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Letter to the Editor

Comment on "Multi-omics analysis of druggable genes to facilitate Alzheimer's disease therapy: A multi-cohort machine learning study"

Dear Editor,

We read with great interest the study "Multi-omics analysis of druggable genes to facilitate Alzheimer's disease therapy: A multi-cohort machine learning study" by Hu et al. [1]. which was recently published on Mar 11, 2025, in *the Journal of Prevention of Alzheimer's Disease*. They identified the different subtypes of Alzheimer's disease (AD) using consensus clustering, extracted key module genes between the two subtypes via weighted correlation network analysis, combined the shared cluster differentially expressed genes, key module genes, and druggable genes to generate 21 hub genes, which were subsequently filtered using various machine learning techniques, and finally conducted a two-sample Mendelian randomization (MR) analysis incorporating the identified druggable genes to ascertain the causal relationships between druggable gene expression and the risk of AD. Although acknowledging the significant contribution of that study, Hu et al. had misunderstood Fig. 8A-B in the section titled "3.7. MR analysis"—they believed that each of the genes *LIMK2*, *MAPK8*, and *NDUFV2* might contribute to an enhanced risk of AD by MR in brain tissues and blood samples [1].

The odds ratio (OR) is a commonly used metric for measuring the magnitude of an effect, particularly in the fields of epidemiological and medical research. It gauges the strength of the association between expo-

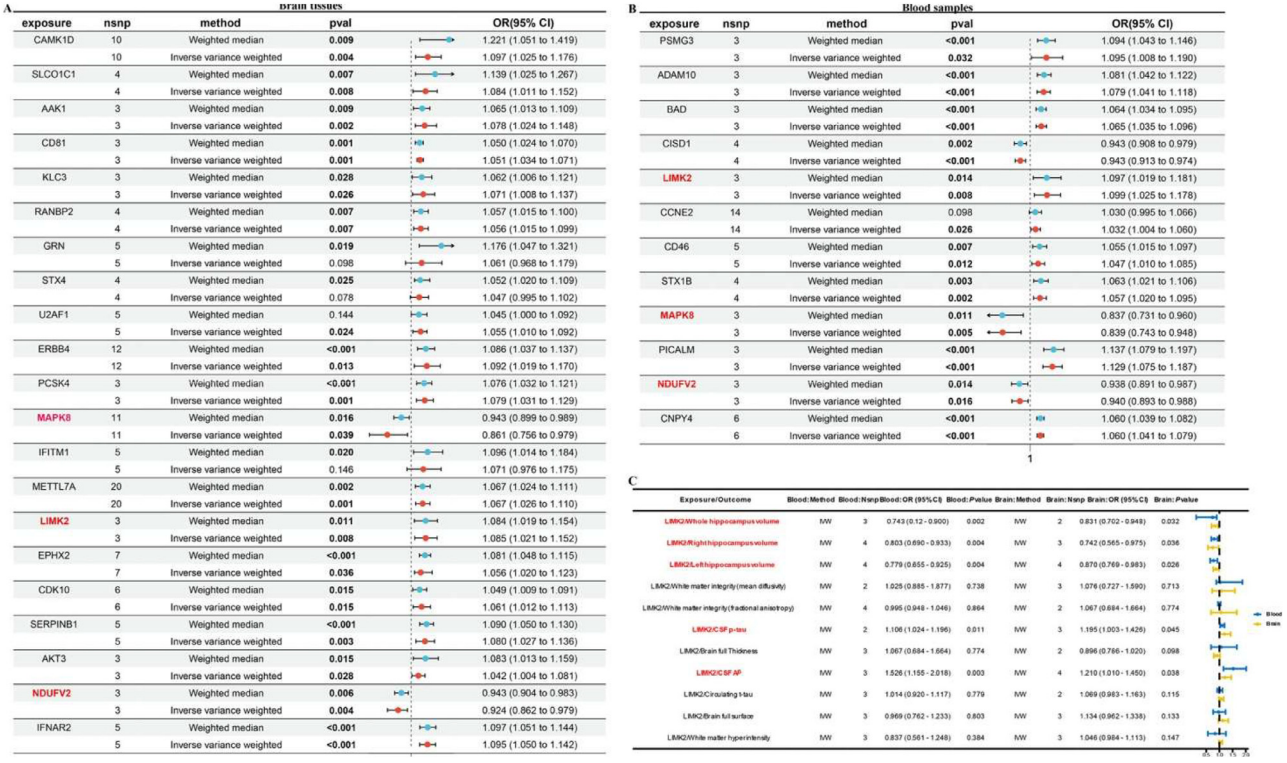

Fig. 8. Identification of hub genes in AD by MR. (**A**) Forest plot for MR results between brain eQTL and AD. (**B**) Forest plot for the MR result between blood eQTL and AD. (**C**) MR results of AD markers and AD outcome in IVW method. (Image source: Hu et al. [1]., Multi-omics analysis of druggable genes to facilitate Alzheimer's disease therapy: A multi-cohort machine learning study).

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sure factors and outcome events by comparing the ratio of the probabilities of an event occurring in the exposed group versus the non-exposed group [2]. Mendelian randomization is a research approach that utilizes natural genetic variation within observational studies to assess the causal effects of modifiable risk factors [3]. In MR analysis, an OR equal to 1 suggests that there is no statistically significant evidence to support a causal effect of genetically predicted changes in exposure levels on the risk of binary outcomes. An OR greater than 1 implies that an increase in the genetically predicted exposure level is causally associated with an elevated risk of binary outcomes, indicating that the exposure serves as a risk factor for the outcome. Conversely, an OR less than 1 indicates a causal relationship between an increase in the genetically predicted exposure level and a reduced risk of binary outcomes, suggesting that the exposure acts as a protective factor for the outcome [4]. Therefore, the accurate interpretation should be that *LIMK2* may elevate the risk of AD attributable to MR, whereas *MAPK8* and *NDUFV2* may mitigate the risk of AD induced by MR (*LIMK2* OR 1.084 (1.019–1.154), *MAPK8* OR 0.943 (0.899–0.989), and *NDUFV2* OR 0.943 (0.904–0.983)) in brain tissues (Fig. 8A), and (*LIMK2* OR 1.097 (1.019–1.181), *MAPK8* OR 0.837 (0.731–0.960), and *NDUFV2* OR 0.938 (0.891–0.987)) in blood samples (Fig. 8B).

To sum up, readers ought to approach the relevant chapters with caution to guarantee precise understanding.

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Declaration of competing interest

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