

LI-FRAUMENI SYNDROME

Li Fraumeni syndrome (LFS) is a clinically and genetically heterogeneous cancer syndrome associated with a wide spectrum of early-onset tumours. Germline mutations in the *TP53* gene predispose individuals to various tumours associated with LFS including early-onset soft tissue sarcomas and premenopausal breast cancer, osteosarcomas, brain cancer, leukemia and adrenal cortical carcinoma. A variety of other neoplasms have also been observed in LFS families. For individuals with an identified *TP53* mutation the risk of developing any invasive cancer is approximately 50% by age 30 and almost 90% by age 60.

GENETICS & CLINICAL CRITERIA

LFS is caused by mutations in the *TP53* gene located on chromosome 17p13.1, and shows an autosomal dominant pattern of inheritance. An individual is at high risk for developing an invasive LFS-related cancer when they have inherited one copy of the altered *TP53* gene.

LFS is diagnosed in individuals who meet the established clinical criteria and/or are found to carry a *TP53* mutation. The "classic" clinical criteria used to diagnose LFS includes: one patient with sarcoma diagnosed under the age of 45; and a first degree relative under the age of 45 with cancer (type not specified); and a third affected first or second-degree relative with either sarcoma at any age or cancer (type not specified) under the age of 45.

The Chompret criteria for LFS is a proband with a tumour belonging to the LFS tumour spectrum before age 46 years; and at least one first or second degree relative with a LFS tumour (except breast cancer if proband has breast cancer) before age 56 years or with multiple tumours; or a proband with multiple tumours, two belonging to the LFS tumour spectrum and the first occurring before age 46 years; or a patient with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history.

The modified inclusion criteria for Li-Fraumeni-like syndrome (Birch's criteria)

is a proband with any childhood cancer or sarcoma, brain tumor, or adrenal cortical tumor diagnosed before 45 years of age; and a first or second-degree relative with a typical LFS cancer at any age; and a first- or second-degree relative with any cancer under the age of 60 years.

TEST METHODS

- Complete sequencing of the coding region and exon/intron boundaries of the *TP53* gene to identify point mutations.
- Quantitative testing of the *TP53* gene to detect larger deletions, using MLPA (Multiplex Ligation-dependent Probe Amplification). Exon 6 is not covered by this analysis.

TEST SENSITIVITY

Approximately 85% of families that meet LFS criteria will have a germline mutation detected by sequence analysis or by MLPA. Whereas approximately 15% of families that meet LFS-like criteria will have a detectable mutation.

WHO SHOULD BE TESTED?

- Individuals meeting one of the LFS clinical criteria.
- Relatives of probands with identified mutations in the *TP53* gene.
- Pregnancies at risk due to family history of LFS with an identified *TP53* family mutation.

POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

Reason for referral	<i>TP53</i> Gene Mutations	Explanation
Diagnosis	None detected	This result is unable to confirm a diagnosis of LFS
Diagnosis	Mutation detected	This result supports a diagnosis of LFS

For More Information

Online Mendelian Inheritance in Man <http://www.ncbi.nlm.nih.gov/omim/> Item # 151623

GeneReviews online clinical information resource <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=li-fraumeni>

To locate a genetics centre near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org



1. Current molecular testing may not detect all possible mutations causing LFS. A negative result does not rule out the possibility that the individual has an unidentified mutation in the *TP53* gene, or a mutation in another cancer-susceptibility gene.

2. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

3. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.