Reviewer's report

Title: Angiotensin-converting enzyme gene insertion/deletion polymorphism in migraine patients

Version: 2 Date: 14 November 2007

Reviewer: Arn van den Maagdenberg

Reviewer's report:

General

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

• Overall: Since the authors did not find an association between ACE polymorphisms and migraine pathophysiology (despite reasonable power), it is rather unexpected that they continued their genetic studies trying to identify a correlation between drug response in migraineurs and the same polymorphisms (and now they lack power). Consequently, it should be advised to remove the section on drug response in case the authors cannot come with a very convincing additional explanation (at various sections of the manuscript) why this section should remain in the paper. Keeping the manuscript as it is, will be confusing to the readers.

• Background: The authors should provide more background information on the function of the RAS system. What is the function of the genes and how does the RAS system relate to migraine pathophysiology? Also they should better explain how an ACE inhibitor and an ARB drug might work in migraine prophylaxis. This is relevant because the authors perform a candidate gene approach, and the a priori hypothesis, that is why ACE polymorphisms might be associated with migraine and the drug response, should be clearly stated.

• Methods: In the methods section, it is stated that genotyping was performed in two locations using different methods. This is highly inappropriate because this might introduce a bias. However, since no association was found it most likely did not affect the outcome of the study. In any case, it should be mentioned whether the ratio between cases and controls was the same between the two genotyped sample sets. Their statement that “control experiments showed allele identification to be the same by both methods” is too vague. Exact procedures should be given.

Although the authors present information on the power of the study for migraine as a phenotype, such data is lacking for the drug study. A detailed description for both power calculations should be included in the methods section.

• Discussion: How strong should the association between responders and ACE genotype be to be valuable in clinical use predicting response in migraine? And
again considering the small sample sizes, what was the power to detect a certain association?

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

• The authors should include a sentence in the methods section of the abstract concerning the ACE genotyping procedure.

• In the abstract section, the description of the results and conclusions are too similar and should be adjusted so that the results section only describes results (‘no genotype differences’, etc), and no subsequent conclusions (‘no association with migraine or correlation with drug response’, etc).

• When the abbreviation ACE is used in the context of gene, it should be written in italics: “ACE gene”.

• Background section: sentence: “In an Australian study … from MwA or MoA.” Should be changed to: In an Australian study, no significant difference in allele or genotype frequencies were found between patients suffering from MwA or MoA and controls.”

• Conclusions section: “There was no difference in genotype…material”: add distribution after the word ‘genotype’.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests