

Ya-Juan Ma

Science Editor

World Journal of Gastrointestinal Oncology

Madrid, August 18th, 2019

Dear Dr. Ya-Juan Ma,

We appreciate the opportunity to submit a revised version of the manuscript entitled **“CURRENT STATUS OF THE GENETIC SUSCEPTIBILITY IN ATTENUATED ADENOMATOUS POLYPOSIS”** (manuscript No 48400; invited manuscript ID 03003789).

This minireview brings up-to-date the genetic knowledge of Attenuated Adenomatous Polyposis syndromes and expounds the difficulties involved in the genetic analysis of a highly heterogeneous condition such as AAP.

We have carefully reviewed the whole manuscript and we hope we have appropriately addressed all the raised concerns and comments of the reviewers. Please, find below the responses to the reviewers' comments. All changes are marked in red in the revised version of the manuscript. English editing certificated by Springer Nature Author Services is provided.

Thank you very much for considering our manuscript for publication in *World Journal of Gastrointestinal Oncology*.

Yours sincerely,

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RESPONSES TO REVIEWERS COMMENTS

First of all, we would like to thank the reviewers for the time spent in reviewing the manuscript and their insightful comments that have resulted in an improved manuscript.

Responses to reviewer 1:

1. *Page 6 line 24 – region starts from codon 177 – check sources:*

Pages 6-7: We have updated the regions and included the citation (number 31 in the bibliography).

2. *Page 12 line 7 – typo, should be gliomas:*

Page 12: Since we are talking about polyposis, we have decided to remove this annotation and refer only to cases with AAP diagnosis.

3. *Page 13 line 28 – needs citation:*

Page 14: We have included the citation (number 99 in the bibliography).

4. *Page 14 line 21 - typo, should be alterations:*

Page 15: We do not agree with this comment. Only truncating mutation or pathogenic alterations in *STK11* are supposed to cause PJS, so we think that in this context, the term of “mutations” is correct.

5. *Page 16 discussion – the first sentence claims that the guidelines have been conservative, while the second claims that the criteria are lax. The second sentence should be revised, as it confuses the reader if the current criteria for genetic testing of AAP are strict or not.*

Page 16: We have changed the term "conservative" for "broad criteria" to better clarify the paragraph.

6. *It's also unclear why would the authors recommend stricter clinical criteria, as multigene panel testing by itself always produces unclassified variants. If I understand this correctly, the authors recommend that the minimal number of adenomas required for genetic testing should go from 10 to 20. However, they do not clarify how that would benefit neither the patient, nor further genetic studies in the field.*

Page 16: We have included a concise explanation regarding the reviewer's concern.

7. The sentence could be changed to: "Nevertheless, the decline in diagnosis rates that comes with the decrease in the adenoma burden shows the necessity of stricter clinical criteria when genetic testing is recommended for AAP predisposition genes."

Pages 17-18: We agree with the reviewer that the proposed sentence is more accurate and we have replaced it.

Responses to reviewer 2:

1. For each predisposition gene mentioned in this article, most of them have only been discussed in mutant types of the genes involved. Rarely did authors describe the mechanism of how gene mutant cause AAP.

We have carefully checked the whole manuscript and we have tried to better explain, briefly, the pathogenesis of the predisposition genes reviewed along the manuscript.

All changes have been marked in red.

The manuscript has been reviewed by an editing company an English certificate is attached in the submission.

Yours sincerely,

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