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DNA palindromes found in cancer

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DNA palindromes appear frequently and are widespread in human cancers, and identifying them could help advance the understanding of genomic instability, according to researchers writing in an advanced online publication of *Nature Genetics* for February 13.

While the scientists did not find similar widespread palindrome formation in four normal cell lines studied, "I anticipate we will identify palindromes on the somatic chromosomes of normal cells that might not have been mapped yet," coauthor Stephen Tapscott of the Fred Hutchinson Cancer Research Center in Seattle told *The Scientist*.

In 2002, Meng-Chao Yao, also of the Hutchinson Center, and colleagues found the molecular mechanisms for palindrome formation in the protozoan *Tetrahymena* were conserved in mammalian cells and that it was an initial, rate-limiting step in gene amplification. Given amplification of large genomic regions contributes to tumor progression, the investigators explored what role DNA palindromes - already known to exist on the normal human Y chromosome - might play in human cancers.

In the current *Nature Genetics* study, Yao's team developed a new method to assess palindrome formation based on what previously made palindromes difficult to study - their propensity for rapid intrastrand base pairing. In the technique, if DNA containing palindromic regions is denatured and rapidly renatured, the results are double-stranded snap-back DNA near palindromic centers and largely single-stranded DNA in nonpalindromic regions. The snap-back DNA is resistant to single-strand - specific nuclease S1, while the rest is sensitive. When the researchers combined their technique with a cDNA-spotted array, widespread palindrome formation was not seen in one breast epithelial or three different fibroblast cell lines.

"The sensitivity is terrific, able to detect signal in a 1:40 dilution from a cell line containing only a couple of copies of the palindrome," Maria Jasin of Memorial Sloan-Kettering Cancer Center in New York, who did not participate in this study, told *The Scientist*. "This research provides another mechanism to investigate genomic instability and therefore will likely become widely used by both cancer and basic researchers."

In the Colo320DM human colon cancer cell line, Tapscott and colleagues found 150 genes tested significantly higher for palindromes than baseline, with significant overlap of palindrome-positive genes with breast cancer cell line MCF7. While most of the palindrome-positive genes seen in Colo320DM and MCF7 are not linked with an increase in gene copy number, as a whole these genes are more likely than any other loci to be amplified.

This indicates "only certain regions might be susceptible to further gene amplification. So the location of a tumor's palindromes might determine its ability to amplify genes and progress to higher stages of cancer," Tapscott said.

Tapscott anticipated that others might criticize the findings because the technique might be measuring unknown features aside from palindromes. "But those features, if they exist, are structures not yet imagined yet," Yao said. The researchers plan experiments with more saturating, as-yet-to-be-

determined array technologies to identify where the posited palindrome centers are to directly verify their structures. In the near term, they also hope to determine the biological significance of the palindromes in tumor progression or potential.

"Their array looks at underlying genomic structure and on a genome-wide scale and high-throughput fashion, and that is really quite new," Thoas Fioretos of Lund University Hospital in Sweden, who did not participate in the study, told *The Scientist*. "We currently know how many individual genes can elicit activity for malignant transformation, but we are not sure what the mechanism is behind the activation of these genes. Their method allows a look at structural genomics features that might make cancer cells susceptible to genomic rearrangements."

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