Eye Disorders Comprehensive Panel: Sequencing and CNV Analysis

**Test Code:** MM030  
**Turnaround time:** 6 weeks  
**CPT Codes:** 81401 x1, 81404 x1, 81406 x1, 81479 x1

### Condition Description

The Eye Disorder Comprehensive Sequencing Panel is an analysis of almost all clinically relevant genes identified as causing syndromic and non-syndromic inherited retinal and choroidal dystrophies, as well as ocular developmental disorders. There is a wide range of genetic and phenotypic heterogeneity in retinal and choroidal disorders making accurate clinical diagnosis difficult especially during early phases of the disease onset.

Retinal disorders can be congenital and present at birth (as in Leber congenital amaurosis), present in early childhood (as in early onset retinitis pigmentosa), or present in mid life (as in pattern dystrophy). The clinical features of retinal disorders include vision loss, vision distortion, loss of peripheral vision, and night blindness. Fundus exam findings can range from almost normal appearance of the retina (as in Leber congenital amaurosis) to pale optic nerve, narrowed arterioles, bone spicules, photoreceptor loss, retinal pigment epithelial changes, and chorioretinal atrophy. The fundus appearance in the end stage of many retinal disorders, such as pattern dystrophy and cone-rod dystrophy, may be similar to that of macular dystrophy or chorioretinal atrophy. Electroretinogram (ERG) findings can range from non-recordable ERG to loss of rod or cone responses and be non-specific. Rarely, characteristic findings in ERG as in congenital stationary night blindness may help in arriving at a more accurate diagnosis. Detailed history and clinical examination, optical coherence tomography (OCT), pattern of visual field loss and ERG may help narrow the selection of disease causing genes or groups of genes.

Some genes on this panel are available as single gene tests or as part of a more clinically specific eye disorders sub-panel (e.g. retinitis pigmentosa). As the distinction between disorders is difficult, the Eye Disorder Comprehensive Sequencing Panel may be ordered as a comprehensive test. Please note that some genes may cause more than one phenotype. In addition to the nuclear genes analyzed, seven targeted mitochondrial DNA mutations are also assessed.

General categorical overview of the eye disorders included on the panel:

- Achromatopsia
- Albinism
- Bardet Biedl Syndrome
- Bradyopsia
- Chorioderemia
- Cone and Cone-rod Dystrophy: 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 the EGL directly.
- Congenital Stationary Night Blindness: Please note, the GRK1 gene is not included on the NGS panel at this time as this gene is only partially annotated in GRCh37. GRK1 will be re-evaluated with the release of GRCh38.
- Flecked Retina Disorders
- Isolated Aniridia
- Joubert Syndrome
- Leber Congenital Amaurosis: Please note, the NMNAT1 gene is not included in the NGS panel at this time due to presence of at least 4 pseudogenes. For clinicians that would like NMNAT1 analysis if all other genes test negative, we request that you contact the EGL directly.
- Leber hereditary optic neuropathy (LHON)
- Microphthalmia, Anterior Segment Dysgenesis, and Related Anomalies
- Neuronal Ceroid-Lipofuscinoses
- Optic Atrophy
- Photoreceptor Dystrophy
- Primary Open Angle Glaucoma
- Retinopathy
- Retinitis pigmentosa and ataxia (NARP)
- Retinitis pigmentosa, AD, AR and X-linked
- Retinoschisis
- Senior Loken Syndrome
- Stargardt's Disease and Macular Dystrophy
- Stickler Syndrome
- Usher Syndrome
- Vitreoretinopathy

Disclaimer: Ordering this panel may result in the identification of a genetic change that predisposes an individual to systemic disorders in addition to eye/retinal disorders. Genetic counseling by qualified genetic counselor or medical geneticist is strongly recommended before ordering any genetic test. Ordering physicians can call EGL Genetics at 470-378-2200 or 855 831-7447 to speak with a laboratory genetic counselor.

References:

- OMIM.
- GeneReviews.
- Emory and Rimoin's Principles and Practice of Medical Genetics, 5th Edition.

### Genes

ABCA4, ABHD12, ADAM9, ADGRV1, AH1, AIPL1, ALMS1, ARL13B, ARL6, ATP13A2, B3GLCT, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7.

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Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to understand the 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 15µg of DNA. Single and multi-exon deletions and duplications are expected to be below the detection limit of this analysis.

Copy Number Analysis: Next generation sequencing (NGS) is used 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 regulatory elements in the region. 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.

Clinical Sensitivity: Unknown. Pathogenic variants in the promoter region, some pathogenic variants in the introns and other regulatory elements may 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 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.

Seven targeted mtDNA pathogenic variants:
- Leber Hereditary Optic Neuropathy (LHON)
  Four pathogenic variants (that account for 90% of cases of LHON) will be detected by this assay: 3460G>A, 14459G>A, & 14484T>C.
- Retinitis Pigmentosa and Ataxia (NARP)
  Two pathogenic variants (that account for 50% of cases of NARP) will be detected by this assay: 8993T>G and 8993T>C.
- Chronic Progressive External Ophthalmoplegia (CPEO)
  One pathogenic variant will be detected by this assay: 3243A>G.

Note: These mtDNA variants will be detected down to approximately 15-20% heteroplasmy.

Specimen Requirements:

Submit only 1 of the following specimen types:

Type: DNA, Isolated

Specimen Requirements:
- Microtainer: 1.0µg
- Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

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

**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.

**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**
- Achromatopsia, Cone, and Cone-rod Dystrophy: Sequencing and Deletion/Duplication Panels.
- Bardet-Biedl Syndrome: Sequencing and Deletion/Duplication Panels.
- Congenital Stationary Night Blindness: Sequencing and Deletion/Duplication Panels.
- Flecked-retina Disorders: Sequencing and Deletion/Duplication Panels.
- Albinism: Sequencing and Deletion/Duplication Panels.
- Joubert Syndrome: Sequencing Panel.
- Macular Dystrophy, Degeneration, Stargardt Disease: Sequencing and Deletion/Duplication Panels.
- Anophthalmia/Microphthalmia/Anterior Segment Dysgenesis/Anomaly: Sequencing Panel.
- Neuronal Ceroid-Lipofuscinoses: Sequencing Panel.
- Retinitis Pigmentosa: Sequencing and Deletion/Duplication Panels.
- Optic Atrophy: Sequencing and Deletion/Duplication Panels.
- Retina/Photoreceptor Dystrophy: Sequencing and Deletion/Duplication Panels.
- Senior-Loken Syndrome: Sequencing and Deletion/Duplication Panels.
- Stickler Syndrome: Sequencing Panel.
- Usher Syndrome: Sequencing Panel.
- Vitreoretinopathy: Sequencing and Deletion/Duplication Panels.
- Eye Disorders: Deletion/Duplication Panel.