Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a rare hereditary cancer predisposition syndrome caused by germline variants in the tumor suppressor gene, *TP53*. Individuals with germline pathogenic variants in *TP53* have a greatly increased risk of developing cancer, often as children or young adults. Tumors most often associated with LFS include breast, osteosarcoma, rhabdomyosarcoma, brain tumors, leukemias, and adrenocortical carcinoma. Germline variants in *TP53* are found in approximately 80% of classic LFS cases.

Tests to Consider

Li-Fraumeni (TP53) Sequencing and Deletion/Duplication 2009313

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Most comprehensive test for LFS

Related Tests

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

Deletion/Duplication Analysis by MLPA 3003144

Method: Multiplex Ligation-dependent Probe Amplification

Use to assess for large deletion/duplication previously identified in a family member

Disease Overview

Prevalence

1/5,000-20,000[1]

Age of Onset

Varies by cancer type

Symptoms

- Predisposition to early-onset and multiple primary cancers:
  - 50% penetrance by age 30
  - 90% penetrance by age 60
- Classic LFS-related cancers:
  - Bone and soft tissue sarcomas
  - Breast cancer (especially premenopausal)
  - Brain tumors (especially choroid plexus)
  - Adrenocortical carcinoma
- Other LFS cancers:
  - Leukemia/lymphoma
  - Lung
  - Colorectal/gastrointestinal
  - Renal cell and other genitourinary
  - Skin
  - Nonmedullary thyroid
  - Early childhood tumors

Diagnostic Issues

TP53 gene variants are common in tumor tissue

- Presence of *TP53* pathogenic variant(s) in tumor does not necessarily imply LFS or Li-Fraumeni-like (LFL) syndrome
- Germline testing is needed to differentiate somatic from constitutional *TP53* gene variant(s)
  - For individuals with an active hematological malignancy, testing on cultured fibroblasts or buccal specimen is required for accurate interpretation of test results

Diagnostic Criteria

- Classic criteria for LFS[2]:
  - Sarcoma diagnosed at <45 years
  - And first-degree relative with cancer <45 years
  - And another first- or second-degree relative with any cancer <45 years or sarcoma at any age

- Chompret criteria[3]:
  - Individual with LFS-related cancer <46 years AND at least one first- or second-degree relative with LFS-related cancer<56 years (except breast cancer if proband has breast cancer) or with multiple primary cancers at any age
  - Individual with at least two LFS-related primary tumors (except multiple breast tumors) first diagnosed <46 years
  - Individual with adrenocortical carcinoma or choroid plexus tumor, regardless of family history

Genetics

Gene

TP53

Inheritance

Autosomal dominant

Penetrance

High (age dependent):

- 50% penetrance by age 30[4]
- 90% penetrance by age 60[4]

Structure/Function

TP53 codes for p53 protein:

- Important tumor suppressor
- Involved in regulation of cell growth, DNA repair, and apoptosis

Variants

- Mostly missense
- Some small deletions and splice site
- Large deletions/duplications are rare
- De novo variants: 7-20% of variants[5]

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity:
  - ~80% of individuals with classic LFS criteria have a detectable *TP53* variant[1,6]
    - ~95% of *TP53* pathogenic variants are sequencing variants; ~1% are large deletions/duplications[1,6]
- Analytical sensitivity/specificity: >95%

Results

- Positive: one pathogenic *TP53* variant detected
  - Individual predicted to be affected with LFS
  - At risk for developing LFS-related cancers
- Negative: no pathogenic *TP53* variant detected
  - Risk for LFS is significantly reduced but not eliminated
- Inconclusive: variant of uncertain clinical significance detected

Limitations

- Not determined or evaluated:
  - Regulatory region variants

    - Deep intronic variants
    - Breakpoints of large deletions/duplications
- Diagnostic errors can occur due to rare sequence variations
- Individuals with hematological malignancies and/or previous allogenic bone marrow transplant should not undergo molecular genetic testing on peripheral blood specimen
    - Testing on cultured fibroblasts or buccal specimen is required for accurate interpretation of test results

References

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