

## *ABCA4, AIPL1, CRX, GUCY2D, RDS (PRPH2), CNGA3, CNGB3, CERKL, and GUCA1A* Gene Analysis in Cone and Cone–Rod Dystrophies

### **Clinical Features:**

Cone-rod dystrophy (CRD) has an estimated prevalence of 1 in 40,000 individuals. CRD presents 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. The electroretinogram (ERG), is distinguished by a more distinctive reduction of the photopic cone b-wave amplitude than the scotopic rod b-wave amplitude, compared to rod degeneration.

### **Inheritance Pattern/Genetics:**

The mode of inheritance for cone or cone rod dystrophies can be X-linked recessive, autosomal recessive (arCRD) and autosomal dominant (adCRD).

ABCA4-related disorders (ATP-binding cassette, sub-family A (ABC1), member 4 protein): autosomal recessive.

AIPL1-related disorders (aryl hydrocarbon receptor interacting protein-like 1 protein): autosomal recessive for LCA, autosomal dominant for CRD.

GUCY2D-related disorders (guanylate cyclase 2D, membrane protein): autosomal recessive for LCA, autosomal dominant for CRD (adCRD).

CRX-related disorders (cone-rod homeobox protein): autosomal dominant.

PRPH2 (RDS)-related disorders (retinal degeneration, slow protein): autosomal dominant, with incomplete penetrance. Digenic inheritance with the ROM1 gene has been reported in adRP.

GUCA1A-related (guanylate cyclase activator 1A protein): autosomal dominant with variable expressivity.

CNGB3-related disorders (cyclic nucleotide-gated channel, beta 3 protein): autosomal recessive

CNGA3-related disorders (cyclic nucleotide-gated channel, alpha protein): autosomal recessive

CERKL-related disorders (ceramide kinase-like protein): autosomal recessive

## **Test Methods:**

Using genomic DNA from the submitted specimen, sequence is obtained and analyzed for exon 13 of the GUCY2D gene, for the coding sequence and splice site junctions of the RDS (exons 1-3), CRX (exons 2-4), GUCA1A (exons 3-6), and the AIPL1 (exons 1-6), CERKL (exons 1-13), CNGB3 (exons 1-18) and CNGA3 (exons 2-8) genes.

GeneDx also offers a panel including the sequencing of all coding exons of the RDS gene as well as the ABCA4 gene and their splice junctions, which are sequenced using a solid-state sequencing-by-synthesis process that allows sequencing a large number of amplicons in parallel. The presence of any potentially disease-associated sequence variant(s) is confirmed by conventional dideoxy DNA sequence analysis.

Each test can be ordered as a reflex test or separately. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

## **Test Sensitivity:**

### **adCRD**

GUCY2D gene: Pathogenic variants in the GUCY2D gene have been identified in 40% of the patients (11 out of 27) with autosomal dominant cone dystrophy, and all mutations were clustered to codon Arg838, in exon 13.<sup>1</sup>

CRX gene: Pathogenic variants in the CRX gene account for 5-12% of the adCRD cases.<sup>2,3,4,5</sup>

AIPL1 gene: An-in-frame deletion located in the C-terminus of the AIPL1 protein appears to be associated with adCORD and juvenile RP.<sup>6</sup>

PRPH2 (RDS): Pathogenic variants probably account for a small number of cone and cone-rod dystrophy cases, with six RDS gene variants reported in well-documented cases of cone and cone-rod dystrophy.<sup>7</sup>

**GUCA1A gene:** Pathogenic variants in the GUCA1A gene have been identified in approximately 16% of patients diagnosed with either autosomal dominant cone dystrophy or autosomal dominant cone-rod dystrophy.<sup>11,12,13</sup>

## **arCRD**

**ABCA4 gene:** It is estimated that ABCA4 pathogenic variants account for arCORD in 24–75% of patients.<sup>8,9,10</sup>

**CNGB3 gene:** Pathogenic variants in the CNGB3 were identified in 5% of arCD individuals (3 out of 60) who developed a progressive loss of cone function during the first two decades of life.<sup>17</sup> These individuals did not have a congenital nystagmus, but had a progressive deterioration of visual acuity, color vision, and photopic electroretinogram. In the same study only a single heterozygous variant likely disease causing, has been identified in ~3% of the probands.

**CNGA3 gene:** A single heterozygous, likely disease causing has been identified in ~7% (4 out of 60) of individuals diagnosed with progressive cone dystrophy.<sup>17</sup>

**CERKL gene:** Pathogenic variants in this gene have also been reported in approximately 2% of autosomal recessive cone-rod dystrophy in patients who tested negative for ABCA4 variants.<sup>14</sup>

## **References:**

1. Kitiratschky et al., (2008) Invest Ophthalmol Vis Sci 49:5015
2. Hamel CP et al., (2007) Orphanet J Rare Dis (1)2:7
3. Rivolta C et al., (2001) Hum Mutat 18: 488-498
4. Freund CL et al., (1997) Cell. 91(4):543- 553
5. Lotery AJ (2000) Arch Ophthalmol]. 118(4):538-43
6. Sohocki et al., (2000) Mol Genet Metab 70:142–150
7. Boon CJ et al., (2008) Prog Retin Eye Res 27:213-35
8. Allikmets, et al (1998) Gene 215: 111-122
9. Cremers F P M et al., (1998) Hum Molec Genet 7: 355-362
10. Klevering B J et al., (2004) Eur J Hum Genet.12(12):1024-32
11. Downes et al., (2001) Arch Ophthalmol 119:96-105
12. Michaelides et al., (2005) Ophthalmology 112:1442-1447
13. Kitiratschy et al., (2009) Human Mutation 30:E782-E796
14. Littink et al., (2010) 51(11):5943-5951
15. Wissinger et al., (2001) Am J Hum Genet 69:722-737
16. Michaelides et al., (2004) Invest Ophthalmol Vis Sci 45(6):1975-1982
17. Thiadens et al., (2010) Ophthalmology 117(4):825-30