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Aggressiveness in cancer is associated with the number of predicted functional mutations in a tumor

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Every malignant tumor has a unique spectrum of 10 to 1,000 of protein mutations. The personalized approach to treatment of cancer calls for determining cancer "driver" mutations for each tumor. The combinatorial diversity of cancer-driving events limits the applicability of statistical methods to determine tumor-specific "driver" mutations among an overwhelming majority of "passengers". Recently, we introduced a functional impact score which assesses the mutation impact from the evolutionary conservation in proteins. Can this score be used to identify non-recurrent driver mutations? Using mutations of TCGA cancer projects, we found that predicted functional mutations tend to be evolutionarily selected as compared to low-scoring and neutral mutations. Using mutation data and clinical information of ten cancers studied in TCGA project, we tested the association between aggressiveness of cancer and various types of genomic alteration, such as missense and truncating mutations, predicted functional mutations and gene copy number alterations. We found that the number of predicted functional mutations is the most discriminative collective marker of outcome for eight of ten studied cancers: the more predicted functional mutations, the poorer outcome. This result underscores the carcinogenic role of predicted functional mutations in rarely mutated genes a mutation "long tail" and suggests that the aggressiveness of cancer may depend rather on the total number of driver mutations than on the specific sets of mutated genes. The reduced sets of predicted functional mutations can significantly facilitate determining genomic markers of outcome, identifying the activated pathways and advancing personalized multi-drug therapy.

Biography

Boris Reva has received his Ph.D in 1992 from The Moscow Institute of Applied Physics. He has published more than 50 papers in the fields of bioinformatics, computational biology and cancer genomics.

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