Reviewer’s report

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

Version: 1 Date: 05 Dec 2017

Reviewer: Karen Friderici

Reviewer's report:

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:

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)."

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.

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.

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