Reviewer's report

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

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Reviewer: Sheng Chih Jin

Reviewer's report:

The authors described a meta-analysis combining the public or published datasets to evaluate the association between Cathepsin D gene C224T and risk for developing AD. They found no association for C224T with AD risk in both Asian and European populations in the combined or stratified analyses. Many aspects of the presentation, statistical analyses, and interpretations are questionable or inappropriate.

1. For the stratified analysis of APOE #4 carriers assuming the dominant model, OR and CI for overall and Caucasians are exactly the same (Page 25, Table 3), which may be due to careless inspection of the manuscript.

2. The title of this abstract does not accurately convey the results and should be modified.

3. How many more samples are added to this meta-analysis compared to the results in the Alzgene webpage? If the difference is negligible, then this manuscript has no contribution to the field.

4. The abstract did not cite references correctly (Line 7, Page 4: should cite the papers that identified the association for C224T.)

5. The authors did not describe the statistical methods (Statistical Analysis, Page 6) in enough details. Please describe which model was used (fixed-effect versus mixed effect). Also, how did you weight the studies in your analyses (sample size versus inverse of the corresponding standard errors)?

6. The authors should round the p values or OR to two places throughout the manuscript.

7. Besides APP, PS1-2, several genes have been identified by GWAS (ex: ABCA7, PICALM and etc.) or sequencing (TREM2) studies, the authors did not give enough information for genetics of Alzheimer's disease (AD). The authored should also described how many phenotypic heritability has been explained by the known AD genes and how many can be explained by known genetic markers found in Cathepsin D in the background.

8. Since the analyses include both early -onset AD and late-onset AD cases, the authors should also list the number of early-onset and late-onset individuals separately in Table 1.

9. Some words used in this manuscript are inexplicit and the authors may misinterpret their results. For example, the authors should describe the known
environmental risk factors and genes affecting AD and cite the references (Background, Line 4, Page 3). In the discussion from the beginning of the Page 12 to the middle of 12, the authored could not draw the conclusion that "the genetic background or environment may not influence the CTSD polymorphism on AD" based on their subgroup analyses by ethnicity. This is clearly an example of misinterpretation since the authors did not conduct any principal component analyses and evaluate the association adjusting for any environment covariates in their models. In addition, in the same paragraph, the authors claimed when stratified by age at onset, there was no difference between early-onset /late-onset cases and controls, and thus they concluded that early-onset and late-onset cases have the same genetic background. This is clearly wrong interpretation. Also, they claimed there was a weak interaction between CTSD T allele and #4 alleles (Discussion, bottom of Page 12). However, their meta-analyses did not suggest any evidence of interaction. These are all examples of overstatements and misinterpretations of their results. I would suggest the authors to conduct more analyses if possible (Ex: PCA, conditional analyses, multivariate analyses) to support their statements or they should modify this paragraph completely.

10. The authored should discuss the limitations of this study in more details. (lack of PCA and statistical analytical strategies, and study design)

11. I think there should be some discussions on whether the authors think the Cathepsin D gene is actually causing AD since a lot of studies are contradictory. Also, are there any other variants in the same gene or other AD related proteins that might be fall into the same functional pathway?

12. This abstract suffered from pool grammars and tons of typos and the authors should find professional language editor to polish the English before submission.

**Level of interest:** An article of limited interest

**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.

**Declaration of competing interests:**

I have no competing interests to declare.