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
  - 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
  - 50% penetrance by age 30
  - 90% penetrance by age 60
- Classic LFSi-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
  - Non-medullary 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 LFL syndrome
- Germline testing is needed to differentiate somatic from constitutional *TP53* gene variant(s)

Diagnostic criteria

- Classic criteria for LFS
  - 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
- LFL syndrome/Chompret criteria
  - Individual with LFS-related cancer <46 years **and** at least one first- or second-degree relative with LFS-related cancer<56 years **or** with multiple primary cancers at any age
  - **Or** individual with at least two LFS-related primary tumors) first diagnosed <46 years
  - **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
  - ~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
  - 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

- Kast K, Krause M, et al. Late onset Li-Fraumeni Syndrome with bilateral breast cancer and other malignancies: case report and review of the literature. BMC Cancer. 2012; 12:217
- Schneider K, Zelley K, Nichols KE, et al. Li-Fraumeni Syndrome. 1999 Jan 19 [Updated 2013 Apr 11]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. (www.ncbi.nlm.nih.gov/books/NBK1311/)