Congenital Hypothyroidism: PAX8 and FOXE1 Gene Sequencing Panel

**Test Code:** PJ  
**Turnaround time:** 6 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). 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.

Studies have shown that 2% of congenital hypothyroidism patients with thyroid dysgenesis have a positive familial history. A segregation analysis led to the conclusion that thyroid developmental abnormalities are compatible with an autosomal dominant mode of inheritance with a low penetrance. 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 (PAX8 2q12-q14), including individuals with positive family histories.

Mutations in the FOXE1 (9q22) gene have also been associated with congenital hypothyroidism, and 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 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.

### Genes

FOXE1, 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 PAX8 gene and the one exon of the FOXE1 gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then 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. Large deletions are not detected by this analysis.

### 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 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) 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

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

Related Tests

- Sequencing of the \textit{PAX8} gene (KF) and the \textit{FOXE1} gene (JQ) are available as individual tests.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by sequencing.
- Prenatal testing 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.