disease in heterozygotes (Rivolta et al. Hum Mut 18:488-498, 2001). PreventionGenetics plans to offer Tests for all genes known to cause LCA, and is committed to add new tests as the remaining LCA genes are discovered.

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 CRX gene:** **\$ 440**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x4	83898	\$ 100	Sequencing x4	83904	\$ 160
Separation x1	83894	\$ 40	Interpretation/Report x1	83912	\$ 70

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

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