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Targeted neurogenesis pathway-based gene analysis identifies *ADORA2A* associated with hippocampal volume in mild cognitive impairment and Alzheimer's disease

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Background: New neurons are generated throughout adulthood in the olfactory bulb and dentate gyrus of the hippocampus, and are incorporated into hippocampal networks during maintenance of neural circuits and in turn contribute to learning and memory. Numerous intrinsic and extrinsic factors such as growth factors, transcription factors, and cell cycle regulators control neural stem cells proliferation, differentiation, and maintenance into mature neurons. However, the genetic mechanisms controlling adult hippocampal neurogenesis remain unclear. We performed a gene-based association analysis of neurogenesis pathway-related candidate genes using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods**:** Neurogenesis-related genes were curated from existing databases (Qiagen RT^2 Profiler PCR Arrays, GoGene and MANGO). The gene list was filtered by AD susceptibility genes from the Alzgene database (http://www.alzgene.org/) and large-scale GWAS (Lambert,et al. 2013, *Nature*). Caucasian non-Hispanic individuals (N=1,525) with AD or mild cognitive impairment (MCI) and cognitively normal older adults from the ADNI cohort with MRI and genotyping data were included. Gene-based association analysis of neurogenesis pathway-related candidate genes was performed. Baseline bilateral hippocampus and hippocampal subfield (CA regions and dentate gyrus) volumes were extracted from MRI and served as phenotypes. Gender, age, intracranial volume, MRI field strength, and diagnosis at scanning were entered as covariates. The empirical *p* value from permutation testing for each gene was adjusted for the number of significant SNPs in each gene.

Results: *ADORA2A* was significantly associated with total hippocampal volume and hippocampal subfield volumes ($p<0.001$). For the most significant SNP (rs9608282) in *ADORA2A*, dosage of the minor allele (T) increased hippocampal volume. rs9608282 was also associated with composite memory score ($p= 0.0076$).

Conclusion: *ADORA2A*-mediated control of neuroinflammation modulates adult neurogenesis and the inhibition of *ADORA2A* prevents Aβ-induced neurotoxicity. Targeted pathway-based genetic analysis combined with brain imaging endophenotypes appears promising to help elucidate disease pathophysiology and identify potential therapeutic targets.

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