Author’s response to reviews

Title: Whole-exome sequencing identified a missense mutation in WFS1 causing low-frequency hearing loss: a case report

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Author’s response to reviews:

Dec 8, 2017

Matteo Pasini
Editorial Board Member
BMC Medical Genetics

Dear Dr. Pasini,

Please find enclosed a revised version of our manuscript (ID: MGTC-D-17-00170R2), entitled “Whole-exome sequencing identified a missense mutation in WFS1 causing low-frequency hearing loss: a case report”, and a point-by-point response to the comments made by the reviewers.
We are pleased to hear the positive response for the publication. With the help of the constructive suggestions and critical comments of the reviewers, we believe that our manuscript has been ready to be published in BMC Medical Genetics.

Thank you again for your prompt handling and advice regarding our submission. We hope that the current version of the manuscript is suitable for publication in BMC Medical Genetics.

Sincerely,

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Technical Comments

1. Title page

Please include the email addresses of all authors in the Title page.

2. Consent for publication

Authors should seek written and signed consent to publish the information from the patient(s) or their guardian(s). The submitted manuscript must include a statement that this consent was obtained in the consent to publish section as detailed in our editorial policies. Please amend this statement accordingly.

Response:

We revised the related issues in the text (yellow colored).

Responses to Reviewer #1

Karen Friderici (Reviewer 1): The authors addressed most of this reviewer's concerns. There are a few remaining points that were either incompletely addressed or introduced new errors. The reference assignments are not correct. There are also some suggested wording changes to consider:

Response:

We thank the reviewer for the detailed comments and reviews. We have added all the revised data and have made the required changes as detailed below.

1. Wording Changes: remove words/letters shown in []

Abstract:

"This missense mutation [was] segregated with [to the] affected status and demonstrated an alteration to an evolutionarily conserved amino acid residue."

Case presentation:

"[even though] since 30-12 (45 years of age) exhibited a degree and pattern of hearing loss similar to
30-22 (14 years of age)."

Response:

Thank you for these detailed comments. Accordingly, we did the word changes.

2. Incompletely addressed:

Background:

"DFNA6/14/38 is rare and found to cause hearing loss in patients with diabetes mellitus and/or an optic atrophy like Wolfram syndrome phenotype [1]." This wasn't removed as stated but the reference was changed.

This sentence is not correct as it stands. In the reference (Mutations in the Wolfram syndrome 1 gene (WFS1) are a common cause of low frequency sensorineural hearing loss) the focus is on DFNA6/14/38 patients who, by definition, are not syndromic. They also point out that many cases of Wolfram Syndrome have hearing loss. It also points out that heterozygous carriers of WFS1 mutations are at increased risk to have hearing loss.

The previous reference used for this sentence (Identification of p.A684V missense mutation in the WFS1 gene as a frequent cause of autosomal dominant optic atrophy and hearing impairment) points out that certain dominant mutations in the WFS1 gene may cause hearing loss accompanied by other syndromic features, in this case optic atrophy.

The salient background points to make are 1: DFNA6/14/38 is usually non-syndromic (no other obvious disease) and caused by dominant mutations in the WFS1 gene. 2: Wolfram Syndrome has an array of features and is caused by recessive mutations in the same gene (WFS1). 3: Some dominant mutations in the WFS1 gene can cause hearing loss with additional clinical features.

Response:

We regret the lack of clarity in this regard. We found that "DFNA6/14/38 is rare and found to cause hearing loss in patients with diabetes mellitus and/or an optic atrophy like Wolfram syndrome phenotype [1]." is not necessary in the context. As the reviewer commented, Wolfram Syndrome has an array of features such as diabetes and optic atrophy and is caused by recessive mutations in the same gene (WFS1), while DFNA1/14/38 is nonsyndromic and caused by dominant mutations in the WFS1 gene. These have been described well in the first and second paragraphs. Therefore, we removed the redundant sentence in the revised manuscript.

3. New or continuing errors
Discussion and Conclusions:

Abstract and Case presentation used pSer807Arg but later switched to p.S807R. Should be consistent.

p.S807 is the correct nomenclature when referring to the position in the unmutated protein.

"Because the S807[R] residue is located in the C terminal domain, the missense mutation at p.S807R affects only a limited number of functions"

Figure 2. A mutation in WFS1 identified using whole-exome sequencing.

(A) Sanger sequencing traces of subjects 30-11, 30-12, 30-21, and 30-22. (B) Multiple sequence alignment of WFS1 among different species. p.S807[R] is well preserved among various species

References:

Please review the references and correct.

Response:

We thank the reviewer for the detailed comments. We corrected the errors and reviewed the references again.

Responses to Reviewer #1

Trevor Lucas (Reviewer 2): In the revised manuscript, the authors have addressed all points raised and detailed all changes in the point-by-point reply.

Response:

Thank you for the positive response.