

# Gene inactivation of PTEN drives cancer predisposition

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An international team of researchers co-led by Cleveland Clinic have identified why patients without PTEN mutations may still experience the high cancer risk associated with PTEN hamartoma tumor syndrome

(PHTS).

In a new study published in the *New England Journal of Medicine*, a research team co-led by Charis Eng, MD, Ph.D., Cleveland Clinic Genomic Medicine Institute, and Pier Paolo Pandolfi, MD, Ph.D., FRCP, University of Turin, Italy, found that mutations to the gene WWPI may be an additional genetic driver of PHTS-associated cancer.

PHTS collectively refers to a spectrum of genetic disorders that carry an [increased risk](#) for benign growths and tumors (i.e., hamartomas), cognitive and behavioral deficits, macrocephaly and certain cancers and that is defined by carrying a germline PTEN mutations. While germline mutations of the tumor suppressor gene PTEN are an established cause of PHTS, approximately 75% of individuals with typical clinical features have been found to carry no PTEN mutations (termed "wildtype").

"Our findings suggest that WWPI mutations may account for at least some portion of the large percentage of these patients we see without PTEN mutations," said Dr. Eng. "Importantly, unlike PTEN, WWPI and the cellular pathway it regulates are druggable targets, a fact that has important implications for [cancer prevention](#) and therapy and may open the door for future drug development studies."

In this study, the researchers analyzed a cohort of PTEN wildtype patients for WWP1 variants, as previous studies have found that the enzyme encoded by WWPI can be overexpressed and/or amplified in multiple types of cancer and can inhibit PTEN function and lead to tumor growth in experimental models.

They identified these variants in a family with a history of oligopolyposis (a condition characterized by abnormal growths on the inner walls of the colon and rectum) and early-onset colon cancers, and an expanded analysis of unrelated patients detected WWP1 germline

variants in 4% of PTEN wildtype individuals with gastrointestinal oligopolyposis as a predominant clinical feature. This is significant because oligopolyposis has long eluded causation. In addition, the researchers found that germline WWP1 variants were significantly enriched in patients affected by sporadic cancers, including cancer types associated with PHTS, particularly colorectal adenocarcinoma and thyroid cancer.

On a mechanistic level, they found that in experimental models certain WWP1 variants lead to abnormal activation of the WWP1 enzyme that inhibits PTEN function and ultimately contributes to cancer development and progression by increasing tumorigenesis.

While additional studies are needed, the researchers conclude that PTEN wildtype patients with germline WWP1 variants may benefit from preventative and/or therapeutic measures that modulate WWP1-PTEN axis.

"These findings are extremely exciting because they implicate WWP1 in the genesis of somatic cancers of multiple histology as well as in dictating cancer susceptibility at large, with important prognostic and therapeutic implications since these class of enzymes are druggable and natural compounds that do so are already available," said Dr. Pandolfi.

Dr. Eng is the inaugural chair of the Genomic Medicine Institute and director of the Center for Personalized Genetic Healthcare. She holds the Sondra J. and Stephen R. Hardis Endowed Chair in Cancer Genomic Medicine. Dr. Pandolfi is professor of [cancer](#) biology and genetics at the University of Turin and Harvard Medical School.

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