Scientists delve into 'black box' of DNA research

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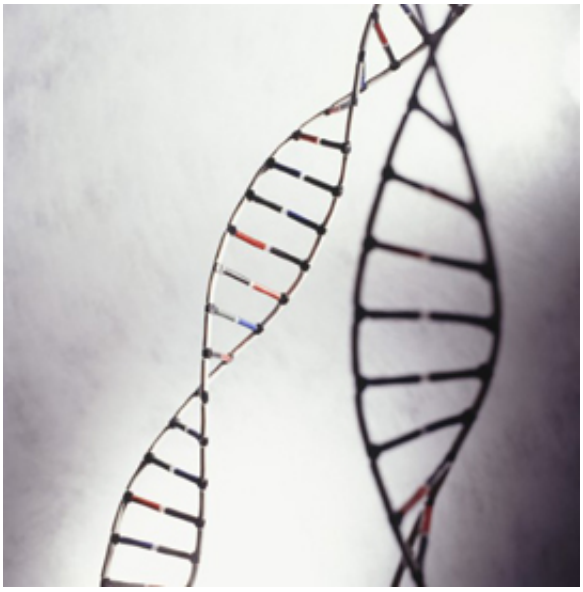

Credit: NIH

Scientists at Florida State University, Baylor College of Medicine and the Broad Institute of Harvard and MIT have broken ground in a little-understood area of human genetics.

In a new study published in the *Proceedings of the National Academy of Sciences*, researchers show that an unusual DNA repeat element on an inactive X chromosome is actually essential to the overall three-dimensional structure of this female-specific genetic phenomenon.

It's what FSU Associate Professor of Biological Science Brian Chadwick describes as the "black box of genome biology."

"These repeat elements are one of the unknowns in our genome," Chadwick said. "Nobody knows where they originated from or why we have retained them, but typically this points to them performing some as of yet unknown important function. The repeats on the X chromosome are particularly intriguing, because they don't behave the way other DNA sequences do."

In nearly all female mammals, there are two X chromosomes. However, one of the chromosomes is almost entirely inactivated, meaning that most genes on the chromosome aren't necessarily dictating a biological function. Since silencing this chromosome is essential for female development, scientists have long been trying to understand how this is achieved and maintained.

While most of the chromosome is packaged into a silent state, there are parts that don't play along. What is unique about most of these parts is that they feature unusual repeat sequences including at one location the extensive tandem repeat called DXZ4.

Similar large repeats exist elsewhere on other chromosomes, and at least one is directly involved in the onset of a common form of muscular dystrophy, while another has been linked to schizophrenia. But why the X chromosome contains these repeats and what they are doing has been a mystery.

Earlier independent work from both groups showed that these repeat elements make frequent contact with one another exclusively on the inactive chromosome, generating what Baylor Assistant Professor and Director of The Center for Genome Architecture Erez Lieberman Aiden coined "superloops."

When Chadwick saw how complementary Aiden's research was, he suggested they team up to tackle the question of function together. In their latest work, the researchers also report that DXZ4 is involved in forming superloops at the inactive X chromosome in rhesus macaque monkeys and mice.

"In principle, the presence of DXZ4 at one end of the human superloops could have been a coincidence," said Aiden, who is also a faculty member at Rice University in Computer Science and at the Center for Theoretical Biological Physics. "But the fact the DXZ4 lies at the site of superloops in all three species was a critical clue."

Chadwick and Aiden employed cutting-edge genome engineering techniques to remove DXZ4 from the inactive X, generating one of the largest engineered deletion in human cells to date, and then applied innovative approaches and microscopic techniques in order to see what exactly would happen if that didn't exist.

The deletion caused a major formation change in the chromosome—it caused the three-dimensional structure of the inactive X DNA to collapse.

"In the absence of this repeat, it significantly alters the folding and organization of the X chromosome," Chadwick said. "It showed for the first time that it was essential for the correct three-dimensional structure of the human chromosome."

"We're entering an exciting new era of genomics," Chadwick said. "We know a lot about basic gene expression and gene structure. But what we don't know is how everything works three dimensionally in the nucleus. Armed with these new genome engineering resources and the state-of-the-art high-throughput genomic analysis tools pioneered by labs such as Dr. Aiden's, we're just starting to pick away at that."

More information: Deletion of DXZ4 on the human inactive X chromosome alters higher-order genome architecture, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1609643113

Provided by Florida State University