Author's response to reviews

Title: ANKS1B is a Smoking-Related Molecular Alteration in Clear Cell Renal Cell Carcinoma

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Author's response to reviews: see over
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RE: MS: 1151436454103326

BMC Urology Editorial Office

Dear Editor-in-Chief,

Enclosed please find our revised manuscript (MS: 1151436454103326) entitled, “ANKS1B is a Smoking-Related Molecular Alteration in Clear Cell Renal Cell Carcinoma”.

We thank the reviewers for their insightful comments and suggestions for improving our manuscript. Below we have provided detailed responses to each of their comments and indicated in bold where we have made changes to the manuscript. In the manuscript itself, we have used bold underlined text to indicate where we have made additions or changes since the last submission. We feel that we have addressed all of the reviewer comments and thus we hope that our manuscript is now suitable for publication in BMC Urology.

If we can be of any further assistance, please do not hesitate to contact us.

Sincerely,

Alexander S. Parker, PhD
Associate Professor of Epidemiology and Urology
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Jeanette E. Eckel-Passow, PhD
Associate Professor of Biostatistics
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Editorial Request:

(1) **Availability of supporting data section.**

We have made the data publically available; however, we will not release the data until our manuscript has been accepted. Additionally, we have added the corresponding section to the end of the manuscript. The reviewers can access our data using the following link: [http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?token=lvgddqciseaakve&acc=GSE46699](http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?token=lvgddqciseaakve&acc=GSE46699).

(2) **Authors contributions.**

We now include all authors’ contributions, as suggested.

(3) **Competing interests.**

We now include a Competing Interests section between the Conclusions and Authors’ Contributions, as suggested.

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**Referee 1**

**Discretionary Revisions:**

Good study, a very sound and scientific approach to explore smoking and its associated risk with ccRCC. The method is sound and results good, however there are some minor points that may be improved (in future studies):

(i) The number of patients is small, and the population is very biased and may not be applicable to the general population.

(ii) Consider using a cohort of patients without kidney cancer as “control”. There may be altered genetic signatures in the non malignancy containing kidney that were also affected by smoking.

(iii) Consider including higher stage/high risk population, as their alteration in gene expression may be more profound, causing more aggressive cancer.

We thank the reviewer for their insightful comments and we will definitely consider these recommendations as we continue our efforts in this area in the future. As acknowledged by the reviewer, we are unable to incorporate these reviewer suggestions in the current study; however, we fully agree and acknowledge that they are important considerations. Particularly, we fully agree (and mention in the Discussion section) that the results discussed in our manuscript require further validation in a more robust study design. In fact, we are using the aforementioned data as preliminary data for an R01 grant submission to conduct a large case-control study that is specifically focused on exploring the association of smoking with molecularly-defined RCC phenotypes (one of which will be expression of ANKS1B).
Referee 2

Discretionary Revisions

(1) I feel that the second paragraph under background is more of a methods paragraph.

Although there are some methodology-related statements in this paragraph, we include this paragraph in the Background section in order to give a brief summary of the manuscript. As such, we would prefer to keep it in the Background section. However, if the editor agrees with the reviewer and would like it to be moved, we will happily oblige.

(2) Also the first paragraph of the discussion reads more like a background paragraph.

As we were writing this manuscript, this paragraph was indeed initially placed in the Background section. However, we ultimately decided to move it to the Discussion section. As currently written, the Background discusses that (1) smoking is an accepted risk factor of ccRCC and (2) that the molecular underpinnings of this association are unknown, thus motivating the importance of the current study. Then, the Discussion starts with a paragraph that discusses the genetics of smoking, followed with a paragraph discussing our genetic results. As such, we feel like the current format is reasonable. However, once again, if the editor agrees with the reviewer and would like this paragraph to be moved, we will happily oblige.

(3) Table 2 is a bit overwhelming. I understand the desire to show the consistency across probesets targeting the same gene, but all of the non-bolded information could be offered under supplemental data.

In reviewing Table 2, we completely agree with the reviewer. Thus, we have now moved the previous Table 2 to Additional File 1. The revised Table 2 now includes only the Affymetrix probesets that were found to have a statistically-significant interaction.

Minor Essential Revisions

(1) Please document supporting literature as to the impact of obesity on ccRCC. It appears that reference 4 addresses obesity as a risk factor, yet in the body of the paper, when obesity is mentioned as a risk factor, there is no citation.

This is an excellent point by the reviewer and as such, we have added appropriate obesity references to the revised manuscript.