Dear Editor,

We would like to submit our manuscript, “*KRAS* allele-specific genetic interactions,” to be published in *Nature Genetics* as an Analysis paper.

Oncogenic mutations to *KRAS* drive a large portion of colorectal adenocarcinoma, lung adenocarcinoma, multiple myeloma, and pancreatic adenocarcinoma tumors. These mutations occur primarily at just four hotspots of this small GTPase, resulting in hyperactivation of the protein and an increase in pro-growth signaling. While many researchers regard these mutations as equivalent, there is mounting evidence that they are in fact distinct, with their differential biochemical and signaling behavior having strong effects on a tumor’s biology (for example, we recently published on the effects of the KRASA146T allele in Poulin *et al.*, 2019).

In this analysis, we sought to identify *KRAS* allele-specific genetic interactions by analyzing the mutations of thousands of tumor samples from these four cancers and the results of a genome-wide CRISPR-Cas9 knockout screen from the Dependency Mapping project. The results of the analysis detailed in the submitted manuscript lead to the following primary conclusions:

1. Using mutational signatures to elucidate the latent mutational processes impacting a tumor, we demonstrated that the frequencies of the various *KRAS* alleles was not solely determined by the active mutagenic forces. This suggested that much of the selection of *KRAS* alleles was driven by the distinct biological properties of the mutant protein.
2. As such, we identified genes that tended to comutate or were less likely to comutate with each *KRAS* allele as these would be cooperating or redundant/inhibitory events, respectively. These interactions described unique biological properties of the alleles that were tissue-specific.
3. The alleles were further characterized by their differential dependency on other genes in the genome. This revealed dependencies on specific genes and cellular processes that were specific to individual alleles.

This analysis presents a unique viewpoint of the highly complex genetic network of *KRAS*. Importantly, this network is both allele- and tissue-specific determined by how the distinct biological properties of the different *KRAS* mutations interact within the existing signaling context of the organ. We believe this is true for all oncogenes, giving this analysis an impact far broader than a single gene. Indeed, we believe this manuscript to be an example of the nuanced information that can only be gleaned from this model of oncogenes, a model that is essential for their complete understanding. For this reason, this study will appeal to the broad and diverse audience of *Nature Genetics*.

Below is a list of recommended referees:

1. Referee One, referee.one@univeristy.edu
2. Referee Two, referee.two@univeristy.edu
3. Referee Three, referee.three@univeristy.edu

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with its submission to *Nature Genetics*.

Poulin *et al*. Tissue-Specific Oncogenic Activity of KRASA146T. *Cancer discovery*, 9(6):738–755, 6 2019.