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Re: *REST* rs3796529 variant does not confer susceptibility to Alzheimer's disease

Kwangsik Nho, PhD¹, Lindsay A. Farrer, PhD², and Andrew J. Saykin, PsyD¹

¹Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN

²Department of Medicine, Neurology, Ophthalmology, and Genetics and Genomics, Boston University School of Medicine, Boston, MA

Liu and colleagues examined summary statistics from the large-scale genome-wide association study (GWAS) by the International Genomics of Alzheimer's Project (IGAP)¹ for the *REST* missense variant (rs3796529) we recently reported to be protective for rate of hippocampal volume loss in individuals with mild cognitive impairment (MCI).² The authors concluded that this variant was not significantly associated with Alzheimer's disease (AD) susceptibility, while noting a trend toward reduced AD risk.

Several aspects of the analysis by Liu and colleagues deserve comment. Our Alzheimer's Disease Neuroimaging Initiative study focused on participants with *APOE* $\epsilon 3/\epsilon 3$ genotype to identify variants independent of the well-established *APOE* $\epsilon 4$ allele AD risk factor, whereas the Liu analysis used all IGAP samples without regard to *APOE* genotype. Second, our discovery group included only participants with MCI rather than AD. Third, instead of binary case–control status, the Nho et al study employed rate of hippocampal atrophy over 2 years as a continuous endophenotype. Quantitative phenotypes provide additional information that may be helpful in differentiating the biological mechanisms by which the identified variants may influence risk or disease characteristics. Given the inherent differences between endophenotype and case–control association analyses, interpretation of differences in results may be challenging. The association with hippocampal volume loss is likely to be more specific in terms of pathways and mechanisms than case status, which is presumably the net result of all pathways contributing to AD, as is tested in a standard case–control GWAS. In sum, Liu and colleagues' findings are interesting and taken together, results from these studies will improve our understanding of the protective role of *REST*. Further studies are needed to clarify the potential contribution of *REST* toward the treatment and prevention of AD.

References

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Potential Conflicts of Interest: Nothing to report.

2. Nho K, Kim S, Risacher SL, et al. Protective variant for hippocampal atrophy identified by whole exome sequencing. *Ann Neurol*. 2015; 77:547–552. [PubMed: 25559091]

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