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

**Test Code:** MM131  
**Turnaround time:** 6 weeks  
**CPT Codes:** 81404 x1, 81406 x1, 81408 x1

### Condition Description

Complete achromatopsia, or rod monochromatism, is an autosomal recessive disease affecting cone function that is characterized by intense photophobia, deficient cone-mediated electrotetroretinogram, 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 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

- **ABC4, ADAM9, AIPL1, BEST1, C8orf37, C8orf37, CACNA1F, CACNA2D4, CDHR1, CEP290, CERKL, CNGA3, CNGB3, CNNM4, CRX, GNAT2, GUCA1A, GUCA1B, GUCA1D, KCNV2, PAX6, PDE6C, PDE6H, PITPNM3, PROM1, PRPH2, RAXX, RBP4, RBM6, RGS6, RGS9B1, RIMS1, RPR2, RPRGRIP1, 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.

**Copy Number Analysis:** Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

### 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. Results of molecular analysis should be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

**Copy Number Analysis:** The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least
3 exons. Smaller (<500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

## Specimen Requirements

**Submit only 1 of the following specimen types**

### Type: Saliva

**Specimen Requirements:**
- Oragene™ Saliva Collection Kit
  - Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**
- Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

### Type: Whole Blood (EDTA)

**Specimen Requirements:**
- EDTA (Purple Top)
  - Infants and Young Children (2 years of age to 10 years old): 3-5 ml
  - Older Children & Adults: 5-10 ml
  - Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
- Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

### Type: DNA, Isolated

**Specimen Requirements:**
- Microtainer
  - 8µg
  - Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
- Refrigerate until time of shipment in 100 ng/µL in 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.