Micro-Changing Short Tandem Repeats: Investigating a Novel Genomic Factor of Polymorphism in 10 Human Cancers

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Replication errors represent two-thirds of cancer mutations. A novel subset, micro-changing short tandem repeats (mcSTRs), lack systematic examination in cancers due to complex chromosomal amplifications and intratumor heterogeneity. This study aimed to determine if mcSTRs are significant cancer mutations by i) identifying mcSTRs' prevalence in cancers, ii) comparing mcSTRs to pathogenic repeats in cancer and other diseases, iii) conducting a case-study on clinically-relevant mcSTRs, and iv) investigating case-study mcSTRs in plasma circulating, cell-free DNA as an early cancer diagnostic biomarker. Using an unpublished ActiveSTRs catalog containing 174,323 population-level STRs, ExpansionHunter analysis on 2,622 genomes spanning 37 cancer types identified mcSTRs (N=182) across 10 cancer types—98% subtype-specific—permitting tissue-of-origin detection. Global mcSTR burden was found to alter TOP1 and MSH2 expression, indicating cancer DNA repair pathway influence. mcSTRs lacked overlap with previous cancer repeats, indicating a novel cancer mutation. Cancer mcSTRs revealed similar genomic qualities to other pathogenic repeats and were associated with survival rate ($p<0.05$), disease-gene annotations ($p<0.005$), and expression ($p<0.01$), indicating influence on cancer severity and regulation. Case-study mcSTRs were experimentally validated in hepatocellular carcinoma (HCC) tumor samples. Regression analysis of eight HCC mcSTRs exhibited 97.8% accuracy in distinguishing tumor-vs-normal sample type, and case-study mcSTR1 was identified in four HCC-extracted plasma DNA. Thus, mcSTRs are viable as an HCC early diagnostic panel. Future investigations on causal mechanisms of mcSTRs in cancers may reveal mcSTRs-based targets as future diagnostics and therapeutics.

Awards Won:

First Award of $5,000

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