

Dear reviewers and editors,

Thank you very much for your advice and comments, which help us improve our manuscript significantly (Manuscript NO.: 59491, Case Report). We have thoroughly revised the manuscript addressing all the advice and comments. Answers to addressing comments are also included in this response letter. We hope that this revised version of manuscript now meets the requirements of reviewers and editors. Please do not hesitate to contact us if you have any further questions or comments.

Sincerely yours,
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Point to point response

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

This case-report with the manuscript ID59491, describes a co-inheritance of *OLFM2* and *SIX6* variants in a JOAG case, which might be effective in the onset of JOAG. This report may enrich the genetic spectrum of JOAG especially in means of co inheritance of variants that might play role in disease onset. Although further investigations on the functional effects of *OLFM2* and *SIX6* variants on JOAG should be performed, the report can be useful at the clinical level in means of identification of further similar cases.

The manuscript represents the corresponding case clearly. The proband includes the mutations on two genes that are inherited from each parent seperately. The parents and the sibling does not represent the disease phenotype but only the proband who harbours both mutations. And the authors claim that there is no mutation on other disease related loci. Co-inheritance of *OLFM2* and *SIX6* variants are not found to be represented in JOAG before although several co-inheritance studies exists seperately for both genes.

The title reflects the main subject of the case-report which is co-inheritance of *OLFM2* and *SIX6* variants in a Chinese family case of JOAG. The abstract summarizes the report in a clear way and the key words reflect the main subject of the report. The information given in the background is sufficient to understand the issue and the work clearly. The methods are described adequtely and are appropriate to reach the primary objectives of the work. The discussion highlights the key points in relevance with the literatüre and reflects the significance of the study.

I think the case report is appropriate for publication after minor revisions.

Response: Thank you so much for your recognition of our work.

My recommendations are as follows:

Methods and results:

- In the whole genome sequencing part, the names (or list) of the reference genes used can be given.

Response: Thank you so much for your comments. In the whole genome sequencing part, we have listed the names of reference genes used in a supplementary table (Page 7, Line 17-19 and supplementary table 1).

- In the whole genome sequencing part, the SNPs positions for some of the major genes that are previously known to affect JOAG phenotype better can be shown as a new figure or as a supplementary figure.

Response: Thanks for your advice. We have summarized the SNPs positions for some of the major genes that are previously reported to affect JOAG phenotype in a supplementary table (Page 7, Line 21-23 and supplementary table 2).

Figures:

- In Figure 2A, the proband should be indicated with an arrow in the pedigree. In the Figure 2B legend, instead of “unaffected families”, the term “unaffected family members” better be used.

Response: Thanks so much for these critical comments. In Figure 2A, we have added an arrow to indicate the proband. In the Figure 2B legend, we replaced the term “unaffected families” with “unaffected family members”. Many thanks again.

- In Figure 3 Legend, B and C should be separated and better be written as: “The mutation and wild type residues for **B**) *OLFM2* p.Arg94 and **C**) *SIX6* p.Ile59 were highlighted with red box.”

Response: Thanks a lot for your suggestion. We have revised the figure 3 legend as “The mutation and wild type residues for B) *OLFM2* p.Arg94 and C) *SIX6* p.Ile59 were highlighted with red box.”

- In Table 1 Legend better be written as: “Primer sequences used for Sanger Sequencing”

Response: Thank you for your kind advice. We have changed “Primers sequence” to “Primer sequences” in Table 1 legend.

Language:

The report is well-organized and the language is clear. There are very few grammar errors that need to be corrected such as:

- Page 3 Line 24-25: Instead of “this co-inherited mutations is”, it should be “these co-inherited mutations are”

Response: We thank the reviewer for the reminding. We have corrected this grammar mistake.

- Page 12 Line 22: The “gene chip based test” better be written as “gene chip-based test”

Response: We really appreciate your recommendations, which help us improve our manuscript significantly. We have revised the term as “gene chip-based test” and thoroughly checked the grammar of our manuscript and corrected grammatical errors.

Informed consent statement is in Chinese. So along with the original one, the English translated one can also be loaded for being able to evaluate.

Response: Thanks for your advice. We translated the original informed consent statement into English and uploaded the file to the submission system.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: None

Response: Thank you very much for your comments.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Thanks for recommending me as a reviewer. This is a meaningful case study. The proband patient was a young male, diagnosed with primary open-angle glaucoma (POAG). at the age of 27. The patient and his unaffected parents who have been excluded from classic genetic mutations for POAG, at Zhongshan Ophthalmic Center, were included to explore for other possible genetic variants through whole genome sequencing (WGS) and bioinformatics analysis. This study is well written overall. If the authors complete minor revisions, it will be a higher quality study. 1. page 6, line 7: If the author describes the subject's past medical history (History of past illness) more specifically, it can help readers understand. 2. page 8, line 16: If the author describes the "treatment" more specifically, it can help the reader understand.

Response: We thank the reviewer for the comments and precious advice.

1. We have supplemented the patient's past medical history in more detail (Page 6, Line 9-10).

2. We have described the "treatment" more specifically as you suggested (Page 8, Line 22-29). Many thanks again.

EDITORIAL OFFICE'S COMMENTS

(1) Science editor: 1 Scientific quality: The manuscript describes a case report of the co-inheritance of OLFM2 and SIX6 variants in a Chinese family with juvenile-onset primary open-angle glaucoma. The topic is within the scope of the WJCC. (1) Classification: Grade B, Grade C and Grade B; (2) Summary of the Peer-Review Report: This is a meaningful case study. It may enrich the genetic spectrum of juvenile-onset primary open-angle glaucoma (JOAG). Although further investigations on the functional effects of OLFM2 and SIX6 variants on JOAG should be performed, the report can be useful at the clinical level in terms of identification of further similar cases. This study is well written overall, and considered publishable after minor revisions. The questions raised by the reviewers should be answered; and (3) Format: There is 1 table and 3 figures. A total of 34 references are cited, including 12 references published in the last 3 years. There are 2 self-citations. 2 Language evaluation: Classification: Grade B, Grade B and Grade A. A language editing certificate issued by Editage was provided.

Response: We thank the science editor for the valuable summative comments. We have thoroughly revised the manuscript addressing all the advice and answered all the questions raised by the reviewers point by point. We have carefully formatted our revised manuscript in strict accordance with the Baishideng Publishing Group (BPG) guidelines and requirements for manuscript revision-case report.

3 Academic norms and rules: The authors provided the CARE Checklist-2016, and the signed informed written consent. The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the CrossCheck detection and Bing search.

Response: Thanks for your kind reminder. We have provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement in the revised file.

4 Supplementary comments: This is an unsolicited manuscript. The study was supported by Guangzhou Science and Technology Plan Project, Guangdong Natural Science Foundation and Research Funds of the State Key Laboratory of Ophthalmology. The topic has not previously been published in the WJCC. The corresponding author has not published articles in the BPG.

5 Issues raised: (1) I found 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); (2) I found the authors did not provide the original figures. 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; (3) Please provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement; and (4) Please provide the audio core tip file. 6 Re-Review: Not required. 7 Recommendation: Conditionally accepted.

Response: Thank you so much for reminding us of the missing points. (1) We have uploaded the approved grant application forms; (2) We have provided the original figure documents and also uploaded the PowerPoint file containing all the original figures which can be reprocessed by the editor; (3) We have submitted the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement; (4) We have submitted the audio core tip file. Many thanks again.

(2) Editorial office director: I have checked the comments written by the science editor.

Response: Thank you so much.

(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 Clinical Cases, 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.

Response: Thanks a lot for careful inspection of the Peer-Review Report, full text of our manuscript, and the relevant ethics documents. We have thoroughly revised the manuscript according to the comments of reviewers and editors, and the format of our manuscript revision-case report strictly follows the guidelines of Baishideng Publishing Group (BPG). We have uploaded all the required documents according to the process you provided. Many thanks for your kind reminder.