**TP53 (p53) Gene Analysis in Li-Fraumeni Syndrome (LFS)**

**Mendelian Inheritance in Man Number:** 151623 (Li-Fraumeni syndrome); 191170 (TP53 gene)

**Clinical features:**

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome with an increased risk to develop (most notably) soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumors, and adrenocortical carcinoma (ACC). Classic LFS and Li-Fraumeni Like (LFL) syndrome are defined based upon the presence of these hallmark tumors in the proband and family members at early ages of onset, as noted in the table below. Those individuals with isolated breast cancer diagnosed at an early age in the absence of a family history suggestive of LFS or LFL rarely have a mutation identified in the TP53 gene (Gonzalez et al., 2009; Ginsburg et al., 2009).

<table>
<thead>
<tr>
<th>Classic Li-Fraumeni Syndrome (Li et al., 1988)</th>
<th>• Proband with sarcoma diagnosed &lt; 45 years of age AND&lt;br&gt;• First degree relative with cancer &lt; 45 years of age AND&lt;br&gt;• Another first or second degree relative with any cancer &lt; 45 years or sarcoma at any age</th>
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<td>Chompret Criteria (Tinat et al., 2009)</td>
<td>• Proband with LFS tumor spectrum &lt; 46 years and a first or second degree relative with LFS tumor (excluding breast cancer) &lt; 56 years of age or with multiple tumors OR&lt;br&gt;• Proband with multiple tumors (except multiple breast tumors), two belonging to the LFS tumor spectrum and one occurring &lt; 46 years of age OR&lt;br&gt;• Proband with adrenocortical carcinoma (ACC) or choroid plexus tumor, regardless of family history</td>
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<td>Li-Fraumeni Like Syndrome (Birch et al., 1994)</td>
<td>• Proband with childhood cancer or sarcoma, brain tumor, or adrenocortical carcinoma &lt; 45 years of age AND&lt;br&gt;• First or second degree relative with a typical LFS tumor at any age AND&lt;br&gt;• First or second degree relative with any cancer &lt; 60 years of age</td>
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<tr>
<td>Li-Fraumeni Like Syndrome (Eeles et al., 1995)</td>
<td>• Two first or second degree relatives with LFS tumors at any age</td>
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</table>

**Inheritance pattern:**

Autosomal dominant with age-related penetrance; penetrance is high. It is estimated that 7-20% of mutations may be de novo (Gonzalez et al., 2009).

**Genetics:**

The TP53 gene, on chromosome 17p13.1, codes for the cellular tumor antigen p53. TP53 is a tumor suppressor that responds to cellular DNA damage by causing cell cycle arrest while transcriptionally activating downstream genes to repair the DNA or induce apoptosis, preventing an abnormal cell from surviving and proliferating.

**Reasons for referral:**

- Confirmation of a clinical diagnosis
- Differentiation between hereditary breast and ovarian cancer syndrome (BRCA1, BRCA2 genes)
- Identification of family members at-risk to develop cancers related to LFS
- To determine an appropriate surveillance and treatment protocol
- Genetic counseling and recurrence risk assessment
- Prenatal diagnosis in families with a known mutation

**Test method:**

For those individuals with LFS or LFL, bi-directional sequence analysis of the complete coding region (exons 2-11) of the TP53 gene is provided. If no mutation is found by sequencing, targeted array CGH analysis with exon-level resolution...
(ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons in the TP53 gene. Mutations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or other appropriate method.

**Mutation spectrum**

The majority of mutations in the TP53 gene reported in the literature are missense mutations; nonsense, splice site, and frameshift mutations have been reported as well. Large partial deletions of the TP53 gene have been reported, but are rare.

**Test sensitivity**

In those individuals meeting clinical criteria for LFS, the likelihood of identifying a mutation in the TP53 gene by sequence analysis is approximately 77% (Varley et al., 2003). The likelihood of identifying a mutation in those individuals with Li-Fraumeni Like (LFL) syndrome by sequence analysis decreases to approximately 40% (Varley et al., 2003). Whole and partial deletions of the TP53 gene are rare, but have been reported in the literature. One study identified a deletion of the TP53 gene in approximately 1% of families with LFS and LFL syndrome that had previously had negative gene sequence analysis (Bougeard et al., 2003).

**Specimen Requirements and Shipping/Handling:**

- **Blood:** A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes:** We cannot accept buccal brush specimens for this test.
- **Prenatal Diagnosis:** For prenatal testing for a known mutation in the TP53 gene, please refer to the specimen requirements table on our website at: [http://www.genedx.com/test-catalog/prenatal/](http://www.genedx.com/test-catalog/prenatal/). Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

**Required Forms:**

- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Li-Fraumeni Syndrome” page on our website: [www.genedx.com](http://www.genedx.com)

**References cited:**