**Pitt-Hopkins Syndrome: TCF4 Gene Sequencing**

**Test Code:** STCF4  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81479 x1

### 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.  
- Carrier testing in adults with a family history of Pitt-Hopkins 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.

### Detection

**Clinical Sensitivity:** Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not 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:** ~99%

### 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

Disclaimer: This information is confidential and subject to change without notice. It may not be reproduced in whole or part unless authorized in writing by an authorized EGL representative.
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.

**Related Tests**

- Deletion/duplication analysis of the *TCF4* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- 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.