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Genetic susceptibility to accelerated cognitive decline in the US Health and Retirement Study

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ABSTRACT

Age-related cognitive decline is a major public health concern facing a large segment of the US population. To identify genetic risk factors related to cognitive decline, we used nationally representative longitudinal data from the US Health and Retirement Study to conduct genome-wide association studies with 5765 participants of European ancestry, and 890 participants of African ancestry. Mixed effects models were used to derive cognitive decline phenotypes from data on repeated cognitive assessments and to perform single nucleotide polymorphism-based heritability estimation. We found 2 independent associations among European-Americans in the 19q13.32 region: rs769449 (APOE intron; $p = 3.1 \times 10^{-20}$) and rs115881343 (TOMM40 intron; $p = 6.6 \times 10^{-11}$). rs769449 was also associated with cognitive decline among African-Americans ($p = 0.005$), but rs115881343 was not. Cross-sectional cognitive function showed moderate heritability (15%–32%) across several age strata (50–59, 60–69, 70–79 years), but the cognitive decline heritability estimate was low (~5%). These results indicate that despite multiple association signals for cognitive decline in the 19q13.32 region, inter-individual variation is likely influenced substantially by environmental factors.

1. Introduction

Based on the 2010 U.S. census, the number of Americans aged 65 years and older is expected to double from ~40 million in 2010 to ~80 million in the next 30 years (Vincent and Velkoff, 2010). Maintaining cognitive health is central to the well-being of aging individuals. Most cognitive domains tend to decline in concert starting around the age of 55 years (Deary et al., 2009; Zelinski and Burnight, 1997), but there is substantial inter-individual variability in the rate at which the decline occurs (Wilson et al., 2002). Although the causes of this variability are not well understood, accelerated decline may be an early sign of cognitive impairment and dementia (Deary et al., 2009; Plassman et al., 2010). Identifying factors that influence the onset and severity of cognitive decline, including genetic factors, is an important step toward developing intervention and treatment strategies.

Twin studies have demonstrated substantial heritability for general cognitive ability (Brandt et al., 1993; McClearn et al., 1997; McGue and Christensen, 2001), as well as for a variety of cognitive domains (Finkel et al., 2005; Lee et al., 2012; Reynolds et al., 2005). However, few twin studies have investigated the heritability of rates of cognitive change over time (Lee et al., 2010; McGue and Christensen, 2002; Reynolds et al., 2002), and these findings generally suggest that non-shared environmental factors are the primary cause of inter-individual differences in rates of decline.

To date, 2 genome-wide association (GWA) studies of cognitive decline have been conducted (Davies et al., 2012; De Jager et al., 2012). Both studies have identified single-nucleotide polymorphisms (SNPs) in the APOE and/or TOMM40 region (19q13.32) that show strong association with cognitive decline. The APOE and TOMM40 genes code for proteins involved with clearance of amyloid-β and mitochondrial functions, respectively, in addition to other functions (Humphries et al., 2005; Mager et al., 2011; Strittmatter et al., 1993). However, the association signals from GWA studies span several genes in the region (Jun et al., 2012), and the causal variant(s) in this region remain unknown.

Here we report a GWA study of cognitive decline using data from the Health and Retirement Study (HRS), a nationally representative longitudinal study of the health and economic well-being of aging individuals, with repeated measurements on cognitive status. In addition to assessing the association of individual SNPs with cognitive decline, we also derive SNP-based

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heritability of cognitive decline, as well as cross-sectional measures of cognitive function at various ages.

2. Methods

2.1. Study participants

The HRS is sponsored by the National Institute on Aging and is coordinated at the University of Michigan ("The Health and Retirement Study: A Longitudinal Study of Health, Retirement, and Aging. Produced and Distributed by the University of Michigan with Funding from the National Institute on Aging [grant number NIA U01AG009740] Ann Arbor, MI." 2013). HRS is an ongoing longitudinal study that began in 1992, with the goal of addressing issues faced by aging individuals transitioning out of the labor force into retirement. The HRS data includes individual-level information on social and economic factors as well as physical health characteristics such as disability and cognitive function. The study is nationally representative with oversampling of African Americans and Hispanic minorities. More than 26,000 subjects aged 50 years and older were enrolled, and interviewed every 2 years, with up to ten waves of data collected.

2.2. Measures of cognitive function

Assessment of cognitive function was based on a reduced version of the telephone interview for cognitive status, which was derived from the Mini-Mental State Exam (Folstein et al., 1975). The battery was designed to be quickly and easily administered over the telephone by lay interviewers, and measured a range of cognitive functions spanning various difficulty levels with sensitivity to changes in cognition over time. We used the summary score of *total cognition*, which consisted of the number of correct responses to all cognitive measures common across Wave 3 (1996) and beyond, with scores ranging from 0 to 35. This measure consisted of the following components: "immediate word recall", "delayed word recall", "serial 7's subtraction", "backwards count", "date naming", "object naming", "President and/or Vice President naming", and "vocabulary". The *total cognition* score was used to derive the cognitive decline phenotype that is the primary outcome for this analysis.

2.3. Construction of cognitive decline phenotype

To obtain cognitive decline measures for each participant, a mixed effects model was used to estimate subject-specific trajectories of cognitive decline. The method is similar to those implemented previously by De Jager et al. (2012) and Davies et al. (2012), and was carried out using the *xtmixed* command along with the *predict* post-estimation command in Stata (version 13.0). The model includes fixed effects terms for sex, age, and linear and quadratic forms of years since baseline visit, wave of entry, and race. Subject-specific random effects in the model accounted for between-individual variation at the age of 50 years (i.e., intercept), and inter-individual variation in the rate of change (i.e., slope) in cognitive function during follow-up. The random effects were assumed to be bivariate normally distributed. Subject-specific intercepts and slopes were obtained for each individual using empirical Bayes estimation. The resulting subject-specific residual slopes were then used as the cognitive decline measure in subsequent GWA analyses and for heritability estimation. Supplementary Fig. 1 shows for 50 random subjects, the observed cognitive trajectories and residual linear cognitive trajectories based on the mixed effects model.

2.4. Genotype data quality control

Germline DNA samples were obtained from 12,507 HRS participants (from blood and saliva samples) and genotyped for >2.5 million SNPs using the Illumina HumanOmni2.5-4v1 array at the Center for Inherited Disease Research. Standard quality control procedures were performed by the Genetics Coordinating Center of the University of Washington (Weir, 2012), which involved checking gender identity, chromosomal anomalies, relatedness, population structure, missing call rates, batch effects, and other sample and SNP quality measures. Subjects of European ancestry were defined as individuals self-identifying as White with relatively homogeneous ancestry, and falling within 1 standard deviation (SD) of all self-identified non-Hispanic Whites for eigenvectors 1 and 2 in the principal components analysis (PCA) of all unrelated study subjects. Subjects of African ancestry were defined as individuals self-identifying as African Americans, and falling within 2 SD of all self-identified African Americans for eigenvector 1, and 1 SD of eigenvector 2 in the PCA of all unrelated study subjects. Filters were implemented using PLINK, including call rates <98%, Hardy-Weinberg $p < 10^{-3}$ within ancestral groups, sex differences in allele frequency ≥0.2 or heterozygosity >0.3, and samples with low quality SNP data (<98% of SNPs successfully measured), evidence of high heterozygosity (i.e., potential contamination) or consanguinity (i.e., inbreeding), and exclusion of 1 individual in each related pair. Only SNPs with study-wide minor allele frequency (MAF) >0.5% within each ancestral group were included in the analysis.

2.5. Genome-wide association analysis

Genome-wide association analysis of the cognitive decline outcome was performed for subjects of European ancestry using linear regression implemented in the PLINK software (version 1.07) (Purcell et al., 2007) using an additive genetic model. To adjust for population substructure among individuals of European ancestry, association analyses were adjusted for the top 5 eigenvectors derived from PCA. Additional conditional analyses were performed by including the top SNP hit as a covariate and analyzing the association of the remaining SNPs with cognitive decline. Regional association plots of the top signals were generated using R script developed by the Broad Institute (http://www.broadinstitute.org/diabetes/scandinavs/figures.html). GWA analysis was also conducted excluding subjects who had reported a doctor-diagnosed memory-related disease (250 of 5765 individuals). GWA analyses were repeated for subjects of African ancestry.

2.6. Estimation of heritability

We estimated the total contribution of genotyped SNPs to cognitive decline as well as cross-sectional cognitive function at various ages by performing a linear mixed-model analysis of variance as implemented in the genome-wide complex trait analysis (GCTA) program (version 1.13) (Yang et al., 2011). GCTA allows the estimation of the proportion of additive genetic variance attributable to all measured SNPs collectively, among unrelated individuals (Yang et al., 2011). To minimize the impact of phenotypic similarity between related individuals because of common environmental factors, we removed an individual from any pairs of close relatives whose estimated genetic relatedness was >0.025. We repeated the above analyses after excluding SNPs in the 2-Mb region surrounding the APOE gene to assess heritability of these cognitive phenotypes that is not because of variants in this region.