Reviewer's report

Title: Cathepsin D C224T polymorphism and risk of Alzheimer's disease: An update meta-analysis

Version: 1 Date: 6 September 2013

Reviewer: Timothy Hohman

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Cathepsin D C224T polymorphism and risk of Alzheimer’s Disease: An update meta-analysis

This manuscript performed a large scale meta-analysis to evaluate the reported relationship between the CTSD C224T polymorphism and risk for Alzheimer’s disease. The work extends a recent combined analysis and meta-analysis performed by Schuur and colleagues in 2011 by including some additional cohorts of Asian descent and a few additional studies with Caucasian participants. Overall, the present paper does not make a large scientific contribution beyond the work of Schuur, and although reports the association is not statistically significant, the overall finding largely aligns with the effects reported previously.

Minor Essential Revisions:

Introduction
1) The introduction was somewhat difficult to follow. I would recommend that the authors bring in a science writer to clear up issues with tense.

2) The authors should offer some possibilities for the disparate findings in the literature, particularly between previously performed meta-analyses. Moreover, how does the approach taken in the current manuscript seek to address these potential confounds?

Method and Results
1) I think it would be helpful to mention how the studies used in the current meta-analysis compare to the previously performed meta-analyses so as to help the reader interpret your results within the framework of the literature.

2) Did the authors perform any type of power analysis to determine what size effect they are powered to detect (given the allele frequency of the C224T polymorphism and the sample size)? The Betram analysis, for example, reports have 80% power to detect odds ratio of 1.2 in SNPs with a minor allele frequency of .20, this type of information would help readers interpret the reported null result.

Discussion
1) The authors report their null finding as contradicting previous reports, but also
mention that the CTSD T allele might confer increased risk for AD in APOE carriers. This is an interesting interpretation given that the trend in APOE carriers (p = 0.07, Table 3) is quite similar to the overall trend in Caucasians (p = 0.082, Table 2).

2) Moreover, the authors report that the trend in APOE carriers is “consistent with the previous meta-analysis” (page 12). However, the Schuur meta-analysis reports an association in APOE non-carriers, both in the cohort introduced in that manuscript and in the Rotterdam cohort. That association did not hold up in the pooled results. In the present manuscript, there is actually a stronger trend (p = 0.052, Table 3) in APOE non-carriers when restricting analyses to Caucasians, which would actually be in line with previous research, and is likely a better analog given the sample in the previous work.

3) More work needs to go into directly comparing the samples, studies, and results of the present meta-analysis with the previous manuscripts. This may help clarify what is novel about the current manuscript and how it differs from the published literature.

Answers to questions from BMC Neurology

1. Is the question posed by the authors well defined?
   The authors could put more work into clarifying how their approach differs from the previously performed meta-analyses, and particularly how it adds to the current findings.

2. Are the methods appropriate and well described?
   Yes

3. Are the data sound?
   Yes

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   No, see above

6. Are limitations of the work clearly stated?
   Yes

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   Yes

8. Do the title and abstract accurately convey what has been found?
Yes

9. Is the writing acceptable?
No, there are serious grammatical errors throughout the text.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.