Reviewer's report

Title: Hearing impairment risk and interaction of folate metabolism related gene polymorphisms in an aging study.

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Reviewer: Jean-Louis Gueant

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Yasue Uchida presents a study of association between the risk intairment Hearing and polymorphisms of methionine synthase (MTR) and MTHFR on 5167 Japanese subjects. The consequences of the polymorphism combinations on folate and homocysteine were also considered. Only one study (Durga et al) has been devoted to the evaluation of MTHFR in Hearing intairment. The merits of the present work were to evaluate MTR and MTHFR in a large sample of subjects and to show a favorable effect of the T allele of MTHFR only in individuals carrying the G allele of MTR.

Main remarks

As there is a gene-gene interaction between MTHFR and MTR, it is important to take into account vitamin B12 and MMA, in addition to folate and homocysteine, as metabolic parameters potentially influenced by MTR.

Minor Notes

- Part of the background summary and the introduction of the article is too long.
- The result section of the summary should be more informative
- The introduction should be shortened; for example, the effects of MTHFR on DNA synthesis etc
- The concentration of homocysteine seemed to be higher in subjects with MTR AA/MTHFR CC genotypes than in subjects MTR GG/MTHFR CC, while the trend was opposite for the various MTR genotypes with MTHFR TT subjects. Ths should evala-uated
- Hardy Weinberg equilibrium should be tested.
- Results obtained after adjustment for age, sex, and other determinants shoulkd be presented in a table.
- Part of the discussion on mechanisms such as epigenetics and DNA methylation are not supported by the experimental section.
- Please, discuss the protective effect of MTHFR TT according to the other determinants of the remethylation pathway (folate status, influence of MTR etc...).

Level of interest: An article of importance in its field
Quality of written English: Acceptable

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