Reviewer’s report

Title: A Six-generation Chinese Family in Haplogroup B4C1C Exhibits High Penetrance of 1555A>G-induced Hearing Loss

Version: 3 Date: 9 July 2010

Reviewer: Regie Santos-Cortez

Reviewer’s report:

Major compulsory revision:

I appreciate that you reworded the conclusion as recommended, however I am still not convinced by your interpretation of results, based on the following:

1. Your covariance analysis reportedly showed that m.1555A>G and aminoglycoside exposure are main influence factors, but this is not included in the manuscript and was not considered as basis for your conclusion. Because it is hard to establish genotype-phenotype correlation based on severity for mitochondrial disorders, it is possible that presence of the m.1555A>G places the individual at risk for hearing loss, but the severity of the disease is based on the interplay of mutation with other factors such as age and aminoglycoside exposure.

2. The conclusion states that nuclear genes (GJB2) and aminoglycosides are responsible for hearing loss in your pedigree, however based on Table 1 only 8/21 individuals with hearing impairment have aminoglycoside exposure, while 8/21 individuals with hearing impairment have GJB2 variants. Note also that all the GJB2 variants in this family were previously documented as benign. On the other hand, all hearing-impaired individuals are m.1555A>G carriers, although 3 hearing individuals are also carriers.

3. If you have information on prevalence of presbycusis and average thresholds by age in your study population, this would help to determine whether the hearing loss in the third generation is more due to age rather than m.1555A>G. Data for presbycusis thresholds from other populations can also be derived. Because age is not included in Table 1, it is hard to determine if the fourth generation would not be affected by presbycusis and so the aminoglycoside exposure and possibly the m.1555A>G variant are stronger predictors of hearing loss. Can it also be possible that the third generation was also exposed to aminoglycosides, but they just did not know or have a poor recollection of it because it happened much farther back in time?

I therefore maintain that your article would highly benefit by the inclusion of statistical evidence of the contribution of the different factors that were phenotyped in this pedigree to the presence and degree of hearing impairment. I am particularly impressed by the amount of phenotyping work you have done, thus I propose that additional statistical work is performed so that more people can benefit from your work. The conclusion should then be rephrased.
accordingly.

Discretionary revision:

In the discussion, the possibility of tissue-specific heteroplasmy which cannot be measured, such as differences in amount of heteroplasmy in blood as compared to the inner ear, can also be considered.

Minor revisions:

Please correct the GJB2 variant I203T in Table 1.

Pedigree drawing, figure 2 and table 1 can be improved with better resolution.

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

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests