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Title: A genetic variation of TGFBR2 as a protective genotype for the development of CRC in men

Manuscript Type: Case-Control Study

Short title: Protective TGFBR2 genotypes in male CRC

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Dear Editor,

Dear Reviewers,

Thank you for your time to review our paper. We acknowledge that our manuscript might have some issues in the conformity with the following comments. We have considered all of them and the corrections, adjustments and enhancements of our paper are highlighted for better comprehension.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

- Thank you for the good overall evaluation of our paper.

Specific Comments to Authors: 1. I wonder whether the author had checked the normality of age and other examination values like TGF β . If those data were skewed distribution, it's not suitable to describe them by Mean (\pm SD).

- Thank you for the valuable note. In fact, we have checked the normality of all parameters via Kolmogorov-Smirnoff testing before deciding which statistical method to apply. The data were not-normally distributed and the non-parametric Mann-Whitney U test was used to compare the mean TGF β 1 levels between CRC patients and controls. Data in figures and text of figures are given as median. In revised version all data in the text

represented as mean (\pm SD) were replaced with median \pm interquartile range (IQR 25-75%), in accordance with the Reviewer's recommendation. We believe that we choose the best and powerful methods to obtain proper and reliable results.

2. I wonder how the study determined the sample size. It would be better If the author could elaborate on it.

- Thank you for the critical point. We calculated the sample size by the GAS Power Calculator, given the significance level $\alpha=0.05$, prevalence = 0.1, the anticipated effect size (Cohen's $d=0.5$), and desired statistical power level $1-\beta = 0.8$, which determined the sample size of cases $n=184$ and controls $n=307$.
- We have added this section in Material and Methods.

3. It would be more concise if the Table 2, 3, and 4 became one table. In other words, three groups (advanced CRC, early CRC, and healthy control) can compare at the same time by other suitable statistics methods.

- We agree with the referee that the results would be more comparable if placed together into one table. However, such table would be very heavy and difficult to wrap in one standard journal page. We have to stick with the recommendations of the journal.
- Additionally, some of the data in these tables should be dropped out, and this is not desirable, because the importance of the results would be diminished.

4. Figure 1 and Figure 2 also could be more concise by integrating counterpart data.

- Thank you for the valuable suggestion. The figures are already combined (A, B, etc.) to provide additional value and meaning of them.

Conclusively, my opinion on this article is a major revision.

- Thank you once again for the valuable comments and for the opportunity to revise our paper.

(1) Science editor: 1 Scientific quality: The manuscript describes a Case Control Study of the Protective genotype of TGFBR2 in male colorectal cancer. The topic is within the scope of the

WJGO. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: The authors should clarify the study determined the sample size. Figures and tables need to be re-organized. The questions raised by the reviewers should be answered; (3) Format: There are 4 tables and 4 figures; (4) References: A total of 37 references are cited, including 5 references published in the last 3 years; (5) Self-cited references: There are 2 self-cited references. 2 Language evaluation: Classification: Grade B. A language editing certificate issued by AJE was provided. The authors are native English speakers. The manuscript is reviewed by a native English speaker. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form and the Written informed consent. and CARE Checklist (2016). No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by Trakia University, Medical Faculty. The topic has not previously been published in the WJGO.

- Thank you for the evaluation of our paper.

5 Issues raised: (1) The language classification is Grade B. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>;

- The paper was once again proofread by another, independent colleague of us.

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

- The approved grant application form is prepared and submitted along with the revised paper and other documents.

(3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

- The original figures were prepared in PowerPoint in a form that can be edited.

(4) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text;

- The section was add at the end of the main text.

and (5) For PMID and DOI numbers of references from English-language journals, please ensure there is a space between the PMID and DOI numbers in the square brackets. PMCID numbers are not necessary. 6 Recommendation: Conditional acceptance.

- The reference list was edited accordingly. All the missing details were added.

(3) *Company editor-in-chief:* I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

- We have provided all the required documents along with the revised version of the manuscript.