Reviewer's report

Title: Molecular epidemiology of deafness in France reclassifies mutations as common polymorphisms in the GJB2 gene

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Reviewer: Richard JH Smith

Reviewer's report:

General

These investigators have studied 159 families presenting with sensorineural deafness and in addition genotyped 3,000 dried blood spots to establish the frequency of GJB2 allele variants in the Languedoc Roussillon region of France.

Discretionary Revisions (which the author can choose to ignore)
None

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

A total of 21 different GJB2 sequence variations were found in the 159 families including three novel variations. In the analysis of the dried blood spots, 22 different GJB2 sequence variations were found. Seven of these allele variants have not been previously reported.

Based on the frequency of three of the allele variants found in the dried blood spot screen, V37I, R127H, and M34T, the authors conclude that these variations represent benign polymorphisms. However, the problem with this conclusion is that the authors have assumed that the phenotype of the persons from whom the dried blood spots were obtained was invariably normal (i.e. that these persons all had normal hearing). This assumption is almost certainly wrong. For example, when mild degrees of hearing loss are considered it is often not until children are of grade school age (at a time when hearing tests are required) that losses of this minor magnitude are detected. For this reason, the authors’ conclusions are not justified and may not be valid. Even their own statistical analysis hints at this. For example, the R127H/M34T genotype was identified twice in their deaf patient cohort but never in the general population (dried blood spots) suggesting that this combined variant may be associated with a hearing-loss phenotype under certain circumstances. Similar likelihood calculations lead to the same conclusion for the M34T/V37I genotype.

In summary, while I agree that the data presented will benefit genetic counseling efforts in this particular region of France, the conclusions the authors draw from their dried blood spot screen are not valid because no phenotypic data are available on these persons and mild degrees of hearing loss are extremely difficult to validate without proper audiometric testing.

What next?: Reject because scientifically unsound
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

None