CRX Gene Analysis in Cone Rod Dystrophy, Leber Congenital Amaurosis and Retinitis Pigmentosa

Clinical Features:
Cone Rod Dystrophy (CRD) present first as a macular disease or as a diffuse retinopathy with predominance of the macular involvement. The clinical signs of CRDs reflect the predominant involvement of cones, leading to decreased visual acuity in the first decade of life. However, in some cases, diffuse retinopathy affects simultaneously cones and rods, resulting in both night blindness and loss of visual acuity. The visual field testing shows central scotomas, while the periphery is spared. Fundus examination shows pigment deposits and retinal atrophy in the macular region. At a later stage, patients are legally blind, even though large parts of the peripheral visual field remain preserved.

Retinitis Pigmentosa (RP) is a group of diseases involving progressive degeneration of the retina that leads to severe visual impairment in the 5th to 6th decade of life. The disorder usually manifests with decline and loss of night vision during adolescence, followed by loss of side vision in young adulthood, and loss of central vision in later life due to the progressive loss of rod and cone photoreceptors. Common symptoms include night blindness and a decreasing visual field, leading to tunnel vision, legal blindness or, in many cases, complete blindness. Clinical hallmarks are an abnormal fundus with bone-spicule deposits, attenuated retinal vessels, abnormal, diminished, or absent electroretinographic findings.

Leber Congenital Amaurosis (LCA) is a group of congenital inherited diseases of the retina that leads to severe early infantile blindness before the age of 1 year. Clinical findings include sensory nystagmus, amaurotic pupils, and a pigmentary retinopathy. Occasionally patients with LCA may have a normal fundus. Other features include keratoconus, cataracts, ptosis, oculodigital phenomenon, vascular attenuation and disk edema. The ERG (electroretinogram) shows a severely reduced scotopic and photopic responses and a normal ERG excludes a diagnosis of LCA.

Genetics:
CRD, RP, and LCA all have an autosomal dominant inheritance pattern, while some rare LCA cases have an autosomal recessive inheritance pattern.

Test Sensitivity:
CRX represents the most common known gene for adCRD with pathogenic variants accounting for 5%-12% of the cases. CRX pathogenic variants contribute to 2%-3% of autosomal dominant LCA and rare cases of autosomal recessive LCA and less than 1% of adRP.

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:

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2. Rivolta C et al., (2001) Hum. Mutat. 18: 488-498.
3. Freund CL et al., (1997) Cell. 91(4):543-553.
4. Lotery AJ (2000) Arch Ophthalmol. 118(4):538-43.