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Breakthrough study finds 'master switches' in colon cancer

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A team of researchers at Case Western Reserve University School of Medicine have identified a new mechanism by which colon cancer develops. By focusing on segments of DNA located between genes, or so-called "junk DNA," the team has discovered a set of master switches, i.e., gene enhancer elements, that turn "on and off" key genes whose altered expression is defining for colon cancers. They have coined the term Variant Enhancer Loci or "VELs," to describe these master switches.

Importantly, VELs are not mutations in the actual DNA sequence, but rather are changes in proteins that bind to DNA, a type of alteration known as "epigenetic" or "epimutations." This is a critical finding because such epimutations are potentially reversible.

Over the course of three years, the team mapped the locations of hundreds of thousands of gene enhancer elements in DNA from normal and cancerous colon tissues, pinpointing key target VELs that differed between the two types.

"What is particularly interesting is that VELs define a 'molecular signature' of colon cancer. Meaning, they are consistently found across multiple independent colon tumor samples, despite the fact that the tumors arose in different individuals and are at different stages of the disease," says Peter Scacheri, PhD, senior author of the study and assistant professor, Genetics and Genome Sciences, School of Medicine, and member, Case Comprehensive Cancer Center at Case Western

Reserve University. "The set of common VELs govern a distinct set of genes that go awry in colon cancer."

"The VELs signature is notable because it cuts through the complexity of the many genes that are changed in colon cancer, to identify genes that are direct targets of alterations on chromosomes", says Sanford Markowitz, MD, PhD, Ingalls Professor of Cancer Genetics in the Division of Hematology-Oncology at the School of Medicine, member, Case Comprehensive Cancer Center, and oncologist at University Hospitals Seidman Cancer Center, whose team collaborated on the study. "The key next step will be to determine whether we can use VELs for 'personalized medicine,' to molecularly define distinct groups of colon cancers that differ in their clinical behavior, and to enable selection of specific drugs that will best treat a given colon tumor."

In addition to finding that VELs are a "signature" of colon cancer, the team showed that genetic variants which predispose individuals to colon cancer are located within VELs. This suggests that individual differences within VELs may play significant roles in determining different individuals' susceptibility to colon cancer.

"Epigenetics has transformed the way we think about genomes. The genetic code isn't just a series of As, Ts, Gs, and Cs strung together. Epigenetic 'marks' on DNA tell genes when, where, and how much to turn on or off to keep cells healthy," says Batool Akhtar-Zaidi, PhD candidate in Dr. Scacheri's lab and lead author of the study. "When this epigenetic machinery is disrupted, as we see with VEL events, this can tip the balance to cancer."

More information: "Epigenomic enhancer profiling defines a signature of colon cancer" is published advanced online in *Science Express*.

Provided by Case Western Reserve University