Published in final edited form as:

Ann Neurol. 2016 February ; 79(2): 335. doi:10.1002/ana.24588.

Reply

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We appreciate Dr. Jiang's and Liu's interest in our recent study, where we reported that the minor allele of a missense variant (rs3796529) in the *REST* gene may be protective for rate of hippocampal volume loss in individuals with mild cognitive impairment (MCI) with *APOE* ε3/ε3 genotype.[1] In their letter, the authors reported that rs3796529 was not significantly associated with the volumes of 7 subcortical regions of human brain determined by magnetic resonance imaging using data from the large-scale genome-wide association study (GWAS) summary statistics from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium.[2]

The authors' negative findings in contrast to the association we reported may be due to numerous differences, including the following factors. First, the ENIGMA consortium included patients diagnosed with anxiety, Alzheimer disease (AD), epilepsy, major depressive disorder, or schizophrenia (>20% of the discovery participants).[2] Although the presence of any diagnosis was used as a covariate in ENIGMA, various neurologic and psychiatric disorders may have differential effects on brain structure volumes, and this may have averaged out any influence of the REST variant. In contrast, the discovery samples in our study included only individuals with MCI, often representing a prodromal stage of AD. Second, the participants of the ENIGMA consortium were aged 9 to 97 years, covering most of the human lifespan,[2] whereas the participants in our study were older adults (mean age = 74.4 years, range = 57.8–85.7 years). Finally, it should be noted that our sample included only participants with *APOE* ε3/ε3 genotype, as it was designed to identify variants independent of the well-established *APOE* ε4 AD risk factor. In contrast, Dr. Jiang and Liu examined GWAS summary statistics obtained using all ENIGMA samples regardless of *APOE* ε4 genotype.[2]

We believe Dr. Jiang's and Liu's negative findings are interesting yet should be interpreted with caution given the marked differences in sample characteristics and study design from the Alzheimer's Disease Neuroimaging Initiative report that addressed a very specific older adult population. The large sample size in ENIGMA should not dissuade further studies, which we believe are warranted to more precisely characterize the association of this and other *REST* variants with subcortical brain structure volumes in cognitively normal older adults as well as those with neurodegenerative disorders.

Potential Conflicts of Interest

Nothing to report.

References

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