

Cowden Syndrome: *PTEN* Gene Deletion/Duplication

Test Code: OW

Turnaround time: 2 weeks

CPT Codes: 81323 x1

Condition Description

PTEN Hamartoma Tumor Syndrome (PHTS) is characterized by hamartomatous tumors and germline *PTEN* mutations. Clinically, PHTS includes Cowden Syndrome (CS), Bannayan-Riley-Ruvalcaba Syndrome (BRRS), Proteus Syndrome (PS), and Proteus-Like Syndrome.

Cowden Syndrome (CS) is a multiple hamartoma syndrome with a high risk of benign and malignant tumors of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules, and present by the late 20s. The lifetime risk of developing breast cancer is 25%-50%, with an average age of diagnosis between 38 and 46 years; the lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is around 10%, and the risk for endometrial cancer may approach 5%-10%.

Bannayan-Riley-Ruvalcaba Syndrome (BRRS) is a congenital disorder characterized by macrocephaly, intestinal polyposis, lipomas, and pigmented macules of the glans penis.

Proteus Syndrome (PS) is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

Proteus-Like Syndrome is undefined, but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

A presumptive diagnosis of PHTS is based on clinical signs. The actual diagnosis of PHTS is made only when a *PTEN* mutation is identified. Approximately 80% of individuals who meet the diagnostic criteria for CS and 60% of individuals with a clinical diagnosis of BRRS have a detectable *PTEN* gene mutation. Approximately 10% of individuals with BRRS who do not have a mutation detected in the *PTEN* coding sequence have large deletions within or encompassing *PTEN*. Preliminary data also suggest that up to 50% of individuals with a Proteus-like syndrome and up to 20% of individuals with Proteus syndrome have *PTEN* mutations.

The *PTEN* gene (10q23.3) has 9 exons. It appears that nuclear PTEN mediates cell cycle arrest, while cytoplasmic PTEN is required for apoptosis. The majority (76%) of germline mutations in *PTEN* result in either truncated protein, lack of protein (haploinsufficiency), or dysfunctional protein. Many missense mutations are functionally null and several act as dominant negatives. When PTEN is absent, decreased, or dysfunctional, phosphorylation of Akt is uninhibited, leading to the inability to activate cell cycle arrest and/or to undergo apoptosis. In addition, through lack of protein phosphatase activity, the mitogen-activated protein kinase (MAPK) pathway is dysregulated, leading to abnormal cell survival.

Sequencing of the *PTEN* gene is recommended after a clinical diagnosis consistent with PHTS, and provides a complementary method to confirm the presence of mutations in a proband, identify at-risk individuals among the proband's relatives, [and provide prenatal diagnosis in families with known mutations](#). For patients with suspected PHTS, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

Visit www.ThinkGenetic.com for patient-friendly information on [Cowden syndrome](#).

Genes

[PTEN](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of PHTS in an individual in whom sequence analysis was negative.
- Individuals at-risk for PHTS due to family history in whom sequence analysis was negative.

Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Detection

Approximately 10% of individuals with BRRS who do not have a mutation detected in the *PTEN* coding sequence have large deletions within/encompassing *PTEN*. Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations.

Results of molecular analysis should be interpreted in the context of the patient's clinical presentation and family history.

Specimen Requirements

Submit only 1 of the following specimen types

Type: Whole Blood (EDTA)

Specimen Requirements:

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old: 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: DNA, Isolated

Specimen Requirements:

Microtainer

3µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Special Instructions

Please submit copies of pedigree or other family history information along with the sample. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition form.

Related Tests

- [Cowden Syndrome: PTEN Gene Sequencing \(OY\)](#) is required before deletion/duplication analysis.
- Prenatal Custom Diagnostics is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.