

August 6, 2014

Dear Editor,

Please find enclosed our revised manuscript (your file name: 11936-review.doc) entitled: 'Identification of candidate colorectal cancer predisposing gene variants in Chinese early-onset and familial cases using whole-exome sequencing' by Jun-Xiao Zhang et al. for publication in the *World Journal of Gastroenterology*.

ESPS Manuscript NO: 11936

The manuscript has been revised according to all suggestions of reviewers:

1 Format has been updated

2 Revisions have been made according to the suggestions of the reviewer:

- (1) **Reviewer's comment 1:** Abstract: In the results section the authors have to cancel "previously" when they talk about unreported, or does it mean "previously reported". I guess this has to be a mistake since they put previously before "unreported"?!
Response: The word "previously" before unreported has been deleted in the revised version.
- (2) **Reviewer's comment 2:** The authors have to explain why they defined early onset CRC patients to be < 40 years. Other authors set the age at < 50 years. A citation would be mandatory.
Response: CRC is commonly thought to be a disease of the elder, with most patients indeed being diagnosed above the age of 50 years. However, patients may develop CRC even ≤ 40 years of age. In order to increase the chance to identify predisposing genes/variants, we strictly selected patients with CRC ≤ 40 years of age, or ≤ 50 years of age with a clear familial aggregation. A relevant citation has been included in the revised version.
- (3) **Reviewer's comment 3:** Page 9, line 15, Results section: change "patients was female" into "patients were female". Grammatically correct would be the plural.
Response: We have changed the "patients was female" into "patients were female" in the revised version.
- (4) **Reviewer's comment 4:** Page 11, line 21: "variants to be damaging or possibly/probably damaging"-I would recommend to use the term "functionally altered or impaired" instead of damaging.
Response: We have changed the term "damaging" into "functionally impaired".
- (5) **Reviewer's comment 5:** Figures 1-3: Increase the size of the letters within the Figures. They are very small and might become unreadable in the final print or PDF version.
Response: We have changed the figures format as suggested by the reviewer.
- (6) **Reviewer's comment 6:** Table 4 and 5: I strongly recommend to remove the question mark in these tables. Instead, use an abbreviation for splice site mutation (i.e. ssm). This sounds more scientifically.
Response: We have change the term "p.?" into "SSM" as abbreviation for splice site mutation in tables 4 and 5.
- (7) **Reviewer's comment 7:** There are some problems with the line spaces throughout some tables (i.e. table 3: line: "Validated by Sanger sequencing" is missing the word "genes". Please reformat/resize the tables otherwise important information might be missing in the final version.
Response: We have changed "Validated by Sanger sequencing" to "Variants/genes validated by Sanger sequencing" and resized the tables.

3 References and typesetting are corrected.

4 With approval of all authors, we have changed the corresponding authorship from professor Ad Geurts van Kessel to professor Jian-Qiu Sheng.

5 We have signed a guarantee letter for the language of the manuscript.

Thank you for considering our revised manuscript for publication in the *World Journal of Gastroenterology*.
On behalf of all co-authors.

Yours sincerely,

Jianqiu Sheng, MD, PhD
Professor, Department of Gastroenterology,
General Hospital of Beijing Military Region
5 Nanmenchang, Dongcheng
Beijing 100700
P.R. China

A handwritten signature in black ink, appearing to read 'Jianqiu Sheng', written in a cursive style.