

PTEN-Related Disorders, Sequencing and Deletion/Duplication

TO CONFIRM A DIAGNOSIS OF PTEN HAMARTOMA TUMOR SYNDROME (PHTS)

Disease Overview

- Germline mutations in the *PTEN* gene can result in several distinct conditions which are collectively referred to as the *PTEN* hamartoma tumor syndrome (PHTS). Associated disorders include Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS), and Proteus-like syndrome (PSL).
- Clinical diagnostic criteria are available for CS and PS.
- Individuals with CS typically demonstrate macrocephaly, facial trichilemmomas, and papillomatous papules. Patients usually present by their late 20s. CS is associated with a high risk of benign and malignant tumors of the thyroid, breast, and endometrium.
 - Pathognomonic clinical criteria for CS include adult-onset Lhermitte-Duclos disease (cerebellar tumors) and mucocutaneous lesions (multiple facial trichilemmomas, multiple palmoplantar keratoses, or oral mucosal papillomatosis in combination with trichilemmomas/keratoses).
 - Major clinical diagnostic criteria include macrocephaly, breast cancer, non-medullary thyroid cancer, and endometrial cancer.
 - The risk of developing breast cancer is 25–50 percent, with an average age of diagnosis between 38 and 46 years.
 - Approximately 3–10 percent of CS patients develop non-medullary thyroid cancer; childhood onset has been reported.
 - Endometrial cancer is estimated to occur in 5–10 percent of women with CS.
 - Minor diagnostic clinical criteria include thyroid lesions, mental retardation, GI hamartomas, fibrocystic breast disease, uterine fibroids, lipomas, fibromas, and GU malformations or tumors (e.g., renal cell carcinoma).
- BRRS is characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, hemangiomas, and pigmented macules of the glans penis.
 - Other features include a high birth weight, developmental delay/mental retardation, a myopathic process in proximal muscles, joint hyperextensibility, scoliosis, and pectus excavatum.
 - In contrast to CS, GI polyps associated with BRRS are more frequently symptomatic.
 - Individuals with BRRS are currently thought to have the same cancer risks as individuals with CS.
- PS is a progressive disorder demonstrating a mosaic distribution of associated lesions.
 - Clinical findings are highly variable and include congenital malformations, hamartomatous tissue overgrowth, hyperostoses, connective tissue nevi, epidermal nevi, dysregulated adipose tissue, vascular malformations, and characteristic facial features.

- Tumors or malignancies are not frequently reported in PS, but all individuals with a *PTEN* germline mutation should follow increased surveillance recommendations.
- PSL refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.
- *PTEN* mutations have also been found in patients who have both autism spectrum disorders and severe macrocephaly (>2.0 standard deviations above the mean).
- Established practice guidelines for tumor surveillance should be followed for individuals with an identified germline *PTEN* mutation or suspected clinical diagnosis of a *PTEN*-related syndrome.

Prevalence

- The prevalence of CS is at least one in 200,000.
- PS is rare, having been reported in approximately 120 patients.
- The prevalence of other *PTEN*-associated conditions is unknown.

Genetics

- The phosphatase and tensin homolog (*PTEN*) tumor-suppressor gene has nine coding exons and is located on chromosome 10q23.3.
- Inheritance of *PTEN*-related syndromes is autosomal dominant. All cases of PS and the majority of CS (50–90 percent) occur due to de novo mutations.
- The penetrance of CS is estimated to be 99 percent by age 30.
- Approximately 85 percent of individuals who meet the diagnostic criteria for CS and 65 percent of individuals with a clinical diagnosis of BRRS have a detectable *PTEN* mutation. Up to 50 percent of individuals with PSL and 20 percent of individuals with PS also carry *PTEN* mutations.
- *PTEN* promoter mutations causing loss of gene function are found in approximately 2 percent of all individuals with CS. Promoter mutations have not been identified in patients with BRRS.
- 10 percent of individuals with BRRS carry large deletions within or encompassing *PTEN*. Such deletions are rare in CS.
- Of patients with autistic spectrum disorders and severe macrocephaly, 10–20 percent carry a *PTEN* mutation.
- Approximately 65 percent of *PTEN* mutations causing CS occur in exons 1–5 of the promoter, while 60 percent of BRRS-causing mutations occur within exons 6–9.
- Some *PTEN* mutations may be associated with multiple phenotypes, as families with both CS and BRRS have been reported.
- *PTEN* gene testing is unlikely to have clinical utility in patients with isolated early-onset breast cancer, BRCA-negative familial breast cancer, or endometrial cancer without other significant signs of CS.

Indications for Ordering

- To confirm a clinical diagnosis of PHTS in a symptomatic individual.
- To determine if at-risk family members have a *PTEN* mutation when the familial mutation is unknown and affected relatives are not available for testing.

Contraindications

- Testing shouldn't be ordered for individuals with a previously identified familial *PTEN* mutation. To test individuals for a specific mutation, it is more cost-effective to order [Familial Mutation, Targeted Sequencing \(ARUP test #2001961\)](#) and provide a copy of the lab report detailing the familial mutation.
- Prenatal testing.

Interpretation

- Identification of a known pathogenic *PTEN* mutation in a symptomatic individual confirms a diagnosis of PHTS.
- Lack of an identifiable *PTEN* mutation in a clinically affected individual decreases but does not exclude a diagnosis of CS/BRRS/PS/PSL. Medical management should rely on clinical findings and family history.
- *PTEN* sequence variants of unknown clinical significance may be detected by sequencing.

Methodology

- Bidirectional sequencing of the *PTEN* coding region, intron-exon borders, and promoter (600 bp region 745 bp upstream of the translation start codon).
- Multiplex ligation-dependent probe amplification (MLPA) of the *PTEN* gene includes all introns and some exons (exons 1, 2, 3, 4, 8, and 9 are not evaluated by MLPA).
- The combined clinical sensitivity of *PTEN* sequencing and deletion/duplication testing is 85 percent for CS, 65 percent for BRRS, 20 percent for PS, 50 percent for PSL, and up to 20 percent for patients with an autism spectrum disorder and significant macrocephaly.
- Analytical sensitivity and specificity of sequencing are 99 percent. Analytic sensitivity and specificity of MLPA are 90 and 98 percent, respectively.

Limitations

- Deep intronic mutations, some regulatory region mutations, and large deletions of exons 1, 2, 3, 4, 8, and 9 are not detected.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Breakpoints of large deletions/duplications detected in *PTEN* will not be determined.

Related Test

[Familial Mutation, Targeted Sequencing \(2001961\)](#)

References

1. Online Gene Tests: *PTEN* Hamartoma Syndrome (PHTS). www.genetests.org (accessed on August 3, 2009).
2. Pilarski R. Cowden syndrome: a critical review of the clinical literature. *J Genet Couns* 2009;18(1):13–27.
3. National Comprehensive Cancer Network. Genetic/familial high-risk assessment: breast and ovarian. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed on December 9, 2009).
4. Biesecker LG, et al. Proteus syndrome: diagnostic criteria, differential diagnosis and patient evaluation. *Am J Med Genet* 1999;84(5):389–95.
5. Varga EA, et al. The prevalence of *PTEN* mutations in a clinical pediatric cohort with autism spectrum disorders, developmental delay, and macrocephaly. *Genet Med* 2009;11(2):111–17.
6. Zhou X, 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;73:404–11.

Test Information

2002470

PTEN-Related Disorders, Sequencing and Deletion/Duplication

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.