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Abstract

Background: Dementia is multifactorial with Alzheimer (AD) and vascular (VaD) pathologies making the largest contributions. There have been over 40 genetic loci associated with AD but genome-wide associations (GWA) underlying VaD remain incompletely identified. The proportion of VaD differs across studies based on study-specific definitions. We hypothesize that common forms of dementia (AD, VaD) will share genetic risk factors. We conducted the largest GWAS to date of VaD and examined the genetic overlap with "all-cause dementia" (ACD).

Method: A total of 293,544 participants from 9 population-based CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) cohorts, 2 national case-control consortia (ADGC, MEMENTO) and the UKBB contributed 23,986 and 2,935 cases of ACD and VaD, respectively. We ran study-specific analyses adjusting for age, sex, and population structure and meta-analyzed summary statistics using the sample size weighted method implemented in METAL, followed by conditional analyses, fine-mapping and bioinformatic exploration of loci.

Result: Genome-wide associations with VaD were identified at the APOE locus and at 5 additional loci. One locus has been previously associated with hippocampal volume, verbal memory and CSF amyloid levels (*ASTN2*); others were near genes associated

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with hypertension, diabetes and hyperlipidemia (Figures 1 and 2). In addition to previously identified AD loci, we identified novel variants associated with ACD. VaD-related loci also showed sub-threshold associations with ACD that were congruent in direction of effect, thus suggesting additional biological targets underlying ACD. We will additionally present results of an ongoing multiethnic GWAS and insights from pathway analyses and bioinformatic parsing of the identified loci.

Conclusion: Although VaD is the second most common cause of dementia, the identification of associated genetic loci has been hindered by the heterogeneity of its definition, which necessitates a large sample size to reach genome-wide significance. The newly identified loci could provide novel insights into the pathophysiological mechanisms of dementia and point to new prevention and treatment strategies.

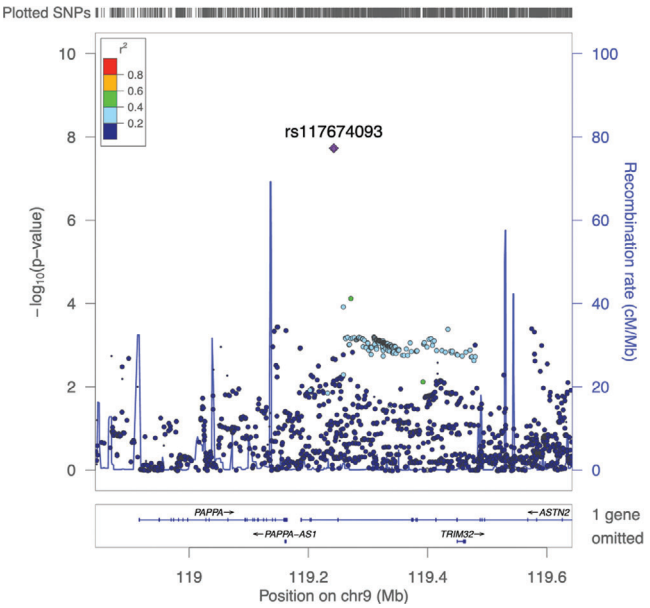

FIGURE 1

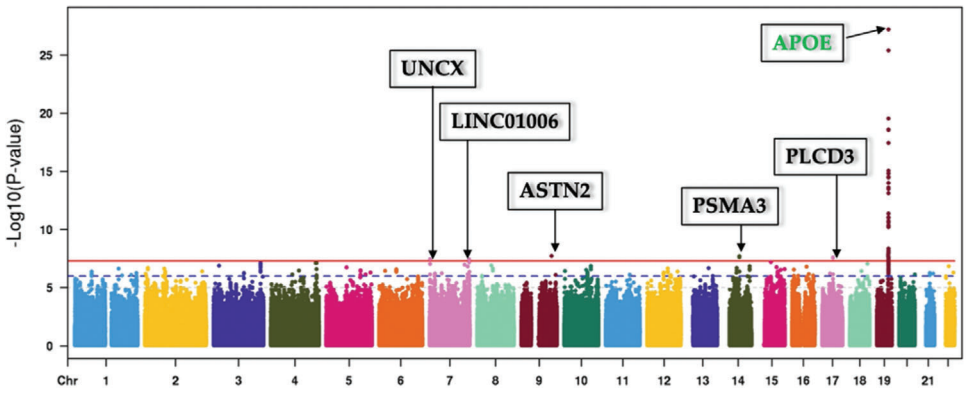

FIGURE 2