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Genome-wide Studies of Verbal Declarative Memory in Nondemented Older People: The Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium

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ABSTRACT

BACKGROUND: Memory performance in older persons can reflect genetic influences on cognitive function and dementing processes. We aimed to identify genetic contributions to verbal declarative memory in a community setting.

METHODS: We conducted genome-wide association studies for paragraph or word list delayed recall in 19 cohorts from the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium, comprising 29,076 dementia- and stroke-free individuals of European descent, aged ≥45 years. Replication of suggestive associations ($p < 5 \times 10^{-6}$) was sought in 10,617 participants of European descent, 3811 African-Americans, and 1561 young adults.

RESULTS: rs4420638, near *APOE*, was associated with poorer delayed recall performance in discovery ($p = 5.57 \times 10^{-10}$) and replication cohorts ($p = 5.65 \times 10^{-8}$). This association was stronger for paragraph than word list delayed recall and in the oldest persons. Two associations with specific tests, in subsets of the total sample, reached genome-wide significance in combined analyses of discovery and replication (rs11074779 [*HS3ST4*], $p = 3.11 \times 10^{-8}$, and rs6813517 [*SPOCK3*], $p = 2.58 \times 10^{-8}$) near genes involved in immune response. A genetic score combining 58 independent suggestive memory risk variants was associated with increasing Alzheimer disease pathology in 725 autopsy samples. Association of memory risk loci with gene expression in 138 human hippocampus samples showed cis-associations with *WDR48* and *CLDN5*, both related to ubiquitin metabolism.

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CONCLUSIONS: This largest study to date exploring the genetics of memory function in ~40,000 older individuals revealed genome-wide associations and suggested an involvement of immune and ubiquitin pathways.

Keywords: Alzheimer disease, Dementia, Epidemiology, Genetics, Population-based, Verbal declarative memory

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The ability to form and retrieve memories is one of the most fundamental and complex aspects of human cognition. Decline in memory performance is a prominent marker of cognitive decline that occurs in late life and is one of the earliest signs of dementia (1,2). Verbal declarative memory, the conscious recall of information that can be retrieved verbally, can be measured using word list and paragraph recall tests. The delayed recall performance of these tests is a powerful predictor of Alzheimer disease (AD) (3).

Cognitive ability and memory performance were shown to be highly heritable (4–7). However, few consistent genetic associations have been described, mostly assessed by candidate gene association studies (8,9). Three genome-wide association studies (GWAS) of verbal declarative memory, on overlapping samples of 333 to 1073 young adults in their twenties, have identified associations of genetic variants in the *KIBRA* and *CTNNBL1* genes with delayed recall (10,11). No GWAS of verbal declarative memory delayed recall performance has been performed in older individuals to our knowledge.

Genetic determinants of verbal declarative memory are likely to differ between young and old individuals, although some may be shared across age groups (4). In young adults, developmental genes determining the neural networks required for learning, storage, and retrieval or genes involved in the molecular mechanisms of memory storage (12) could be expected to harbor most susceptibility variants. In older individuals, variants in genes involved in brain aging and neurodegenerative disease may be more likely revealed (13).

Our aim was to identify genetic variants associated with memory performance in late middle-aged and older individuals. We conducted a meta-analysis of GWAS for delayed recall performance in tests of verbal declarative memory in 29,076 older community-based individuals and sought replication and extension of findings in 13,998 independent older participants (10,617 of European descent and 3381 African-Americans) and 1561 young adults.

METHODS AND MATERIALS

GWAS Study Population

Analyses were performed in 19 population-based cohorts participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium (Section 2, Table S1 in Supplement 1). All subjects were aged ≥45 years and dementia and stroke free at cognitive assessment. The study population comprised 29,076 participants of European ancestry, including 6674 participants with paragraph recall and 24,604 participants with word list recall tests. Each cohort secured approval from institutional review boards, and all participants provided written informed consent for study participation, cognitive testing, and use of DNA for genetic research. None of these studies have previously published GWAS for delayed recall performance in tests of verbal declarative memory.

Memory Tests

Participants were administered one or both types of verbal declarative memory tests: word list delayed recall (WL-dr) and paragraph delayed recall (PAR-dr). WL-dr comprised tests using visually or verbally presented word lists, with or without semantic relatedness between the words; PAR-dr comprised tests using one or two verbally presented stories (Figure 1; Table S2 in Supplement 1). Participants were asked to remember as many words or paragraph elements as possible after a specified delay interval, preceded by an immediate recall task (Section 3 in Supplement 1). We decided a priori to run both global meta-analyses combining all tests and meta-analyses combining similar tests. Indeed, different memory tests may involve partly distinct neural networks and mechanisms (Section 3 in Supplement 1). Meta-analyses thus comprised a combination of all measures of delayed recall (ALL-dr; n = 29,076), PAR-dr (n = 6674), WL-dr (n = 24,604), and various subtypes of WL-dr tests, including Consortium to Establish a Registry for Alzheimer's Disease delayed recall (CERAD-dr, n = 4,274), Delayed Word Recall Test (n = 9,188), Rey Auditory Verbal Learning Test (RAVLT-dr, n = 4,274), California Verbal Learning Test (CVLT-dr, n = 2,950), and Hopkins Verbal Learning Test (n = 331) (Figure 1).

Genotyping and Imputation

The consortium was formed after the individual studies had finalized their GWAS platforms; hence, the studies included used different platforms. Genotyping platforms are described in Table S4 in Supplement 1. Imputation to nonmonomorphic, autosomal single nucleotide polymorphisms (SNPs) from the HapMap CEU (Utah residents with Northern and Western European ancestry from the CEPH collection) panel was performed with standard quality control filters (Section 4, Tables S5 and S6 in Supplement 1). *APOE*-ε genotypes are not available on the GWAS arrays; however, *APOE*ε had been genotyped separately in most cohorts.

Discovery GWAS

Within each cohort, a linear regression model was used to evaluate the association of raw scores for delayed recall (number of words or story elements recalled) with the number of minor alleles (0 to 2) at each SNP. Analyses were adjusted for age and sex and, if relevant, study site, familial structure, and population substructure (Section 5 in Supplement 1). We additionally adjusted for educational achievement (Table S1 in Supplement 1) in a secondary model only, as this could weaken associations with developmental genes that may impact educational attainment.