

Ciliopathies Panel: Sequencing and CNV Analysis

Test Code: MCIL1

Turnaround time: 6 weeks

CPT Codes: 81404 x1, 81406 x1, 81405 x1

Condition Description

The ciliopathies are a group of disorders caused by mutations in genes that encode proteins involved in the formation and function of cilia. Cilia are microtubule-based, hair-like cytoplasmic extensions that extend from the cell surface. The cilium is a highly conserved organelle that is structurally complex with approximately 1000 different recognized polypeptides.

Cilia can be classified as either motile cilia or primary cilia (often called sensory cilia). Motile cilia, sometimes referred to as flagella, are typically found on epithelia cells that line the brain ventricles, oviducts, and respiratory tract. They can appear in bundles of 200-300 and can create movement of the extracellular fluid. Primary cilia are found on the surface of almost all cell types. They sense a wide variety of extracellular signals and transmit them to the interior of the cell. They are critical for developmental and physiological functions. Recent research suggests that motile cilia can be chemosensory as well.

Cilia are a component of almost all cells, so defects in the cilia can lead to conditions that have features involving multiple organ systems, such as renal disease, cerebral anomalies, and retinal degeneration. Additional features include diabetes, skeletal dysplasia, obesity, and congenital fibrocystic diseases of the pancreas and liver; however, the specific phenotype depends on the specific cilia involved.

Diseases tested by the panel include primary ciliary dyskinesia, nephronophthisis, Senior-Loken syndrome, Leber congenital amaurosis, Meckel-Gruber syndrome, Joubert and related syndromes, Bardet-Biedl syndrome, and many others. Please refer to the below list for all genes on the ciliopathies panel.

References:

- Ferkol and Leigh, (2011), *J Pediatr*, 160:366-371.
- Hildebrandt *et al.*, (2011), *New Engl J Med*, 364:1533-1543.
- Ware *et al.*, (2011), *Proc Am Thorac Soc*, 8:444-450.
- Waters and Beales, (2011), *Pediatr Nephrol*, 26:1039-1056.

Genes

[ACVR2B](#), [ADGRV1](#), [AHI1](#), [AIPL1](#), [ARL13B](#), [ARL6](#), [ATXN10](#), [B9D1](#), [B9D2](#), [BBS1](#), [BBS10](#), [BBS12](#), [BBS2](#), [BBS4](#), [BBS5](#), [BBS7](#), [BBS9](#), [CC2D2A](#), [CCDC28B](#), [CCDC39](#), [CCDC40](#), [CDH23](#), [CEP164](#), [CEP290](#), [CEP41](#), [CFTR](#), [CLRN1](#), [CPLANE1](#), [CRB1](#), [CRELD1](#), [CRX](#), [DNAAF1](#), [DNAAF2](#), [DNAAF3](#), [DNAH11](#), [DNAH5](#), [DNAI1](#), [DNAI2](#), [DNAL1](#), [DYNC2H1](#), [EVC](#), [EVC2](#), [FOXH1](#), [GDF1](#), [GLIS2](#), [GUCY2D](#), [HYLS1](#), [IFT43](#), [IFT80](#), [IMPDH1](#), [INVS](#), [IQCB1](#), [KCNJ13](#), [KIF7](#), [LCA5](#), [LEFTY2](#), [LRAT](#), [MKKS](#), [MKS1](#), [MYO7A](#), [NEK1](#), [NEK8](#), [NKX2-5](#), [NME8](#), [NODAL](#), [NPHP1](#), [NPHP3](#), [NPHP4](#), [OFD1](#), [PCARE](#), [PCDH15](#), [PKD2](#), [PKHD1](#), [RD3](#), [RDH12](#), [RPE65](#), [RPGR](#), [RPGRIP1](#), [RPGRIP1L](#), [RSPH4A](#), [RSPH9](#), [SCNN1A](#), [SCNN1B](#), [SCNN1G](#), [SDCCAG8](#), [SPATA7](#), [TCTN1](#), [TCTN2](#), [TMEM138](#), [TMEM216](#), [TMEM231](#), [TMEM237](#), [TMEM67](#), [TOPORS](#), [TRIM32](#), [TSC1](#), [TSC2](#), [TTC21B](#), [TTC8](#), [TULP1](#), [UMOD](#), [USH1C](#), [USH1G](#), [USH2A](#), [VHL](#), [WDPCE](#), [WDR19](#), [WDR35](#), [WHRN](#), [XPNPEP3](#), [ZIC3](#), [ZNF423](#)

Indications

This test is indicated for:

- Individuals with a suspected ciliopathy.

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

Next Generation Sequencing: Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/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: DNA, Isolated

Specimen Requirements:

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ 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.

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: 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.

Related Tests

- Individual gene sequencing and deletion/duplication analysis is available for some genes on this panel.
- A comprehensive Eye Disorders Panel is also available.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Ciliopathies: Deletion/Duplication Panel.