CFC1 gene encodes the Cripto, FRL-1, cryptic family 1 protein, a member of the EGF-CFC family. Proteins in this family share a variant EGF-like motif, a conserved cysteine-rich domain and a C-terminal hydrophobic region. They are involved in signalling during embryonic development. CFC1 is necessary for patterning the left-right embryonic axis. CFC1 gene contains 6 coding exons and spans over 6.7 kb, and has been mapped to chromosome 2q21.1. Alternative spliced transcripts encoding multiple isoforms have been observed for this gene. Mutations in this gene are associated with defects in organ development, including autosomal visceral heterotaxy and congenital heart disease. They were causes of double-outlet right ventricle, autosomal visceral heterotaxy 2 and dextro-looped 2 transposition of the great arteries. CFC1 mutations demonstrate autosomal dominant inheritance with a broad range of clinical severity both within and between families. Definitive genotype/phenotype correlations have not been described.

The John Welsh Cardiovascular Diagnostic Laboratory offers molecular genetic testing for CFC1 mutations. Individuals are tested by DNA sequencing of the coding exons of the CFC1 gene. We strongly recommend initial testing of a clearly affected individual, if available, in order to provide the greatest test sensitivity and clearest interpretation of results for subsequent family members. Genetic counseling is recommended for all individuals.

**Reasons for Referral**

Molecular confirmation of the diagnosis of congenital heart disease (CHD) and autosomal visceral heterotaxy.

**Methodology**

Genomic DNA is analyzed for CFC1 mutations by DNA sequencing of the coding exons of the CFC1 gene, as well as the exon/intron junctions and a portion of the 5’ and 3’ untranslated region. Patient DNA is sequenced in both the forward and reverse orientations. If a mutation is identified, additional family members are analyzed only for the familial mutation by automatic fluorescent DNA sequencing.

**Service Fees**

<table>
<thead>
<tr>
<th></th>
<th>Direct and Institutional Billing</th>
<th>CPT Codes</th>
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</thead>
<tbody>
<tr>
<td>Index Case (Male or Female)</td>
<td>$600 per sample</td>
<td>81405</td>
</tr>
<tr>
<td>Additional Family Members</td>
<td>$300 per sample; known familial mutation only</td>
<td>81403</td>
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**Sensitivity**

DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons 1-6 of CFC1.

**Specimen Requirements**

- **Blood (preferred):** EDTA (purple-top) tubes: *Adult:* 5 cc  *Child:* 5 cc  *Infant:* 2-3 cc
- **Tissue:** Frozen (preferred), RNAlater
- **Other Body Fluids or Formalin-fixed, Paraffin-embedded Tissue:** Call to inquire

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