PALINDROMES, HAIRPINS, AND COMPLEX REARRANGEMENTS: THE CASE OF 16P13.3

Genomic palindromes are DNA sequences arranged as inverted repeats, meaning that the two strands contain mirror-image sequences. Such structures are intrinsically unstable because the DNA can fold back on itself and form secondary structures, such as hairpins or cruciforms. These non-B DNA conformations interfere with normal DNA replication and repair, can stall or collapse replication forks, and are well known to promote double-strand breaks (DSBs). In short, palindromic architecture creates a physical fragility of the DNA molecule.

This principle has been beautifully illustrated by the work of Beverly Emanuel's group and others on recurrent translocations mediated by short AT-rich palindromic repeats (PATRRs), most famously the t(11;22). In those cases, relatively small palindromes form hairpin or cruciform structures, break, and are then mis-repaired, leading to highly recurrent, stereotyped balanced translocations, often arising during meiosis.

The situation at 16p13.3 described by Fasham et al. (1) is conceptually related but structurally very different. Here, the rearrangements are driven by a much larger palindromic architecture, spanning hundreds of kilobases and embedded in a region rich in segmental duplications. Such a large palindrome is again expected to form secondary structures and to be prone to breakage or replication fork collapse, but the repair does not typically produce a simple translocation. Instead, because of the local genomic architecture and the abundance of homologous sequences, the outcome is a variety of complex intrachromosomal rearrangements.

In practice, this means that the instability of the 16p13.3 palindrome is resolved by error-prone repair or replicative mechanisms (such as template switching), generating complex copy-number structures, most often inverted duplications and duplication–triplication architectures, rather than simple reciprocal exchanges.

The study shows that this locus behaves as a highly unstable, palindrome-driven rearrangement hotspot, explaining why patients present with a characteristic spectrum of complex duplications involving 16p13.3. Importantly, these copy-number variants cause a recognizable and severe clinical phenotype, marked by early-onset progressive ataxia, cognitive decline, and cerebellar atrophy.

1. https://www.ncbi.nlm.nih.gov/pubmed/41349538