Reviewer’s report

Title: ApoE4: an emerging therapeutic target for Alzheimer's disease

Version: 0 Date: 03 Dec 2018

Reviewer: Takahisa Kanekiyo

Reviewer’s report:

This is a timely and important review summarizing the current evidence regarding ApoE4's risk for Alzheimer's disease (AD) and discussing the potential of targeting ApoE4 as a therapeutic approach for the disease. Although this reviewer does not find any major flaws, there are several comments to improve the review manuscript.

1. Recent findings have suggested that ApoE4 is predominantly involved in Aβ aggregation stage in accelerating amyloid pathology (DOI: 10.1016/j.neuron.2017.11.014; DOI: 10.1016/j.neuron.2017.11.013), which should be discussed. For ApoE4-targeted therapy in AD, the timing of treatment might be critical to be effective.

2. APOE4's effects may be different depending on sex, which should be considered in designing ApoE4-targeted therapy.

3. While ApoE4 is likely associated with the risk for DLB and synucleinopathy, there is no discussion of this point. The contribution of APOE genotype to tauopathy should be also discussed more comprehensively.

4. There is a controversy regarding whether ApoE4 really functions as a transcription factor. Authors need to describe this section with more balanced view.

5. CRISPR is a strong tool to investigate ApoE4 function in vitro and to generate animal models. However, there is a substantial technical limitation to edit APOE gene using current CRISPR techniques in adult human.

6. Whenever ApoE genes are indicated, all letters should be italicized in upper-case.

7. To be an unbiased review, only published studies should be cited. Thus, the last sentence in page 13 should be removed.

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