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Genetics/genetic factors of Alzheimer's disease

Common and rare variants in Alzheimer's disease genes are associated with episodic memory in South Asians from the LASI-DAD study

Wei Zhao[1] | Jennifer A. Smith[1] | Miao Yu[1] | Priya Moorjani[2] | Andrea Ganna[3] | Aparajit Ballav Dey[4] | Jinkook Lee[5] | Sharon L.R. Kardia[1]

[1] University of Michigan School of Public Health, Ann Arbor, MI, USA

[2] University of California, Berkeley, Berkeley, CA, USA

[3] Institute for Molecular Medicine Finland, Helsinki, Finland

[4] All India Institute of Medical Science, New Delhi, India

[5] University of Southern California, Los Angeles, CA, USA

Correspondence
Wei Zhao, University of Michigan School of Public Health, Ann Arbor, MI, USA.
Email: zhaowei@umich.edu

Abstract

Background: Many risk loci for Alzheimer's disease (AD) have been identified in genome wide association studies (GWAS) conducted primarily in European ancestry (EA). We previously investigated whether SNPs identified in EA were associated with episodic memory in South Asians, and failed to find an association for the majority of SNPs. Due to genetic heterogeneity among different race/ethnic groups, risk SNPs identified in EA GWAS may not be as strongly associated in different ethnicities. Genes, however, have the same function across ethnicities. The goal of this study was to use a gene-based approach to investigate the association between 39 known risk genes for AD and episodic memory in 937 South Asians from the Diagnostic Assessment of Dementia for the Longitudinal Aging Study of India (LASI-DAD).

Method: Participants were genotyped using the Illumina Global Screening Array and imputed to 1000G Phase 3v5. We used a gene-based approach, the sequence kernel association test (SKAT and SKAT-O), to assess the joint effects of all SNPs simultaneously within each risk gene on two episodic memory scores (total and delayed word recall) after controlling for age, gender, and population structure. We used two weighting schemes: equal weight for all SNPs/variants (beta(1,1)), and upweighting of rare variants (beta(1,25)).

Result: Preliminary analyses showed that 7 genes (*APOE*, *ADAMTS1*, *RIN3*, *IQCK*, *KAT8*, *HLA-DRB5*, *EPHA1*) were associated with total learning score and 2 genes (*ADAMTS1*, *CLU*) were associated with delayed recall score using the equal SNP/variant weighting approach at a nominal p-value ($p < 0.05$). Using the rare variant weighting approach, 5 genes (*APOE*, *ADAMTS1*, *KAT8*, *RIN3*, *HLA-DRB5*) were associated with total learning score and 2 genes (*ADAMTS1* and *ABCA7*) were associated with delayed recall score.

Conclusion: Given that variation in only one gene was associated with both total learning and delayed recall, different biological mechanisms may be involved in these traits. Moreover, the association of the majority of genes was driven by both common and rare variants, whereas only a few associations were driven largely by rare variants. Future work is needed to identify the specific variants that influence episodic memory in South Asians.