Genetic architecture of age-related cognitive decline in African Americans

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ABSTRACT

Objective: To identify genetic risk factors associated with susceptibility to age-related cognitive decline in African Americans (AAs).

Methods: We performed a genome-wide association study (GWAS) and an admixture-mapping scan in 3,964 older AAs from 5 longitudinal cohorts; for each participant, we calculated a slope of an individual’s global cognitive change from neuropsychological evaluations. We also performed a pathway-based analysis of the age-related cognitive decline GWAS.

Results: We found no evidence to support the existence of a genomic region which has a strongly different contribution to age-related cognitive decline in African and European genomes. Known Alzheimer disease (AD) susceptibility variants in the ABCA7 and MS4A loci do influence this trait in AAs. Of interest, our pathway-based analyses returned statistically significant results highlighting a shared risk from lipid/metabolism and protein tyrosine signaling pathways between cognitive decline and AD, but the role of inflammatory pathways is polarized, being limited to AD susceptibility.

Conclusions: The genetic architecture of aging-related cognitive in AA individuals is largely similar to that of individuals of European descent. In both populations, we note a surprising lack of enrichment for immune pathways in the genetic risk for cognitive decline, despite strong enrichment of these pathways among genetic risk factors for AD. Neurology Genet 2017;3:e125; doi: 10.1212/NXG.0000000000000125

GLOSSARY

African American; Alzheimer disease; CHAP = Chicago Health and Aging Project; EA = European ancestry; GWAS = genome-wide association study; IIDP = Indianapolis-Ibadan Dementia Project; MAP = Rush Memory and Aging Project; MARS = Minority Aging Research Study; ROS = Religious Orders Study; SNP = single nucleotide polymorphism.

Aging-related cognitive decline is a multifactorial process and is likely to be promoted by accumulated brain injury due to chronic conditions of aging, including Alzheimer disease (AD), cardiovascular brain factors, type II diabetes mellitus, cerebrovascular diseases, and inflammatory diseases.

When trajectories of cognitive decline are compared between individuals of African American (AA) ancestry and individuals of non-Hispanic European ancestry (EA), there is no appreciable difference at the average rate of decline in these 2 populations. However, differences in the prevalence and effect size of different risk factors for cognitive decline—such as AD, small and

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large vessel neurovascular disease, and lipid profiles—have been noted previously.7,8 These differences suggest that it is important to explore the role of such risk factors in distinct human populations so that interventions to mitigate cognitive decline can be more effectively targeted.

To identify genetic loci influencing age-related cognitive decline in AAs, we first used admixture mapping, an approach that scans the genome for disease-related genetic variants that differ in frequency across populations.9 In addition, we performed a genome-wide association study (GWAS) using the same 3,964 AA participants and outcome measure to identify genetic variants that are associated with the individual’s trajectory of cognitive decline. We evaluated the mechanism of the association by examining pathologic phenotypes, gene expression, and biological pathway data. Together, these analyses shed light on the role of genetic ancestry and on genes and pathways that contribute to the pathogenesis of age-related cognitive decline in AAs.

**RESULTS**

**Demographic and phenotypic characteristics of participants.** After stringent data quality control, 3,964 AA individuals from 5 study cohorts (CHAP, IIDP, ROS, MAP, and MARS) were available for our analysis (table e-2). All of these cohorts recruit participants who are older than 65 years and do not have dementia at the time of enrollment. The participants are then followed longitudinally using a battery of cognitive tests. A subject’s performance on each test was standardized, and an average aggregate measure of global cognitive performance was computed for each evaluation.14 Each individual had 2 or more neuropsychological evaluations, and a linear mixed-effects model was used to calculate a residual that captures the slope of an individual’s global cognitive change (figure e-2; e-Methods). This residual was then used as a quantitative trait in our analyses, as we have done in a prior GWAS.19

**Genome-wide admixture scan for age-related cognitive decline.** To examine whether genetic ancestry influences age-related cognitive decline in AA participants, we conducted a genome-wide admixture study. This technique estimates the proportion of African or EA that is present at every point in the genome of each individual. The estimated average percentage of EA in the AA participants used in this analysis was 21.2 ± 12.3%, consistent with other studies of AA participants8,20 (figure e-3).

In our primary analysis, we performed a quantitative admixture evaluation14, which associates local ancestry to the continuous phenotype—in this case, the slope of cognitive decline. The quantitative
admixture scan did not identify any single region of the genome that meets the stringent threshold of genome-wide significance \( (p < 1 \times 10^{-5}) \) (figure 1A). We also conducted a different admixture scan using an “extreme of outcome” strategy. Specifically, we defined the top 20% of individuals \( (n = 792) \) in the distribution of cognitive decline trajectories as “cases” and the 20% with lowest cognitive decline trajectories as “controls.” In this analysis, we observed no admixture peak of excess European or African ancestry in the cases relative to the control participants, consistent with the results of the quantitative admixture scan (figure 1B). However, while no single chromosomal region shows a statistically significant difference in ancestry, we find that cases have a higher proportion of African ancestry across their genome compared to controls \( (80.0\% \pm 11.4\% \text{ African ancestry in cases and } 78.4\% \pm 13.3\% \text{ in controls}; t \text{ test } p < 0.0001) \). This result suggests that there may be several different regions of the genome that contain risk alleles that are more frequent in AA populations but that each of them may have only a modest influence on the risk of cognitive decline.

**GWAS for age-related cognitive decline.** While genetic ancestry at any single locus does not appear to have a strong role in age-related cognitive decline, genetic variants do influence this trait.\(^{19,21-24}\) We therefore proceeded with a GWAS meta-analysis across the 5 AA cohorts \( (n = 3,964 \text{ participants}) \) to identify common genetic variants that contribute to age-related cognitive decline. Quantile-quantile plots of the distribution of test statistics showed little deviation from the expected null distribution over most of the genome (figure 2A), and the genomic inflation factor \( (\lambda_{GC}) \) was 0.997, indicating no substantial population stratification in the study.

The top results of the GWAS are listed in table 1. As expected, common variants such as rs429358 that partially reflect the effect of the \( APOE \) locus\(^{7,25}\) showed association at a genome-wide level of significance, consistent with the previously reported role of the \( APOE e4 \) haplotype in cognitive decline.\(^{19}\) In addition to \( APOE \), we discovered 20 loci with suggestive \( (p < 10^{-6}) \) and 4 loci (nearest genes are \( TRPS1, TEK, GABRA4, \) and \( ZNF737 \)) with highly suggestive \( (p < 10^{-7}) \) levels of association to the rate of cognitive decline in our study (table 1; figure 2B).

The highly suggestive variant rs16885997 is located 911 kb from \( TRPS1 \), a gene encoding a zinc finger transcription factor that represses GATA-regulated genes and binds to a dynein light chain protein. Of interest, the \( TRPS1 \) haplotype associated...
with a higher rate of cognitive decline has previously been associated with greater total cholesterol levels, suggesting a possible link with neurovascular disease.

A complementary strategy to evaluate the role of the 4 highly suggested loci involves their evaluation in network analyses: specifically, we assessed whether the genes found within these 4 loci connect to an existing AD susceptibility network. Of interest, in a protein-protein interaction analysis using DAPPLE, the \( \text{TEK} \) gene on chr 9p21 (table 1) interacts with validated AD susceptibility genes identified in a recent GWAS including \( \text{CD2AP} \), \( \text{PTK2B} \), \( \text{BIN1} \), and \( \text{INPP5D} \) (figure e-4). This network analysis is significant (permuted \( p = 0.021 \)), suggesting that the \( \text{TEK} \) locus may have a role in cognitive decline through an effect on known AD susceptibility networks.

Since AD susceptibility alleles have been reported to influence the trajectory of cognitive decline, we also evaluated the role of the known AD risk alleles discovered in EA participants in our AA results. As outlined in table e-3, we find evidence that the index SNPs in the \( \text{ABCA7} \) and \( \text{MS4A} \) loci are associated with age-related cognitive decline in AAs using a gene-based multiple hypothesis correction.

Immune system–mediated pathways are enriched in the AD GWAS but not in cognitive decline. To systematically identify biological connections between putative susceptibility loci in our analysis, we conducted a pathway enrichment analysis using MAGENTA software and highly curated databases as pathway information resources. We found evidence of enrichment of associations involved in lipid/cholesterol metabolism and protein tyrosine kinase signaling pathways in relation to cognitive decline in AA participants (figure 3). We replicated the role of these 2 pathways in an analysis of the same trait in the participants of EA from the ROS and MAP cohorts (table e-4).
We then compared our pathway enrichment results for cognitive decline with results for AD susceptibility using data from a recent large AD GWAS.25 In the AD GWAS pathway analysis, we found that cholesterol/lipid metabolism and immune processes were enriched \( (p < 10^{-3}; \text{false discovery rate } 0.1) \).

When comparing our AA cognitive decline results with the results of a similar analysis in relation to AD in AA participants using a recently published study,7 we find that "lipid/cholesterol metabolism" and "protein kinase signaling processes" are enriched in both analyses, but we observed striking polarization of immunity-related pathways in the AD GWAS (figure 3; table e-3). The pathways including "complement activation," "interferon-mediated immunity," and "NF-kappaB cascade" are enriched for AD GWAS results but not for loci associated with cognitive decline (figure 3). These results suggest that, proportionally, the involvement of innate immunity may be much more important in AD than that in aging-related cognitive decline.

**DISCUSSION** Our large study represents an important step forward in understanding the role of genetic risk factors in aging-related cognitive decline in the AA population. We were well powered to find susceptibility loci of an even modest effect in our

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**Table 1** Top results of genome-wide scan for the rate of age-related cognitive decline in African Americans

| Single nucleotide polymorphism | Allele | Minor allele frequency | \( \beta \) | \( p \) Value (meta-analysis) | Nearest gene(s) |
|--------------------------------|--------|------------------------|------|------------------------------|-----------------|
| rs429358                       | C/T    | 0.198                  | -0.01| 1.92E-14                     | TOMM40, APOE    |
| rs16885997                     | T/G    | 0.077                  | -0.009| 2.52E-07                     | TRPS1, CSM03    |
| rs73643144                     | C/T    | 0.103                  | -0.007| 4.10E-07                     | TEK, ncRNA32    |
| rs17641411                     | T/C    | 0.013                  | -0.026| 5.05E-07                     | COX7B2, GABRA4  |
| chr19:20843676                 | G/A    | 0.022                  | -0.037| 7.43E-07                     | ZNF737, ZNF626  |
| chr10:114847180                | T/A    | 0.016                  | -0.029| 1.22E-06                     | VTI1A, TCF7L2   |
| chr1:3293503                   | G/T    | 0.011                  | -0.048| 1.31E-06                     | ACTRT2, PRDM16  |
| chr5:76620888                  | C/T    | 0.017                  | -0.012| 1.35E-06                     | C16orf13, UBE2CBP |
| chr3:29995897                  | G/A    | 0.034                  | -0.016| 1.47E-06                     | AZI2, ZCWDP2    |
| chr15:82531032                 | T/C    | 0.035                  | -0.019| 2.04E-06                     | EFTUD1, FAM154B |
| chr16:6473466                  | T/G    | 0.017                  | -0.018| 2.28E-06                     | TMEM114, C16orf68 |
| rs10865419                     | C/A    | 0.152                  | -0.007| 2.54E-06                     | C2orf5, LRRTM4  |
| rs4719128                      | T/C    | 0.302                  | -0.004| 2.70E-06                     | AUTS2, WBSCR17  |
| chr20:54981371                 | C/T    | 0.025                  | -0.032| 3.03E-06                     | CSTF1, CASS4    |
| chr12654437                    | G/T    | 0.363                  | 0.004 | 4.43E-06                     | GRAMD1A, TTLL2  |
| rs2717504                      | G/C    | 0.205                  | 0.005 | 4.78E-06                     | VIT, STRN       |
| rs6939297                      | A/G    | 0.066                  | -0.009| 4.97E-06                     | SCAND3, RPSAP2  |
| chr14:30517407                 | A/G    | 0.011                  | -0.02 | 5.42E-06                     | G2E3, SCFD1     |
| chr2:235031272                 | A/G    | 0.016                  | -0.031| 6.33E-06                     | SPP2, ARL4C     |
| rs2343732                      | C/T    | 0.113                  | -0.007| 6.42E-06                     | PDGFC, GLRB     |

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**Figure 3** Pathway enrichment analysis of African American age-related cognitive decline and Alzheimer disease genome-wide association studies

The figure plots the \(-\log_{10} \text{false discovery rate (FDR \( q \) value)}\) derived using MAGENTA for pathways enriched in association for Alzheimer disease susceptibility on the y axis, and the results of the same analysis for the genetic architecture of aging-related cognitive decline that we define in our participants on the x axis. The dotted lines denote the threshold of significance (FDR < 0.05) in each analysis. Each point represents one pathway; enriched pathways are color coded with the color key included at the top right aspect of the figure. Selected pathways are annotated to illustrate the types of pathways that we find to be enriched.
admixture analysis, but we failed to find any single locus with a significant association in this analysis that relies on differences in the genetic risk between the AA and EA populations. Thus, we have not found evidence to support the existence of genetic risk factors that are unique to AA individuals and have a strong effect on aging-related cognitive decline at the population level.

Nonetheless, the greater average proportion of African ancestry in AA individuals with more rapid cognitive decline suggests that there are likely to be a number of genetic risk factors that, while shared between African and European populations, may have a more detrimental role in AA participants. Such a variant may have a more detrimental role for the AA population because of an increase in frequency, a larger effect size, or an interaction with an environmental variable that is enriched in AA individuals.

Our study holds many other intriguing results that warrant further investigation such as the low frequency variants that are strongly associated with cognitive decline in AA individuals and are not found in EA individuals. This prevents us from evaluating these variants in existing data from EA participants, and thus, replication in large cohorts of AA participants will be necessary to validate these observations. Similarly, the other suggestive association of the TEK locus, which connects to a pathway of validated AD susceptibility genes, will require further investigation in AA participants given the very low frequency of the risk allele in EA populations. Finally, we also examined the role of the most suggestively associated variants in the published results of the AD GWAS in AA participants, and we saw no association with this different trait, although this study is not powered to rule out a modest effect in AD for the variants that we report in this study.

Leveraging several large recent studies of AD and cognitive decline in AA and EA participants in addition to our new AA study, we report an intriguing perspective on broader patterns in the genetic architecture of AD and cognitive decline. The fact that certain pathways are significantly enriched for associations with both traits is not surprising since AD is an important driver of cognitive decline in older age. However, the degree of polarization in the enrichment of immune pathways is striking and was unexpected. While there are certainly some susceptibility variants for cognitive decline with presumed effects on immune function (such as MS4A genes and perhaps TRPS1), the relative role of immune pathways is clearly different in terms of susceptibility to these 2 conditions. This is important in prioritizing target validation and drug discovery efforts in shared pathways as well as framing the deployment of compounds that may be discovered in the future: patient stratification may be required to develop an optimal therapy for an individual, based on the relative role of different pathophysiologic processes that contribute to that individual’s cognitive decline.

Overall, this study illustrates the successful application of a study design that does not target cognitive performance in older age—which is an amalgam of the effects of developmental factors, life experience, and degenerative processes—but rather targets cognitive decline. This trait allows us to specifically interrogate the genetic architecture of factors that contribute to cognitive loss with age, which occurs in all participants, regardless of their maximal cognitive attainment. Our focus on cohorts that represent samples of the older population makes our results relevant to the experience of our aging population, particularly the AA population. Our pathway analyses are consistent with the narrative that neurovascular risk factors, as well as AD risk factors, are important for cognitive well-being in older age in AA individuals and individuals of other ancestries. The admixture analyses highlight the fact that there are probably no genetic risk factors for cognitive decline that are common and unique to populations with African ancestry; such genetic risk factors appear to be present in both the European and African component of an AA individual’s genome, but the allele frequency and effect size of a susceptibility variant can vary between populations, making an allele easier to discover in one or another population.

**AUTHOR CONTRIBUTIONS**

Towfique Raj and Lori B. Chibnik: analysis. Cristin McCabe: data generation. Andus Wong: interpretation of data. Joseph M. Replogle and Lei Yu: analysis. Sujuan Gao, Frederick W. Unverzagt, and Barbara Stranger: interpretation of data. Jill Murrell, Lisa Barnes, Hugh C. Hendrie, and Tatiana Foroud: provided samples. Anna Kritchovsky: interpretation of data. David A. Bennett: provided samples. Kathleen S. Hall: provided samples and study design. Denis A. Evans: provided samples. Philip L. De Jager: study design, data generation, analysis, and interpretation of data.

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**DISCLOSURE**

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