Two new genetic mutations associated with Cowden syndrome

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Cleveland Clinic researchers from the Lerner Research Institute have uncovered two new genes associated with Cowden syndrome (CS) according to a new study, published today in the online version of the *American Journal of Human Genetics*.

Cowden syndrome is a difficult-to-recognize, under-diagnosed condition that carries high risks of breast, thyroid, and other cancers. The discovery of the two new genes – led by Charis Eng, MD, Ph.D., Chair and Founding Director of the Cleveland Clinic's Lerner Research Institute's Genomic Medicine Institute – will promote diagnosis and clinical management of the disease, while also assisting in predictive genetic testing and genetic counseling.

Researchers performed genetic sequencing on DNA from individuals with CS who have none of the known genetic alterations associated with CS. State-of-the-art technology was used to identify a high prevalence of mutations in the PIK3CA and AKT1 genes, which are involved in cancer-related signaling pathways.

In tracing the root causes of CS, Dr. Eng has previously identified many genetic alterations that promote the disease, beginning with mutations in the first gene ever to be associated with CS, the tumor suppressor, PTEN, along with the SDHB/D and KLLN genes, identifying their connection with PTEN in cancer.

"Gene-enabled risk assessment and management begins with the

identification of all the genes that, when mutated, account for as many or all the individuals with a particular syndrome, in this case CS," said Dr. Eng. "We started with only PTEN, and now we know that SDHB/D, KLLN, PIK3CA and AKT1 account for CS. Each also brings differing risks of breast, thyroid and other cancers, and so this discovery directly aids genetic counseling and clinical management."

This research comes on the heels of two new discoveries by Dr. Eng, both related to Cowden syndrome and the PTEN gene, that were recently published in the Journal of Clinical Endocrinology & Metabolism.

In a Nov. 1 paper, Dr. Eng and her team reported on uncovered, untapped, diagnostic and prognostic pathways for cancers related to the compromised PTEN tumor suppressor.

This discovery that PTEN disrupts cancer signaling pinpoints a novel target for future treatment and diagnosis. This type of location-specific strategy is important in both heritable and sporadic cancers.

In another paper published Dec. 1, Dr. Eng and her team identified a screening biomarker in thyroid cancers that revealed inherited predisposition in Cowden syndrome patients. With the increasing incidence of thyroid cancer over the last few years, having a biomarker to screen for an inherited mutated PTEN tumor suppressor gene would accelerate follow-up for affected individuals.

After a five-year, multi-center study of patients with Cowden syndrome and Cowden-like syndrome, characterized in part by PTEN mutations, researchers have concluded that a simple blood test may screen for individuals carrying increased cancer risk. Until now, only four clinical factors were known to predict an inherited PTEN mutation – and this study's blood test out-predicts them all. Future studies testing thyroid tissue itself may reveal additional biomarkers.

Provided by Cleveland Clinic