

Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 21734

Title: Genomic characterization of esophageal squamous cell carcinoma: insights from next-generation sequencing

Professor Ze-Mao Gong

Scientific editor / World Journal of Gastroenterology

Dear Prof. Gong:

Thank you very much for sparing your time on reviewing our manuscript stated above. We have substantially revised our manuscript as suggested as follows. Furthermore, some other parts of the text were also altered in order to maintain over-all consistency and integrity of the manuscript, which was disrupted by the revision. This manuscript was reviewed by a professional language editing company.

I think the quality of the manuscript greatly improved by the invaluable suggestions from yourself and the other reviewers. I hope this revised manuscript will meet the quality to be published in *World Journal of Gastroenterology* this time. All changes are highlighted in yellow in the revised manuscript.

We also submit the Conflict-of-Interest Statement form, the Copyright Assignment form, the Language Certificate, and the Audio core tip.

Thank you very much for your kind consideration.

Sincerely yours,

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Author Response:

We thank the editor and all reviewers for their critical reading of our manuscript and for giving us many insightful comments. According to those comments, we modified our manuscript and figures. As a result, our revised paper is much improved. We incorporated most of reviewers' suggestions, and our response to each comment is shown below.

Our responses to comments of Scientific Editor

1. We have revised "Author contributions".
2. We have added "Driver mutation" to keyword list.
Key words: Esophageal squamous cell carcinoma; Next-generation sequencing; Somatic mutation; Driver mutation; Copy number variant
3. We have corrected references per your journal's style.
4. We have supplied figures in PPT format.
5. We have italicized gene names in Figure 2.

Reviewer #00503623

This well written review details recent advance in esophageal cancer characterization, with the application of NCS technique in cancer genomic studies of ESCC, as well as points to future possibilities of applying the results to facilitate the targeted therapies. The manuscript is well illustrated and the

content supported by 78 references.

We greatly appreciate the reviewer's comment.

Minor comment: Page 11 under RTK MAPK-PI3K In this section you are stressing overexpression of EGFR as the major feature of ESCC, whereas the more recent data point to the role of EGFR ligand shedding in the inflammatory process as well as cancer. Hence, the suggested references should be included and discussed in the context to broaden the scope. See Molecular Cell, vol. 37, pp.551-566, 2010) and OA Inflammation 2013 Apr 01;1(1):1.

Response:

According to the comment of the reviewer, we have cited the references. Additionally, we mentioned the following sentences in the revised manuscript. (page 13, lines 10-15)

“Moreover, EGFR transactivation via ectodomain shedding of EGFR ligands plays a role in inflammation as well as tumor growth and metastasis. A recent report demonstrated that targeting the sheddase activity of ADAM17, which is responsible for the release of multiple EGFR ligands, decreased head and neck squamous cell carcinoma cell viability and motility through blocking of the EGFR pathway.”

Reviewer #01557562

This paper is a well-written review article concerning a current overview of the somatic genetic alterations in ESCC by being emphasized from the recent results of large-scale sequencing efforts using next-generation sequencing (NGS) technology. In the review article, the author well summarized the previous

reports and addressed the problems. After minor revisions, this article would be improved and potentially acceptable for publication in World Journal of Gastroenterology.

We greatly appreciate the reviewer's comment.

Comments 1. The authors cited 5 famous articles (ref. 31-35) about genomic alterations in ESCC using NGS. However, explanation of the information including the frequency of genomic mutation of TP53, NOTCH1, PI3K and CCND1 was not sufficient.

Response:

We greatly appreciate the reviewer's instructive comments. According to the suggestion of the reviewer, we have summarized frequently altered genes in ESCC, as identified in these five studies (TP53, NOTCH1, PIK3CA, CDKN2A, CCND1 and FAT1). The results are presented in Table 3.

2. Page 11, line 4 (... mutation rate of 14-33%), some citations should be added.

Response:

According to the comment of the reviewer, we have cited the references.

3. Page 11, line 10 (... through to lead to a loss of function.), some citations should be added.

Response:

According to the comment of the reviewer, we have cited the references. We have also edited the sentence in the revised manuscript to avoid misleading.

(page 12, lines 8-11)

"When we characterized the distribution of *NOTCH1* somatic mutations obtained from the two studies, most *NOTCH1* mutations observed in ESCC affect the epidermal growth factor (EGF)-like ligand-binding domain (56%, 30 of 54) and are thought to lead to a loss of function."

4. Page 13, line 6 (... over 70% of ESCC samples.), some citations should be added.

Response:

According to the comment of the reviewer, we have cited the references.

Reviewer #00052396

An interesting and thoughtful review for gastroenterologists

We greatly appreciate the reviewer's comment.