Reviewer's report

Title: Lack of association between PRNP 1368 polymorphism and Alzheimer's disease or vascular dementia

Version: 2 Date: 25 November 2008

Reviewer: Maaike Schuur

Reviewer's report:

Major Compulsory Revisions:

Background:
1. Line 8-12: this sentence is hard to follow, and maybe interpreted wrongly by readers.
2. Line 18-19: what do the authors mean by the second part of the sentence: 'including a role for oxidative stress and the occurrence of dementia'. This part does not seem to be related to the first part of the sentence. It is not clear what it means.

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3. Line 13: ‘In a British..’ the link with previous sentences is missing. This sentence appears out of the blue.

Methods:
4. The authors did not describe how they ascertained their cases, there is no description on where the patients where seen, who diagnosed them, whether the researchers verified the diagnosis, examined them or only took blood, and in which period they were seen, etc. The authors should describe this more extensively. Now it is not clear what procedures were followed.
5. The authors do not report on the models they used in their analyses. It is not clear for which covariates they adjusted, and what models they applied. The authors should add this to the description on statistical analyses.
6. Also, the authors do not describe the haplotype analysis, while this is important information to the methods.

Discussion:
7. The authors don’t speculate on the reason why they didn’t find an association. While it would add more strength to the discussion if they did.
8. The authors should add a power calculation.
9. The last paragraph on page 11 appears just like that. There is no link to previous paragraphs.

Minor Essential Revisions:
Abstract:
10. Line 5: please change ‘another’ in ‘other’
11. Line 6-8: The idea behind this sentence is not clear. It would aid if this sentence was introduced in the previous sentence.

Background:
12. Line 3: it is a very brief description of the clinical characteristic of AD. This can be discussed more extensively.
13. Line 14: can easily be omitted.

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14. Line 16: second part: ‘the association study between..’ can be formulated differently, it is not clear what the authors want to state here.

Methods:
15. Line 20: the authors do not say in which group (patients or controls) the genotype were in HWE. This would be helpful in this part.

Results:
16. Line 8-10: the conclusion in this sentences does not fit the results. They authors stratified on gender, and conclude that there was no association between the polymorphism and gender, while in fact they did not test this.
17. Line 17-18: The authors mention that 1 haplotype was associated with VaD, but in the next sentence they conclude that the PRNP 1387 polymorphism was not associated with the disease. It is not clear on the basis of which findings, the authors conclude this. The sentence can be deleted here, and pasted to the conclusions.

Discussion:
18. Page 10, Line 2: which mechanisms do the authors mean. Genetic mechanisms?
19. Page 10, Line 4: please change ‘has’ into ‘have’
20. Page 10, Line 19-20: ‘recently, there has been growing ..’ It would be better if the authors would explain why there is growing concern. Has it been reported in other studies? Has it been linked to AD before? What might be the pathway?
21. It is not clear why the authors choose the 1386 polymorphism to study, when there is so little evidence from other studies. What is their hypothesis on this polymorphism? What role can it play? Why would this be the most important one, and what role does it play, compared to other polymorphisms?
22. It would be of additional value if the authors would speculate on the possible implications of this study to future work? And how to proceed form here?

Tables

Minor Essential Revisions:
23. Table 2 and 3 can be combined.
24. The authors should add a legend with information on the numbers that are depicted in the tables.
25. Abbreviations are different between tables, please make them consistent, and add a legend with the meaning of these.

**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, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.