

PTEN-RELATED DISORDERS

Comprehensive Test - Test 1

- updated 09-21-09

DESCRIPTION

Mendelian Inheritance in Man number: [*601728](#) (*PTEN* gene); [158350](#) (Cowden syndrome, CS); [153480](#) (Bannayan-Riley-Ruvalcaba syndrome, BRRS); [176920](#) (Proteus syndrome, PS); [605309](#) (Macrocephaly/Autism syndrome)

Click here for [Gene Reviews](#) Clinical Summary.

PTEN hamartoma tumor syndrome (PHTS) includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS), and Proteus-like syndrome. This group of disorders shares significant clinical overlap [[Eng, 2003](#)]. Each of these disorders is inherited in an autosomal dominant manner, and de novo mutations are common.

1. **CS** is a multiple hamartoma syndrome with a high risk of benign and malignant tumors of the thyroid (10%), breast (25-50%), and endometrium (10%). Most patients usually have macrocephaly and pathognomonic mucocutaneous lesions, including trichilemmomas, papillomatous papules, and acral and plantar keratoses. Other tumors include hamartomatous polyps of the GI tract, fibrocystic disease of the breast, fibromas, cerebellar dysplastic gangliocytoma (Lhermitte-Duclos disease), skin cancers, renal cell carcinomas, uterine leiomyoma, and brain tumors as well as vascular malformations affecting any organ.
2. **BRRS** is characterized by macrocephaly, intestinal polyposis, lipomas, and pigmented macules of the glans penis. Other common features include developmental delay, mental retardation, hamartomatous polyps of the GI tract, a myopathic process in proximal muscles, joint hyperextensibility, pectus excavatum, and scoliosis. Individuals with BRRS who have *PTEN* gene mutations are thought to have the same cancer risks as individuals with CS.
3. **PS** is a complex, highly variable disorder consisting variably of disproportionate, asymmetric overgrowth of body parts; cerebriform connective tissue nevi; epidermal nevi; vascular malformations of the capillary, venous, and lymphatic types; dysregulated adipose tissue; and hyperostoses [[Cohen, 2005](#)]. Unusual tumor types have been observed, such as cystadenoma of the ovary, various types of testicular tumors, central nervous system tumors, and parotid monomorphous adenomas. Somatic mosaicism, lethal in the nonmosaic state, is the present hypothesis for PS.
4. **Proteus-like syndrome** is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.
5. **Macrocephaly/Autism Syndrome** is one of *PTEN*-related disorders. Autism is associated with macrocephaly in approximately 20% of cases. Several studies

have shown that *PTEN* mutations can be found in a subset of individuals who present with autism and macrocephaly, with or without the presence of other features of *PTEN*-related tumor syndrome [[Butler et al. 2005](#), [Buxbaum et al. 2007](#), [Goffin et al. 2001](#), [Herman et al. 2007](#)]. Therefore, *PTEN* sequence analysis may be considered as additional testing when other genetic causes of autism have been ruled out through the autism panel.

INDICATIONS FOR DIRECT TESTING

- Individuals suspected to have *PTEN*-related disorders
- Individuals who seek confirmation of a clinical diagnosis

TESTING METHODOLOGY

We offer a **two-tiered** approach to testing.

First, the entire coding region and core promoter is analyzed by direct sequencing. This can be accomplished either using an RNA core assay (**Tier 1-RNA based**), starting from a fresh EDTA blood sample and short-term lymphocyte culture or starting from a DNA sample, if no fresh blood sample can be obtained/shipped (**Tier 1-DNA based**). If no clearcut pathogenic mutation is identified, MLPA analysis to detect copy number changes is performed (**Tier 2**). Copy number changes are confirmed using qPCR and/or long range RT-PCR and/or aCGH. Mutations screened for include truncating mutations (nonsense, frameshift, splicing mutations), missense mutations, multi-exon deletions and total gene deletions. Deep intronic splice mutations will only be detected using Tier1-cDNA based.

Testing can be ordered as:

Test 1, Tier 1 and proceed with Tier 2 as needed- cDNA or gDNA-based
(\$1100 or \$1400)

Test 1, Tier 1 *only* -cDNA or gDNA-based (\$1100)

Test 1, Tier 2 *only* (\$300)

Sequencing of the core promoter region only (\$350).

Test sensitivity varies depending on the clinical diagnosis. The sequencing approach used by MGL will identify >99% of intragenic minor lesion mutations in the *PTEN* gene. Partial or whole gene deletions/duplications can be detected by MLPA copy number analysis.

SPECIMEN REQUIREMENTS

We require 10 milliliters of whole blood. Blood samples must be collected in EDTA (purple topped) tubes. For pediatric patients or those for whom venipuncture is very difficult, please send a minimum of 3 ml in EDTA. **Please note that if you order *PTEN* gene testing in addition to Fragile X testing for pediatric patients, we require a minimum of 5 milliliters of whole blood.**

TRANSPORT

If specimen is from clinics within UAB or Kirklin Clinic, please call 934-5562 for pick-up. If specimens are being sent from some other location, please ship via UPS or Federal Express.

IMPORTANT!

Blood specimens must be kept at room temperature and received within 60 hours of collection.

1. DO NOT SHIP ON ICE.
2. Be sure that the shipping air bill is marked “**Priority**”, either Domestic or International.
3. Specimens must be packaged to prevent breakage and absorbent material must be included in the package to absorb liquids in the event that breakage occurs. Also, the package must be shipped in double watertight containers (e.g. a specimen pouch + the shipping companies Diagnostic Envelope). **You can use our collection kits, which we will send to physicians directly upon request.**
4. Please contact us (Email – mgl@genetics.uab.edu, Phone – 205-934-5562) prior to sample shipment and provide us with the **date of shipment** and the **tracking number** of the package, so that we can better ensure receipt of the samples within the 60-hour window. Please include the form for customs. This is especially important for samples sent from outside the US.

TURN AROUND TIME

Tier 1 and Tier 2: 5 weeks

Copy number analysis by MLPA: 2-3 weeks

CPT CODES AND PRICES

Please note that prices listed correspond to institutional rates; please contact the lab for insurance rates.

Tier 1 RNA-based- Sequence Analysis of the coding region and core promoter
\$1100, -USD ([currency converter](#))
83891 (x2), 83894 (x2), 83898 (x2), 83904 (x8), 83912 (x1), 83913 (x1), 88230 (x1)

Tier 1 DNA-based- Sequence Analysis of the coding region and core promoter region: \$1100, -USD ([currency converter](#))
83891 (x1), 83894 (x10), 83898 (x10), 83904 (x20), 83912 (x1)

Tier 2- Copy Number Analysis by MLPA:
\$300, -USD ([currency converter](#))
83891 (x1), 83896 (x3), 83898 (x3), 83909 (x3), 83912 (x1)

Promoter Sequence Analysis only:
\$350, -USD ([currency converter](#))
83891 (x1), 83894 (x2), 83898 (x2), 83904 (x4), 83912 (x1)

*Please note that promoter sequence analysis is part of the *PTEN* Tier 1 analysis, but can be requested as a stand-alone test at \$350,-USD

REQUIRED FORMS

[PTEN Test Requisition including the phenotypic data form.](#)
[Form for customs \(International shipment\)](#)

Note: Requests for Molecular Genetic testing for *PTEN* will **not** be accepted for the following reasons:

- No label (patient's full name and date of collection) on the specimens
- No referring physician's or genetic counselor's names and addresses
- No billing information
- No informed consent
- **No phenotypic checklist**

For more information, test requisition forms, or sample collection and mailing kits, please call: 205-934-5562.

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