Joubert Syndrome: Sequencing Panel

**Test Code:** MM136  
**Turnaround time:** 6 weeks  
**CPT Codes:** 81406 x1

### Condition Description

Joubert syndrome (JS) is an autosomal recessive multisystem disease characterized by cerebellar vermis hypoplasia with prominent superior cerebellar peduncles (resulting in the 'molar tooth sign', or MTS, on axial MRI), intellectual disability, hypotonia, irregular breathing pattern, and eye movement abnormalities. Some individuals with JS have retinal dystrophy and/or progressive renal failure characterized as nephronophthisis. The disorder in such patients is referred to as cerebellooculorenal syndrome, or CORS. Individuals with a mild form of JS have been shown to have a homozygous deletion of the NPHP1 gene identical, by mapping, to that in subjects with nephronophthisis alone. Please note, the CEP164 gene is not included in the NGS panel at this time due to presence of at least one pseudogene. For clinicians that would like CEP164 analysis in the event that all other genes test negative, we request that you contact EGL directly. Please note, the TMEM138 and TMEM231 genes are not included on the NGS panel at this time as these genes are only partially annotated in hg19. TMEM138 and TMEM231 will be re-evaluated with the release of hg20.

### References:
- OMIM  
- GeneReviews

### Genes

AH1, ARL13B, CC2D2A, CEP290, CEP41, CPLANE1, KIF7, NPHP1, QFD1, RPGRIP1L, TCTN1, TCTN2, TCTN3, TMEM216, TMEM237, TMEM67, TTC21B, ZNF423

### Indications

This test is indicated for:  
- Confirmation of a clinical diagnosis of Joubert syndrome.  
- Carrier testing in adults with a family history of Joubert syndrome.

### 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

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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: 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: 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**

- Eye Disorders: Comprehensive Sequencing and Deletion/Duplication Panels
- Joubert Syndrome: Deletion/Duplication Panel