CNTNAP2-related Disorders: CNTNAP2 Gene Deletion/Duplication

**Condition Description**

**Pitt-Hopkins-Like Syndrome-1**
Pitt-Hopkins-like syndrome-1 and Pitt-Hopkins-like syndrome-2 are inherited in an autosomal recessive manner and are caused by mutations in the genes CNTNAP2 (7q35) and NRXN1 (2p16.3) respectively. Both of these conditions resemble Pitt-Hopkins syndrome, caused by mutation of the TCF4 gene, with regard to the distinctive facial features, severe intellectual disability and breathing abnormalities; however, there is a phenotypical difference. While speech is severely impaired, individuals with mutation the CNTNAP2 or NRXN1 gene have normal or mildly delayed motor milestones.

Please note that this test is for the CNTNAP2 gene only.

**Cortical Dysplasia-Focal Epilepsy Syndrome**

In Old Order Amish children, Strauss et al. (2006) identified a homozygous mutation of the CNTNAP2 gene (7q35-q36) that causes focal epilepsy, cortical dysplasia, reduced deep-tendon reflexes, and relative macrocephaly. The focal seizures begin in early childhood and do not respond to therapy. After the onset of seizures, language regression, hyperactivity, intellectual disability, and impulsive and aggressive behavior are observed.

For patients with suspected CNTNAP2-related disorders, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**References:**

- OMIM #604569: CNTNAP2 gene
- OMIM #610042: Cortical Dysplasia-Focal Epilepsy syndrome
- OMIM #610954: PTHS

**Genes**

**CNTNAP2**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of CNTNAP2-related disorders in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of CNTNAP2-related disorders in whom sequence analysis was negative.

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:
In EDTA (purple top) or ACD (yellow top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequence analysis of the CNTNAP2 gene is available and is required before deletion/duplication analysis.
- Sequencing and deletion/duplication analysis of the TCF4 and NRXN1 gene are available.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90+ genes.