Measuring the overall functional burdening of passenger mutations in cancer genomes -- in the PCAWG project.

Measuring the overall functional burdening & selective effect of passenger mutations in cancer genomes -- in the PCAWG project.

Overall functional burdening & selective effect of passenger mutations in cancer genomes

passenger mutations in 2800 cancer genomes: overall functional burdening & selective effects [[LS votes]]

passenger mutations in 2800 cancer genomes: overall burdening & selective effects

Extended Abstract

A typical tumor has thousands of genomic variants, yet very few of these (<5/tumor[1]) are thought to drive tumor growth. The remaining variants, termed passengers, represent the majority of all variants in cancer samples, and their functional consequences are poorly understood. Furthermore, the bulk of these passengers fall within noncoding regions of the genome. These passengers can be further subdivided into neutral and impactful based on their functional impact on the genome. As expected, low-impact passengers are inconsequential for tumor progression. However, impactful passengers can alter gene expression or activity, and while some of these changes are irrelevant, others may promote or inhibit tumor cell growth and survival, as is the case in *latent driver variants* [2,3] and *deleterious passengers*[4], respectively. In this work, we explore the landscape of passengers in various cancer cohorts by leveraging extensive pan-cancer variation data from ~2800 uniformly processed whole cancer genomes. More specifically, we annotate and evaluate the impact of each variant, including SNVs, INDELs and SVs in the pan-cancer dataset. Subsequently, we integrate their annotations and impact scores to quantify the overall burdening of various functional elements in cancer genomes. Furthermore, we also show how overall functional burdening correlates with age at cancer diagnosis, patient survival time, and tumor clonality.

In order to substantiate the presence of various categories of passenger variants, we surveyed the functional impact distribution of variants in the pan-cancer dataset. Based on canonical classification of cancer variants as passenger and drivers, one might expect their functional impact score distribution to be unimodal and centered around 0 (as a result of a large number of neutral passengers), along with a tail in the high-impact score regime, corresponding to putative drivers. However, inspection of variant functional impact scores across cancer cohorts reveals that pan-cancer variants can be broadly classified into three distinct subgroups. The upper and the lower extreme of scored variants comprises of ~23 and ~13,500 thousand noncoding variants per patient, which fall under traditional definitions of high-impact putative driver variants and neutral passengers, respectively. In contrast, the intermediate functional impact regime comprises of *impactful passengers* (~3,500 thousand noncoding variants per patient), which can further influence cancer progression by acting as latent drivers or through large burdening of various functional elements. Interestingly, there is a significant depletion of such mildly deleterious variants in the germline of these cancer cohorts. As expected, the germline genome comprises of mostly neutral variants with very few high-impact alterations. Furthermore, it's expected that, presence of these impactful passengers varies among different genomic elements as well as different cancer cohorts. Consequently, we comprehensively analyzed the overall burdening of various genomic elements,

including TF (transcription factor) motifs in the pan-cancer variant dataset. The presence of a variant within a TF binding site can lead to either the creation or destruction of binding motifs. In both cases, we observe differential burdening of *impactful variants* among different cancer cohorts. Furthermore, the selective enrichment or depletion of impactful variant*s* in different TF motifs suggest distinct alteration profiles associated with different components of regulatory networks in various cancers.

Additionally, we explored the role of impactful variations in cancer evolution by integrating sub-clonal information and allele frequencies along with functional burdening measure of pan-cancer variants. Intuitively, one would expect that high impact mutations should either achieve higher frequency if they are advantageous, or lower/non detectable if deleterious. Interestingly, we observed that high functional impact passenger variants along with LOF variants have a higher allelic frequency and a higher prevalence in parental subclones, signifying their important role in the early phases of cancer progression, or potentially providing a higher fitness advantage.

We next sought to examine whether impactful passengers might exert a clinically meaningful effect on tumor progression. Therefore, we performed survival analysis to see if impact burden predicted patient survival within individual cancer subtypes. These correlations varied substantially in different cancer types. For instance, we observed that functional mutation burden predicted substantially earlier death in chronic lymphocytic leukemia(CLL) and substantially prolonged survival in Kidney-RCC (renal clear cells), respectively. These results lend support to the hypothesis that functional passengers are clinically meaningful. More specifically, the results suggest that latent drivers are more important than deleterious passengers in CLL, but that the situation is reversed in RCC. This divergence can be explained by appealing to the large share of missing drivers in CLL, which suggests a greater role for latent drivers in CLL.

In conclusion, our work highlights an important subset of the coding and noncoding variants that were originally identified as "passenger variants", nonetheless show biologically and clinically relevant functional roles across a range of cancers.

References

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