The human LDLR gene encodes a product containing 860 amino acids and encompasses 18 exons. It is located at 19p13.2. The low density lipoprotein receptor (LDLR) gene family consists of cell surface proteins involved in receptor-mediated endocytosis of specific ligands. Low density lipoprotein (LDL) is normally bound at the cell membrane and taken into the cell ending up in lysosomes where the protein is degraded and the cholesterol is made available for repression of microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis. At the same time, a reciprocal stimulation of cholesterol ester synthesis takes place. Mutations in the LDLR gene cause an inherited form of high cholesterol called familial hypercholesterolemia. More than 1,000 mutations have been identified in this gene. Some of these genetic changes reduce the number of low-density lipoprotein receptors produced within cells. Other mutations disrupt the receptor's ability to remove low-density lipoproteins from the blood. As a result, patients with mutations in the LDLR gene have very high blood cholesterol levels. LDLR 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 LDLR mutations. Individuals are tested by DNA sequencing of the coding exons of the LDLR 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 familial hypercholesterolemia.

**Methodology**

Genomic DNA is analyzed for LDLR mutations by DNA sequencing of the coding exons of the LDLR 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>Direct and Institutional Billing</th>
<th>CPT Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index Case (Male or Female)</td>
<td>$1000 per sample</td>
</tr>
<tr>
<td>Additional Family Members</td>
<td>$300 per sample; Known familial mutation only</td>
</tr>
</tbody>
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**Sensitivity**

DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons 1-18 of LDLR.

**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 and Formalin-fixed, Paraffin-embedded Tissue**: Call to inquire

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