

Dear Professor Ma:

Manuscript NO: 59518

Title: Mining TCGA database for tumor mutation burden and their clinical implications in gastric cancer

Thank you for your letter and the reviewer's comments concerning our manuscript. These comments are all valuable and very helpful for revising and improving our paper. According to the suggestions of the science editor, we have added the "article highlights" section at the end of the main text. Besides, we have studied the reviewers' comments very carefully and have tried our best to improve the manuscript. The followings are our point-by-point responses to the original reviewers' remarks underneath each comment. Revised portions are marked in yellow in the revised version of the manuscript. I hope that the adjustments made to the manuscript are satisfactory, and I am looking forward to your correspondence!

All the best.

Yours Sincerely,

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Answering reviewer 03388124:

Thank you very much for your kind response to this manuscript. We should like to express our appreciation to you. We also carefully proof-read the language, data, and references in our manuscript. I hope that the revised manuscript is now suitable for publication.

Answering reviewer 03017551:

Thank you for your letter. We are pleased to note the favorable comments. I hope that the revised manuscript is now suitable for publication.

Answering reviewer 00073640:

Thank you very much for your comments and suggestions, which are very valuable for us to improve and revise our paper. We have made revisions or explanations point by point. Revised portions are marked in yellow in the paper.

1. Please check the grammar – for instance page 4/49 – Core tip section – first sentence – there is probably missing something (is?) in the first sentence: “Core tip: Whether tumor mutation burden (TMB) associated with favorable prognosis remained controversy in various cancers.”

Answer: Thank you for your careful review. We are deeply sorry for the incorrect statement and we are appreciated that you offer us a valuable opportunity to modify it. We have replaced the statement “Whether tumor mutation burden (TMB) associated with favorable prognosis remained controversy in various cancers” with “Whether tumor mutation burden (TMB) was associated with favorable prognosis remained controversy in various cancers”. Corresponding statements have been modified in the core tip section of the revised manuscript on page 4, highlighted in yellow.

2. Figure 8: please include in the legend what bullet with the number (17-22miRNAs) denotes.

Answer: We are very sorry for the ambiguous statement and thank you for giving us the opportunity to explain it. Each category in figure 8 is depicted

using its GO or KEGG entry name (Y axis), the enrichment p value (bubble color), the number of targeted genes (X axis), and the number of targeting miRNAs (bubble size). If the number of miRNAs is 17, it means that 17 of the selected miRNAs from the miRNA-based signature seem to share the same functionality^[1]. Corresponding statements have been added in the figure legends section of the revised manuscript on page 31, highlighted in yellow.

3. Figure S1: there are 2 times $P < 0.001$ (* and .) but on the figure there are only * - was these error?

Answer: Thank you for your careful review. We are deeply sorry for the errors in the figure S1 and we are appreciated that you offer us a valuable opportunity to modify it. We have redrawn the figure S1. Statistical significance is expressed as ^a $P < 0.001$ and ^b $P < 0.05$ in the revised figure S1. More details about figure S1 have been added in the Supplementary material.

4. Table S1: colorectal cancer patients – please correct into gastric cancer patients.

Answer: We are very sorry for the incorrect statement and thank you for giving us the opportunity to modify it. We have replaced the statement “colorectal cancer patients” with “gastric cancer patients” in the Table S1. Besides, we have carefully checked the entire manuscript for consistent formatting, typos and corrected the errors.

Reference

1 **Paraskevopoulou MD**, Vlachos IS, Hatzigeorgiou AG. Diana-tarbase and diana suite tools: Studying experimentally supported microrna targets. *Curr Protoc Bioinformatics* 2016; 55: 12.14.11-12.14.18 [PMID: 27603020 DOI: 10.1002/cpbi.12]