

GUCY2D Gene Analysis in 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:

Autosomal dominant (CRD), Autosomal Recessive (LCA)

Test Sensitivity:

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 (Kitiratschky et al., 2008).

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 were 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:

1. Kitiratschky et al., (2008) Invest Ophthalmol Vis Sci 49:5015
2. Wissinger et al., (2001) Am J Hum Genet 69:722-737
3. Michaelides et al., (2004) Invest Ophthalmol Vis Sci 45(6):1975-1982