KILLIN Gene Discovery Stirs Up Research on Cowden Syndrome Cancers

By Charlie Schmidt

Researchers at the Cleveland Clinic have identified what appears to be a powerful gene predictor for cancer among some patients with Cowden syndrome (CS) or Cowden-like syndrome (CLS)—rare, inherited conditions characterized in part by the presence of benign neoplasms throughout the body. Published in the *Journal of the American Medical Association* in December, the findings show that up to 85% of CS/CLS patients who have breast cancer also have a compromised gene called KILLIN. Moreover, CS/CLS patients with compromised KILLIN also have much higher risks for kidney cancer than those CS/CLS patients without it.

The study’s authors emphasize that other studies must still replicate these findings. But if the results hold up, KILLIN could be one of the strongest genetic cancer risk factors discovered—on par with BRCA1 and BRCA2, albeit for this more limited CS/CLS population, according to the study’s corresponding author, Charis Eng, M.D., Ph.D.

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“We don’t know,” Eng said.

Eng came across KILLIN while looking for the genetic cause of CS among patients who don’t have germline PTEN mutations. She and her team started with 2,000 CS/CLS patients in the United States. From that group, they selected 123 individuals with pristine PTEN and an absence of nearby germline anomalies. Eng’s initial hypothesis was that although these patients don’t have mutated PTEN, perhaps epigenetic mutations—methyl groups sticking to the sequence that interfere with the gene’s ability to make protein—could compromise the gene.

The team did find that PTEN is often hypermethylated, meaning that the methyl groups stick to its promoter, the “on switch” for protein transcription. Unexpectedly, though, PTEN could still function normally despite these methyl groups. But when Eng looked more closely at the surrounding sequences, she found that hypermethylation had compromised PTEN’s next-door neighbor: KILLIN. From that finding, she
deduced that KILLIN and PTEN share the same promoter but that hypermethylation affects only KILLIN’s expression.

Pen Liang, Ph.D., and colleagues from the Vanderbilt–Ingram Cancer Center in Nashville, Tenn., discovered KILLIN in 2008. These scientists also found that the tumor suppressor p53 regulates both KILLIN and PTEN. In her current research, Eng showed that hypermethylation of the PTEN/KILLIN promoter disrupts p53’s regulation of KILLIN but not that of PTEN. When KILLIN becomes dysfunctional because of inadequate p53 regulation, Eng proposed, cells proliferate abnormally, which produces hamartomas and could lead to cancer.

Concerns Over Limited Data
Ben Ho Park, M.D., Ph.D., an oncologist and associate professor at the Johns Hopkins University School of Medicine in Baltimore, described Eng’s findings as provocative in that they open new lines of research. But Park is not convinced that KILLIN is a bona fide tumor suppressor gene, like PTEN.

To qualify as a tumor suppressor gene, Park said, KILLIN would have to satisfy the Knudsen “two hit” hypothesis (first described by Alfred G. Knudsen, M.D., Ph.D., from Philadelphia’s Fox Chase Cancer Center). According to Knudsen’s hypothesis, which isn’t universally accepted, Park said, tumor suppressor genes allow uncontrolled cell growth only when
both their alleles are silenced. Eng still has not demonstrated that for KILLIN. Moreover, Eng didn’t test unaffected CS family members and so could not confirm the absence of PTEN/KILLIN hypermethylation in these individuals.

“I’m somewhat concerned that [these] results are overstated,” Park said. “In my view, it’s premature to say this KILLIN is definitely a causal gene for CS/CLS that warrants changes in screening policy.” To that, Eng responded that for now, patients should be screened for KILLIN only in research settings designed to validate her recent findings.

Now PTEN testing is offered on the basis of medical and family history, either to link what looks like CS to a molecular cause or to assess risks for CS-related cancers among unaffected family members. A positive PTEN finding might lead to heightened cancer surveillance, for instance, by substituting magnetic resonance imaging for mammography in breast cancer screening, according to Kathleen Hruska, Ph.D., an associate science director of GeneDx, a molecular diagnostics company in Gaithersburg, Md. If Eng’s results hold up, said Hruska, then suspected CS patients with breast or renal cell cancer might be tested for KILLIN in advance of PTEN, given that the new gene may turn out to be a more powerful risk factor for these illnesses.

Current CS screening guidelines from the National Comprehensive Cancer Network (NCCN) recommend breast magnetic resonance imaging for CS patients beginning at age 30–35 years and thyroid cancer surveillance with ultrasound beginning at age 18. (In a new report published in *Hereditary Cancer in Clinical Practice* on June 17, Eng et al. argue for screening at younger ages.) NCCN’s guidelines make no recommendation with respect to kidney cancer screening, but according to Ken Offit, M.D., chief of the clinical genetics service at the Memorial Sloan–Kettering Cancer Center in New York, that may soon change. Offit sits on NCCN’s CS expert panel. Eng’s results, he said, add to evidence of kidney cancer risk among CS patients. On the basis of these results, NCCN may recommend renal ultrasound or some other form of cross-sectional kidney imaging in CS patients later this year, he said. Offit disagrees with Park’s view of the data, suggesting that screening for KILLIN in PTEN-negative CS families now seems sensible.

**New Epimutation**

More intriguing than the screening implications of Eng’s findings, in Offit’s view, are their implications for research into familial cancer syndromes. The findings appear to show that PTEN/KILLIN hypermethylation can be inherited—making it one of the few examples of a gene risk factor passing through generations with no change to DNA. This example is now the third of an inherited epigenetic mutation involved in the mechanism for cancer susceptibility, Offit said. The other two target the MSH2 and MHL1 genes, both implicated in familial colon cancer.

Such epimutations pose vexing challenges for genetic counseling. For instance, whereas inheritance of MSH2 epimutations follows a straightforward, autosomal-dominant (i.e., Mendelian) pattern, non-Mendelian inheritance has been observed for MSH1, possibly because methylation is reversible. “So, when we find epimutations in MSH1, we advise testing of as many family members as possible and intensified colon cancer screening for those found to carry the mutation,” he said.

Eng’s results, Offit added, suggest a possible Mendelian inheritance pattern for KILLIN, but the data are so far too limited to state this conclusively. Therefore, the possibility of more complex transmission patterns remains. “It seems prudent to follow the MSH1 model and test as many CS family members as possible for KILLIN as possible, until the mode of transmission can be worked out,” he said.

Eng said she plans to continue testing CS family members for KILLIN hypermethylation and that she has assembled a new cohort to test the validity of her findings.