Gene Sequencing

mutations. Clinically, PHTS includes the PTEN gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is used for patient-friendly information on the PTEN gene mutation. Approximately 10% of individuals with BRRS who do not have a mutation detected in the PTEN (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.

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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.


Genes

PTEN

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of PHTS or autism with macrocephaly.
- Individuals at-risk for PHTS or autism with macrocephaly due to family history.

Methodology

PCR amplification of 9 exons contained in the PTEN gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and will not detect large deletions.

Detection

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/encircling PTEN. Preliminary data also suggest that up to 50% of individuals with Proteus-like syndrome and up to 20% of individuals with Proteus syndrome have PTEN mutations. Approximately 20% of individuals with autism spectrum disorders and macrocephaly have germline PTEN mutations. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions cannot be detected by this analysis.

Analytical Sensitivity: ~99%.

### Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

#### Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

#### Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection 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.

### Related Tests

- **Cowden Syndrome: PTEN Gene Deletion/Duplication (OW)** is available for those individuals in whom sequence analysis is negative.
- **Known Mutation Analysis (KM)** is available to family members if mutations are identified by sequencing.
- **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.