Reviewer's report

Title: A Novel Pathogenic Variant in OSBPL2 Linked to Hereditary Late-onset Deafness in a Mongolian Family

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Reviewer: Barbara Vona

Reviewer's report:

The manuscript entitled "A novel mutation in OSBPL2 linked to hereditary delayed deafness in a Mongolian family" by Wu et al. describes a large multi-generational Mongolian family presenting with autosomal dominant non-syndromic hearing loss that was resolved through the identification of a two base pair deletion in the gene OSBPL2. This gene has only been described in two families prior to this manuscript—one in a large Chinese family, the other in a large German family. The hearing loss is postlingual and progressive, which appears to be a characteristic hallmark of hearing loss due to OSBPL2 variants. The main message of the manuscript is clear. However, I feel that some basic aspects of the study are missing, which I will describe in detail below. I also found the writing style distracting at times. I have also outlined suggestions for improvement below (note: this is not a comprehensive list). Otherwise, I found it interesting that since 2014/2015, only two previous families with hearing loss due to frameshift variants in OSBPL2 have been identified, which is remarkable considering the prevalent use of high-throughput sequencing methods in clinical and research settings. Also remarkable is the close proximity of these variants reported so far.

Major points for revision:

-Abstract: clarify the last sentence of the "objective" sub-section "...to provide a new candidate gene for the early genetic screening and diagnosis of this disease."

-Introduction: I encourage the authors to use a different sentence that describes the number of genes that have been identified using next generation sequencing, as the original 230 rare disease genes discovered by next generation sequencing is from Boycott et al., 2014, which is a bit outdated in this fast paced field (or remove this sentence). Otherwise, I found it interesting that since 2014/2015, only two previous families with hearing loss due to frameshift variants in OSBPL2 have been identified, which is remarkable considering the prevalent use of high-throughput sequencing methods in clinical and research settings. Also, highlight that this is the third family reported with hearing loss due to OSBPL2 frameshift variants.

-Methods:

-I noticed many details pertaining to the genome sequencing methodology and analysis were missing. In particular: (1) what was the type of genome sequencing kit used, what other details about sequencing can be provided, which sequencer was used for sequencing? (2) What other databases and bioinformatics tools were used for variant prioritization? (3) How were the data filtered and what conventions were used for variant prioritization? (4) Were there any other
candidate variants identified? (5) What was the average coverage of the genome data and of the variant?

-Which family members were involved in co-segregation testing or was it only limited to the five that were also genome sequenced? This will help understand the extent of the co-segregation analysis that was performed.

-Add the ref seq NM_ID

Results:

-Was there any evidence of incomplete penetrance?

-What was the age of onset for each respective individual from whom audiological measurements were obtained? Also, what was the age at testing of each individual in Figure 2? Are serial audiograms available from individuals? This would be very helpful to gain insight into the rate of progression.

-What were the results of tympanometry?

-I noticed an air-bone gap in Figure 2B. Was this testing repeated in the individual? Is there any explanation for this or is this also an aspect hearing loss due to OSBPL2?

-The first mention of the c. position of the frameshift should also include the p. position details.

-Discussion:

-Much of the first paragraph is more suitable to an introduction to the topic. Consider moving some of the text to the introduction.

-Figures: I would recommend some re-organizing of figures, to reduce the overall number and add to the impact of each figure

-Figure 1: I would recommend integrating the segregation results into this figure, either via genotype or +/- (for heterozygous) and +/+ for wild type result directly below the pedigree symbol for each respective individual. This helps to clarify who was recruited/tested.

-Figure 2: Describe A, B, C, D in the legend.

-Figure 4: It is not necessary for this figure to be presented in the manuscript. It could either be removed entirely or moved to a supplementary section (Additional files). If this figure is moved, how long was the amplicon?
-Figure 5: consider moving this figure to a subfigure of Figure 1 (Figure 1A could be the pedigree, Figure 1B could be the Sanger sequencing validation).

Table 2: include the reference for the transcript (NM_) here and add the human genome build information.

Minor points for revision:

English improvements:

Abstract:

-Results sub-section:

-...19 of them were diagnosed with post lingual deafness with the age of onset between 10 and 40 years...

-Patients with hearing loss showed bilateral symmetry and mild to severe sensorineural deafness.

-Whole genome sequencing identified a novel pathogenic frameshift mutation (c.158_159delAA) in the gene OSBPL2…

-Conclusion sub-section:

-Our finding expands the mutational spectrum of…

-Introduction:

-Deafness is a defect of the human auditory system…

-…with genetic factors contributing to the majority…

-….50% to 60% of hearing loss is inherited…

-Check the word "posterior"

-…we applied whole genome sequencing…

-Materials and Methods:

-extremely severe could be revised to profound

-Results:

-All affected subjects had no history of ototoxic drug use…
- Hearing tests were diagnosed as bilaterally symmetric…

- We next sought to confirm the frameshift…associated with the hearing loss in this family.

- Discussion:

- Check the word "posterior" at the end of the first paragraph.

- In this study, a new frameshift mutation…in OSBPL2 was found in a family with hereditary delayed…

- OSBPL2 encodes a receptor…, which play an important…

- However, in this study we did not detect any blood lipid abnormalities in individuals with hearing loss, suggesting the…

- OSBPL2 is highly expressed in the inner and outer hair cells of the mouse cochlea.

- However, this hypothesis needs to be tested…in the cochlea by studying mice with OSBPL2 deficiency.

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

No

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

Unable to assess

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

Yes

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.

I am able to assess the statistics
Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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