Study evaluates association of genetic factors and brain imaging findings in Alzheimer's disease

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By investigating the association between genetic loci related to Alzheimer's disease and neuroimaging measures related to disease risk, researchers may have uncovered additional evidence that several previously studied genetic variants are associated with the development and progression of Alzheimer's disease and also may have identified new genetic risk factors for further study, according to a report in the June issue of *Archives of Neurology*.

"The mechanisms underlying Alzheimer's disease onset and progression remain largely unexplained," the authors write as background information in the article. Twin studies have suggested that the condition is 60 percent to 80 percent heritable. Until recently, only one genetic variant—known as APOE—was shown to influence Alzheimer's disease risk and age at onset. However, new findings from genome-wide association studies have identified three additional loci (specific locations of genetic variants on chromosomes) that confer risk of Alzheimer's disease.

Neuroimaging measures—including the volume of hippocampus, amygdala and other brain structures—also correlate with the risk and progression of Alzheimer's disease. "The demonstration that recently discovered genetic risk factors for Alzheimer's disease also influence these neuroimaging traits would provide important confirmation of a role for these genetic variants and suggest mechanisms through which

they might be acting," the authors write.

Alessandro Biffi, M.D., and Christopher D. Anderson, M.D., of Massachusetts General Hospital, Boston, and Broad Institute, Cambridge, Mass., and colleagues studied the associations between genes and neuroimaging results among 168 individuals with probable Alzheimer's disease, 357 with mild cognitive impairment (a precursor to Alzheimer's disease) and 215 who were cognitively normal.

The four loci previously associated with Alzheimer's disease were assessed, along with six neuroimaging traits linked to Alzheimer's disease. The APOE gene had the strongest association with clinical Alzheimer's disease, and was associated with all the neuroimaging traits except one. The other candidate genes showed a significant cumulative effect on the neuroimaging measures analyzed.

"Our results indicate that APOE and other previously validated loci for Alzheimer's disease affect clinical diagnosis of Alzheimer's disease and neuroimaging measures associated with disease," the authors write. "These findings suggest that sequence variants that modulate Alzheimer's disease risk in recent genome-wide association studies may act through their influence on neuroimaging measures."

In addition, the genetic analysis of neuroimaging traits identified two new target gene locations—BIN1 and CNTN5—of heightened interest for their relationship with Alzheimer's disease. "Although our results for these loci can only be considered preliminary, they may help prioritize targets for future genetic studies and genome-wide association studies in Alzheimer's disease, particularly given their association with neuroimaging correlates of Alzheimer's disease and disease status," the authors write. They add that independent evidence for an association between the BIN1 gene location and Alzheimer's disease emerged in a recent meta-analysis.

More information: Arch Neurol. 2010;67[6]:677-685.