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

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 variant identified in the TP53 gene.[5,4]

Classic Li-Fraumeni Syndrome: Proband with sarcoma diagnosed < 45 years of age AND first degree relative with cancer <45 years of age AND another first or second degree relative with any cancer <45 years or sarcoma at any age.[7]

Chompret Criteria: Proband with LFS tumor spectrum <46 years and a first or second degree relative with LFS tumor (excluding breast cancer) <56 years of age or with multiple tumors. OR Proband with multiple tumors (except multiple breast tumors), two belonging to the LFS tumor specrum and one occurring <46 years of age. OR Proband with adrenocortical carcinoma (ACC) or choroid plexus tumor, regardless of family history.[8]

Li-Fraumeni Like Syndrome: Proband with childhood cancer or sarcoma, brain tumor, or adrenocortical carcinoma < 45 years of age AND first or second degree relative with a typical LFS tumor at any age AND first or second degree relative with any cancer <60 years of age.[1]

Li-Fraumeni Like Syndrome: Two first or second degree relatives with LFS tumors at any age.[3]

Inheritance Pattern/Genetics:

Autosomal dominant with age-related penetrance; penetrace is high. It is estimated that 7-20% of variants may be de novo.[6]

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.

Test Methods:

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 variant 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. Variants 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.

Test Sensitivity:

In those individuals meeting clinical criteria for LFS, the likelihood of identifying a variant in the TP53 gene by sequence analysis is approximately 77%.[9] The likelihood of identifying a variant in those individuals with Li-Fraumeni Like (LFL) syndrome by sequence analysis decreases to approximately 40%.[9] 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.[2]

References:

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