Congenital Hypothyroidism: \textit{PAX8} Gene Sequencing

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

### 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) \cite{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. However, if thyroid hormone therapy is not initiated within the first two months of life, congenital hypothyroidism can cause severe neurological, mental, and motor damage (cretinism). In the United States and many other countries, all newborns are tested for congenital hypothyroidism.

Studies have shown that 2\% of congenital hypothyroidism patients with thyroid dysgenesis have a positive familial history \cite{2}. A segregation analysis led to the conclusion that thyroid developmental abnormalities are compatible with an autosomal dominant mode of inheritance with a low penetrance \cite{3}. Mutations in many genes are known to cause congenital hypothyroidism. Multiple affected individuals have been shown to be heterozygous for mutations in the Paired Box Gene 8 (\textit{PAX8} 2q12-q14), including individuals with positive family histories \cite{4-8}.

**References:**

### Genes

\textit{PAX8}

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of congenital hypothyroidism.

### Methodology

PCR amplification of 11 exons contained in the \textit{PAX8} 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.

### Detection

Clinical Sensitivity: unknown. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions will not be detected by this analysis.

Analytical Sensitivity: \( \sim 99\% \). Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

### Specimen Requirements

**Submit only 1 of the following specimen types**

**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

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Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
- 8µg

Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**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.

**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.