New cancer genes identified, opening door to targeted treatments

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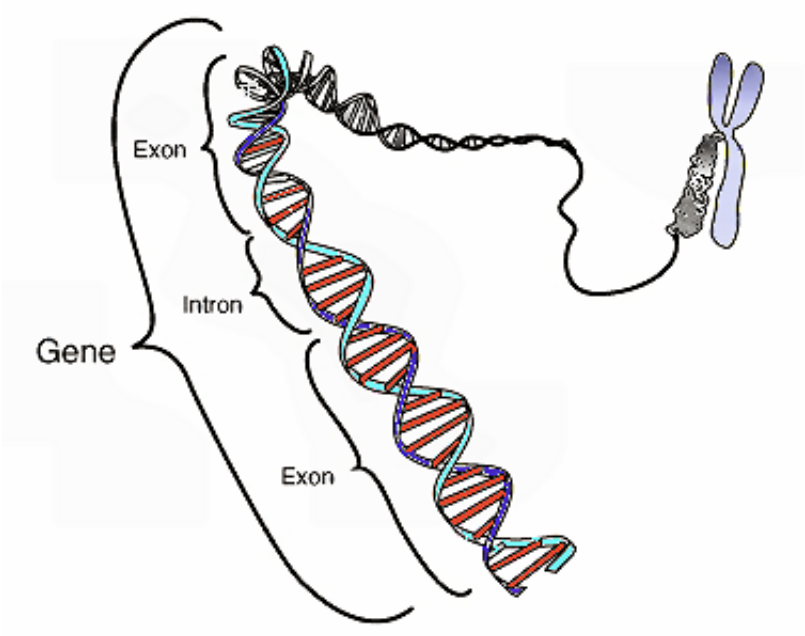

This image shows the coding region in a segment of eukaryotic DNA. Credit: National Human Genome Research Institute

In a discovery that could lead to more targeted and effective treatments for certain lung and prostate cancers, researchers at the University of Virginia School of Medicine have identified two new cancer-causing gene mutations - mutations that may be particularly susceptible to cancer-fighting drugs already approved by the federal Food and Drug Administration. One of the gene mutations also may play a key role in early menopause.

'The Perfect Hammer'

The discovery suggests that cancers with the newly discovered mutations in the MCM8 and MCM9 genes likely will respond extremely favorably to the same chemotherapy drugs that have already proven effective against breast cancers with the well-known BRCA1 and BRCA2 gene mutations.

"One of the biggest problems in cancer is that we hit everything with the same hammer, and consequently some cancers are responsive and others are not.

Imagine if you could find the perfect hammer for the nail - the famous personalized therapy," said lead researcher Anindya Dutta, MD, PhD. "If a patient has BRCA1 and BRCA2 mutations, then the perfect hammer is cisplatin and olaparib. Similarly, [for other cancers,] if you could break them up into those with mutations in MCM8 and MCM9, and then hit them hard with olaparib and cisplatin, we predict that there will be much better responsiveness."

Missing DNA Repairmen

Dutta's new research shows that the MCM8 and MCM9 genes produce proteins that play a critical role in homologous recombination, a method cells use to repair double-strand breaks in our DNA. Such breaks are thought to occur commonly—perhaps thousands of times in each cell's life—but the vital repair proteins appear to be missing in cancers with MCM8 and MCM9 mutations. That defect could be the cancer cells' downfall, theoretically making them "superbly sensitive" to cisplatin and other drugs already developed to battle BRCA1 and BRCA2 mutations, said Dutta, chairman of UVA's Department of Biochemistry and Molecular Genetics.

As of now, there is no commercially available diagnostic test for the MCM8 and MCM9 mutations, though they could be revealed via whole genome sequencing. Dutta, however, says that a much simpler test can be designed; he'd also like to see a clinical trial to determine the effectiveness of cisplatin and olaparib in battling cancers with the MCM8 and MCM9 mutations.

Dutta's research also notes the correlation of genetic inactivation of the MCM8 gene and the early onset of menopause, also known as premature ovarian failure. That will give scientists a new avenue to explore as they seek to better understand the condition.

Findings Published

The findings have been detailed in a paper published online by *Nature Communications*. It was authored by Kyung Yong Lee, Jun-Sub Im, Etsuko Shibata, Jonghoon Park, Naofumi Handa, Stephen C. Kowalczykowski and Dutta.

Provided by University of Virginia