Reviewer's report

Title: Screening mutations of the Otoferlin gene (OTOF) in Chinese patients with auditory neuropathy, including a familial case of temperature-sensitive auditory neuropathy

Version: 2 Date: 16 December 2009

Reviewer: Zubair Ahmed

Reviewer's report:

Review of Wang et al., 2009

In this paper, the authors retrospectively studied Chinese 73 unrelated auditory neuropathy patients (including one temperature sensitive AN patient) diagnosed by certain clinical criteria. They performed a molecular screening of the DNA samples from the 73 AN patient and 92 ethnicity matched controls for mutations of OTOF. They observed only three single heterozygotes and one compound heterozygote of OTOF among 73 AN patients. Temperature sensitive AN patient turned out to be the only patient carrying two mutant alleles of OTOF. The five mutations that they found were all novel. They concluded that Chinese have a unique mutation spectrum of the OTOF gene.

This is a paper with a sound rationale and relatively interesting data showing the low genetic load of OTOF to Chinese AN patients and on the Chinese temperature-sensitive AN patient (probably second case reported thus far in the literature). However their discussion is not well written, their literature review was not thorough, and more importantly, I do not think that a current conclusion is the best conclusion that they can draw from their data. For example, in the discussion, they should at least briefly address why they considered those three single heterozygous mutations to contribute to the phenotype. Do they think that there are non-detected, second mutations of OTOF? This should have been addressed.

Given that there is actually only one AN patient with two mutant allele, the genetic load of OTOF to Chinese AN patients appears to be much lower, compared with that from other published reports with Spanish (Rodriguez-Ballesteros et al., 2008) and Caucasian (Varga et al., 2006) population. Rodriguez-Ballesteros et al (2008) reported that 13/15 AN patients have two mutant alleles of OTOF. Authors described that OTOF mutations are responsible for 2~3% of AN patients all though the manuscripts but this is not true (see below). Therefore, a better conclusion of this paper would be that “A genetic load of OTOF to Chinese AN appears to be lower in contrast to Spanish and Caucasian population and other genetic or environmental etiology of AN should be searched in Chinese population”, even if we assume that those three single heterozygotes are AN patients due to recessive OTOF mutations.

Other comments
Title
In the title, ….Otoferlin gene (OTOF)…. is not correct. Otoferlin is the encoded protein name and the HUGO approved gene name is OTOF. Please revise the title.

Background
(3rd paragraph in p4)
Authors described that that OTOF is responsible 2~3% of NSRAN in Spanish and Caucasians.
But this is not true, OTOF is responsible for 2~3% of non-syndromic HL (not NSRAN) in these population.

Result
For the temperature sensitive AN case, the clinical details have been published early in Chinese language and is not readily available through PubMed in English language so it will be appropriate to present some of the audiometric data for this subject as a figure in this study. In my opinion this is more important information to have than table 1.

Discussion
In the discussion section authors did not provide any hypothesis or suggestion regarding the sensitivity of some mutations to temperature to show the phenotype. A paragraph in the discussion about author’s opinion will be helpful.
(Last paragraph, P9)
Authors mentioned about Spanish, Caucasians, Pakistani populations, but they did not cite Choi et al., 2009 with Pakistani population.

(1st paragraph, P10)
“Our perception is supported by~ “

Figures
Figure 2, no need to show the chromatograms for a polymorphism p.A53T.
Figure 2, it will be easy to read the chromatograms if the figure is colored. For 2975_2978delAG, based on the current figure, it looks like there is deletion of “GT” not “AG” but again without color traces it is impossible to read the allele call. Also the nucleotide bases given for patient and I think his mother (what is panel “c”, not mentioned in the figure legend) after the mutation should be “N N N Ns” as due to frameshift all the peaks are two different bases at each position and writing ‘N’ at each position is more appropriate than “A C T C T C G T”.
Figure 2, as the nucleotidesequences are given so please write the cDNA change nomenclature rather than protein change R1607W.
For clustal W alignment in figure 1, please also show species like drosophila.
p.E594 and p.R1607 are not conserved in drosophila and it will be nice to point out non-conservation of some of these alleles across different species.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests