Li-Fraumeni Syndrome

Indications for Ordering

• Confirm clinical diagnosis of classic Li-Fraumeni syndrome (LFS) or Li-Fraumeni-like syndrome (LFL)
• Family history of known germline TP53 gene variant

Test Description

• Bidirectional sequencing of all coding regions and intron/exon boundaries of the TP53 gene
• Multiplex ligation-dependent probe amplification to detect large TP53 deletions/duplications

Tests to Consider

Typical testing strategy

• When specific familial TP53 pathogenic variant is known, use targeted testing for symptomatic and asymptomatic family members
• When no known TP53 pathogenic variant in family, test symptomatic family member
  o If variant is identified, test at-risk relatives for specific variant
• If no symptomatic individual is available for testing, test family member most likely to have variant based on family history

Primary tests
Li-Fraumeni (TP53) Sequencing and Deletion/Duplication
2009313
• Most comprehensive test for LFS
Li-Fraumeni (TP53) Sequencing 2009302
• Appropriate initial test for LFS

Related test
Familial Mutation, Targeted Sequencing 2001961
• Useful when a pathogenic familial variant identifiable by sequencing in known

Disease Overview

Prevalence – 1/5,000-20,000

Age of onset – varies by cancer type

Symptoms

• Predisposition to early-onset and multiple primary cancers
  o 50% penetrance by age 30
  o 90% penetrance by age 60
• Classic LFS-related cancers
  o Bone and soft tissue sarcomas
  o Breast cancer (especially premenopausal)
  o Brain tumors (especially choroid plexus)
  o Adrenocortical carcinoma
• Other LFS cancers
  o Leukemia/lymphoma
  o Lung
  o Colorectal/gastrointestinal
  o Renal cell and other genitourinary
  o Skin
  o Non-medullary thyroid
  o 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 LFL syndrome
• Germline testing is needed to differentiate somatic from constitutional TP53 gene variant(s)

Diagnostic criteria

• Classic criteria for LFS
  o Sarcoma diagnosed at <45 years
  o And first-degree relative with cancer <45 years
  o And another first- or second-degree relative with any cancer <45 years or sarcoma at any age
• LFL syndrome/Chompret criteria
  o Individual with LFS-related cancer <46 years and at least one first- or second-degree relative with any cancer <56 years or with multiple primary cancers at any age
  o Or individual with at least two LFS-related primary tumors) first diagnosed <46 years
  o Or individual with adrenocortical carcinoma or choroid plexus tumor, regardless of family history

Genetics

Gene – TP53

Inheritance – autosomal dominant

Penetrance – high (age dependent)
Structure/function
TP53 codes for p53 protein
• Important tumor suppressor
• Involved in regulation of cell growth, DNA repair, and apoptosis

De novo variants – ~20% of variants

Variants
• Mostly missense
• Some small deletions and splice site
• Large deletions/duplications are rare

Test Interpretation

Sensitivity/specificity
• Clinical sensitivity
  o ~80% of individuals with classic LFS criteria have a detectable TP53 variant (Kast, 2012; Schneider, 2013)
    ▪ Primarily sequence variants
    ▪ ~1% are large deletions/duplications
• Analytical sensitivity/specificity – >95%

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

Limitations
• Not determined or evaluated
  o Regulatory region variants
  o Deep intronic variants
  o 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
  o Testing on cultured fibroblasts or buccal specimen is required for accurate interpretation of test results

References