Congenital Hypothyroidism: \textit{FOXE1} Gene Sequencing

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

\textbf{Condition Description}

Congenital hypothyroidism occurs when the thyroid gland fails to develop or function properly. In 80-85\% of cases, the thyroid gland is absent (agenesis), ectopically located, and/or severely reduced in size (hypoplasia) [1]. In the remaining cases, a normal-sized or enlarged thyroid gland is present, but production of thyroid hormones is decreased or absent. If treatment begins in the first month after birth, infants usually develop normally. When thyroid hormone therapy is not initiated within the first two months of life, however, congenital hypothyroidism can cause severe neurologic, mental, and motor damage (cretinism). In the United States and many other countries, all newborns are tested for congenital hypothyroidism.

Mutations in the \textit{FOXE1} (9q22) gene have been associated with Bamforth Lazarus syndrome (BLS). In addition to congenital hypothyroidism, other characteristics of BLS can include bilateral choanal atresia, cleft palate, bifid epiglottis, and spiky or curly hair. Hypothyroidism can be due to athyreosis or a nonfunctional eutopic thyroid. Sequencing of the \textit{FOXE1} gene is recommended after a biochemical diagnosis of congenital hypothyroidism that presents with the characteristics listed above. It can be used to confirm the presence of mutations in a proband, identify carriers among the proband’s relatives, and provide prenatal diagnosis in families with known mutations.

Please \textbf{click here} for the OMIM summary on this condition.

\textbf{Genes}

\textit{FOXE1}

\textbf{Indications}

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of congenital hypothyroidism presenting with choanal atresia, cleft palate, and spiky hair.

\textbf{Methodology}

PCR amplification of the one exon contained in the \textit{FOXE1} gene is performed on the patient’s genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions using automated fluorescence dideoxy sequencing methods. The patient’s gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

\textbf{Detection}

\textbf{Clinical Sensitivity:}

- 4/4 alleles identified in brothers  
- 4/4 alleles identified in siblings  
- 2/2 alleles identified in a female (See OMIM 602617)

\textbf{Analytical Sensitivity: \sim 99\%. Results of molecular analysis should be interpreted in the context of the patient’s biochemical phenotype.}

\textbf{Specimen Requirements}

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

\textbf{Type: DNA, Isolated}

\textbf{Specimen Requirements:}

- Microtainer 8µg  
- Isolation using the PerkinElmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

\textbf{Specimen Collection and Shipping:}

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

\textbf{Type: Saliva}

\textbf{Specimen Requirements:}

- Oragene™ Saliva Collection Kit  
- 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: 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.

**Special Instructions**

Please submit copies of diagnostic biochemical test results along with the sample. Contact the laboratory if further information is needed.

**Related Tests**

- **Known Mutation Analysis (KM)** is available to family members if mutations are identified by sequencing.
- Prenatal Custom Diagnostics is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.