**Reviewer’s report**

**Title:** Genotype-phenotype correlation analysis of MYO15A variants in autosomal recessive non-syndromic hearing loss

**Version:** 0  **Date:** 06 Jan 2019

**Reviewer:** Thomas Friedman

**Reviewer’s report:**

MGTC-D-18-00494 manuscript "Genotype-phenotype correlation analysis of MYO15A variants in autosomal non-syndromic hearing loss" is suitably crafted and scholarly. The authors have added 16 novel variants of MYO15A segregating in the Han community to the nearly 200 variants of MYO15A reviewed in Rehman et al., 2016 (PMID: 27375115). More recently, Richard et al., 2018 (PMID: 30303587) added additional novel variants of MYO15A that the authors of MGTC-D-18-00494 missed.

Listed below are suggested edits and corrections.

**Background**

Variants of HGF, CIB2, MYO7A and TMC1 are also worldwide major contributors to autosomal nonsyndromic hearing loss.

Line 56, The prevalence of MYO15A variants in the Pakistani population is 5.7% as reported in Richard et.al, 2018.

Myosin 15 is a member of a superfamily of unconventional myosin not actin.  

No need to mention phenotypes after "severe to profound congenital sensorineural deafness".

Background (Conclusion, last sentence), Revise the sentence "was the first study … in different populations…" Please see Supp. Table S1 of Rehman et al., 2016 where the country of origin/ethnicity was noted. Maybe this manuscript is the first to make a nice figure of these data. Is that worth boasting about?

In mouse, the official name of the gene is Myo15 (with a superscript for the allele), not Myo15a. See the JAX entry http://www.informatics.jax.org/searchtool/Search.do?query=myo15&submit=Quick%0D%0ASe arch

Materials and methods, The authors indicate that they reviewed the literature up to October 22, 2018. Recently, Richards et al. 2018 reported three additional likely pathogenic variants of MYO15A segregating with deafness in Pakistani families. For completeness, the authors of
MGTC-D-18-00494 might want to add these new variants to their figures 2 and 4. Additionally, please update following variants: c.9229+2T>C and c.6178-2A>G from Rehman et.al, 2016.

Authors have mentioned that individuals ascertained for the study had mild to moderate hearing loss. Yet in Figure 2, p.Gln1510* and p.Ile1311Thr are colored brown indicating "variants without reported hearing loss".

In Figure 4, p.Ile1311Thr is noted below the schematic, which are "variants without known zygosity". Yet, in that manuscript, the authors show pedigrees with genotypes that indicate p.Ile1311Thr is segregating in an autosomal recessive manner.

Some variants from Rehman et.al 2016 are not written correctly in Figure 2 and in Figure 4. Please omit "V" from p. Gly1315Glu in Figure 4.

The correct nomenclature for p.Gln3403delinsProThrArgValQGlyLeu in Figure 2 and 4 is p.Gln3403delinsProThrArgProValGlnLeu.


What "genomic enrichment platform to capture exons" was used in the authors' study? Were there any common genetics variants of other genes responsible for deafness in the Han community that were pre-screened before your targeted capture?

Spell out BWA and GATK?

Mutation analysis and control screening

Line 56, "PolyPhen-2 analyses (http://genetics.bwh.harvard.edu/pph2/) and Mutation Taster (http://www.mutationtaster.org) were performed". Omit "analyses" after PolyPhen-2 and move to the end of the sentence.

Line 15, "whether the potential mutations in pathogenic genes co-segregated with the disease phenotype in these families". Genes are not pathogenic, but variants of genes can be.

Line 26, Consider "ethnically matched controls" instead of "local controls".

Results

Line 56, "potentially pathogenic variants of MYO15A variants". Delete the second "variant" in this sentence.
What is meant by "Subsequent Sanger sequencing"? Never heard of the "subsequent" version of Sanger sequencing.

There is a Section 3.2 and a Section 3.3 but no Section 3.1.

End of Section 3.2, remove the extra period after "audiometry".

Section 3.3, The authors state that "There were 136 reported MYO15A variants in individuals from the Middle East, which is the greatest number of MYO15A variants in all populations". Add a reference to support this statement.

Discussion, Human and mouse MYO15A/Myo15 have 67 exons not 66 exons. See Rehman et al., 2016. An additional protein coding, alternatively spliced exon was reported in Rehman et al., and it is located between the giant exons 2 and exon 3.

At least on function of the large N-terminus of myosin 15 was reported in Fang et al., 2016, eLife PMID: 26974472. The 133-kDa N-terminal domain enables myosin 15 to maintain mechanotransducing stereocilia and is essential for hearing.

Line 56, "FERM" not "ERM".

What is ADNSL? Spell out and correct it.

"IQ" not "IQ3. Correct in the text and figures

In the section on "Availability of data and material" Who decides if a request is "reasonable"? Where can one find the written guidelines used to establish a request as "reasonable" or "unreasonable"? Are there guidelines for sharing that authors must abide by if you publish in BMC Medical Genetics? I suggest deleting the word "reasonable".

The Acknowledgement section of the manuscript is duplicated (i.e there are two copies).

Many of the references are not formatted correctly for BMC Medical Genetics. The first letter of each word of a journal name is capitalized.

The font size for words and variants in the pedigree figure are way too tiny to read. There is plenty of room to use a much larger font size.

Figure 2b, The word "Exon" on the left side above the schematic drawing doesn't make sense. Put it either above exon 1 or remove it.

Figure 2c, correct spelling of "phenotype" not "phenotype".

Figure 3, State in the legend the meaning of the numbers after the name of each country.

Figure 3 legend "The number of previously reported MYO15A variants with a milder auditory
phenotype in four periods" which is referred to as less serious in the figure.

Figure 4 legend, for "variants without known zygosity", consider "variants of unknown zygosity".

**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.

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.

Not relevant to this manuscript

**Quality of written English**
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?
4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal.