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ALZHEIMER DISEASE:

'Generation Next' in Alzheimer disease genetic studies

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Abstract

A recent study has used whole-exome sequencing, an 'extreme trait' design and imaging genetics to identify coding variants associated with hippocampal volume loss in Alzheimer disease. The research highlights the utility of next-generation sequencing and association studies involving quantitative traits for discovery of disease-related variants in neurodegeneration.

The Human Genome Project was completed in 2003. Since then, the human genome has been intensively studied for genes that associate with human diseases. Neurodegenerative diseases have been an important focus of such efforts owing to ageing populations and the increasing burden of such diseases on society. A recent study by Nho *et al.*,¹ which investigated novel risk variants for neurodegeneration, has contributed important findings to this body of research.

The past decade has witnessed the discovery and validation of more than a dozen Alzheimer disease (AD) risk genes.^{2,3} These discoveries originated from large genome-wide association studies (GWAS) that investigated the genetic make-up of tens of thousands of individuals with AD and healthy elderly controls for the presence of disease-associated variants. The validity of the data has been rigorously tested using stringent genome-wide multiple comparison correction and replicated in other large genomic datasets. Yet the GWAS approach, as powerful as it is, has three crucial short-comings: sparse sampling of the genome, exclusive reliance on statistical power without requirement of plausible functional relation to the disease of interest, and the case-control design. The case-control design has limited discovery power when applied to neurodegenerative disorders with a protracted presymptomatic course, such as AD, as many cognitively normal individuals who are selected as controls might be in the latent stages of the disorder.

In the new study, Nho *et al.*¹ identified two novel risk variants for neurodegenerative disease through application of an unconventional but powerful and scientifically grounded genetic discovery strategy to data from the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI-1). The researchers substituted the case-control design with the 'extreme trait' design. For this approach, they selected eight individuals with mild cognitive impairment

(MCI) who had extensive hippocampal tissue loss over 2 years, and compared them with eight demographically matched ADNI-1 MCI controls who had minimal hippocampal volume loss over the same period of time.

The selection of hippocampal atrophy as a quantitative trait for extreme MCI case–MCI control selection is scientifically reasonable as hippocampal atrophy is the most established biomarker of neurodegeneration in AD.^{4,5} The selection of MCI individuals who were homozygous carriers of the apolipoprotein E (*APOE*) $\epsilon 3$ allele enabled detection of risk variants that are independent of *APOE* $\epsilon 4$ —the strongest genetic risk factor for AD.

Next, Nho *et al.*¹ conducted whole-exome sequencing on the genomic DNA samples provided by the 16 selected MCI individuals, and determined the genetic variability at all coding sites for variants that are observed with >50% frequency in the cases and absent in the controls. This screening of 89,400 single nucleotide polymorphisms (SNPs) resulted in discovery of 57 nonsynonymous SNPs that met the prevalence criteria specified above. Of these SNPs, the researchers focused on two: the rs9610775 variant in the caspase recruitment domain family, member 10 (*CARD10*) gene, and the rs1136410 variant in the poly(ADP-ribose) polymerase-1 (*PARP1*) gene. Both SNPs show minor allele frequency >10% among European Americans, and both were seen in six of eight cases and none of the controls.

Researchers are increasingly adopting well-established quantitative disease endophenotypes instead of the case–control design in genetics, as the former approach not only assures superior statistical power but can provide evidence with regard to gene function and disease mechanism.^{6–10} The third innovation in the study by Nho *et al.*¹ came from the use of imaging genetics approaches. These analyses were done in all *APOE* $\epsilon 3$ homozygote MCI ADNI-1 participants. The researchers investigated the strength of association of the two SNPs of interest with cortical and hippocampal atrophy. Conventional (hippocampal volumetric and voxel-based morphology) and modern (cortical thickness mapping with Freesurfer) methods were employed. Both SNPs were associated with hippocampal and cortical atrophy and were, therefore, considered to be linked with neurodegenerative aspects of AD.

Finally, validation of the findings was sought in a meta-analysis of several independent imaging genomic cohorts. This validation confirmed the association of rs1136410 with hippocampal volume in *APOE* $\epsilon 3$ homozygotes.

The innovative study design used by Nho and colleagues¹ make this investigation one of the most progressive AD genetic risk studies to date. Two key strengths are the focus on genetic discovery in cognitively affected but nondemented individuals, and the study of genetic variability in the extremes of a well-established neurodegenerative phenotype. Individuals with MCI who have extensive hippocampal atrophy are likely to harbour AD pathology. The only caveat is that without evidence of ongoing amyloid pathology from either amyloid PET scans or measurement of cerebrospinal amyloid- β levels, the possibility remains that the hippocampal atrophy could be attributable to causes other than prodromal AD, such as hippocampal sclerosis.

The whole-exome sequencing approach guarantees capture of all genetic variability at coding sites in the study discovery cohort. The limitation of this part of the study by Nho *et al.*¹ lies in the small sample size, which would encompass only a proportion of existing risk variants for AD. Larger sequencing studies with longitudinal follow-up will undoubtedly uncover additional AD-associated variants.

Many researchers are becoming increasingly sceptical about the power of statistical genetics to enable complete understanding of the genetic map of sporadic AD. The field is in need of a transition away from the statistically governed methodologies and towards quantitative trait association genetics. Such an approach, especially when coupled with whole-exome or whole-genome sequencing, will no doubt lead to discovery of a substantial portion of the missing heritability in AD, improve our understanding of disease mechanisms, and enable plausible biological effects of the involved genes to be determined. Adoption of quantitative trait association genetics will also pave the way to genomic medicine, including individualized risk assessment, improved diagnostic accuracy and patient-specific disease prevention and treatment plans.

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