Non-B DNA Conformations, Mutagenesis and Disease

Robert D. Wells*
Institute of Biosciences and Technology
Texas A&M System Health Science Center
2121 W. Holcombe Blvd.
Houston, TX 77030-3303, USA
rwells@ibt.tamhsc.edu

A veritable explosion has taken place in recent years in our molecular (nano) comprehension of the etiology of genomic disorders. These processes are mediated by the formation of non-B DNA structures at certain locations in chromosomes which serve as sites of double-strand breaks as mediated by recombination-repair. Simple repeating DNA sequences adopt non-B DNA conformations (such as triplexes, cruciforms, slipped structures, left-handed Z-DNA and tetraplexes). These non-B DNA structures are mutagenic. The mutagenesis is due to the non-B DNA conformation rather than to the DNA sequence per se in the orthodox right-handed Watson-Crick B-form. The human genetic consequences of these non-B structures are ~20 neurological diseases, ~50 genomic disorders (caused by gross deletions, inversions, duplications and translocations), and several psychiatric diseases involving polymorphisms in simple repeating sequences. The neurological diseases include myotonic dystrophy, fragile X syndrome, and Friedreich Ataxia; the genomic disorders include adrenoleukodystrophy, follicular lymphomas, and spermatogenic failure; and the psychiatric diseases include schizophrenia and bipolar affective disorder. Thus, the convergence of biochemical, genetic and genomic studies has demonstrated a new paradigm implicating the non-B DNA conformations as the mutagenesis specificity determinants, not the sequences as such.

References.

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