Reviewer's report

Title: Pathogenic substitution of IVS15+5G>A in SLC26A4 in patients of Okinawa Islands with enlarged vestibular aqueduct syndrome or Pendred syndrome

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Reviewer: Philine Wangemann

Reviewer's report:

This paper focuses on 22 patients from Okinawa island presenting with Pendred syndrome and Enlarged Vestibular Aqueduct and evaluates hearing and balance, provides detailed computer tomography evaluations of both temporal bones, thyroid function and thyroid status of the patients. The data are well presented and a novel mutation spectrum is identified in residents of the Okinawa island. The prevalent sequence variant, IVS15+5G>A, was identified as pathogenic based on the finding that it leads to a loss of exon 15 expression.

Major Compulsory Revisions

1) The clinical data are summarized in Table 1 and this summary notes whether or not 'vertigo' was present. Neither in the Method, Results or Discussion sections 'vertigo' is mentioned. The method by which 'vertigo' was determined needs to be reported. What criteria were used in the diagnosis a balance disorders? What tests were done? Is the entry based on patients’ self-reporting of past episodes? These data need to be made available. A discussion on balance deficits associated with Pendred syndrome and Enlarged Vestibular Aqueduct would be a valuable contribution to the literature.

2) The statement that "no significant differences were found in hearing levels among the 5 genotypes" needs to be modified to point out that no significant differences were expected due to the small sample of only 22 patients.

3) Li et al 1998 (PMID: 9500541) was the first to make the association between SLC26A4 (called PDS at the time) and hearing loss associated with Enlarged Vestibular Aqueduct (DFNB4). Li et al should be cited.

Minor Essential Revisions

1) Yang et al 2005 did not find a difference in the amount of RT-PCR products in materials from patients carrying the IVS15+5G>A variant. The present discussion of these data would benefit from reporting the location of primers that were used by Yang et al 2005 and that the patients in Yang et al 2005 were heterozyote so that Yang et al most likely amplified the non-mutated allele.

Level of interest: An article of outstanding merit and interest in its field
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