Researchers discover link between DNA palindromes and disease

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In the past 10 years, researchers in genome stability have observed that many kinds of cancers are associated with areas where human chromosomes break. More recently, scientists have discovered that slow or altered replication causes chromosomal breaking. But why does DNA replication stall?

In a Tufts University study published in the July 14 issue of "Proceedings of the National Academy of Sciences," a team of biologists have found a relationship between peculiar DNA sequences named palindromes and replication delays.

Sergei Mirkin, White Family Professor of Biology at Tufts' School of Arts and Sciences, along with his graduate student Irina Voineagu and collaborators Kirill Lobachev and Vidhya Narayanan from the Georgia Institute of Technology explored the heretofore elusive function of long palindromes in DNA replication. Mirkin's research was funded by the National Institutes of Health.

Mirkin and his team studied palindrome behavior in bacterial, yeast and mammalian cells because they allowed them to monitor DNA replication in a more detailed way than looking at actual human chromosomes. Based on previous studies in model systems, they expect their results to be applicable for human chromosomes.

Abnormally shaped DNA blocks molecule's

replication

In the context of everyday life, palindromes are quite common, said Mirkin. They are words, phrases, numbers or other sequences of units that read the same way in either direction. "We all enjoy palindromes in everyday language, such as 'A man, a plan, a canal – Panama!' They are short, make perfect sense and are easy to remember," he explained. The problems begin when they become longer. "They stop making sense," he said. "For example, say 'A man, a plan, a cat, a ham, a yak, a yam, a hat, a canal-Panama!'"

Past DNA research had shown that long palindromes change the shape of the molecule from a double helix into a hairpin or cruciform like structure in a test tube. It was not known, however, whether these changes can occur inside cells and, if so, affect DNA functioning. In this study, the researchers found that large palindromes stall the replication machinery.

"Replication is carried out by a complex and sophisticated machinery, which has many levels of checks and balances to prevent 'typos' from happening. Long DNA palindromes, however, can occasionally jam this powerful replication machinery," Mirkin explained. The researchers were also able to pinpoint the exact structure causing DNA malfunction. "In all cases it was the formation of the hairpin-like DNA structure in a palindrome that caused the replication to stall," he said.

Other scientists have previously found that when replication slows down, chromosomes break. "Stalled DNA replication could result in the chromosomal breakage during cell division, explaining why DNA palindromes are genomic weak spots."

The study of yeast cells yielded an additional finding. Mirkin and his team found that two proteins within the cell - Tof1 and Mrc1 - enabled

replication to proceed through the hairpin-like DNA structures. "These proteins might be key players in protecting the genome from breaking at DNA palindromes," said Mirkin.

Mirkin said he has begun experiments to see if the same results will be observed with human homologues of these proteins.

Source: Tufts University/PhysOrg.com