There goes the neighborhood: Changes in chromosome structure activate cancer-causing genes

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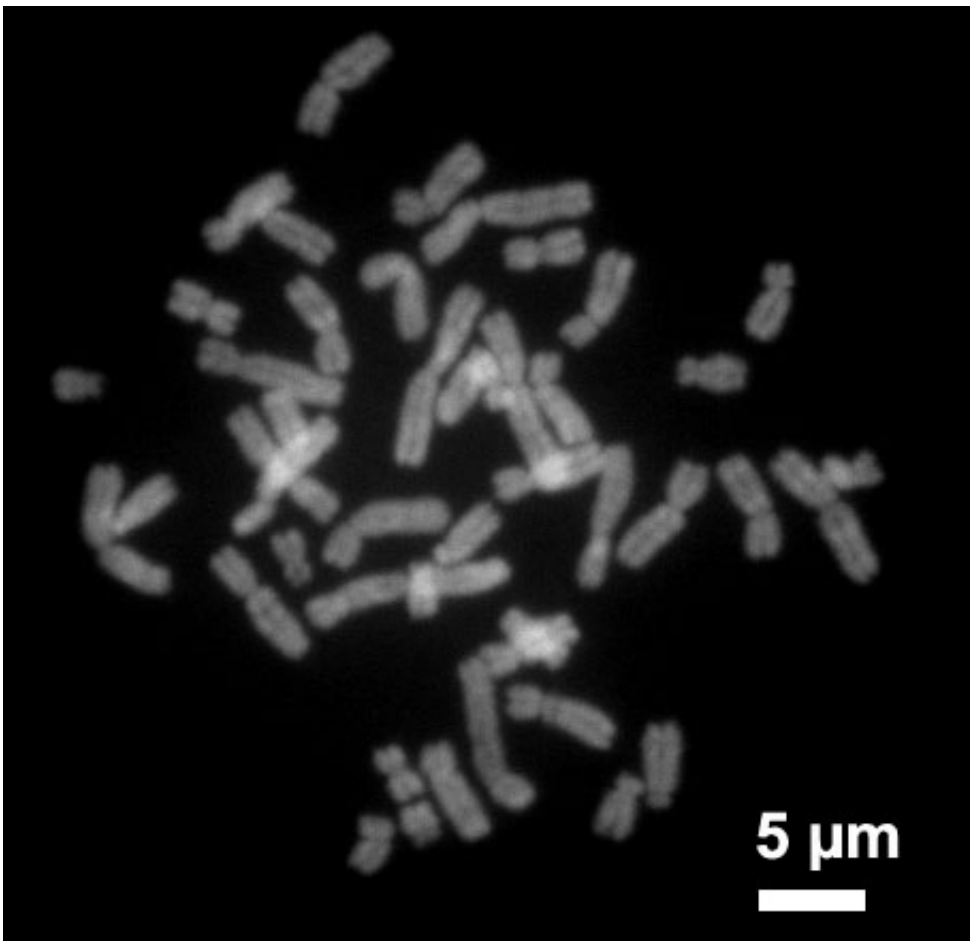

Human chromosomes during metaphase. Credit: Steffen Dietzel/Wikipedia

In a finding with enormous implications for cancer diagnostics and

therapeutics, Whitehead Institute scientists have discovered that breaches in looping chromosomal structures known as "insulated neighborhoods" can activate oncogenes capable of fueling aggressive tumor growth.

"This new understanding of the role of chromosome structure in cancer gene misregulation reveals the powerful influence of the genome's structure in human health and disease," says Whitehead Member Richard Young, whose lab's research is reported online this week in the journal *Science*.

Young's most recent findings build on previous work in which the lab charted human genome structure and described its influence on gene control in healthy cells. By mapping the genome's three-dimensional (3D) conformation, researchers found that key genes controlling cell identity are found in insulated neighborhoods, whose loops are maintained through anchor sites bound by the protein CTCF. All essential gene regulation, including control of proper activation and repression, takes place within these enclosed neighborhoods.

The scientists had also found that these CTCF loop anchor sites are maintained across various cell types in the human body and highly conserved in primate genomes, emphasizing their importance in normal development. Such widespread structural conservation led the researchers to hypothesize that disruptions in genome conformation might be associated with disease, including cancer.

Sure enough, subsequent systematic genomic analysis of >50 cancer cell types revealed mutations affecting CTCF anchor sites, leading to the loss of insulated neighborhood boundaries. Such neighborhood breaches were found especially frequently in T-cell acute lymphoblastic leukemia, esophageal and liver carcinoma, and in some cases allowed enhancer elements to contact and activate previously silent oncogenes.

"We hadn't known if these types of mutations contributed to cancer," says Young. "Now we have multiple examples where these disruptions activate oncogenes that play major roles in tumorigenesis."

Researchers in Young's lab note that this oncogenic mechanism is not only widespread in cancer, but may be valuable for identifying the key genes that drive poorly understood cancers.

"In some cancers, such as esophageal carcinoma, the most frequent genetic mutation occurs at the CTCF sites, which is quite striking," says Denes Hnisz, a postdoctoral researcher in the Young lab and co-first author of the *Science* paper. "In addition, there are still many cancers whose driver mutations and oncogenes are not known and mapping altered structures may reveal the key oncogenes in these cancers."

In a final step confirming the relationship between structural disruption and oncogenesis, Hnisz and co-first author Abe Weintraub, a graduate student in Young's lab, used genome editing techniques to introduce CTCF anchor site deletions in non-malignant cells. These mutations were sufficient to activate oncogenes that are silent in normal cells.

The new findings suggest that future mapping of genome structure in individual patient cancers may improve diagnosis and help guide treatment protocols. "Now that we understand how perturbations in the genome's structure can contribute to oncogenesis, we're developing strategies to efficiently diagnose and potentially fix these faulty neighborhoods," says Weintraub.

More information: "Activation of proto-oncogenes by disruption of chromosome neighborhoods," *Science*, (2016). DOI: 10.1126/science.aad9024