MICRO-CHANGING SHORT TANDEM REPEATS

INVESTIGATING A NOVEL GENOMIC FACTOR OF POLYMORPHISM IN 10 HUMAN CANCERS

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My research focuses on discovering new, previously undiscovered cancer DNA mutations that allow for potential early cancer detection via blood tests.

Abstract

Replication errors represent two-thirds of genetic cancer mutations. A newly discovered subset are micro-changing short tandem repeats (mcSTRs). These mcSTRs are unique, where we are looking for small variations upon an expected DNA tandem repeat size (rather than typically looking for large changes in size). These mcSTRs have yet to be analyzed in cancers due to complexities caused by the sheer number of mutations occuring in cancer, which results in technological difficulties identifing mcSTRs. 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. By developing tools to eliminate false-positive signals and prioritize highly-mutating regions of the human genome, computational analysis on 2,622 genomes spanning 37 cancer types identified 182 mcSTRs across 10 cancer types—98% specific to one cancer type. Global mcSTR burden was found to alter DNA repair gene pathways, and lacked overlap with previous cancer repeats, indicating a completely new cancer mutation. Cancer mcSTRs seemed to be structurally similar to other known repeats that cause disease, and were correlated with patient survival rate and disease-gene precedence in literature, 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 nearly 98% accuracy in distinguishing tumor-vs-normal sample type, meaning they could be effectively used as an early diagnostic tool. Plus, mcSTRs were successfully identified in cell-free DNA in plasma samples of cancer patients. Thus, mcSTRs are viable as an HCC early diagnostic blood test. Future investigations on causal mechanisms of mcSTRs in cancers may reveal mcSTRs-based targets as future diagnostics and therapeutics.