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Domain-restricted mutation analysis to identify novel driver events in human cancer

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Abstract

Analysis of mutational spectra across various cancer types has given valuable insights into tumorigenesis. Different approaches have been used to identify novel drivers from the set of somatic mutations, including the methods which use sequence conservation, geometric localization and pathway information. Recent computational methods suggest use of protein domain information for analysis and understanding of the functional consequence of non-synonymous mutations. Similarly, evidence suggests recurrence at specific position in proteins is robust indicators of its functional impact. Building on this, we performed a systematic analysis of TCGA exome derived somatic mutations across 6089 PFAM domains and significantly mutated domains were identified using randomization approach. Multiple alignment of individual domain allowed us to prioritize for conserved residues mutated at analogous positions across different proteins in a statistically disciplined manner. In addition to the known frequently mutated genes, this analysis independently identifies low frequency Meprin and TRAF-Homology (MATH) domain in Speckle Type BTB/POZ (SPOP) protein, in prostate adenocarcinoma. Results from this analysis will help generate hypotheses about the downstream molecular mechanism resulting in cancer phenotypes.

References


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