Neuronal Ceroid-Lipofuscinoses Panel: Sequencing and CNV Analysis

Condition Description

As a group, the neuronal ceroid-lipofuscinoses (NCL and also known as Batten disease) are progressive autosomal recessive lysosomal storage disorders causing neurodegenerative disease. The clinical spectrum is characterized by vision loss, seizures, cognitive decline, motor decline, and early demise. The clinical spectrum can be divided into the following phenotypes based on age of onset and symptom presentation: infantile; late-infantile; juvenile; adult; and Northern epilepsy. Both genetic and allelic heterogeneity exist and current classifications are made using the gene and age at symptom presentation. The classic late infantile and juvenile forms are more common. The classic late infantile form (CLN2 disease) presents between two and four years of age with seizures and ataxia followed by cognitive and motor decline. Vision also deteriorates and a tapetoretinal degeneration eventually causes blindness. The clinical course typically results in a life expectancy from six years to adolescence. In the classic juvenile form (CLN3 disease), the first clinical sign, typically evident between four and ten years of age, is retinitis pigmentosa resulting in decreased central vision and complete blindness eventually follows. Cognitive decline is apparent usually by age ten and insomnia is common with seizures following in subsequent years. Additionally, speech disturbances, a Parkinsonian-like gate, depression, agitation and hallucinations are some of the common clinical features. Worsening seizures are evident with disease progression and individuals may survive into their 30s.

Please note that the DNAJC5 gene, identified in adult onset autosomal dominant NCL, is not included in this NGS panel due to the presence of at least one pseudogene. For clinicians that suspect autosomal dominant NCL and would like DNAJC5 analysis in the event that all other genes test negative, we request that you contact the EGL directly.


References:

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

Genes

ATP13A2, CLN3, CLN5, CLN6, CLN8, CTSD, GRN, KCTD7, MFSD8, PPT1, TPP1

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of NCL.
- Carrier testing in adults with a family history of NCL.

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

Sequencing

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 and depth of coverage.
context, size of exon(s) involved and depth of coverage.

### Specimen Requirements

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

#### 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: Saliva

**Specimen Requirements:**
- Oragene™ Saliva Collection Kit
- Oragene™ 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: 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 Disorder: Comprehensive Sequencing and Deletion/Duplication Panels
- Neuronal Ceroid-Lipofuscinoses: Deletion/Duplication Panel