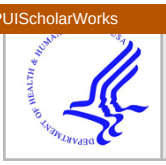

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Two novel loci, *COBL* and *SLC10A2*, for Alzheimer's disease in African Americans

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Supplementary data

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Abstract

Introduction—African Americans' (AAs) late-onset Alzheimer's disease (LOAD) genetic risk profile is incompletely understood. Including clinical covariates in genetic analyses using informed conditioning might improve study power.

Methods—We conducted a genome-wide association study (GWAS) in AAs employing informed conditioning in 1825 LOAD cases and 3784 cognitively normal controls. We derived a posterior liability conditioned on age, sex, diabetes status, current smoking status, educational attainment, and affection status, with parameters informed by external prevalence information. We assessed association between the posterior liability and a genome-wide set of single-nucleotide polymorphisms (SNPs), controlling for *APOE* and *ABCA7*, identified previously in a LOAD GWAS of AAs.

Results—Two SNPs at novel loci, rs112404845 ($P = 3.8 \times 10^{-8}$), upstream of *COBL*, and rs16961023 ($P = 4.6 \times 10^{-8}$), downstream of *SLC10A2*, obtained genome-wide significant evidence of association with the posterior liability.

Discussion—An informed conditioning approach can detect LOAD genetic associations in AAs not identified by traditional GWAS.

Keywords

Alzheimer's disease; Genome-wide association study (GWAS); African Americans; Informed conditioning on clinical covariates; *COBL*; *SLC10A2*; *APOE*; *ABCA7*; Age; Sex differences; Diabetes; Smoking; Education; Resveratrol

1. Introduction

Late-onset Alzheimer's disease (LOAD) in African Americans (AAs) is influenced by multiple genetic, clinical, and environmental factors [1–3]. AAs are at increased risk of LOAD compared with non-Hispanic whites [4–6]. Nonetheless, knowledge about the genetic architecture of LOAD comes disproportionately from studies of non-Hispanic whites. The relative lack of data presents a substantial barrier to understanding LOAD

mechanisms in AAs [3]. The *APOE* ε4 allele is a well-established genetic risk factor for LOAD in AAs [7]. Whereas >20 LOAD risk genes have been identified from genome-wide association studies (GWASs) for non-Hispanic whites, only two loci have been identified from GWAS for AAs [1,8]. A GWAS by Reitz et al. [1] found that, in addition to the *APOE* ε4 allele, a variant in the *ABCA7* gene (rs115550680) was significantly associated with LOAD in AAs.

Most genetic association studies in LOAD, including those of AAs, adjust for age, sex, and population substructure (PC) only. For quantitative traits analyzed by linear regression, introducing other nonconfounding covariates into a genetic study could enhance detection of additional loci by accounting for some of the variance in the outcome. However, for case-control association studies, including nonconfounding covariates in a logistic regression model can actually reduce power to detect an association because case-control ascertainment can create an artificial correlation between the genetic variant and a covariate, and each additional covariate reduces the precision of estimates [9,10]. Zaitlen et al. [11] recently showed that using an informed conditioning approach, nonconfounding covariates could be included in a case-control study with an increase in power compared with models that do not include covariates. Informed conditioning is based on the liability threshold model with parameters informed by external prevalence information. In this approach, first a liability model is constructed using covariates' independent effect estimates, in the form of trait prevalences at different covariate levels. Next, an association is tested between a genetic variant and the residuals from the liability model [11]. Informed conditioning has been applied with success to other phenotypes including stroke, type-2 diabetes, prostate cancer, lung cancer, breast cancer, reheumatoid arthritis, age-related macular degeneration, and end-stage kidney disease [11,12]. In the present study, we conducted a GWAS in the AA cohort of Reitz et al. [1], employing informed conditioning on LOAD status and several well-established LOAD risk factors, obtaining genome-wide significant evidence of association at two novel loci.

2. Methods

2.1. Study population

Study population included 1825 well-characterized AA LOAD cases and 3784 cognitively normal AA controls from 9 Alzheimer's Disease Genetic Consortium (ADGC) datasets: Adult Changes in Thought, Alzheimer's Disease Centers 1&2 (ADC1&2), ADC3, ADGC, Chicago Health and Aging Project (CHAP), Indianapolis, Genetic and Environmental Risk Factors for Alzheimer Disease Among AAs (GenerAAtions), Multi-Institutional Research on Alzheimer Genetic Epidemiology (MIRAGE) 300k, and MIRAGE 660k. The ADGC dataset contained participants from several studies including the AA AD Genetics Study, the ADCs, CHAP, Mayo Clinic, Mount Sinai School of Medicine, Religious Orders Study/ Memory and Aging Project/Minority Aging Research Study (MARS)/Rush Clinical Core (CORE), University of Miami (UM)/Vanderbilt University (VU), University of Pittsburgh, Washington Heights Columbia Aging Project, and Washington University. A detailed description of subject recruitment and phenotyping has been described previously [1]. Two of these studies were family based (i.e., contained related participants: MIRAGE and

GenerAAtions), whereas the other studies included only unrelated participants. Age of symptom onset was available for most cases. For the remaining cases, surrogate age information was available (age at ascertainment for Indianapolis, age at diagnosis for CHAP and MARS/CORE, and age at death for autopsy cases from UM/VU). Age of last examination or age of death was available for controls. We excluded cases younger than age 60. Ascertainment of additional risk factor data (educational attainment, diabetes status, and current smoking status) in each parent study has been described previously [13–20]. For the present study, we defined low educational attainment as ≤8 years of education. Because only a subset of the subjects from the ADGC dataset had additional risk factor data available, we divided the dataset into those with new risk factor data (ADGC1) and those without new risk factor data (ADGC2). Individuals were recruited under protocols approved by the appropriate institutional review boards.

2.2. Procedures

Details of genotyping (including platforms), quality control (including call rates, Hardy-Weinberg equilibrium, discordance with ascertained sex and latent relatedness), and derivation of principal components to adjust for PCs were described previously [1]. Briefly, we used directly measured *APOE* genotypes. We estimated haplotypes using SHAPEIT [21] and then imputed allele dosages for each dataset separately using IMPUTE2 [22] and 1000 Genomes reference haplotypes (March 2012). We excluded imputed single-nucleotide polymorphisms (SNPs) with an imputation quality estimate of R^2 ≤0.40. In the unrelated cohorts, we did not exclude SNPs based on minor allele frequency (MAF) because their inclusion did not lead to *P*-value inflation. In the family-based cohorts, we excluded SNPs with MAFs <0.05. We derived principal components using EIGENSTRAT [23] separately for each dataset using a set of genotyped SNPs common to all genotyping platforms.

2.3. Calculation of the posterior mean residual liability score

An informed conditioning approach leverages external conditional prevalence data from the epidemiological literature. AA-specific prevalences of LOAD conditioned on LOAD risk factors (age, sex, education, current smoking status, and diabetes) have not been presented in the epidemiological literature. Therefore, we estimated the prevalences of LOAD in AAs >65 years of age, conditioned on a given LOAD risk factor (RF), based on published ancestry-nonspecific relative risks (RRs) of LOAD with respect to the RF [4–6,24,25], published prevalence of each RF (*P*(RF)) in AAs [26–29] (Supplementary Table 1), and estimated prevalence of LOAD in AAs (*P*(LOAD)) (Table 1). We assumed that RRs do not differ by ancestry [3,30–34]. The conditional prevalence of LOAD for a given RF, *P*(LOAD|RF), is related to the RR as follows:

$$P(\mathrm{LOAD}|\mathrm{RF}) = \mathrm{RR} * P(\mathrm{LOAD}|{\sim}\mathrm{RF}), \text{where} {\sim}\mathrm{RF} \text{ is the absence of the RF.} \quad (1)$$

where ~ RF is the absence of the RF.

The law of total probability,

$$P(\mathrm{LOAD})=P(\mathrm{LOAD}|\mathrm{RF})*P(\mathrm{RF})+P(\mathrm{LOAD}|\sim\mathrm{RF})*P(\sim\mathrm{RF}), \quad (2)$$

can be used to rewrite the conditional prevalence as follows:

$$P(\mathrm{LOAD}|\mathrm{RF})=\frac{\mathrm{RR}*P(\mathrm{LOAD})}{P(\sim\mathrm{RF})+\mathrm{RR}*P(\mathrm{RF})} \quad (3)$$

We used equation 3 to calculate the LOAD conditional prevalences in AAs for each of the five LOAD risk factors (Table 1).

An informed conditioning approach, described by Zaitlen et al. [11], models an unobserved underlying quantitative trait, ϕ, called the liability:

$$\phi=\sum_{j=1}^{J} c_j(t_j-\bar{t}_j)+m+\varepsilon, \quad (4)$$

where c_j is a parameter estimating the effect of a given covariate j on the liability scale, t_j is the value of covariate j, and m is a parameter that determines the population prevalence p of LOAD at the covariate mean $\bar{t}_j$ such that ϕ is the normal cumulative distribution function and $\phi(-m) = P(x > -m) = p$. Finally, $\varepsilon = \gamma g + N(0,1)$ where γ is the effect size of the candidate SNP with genotype g normalized to mean 0 and $N(0,1)$ is the standard normal distribution. Multiple covariates are treated independently, but parameters are estimated jointly. A subject is a case if $\phi \geq 0$ and is a control otherwise.

We estimated parameters for two models because the additional risk factor data were missing for a subset of study subjects. The first model included all LOAD risk factors and their corresponding external conditional prevalence estimates, whereas the second model included only age and sex as LOAD risk factors and their corresponding external conditional prevalence estimates. We used these models to calculate the posterior mean residual liability score (hereafter called the LOAD liability score) for each subject given their LOAD and risk factor status. We used the LTSOFT computer program [11,35] for modeling the LOAD liability and for generating the LOAD liability score.

2.4. Association analyses

For mean age, sex, current smoking status, diabetes status, mean education level, *APOE* ε4 genotype, and rs115550680 MAF, we compared cases with controls in unadjusted models by meta-analyzing the ln odds ratio for categorical variables and standardized mean difference for continuous variables using a fixed-effects model with inverse variance weights. We conducted genome-wide association with the LOAD liability score using linear regression in each of the unrelated cohorts and linear generalized estimating equations (GEEs) in each family-based cohort, as the GEE method is robust to nonindependence of error terms within a family [36]. Association tests were adjusted for three PCs, *APOE* ε4 dosage, and dosage

of the minor allele of *ABCA7* SNP rs115550680. Association tests were carried out using R version 3.1.2 software [37]. Results were combined across datasets by meta-analyzing the regression estimates after applying genomic control adjustments using a fixed-effects model with inverse variance weights, as implemented in METAL [38]. The test statistic was the meta-analyzed regression estimate divided by its standard error. Several post hoc analyses were conducted for top-ranked loci. We evaluated several logistic regression models using LOAD case-control status as the outcome with different sets of covariates. In addition, we analyzed a liability model that included the full set of clinical variables but that did not include *APOE* ε4 genotype and rs115550680 minor allele dosage as covariates.

3. Results

Table 2 shows characteristics for each dataset. In unadjusted models, older age, lower educational attainment, *APOE* ε4 genotype, and rs115550680 minor allele (G) dosage were associated with LOAD risk. Current smoking and diabetes were associated with reduced risk. Female sex was not associated with LOAD status. The conditional prevalence estimates of LOAD in AAs >65 years of age that were calculated based on published LOAD RF prevalences and LOAD RRs with respect to the RFs (Supplementary Table 1) are listed in Table 1.

A total of 19,725,427 SNPs passed quality control and were included in the GWAS. For individual datasets, the genomic inflation factor λ ranged from 0.984 to 1.127. There was no evidence of inflation of test statistics in the meta-analyzed LOAD liability model (λ = 0.993, Supplementary Fig. 1). We found genome-wide significant associations ($P <= \times 10^{-8}$) using informed conditioning in two distinct regions, 200-kb upstream of cordon-bleu WH2 repeat protein (*COBL*) and 30-kb downstream of solute carrier family 10, member 2 (*SLC10A2*) (Table 3). For the top SNP in each region (*COBL*: rs112404845, *SLC10A2*: rs16961023), the effect was in the same direction for all datasets (Figs. 1 and 2) and the final liability model showed a smaller *P* value than the logistic models by one to two orders of magnitude (Table 3).

Because both variants were imputed and relatively rare, we compared allele dosages from imputation with direct genotyping. For rs112404845 (imputation quality range [using the IMPUTE2 information metric]: 0.905–1.039), we Sanger sequenced 20 predicted risk-allele carriers and an equal number of noncarriers. We found perfect correlation between the imputed dosage and direct genotype. For rs16961023 (imputation quality range: 0.598–0.917), we used a Taqman assay to directly genotype 35 predicted risk allele carriers and 1720 noncarriers from the ADGC1 and ADGC2 datasets. As expected based on the imputation quality (ADGC1 = 0.704, ADGC2 = 0.679), the correlation between direct genotype and imputed dosage (ADGC1 = 0.736, ADGC2 = 0.565) was adequate. When we repeated our association analysis across all datasets, among subjects with imputed posterior probabilities >0.8, using best-guess genotype, there was a reduction in effect size from 0.41 to 0.33.

Supplementary Table 2 shows SNPs with suggestive associations ($P <= \times 10^{-6}$) using informed conditioning. No loci identified as risk factors for LOAD in GWAS in white non-

Hispanics showed suggestive associations. As a positive control, we compared the effect of the *ABCA7* rs115550680 variant in a logistic model that controlled for age, sex, current smoking status, diabetes status, educational attainment, and PCs with the liability model. Using the informed conditioning approach, the *P* value decreased by a half order of magnitude in the liability model compared with a logistic model (Supplementary Table 3).

4. Discussion

In this study, we conducted a GWAS in AAs, employing informed conditioning on LOAD status and well-established LOAD risk factors including age, sex, diabetes status, current smoking status, and educational attainment. Our model is informed by external prevalence data from the epidemiological literature. Using this approach, which has been shown to outperform standard case-control association tests [11,12], we identified two genome-wide significant novel LOAD loci, upstream of *COBL* and downstream of *SLC10A2*.

COBL is predominantly expressed in brain, and its protein product regulates neuron morphogenesis. It mediates actin nucleation, ensuring that neurites form, elongate, and branch correctly to produce functional neuronal networks. In Cobl-deficient dissociated hippocampal neurons, neurite and dendritic branch point numbers were significantly reduced [39]. An SNP approximately 500-kb upstream of *COBL* was implicated in posttraumatic stress disorder in cohorts with European [40] and African ancestry [41]. Rs112404845, the top SNP in the *COBL* region in our study, is located 200-kb upstream of *COBL* and is present only in persons with African ancestry (MAF = 0.012 in the 1000 Genomes reference panel). This may explain why *COBL* has not been recognized previously as an AD risk gene. Variation at rs112404845 leads to a Pax-4 regulatory motif change. Rs113739092, an SNP in linkage disequilibrium with rs112404845 ($r^2 = 0.64$) and which achieved a *P* value of 1.3×10^{-5}, is an enhancer histone mark in brain [42].

SLC10A2 encodes a sodium/bile acid cotransporter that is essential for cholesterol homeostasis. Mutations in *SLC10A2* have been found in cases of familial hypercholesterolemia [43]. Several other genes implicated by GWAS in LOAD pathogenesis function in cholesterol metabolism include *APOE*, *CLU*, *ABCA7*, and *SORL1* [44]. Although its function is best understood in the small intestine [45], *SLC10A2* also is expressed in brain [46]. Resveratrol, a chief constituent of red wine, inhibits *SLC10A2* expression and function through a Sirt1 (sirtuin 1)–independent manner [47]. Potentially an exciting therapy for LOAD, resveratrol reduces amyloid plaque pathology in AD animal models [48] and has been shown to be safe and well-tolerated in a large phase 2 LOAD clinical trial [49]. Although resveratrol's antiamyloidogenic effects have been suggested to be mediated by Sirt1 [50], our findings indirectly suggest that resveratrol may affect AD through multiple mechanisms. Rs16961023, the most significantly associated SNP in the *SLC10A2* region in our study, is located 30-kb downstream of *SLC10A2*. Variation at rs16961023 leads to an Egr-1 regulatory motif change [42]. In the 1000 Genomes reference panel, the rs16961023 minor allele is infrequent among persons with African ancestry (MAF = 0.02) and rare among persons with European ancestry (MAF = 0.004), but is common in East Asians (MAF = 0.15).We previously conducted a GWAS for LOAD case/control status in a Japanese cohort [51] but did not find any nominally associated SNPs at this locus.

Genetic association findings may be specific to a particular ethnic background, especially when variants are rare [52].

Current smoking has been found to increase LOAD risk in meta-analyses [24]; however, in this study, it was more frequent in LOAD controls than in LOAD cases when we combined the datasets. Ascertainment bias may explain this finding because our datasets are a mixture of clinic-and community-based studies. Cases disproportionately come from the clinic-based studies, whereas controls disproportionately come from the community-based studies. Typically, clinic-based cohorts have fewer vascular risk factors, including smoking, than their community-based counterparts [53]. Alternatively, survival bias may explain this finding, as smokers with LOAD may have died before entering the study [54]. Although early cross-sectional case-control studies observed that smoking was associated with a reduced risk of LOAD, a meta-analysis that included 23 longitudinal studies found that smoking increased risk [55]. That smoking occurs in our combined cohort at such a different relative rate than what is observed in the epidemiological literature emphasizes the importance of the informed conditioning approach, which makes use of external prevalence data.

Our study has several potential caveats. Because LOAD conditional prevalence data for AAs have not been reported, we estimated these values using available relative risk data that are not ancestry specific and therefore assumed that LOAD relative risks do not differ by ancestral population. Support for this assumption comes from review of the literature that shows the relative risks of dementia, LOAD, and/or cognitive decline for age, sex, diabetes status, smoking status, and educational attainment do not appear to differ significantly by ancestry [3,30–34]; however, this warrants further investigation. This concern is further lessened by a simulation study showing that moderate misspecification of model parameters did not reduce power and that even when parameters were misspecified by a large amount (up to 100%), the model still performed at least and logistic regression [11].

It should also be noted that the genome-wide significant variants near *COBL* and *SLC10A2* have low frequency (0.01–0.02). By comparison, SNPs with MAF <0.05 were not analyzed in the GWAS of Reitz et al. [1] because genotype imputation quality was poor for low-frequency SNPs using the older 1000 Genomes reference panel. Using a newer reference panel, we were able to include low-frequency variants with improved imputation quality. For rs112404845, the top SNP in the *COBL* region, imputation quality, and correlation between imputed and direct genotype dosages were excellent, suggesting that our association findings were unlikely to be influenced by imputation quality. However, for rs16961023, the top SNP in the *SLC10A2* region, imputation quality, and correlation between imputed and direct genotype dosages were similar, but only adequate, and there was a reduction in effect size when we repeated our association analysis among subjects with imputed posterior probabilities >0.8. It appears that subjects with less certain genotype probabilities may contribute disproportionately to the association signal, and, therefore, the *SLC10A2* finding warrants cautious optimism. Finally, inclusion of low-frequency variants in GWAS can increase genomic inflation [56]. However, despite inclusion of low-frequency variants in our study, we did not see evidence of inflation ($\lambda = 0.993$, Supplementary Fig. 1).

Although *COBL* and *SLC10A2* are attractive candidate genes, variants identified through GWAS may not be causal and do not necessarily act at the gene closest to them. Therefore, it is only speculative that these genes are the causal risk factors for LOAD in AAs and that the identified variants have an effect on AD via the proposed regulatory mechanisms. Finally, our findings should be regarded with measured enthusiasm until they are confirmed in independent samples of AAs. Unfortunately, to our knowledge, additional large AA LOAD cohorts with genotype data are not currently available. Therefore, validation of the role of these loci in AD will likely require experimental evidence.

Taken together, these findings suggest that an informed conditioning approach can be used to identify new genetic associations for complex genetic traits where risk is a mix of genetic and environmental factors. Our success in using informed conditioning to identify new risk loci for AD mirrors the success of informed conditioning in GWASs of other phenotypes [11,12]. This work furthers our understanding of the biological underpinnings of AD in AAs. Functional studies are needed to determine whether *COBL* and *SLC10A2* are suitable targets for development of novel therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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RESEARCH IN CONTEXT

1. Systematic review: The authors are members of the Alzheimer's Disease Genetics Consortium and therefore are familiar with emerging pertinent literature. PubMed searches were conducted to identify other relevant publications. References that informed the novel approach and that support the significance of the identified risk loci are cited.
2. Interpretation: Although >20 late-onset Alzheimer's disease (LOAD) risk genes have been identified from genome-wide association studies (GWASs) for non-Hispanic whites, this report identifies only the third and fourth loci from GWAS associated with LOAD for African Americans (AAs). The *COBL* and *SLC10A2* loci provide further evidence that axonal integrity and cholesterol homeostasis underlie LOAD pathophysiology.
3. Future directions: The study findings should be confirmed in independent AA samples. Unfortunately, additional large AA LOAD cohorts with genotype data are not currently available. Functional studies are needed to determine whether *COBL* and *SLC10A2* are suitable targets for development of novel therapies.

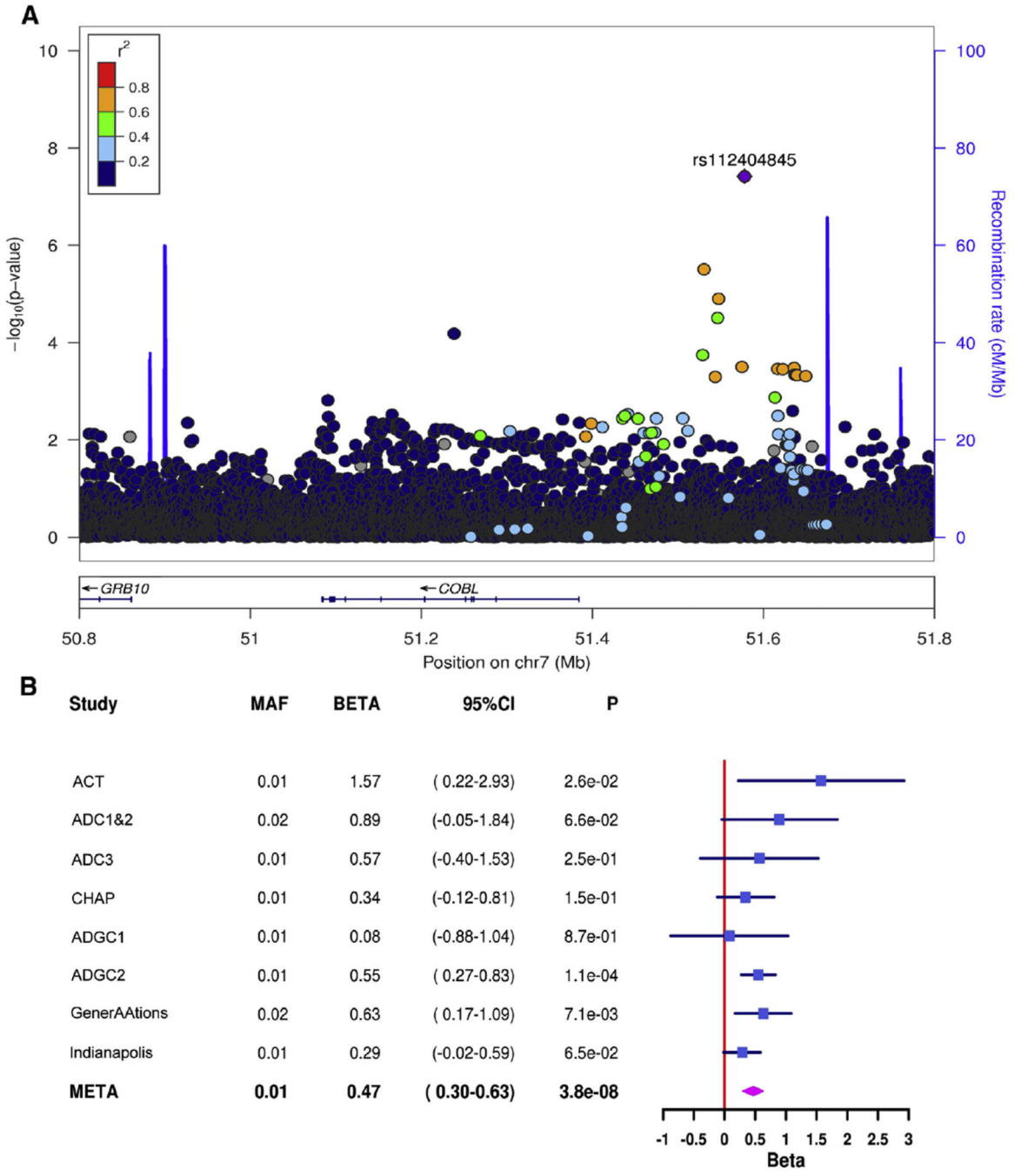

Fig. 1.

(A) Regional association plot of the *COBL* region on chromosome 7 and (B) forest plots for rs112404845, the top single-nucleotide polymorphism in the region. Abbreviations: ACT, Adult Changes in Thought; ADC, Alzheimer's Disease Center; ADGC, Alzheimer's Disease Genetics Consortium; CHAP, Chicago Health and Aging Project; CI, confidence interval; *COBL*, Cordon-Bleu WH2 Repeat Protein; GenerAAtions, Genetic and Environmental Risk Factors for Alzheimer Disease among African Americans; and MAF, minor allele frequency.

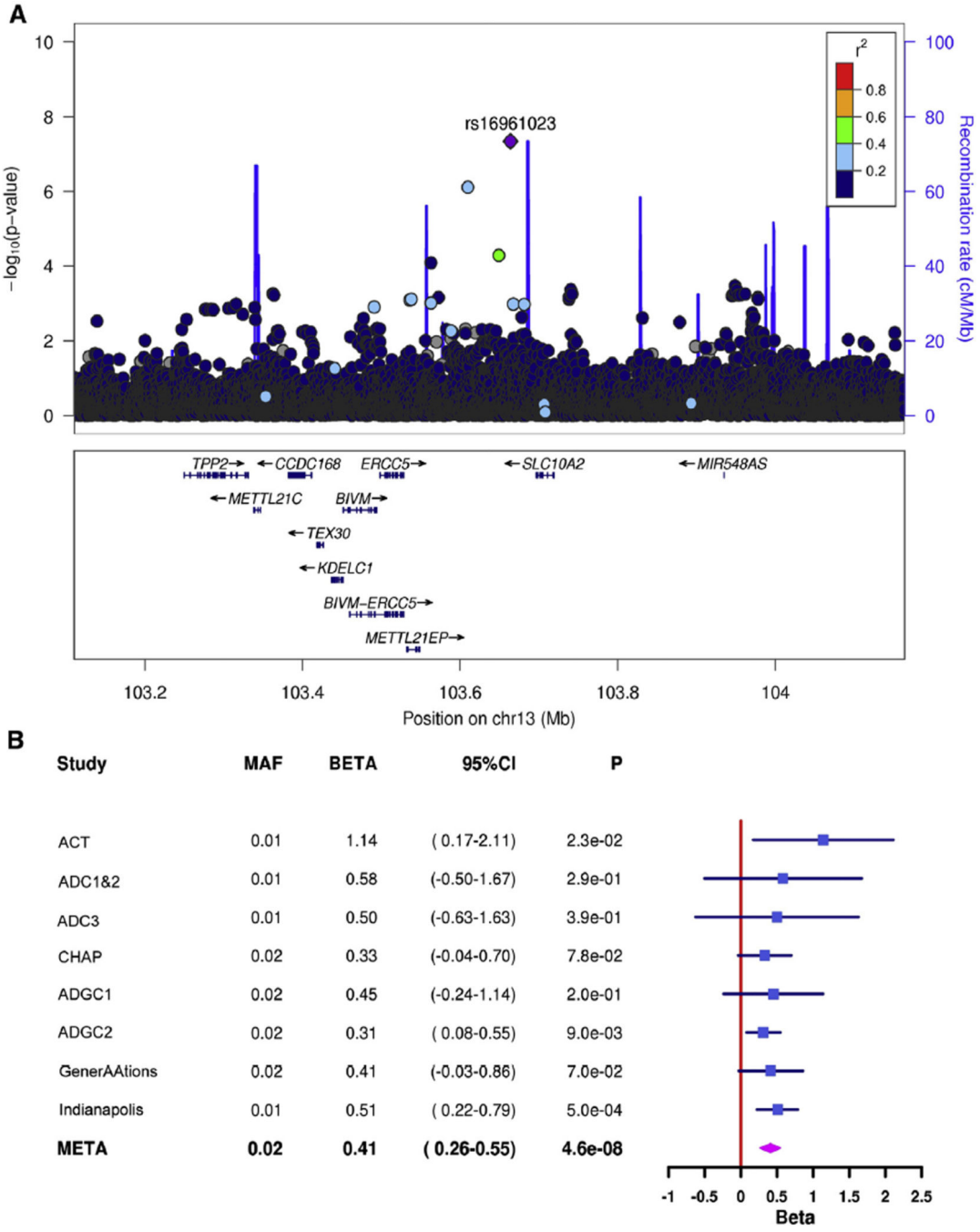

Fig. 2.

(A) Regional association plot of the *SLC10A2* region on chromosome 13 and (B) forest plots for rs16961023, the top single-nucleotide polymorphism in the region. Abbreviations: ACT, Adult Changes in Thought; ADC, Alzheimer's Disease Center; ADGC, Alzheimer's Disease Genetics Consortium; CHAP, Chicago Health and Aging Project; CI, confidence interval; GenerAAtions, Genetic and Environmental Risk Factors for Alzheimer Disease

among African Americans; MAF, minor allele frequency; and *SLC10A2*, solute carrier family 10, member 2.

Table 1

Estimated conditional prevalence of AD in African Americans .65 years of age

Trait	Conditional prevalence
Age	
65–74	0.062
75–84	0.326
≥85	0.598
Sex	
Male	0.172
Female	0.242
Education	
Low	0.305
High	0.192
Current smoker	
No	0.190
Yes	0.302
Diabetes	
No	0.188
Yes	0.275
Overall	0.215

Table 2

Characteristics of datasets

Dataset		*N* (%)	Mean age (SD)	Women (%)	Current smoker (%)	Diabetes (%)	Mean education level (SD)	*APOE*−/−* (%)	*APOE*−/4* (%)	*APOE* 4/4 (%)	rs115550680 MAF† (INFO)	
ACT	Case	32 (32.99)	83.16 (5)	24 (75)	4 (12.5)	0 (0)	11.85 (3.67)	15 (46.88)	12 (37.5)	4 (12.5)	0.16	(0.94)
	Control	65 (67.01)	79.23 (6.21)	38 (58.46)	33 (50.77)	20 (30.77)	13.64 (3.56)	42 (64.62)	20 (30.77)	0 (0)	0.06	
ADC1&2	Case	59 (44.7)	75.69 (7.3)	36 (61.02)	1 (1.69)	0 (0)	12.43 (3.68)	17 (28.81)	33 (55.93)	8 (13.56)	0.08	(0.91)
	Control	73 (55.3)	72.95 (7.58)	58 (79.45)	36 (49.32)	26 (35.62)	14.94 (2.97)	42 (57.53)	25 (34.25)	2 (2.74)	0.05	
ADC3	Case	162 (59.12)	79.88 (7.22)	118 (72.84)	60 (37.04)	37 (22.84)	12.13 (3.15)	39 (24.07)	78 (48.15)	17 (10.49)	0.08	(0.99)
	Control	112 (40.88)	74.28 (7.55)	91 (81.25)	58 (51.79)	27 (24.11)	15.06 (3.05)	62 (55.36)	39 (34.82)	4 (3.57)	0.08	
CHAP	Case	114 (20.84)	81.82 (5.93)	71 (62.28)	60 (52.63)	24 (21.05)	10.98 (3.57)	67 (58.77)	41 (35.96)	5 (4.39)	0.09	(0.88)
	Control	433 (79.16)	78 (6.62)	290 (66.97)	230 (53.12)	50 (11.55)	12.81 (2.87)	261 (60.28)	153 (35.33)	12 (2.77)	0.05	
Indianapolis	Case	173 (14.72)	83.6 (6.74)	108 (62.43)	90 (52.02)	43 (24.86)	9.43 (3.47)	78 (45.09)	75 (43.35)	20 (11.56)	0.10	(0.94)
	Control	1002 (85.28)	82.88 (5.31)	663 (66.17)	625 (62.38)	410 (40.92)	11.25 (2.71)	670 (66.87)	298 (29.74)	34 (3.39)	0.06	
ADGC1‡	Case	267 (52.56)	79.29 (7.24)	185 (69.29)	123 (46.07)	50 (18.73)	10.91 (3.83)	61 (22.85)	49 (18.35)	10 (3.75)	0.08	(0.88)
	Control	241 (47.44)	80.68 (6.87)	169 (70.12)	121 (50.21)	50 (20.75)	13.32 (3.4)	138 (57.26)	59 (24.48)	3 (1.24)	0.06	
ADGC2‡	Case	554 (28.4)	77.86 (8.31)	415 (74.91)	—	—	—	222 (40.07)	248 (44.77)	75 (13.54)	0.07	(0.87)
	Control	1397 (71.6)	73.12 (8.22)	1056 (75.59)	—	—	—	903 (64.64)	431 (30.85)	41 (2.93)	0.06	
MIRAGE 300k	Case	58 (57.43)	72.69 (7.46)	40 (68.97)	27 (46.55)	12 (20.69)	11.34 (4.7)	15 (25.86)	33 (56.9)	10 (17.24)	0.13	(0.69)
	Control	43 (42.57)	73.12 (8.23)	30 (69.77)	23 (53.49)	9 (20.93)	11.21 (4.48)	20 (46.51)	21 (48.84)	2 (4.65)	0.13	
MIRAGE 660k	Case	164 (42.82)	72.95 (6.82)	119 (72.56)	56 (34.15)	45 (27.44)	9.17 (5.24)	53 (32.32)	77 (46.95)	33 (20.12)	0.13	(0.89)
	Control	219 (57.18)	73.39 (8.28)	159 (72.6)	72 (32.88)	48 (21.92)	10.71 (5.1)	121 (55.25)	88 (40.18)	9 (4.11)	0.08	
GenerAAtions	Case	242 (54.88)	80.21 (6.6)	138 (57.02)	—	—	—	88 (36.36)	112 (46.28)	26 (10.74)	0.09	(0.88)
	Control	199 (45.12)	78.49 (6.7)	118 (59.3)	—	—	—	114 (57.29)	63 (31.66)	6 (3.02)	0.07	
	P value§	—	7.23×10^{-28}	0.11	5.01×10^{-4}	0.11	1.03×10^{-45}	1.43×10^{-53}		5.90×10^{-30}	6.12×10^{-5}	

Abbreviations: ACT, Adult Changes in Thought; ADC, Alzheimer's Disease Center; ADGC, Alzheimer's Disease Genetics Consortium; *APOE*, apolipoprotein E; CHAP, Chicago Health and Aging Project; GenerAAtions, Genetic and Environmental Risk Factors for Alzheimer's Disease among African Americans; INFO, information metric for imputation quality from IMPUTE2; MAF, minor allele frequency; MIRAGE, Multi-Institutional Research on Alzheimer Genetic Epidemiology; SD, standard deviation.

*(–) refers to all non–*APOE* ε4-containing genotypes (*APOE* 3/3, *APOE* 2/3, *APOE* 2/2).

†Imputed single-nucleotide polymorphism, minor allele = G, major allele = A.

‡Samples genotyped by the ADGC for this project were received from the African American Alzheimer's Disease Genetics Study, the ADCs, CHAP, Mayo Clinic, Mount Sinai School of Medicine, Religious Orders Study/Rush Memory and Aging Project/Minority Aging Research Study/Rush Clinical Core, University of Miami/Vanderbilt University, University of Pittsburgh, Washington Heights Columbia Aging Project, and Washington University.

§Comparison of cases with controls; results were combined across datasets by meta-analyzing the ln odds ratio for categorical variables and standardized mean difference for continuous variables using a fixed-effects model with inverse variance weights.

Table 3

Logistic and liability models for the top independent SNPs to achieve genome-wide significance in the liability model

Chrom	Gene	SNP	BP	Minor allele*	Major allele	MAF	Model	Covariates	Effect size†	95% CI	*P* value
7	*COBL*	rsl12404845	51578022	T	A	0.01	Logistic	Age, sex, three principal components	3.28	1.71–4.85	1.22×10^{-6}
							Logistic	Age, sex, smoking, diabetes, education, three principal components	3.59	1.76–5.41	8.70×10^{-7}
							Liability: age, sex, smoking, diabetes, education	Three principal components	0.46	0.28–0.64	1.28×10^{-7}
							Liability: age, sex, smoking, diabetes, education	*APOE* ε4, rsl 15550680, three principal components	0.47	0.29–0.65	3.82×10^{-8}
13	*SLC10A2*	rsl6961023	103663945	G	C	0.02	Logistic	Age, sex, three principal components	2.77	1.65–3.89	8.01×10^{-7}
							Logistic	Age, sex, smoking, diabetes, education, three principal components	2.68	1.52–3.84	7.92×10^{-6}
							Liability: age, sex, smoking, diabetes, education	Three principal components	0.41	0.25–0.57	1.03×10^{-7}
							Liability: age, sex, smoking, diabetes, education	*APOE* ε4, rsl 15550680, three principal components	0.41	0.27–0.55	4.59×10^{-8}

Abbreviations: *APOE*, apolipoprotein E; BP, base pair position; Chrom, chromosome; CI, confidence interval; COBL, cordon-bleu WH2 repeat protein; MAF, minor allele frequency; SLC10A2, solute carrier family 10, member 2; SNP, single-nucleotide polymorphism.

*Effect allele.

†Odds ratios (ORs) for logistic models and beta coefficients for liability models. Note ORs and beta coefficients are not on the same scale and cannot be compared. Effect is for the minor allele.