Reviewer’s report

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

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Reviewer: Trevor Lucas

Reviewer's report:

General comments:

The authors investigated the genetic cause of non-syndromic hearing loss (NSHL) at mid-to-low frequencies in a small Korean family with a presumed dominant inheritance. The observed hearing loss profile is typical of mutations in the Wolfram syndrome 1 gene (WFS1), which was indeed found to be causative by whole-exome sequencing (WES) in an index patient. The identified variant had previously been described in a UK family with the same disease phenotype. The results presented in the manuscript contribute to the specific characterization of the WFS1 mutational landscape in Asia and the Korean population, in particular. The pursued screening strategy should be improved and specified. The manuscript contains a number of minor errors, conflicting statements and misleading or repetitive formulations. Grammar and syntax mistakes as well as inconsistent hyphenation throughout call for proofreading by a native speaker in a revised manuscript.

Specific comments:

The authors state 'This is the first report to describe a pathological mutation in WFS1 among Korean patients' and 'Our description of the p.S807R (c.2419A→C) mutation in WFS1 is the first report of a mutation associated with LF-NSHL in Korean patients'. However, another WFS1 mutation has been described among Koreans linked to NSHL (Choi B. Y. et al. Diagnostic application of targeted resequencing for familial nonsyndromic hearing loss. PLoS One 8, e68692 2013). This paper should be cited in the revised manuscript.

The authors state 'According to the The Hereditary Hearing loss Homepage (http://hereditaryhearingloss.org), autosomal dominant, non-syndromic hearing loss is hereditary and known to be associated with 41 genetic loci.' The number of genetic loci should be updated. The sentence is also repetitive since autosomal dominant hearing loss is always hereditary.

The authors state '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 [6]'. DFNA6/14/38 causes non-syndromic hearing loss. The publication reports the occurrence of autoimmune diseases
(Crohn's disease and Graves' disease) in two members of a family with non-syndromic hearing loss. This should be corrected.

Two different numbers of reported WFS1 mutations are given with reference to different sources. Background: 'To date, approximately 300 mutations in WFS1 have been reported (https://lovd.euro-wabb.org/home.php?select_db=WFS1). ' Discussion and Conclusions: 'To date, more than 250 mutations in the WFS1 gene have been reported worldwide (http://www.hgmd.cf.ac.uk/ac/index.php). ' This should be clarified.

In the sentence 'Most mutations in WFS1 have been identified in exon 8 and, moreover, in exons 3, 4, 5, and 66-8." Correct to read '6-8'.

The authors state 'Using whole exome sequencing (WES), we examined a Korean family (Yonsei University Hearing Loss [YUHL] 30) and identified a novel missense mutation, c.2419A→C (p.Ser807Arg), in the WFS1 gene.' The mutation is not novel and this should be corrected.

The hearing loss in the family under study is first characterized as progressive, then as non-progressive. Abstract: 'Audiological evaluation of the affected subjects revealed progressive LF-NSSH, with early onset at 10 years of age, but not to a profound level.' Case presentation: "Notably, it did not appear that hearing loss was progressive, even though 30-12 (45 years of age) exhibited a degree and pattern of hearing loss similar to 30-22 (14 years of age). This should be clarified. The patient designations should also be renamed appropriately for publication.

The sentence 'While hearing function at frequencies between 2000 Hz and 8000 Hz was well preserved, hearing threshold was decreased up to 50-60 dB HL at frequencies ≤ 2000 Hz in the two affected subjects' should be changed. The threshold is increased, not decreased. The hearing loss is said to affect low frequencies in the title and abstract, mid-to-low frequencies in the background and case presentation and only mid-frequencies in the legend to figure 1. This should be changed and the international criteria used for defining degrees of hearing loss (mild to profound) added to the manuscript.

Allele frequency data should reference gnomAD rather than the ExAC database (gnomad.broadinstitute.org/) throughout the manuscript.

Table 1

According to Table 1, common variants, variants detected in controls and synonymous variants were excluded. It is not clear how the remaining 622 variants were narrowed down to the mutation in WFS1. The authors state 'There were 553 missense variants; variants in WFS1 (c.2419A→C; p.Ser807Arg) remained after filtering and inspection of WES data (Tables 1 and 2). ' This suggests that only missense variants were considered. Why? 'Variants which are
nonsynonymous or located in splice junction' should be changed to '…located in a splice site'. In addition, the 'Variants which are not common dbSNP138 (MAF>1%) (A)' are greater than the total number of variants. The GnomAd database should be used for allele frequencies. A 1% cut-off for variant identification is at least a thousand-fold too high for low frequency AD deafness. It is therefore not clear how WFS1 is identified as a 'surviving gene'.

Table 2 is superfluous. Additional information contained within the table (PolyPhen-2, PROVEAN, MT) should be incorporated into the text.

Discussion and Conclusions

It is unclear what strategy was pursued and how WES was selected as the method of choice. It is stated that 'the majority of mutations associated with LF-NSHL are, in fact, missense mutations located in exon 8, whereas those linked to Wolfram syndrome are frameshift and nonsense mutations' and that the hearing loss profile of the family under study 'is unique only in hearing loss associated with mutations in WFS1; thus, screening of WFS1 is a reasonable first step in cases of suspected LF-NSHL without progression to a profound level.' This and table 1 lead to the assumption that the authors were specifically looking for missense mutations in WFS1. In that case, the aim and strategy need to be specified.

Figure 2

Fig 2A: Protein designations should be aligned correctly. Throughout the manuscript, p.Ser807Arg should consistently be used to designate the mutation and amino acid position. The Danio rerio alignment is missing.

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

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Needs some language corrections before being published

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