

Cone-Rod Dystrophies Panel

CRD PANEL GENE LIST:

ABCA4, ADAM9, AIPL1, BEST1, C8ORF37, CABP4, CACNA1F, CDH3, CDHR1, CEP290, CERKL, CNGA3, CNGB3, CRX, DRAM2, ELOVL4, GUCA1A, GUCY2D, PAX6, PITPNM3, POC1B, PROM1, PRPH2 (RDS), RAB28, RAX2 (QRX), RDH5, RIMS1, RPGR, RPGRIP1, SEMA4A, TLL5

CLINICAL FEATURES:

Cone-rod dystrophy (CRD) is a group of inherited eye disorders affecting the cone and rod cells, or light sensitive cells, of the retina.¹ As these cells deteriorate, individuals with cone-rod dystrophy experience progressive vision loss.¹ CRD has an estimated prevalence of 1 in 40,000 individuals¹ and is characterized by predominantly cone impairment, later followed by rod involvement.¹ In some cases, the retinopathy affects both cones and rods simultaneously. The clinical signs of CRD reflect the predominant involvement of cones, presenting as decreased visual acuity with or without nystagmus in the first decade of life. Patients also experience progressive central vision loss, photophobia, and color vision abnormalities. When cones and rods are affected, individuals have both night blindness and loss of visual acuity.^{1,8} Later in life, patients become legally blind even though large parts of the peripheral visual field may remain preserved.

Visual field testing shows central scotomas while the periphery is spared. Fundus examination shows pigment deposits and retinal atrophy in the macular region. 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.¹

CRD frequently presents as non-syndromic, but it is also associated with disorders such as Bardet-Biedl syndrome, spinocerebellar ataxia 7, and Jalili syndrome.⁸ Clinical and genetic overlap also exists between CRD and other inherited retinal disorders. At advanced stages, as both cone and rod impairment occurs, diagnosis mimics that of rod-cone dystrophy, or Retinitis Pigmentosa (RP). Moreover, many genes causing CRD also cause RP, Leber congenital amaurosis (LCA) and achromatopsia.

The CRD panel may clarify a clinical diagnosis or identify a genetic diagnosis for CRD or a CRD-related disorder. If a genetic diagnosis is found, genetic testing and recurrence risk information would be available for at-risk family members. In addition, having an identified genetic diagnosis may or may not impact medical management or treatment of the condition.

GENETICS:

Autosomal recessive, autosomal dominant, or X-linked.

TEST METHODS:

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving

coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. 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.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

TEST SENSITIVITY:

According to a recent meta-analysis, autosomal recessive, autosomal dominant, and x-linked CRD make up an estimated 77%, 22%, and 1% of all CRD, respectively.⁹ In addition, ABCA4, GUCY20, and RPGR are the most common causes of AR, AD, and XL CRD, correspondingly. Many causes of CRD have yet to be elucidated, as it is reported that only approximately 25% of CRD are genetically resolved.^{7,9}

AUTOSOMAL RECESSIVE:

ABCA4 gene: It is estimated that ABCA4 variants account for arCRD in 16% of cases.⁹

Reports have been as high as 24–75% in smaller study groups.^{3,4,5}

ADAM9 gene: ADAM9 gene variants are rare, accounting for <1% of arCRD.^{9,10}

C8ORF37 gene: Variants in C8ORF37 are rare, accounting for <1% of arCRD.^{9,12} **CABP4 gene:** CABP4 gene variants are rare, as they have only been identified in a small subset of families with cone-rod synaptic disorder.²⁸

CDH3 gene: Variants in the CDH3 gene cause hypotrichosis with juvenile macular dystrophy, a condition characterized by CRD and sparse hair. Hypotrichosis with juvenile macular dystrophy is rare, as it has only been reported in a small subset of families.^{13,14}

CDHR1 gene: Variants in the CDHR1 gene are rare, accounting for <1% of arCRD.^{9,15} **CEP290 gene:** CEP290 gene variants account for approximately 22% of Leber congenital amaurosis cases and have been reported in individuals with Joubert, Senior-Loken, Meckel, and Bardet-Biedl syndromes.³²

CERKL gene: Variants in this gene are estimated to account for 1% of cases.⁹ Additionally, they have been reported in approximately 2% of autosomal recessive cone-rod dystrophy in patients who tested negative for ABCA4 variants.⁶

CNGA3 gene: CNGA3 variants causing CRD are rare.¹⁶ CNGA3 pathogenic variants are estimated to be the underlying cause of achromatopsia in 36% of patients.⁹

CNGB3 gene: Variants in the CNGB3 were identified in <1% of individuals with arCRD.⁹

CNGB3 pathogenic variants make up about 59% of individuals with achromatopsia.⁹

DRAM2 gene: Variants causing arCRD are rare and have been reported in few families.^{17,18}

POC1B gene: POC1B variants are rare and have been reported in few families.^{19,20}

RAB28 gene: RAB28 variants were identified in <1% of individuals with arCRD.^{9,22}

RDH5 gene: Variants in the RDH5 gene account for an unknown number of individuals with CRD, however, in smaller studies the identification of RDH5 variants in individuals with fundus albipunctatus has ranged from 75% to 100%.^{29,30}

RPGRIP1 gene: Variants in the RPGRIP gene were identified in <1% of individuals with arCRD.⁹

SEMA4A gene: Compound heterozygotic variants in the SEMA4A gene are rare, as they were identified in two individuals with CRD.²³

TLL5 gene: Variants in the TLL5 gene are rare, as they have only been identified in a small subset of families with CRD.^{24,25}

AUTOSOMAL DOMINANT:

AIPL1 gene: Variants were identified in <1% of adCRD cases.⁹ An-in-frame deletion located in the C-terminus of the AIPL1 protein appears to be associated with adCRD and juvenile RP.² The AIPL1 gene variants are often associated with arLCA, accounting for 5% of cases.¹¹ **BEST1 gene:** BEST1 gene variants commonly cause bestrophinopathy and vitelliform macular dystrophy, and have been described in few individuals with MRCS syndrome characterized by, microcornea, rod-cone dystrophy, early-onset cataracts, and posterior staphyloma.³¹

ELOVL4 gene: Variants in the ELOVL4 gene have been associated with Stargardt disease in a small subset of families.³³

GUCY2D gene: Variants in the GUCY2D gene have been identified in approximately 8% of individuals with adCRD.⁹

CRX gene: Variants in the CRX gene account for 4% of adCRD cases.⁹

PAX6 gene: PAX6 gene variants cause a number of diverse ocular manifestations including aniridia, Peters' anomaly, and microphthalmia.³⁴ Many occur with neurological abnormalities.³⁴ **PROM1 gene:** Variants in the PROM1 were identified in about 1% of individuals with adCRD and <1% of individuals with arCRD.^{9,21}

PRPH2 (RDS) gene: Variants account for approximately 2% of adCRD cases.⁹

GUCA1A gene: GUCA1A gene variants have been identified in about 3% of adCRD cases.⁹

PITPNM3 gene: Variants in the PITPNM3 gene have been identified in approximately 1% of adCRD cases.⁹

RAX2 (QRX) gene: Variants in the RAX2 gene are rare, as they have only been identified in a small subset of families with CRD.^{26,27}

RIMS gene: Variants account for <1% of adCRD cases.⁹

X-LINKED:

CACNA1F gene: Variants account for approximately 3% of xICRD cases.⁹

RPGR gene: Variants in the RPGR gene account for approximately 53% of xICRD cases.⁹

Gene	Protein	Inheritance	Disease Associations
ABCA4	ATP-binding cassette, subfamily A, member 4	AR	CRD, RP, Stargardt disease, retinal dystrophy, fundus flavimaculatus
ADAM9	A disintegrin and metalloproteinase domain 9	AR	CRD
AIPL1	Aryl hydrocarbon-interacting receptor protein-like 1	AD/AR	CRD, LCA, juvenile RP
BEST1	Bestrophin 1	AD	Bestrophinopathy, macular dystrophy, MRCS, RP
C8ORF37	Chromosome 8 open reading frame 37	AR	CRD, RP, Bardet-Biedl syndrome
CABP4	Calcium binding protein 4	AR	Cone-rod synaptic disorder
CACNA1F	Calcium channel, voltage-dependent, alpha-1F subunit	XL	CRD, CSNB, Aland Island eye disease

CDH3	Cadherin 3	AR	Hypotrichosis with juvenile macular dystrophy
CDHR1	Cadherin-related family, member 1	AR	CRD, RP
CEP290	Centrosomal protein 290-KD	AR	LCA, Joubert, Meckel, SeniorLoken, and Bardet-Biedl syndromes
CERKL	Ceramide kinase-like	AR	CRD, RP
CNGA3	Cyclic nucleotide-gated channel, alpha-3	AR	CRD, achromatopsia, LCA, cone dystrophy, CSNB
CNGB3	Cyclic nucleotide-gated channel, beta-3	AR	CRD, achromatopsia
CRX	Cone-rod homeoboxcontaining gene	AD	CRD, RP, LCA, macular dystrophy
DRAM2	Damage-regulated autophagy modulator 2	AR	CRD, RP
ELOVL4	Elongation of very long chain fatty acids-like 4	AD	Stargardt disease, spinocerebellar ataxia, ichthyosis
GUCA1A	Guanylate cyclase activator 1A	AD	CRD, cone dystrophy
GUCY2D	Guanylate cyclase 2D, membrane	AD/AR	CRD, LCA, RP
PAX6	Paired box gene 6	AD	Peters anomaly, aniridia, glaucoma, cataracts, microphthalmia, keratitis, neurologic abnormalities
PITPNM3	Phosphatidylinositol transfer protein, membraneassociated, 3	AD	CRD
POC1B	Centriolar protein chlamydomonas, B	AR	CRD
PROM1	Prominin 1	AR	CRD, RP, Stargardt disease
PRPH2 (RDS)	Peripherin 2	AD/AR	CRD, RP, LCA, Stargardt disease, cone dystrophy, other retinal dystrophies
RAB28	Ras-associated protein 28	AR	CRD
RAX2 (QRX)	Retina and anterior neural fold homeobox 2	AD	CRD
RDH5	Retinol dehydrogenase 5	AR	Fundus albipunctatus
RIMS1	Protein regulating synaptic membrane exocytosis 1	AD	CRD

<i>RPGR</i>	Retinitis pigmentosa GTPase regulator	XL	CRD, RP
<i>RPGRIP1</i>	Retinitis pigmentosa GTPase regulator- interacting protein	AR	CRD, LGA
<i>SEMA4A</i>	Semaphorin 4A	AR/AD	CRD, RP
<i>TTL5</i>	Tubulin tyrosine ligase-like family, member 5	AR	CRD, RP

REFERENCES:

- Hamel CP et al., (2007) Orphanet J Rare Dis (1)2:7
- Sohocki et al., (2000) Mol Genet Metab 70:142-150
- Allikmets, et al (1998) Gene 215: 111-122
- Cremers F P M et al., (1998) Hum Molec Genet 7: 355-362
- Klevering B J et al., (2004) Eur J Hum Genet.12(12):1024-32
- Littink et al., (2010) 51(11):5943-5951
- Thaidens et al., (2012) Ophthalmology 119(4): 819-26
- Boulanger-Scemama et al., (2015) Orphanet J Rare Dis 10: 85
- Roosing S et al., (2014) Prog Retin Eye Res 42:1-26
- El-Haig WM et al., (2014) Br J Ophthalmol 98(12): 1718-23
- Aboshiha et al., (2015) Ophthalmology 122:862-864
- Rahner et al., (2016) Ophthalmic Genet 37(3): 294-300
- Khan and Bolz (2016) Ophthalmic Genet 37(3): 301-6
- Sprecher et al., (2001) Nature Genet 29: 134-136
- Nikopoulos K (2015) Sci Rep 5:13902
- Shaikh RS (2015) Eur J Hum Genet 23(4): 473-80
- El-Asrag ME (2015) Am J Hum Genet 96(6): 948-54
- Sergouniotis PI et al., (2015) Invest Ophthalmol Vis Sci 56(13): 8083-90
- Roosing S et al., (2014) Am J Hum Genet 95(2): 131-42
- Durlu YK et al., (2014) JAMA Ophthalmol 132(10) 1185-91
- Beryozkin A (2014) Invest Ophthalmol Vis Sci 52(2): 1149-60
- Riveiro-Alvarez (2015) JAMA Ophthalmol 133(2):133-9
- Abid et al., (2006) J Med Genet 43:378-381
- Sergouniotis (2014) Am J Hum Genet 94(5): 760-9
- Bendoni et al., (2016) 25(20): 4546-4555
- Wang et al., (2004) Hum Mol Genet 13(10): 1025-40
- Yang et al., (2015) JAMA Ophthalmol 133(6):653-61
- Khan et al. (2013) Br J Ophthalmol 97 (3):262-5
- Nakamura et al., (2000) Invest Ophthalmol Vis Sci 41(12):3925-32
- Nakamura et al. (2003) Doc Ophthalmol 107(1):3-11
- Boon et al. (2009) Progress In Retinal And Eye Research 28 (3):187-205
- Perrault et al. (2007) Human Mutation 28 (4):416
- Bernstein et al. (2001) Investigative Ophthalmology & Visual Science 42 (13):3331-6
- Dansault et al. (2007) Molecular Vision 13 :511-23