Pitt-Hopkins-like Syndrome-2: \textit{NRXN1} Gene Sequencing

\textbf{Test Code: SNRXN}
\textbf{Turnaround time: 4 weeks}
\textbf{CPT Codes: 81479 x1}

\section*{Condition Description}

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 \textit{CNTNAP2} (7q35) and \textit{NRXN1} (2p16.3) genes respectively. Both of these conditions resemble Pitt-Hopkins syndrome, caused by mutation of the \textit{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 \textit{CNTNAP2} or \textit{NRXN1} gene have normal or mildly delayed motor milestones.

Please note that this test is for the \textit{NRXN1} gene only.

For patients with suspected Pitt-Hopkins-like syndrome-2, 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.

\section*{References:}

- OMIM \#600565: \textit{NRXN1} gene
- OMIM \#610954: PTHS

\section*{Indications}

This test is indicated for:

- \begin{itemize}
  
  \item Confirmation of a clinical diagnosis of Pitt-Hopkins-like syndrome-2.
  \item Carrier testing in adults with a family history of Pitt-Hopkins-like syndrome-2.
  \end{itemize}

\section*{Methodology}

\textbf{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.

\section*{Detection}

\textbf{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.

\textbf{Analytical Sensitivity: \~99\%}

\section*{Specimen Requirements}

\textbf{Submit only 1 of the following specimen types}

\textbf{Type: DNA, Isolated}

\textbf{Specimen Requirements:}

\begin{itemize}
  
  \item Microtainer
  \item 8\textmu g
  \end{itemize}

Isolation using the Perkin ElmerChemagenChemagen Automated Extraction method or Qiagen\textsuperscript{TM} Puregene kit for DNA extraction is recommended.

\textbf{Specimen Collection and Shipping:}

Refrigerate until time of shipment in 100 ng/\textmu L in TE buffer. Ship sample at room temperature with overnight delivery.

\textbf{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 24 hours of collection. Do not refrigerate or freeze.

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.

Related Tests
- Deletion/duplication analysis of the NRXN1 gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Sequencing and deletion/duplication analysis of the CNTNAP2 and TCF4 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.