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Researchers shed new light on the genetics of memory performance

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In the largest study of the genetics of memory ever undertaken, an international researcher team including scientists from Boston University School of Medicine (BUSM), have discovered two common genetic variants that are believed to be associated with memory performance. The findings, which appear in the journal *Biological Psychiatry*, are a significant step towards better understanding how memory loss is inherited.

Longer life spans and the increased prevalence of memory impairment and dementia world-wide underscore the critical public health importance of efforts aimed at deciphering the underlying mechanisms of human memory.

The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium was developed to facilitate the study of the entire genome through pooling of data from research centers all across the world. Nearly 30,000 participants who did not have dementia were included in the study. Each participant completed memory tests, such as word recall, and their entire genome was genotyped. Using sophisticated statistical analysis, the genome was examined for segments that were associated with low memory scores.

The researchers found genetic variants near the Apolipoprotein E gene, known to harbor an increased risk of dementia (especially Alzheimer disease), were associated with poorer memory performance, mostly so in the oldest participants and for the short story recall. In a sub-study with

post-mortem brain samples, participants with an increasing load of memory risk variants also had more pathological features of Alzheimer disease, perhaps reflecting in some instances early pre-clinical stages of the disease.

According to the researchers two additional regions of the genome, pointing to genes involved in immune response, were associated with the ability to recall word lists, providing new support for an important role of immune system dysfunction in age-related memory decline. "Interestingly genetic variants associated with memory performance also predicted altered levels of expression of certain genes in the hippocampus, a key region of the brain for the consolidation of information. These were mainly genes involved in the metabolism of ubiquitin that plays a pivotal role in protein degradation," explained lead author Stéphanie Debette, MD, PhD, adjunct associate professor of neurology at BUSM.

This unprecedented world-wide collaboration has generated novel important hypotheses on the biological underpinnings of memory decline in old age, however the researchers caution that more research is clearly needed to confirm these findings. "The differential associations according to memory test characteristics and age should be accounted for in future studies. Exploring other types of genetic variation, including rare variants and epigenetic modifications, will be crucial to decipher the full spectrum of memory heritability," added Debette.

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