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Age-at-Onset in Late Onset Alzheimer Disease is Modified by Multiple Genetic Loci

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Abstract

Importance—As *APOE* locus variants contribute to both risk of late-onset Alzheimer disease and differences in age-at-onset, it is important to know if other established late-onset Alzheimer disease risk loci also affect age-at-onset in cases.

Objectives—To investigate the effects of known Alzheimer disease risk loci in modifying age-at-onset, and to estimate their cumulative effect on age-at-onset variation, using data from genome-wide association studies in the Alzheimer's Disease Genetics Consortium (ADGC).

Design, Setting and Participants—The ADGC comprises 14 case-control, prospective, and family-based datasets with data on 9,162 Caucasian participants with Alzheimer's occurring after age 60 who also had complete age-at-onset information, gathered between 1989 and 2011 at multiple sites by participating studies. Data on genotyped or imputed single nucleotide polymorphisms (SNPs) most significantly associated with risk at ten confirmed LOAD loci were examined in linear modeling of AAO, and individual dataset results were combined using a random effects, inverse variance-weighted meta-analysis approach to determine if they contribute to variation in age-at-onset. Aggregate effects of all risk loci on AAO were examined in a burden analysis using genotype scores weighted by risk effect sizes.

Main Outcomes and Measures—Age at disease onset abstracted from medical records among participants with late-onset Alzheimer disease diagnosed per standard criteria.

Results—Analysis confirmed association of *APOE* with age-at-onset (rs6857, $P=3.30\times10^{-96}$), with associations in *CR1* (rs6701713, $P=7.17\times10^{-4}$), *BIN1* (rs7561528, $P=4.78\times10^{-4}$), and *PICALM* (rs561655, $P=2.23\times10^{-3}$) reaching statistical significance ($P<0.005$). Risk alleles individually reduced age-at-onset by 3-6 months. Burden analyses demonstrated that *APOE* contributes to 3.9% of variation in age-at-onset ($R^2=0.220$) over baseline ($R^2=0.189$) whereas the other nine loci together contribute to 1.1% of variation ($R^2=0.198$).

Conclusions and Relevance—We confirmed association of *APOE* variants with age-at-onset among late-onset Alzheimer disease cases and observed novel associations with age-at-onset in *CR1*, *BIN1*, and *PICALM*. In contrast to earlier hypothetical modeling, we show that the combined effects of Alzheimer disease risk variants on age-at-onset are on the scale of, but do not exceed, the *APOE* effect. While the aggregate effects of risk loci on age-at-onset may be significant, additional genetic contributions to age-at-onset are individually likely to be small.

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Keywords

Alzheimer Disease; Alzheimer Disease Genetics; Alzheimer's Disease - Pathophysiology; Genetics of Alzheimer Disease; Aging

INTRODUCTION

Alzheimer Disease (AD) [MIM 104300] affects more than 13% of individuals aged 65 years and older, and its prevalence increases with age, occurring in fewer than 1% of those age 65 years and younger and in as much as 40% of the population after age 90.[1-4] While genetic studies of late-onset Alzheimer Disease (LOAD) confirmed at least ten loci contributing to risk of disease, including APOE, PICALM, CLU, CR1, BIN1, CD2AP, EPHA1, MS4A4A, CD33, and *ABCA7*,[5,6] genes modifying age-at-onset (AAO) of LOAD have not been widely studied. Earlier linkage and candidate gene studies identified only a few loci possibly underlying variation of AAO (e.g., *GSTO1*),[7] but only variation in the *APOE* region has been consistently confirmed.[8-12]

A multitude of studies have attempted to identify susceptibility genes for AAO in AD. The first study to identify a genetic association with AAO showed a lower mean AAO among cases for each additional copy of the ε4 allele at the *APOE* locus on chromosome 19q (0 copies: 84.3 years; 1 copy: 75.5; 2 copies: 68.4),[13] a finding which has since been replicated.[14] Subsequent genome-wide linkage scans examining AAO in AD patients and unaffected family members (using age at study entry) found suggestive evidence of linkage on chromosome 19 to *APOE* (LOD = 3.28),[15] which was confirmed in later studies.[16] Multiple studies identified other suggestive linkage signals on chromosomes 4q, 8q,[16] 1q, 6p,[17] 7q, 15, and 19p[18] in Caucasian families, and chromosomes 5q, 7q, 14q, and 17q[19] in Caribbean Hispanics, though the specific loci driving these linkage signals remain unknown. More recently, an AAO GWAS in 2,222 Caucasian AD cases confirmed association at *APOE*, and also found strong evidence of association (P=4.95×10^{-7}) on chromosome 4q31.3 in the gene *DCHS2*.[20]

The lack of overlap in the regions identified across these studies may have resulted from differences in the approaches applied, such as varied strategies for censoring unaffected pedigree members and differences in covariates adjusted for in analyses. Reduced statistical power from the limited availability of extended families for analysis may also have contributed to the differences in findings between these early linkage and association studies. The high variability in approaches and findings highlights the need for a more comprehensive approach to identify genetic risk factors which may influence LOAD AAO as well as LOAD risk directly. Notably, variants in the ten confirmed LOAD risk loci have not been examined for their possible influence on AAO among LOAD cases.

Using data from 9,162 LOAD cases from a recent genome-wide association study (GWAS) of LOAD by the Alzheimer's Disease Genetics Consortium,[6] we examined whether variants most significantly associated with LOAD risk in 10 LOAD loci are also associated with differences in AAO among LOAD cases. Furthermore, we used a genetic burden analysis

approach to determine the proportion of variation in AAO accounted for by variants in these established LOAD risk genes.

MATERIALS AND METHODS

Ascertainment and Collection of Genotypic and Phenotypic Data

A detailed description of ascertainment and the collection of genotype and phenotype data in the individual datasets of the ADGC is available elsewhere.[6] Briefly, subjects in each dataset (eTable 1) were genotyped using either Illumina or Affymetrix commercially-available GWAS high-density SNP genotyping microarrays. All LOAD subjects met NINCDS/ADRDA criteria for definite, probable or possible LOAD,[21] and age-at-onset (AAO) of LOAD, which was abstracted from medical records for most subjects, was defined as the age when LOAD-related symptoms manifested, as reported by the subject or an informant. Age-at-ascertainment (WU, ADNI) was substituted for datasets lacking AAO information (eTable 1). Unaffected subjects and LOAD cases lacking AAO information, cases with an age-at-onset or age-at-death less than 60 years, and non-Caucasians of European ancestry were excluded from the association analyses. *Post hoc* analyses revealed no significant differences in association findings between subjects with age-at-onset and those with age-at-ascertainment information (data not shown).

Quality Control

Subjects were excluded if Affymetrix chip genotypes were called for fewer than 95% of SNPs or if Illumina chip genotypes were called for fewer than 98% for SNPs. Additionally, samples were excluded if reported gender differed from genetic gender by X-chromosome analysis (PLINK software).[22] Samples were dropped from family datasets if reported relationships differed from estimated relatedness from IBD using the program PREST.[23] If samples were duplicated in different datasets, only one sample per duplicate pair was kept in analysis. After exclusions, data on 9,162 cases remained for subsequent analyses.

After sample quality control, genotyped SNPs were excluded from analysis if their minor allele frequencies (MAF) were less than 0.02 for Affymetrix chips or less than 0.01 for Illumina chips, or if the SNPs were observed to be out of Hardy-Weinberg equilibrium with $P<10^{-6}$. Imputed SNPs were excluded if the quality score ("Info" from IMPUTE2)[24] was less than 0.50. Genome-wide genotype imputation was performed in each cohort using IMPUTE2 software[24] with 1000 Genomes (December 2010 release) CEPH Utah pedigree (CEU) reference haplotypes. Imputation quality was assessed using the 'Info' statistic, and only SNPs imputed with Info ≥0.50 were included in analysis. The ten SNPs examined here were among the common set of SNPs produced in imputation.

Statistical Analysis

We performed association analysis on individual datasets assuming an additive model on log-transformed age-at-onset with covariate adjustment for population substructure. For cases from case-control datasets, linear regression was performed in PLINK,[22] while for analysis of cases from family datasets (used only in the primary analysis of risk variants), generalized estimating equations (GEE) with a linear model as implemented in the R

statistical package[25] were used. To account for the effects of population substructure, we performed a principal components (PC) analysis on cases within each dataset using EIGENSTRAT[26] on a subset of 21,109 SNPs common to all genotyping platforms. The first three PCs from analysis were incorporated in our minimal model for covariate adjustment. We also performed analyses conditioning on the major AAO-modifying effects of *APOE* through an extended model of covariate adjustment which included sex and number of *APOE* ε4 alleles (0, 1, or 2). Results from individual datasets were combined in the *meta*-analysis using inverse-variance weighting as implemented in METAL,[27] applying a genomic control to each dataset. With this set of 9,162 cases, we expected to have 80% power to detect loci with as little effect as 9 months difference in AAO per allelic copy for very common variants (MAF>0.34), with power to detect 1 year difference in AAO per allelic copy for variants of even modest frequency (MAF>0.14).[28]

We performed a discovery genome-wide association meta-analysis among 6,143 cases in 10 ADGC case-control datasets to determine whether SNPs with more modest LOAD risk associations may contribute to differences in AAO, and to assess genetic burden attributable to these variants. Methods, results, and a brief summary are provided in the eAppendix.

In addition to association meta-analysis, we performed genetic burden analyses to determine the percent contribution of LOAD susceptibility SNPs in ten LOAD candidate genes to variation in AAO. Risk-weighted genetic burden analyses of AAO linearly modeled locus-specific effects as the product of the meta-analysis-estimated effect size (across-study change in AAO for each copy of the minor allele) and the dosage of the minor allele (scale 0-2; estimated from genotype-specific imputation probabilities), and were implemented in analyses of risk variants. Additional covariate adjustment in the burden model included covariates for population substructure from principal components analysis and dataset-specific effects.

RESULTS

ADGC Data Characteristics

Descriptive characteristics of the individual ADGC datasets are shown in eTable 1. There were more female cases (N = 5,480; 60%) than males. The mean age-at-onset of was 74.3 years (y) (standard deviation = 7.64 y) for the entire group. Several datasets had later ages at onset; two of these were population-based cohorts of aging and memory loss, ROSMAP [mean AAO (SD) = 85.6 y (6.26 y)] and ACT [mean AAO (SD) = 83.9 y (4.76 y)], and one case-control dataset, OHSU, which intentionally ascertained individuals with later age-at-onset [mean AAO (SD) = 86.1 y (5.53 y)]. While data from these studies did not largely change the patterns of association observed (data not shown) in association testing, we performed several sub-analysis to assess their effect on the genetic burden analyses as described below.

LOAD Susceptibility Variant Associations with AAO

We confirmed the association of the *APOE* ε4 allele with lower AAO, with each additional copy of the ε4 allele reducing AAO by 2.45 years (β=−2.45; P=3.30×10^{-96}). Examining the

variants most strongly associated with LOAD in nine genomic regions with genome-wide statistically significant associations in our GWAS of LOAD risk (Table 1),[6] we observed that several LOAD risk loci also demonstrated statistically significant associations ($P<0.005$) with AAO, including rs6701713 in *CR1* ($P=7.17\times10^{-4}$), rs7561528 in *BIN1* ($P=4.78\times10^{-4}$), rs561655 in *PICALM* ($P=0.00223$). Both rs6701713 in *CR1* and rs7561528 in *BIN1* demonstrated a reduced age-at-onset for each copy of the risk variant with each copy of the risk allele A at rs6701713 (MAF=0.24) advancing AAO by approximately five months [β (95% CI): −0.41 (−0.65, −0.17)], and each copy of the risk allele A at rs7561528 (MAF=0.37) advancing AAO by slightly less than four months [β (95% CI): −0.31 (−0.52, −0.09)]. In contrast, each copy of the more common risk allele (A; frequency=0.62) at rs561655 in the *PICALM* gene corresponded with earlier onset by approximately four months [β (95% CI): −0.33 (−0.55, 0.12)]. These patterns of association remained largely unchanged after adjustment for *APOE* ε4 allele dose and sex for the *CR1* and *BIN1* variants [rs6701713: −0.41 (−0.69, −0.12), $P=0.00488$; rs7561528: −0.32 (−0.57, −0.08), $P=0.00985$]. While the size and direction of the association remained the same as in the minimally adjusted model, the association of the *PICALM* variant demonstrated only marginal significance after this additional adjustment [rs561655: 0.32 (0.07, 0.57), $P=0.0112$]. Investigation of AAO associations in the vicinity of these AD risk variants revealed no substantially different associations among nearby variants. Directions of variant effects were concordant between AD risk and AAO; all variants that increase risk also lower AAO.

Genetic Burden Analysis of AAO with LOAD Risk Variants

We examined the genetic burden of *APOE* and the LOAD risk variants in the nine genomic regions on variation in AAO (Table 2) in the 14 ADGC datasets with complete AAO data. In our baseline model, 19% of the variation in AAO ($R^2=0.189$) was accounted for by population substructure and study-specific effects. The independent contributions of dosage of the *APOE* ε4 allele to genetic burden was roughly 3.1% of AAO variation ($R^2=0.220$) while the cumulative effect of the nine LOAD risk variants was 0.93% ($R^2=0.198$), together accounting for approximately 4.1% of genetic variation in AAO ($R^2=0.229$). Excluding study-specific effects, *APOE* accounts for 3.9% of the remaining variation, the nine LOAD risk variants account for another 1.1%, for a combined contribution of 5% of the variation of AAO. Variant effects in burden modeling were consistent with the association results for individual variants described above.

To determine whether ascertainment differences may have influenced the amount of variation in AAO attributable to LOAD risk variants, we examined the effects of the three datasets with much later average AAO (ACT, OHSU, and ROSMAP) and the two-family based datasets (NIA-LOAD and MIRAGE) on genetic burden analyses. In analyses excluding the datasets with later average AAO (eTable 2), we found that these datasets account for much of the dataset-specific AAO variation, reducing the effect of dataset on AAO variation from nearly 19% to 1.7% ($R^2=0.0165$). In these analyses, after excluding dataset-specific effects, the percent variation attributable to *APOE* was slightly lower at 3.6% ($R^2=0.0523$), the effect attributable to the nine LOAD risk variants was similar to before at 1.1% ($R^2=0.0270$), and the combined contribution of both was observed to be 4.7%

(R^2=0.0631). Removal of the family datasets (eTable 3) did not appreciably change the variation attributable to study-specific effects (R^2=0.221), nor did it substantially change the relative effects of *APOE* and the 9 LOAD risk variants on AAO variation.

DISCUSSION

Our analysis of more than 9,000 LOAD cases with age-at-onset information is the largest genetic study of LOAD AAO to date. Examining AAO associations at LOAD risk loci, we confirmed the association of *APOE* region variation with AAO and found additional strong associations with AAO among variants at three of the other nine established risk loci (*CR1*, *BIN1*, and *PICALM*). Burden analysis demonstrated that the cumulative variation explained by SNPs at nine LOAD risk loci was about a third as much as the percent variation in AAO from *APOE*, The smaller effect of *APOE* ε4 on differences in AAO here (3-4%) than in previous studies (7-9%)[29] may be due to differences in study design; for instance, all previous estimates were made in multiplex pedigrees, whereas most cases examined here were unrelated (2,302 of 9,162 [25.1%] of cases were from family datasets). However, in addition to confirming the predominance of the effect of *APOE* on AAO, we showed that the cumulative effects of risk loci associated with AAO may have an effect of similar scale on AAO. In our secondary analysis of genome-wide association, cumulative effects on genetic burden of SNPs associated with AAO but with little or no effect on LOAD risk accounted for more variation in AAO compared to the non-*APOE* risk variants (2.2% vs. 1.1%), but were still dwarfed by the effects of *APOE* on variation in AAO (~4%).

Several previous studies have suggested potential associations of risk variants at these loci with AAO. A recent study using a small subset of the cases used in this study (ADC1-3; n=2,569) identified an association with a *PICALM* risk variant (rs3851179, P=0.008.6×10^{-3}).[10] A study of the expression of the 10 LOAD risk genes in parietal lobe neurons from an autopsy series of AD brains demonstrated nominally significant evidence of an association between reduced *BIN1* expression levels and earlier AAO (P=0.041),[30] as well as an association with a longer duration of disease. A study by Jones et al. (2013)[31] among persons with Down Syndrome, which is typically associated with elevated AD risk at an earlier AAO, showed risk variants in *APOE* (P=0.014) and *PICALM* (P=0.011) to be correlated with lower AAO in AD patients with Down syndrome.

Daw et al analyzed families with a high burden of AD and later age of onset in a multiplex family data set[29] and found evidence for at least four additional genes with major effects on variation in AAO as large as those of *APOE*. The lack of major AAO-modifying effects outside of *APOE* in our study is not consistent with the Daw et al study and may reflect genetic heterogeneity of age-at-onset genetics within late-onset AD or, more likely, indicate the existence of large effect modifiers enriched in families with multiple affected members. *APOE*-related survival effects may have further complicated the identification of AAO-modifying genes. Furthermore, other genetic mechanisms including the effects of rare variants, epigenetic modification, and gene-environment interactions, which have been reported to influence dementia risk and cognitive decline,[32-37] may also contribute to variation in age at onset of AD. Identification of other genetic modifiers of age-at-onset through studies of larger samples of LOAD cases and studies using next-generation

sequencing approaches which can more thoroughly interrogate the genome may yet yield additional genetic risk factors that influence age-at-onset and provide new insights into LOAD pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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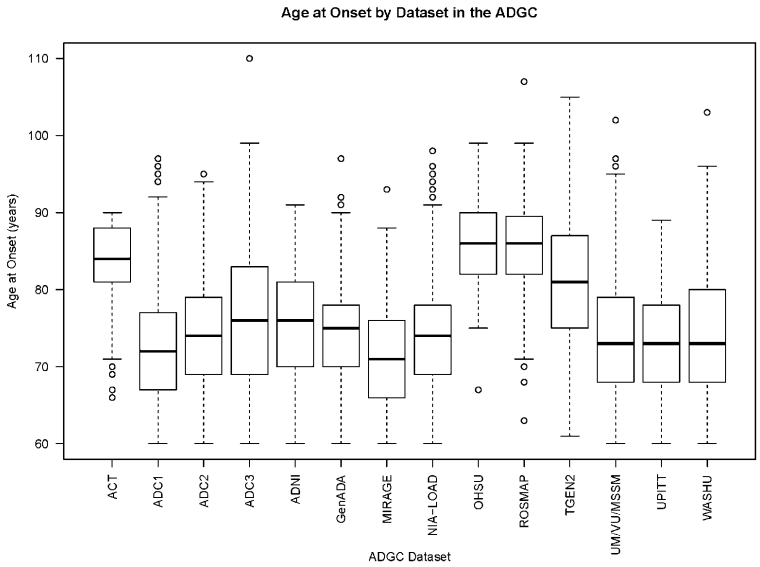

Figure 1. Boxplots for age-at-onset (AAO) by ADGC dataset

Table 1

Association with age-at-onset (AAO) of SNPs most significantly associated with LOAD in nine genomic regions and *APOE*

SNPs presented demonstrated strongest associations within each of ten genomic regions with associations of genome-wide statistical significance ($P \leq 5.0\times10^{-8}$) with LOAD risk. *P*-values for AAO associations exceeding the multiple hypothesis testing threshold (P<0.005) are shown in bold

SNP	CH:MB	Nearest Gene	MA	MAF	AAO (Minimal Adjustment Model)			AAO (Extended Adjustment Model)			LOAD Risk (from Naj et al.)	
					β (95% CI)	*P*	Het *P*	*β* (95% CI)	*P*	Het *P*	OR (95% CI)	*P*
rs6701713	1:207.8	*CR1*	A	0.24	−0.41 (−0.65, −0.17)	**7.17×10^{-4}**	0.405	−0.41 (−0.69, −0.12)	4.88×10^{-3}	0.422	1.16 (1.11, 1.22)	4.6×10^{-10}
rs7561528	2:127.9	*BIN1*	A	0.37	−0.31 (−0.52, −0.09)	**4.78×10^{-4}**	0.855	−0.32 (−0.57, −0.08)	9.85×10^{-3}	0.684	1.17 (1.13, 1.22)	4.2×10^{-14}
rs9349407	6:47.5	*CD2AP*	C	0.32	−0.03 (−0.25, 0.19)	0.765	0.266	−0.14 (−0.40, 0.11)	0.273	0.860	1.12 (1.07, 1.18)	1.0×10^{-6}
rs11767557	7:143.1	*EPHA1*	C	0.18	0.03 (−0.26, 0.32)	0.830	0.861	0.07 (−0.24, 0.39)	0.659	0.657	0.87 (0.83, 0.92)	2.4×108^{-7}
rs1532278	8:27.5	*CLU*	T	0.37	0.05 (−0.18, 0.28)	0.661	0.137	0.0038 (−0.26, 0.27)	0.977	0.108	0.89 (0.85, 0.93)	8.3×10^{-8}
rs4938933	11:60.0	*MS4A4A*	C	0.36	0.09 (−0.14, 0.31)	0.448	0.454	0.018 (−0.23, 0.27)	0.8874	0.584	0.88 (0.85, 0.92)	1.7×10^{-9}
rs561655	11:85.8	*PICALM*	G	0.38	0.33 (−0.12, 0.55)	**2.23×10^{-3}**	0.915	0.32 (0.07, 0.57)	0.0112	0.957	0.87 (0.84, 0.91)	7.0×10^{-11}
rs3752246	19:1.1	*ABCA7*	G	0.34	−0.27 (−0.55, 0.02)	0.0640	0.700	−0.19 (−0.51, 0.13)	0.242	0.748	1.15 (1.09, 1.21)	5.8×10^{-7}
Haplotype (rs7412/ rs429358)	19:45.4	APOE	ε4	0.35	−2.45 (−2.68, −2.21)	**3.30×10^{-96}**	0.0941	−0.24 (−0.75, 0.27)	0.360	0.874	3.02 (2.86, 3.20)	2.18×10^{-320}
rs3865444	19:51.7	*CD33*	A	0.20	0.10 (−0.13, 0.33)	0.377	0.596	0.13 (−0.13, 0.38)	0.338	0.872	0.89 (0.86, 0.93)	1.1×10^{-7}

CH:MB, chromosome:position (in mega base pairs, build 19); MA, minor allele; MAF, minor allele frequency; β, Beta coefficient for AAO from meta-analysis (# years difference in AAO per copy of the minor allele); OR, odds ratio; 95% CI, 95% Confidence Interval; P, P-value; Het *P*, *P*-value for heterogeneity across studies.

Table 2

Risk-weighted burden analysis results for *APOE* and 9 LOAD Candidate Genes

Beta coefficients (β), 95% Confidence Intervals, and P-values are from four logistic regression models examining weighted scores for the peak SNP associations in *APOE* and 9 LOAD candidate genes. Scores are the product of the log-transformed odds ratio for each SNP association multiplied by minor allele dosage from imputed genotype probabilities.

	Model 1: Adjustment for PCs & Site		**Model 2: Adjustment for Model 1 + APOE**		**Model 3: Adjustment for Model 1 + 9 LOAD Genes**		**Model 4: Adjustment for Model 1 + APOE + 9 LOAD Genes**	
	***β*(95% CI)**	***P***	***β*(95% CI)**	***P***	***β*(95% CI)**	***P***	***β*(95% CI)**	***P***
(Intercept)	74.2 (73.5, 75.0)	<10-32	70.6 (69.8, 71.4)	$<10^{-32}$	72.9 (71.6, 74.1)	$<10^{-32}$	69.1 (67.9, 70.4)	$<10^{-32}$
CR1 Score	--	--	--	--	1.01 (0.59, 1.43)	2.66×10^{-6}	1.01 (0.60, 1.43)	1.51×10^{-6}
BIN1 Score	--	--	--	--	−0.97 (−1.45, −0.50)	5.27×10^{-5}	−1.04 (−1.51, −0.58)	9.99×10^{-6}
CD2AP Score	--	--	--	--	−0.51 (−1.00, −0.03)	0.0381	−0.43 (−0.90, 0.05)	0.0764
EPHA1 Score	--	--	--	--	−0.73 (−1.49, 0.03)	0.0586	−0.67 (−1.41, 0.07)	0.0778
CLU Score	--	--	--	--	0.83 (0.36, 1.29)	4.63×10^{-4}	0.89 (0.44, 1.35)	1.11×10^{-4}
MS4A4A Score	--	--	--	--	0.87 (0.34, 1.40)	0.00120	0.91 (0.39, 1.43)	5.58×10^{-4}
PICALM Score	--	--	--	--	1.11 (0.63, 1.59)	6.78x10−6	1.03 (0.56, 1.51)	1.83×10^{-5}
ABCA7 Score	--	--	--	--	0.92 (0.35, 1.50)	0.00164	0.97 (0.41, 1.53)	7.35×10^{-4}
CD33 Score	--	--	--	--	−0.84 (−1.41, −0.28)	0.00315	−0.81 (−1.36, −0.26)	0.00405
APOE Score	--	--	−0.77 (−0.85, −0.70)	1.03×10^{-79}	--	--	-0.78 (−0.86, −0.70)	5.48×10^{-81}
ACT	9.67 (8.62, 10.7)	3.31×10^{-72}	10.3 (9.30, 11.4)	1.10×10^{-84}	11.15 (9.64, 12.66)	8.89×10^{-47}	11.9 (10.42, 13.39)	6.69×10^{-55}
ADC1	−1.76 (−2.60, −0.93)	3.66x10−5	0.54 (−0.32, 1.39)	0.219	−1.74 (−2.81, −0.67)	0.00139	0.62 (−0.45, 1.70)	0.256
ADC2	−i.03 (−1.96, −0.10)	0.0294	−1.47 (−2.38, −0.56)	0.00157	0.33 (−1.20, 1.87)	0.671	−0.09 (−1.59, 1.42)	0.909
ADC3	0.19 (−0.74, 1.13)	0.684	0.40 (−0.52, 1.32)	0.393	1.17 (−0.68, 3.02)	0.215	1.31 (−0.50, 3.13)	0.155
ADNI	−1.20 (−2.57, 0.18)	0.0882	−0.91 (−2.26, 0.44)	0.187	−0.26 (−1.90, 1.39)	0.758	0.22 (−1.39, 1.84)	0.787
GenADA	0.36 (−0.57, 1.28)	0.449	−1.42 (−2.34, −0.50)	0.00258	2.46 (1.19, 3.72)	1.39×10^{-4}	0.79 (−0.46, 2.04)	0.216
LOAD	−0.67 (−1.49, 0.15)	0.111	0.42 (−0.40, 1.23)	0.316	−0.37 (−1.55, 0.80)	0.533	0.77 (−0.38, 1.93)	0.190
MIRAGE	−3.08 (−4.04, −2.11)	4.66×10^{-10}	0.37 (−0.64, 1.38)	0.472	−2.17 (−3.51, −0.83)	0.00146	1.36 (0, 2.72)	0.0504
OHSU	11.9 (10.5, 13.3)	2.06×10^{-59}	12.5 (11.1, 13.9)	5.29×10^{-68}	13.55 (11.72, 15.39)	5.32×10^{-47}	14.4 (12.6, 16.2)	1.16×10^{-54}
ROSMAP	11.4 (10.3, 12.5)	6.52×10^{-90}	9.21 (8.11, 10.3)	4.63×10^{-60}	13.26 (11.57, 14.95)	1.34×10^{-52}	11.22 (9.55, 12.9)	3.11×10^{-39}
TGEN2	0.55 (−1.03, 2.13)	0.494	0.69 (−0.86, 2.24)	0.385	1.47 (−3.09, 6.03)	0.528	1.55 (−2.92, 6.03)	0.497
UM/VU/MSSM	−0.33 (−1.20, 0.53)	0.449	−0.6 (−1.45, 0.25)	0.165	1.18 (−0.10, 2.46)	0.0704	0.92 (−0.33, 2.18)	0.149

	Model 1: Adjustment for PCs & Site		Model 2: Adjustment for Model 1 + APOE		Model 3: Adjustment for Model 1 + 9 LOAD Genes		Model 4: Adjustment for Model 1 + APOE + 9 LOAD Genes	
	***β*(95% CI)**	***P***	***β*(95% CI)**	***P***	***β*(95% CI)**	***P***	***β*(95% CI)**	***P***
UPITT	−1.33 (−2.18, −0.47)	0.0233	−0.61 (−1.45, 0.23)	0.155	0.7 (−0.54, 1.94)	0.267	1.38 (0.16, 2.59)	0.0261
PC1	6.76 (3.09, 10.4)	3.10×10^{-4}	6.16 (2.56, 9.76)	8.01×10^{-4}	7.04 (3.38, 10.7)	1.61×10^{-4}	6.44 (2.85, 10.02)	4.32×10^{-4}
PC2	1.12 (−2.60, 4.84)	0.554	1.99 (−1.66, 5.64)	0.285	0.81 (−2.90, 4.51)	0.670	1.65 (−1.98, 5.28)	0.372
PC3	−0.89 (−4.54, 2.77)	0.634	−0.34 (−3.93, 3.24)	0.852	−1.07 (−4.71, 2.57)	0.564	−0.5 (−4.07, 3.06)	0.782
F (df_1, df_2)	164.2 (13, 9114)		184.8 (14, 9113)		103.3 (22, 9105)		119.1 (23, 9104)	
P	$<10^{-100}$		$<10^{-100}$		$<10^{-100}$		$<10^{-100}$	
Multiple R^2	0.1898		0.2211		0.1998		0.2313	
Adjusted R^2	0.1886		0.2199		0.1979		0.2294	