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Beyond PTEN: Alternate genes linked to breast, thyroid and kidney cancer predisposition

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A new discovery may lead to more effective screening and treatment for patients with a difficult to recognize syndrome characterized by tumor-like growths and a high risk of developing specific cancers. The research, published by Cell Press in the August 7 issue of the *American Journal of Human Genetics,* is the first in over thirteen years to identify an alternate susceptibility gene for Cowden syndrome (CS) and related disorders.

Mutations of the common tumor suppressor PTEN are associated with most cases of CS, a poorly recognized, inherited cancer syndrome that causes benign and malignant breast, thyroid and uterine tumors. However, about 15% of CS patients do not exhibit PTEN mutations and the cause for the disorder in these patients is unknown. Further, many patients present with a poorly understood CS-like syndromes that do not meet the diagnostic guidelines for CS. "Other susceptibility genes for CS and CS-like phenotypes must exist," says lead study author Dr. Charis Eng, the Hardis Chair and Director of the Genomic Medicine Institute at the Cleveland Clinic.

Succinate dehydrogenase (SDH) is a mitochondrial enzyme that is responsible for energy production and is therefore vital to all organs and organisms. Mutations in both copies of the SDH genes cause a rare devastating brain and heart condition resulting in death in infancy and childhood. Surprisingly, mutations in one of the pair of genes for various

forms of SDH (referred to as SDHx) have been linked to a group of rare tumors called paragangliomas and pheochromocytomas. Dr. Eng noticed, however, that 1-5% of individuals with these rare tumors also had thyroid cancers similar to those observed in CS and CS-like patients. "We hypothesized that SDHx might represent susceptibility genes, other than PTEN, for CS/CS-like syndromes," explains Dr. Eng.

Dr. Eng and colleagues screened samples from CS/CS-like individuals that did not possess PTEN mutations for mitochondrial dysfunction. They identified a subset of patients with CS or CS-like syndrome that had various SDH mutations that were unrelated to PTEN mutations. Compared with PTEN mutation positive CS/CS-like individuals, those with SDH mutations exhibited a consistently increased risk for breast, thyroid and kidney cancers. Interestingly, in the absence of PTEN alteration, CS/CS-like-related SDH mutations exhibited perturbations of cellular signaling pathways similar to those seen in PTEN dysfunction.

"Our data have important implications for both patient care and genetic counseling. I would like to see others independently repeat our observations. Nonetheless, clinicians should consider SDH testing for PTEN mutation-negative CS/CS-like individuals, especially if these individuals have a strong personal history and/or family history of breast, thyroid or kidney cancer. In fact, patients with SDHx mutation should be more rigorously screened for these cancers compared to those with PTEN mutations," concludes Dr. Eng.

Source: Cell Press