

# Study finds genes associated with hippocampal atrophy

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In a genome-wide association (GWA) study, researchers from Boston University Schools of Medicine (BUSM) and Public Health (BUSPH) have identified several genes which influence degeneration of the hippocampus, the part of the brain most associated with Alzheimer disease (AD). The study, which currently appears online as a Rapid Communication in the *Annals of Neurology*, demonstrates the efficacy of endophenotypes for broadening the understanding of the genetic basis of and pathways leading to AD.

AD is a progressive [neurodegenerative disorder](#) for which there are no [prevention methods](#). Available drugs only marginally affect [disease severity](#) and progression, making AD effectively untreatable.

GWA studies using very large samples have increased the number of robust associations to 10 genes, including APOE. However, these genes account for no more than 35 percent of the inherited risk of AD and most of the genetic underpinning of the disorder remains unexplained. According to the researchers, [magnetic resonance imaging](#) (MRI) of the brain provides in vivo quantitative measures of neurodegenerative and cerebrovascular [brain injury](#) that may represent AD-related changes long before clinical symptoms appear. These measures are more powerful than comparisons of individuals with AD with cognitively healthy persons because they avoid misclassification of normal persons who will develop disease in the future.

BUSM researchers conducted a two-stage GWA study for quantitative measures of hippocampal volume (HV), total cerebral volume (TCV) and [white matter](#) hyperintensities (WMH). Brain MRI measures of HV, TCV and WMH were obtained from 981 Caucasian and 419 African-American AD cases and their cognitively normal siblings in the MIRAGE (Multi Institutional Research in Alzheimer's Genetic Epidemiology) Study. In

addition, similar MRI measures were obtained from 168 AD cases, 336 individuals with [mild cognitive impairment](#) and 188 controls (all Caucasian) in the AD Neuroimaging Initiative (ADNI) Study. The MIRAGE Caucasian families and ADNI subjects were included in the first stage and the MIRAGE African American families were added in stage two. Results from the two Caucasians data sets were combined by meta-analysis.

In stage two, one genetic marker (i.e. single nucleotide polymorphism or SNP) from each of the gene regions that were most significantly associated with AD in the Caucasian data sets was evaluated in the African-American data set.

Novel genome-wide significant associations were observed for HV with SNPs in the APOE, F5/SELP, LHFP, and GCFC2 gene regions. All of these associations were supported by evidence in each data set.

"Our two-stage GWAS identified highly significant associations between a measure of degeneration in the brain region most strongly correlated with AD and several genes in both Caucasian and African American samples containing AD, cognitively impaired and cognitively healthy subjects. One of these associations was with the ?4 variant of APOE which is the most well-established genetic risk factor for AD.

Other associations were demonstrated with markers in F5/SELP, LHFP, and GCFC2, genes not previously implicated in this disease" explained senior author Lindsay Farrer, PhD, chief of biomedical genetics at BUSM. He also noted, "previous studies showed that blood level of P-selectin (the protein encoded by SELP) has been correlated with rate of cognitive decline in AD patients."

Farrer believes it is very likely that the number and specificity of these associations will increase in

future studies using larger samples and focused on additional precise structural and functional MRI measures. "These findings will inform experiments designed to increase our understanding of disease-causing mechanism and may lead to new therapeutics targets," added Farrer.

Provided by Boston University Medical Center

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