**Condition Description**

Pitt-Hopkins syndrome (PTHS) is characterized by severe intellectual disability, speech delays, and developmental delays. Additional variable anomalies include distinctive facial features, such as a beaked nose and wide mouth with cupid's-bow-shaped upper lip, intermittent hyperventilation followed by apnea, microcephaly, seizures, ataxic gait, and a happy personality. The features of PTHS overlap with Angelman syndrome and Rett syndrome and PTHS should be considered in the differential diagnosis of severe intellectual disability. Heterozygous mutations or deletions in the TCF4 gene (18q21.2) cause autosomal dominant PTHS. The mutation spectrum in patients with TCF4 mutations consists of 40% point mutations, 30% small deletions/insertions and 30% deletions. The majority of mutations in TCF4 are de novo.

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 PTHS 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 mutations in the CNTNAP2 or NRXN1 gene have normal or mildly delayed motor milestones.

Please note that this test is for the TCF4 gene only.

For patients with suspected Pitt-Hopkins syndrome, 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 #602272: TCF4 gene
- OMIM #610954: PTHS

**Genes**

TCF4

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of Pitt-Hopkins syndrome in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of Pitt-Hopkins syndrome 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) 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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Sequence analysis of the TCF4 gene is available and is required before deletion/duplication analysis.
- Sequencing and deletion/duplication analysis of the CNTNAP2 and NRXN1 genes 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.