

TP53 Gene Analysis in Li-Fraumeni Syndrome

Disorder Also Known As: LFS, SBLA syndrome

Clinical Features:

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome with a high risk of childhood- and adult-onset cancers. While breast cancer, soft tissue sarcomas, brain tumors, osteosarcomas, and adrenocortical carcinomas account for 70-77% of LFS-associated tumors, other cancers have been reported in association with LFS, including ovarian, gastrointestinal, pancreatic, genitourinary, skin, renal, thyroid, prostate, and lung cancers as well as leukemia, lymphoma, and neuroblastomas.^{1,2} The risk for males and females with a germline *TP53* pathogenic variant to develop cancer by age 60 is estimated to be 88% and 95%, respectively.³ The chance of a second primary cancer diagnosis within ten years of the first cancer diagnosis is approximately 50% for both men and women.³ Radiation-induced second malignancies have been reported in individuals with LFS, suggesting that radiation may increase *TP53* pathogenic variant carriers' risk for subsequent cancers within the radiation field.^{4,5}

Inheritance Pattern:

LFS is inherited in an autosomal dominant manner. Approximately 24% of LFS cases are *de novo* (new).⁶

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *TP53* are PCR amplified and capillary sequencing is performed. Bi directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. Data analysis is performed using gene-specific filtering. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of *TP53* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of Li-Fraumeni syndrome as outlined above. Sequencing and deletion/duplication analysis are expected to identify pathogenic variants in up to 80% of families with features of Li-Fraumeni syndrome, with large rearrangements accounting for <5% of all pathogenic variants.^{4,7}

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

References:

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