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*	rs112404845	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, rs115550680, three principal components	0.47	0.29–0.65	3.82×10^{-8}
13	*SLC10A2*	rs16961023	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, rs115550680, 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.

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