PTEN Gene Analysis in PTEN Hamartoma Tumor Syndrome

Disorder Also Known As: PTHS; Cowden syndrome, Bannayan-Riley-Ruvalcaba Syndrome, Proteus syndrome/Proteus-like syndrome

Clinical Features:

PTEN hamartoma tumor syndrome (PHTS) describes individuals with Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome, and other conditions found to have a germline pathogenic variant of the *PTEN* tumor suppressor gene. Individuals with PHTS are at increased risk for benign and malignant tumors as well as neurodevelopmental issues. Breast (77-85% lifetime risk), thyroid (35-38% lifetime risk), and endometrial cancers (21-28% lifetime risk) are most common in individuals with PHTS; however renal, colorectal, and melanoma skin cancers have also been reported.[1–3] While most cancers are diagnosed in adulthood, thyroid, genitourinary, and other malignancies have been reported in childhood.[4–6] Common benign neoplasias in individuals with PHTS include gastrointestinal polyposis, beign mucocutaneous lesions of diverse histologies, and other benign lesions affecting the organs at increased cancer risk.[7–9] *PTEN*-related hamartomas of soft tissue (PHOSTs) and arteriovenous malformations may develop in childhood or adulthood.[10,11] Dysplastic cerebellar ganglioctyoma, also called Lhermitte-Duclos disease, is estimated to occur in less than 10% of individuals with PHTS.[3]

Apart from tumor development, individuals with PHTS often have increased head circumference and are at risk of having autism or neurocognitive delay. Macrocephaly is the most common feature observed, identified in 94% of affected individuals.[12] In addition, within a series of children with macrocephaly and autism, up to 17% were found to have PHTS.[13]

Inheritance Pattern:

PHTS is inherited in an autosomal dominant manner. At least 10% of *PTEN* pathogenic variants are estimated to occur *de novo* (new).[14]

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *PTEN* are PCR amplified and capillary sequencing is performed. Approximately nucleotides c.-700 through c.-1300 in the promoter region are also captured. Bi directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines.

Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

For patients who have had *PTEN* testing performed previously at GeneDx, prior to availability of promoter sequencing and/or deletion testing, GeneDx also offers promoter sequencing and/or deletion/duplication testing by ExonArrayDx as separate tests. If interested, contact GeneDx to order.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of *PTEN* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of PHTS as outlined above. The likelihood of detecting a pathogenic variant in *PTEN* varies according to phenotype. For those probands with Cowden syndrome, sequence analysis of the coding and promoter regions is expected to detect 47%-80% of causative variants, while large deletions and duplications have been reported.[9,15,16] For individuals with Bannayan-Riley-Ruvalcaba syndrome, ~60% of causative pathogenic variants will be detected by sequencing while 11% will be detected by deletion/duplication analysis.[15,17,18]

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

References:

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