Dear Editor-in-Chief:

We respectfully submit the manuscript, entitled “*TOMM40 genetic variants cause neuroinflammation in Alzheimer's disease*”, for consideration as a “**Research Article**” in the “***International Journal of Molecular Sciences***”. This manuscript has not been simultaneously considered by another journal.

It suggests that mitochondrial dysfunction is linked to neuroinflammation. Translocase of outer mitochondrial membrane 40 (TOMM40) is located in the outer membrane of mitochondria. TOMM40 genetic variants may be involved in mitochondrial function and increase the risk of Alzheimer’s disease (AD). However, the role of TOMM40 in neuroinflammation of AD remains unclear. In this study, four exonic variants within *TOMM40-APOE* region (rs772262361, rs157581, rs11556505, rs440446) were identified from 80 AD patients by using next-generation sequencing. Four functional variants were further evaluated in 213 normal control, 393 AD patients and 1025 controls from Taiwan biobank. Two TOMM40 missense variant rs157581 (c.339T>C, p.Phe113Leu) and rs11556505 (c.393C>T, p.Phe131Leu) were linked to increased AD susceptibility. Our results demonstrated that TOMM40 genetic variants, but not wild-type (WT) TOMM40, cause microglial activation. TOMM40 missense variants activate NF-κB cascade and NLRP3 inflammasome activation in BV2 microglial cells. Moreover, TOMM40 genetic variant upregulated pro-inflammatory cytokines in microglia cells expressing (F113L) and (F131L) TOMM40, leading to loss of hippocampal neurons. The plasma levels of inflammatory cytokines, including IL-6, IL-18, IL-33 and COX-2, were significantly upregulated in AD patients carrying TOMM40 variants. AD patients carrying TOMM40 genetic variants displayed the upregulated level of inflammatory cytokines.

Thank you in advance for considering our manuscript for publication in “***International Journal of Molecular Sciences***”. We look forward to your timely decision regarding its suitability.

Sincerely yours,

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