PTEN Gene Analysis in PTEN-related disorders (Cowden Syndrome, Bannayan-Riley-Ruvalcaba Syndrome, and Proteus Syndrome/-like syndrome)

Disorder also known as: PTEN Hamartoma Tumor Syndrome (PHTS)

Clinical Features:
The 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.[1]

CS is characterized by increased risk for both benign and malignant tumors of the breast, thyroid, and endometrium. Affected individuals have macrocephaly and almost all will develop the pathognomonic mucocutaneous lesions by the third decade of life, including trichilemmomas, papillomatous papules, and acral and plantar keratoses. Affected females also have a high rate of benign breast disease. Hamartomatous polyposis of the GI tract can be observed, but is rarely symptomatic.

BRRS is a congenital disorder characterized by macrocephaly, intestinal polyposis, lipomas, and enlargement and spotty pigmentation of the glans penis. Other common features may include: high birth weight, mild to severe mental retardation with delayed motor and speech development, proximal muscle weakness, joint hyperextensibility, macrodactyly, pectus excavatum, and scoliosis. Hamartomatous GI polyps are observed in ~45% of affected individuals. The cancer risks in patients with BRRS who harbor PTEN gene variants are thought to be similar to that of individuals with CS.

PS/PS-like (PSL) is an extremely rare congenital disorder with generalized, unilateral, or localized hamartomatous overgrowth of any tissue. Unusual malignancies have been observed, such as cystadenoma of the ovary, testicular tumors, central nervous system tumors, and parotid monomorphic adenomas.

Inheritance Pattern/Genetics:
Each of these disorders is inherited in an autosomal dominant manner; de novo variants are common.

Test Methods:
GeneDx now offers a comprehensive PTEN analysis that includes gene sequencing and deletion/duplication testing. Using DNA from the submitted specimen, bi-directional sequence

of the coding exons 1-9 and the core promoter region (approximately from c.-700 to c.-1300) is obtained and analyzed. Concurrently, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons of this gene or the 5' regulatory region (promoter and E-box element). Any variant/deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR or another appropriate method.

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.

Test Sensitivity:

Test sensitivity varies depending on the clinical diagnosis. The sequencing approach used by GeneDx will identify >99% of existing small, intragenic variants in the PTEN gene but not partial or whole gene deletions which can be detected by ExonArrayDx deletion/duplication testing.

In CS, germline PTEN variants identifiable by DNA sequencing were found in up to 81% of patients. Approximately 13% of patients (4 out of 30) with CS/CS-like phenotype without an identifiable PTEN variant in the coding exons have a deletion involving exon 1 and/or the upstream promoter region, including an E-box element mediating transcription activation. In addition, ~ 9% of CS patients (9 out of 95) are expected to have a point variant in the PTEN core promoter region.

Approximately 60% of patients with BRRS have a PTEN variant identifiable by sequencing. Of the remaining patients, 11% (3 of 27) have a heterozygous partial or complete gene deletion including at least exons 1-5.[2-4]

Overall, ~25% of patients with PS/PSL (7 out of 29), have been found to have PTEN variants.[5-8] This sensitivity data suggest that PS/PSL may be considered to be part of PHTS, but it also is believed that additional susceptibility genes for PS/PSL will be found.

References:

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