The CBL gene is located at 11q23.3 and encodes RING finger E3 ubiquitin ligase that mediates the transfer of ubiquitin from ubiquitin conjugating enzymes (E2) to specific substrates. This protein also contains an N-terminal phosphotyrosine binding domain that allows it to interact with numerous tyrosine-phosphorylated substrates and target them for proteasome degradation. The cbl protein is a negative regulator of many signal transduction pathways. Mutations in this gene are associated with Noonan syndrome-like disorder and cardiomyopathy. These mutations are passed on in an autosomal dominant fashion. Definitive genotype/phenotype correlations have not been described.

The John Welsh Cardiovascular Diagnostic Laboratory offers molecular genetic testing for CBL mutations. Individuals are tested by DNA sequencing of the coding exons of the CBL 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 Noonan syndrome-like disorder and cardiomyopathy.

**METHODOLOGY**

Genomic DNA is analyzed for CBL mutations by DNA sequencing of the coding exons of the CBL 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>
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<th>Direct and Institutional Billing</th>
<th>CPT Codes</th>
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<tbody>
<tr>
<td>Index Case (Male or Female)</td>
<td>$1,100 per sample</td>
<td>81406</td>
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<tr>
<td>Additional Family Members</td>
<td>$300 per sample; Known familial mutation only</td>
<td>81403</td>
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</table>

**SENSITIVITY**

DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons 1-16 of CBL.

**SPECIMEN REQUIREMENTS**

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

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