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Genome-wide association study of temporal lobe structure identifies novel quantitative trait loci for neurodegeneration in Alzheimer's disease

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Abstract: Temporal lobe atrophy is a characteristic feature of many common neurological and psychiatric disorders, including Alzheimer's disease (AD) and mild cognitive impairment (MCI), which carries a 5-fold increased risk for subsequent development of AD. As progressive temporal lobe and hippocampal atrophy may mediate the link between genes and behavioral deficits, genes associated with structural degeneration may help to identify molecular mechanisms involved in cognitive decline and disease progression.
To identify specific genes influencing brain structure, the Alzheimer's Disease Neuroimaging Initiative (ADNI) collected whole-brain MRI and genome-wide genotype data in 793 subjects with AD, MCI, and healthy elderly controls. Two image-derived measures were analyzed: (1) temporal lobe atrophy, computed using an automated method (tensor-based morphometry), and (2) hippocampal volume, measured bilaterally with an automatic recognition algorithm. Genome-wide information at 620,901 markers was genotyped on an Illumina 610 Quad microarray platform. After excluding markers that did not satisfy quality control measures, 545,872 SNPs (single nucleotide polymorphisms) were tested for association with temporal lobe atrophy and hippocampal volume. Only Caucasian subjects (non-Hispanic; N=722) were included to reduce population stratification effects. Genome-wide association analysis using temporal lobe atrophy and hippocampal volume as quantitative phenotypes controlling for age and sex revealed two SNPs that survived the conventional genome-wide significance threshold of $P<5x10^{-7}$. One significantly associated SNP, rs10845840, is located on chromosome 12 within the *GRIN2B* gene, which encodes the regulatory subunit 2B (NR2B) of the *N*-methyl-*D*-aspartate (NMDA) glutamate receptor. NMDA receptors have long been implicated in long-term potentiation, a key process in learning and memory; overexpression of this gene in mice enhances learning and memory. Pharmaceutical blockade of NMDA channels also limits excitotoxic cell death.
These associations require replication, but they suggest that large-scale imaging projects will help discover genes that influence brain structure.

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Presentation Preference (Complete): Nanosymposium Preferred
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Briefly explain (500 characters) the timeliness and importance of your research, and the overall theme of your abstract.

If you are the creator of your linking group provide this explanation for your entire group. : This study is one of the first genome-wide association studies using neuroimaging phenotypes as quantitative traits. We combined methods from genomics and imaging and found a polymorphism in an NMDA receptor subunit that potentially influences brain atrophy and Alzheimer's disease, having broad implications for the study of Alzheimer's disease pathways.

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