TRANSPOSABLE ELEMENTS (TE) IN CANCER AND IN EVOLUTION

A recent study of tumors with exceptionally high LINE-1 (L1) activity was published in Science (1). In just ten highly active tumors, more than 6,000 somatic L1 insertions were identified using long-read sequencing. Most were the expected 5'-truncated insertions. However, a small but significant fraction proved far more consequential. Rather than simply inserting into new loci, some L1 events bridged distant chromosomal breaks, generating deletions, inversions, duplications, and reciprocal translocations between non-homologous chromosomes. These rearrangements arise early during tumorigenesis and were propagated through subsequent clonal expansions, thus, supposedly, making a substantial contribution to the evolutionary trajectory of the tumor.
This same grammar that governs structural variation in tumors operates in the germline. The mechanism is the same; only the clock changes, it just runs much faster in cancer.

Recombination between non-allelic transposable elements, generating deletions, copy number variants, and chromosomal rearrangements, has been extensively documented by Lupski and colleagues in the human population (2). When a deletion generated by repeat-mediated recombination becomes fixed in a population, it effectively disappears from the radar of present-day population studies. To uncover these “ghost” events, Batzer and colleagues (3) compared the human and chimpanzee genomes. They identified hundreds of human-specific deletions, totaling roughly 400 kb of DNA, mediated by Alu–Alu recombination. Many of these occurred within or near genes, and some removed functional exons that were present in our common ancestor.
Across tumors, populations, and species divergence, the underlying mechanism remains strikingly consistent. Transposable elements provide dispersed homologous substrates; DNA repair pathways resolve breaks between them; rearrangements arise. Selection then determines their fate.

1. 10.1126/science.aee4513
2. 10.1101/gr.229401.117
3. 10.1086/504600