Reviewer's report

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

Version: 1 Date: 18 Sep 2018

Reviewer: Shiwani Sharma

Reviewer's report:

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?

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.

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

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

3. According to Figure 2, the identified mutation is present in 4 female carriers not 3, as stated in the Results.

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

5. 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.

6. 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 we corrected, for publication.

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.

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.

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

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript
Quality of written English
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Needs some language corrections before being published

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