Reviewer’s report

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

Version: 0 Date: 08 Aug 2017

Reviewer: Karen Friderici

Reviewer's report:

The authors have provided a convincing argument that the mutation p.S807R in WFS1, identified by WES is the causative mutation for Low Frequency Non-Syndromic Hearing Loss in this family:

LF hearing loss pattern typical of WFS1 mutation: non-profound, LF only

Apparently Autosomal dominant

Evolutionary conserved amino acid

Previously found as causative mutation in family based on linkage mapping

Critique:

Background:

Dominant mutations in the WFS1 gene typically cause an unusual form of hearing loss that involves only low frequency and does not progress to profound hearing loss. However, there are several reports of dominant mutations that cause, in addition to hearing loss, some of the symptoms of Wolfram Syndrome; that is, diabetes and optic neuropathy.

In the background page 4 lines 47-52 it is not clear that the majority of cases DFNA6/14/38 are non-syndromic and only a few reports describe other clinical features. This sentence should be reworded.

Case presentation:

It is important that case studies, where mutation is identified, present as complete a clinical picture as possible.
Page 5 line 24 states that subjects did not exhibit any syndromic phenotypes but it would be helpful to know that diabetes and optic neuropathy were actually ruled out, or at least how the non-syndromic nature of their clinical presentation was established.

Were other audiological tests besides pure tone audiometry performed? The abstract says audiological evaluations "including" pure tone audiometry; this implies other audiological evaluations were done. What were they and what were the results? What were the results of temporal bone CT? The authors state that imaging was performed "including" temporal bone CT; again this implies that other imaging was also performed…is this the case? If so what other tests?

Whole Exome Sequencing (WES) is an appropriate first approach to identifying the causative mutation in this case with few family members. Table 1 appears to have an error since there are more variants not common in dbSNP than there were total variants detected. It is not clear how 622 potential disease-causing variants were distilled down to the WFS1 mutation. Was it chosen exclusively because it was the clear candidate. If so please state that.

The authors suggest that the p.S807R mutation may represent a hot spot for mutation because it has been found now in two different ethnic backgrounds. This speculation should be better supported. There is the possibility of recent or distant admixture. This could be addressed by looking at the WES data. Are there other variants in the WFS1 gene? Were those absent in the UK family with the same mutation? Is there evidence for or against other European variants using the distribution of variants identified in the WES data?

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If not, please specify what is required in your comments to the authors.

No

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Yes

**Are the conclusions drawn adequately supported by the data shown?**
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Not relevant to this manuscript

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