Reviewer's report

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

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Reviewer: Shiwani Sharma

Reviewer's report:

In this manuscript the authors through whole exome sequencing (WES) report identification of a novel truncating mutation in the NHS gene in a Chinese family with Nance-Horan syndrome and attempt to draw genotype-phenotype correlations on the basis of reported pathogenic variants and chromosomal aberrations in this gene.

Nance-Horan syndrome is an X-linked disease with variable clinical manifestations except bilateral congenital cataracts are present in all affected males. Thus molecular diagnosis provides confirmation of clinical diagnosis of the disorder. The novel mutation identified in the NHS gene in this study though may be the cause of the genetic disorder in the affected family the manuscript does not present sufficient clinical data, except for a description in the text, to demonstrate the presence of Nance-Horan syndrome in the proband or his maternal uncle. The proband's teeth appear quite normal from the dental image shown in Figure 1. The possibility of presence of a pathogenic segregating mutation elsewhere in the genome has also not been excluded. Thus this reviewer has some doubt about the conclusion of this study.

Specific comments:

Major –

1. Can the authors present clinical data showing facial dysmorphism in the proband and/or his uncle?

2. If the aim of the study was to screen known cataract causing genes for a pathogenic variant in the proband then what was the premise of initially analysing the entire WES data for variants with <0.01 MAF? Why not limit the analysis to known cataract causing genes? As the entire WES data has been analysed, do any of the other 128 potentially pathogenic variants present in the proband segregate with the disease in the family? How confident are the authors that the identified variant in NHS is the only pathogenic variant present in this family?

3. According to the Cat-Map database (Shiels et al, Mol Vis 2010) more than 50 pathogenic mutations including 8 chromosomal aberrations have been reported in the NHS gene. For
drawing any meaningful genotype-phenotype correlations, all the reported genetic defects in the gene should be considered. Some of the cases reported in the literature to have X-linked cataract due to mutation/aberration of NHS gene also have other features such as congenital heart defects. These features should also be considered while drawing genotype-phenotype correlations.

4. The Discussion could be more comprehensive and discuss the findings of the study in the context of implication of NHS gene in the syndrome including the effect of the identified mutation on the protein and its function, correlation with the phenotype and similarity/difference from other reported mutations in the gene.

5. Please correct the language and grammar in the manuscript and avoid the use of casual expressions.

Minor –

1. Please move clinical information of the proband and the family members, and WES results from the Methods to the Results section.

2. Please revise Figure legends so that they provide complete and accurate details about the figures.


4. Please see that formatting of references conforms to the Journal style.

5. In Figure 2, were individuals III:2-III:5 included in the study? Why are they numbered?
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.

Unable to assess

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
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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