Reviewer’s report

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

Version: 2 Date: 7 June 2010

Reviewer: Regie Santos-Cortez

Reviewer’s report:

The authors report on a multi-generational family with maternally inherited hearing impairment due to the mitochondrial variant 1555A>G. They must be congratulated for their efforts to comprehensively elucidate the cause of hearing impairment in this family by performing non-standard audiogram testing including high frequencies >4kHz, history of aminglycoside exposure, mitochondrial haplotype analysis and GJB2 sequencing.

Major revision:

Despite the availability of comprehensive data on modifying factors for 1555A>G penetrance, the question on how much these modifiers affect the phenotype is left largely unanswered. It is also not clear whether the high-frequency loss in some individuals is due to the 1555A>G variant, to GJB2 variants or the aminglycoside exposure. It is suggested that the authors consult a statistician if further analysis can be performed (e.g. linear regression using hearing thresholds per frequency as dependent variable, presence of 1555A>G variant as independent variable, and GJB2 variant, aminglycoside exposure and age at audiogram testing as covariates). This is important considering that a summary description using average threshold per ear and audiogram shape does not fully reflect the phenotypic information available for each family member. Audiogram data on unaffected relatives would be helpful to carry out such an analysis. The authors are urged to review the classic work of Prof. Patrick LM Huygen (from University Medical Centre Nijmegen, the Netherlands) on audiogram analysis for families with genetic hearing impairment.

Discretionary revision:
Wording of the title can be improved.

Minor revision:

Similarly the conclusion can be reworded to have a clearer message and stronger impact.

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

Quality of written English: Acceptable

Statistical review: Highly suggested to consult a statistician

Declaration of competing interests: I declare that I have no competing interests

**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