PTEN-Related Disorders

Indications for Ordering

- Confirm clinical diagnosis of *PTEN* hamartoma tumor syndrome (PHTS)
- Determine if at-risk family members have a *PTEN* variant when a familial variant is unknown and affected relatives are unavailable for testing

Test Description

- Polymerase chain reaction and bidirectional sequencing of *PTEN* coding regions, intron/exon boundaries, and promotor (600 bp region745 bp upstream of translation start codon)
- Multiplex ligation-dependent probe amplification of *PTEN* coding regions

Tests to Consider

Primary tests

PTEN-Related Disorders (*PTEN*) Sequencing and Deletion/Duplication 2002470

- Preferred initial diagnostic and predictive test for *PTEN*-related disorders

PTEN-Related Disorders (*PTEN*) Sequencing 2002722

- Acceptable initial diagnostic and predictive test for *PTEN*-related disorders

Related test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence

- Cowden syndrome (CS) – at least 1/200,000
- Proteus syndrome (PS) – rare
  - ~120 reported cases
- Other *PTEN*-associated conditions – unknown

Symptoms

- Germline variants in *PTEN* gene cause several syndromes collectively referred to as PHTS
  - Associated disorders include
    - CS
    - Bannayan-Riley-Ruvalcaba syndrome (BRRS)
    - PS
    - Proteus-like syndrome (PLS)

For disease descriptions, see table below

- Established practice guidelines for tumor surveillance should be followed for individuals with an identified germline *PTEN* variant or suspected clinical diagnosis of a *PTEN*-related syndrome

Genetics

Gene – *PTEN*

Inheritance – autosomal dominant

Penetrance

CS – 99% by age 30

De novo variants – all cases of PS and 50-90% of CS

Variants

- Some variants may be associated with multiple phenotypes
- Type of variant detected may differ by phenotype
- Promoter variants
  - ~10% of individuals with CS do not have a *PTEN* sequence variant (Zhou, 2003)
  - Have not been identified in patients with BRRS
- Large deletions
  - 10% of individuals with BRRS do not have a *PTEN* sequence variant (Zhou, 2003)
  - Rare in CS
- Exon location
  - 65% of variants causing CS occur in exons 1-5 or the promoter
  - 60% of variants causing BRRS occur within exons 6-9

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - 25-85% for CS in individuals meeting strict diagnostic criteria (Marsh, 1998; Tan 2011)
  - 65% for BRRS (Marsh, 1998; Zhou, 2003)
  - 20% for PS (Zhou, 2001)
  - 50% for PSL (Zhou, 2001)
  - Up to 20% for autism spectrum disorder with significant macrocephaly (Butler, 2005)
- Analytical sensitivity/specificity
  - Sequencing – 99%
  - MLPA – 90% and 98% respectively

Results

- Positive – pathogenic variant in *PTEN* was identified
  - Confirms diagnosis of PHTS
- Negative – no variant detected
  - Decreases, but does not exclude, the probability of a *PTEN*-related disorder
- Sequence variants of unknown clinical significance may be detected

Limitations

- Deep intronic variants and some regulatory region variants are not detected
- Large deletions/duplications of exon 3 may not be detected
- Breakpoints for large deletions/duplications will not be determined
- Diagnostic errors can occur due to rare sequence variations

References

- Butler MG, Dasouki MJ, et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. J Med Genet. 2005;42(4):318-321
- Marsh DJ, Coulon V, et al. Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet. 1998;7(3):507-515
- Tan MH, Mester J, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. Am J Hum Genet. 2011;88(1):42-56
- Zhou X, Hampel H, et al. Association of germline mutation in the PTEN tumour suppressor gene and Proteus and Proteus-like syndromes. Lancet. 2001;358:210-211
- Zhou XP, Waite KA, et al. Germline PTEN promoter mutations and deletions in Cowden/Bannayan-Riley-Ruvalcaba syndrome result in aberrant PTEN protein and dysregulation of the phosphoinositol-3-kinase/akt pathway. Am J Hum Genet. 2003;73(2):404-411

PHTS			
Syndrome	**Age of onset**	**Diagnostic Criteria**	**Tumor Risks**
CS	By late 20s	• Pathognomonic ○ Adult-onset Lhermitte-Duclos disease (cerebellar tumors) ○ Mucocutaneous lesions ▪ Facial trichilemmomas ▪ Palmoplantar keratoses ▪ Oral mucosal papillomatosis in combination with trichilemmomas/ keratoses • Major ○ Macrocephaly ○ Breast cancer ○ Nonmedullary thyroid cancer ○ Endometrial cancer • Minor ○ Thyroid lesions ○ Intellectual disability ○ Fibrocystic breast disease ○ GI hamartomas ○ Uterine fibroids ○ Lipomas/fibromas ○ GU malformations/tumors	• Breast disease ○ Benign disease – up to 67% ○ Breast cancer ▪ Lifetime risk – 25-85% ▪ Average age at diagnosis – 38-46 years • Thyroid disease ○ Benign – thyroid nodules, adenomas, goiter in up to 75% ○ Nonmedullary thyroid cancer ▪ Lifetime risk – ~35% ▪ Childhood onset has been reported • Endometrial disease ○ Benign disease – uterine fibroids common ○ Endometrial cancer – lifetime risk of ~25% • Gastrointestinal disease ○ Benign – >90% with polyps ○ Colorectal cancer – lifetime risk of ~9% • Renal disease ○ Renal cell carcinoma – ~35% • Other ○ Melanoma – lifetime risk of >5% ○ Brain tumors – occasional

PHTS			
Syndrome	**Age of onset**	**Diagnostic Criteria**	**Tumor Risks**
BRRS	Birth to early childhood	• Diagnostic criteria not set but heavily based on the following ○ Macrocephaly ○ Intestinal hamartomas ○ Polyposis ○ Lipomas ○ Hemangiomas ○ Pigmented lesions of the glans penis	• Same cancer risks as CS if *PTEN* variant present
BRRS	Birth to early childhood	• Additional ○ High birth weight ○ Developmental delay ○ Intellectual disability ○ Proximal myopathy ○ Joint hyperextensibility ○ Pectus excavatum ○ Scoliosis	
PS	Infancy	• Major ○ Mosaic distribution of lesions ○ Progressive course ○ Sporadic occurrence • Additional ○ Connective tissue nevi ○ Epidermal nevus ○ Disproportionate overgrowth in limbs, skull, vertebrae, viscera ○ Specific tumors before end of second decade ▪ Bilateral ovarian cystadenoma ▪ Parotid monomorphic adenoma ○ Dysregulated adipose tissue ○ Vascular malformations – capillary, venous and/or lymphatic ○ Facial phenotype ▪ Dolichocephaly ▪ Long face ▪ Low nasal bridge ▪ Wide or anteverted nares ▪ Open mouth at rest ▪ Minor downslanting of palpebral fissures	• Tumors and malignancies are not common • Reported ○ Cystadenoma of the ovary ○ Testicular tumors ○ Central nervous system tumors ○ Parotid monomorphic adenomas
PLS	Infancy	Clinical features of PS which do not meet diagnostic criteria for PS	