Achromatopsia, Cone, and Cone-rod Dystrophy: Sequencing Panel

Condition Description

Complete achromatopsia, or rod monochromatism, is an autosomal recessive disease affecting cone function that is characterized by intense photophobia, deficient cone-mediated electroretinogram, reduced visual acuity, a normal or near normal fundus appearance, pendular nystagmus, and impaired color discrimination for all cone classes. Temporal optic atrophy, a slight macular retinal pigment epithelial disturbance, may also be seen on fundus exam. Pathogenic variants in five different genes have been identified as causing achromatopsia (CNGB3, CNGA3, GNAT2, PDE6C, and PDE6H). Thus far, most pathogenic variants have been identified in the CNGB3 and CNGA3 genes.

Cone dystrophies are diagnosed by an abnormal or nonrecordable photopic ERG and a normal scotopic ERG, while peripheral visual fields remain normal. All three inheritance patterns, autosomal dominant, autosomal recessive, and X-linked, have been found in the cone degenerations. Symptoms of cone dysfunction include loss of visual acuity, photophobia (light intolerance), and progressive color vision loss. Retinal pigment epithelial loss and pigment deposition may be seen in later stages. Mild to severe temporal optic atrophy, bull's eye maculopathy with or without tapetal reflexes or macular atrophy may be seen.

Cone-rod dystrophy (CORD) is characterized by an initial loss of color vision and visual acuity, followed by nyctalopia (night blindness) and loss of peripheral visual fields. In extreme cases, these progressive symptoms are accompanied by widespread, advancing retinal pigmentation and chorioretinal atrophy of the central and peripheral retina.

These conditions can have overlapping clinical presentations. Please note, the RAB28 gene is not included on the NGS panel at this time due to the presence of at least 2 pseudogenes. For clinicians that would like RAB28 analysis if all other genes test negative, we request consultation with EGL directly.

References:
- OMIM
- GeneReviews

Genes

ABCA4, ADAM9, AIPL1, BEST1, C8orf37, C8PBP4, CACNA1F, CACNA2D4, CDHR1, CEP290, CERKL, CNGA3, CNGA3, CNNM4, CRX, GNAT2, GUCA1A, GUCA1B, GUCY2D, KCNV2, PAX6, PDE6C, PDE6H, PITPNM3, PROM1, PRPH2, RAX2, RBP4, RDS2, RGS9, RGS9BP1, RIMS1, RPGR, RPGRIP1, SEMA4A, UNC119

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of achromatopsia, cone, and cone-rod dystrophy.
- Carrier testing in adults with a family history of achromatopsia, cone, and cone-rod dystrophy.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

Clinical Sensitivity: Unknown. Pathogenic variants in the promoter region, some pathogenic variants in the introns and other regulatory element pathogenic variants cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%.

Specimen Requirements

Submit only 1 of the following specimen types

Type: Whole Blood
Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Ship sample at room temperature with overnight delivery.

**Type: Isolated DNA**

Specimen Requirements:

In microtainer: 60 ug

Isolation using the Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping: Refrigerate until time of shipment in 100 ng/ul of TE buffer. Ship sample at room temperature with overnight delivery.

**Special Instructions**

Please include fundus photographs, electroretinogram (ERG) findings, visual field findings, and visual acuity, if available, for expert review and clinical correlation with test results.

**Related Tests**

- Eye Disorders: Comprehensive Sequencing and Deletion/Duplication Panels.
- Achromatopsia, Cone, and Cone-rod Dystrophy: Deletion/Duplication Panel.