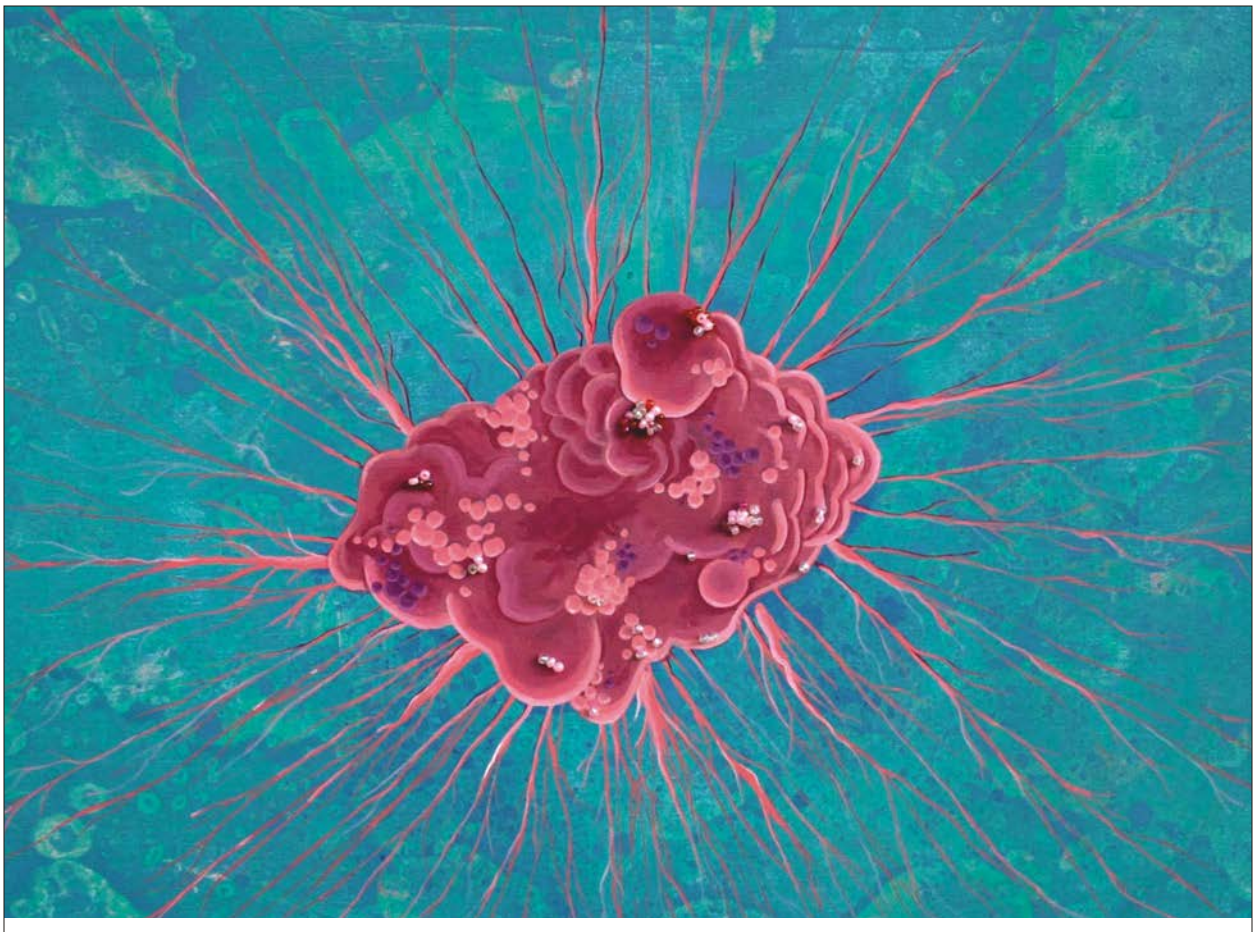

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Gene Alteration Identified That Predisposes to Syndrome With High Risk of Cancer

Researchers have identified a new genetic alteration that predisposes individuals to Cowden syndrome, a rare disorder that is characterized by high risks of breast, thyroid and other cancers, according to preliminary research published in the December 22/29 issue of JAMA.

A majority of patients with Cowden syndrome, which occurs in approximately 1 in 200,000 live births, and a small minority of patients with Cowden-like syndrome, have mutations in the tumor suppressor PTEN gene. These mutations are associated with increased risk of various malignancies, approximately 10 percent lifetime risk for thyroid cancer, and as much as 50 percent lifetime risk for female breast cancer over the general population, according to background information in the article. "A large heterogeneous group of individuals with Cowden-like syndrome, who have various combinations of Cowden syndrome features but who do not meet Cowden syndrome diagnostic criteria, have PTEN mutations less than 10 percent of the time, making molecular diagnosis, prediction, genetic counseling, and risk management challenging."

Other mechanisms of loss of function could result in underexpression of PTEN or of KILLIN, a novel tumor suppressor gene lying right next to PTEN, which may account for the remainder of Cowden syndrome and Cowden-like syndrome. "In the context of a difficult-to-recognize syndrome, identification of additional cancer predisposition genes would facilitate molecular diagnosis, genotype-specific predictive testing of family members who are as yet clinically unaffected, genetic counseling, and medical management," the authors write.

Included in the objectives of a study conducted by Charis Eng, M.D., Ph.D., of the Cleveland Clinic, and colleagues, was to determine the likelihood of KILLIN as a predisposition gene in patients with Cowden syndrome or Cowden-like syndrome, because of its similar function to PTEN. The study included analysis of nucleic acids from 123 patients with Cowden syndrome or Cowden-like syndrome and 50 unaffected individuals without PTEN variants, which were genetically analyzed for expression of PTEN and KILLIN from August 2008 -- June 2010. Prevalence of cancers between groups was compared.

Among the findings of the researchers was that KILLIN is a predisposition gene for Cowden syndrome and Cowden-like syndrome. Individuals with KILLIN-promoter methylation (turns gene off) had a 3-fold increased prevalence of breast cancer (35/42 vs. 24/64) and a greater than 2-fold increase of kidney cancer (4/45 vs. 6/155) over individuals with germline (the cell line from which egg or sperm cells [gametes] are derived) PTEN mutations.

"By discovering another cancer predisposition gene, we have added to the sensitivity of molecular diagnosis and predictive testing becomes possible. Importantly, genetic counseling and gene-informed risk assessment and management become evidence based," the researchers write. "The current national practice guidelines for individuals with PTEN germline mutations includes heightened surveillance of the female breasts and thyroid, but do not have awareness of renal cancer risk. If our observations of 2- to 3-fold increased risks of renal and/or breast cancer with KILLIN germline methylation over those of PTEN mutation holds, then extra vigilance for the organs at risk, breast and kidneys, is warranted. The KILLIN-associated breast cancer risks would parallel those conferred by germline BRCA1/2 mutations."

"If these data can be and must be replicated independently, then a hypothetical schema for prioritizing gene testing could be as follows: (1) individuals with classic Cowden syndrome should be offered PTEN testing first; (2) those found not to have germline PTEN mutations should then be

offered KILLIN epigenetic [affects expression of genes without mutation] analysis, in the setting of genetic counseling; and (3) individuals with classic Cowden syndrome without germline PTEN mutation (80 percent are mutation-positive) and without KILLIN epigenetic inactivation (half of the 20 percent should have KILLIN epigenetic inactivation) should then be offered SDHB/D [a type of genes] testing (10 percent of the 20 percent should have SDHB/D mutation). Altogether, therefore, PTEN, KILLIN, and SDHB/D should then account for 92 percent of all classic Cowden syndrome," the authors write.

Editorial: PTEN Promoter Silencing and Cowden Syndrome

In an accompanying editorial, Danijela Jelovac, M.D., and Ben Ho Park, M.D., Ph.D., of the Johns Hopkins University School of Medicine, Baltimore, write that the findings from this study must be cautiously viewed as a foundation for further research that may allow for the unambiguous demonstration of the role of KILLIN in Cowden syndrome and Cowden-like syndrome.

"In addition, the findings by Bennett et al propose a new model whereby heritable epigenetic regulation in neighboring genes could account for a number of familial cancer syndromes, where no germline mutations have been found. If true, the results of this work could have even greater significance for researchers and physicians and, most importantly, for the families and patients affected by this often devastating group of disorders."

Kristi L. Bennett, Jessica Mester, Charis Eng. Germline Epigenetic Regulation of KILLIN in Cowden and Cowden-like Syndrome. JAMA, Dec 22, 2010 DOI: 10.1001/jama.2010.1877