DNA caught rock 'n rollin' (w/ Video)

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(PhysOrg.com) -- DNA, that marvelous, twisty molecule of life, has an alter ego, research at the University of Michigan and the University of California, Irvine reveals.

On rare occasions, its building blocks "rock and roll," deforming the familiar double helix into a different shape.

"We show that the simple DNA double helix exists in an alternative form—for one percent of the time—and that this alternative form is functional," said Hashim M. Al-Hashimi, who is the Robert L. Kuczkowski Professor of Chemistry and Professor of Biophysics at U-M. "Together, these data suggest that there are multiple layers of information stored in the genetic code." The findings were published online Jan. 26 in the journal *Nature*.

It's been known for some time that the DNA molecule can bend and flex, something like a rope ladder, but throughout these gyrations its building blocks—called bases—remain paired up just the way they were originally described by James Watson and Francis Crick, who proposed the spiral-staircase structure in 1953. By adapting nuclear magnetic resonance (NMR) technology, Al-Hashimi's group was able to observe transient, alternative forms in which some steps on the stairway come apart and reassemble into stable structures other than the typical Watson-Crick base pairs.

The question was, what were these alternative stable structures?

"Using NMR, we were able to access the chemical shifts of this alternative form," said graduate student Evgenia Nikolova. "These chemical shifts are like fingerprints that tell us something about the structure." Through careful analysis, Nikolova realized the "fingerprints" were typical of an orientation in which certain bases are flipped 180 degrees.

"It's like taking half of the stairway step and flipping it upside down so that the other face now points up," said Al-Hashimi. "If you do this, you can still put the two halves of the step back together, but now what you have is no longer a Watson-Crick base pair; it's something called a Hoogsteen base pair."

"Using computational modeling, we further validated that individual bases can roll over inside the double helix to achieve these Hoogsteen base pairs," said Ioan Andricioaei, an associate professor of chemistry at the University of California, Irvine.

Hoogsteen base pairs have previously been observed in double-stranded DNA, but only when the molecule is bound to proteins or drugs or when the DNA is damaged. The new study shows that even under normal circumstances, with no outside influence, certain sections of DNA tend to briefly morph into the alternative structure, called an "excited state."

Previous studies of DNA structure have relied mainly on techniques such as X-ray and conventional NMR, which can't detect such fleeting or rare structural changes.

"These methods do not capture alternative DNA structural forms that may exist for only a millisecond or in very little abundance, such as one percent of the time," said Al-Hashimi. "We took new solution NMR methods that previously have been used to study rare deformations in proteins and adapted them so that they could be used to study rare states in nucleic acids. Now that we have the right tools to look at these so-called excited states, we may find other short-lived states in DNA and RNA."

Because critical interactions between DNA and proteins are thought to be directed by both the sequence of bases and the flexing of the molecule, these excited states represent a whole new level of information contained in the genetic code, Al-Hashimi said.

In addition to Al-Hashimi, Nikolova and Andricioaei, the paper's authors are undergraduate student Abigail Wise and assistant professor of biological chemistry Patrick O'Brien of U-M and postdoctoral researcher Eunae Kim of the University of California, Irvine.

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