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Give and take: 'Z-philic' A...A mismatch in a GAC repeat promotes interaction with Z α binding domain of human ADAR1 protein

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Tandem repeats or microsatellites are abundant in eukaryotic genomes and are polymorphic in nature. Abnormal expansion of such tandem repeats in different sequence contexts cause many incurable genetic diseases. These over expansions lead to genome instability irrespective of its location in the genome by forming unusual secondary structures comprising of non-canonical base pairs. By employing molecular dynamics simulation technique, here we investigate the structural traits of DNA d(GAC)6.d(GAC)6 hairpin containing A...A mismatch that is associated with pseudoachondroplasia and multiple epiphyseal dysplasias. Results show local B-to-Z DNA formation akin to d(CAG)6.d(CAG)6 repeat. This finding is further corroborated by titrating d(GAC)5.d(GAC)5 with different concentrations of salt (NaCl) and Z α binding domain of human ADAR1 protein using circular dichroism studies. Comparison of canonical d(GAC)5.d(GTC)5 with non-canonical d(GAC)5.d(GAC)5 duplexes confirms that non-isosterisity of A...A mismatch impels Z-DNA formation in the latter, thereby, facilitating the binding with Z α binding domain of human ADAR1 protein. As this is the first study that shows the binding of A...A mismatch containing d(GAC)5.d(GAC)5 duplex with an Z-DNA binding protein, it opens up a new avenue to investigate the role of Z-DNA binding proteins in trinucleotide repeat expansion disorders. Further, even a single A...A mismatch that intervenes canonical base pairs in the following sequence contexts: 5'GAA-3'CAT, 5'GAG-3'CAC, 5'AAC-3'TAG, 5'AAG-3'TAC, 5'TAA-3'AAT, 5'TAT-3'AAA, 5'CAA-3'GAT and 5'AAT-3'TAA (A...A mismatch underlined) also forms B-Z junction at the mismatch site. Such B-Z transition imposed by non-canonical A...A mismatch irrespective of the flanking sequence may have an impact on binding with mismatch repair or regulatory proteins and the accompanying biological processes.

Biography

Rathinavelan has completed her PhD from Department of Crystallography and Biophysics, University of Madras. Subsequently, she did her postdoctoral studies from Center for Bioinformatics/Department of Molecular Biosciences, The University of Kansas, US. Currently, she is working as an Assistant Professor in IIT Hyderabad and she has published more than 10 research papers in reputed journals.

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