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DNA secondary structures and epigenetic determinants of cancer genome evolution

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An unstable genome is a hallmark of many cancers. It is unclear, however, whether mutagenic features that drive somatic alterations in cancer are encoded in the genome sequence, and whether they operate in a tissue- specific manner. Here we perform a genome-wide analysis of 663,446 DNA breakpoints associated with somatic copy-number alterations (SCNAs) from 2,792 cancer samples classified into 26 cancer subtypes. We find that many SCNA breakpoints are spatially clustered in cancer genomes; some breakpoint hotspots are shared across evolutionary timescales (i.e. with personal genomes). We establish that there is a significant enrichment for G-quadruplex (G4) sequences in the vicinity of SCNA breakpoints, and that SCNAs display a strand bias consistent with G4-mediated structural alterations. Integrating methylation data from multiple cancer-types, we report that sites of DNA breakpoint hotspots that are rich in G4 sequences are also significantly enriched for hypomethylation. We propose that abnormal hypomethylation in genomic regions that are enriched in G4 sequences is a key mutagenic factor driving tumorigenesis, thus suggesting a mechanistic model for the generation of tissue-specific mutational landscapes in cancer.

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