**Passenger mutations in 2500 cancer genomes: Overall molecular functional impact and consequences**

***Abstract***

The Pan-cancer Analysis of Whole Genomes (PCAWG) project provides an unprecedented opportunity to comprehensively characterize a vast set of uniformly annotated coding and non-coding mutations present in thousands of cancer genomes. Classical models of cancer progression posit that only a small number of these mutations strongly drive tumor progression and that the remaining ones (termed “putative passengers”) are inconsequential for tumorigenesis. In this study, we leveraged the comprehensive variant data from PCAWG to ascertain the molecular functional impact of each variant. The predicted impact distribution of PCAWG mutations shows that, in addition to high- and low-impact mutations, there is a group of medium-impact putative passengers predicted to influence gene expression or activity. Moreover, the predicted functional impact relates to the underlying mutational signature: different signatures confer divergent impact, differentially affecting distinct regulatory subsystems and categories of genes. We also find that impact varies based on subclonal architecture (i.e., early vs. late mutations) and can be related to patient survival. Finally, we note that insufficient power due to the limitation in cohort sizes precludes identification of weak drivers using standard recurrence-based approaches. To address this, we adapted an additive effects model derived from complex trait studies to show that aggregating the functional impact of putative passenger variants (i.e. including yet undetected weak drivers) provides significant predictability (12.5% additive variance) for cancer phenotypes beyond the PCAWG identified driver mutations. This framework allowed us to estimate the frequency of potential weak driver mutations in the subset of PCAWG samples lacking well-characterized driver alterations.