Review of: "RAS mutations that have a major impact on current cancer genomic medicine"

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Potential competing interests: No potential competing interests to declare.

The manuscript entitled “RAS mutations that have a major impact on current cancer genomic medicine” by Hayashi et al. stated that the silent KRAS variants may be of concern in genetic medicine of cancer. They deeply referred the Kobayashi et al. (Nature 603, pages335–342 (2022)) and they detect similar mutations in their own samples. Unfortunately, the authors misunderstood the Kobayashi et al. paper and stated many KRAS p.Q61 mutations with cryptic splice donor site at codon 60 of KRAS gene. The sequence of human KRAS p.G60 (c.GGU) has intrinsic cryptic splice donor site at the second and third letters. Kobayashi et al. identified that some of the p.Q61 mutations may activate the cryptic donor site as an exonic splicing enhancer and additional mutations at the third letter of codon 60 can avoid the activation of newly developed splicing enhancer by p.Q61 mutation. Without the Q61 mutation, the cryptic splice donor site may not be activated. The manuscript by Hayashi et al. is based on this misunderstanding of the Kobayashi et al. Nature paper and insufficient surveyed of their own data. The reviewer recommends “reject” to this manuscript.

Minor comments

1. The authors included AMED as their second affiliations but AMED is a funding agency and the authors should not belong the funding agency to receive scientific grants.

2. They did not discuss the patients’ mutations with genomic alteration data in the comprehensive cancer genome profiling data but amino acid substitutions. They might have observed double nucleotides substitutions in some KRAS Q61K mutations. They referred ENTREZ sequence data but that is nonsense.

3. They missed citation information for ref. 8. They should add “ Nature” to finish citation.