Author’s response to reviews

Title: Whole Exome Sequencing Identified a Novel Truncation Mutation in the NHS Gene Associated with Nance-Horan Syndrome

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Dear Editor-in-Chief,

Thank you for your kindly suggestions on our manuscript entitled “Whole Exome Sequencing Identified a Novel Truncation Mutation in the NHS Gene Associated with Nance-Horan Syndrome”. We appreciate the reviewers’ commentary very much. Per editor’s request, the current revision has been modified to address all of the comments from reviewers, and changes are highlighted using ‘track changes’ in the manuscript. Detailed point-by-point responses are given below.

Thank you and best regards,

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Editor Comments:
While the authors have addressed most of the reviewers comments, the manuscript stills needs revising before being considered for acceptance. As Reviewer 1 points out, the authors need to be more cautious/conservative in their conclusions; the inclusion of several additional discussion points will help support the appropriate conclusions from the data. Language, grammatical and proofing errors still need to be addressed by a native English speaker.

Response: We thank the editor’s comments. We added several additional discussion points in Discussion-page 7, line 1-8. And the conclusion had been re-edited in the Abstract-Conclusion-page 2, line 21-25 and page 3, line 1-2; Conclusion-page 10, line 3-13. Additionally, the language, grammatical and errors had been re-addressed in the whole manuscript. Also, this manuscript had been edited and polished by the editor from Springer Nature Author Services system (English Language Editing: Gold).

Reviewer reports:
Shiwani Sharma, PhD (Reviewer 1): Thank you to the authors for the revised manuscript. They have addressed some of the comments raised by this reviewer. Additional comments on the revised manuscript are the following.

Main comments-
1. The results do not support the conclusions of the study. The finding of a potential pathogenic mutation is a family with subtle features of possibly Nance-Horan syndrome instead of improving the genotype-phenotype correlation, only adds another mutation to the list of causative mutations for this syndrome. Can the authors draw some definitive conclusions from the review of genetic defects reported in or involving NHS gene included in the manuscript?
Response: We thank the reviewer’s comments. We have re-addressed the conclusions of the study and drew some definitive conclusions to the study in Abstract-Conclusion-page 2, line 21-25 and page 3, line 1-2; Conclusion-page 10, line 3-13.

2. According to the clinical photographs shown in Figure 1, the proband does not appear to present with diastema. The authors mention self reported nystagmus in the affected individual II:5. Did he present with nystagmus at the time of recruitment in this study? If not, when did his nystagmus resolve and was it related to the syndrome? This point warrants a discussion.

Response: We thank the reviewer’s comments. We have removed the description of ‘diastema’ in the proband in Figure legends-page 16, line 3. And individual II:5 did present with nystagmus, which had not been resolved at the time of recruitment in our study. Based on the previous study, the nystagmus might relate to NHS. And we added this information in Results-page 6, line 4-5.

3. Can the authors include facial photographs of the affected individuals to increase confidence in clinical diagnosis of the disorder in this family?

Response: We thank the reviewer’s comments. We provided the facial photographs of the affected individuals as attachment. However, we have signed the informed consent with the participants to make sure of the privacy protection, the facial photographs only for review, never for publication. Thank you.

4. Were the carrier females examined for lens opacity and vision? Please comment.

Response: We thank the reviewer’s comments. In this study, the carrier females were not examined for lens opacity and vision, since they live far away from Beijing, and they don’t think they have visual impairment. We have added this comment in Results-page 6, line 7-8; and Discussion-page 7, line 10-14.
5. According to Figure 2, the identified mutation is present in 4 female carriers not 3, as stated in the Results.

Response: Thanks. We have corrected the number in Results-page 6, line 20.

6. The results of the study haven't been discussed in the Discussion section.

Response: We thank the reviewer’s comments. We added the discussion of the results in the Discussion-page 7, line 2-8.

7. The statement in the Discussion, ”One study suggested that a lack of functional NHS protein causes NHS, whereas aberrant transcription of the NHS gene leads to a milder X-linked cataract phenotype [10]” is slightly mis-leading. The cited study reported a copy-number variation including NHS, predicted to result in altered expression levels of NHS, to underlie X-linked cataract in a family.

Response: We thank the reviewer’s comments. We have revised the statement in Discussion-page 8, line 5-8.

8. Although the authors have sought assistance of a native English speaker while revising the manuscript, the manuscript still has numerous language, grammatical and proofing errors that must be corrected, for publication.

Response: We thank the reviewer’s suggestion. The language, grammatical and errors had been re-addressed in the whole manuscript. Also, this manuscript had been edited and polished by the editor from Springer Nature Author Services system (English Language Editing: Gold).
Minor comments-

1. In Supplementary file 4 list the mutations leading to Nance-Horan syndrome in the order of their genomic location, including the mutation found in the present study. Please indicate the protein changes caused by the listed splice mutations.

Response: We thank the reviewer’s suggestions. We have re-sorted the mutations in the Supplementary file 4, and they all in the order of the genomic location. And the protein changes caused by the splice mutation had also been indicated in the excel file.

2. In Figure 2, change the mutation found in NHS gene in the proband and his uncle to 'hemizygous' from 'homozygous' because the gene is located on X-chromosome.

Response: We thank the reviewer’s correction. And we have changed the ‘homozygous’ into ‘hemizygous’ in Figure legends-Page 16, line 10.

3. For figures with multiple panels, both in the main manuscript and supplementary material explain what is shown in each panel, in the figure legend.

Response: We thank the reviewer’s suggestions. We have added the description for each of the figure panel in the main manuscript and the supplementary material in Figure legends-Page 16, line 2-11, 18-20. And figure legend for Supplementary file 4 has been added in Figure legends-page 17, line 5-7.

4. Methods - Page 6, line 13 - should be 'examined' not 'detected'.

Response: We thank the reviewer’s correction. We have revised the word in Methods-Page 4, line 20.
John Rosendahl Østergaard (Reviewer 2): All my concerns have been taken into consideration in the revised article and the paper has improved a lot. Only few misprints are left.

Response: We thank the reviewer’s comments. The language, grammatical and errors had been re-addressed in the whole manuscript. Also, this manuscript had been edited and polished by the editor from Springer Nature Author Services system (English Language Editing: Gold).