Original Investigation

Effects of Multiple Genetic Loci on Age at Onset in Late-Onset Alzheimer Disease
A Genome-Wide Association Study

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IMPORTANCE Because *APOE* locus variants contribute to risk of late-onset Alzheimer disease (LOAD) and to differences in age at onset (AAO), it is important to know whether other established LOAD risk loci also affect AAO in affected participants.

OBJECTIVES To investigate the effects of known Alzheimer disease risk loci in modifying AAO and to estimate their cumulative effect on AAO variation using data from genome-wide association studies in the Alzheimer Disease Genetics Consortium.

DESIGN, SETTING, AND PARTICIPANTS The Alzheimer Disease Genetics Consortium comprises 14 case-control, prospective, and family-based data sets with data on 9162 participants of white race/ethnicity with Alzheimer disease occurring after age 60 years who also had complete AAO information, gathered between 1989 and 2011 at multiple sites by participating studies. Data on genotyped or imputed single-nucleotide polymorphisms most significantly associated with risk at 10 confirmed LOAD loci were examined in linear modeling of AAO, and individual data set results were combined using a random-effects, inverse variance–weighted meta-analysis approach to determine whether they contribute to variation in AAO. 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 LOAD diagnosed per standard criteria.

RESULTS Analysis confirmed the association of *APOE* with earlier AAO ($P = 3.3 \times 10^{-96}$), with associations in *CR1* (rs6701713, $P = 7.2 \times 10^{-4}$), *BIN1* (rs7561528, $P = 4.8 \times 10^{-4}$), and *PICALM* (rs561655, $P = 2.2 \times 10^{-3}$) reaching statistical significance ($P < .005$). Risk alleles individually reduced AAO by 3 to 6 months. Burden analyses demonstrated that *APOE* contributes to 3.7% of the variation in AAO ($R^2 = 0.256$) over baseline ($R^2 = 0.221$), whereas the other 9 loci together contribute to 2.2% of the variation ($R^2 = 0.242$).

CONCLUSIONS AND RELEVANCE We confirmed an association of *APOE* (OMIM 107741) variants with AAO among affected participants with LOAD and observed novel associations of *CR1* (OMIM 120620), *BIN1* (OMIM 601248), and *PICALM* (OMIM 603025) with AAO. In contrast to earlier hypothetical modeling, we show that the combined effects of Alzheimer disease risk variants on AAO are on the scale of, but do not exceed, the *APOE* effect. While the aggregate effects of risk loci on AAO may be significant, additional genetic contributions to AAO are individually likely to be small.

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Alzheimer disease (AD) (OMIM 104300) affects more than 13% of individuals 65 years and older, and its prevalence increases with age, occurring in less than 1% of those 65 years and younger and in up to 40% of the population after age 90 years.[1-4] While genetic studies[5,6] of late-onset AD (LOAD) confirmed at least 10 loci contributing to risk of disease, including *APOE*, *PICALM*, *CLU*, *CR1*, *BIN1*, *CD2AP*, *EPHA1*, *MS4A4A*, *CD33*, and *ABCA7*, genes modifying age at onset (AAO) of LOAD have not been widely studied. Earlier linkage and candidate gene studies identified a few loci possibly underlying variation of AAO (eg, *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[13] to identify a genetic association with AAO showed a lower mean AAO among affected participants with AD for each additional copy of the ε4 allele at the *APOE* locus on chromosome 19q (84.3 years for 0 copy, 75.5 years for 1 copy, and 68.4 years for 2 copies), a finding that has since been replicated.[14] Subsequent genome-wide linkage scans examining AAO in patients with AD and unaffected family members (using age at study entry) found suggestive evidence of linkage on chromosome 19 to *APOE* (logarithm of odds [LOD], 3.28),[15] which was confirmed in later investigations.[16] Multiple studies identified other suggestive linkage signals on chromosomes 4q, 8q, 1q, 6p, 7q, 15, and 19p[16-18] in families of white race/ethnicity and on chromosomes 5q, 7q, 14q, and 17q[19] in Caribbean Hispanics, although the specific loci driving these linkage signals remain unknown. More recently, an AAO genome-wide association study[20] (GWAS) in 2222 AD patients of white race/ethnicity confirmed an association at *APOE* and found strong evidence of association ($P = 5.0 \times 10^{-7}$) on chromosome 4q31.3 in the *DCHS2* gene.

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 that may influence LOAD AAO, as well as LOAD risk directly. To date, variants in the 10 confirmed LOAD risk loci have not been examined for their possible influence on AAO among affected participants with LOAD.

Using data from 9162 affected participants with LOAD from a GWAS of LOAD by the Alzheimer Disease Genetics Consortium (ADGC),[6] we examined whether variants most significantly associated with LOAD risk in 10 LOAD loci are also associated with differences in AAO among affected participants with LOAD. 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.

Methods

Ascertainment and Collection of Genotype and Phenotype Data

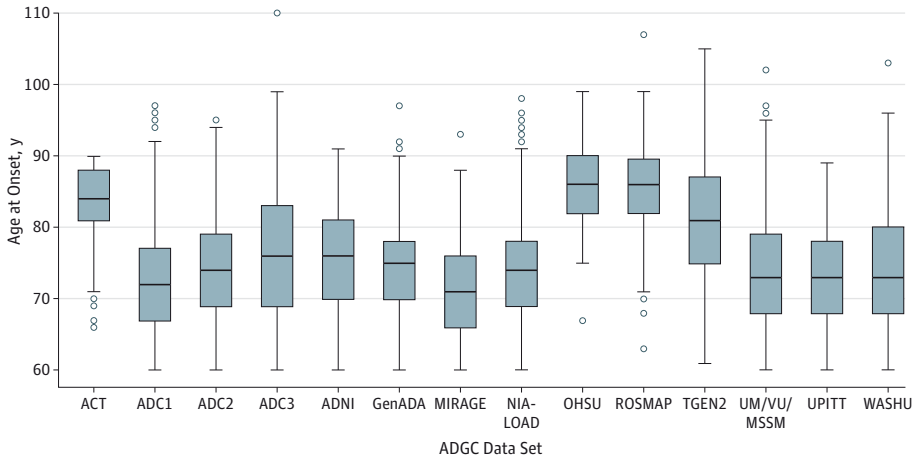
The ADGC comprises 14 case-control, prospective, and family-based data sets with data on 9162 participants of white race/ethnicity with AD occurring after age 60 years who also had complete AAO information, gathered between September 1989 and January 2011 at multiple sites by participating studies. The ADGC received approval for analysis and use of data from the University of Pennsylvania Institutional Review Board. Participants' written or oral consents were obtained by their originating studies. A detailed description of ascertainment and the collection of genotype and phenotype data in the individual data sets of the ADGC is available elsewhere.[6] Briefly, individuals in each data set (eTable 1 in the Supplement) were genotyped using commercially available GWAS high-density single-nucleotide polymorphism (SNP) genotyping microarrays (Illumina or Affymetrix). All individuals with LOAD met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for definite, probable, or possible LOAD,[21] and AAO of LOAD, which was abstracted from medical records for most individuals, was defined as the age when LOAD-related symptoms manifested, as reported by the individual or by an informant. Age at ascertainment was substituted for data sets lacking AAO information (Washington University in St Louis and Alzheimer's Disease Neuroimaging Initiative) (eTable 1 in the Supplement). Unaffected individuals and affected participants with LOAD lacking AAO information, those with an AAO or age at death younger than 60 years, and individuals of nonwhite race/ethnicity with European ancestry were excluded from the association analyses.

Quality Control

Individuals were excluded if Affymetrix chip genotypes were called for less than 95% of SNPs or if Illumina chip genotypes were called for less than 98% of SNPs. In addition, samples were excluded if reported sex differed from genetic sex by X-chromosome analysis (PLINK; http://pngu.mgh.harvard.edu/purcell/plink/).[22] Samples were dropped from family data sets if reported relationships differed from relatedness from identity by descent (IBD) estimation (using PREST; http://fisher.utstat.toronto.edu/sun/Software/Prest/).[23] If samples were duplicated in different data sets, only one sample per duplicate pair was kept in the analysis. After exclusions, data on 9162 affected participants remained for subsequent analyses.

After sample quality control, genotyped SNPs were excluded from the analysis if their minor allele frequencies (MAFs) 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; http://mathgen.stats.ox.ac.uk/impute/impute_v2.html)[24] was less than 0.50. Genome-wide genotype imputation was performed in each cohort using IMPUTE2 software[24] with all available reference haplotypes from 1000 Genomes (December 2010

Figure. Age at Onset by Alzheimer Disease Genetics Consortium (ADGC) Data Set



ACT indicates Adult Changes in Thought; ADC, Alzheimer Disease Center; ADNI, Alzheimer's Disease Neuroimaging Initiative; GenADA, Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's Disease; MIRAGE, Multi-Institutional Research on Alzheimer Genetic Epidemiology; NIA-LOAD, National Institute on Aging–Late-Onset Alzheimer Disease; OHSU, Oregon Health & Science University; ROSMAP, Religious Orders Study/Memory and Aging Project; TGEN2, Translational Genomics Research Institute 2; UM/VU/MSSM, University of Miami/Vanderbilt University/Mount Sinai School of Medicine; UPITT, University of Pittsburgh; and WASHU, Washington University in St Louis.

release; http://www.1000genomes.org/announcements/june-2011-data-release-2011-06-23). Imputation quality was assessed using the Info statistic, and only SNPs imputed with an Info of 0.50 or higher were included in the analysis. The 10 SNPs examined herein were among the common set of SNPs produced in imputation.

Statistical Analysis

We performed association analysis on individual data sets assuming an additive model on log-transformed AAO with covariate adjustment for population substructure. For cases from case-control data sets, linear regression was performed in PLINK,[22] while for analysis of cases from family data sets (used only in the primary analysis of risk variants), generalized estimating equations with a linear model as implemented in a statistical package (R; http://www.r-project.org/)[25] were used. To account for the effects of population substructure, we performed a principal components analysis on affected participants within each data set (using EIGENSTRAT; http://genepath.med.harvard.edu/~reich/EIGENSTRAT.htm)[26] on a subset of 21 109 SNPs common to all genotyping platforms. The first 3 principal components from the 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 that included sex and the number of *APOE* ε4 alleles (0, 1, or 2). Results from individual data sets were combined in the meta-analysis using inverse variance weighting (as implemented in METAL; http://www.sph.umich.edu/csg/abecasis/metal/),[27] applying a genomic control to each data set. With this set of 9162 affected participants, for 10 focused independent hypothesis tests, we expected to have greater than 80% power to detect loci at $\alpha = 0.05$ with as little effect as 5 months' difference in AAO per allelic copy for very common variants (MAF, 0.30), and greater than 80% power to detect 8 months' difference in AAO per allelic copy for variants of modest or low frequency (MAF, 0.10).[28]

Because of limitations in the availability of genotyped replication data sets with similar AAO phenotypes and ascertainment, we performed a discovery genome-wide association meta-analysis among 6143 cases in 10 ADGC case-control data sets to determine whether SNPs with weak or no LOAD risk associations may contribute to differences in AAO, as well as to assess the genetic burden attributable to these variants. Methods, results, and a brief summary are provided in the eAppendix, eFigure, and eTables 5-9 in the Supplement. Replication data on affected participants from 6 new ADGC data sets (described in the Methods subsection of the eAppendix in the Supplement) were also examined.

In addition to association meta-analysis, we performed several genetic burden analyses to determine the percentage contribution of LOAD susceptibility SNPs in 10 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 LOAD risk (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 data set–specific effects. We also performed a score-based genetic burden analysis of AAO using a risk genotype score derived from summing dosages of the risk alleles at the 10 LOAD risk loci examined.

Results

ADGC Data Characteristics

Descriptive characteristics of the individual ADGC data sets are summarized in eTable 1 in the Supplement. There were more female affected participants (5480 [59.8%]) than male affected participants. The mean (SD) AAO was 74.3 (7.6) years for the entire group. Several data sets had later ages at onset (**Figure**). Two of these were population-based cohorts of aging and memory loss, Religious Orders Study/Memory and Aging Project (mean [SD] AAO, 85.6 [6.3] years) and Adult Changes

Table 1. Association With Age at Onset of SNPs Most Significantly Associated With LOAD in 9 Genomic Regions and *APOE*[a]

					Age at Onset						LOAD Risk	
					Minimal Adjustment Model			Extended Adjustment Model				
SNP	CH:MB	Nearest Gene	Minor Allele	MAF	β (95% CI)	*P* Value	*P* Value for Het	β (95% CI)	*P* Value	*P* Value for Het	OR (95% CI)	*P* Value
rs6701713	1:207.8	*CR1*	*A*	0.24	−0.41 (−0.65 to −0.17)	7.2×10^{-4}	.405	−0.41 (−0.69 to −0.12)	4.9×10^{-3}	.422	1.16 (1.11 to 1.22)	4.6×10^{-10}
rs7561528	2:127.9	*BIN1*	*A*	0.37	−0.31 (−0.52 to −0.09)	4.8×10^{-4}	.855	−0.32 (−0.57 to −0.08)	9.9×10^{-3}	.684	1.17 (1.13 to 1.22)	4.2×10^{-14}
rs9349407	6:47.5	*CD2AP*	*C*	0.32	−0.03 (−0.25 to 0.19)	.765	.266	−0.14 (−0.40 to 0.11)	.273	.860	1.12 (1.07 to 1.18)	1.0×10^{-6}
rs11767557	7:143.1	*EPHA1*	*C*	0.18	0.03 (−0.26 to 0.32)	.830	.861	0.07 (−0.24 to 0.39)	.659	.657	0.87 (0.83 to 0.92)	2.4×10^{-7}
rs1532278	8:27.5	*CLU*	*T*	0.37	0.05 (−0.18 to 0.28)	.661	.137	0.0038 (−0.26 to 0.27)	.977	.108	0.89 (0.85 to 0.93)	8.3×10^{-8}
rs4938933	11:60.0	*MS4A4A*	*C*	0.36	0.09 (−0.14 to 0.31)	.448	.454	0.018 (−0.23 to 0.27)	.887	.584	0.88 (0.85 to 0.92)	1.7×10^{-9}
rs561655	11:85.8	*PICALM*	*G*	0.38	0.33 (−0.12 to 0.55)	2.2×10^{-3}	.915	0.32 (0.07 to 0.57)	.011	.957	0.87 (0.84 to 0.91)	7.0×10^{-11}
rs3752246	19:1.1	*ABCA7*	*G*	0.34	−0.27 (−0.55 to 0.02)	.064	.700	−0.19 (−0.51 to 0.13)	.242	.748	1.15 (1.09 to 1.21)	5.8×10^{-7}
Haplotype rs7412/ rs429358	19:45.4	*APOE*	ε4	0.35	−2.45 (−2.68 to −2.21)	3.3×10^{-96}	.094	−0.24 (−0.75 to 0.27)	.360	.874	3.02 (2.86 to 3.20)	2.2×10^{-320}
rs3865444	19:51.7	*CD33*	*A*	0.20	0.10 (−0.13 to 0.33)	.377	.596	0.13 (−0.13 to 0.38)	.338	.872	0.89 (0.86 to 0.93)	1.1×10^{-7}

Abbreviations: β, β Coefficient for age at onset from the meta-analysis (the number of years' difference in age at onset per copy of the minor allele); CH:MB, chromosome:position (in megabases, build 19); LOAD, late-onset Alzheimer disease; MAF, minor allele frequency; OR, odds ratio; *P* Value for Het, *P* value for heterogeneity across studies; SNP, single-nucleotide polymorphism.

[a] The SNPs presented demonstrated strongest associations within each of 10 genomic regions having associations of genome-wide statistical significance ($P \leq 5.0 \times 10^{-8}$) with LOAD risk. *P* values for age-at-onset associations exceeding the multiple hypothesis testing threshold ($P < .005$) are shown in boldface.

in Thought (mean [SD] AAO, 83.9 [4.8] years). A third was a case-control data set, Oregon Health & Science University, which intentionally ascertained individuals with later AAO (mean [SD] AAO, 86.1 [5.5] years). While data from these studies did not largely change the patterns of association observed (data not shown) in association testing, we performed several subanalyses to assess their effect on the genetic burden analyses as described below.

LOAD Susceptibility Variant Associations With AAO

We confirmed an association of the *APOE* ε4 allele with lower AAO, with each additional copy of the ε4 allele reducing AAO by 2.45 years ($\beta = -2.45$, $P = 3.3 \times 10^{-96}$). Examining the variants most strongly associated with LOAD in 9 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 ($P < .005$) with AAO, including rs6701713 in *CR1* ($P = 7.2 \times 10^{-4}$), rs7561528 in *BIN1* ($P = 4.8 \times 10^{-4}$), and rs561655 in *PICALM* ($P = 2.2 \times 10^{-3}$). Both rs6701713 in *CR1* and rs7561528 in *BIN1* demonstrated a reduced AAO for each copy of the risk variant, with each copy of the risk allele *A* at rs6701713 (MAF, 0.24) advancing AAO by approximately 5 months ($\beta = -0.41$; 95% CI, −0.65 to −0.17) and with each copy of the risk allele *A* at rs7561528 (MAF, 0.37) advancing AAO by slightly less than 4 months ($\beta = -0.31$; 95% CI, −0.52 to −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 4 months ($\beta = -0.33$; 95% CI, −0.55 to 0.12). These patterns of association remained largely unchanged after adjustment for *APOE* ε4 allele dosage and sex for the *CR1* variant (rs6701713; $\beta = -0.41$; 95% CI, −0.69 to −0.12; $P = 4.9 \times 10^{-3}$) and for the *BIN1* variant (rs7561528; $\beta = -0.32$; 95% CI, −0.57 to −0.08; $P = 9.9 \times 10^{-3}$). 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; $\beta = 0.32$; 95% CI, 0.07-0.57; $P = .011$). 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. We examined these associations in a limited replication data set of 1978 cases from 6 newly available ADGC case-control data sets (described in the eAppendix in the Supplement). Although similar directionality of effects on AAO were observed for all the LOAD risk variants (eTable 2 in the Supplement), other than *APOE*, none of the AAO associations of *CR1*, *BIN1*, and *PICALM* variants in the replication data set of less than 2000 affected participants were nominally significant ($P < .05$). Power with these data are limited in a data set of 1978, and for a variant of MAF of 0.20, there is 80% power to detect at a difference in AAO of about 10 months at $\alpha = 0.05$, whereas for a variant of MAF of 0.30, 80% power can detect a 9-month AAO difference.

Genetic Burden Analysis of AAO With LOAD Risk Variants

We examined the genetic burden of *APOE* and the LOAD risk variants in the 9 genomic regions on variation in AAO (**Table 2**) in the 14 ADGC data sets with complete AAO data. In our base-

Table 2. Risk-Weighted Burden Analysis Results for *APOE* and 9 LOAD Candidate Genes[a]

	Model							
	1, Adjustment for PC and Site		2, Adjustment for Model 1 and *APOE*		3, Adjustment for Model 1 and 9 LOAD Genes		4, Adjustment for Model 1, *APOE*, and 9 LOAD Genes	
Variable	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Intercept	74.3 (73.5 to 75.0)	$<10^{-32}$	75.9 (75.2 to 76.7)	$<10^{-32}$	75.4 (74.3 to 76.5)	$<10^{-32}$	77.1 (76.0 to 78.1)	$<10^{-32}$
CR1 score	NA	NA	NA	NA	−0.27 (−0.49 to −0.04)	.021	−0.25 (−0.47 to −0.03)	.024
BIN1 score	NA	NA	NA	NA	−0.27 (−0.46 to −0.07)	.007	−0.29 (−0.48 to −0.1)	.003
CD2AP score	NA	NA	NA	NA	−0.05 (−0.26 to 0.17)	.671	−0.09 (−0.30 to 0.12)	.398
EPHA1 score	NA	NA	NA	NA	0.02 (−0.23 to 0.27)	.878	0.03 (−0.22 to 0.27)	.823
CLU score	NA	NA	NA	NA	−0.08 (−0.29 to 0.14)	.488	−0.08 (−0.28 to 0.13)	.462
MS4A4A score	NA	NA	NA	NA	−0.08 (−0.27 to 0.12)	.459	−0.09 (−0.28 to 0.11)	.378
PICALM score	NA	NA	NA	NA	−0.27 (−0.47 to −0.07)	.010	−0.24 (−0.44 to −0.04)	.018
ABCA7 score	NA	NA	NA	NA	−0.19 (−0.45 to 0.07)	.143	−0.18 (−0.44 to 0.07)	.151
CD33 score	NA	NA	NA	NA	−0.02 (−0.23 to 0.20)	.862	−0.08 (−0.29 to 0.13)	.458
APOE score	NA	NA	−0.81 (−0.89 to −0.73)	2.9×10^{-90}	NA	NA	−0.78 (−0.86 to −0.7)	5.2×10^{-78}
ACT	9.61 (8.57 to 10.65)	1.3×10^{-71}	8.97 (7.95 to 9.99)	1.6×10^{-65}	9.68 (8.65 to 10.7)	2.0×10^{-74}	9.06 (8.05 to 10.1)	2.4×10^{-68}
ADC1	−1.81 (−2.65 to −0.98)	2.2×10^{-5}	−1.99 (−2.80 to −1.17)	1.9×10^{-6}	−1.78 (−2.60 to −0.95)	2.5×10^{-5}	−1.94 (−2.74 to −1.13)	2.6×10^{-6}
ADC2	−1.1 (−2.03 to −0.18)	.020	−0.82 (−1.73 to 0.08)	.074	−1.09 (−2.01 to −0.18)	.019	−0.82 (−1.71 to 0.07)	.072
ADC3	0.15 (−0.78 to 1.08)	.755	0.48 (−0.43 to 1.39)	.300	0.19 (−0.73 to 1.11)	.684	0.52 (−0.38 to 1.42)	.260
ADNI	−1.33 (−2.71 to 0.04)	.058	−1.08 (−2.42 to 0.26)	.115	−1.31 (−2.66 to 0.05)	.059	−1.05 (−2.37 to 0.28)	.120
GenADA	0.32 (−0.60 to 1.24)	.490	−0.55 (−1.46 to 0.35)	.229	0.41 (−0.50 to 1.32)	.375	−0.43 (−1.32 to 0.46)	.344
NIA-LOAD	−2.93 (−3.80 to −2.06)	4.2×10^{-11}	−2.24 (−3.09 to −1.39)	2.7×10^{-7}	−2.86 (−3.71 to −2.00)	7.5×10^{-11}	−2.18 (−3.02 to −1.34)	4.0×10^{-7}
MIRAGE	−3.26 (−4.23 to −2.28)	6.7×10^{-11}	−3.01 (−3.96 to −2.05)	6.8×10^{-10}	−3.30 (−4.26 to −2.33)	2.3×10^{-11}	−3.02 (−3.96 to −2.07)	4.0×10^{-10}
OHSU	11.7 (10.3 to 13.2)	9.9×10^{-58}	11.3 (9.94 to 12.72)	1.3×10^{-56}	12.0 (10.5 to 13.4)	2.7×10^{-61}	11.6 (10.2 to 12.9)	4.3×10^{-60}
ROSMAP	11.3 (10.2 to 12.4)	1.9×10^{-88}	10.6 (9.52 to 11.7)	5.3×10^{-82}	11.4 (10.3 to 12.5)	3.2×10^{-92}	10.7 (9.66 to 11.8)	9.4×10^{-86}
TGEN2	0.26 (−1.31 to 1.84)	.742	0.67 (−0.87 to 2.21)	.395	0.5 (−1.06 to 2.05)	.532	0.89 (−0.64 to 2.41)	.254
UM/VU/MSSM	−0.40 (−1.26 to 0.47)	.369	−0.55 (−1.39 to 0.29)	.200	−1.95 (−3.03 to −0.87)	4.2×10^{-4}	−2.44 (−3.50 to −1.39)	6.2×10^{-6}
UPITT	−1.39 (−2.25 to −0.54)	.001	−1.22 (−2.06 to −0.39)	.004	−1.41 (−2.26 to −0.57)	.001	−1.22 (−2.04 to −0.39)	.004
PC1	17.6 (7.50 to 27.6)	6.2×10^{-4}	18.9 (9.09 to 28.72)	1.6×10^{-4}	−26.3 (−38.8 to −13.9)	3.6×10^{-5}	−20.8 (−33.0 to −8.62)	8.3×10^{-4}
PC2	35.4 (25.6 to 45.2)	1.7×10^{-12}	32.3 (22.7 to 41.9)	4.1×10^{-11}	7.62 (−3.02 to 18.3)	.160	6.39 (−4.00 to 16.8)	.228
PC3	0.38 (−9.54 to 10.3)	.939	−5.07 (−14.8 to 4.63)	.306	−4.34 (−17.0 to 8.35)	.503	−12.1 (−24.53 to 0.33)	.056
F score	$146.7_{16,8228}$		$169.5_{17,8227}$		$97.02_{25,7479}$		$111.5_{26,7478}$	
P value	2.2×10^{-16}		2.2×10^{-16}		2.2×10^{-16}		2.2×10^{-16}	
Multiple R^2	0.222		0.2594		0.2449		0.2794	
Adjusted R^2	0.2205		0.2579		0.2424		0.2769	

Abbreviations: ACT, Adult Changes in Thought; ADC, Alzheimer Disease Center; ADNI, Alzheimer's Disease Neuroimaging Initiative; β, β coefficient; GenADA, Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's Disease; LOAD, late-onset Alzheimer disease; MIRAGE, Multi-Institutional Research on Alzheimer Genetic Epidemiology; NA, not applicable; NIA-LOAD, National Institute on Aging–Late-Onset Alzheimer Disease; OHSU, Oregon Health & Science University; PC, principal components; ROSMAP, Religious Orders Study/Memory and Aging Project; TGEN2, Translational Genomics Research Institute 2; UM/VU/MSSM, University of Miami/Vanderbilt University/Mount Sinai School of Medicine; UPITT, University of Pittsburgh.

[a] *P* values are from 4 linear regression models of age at onset examining weighted scores for the peak single-nucleotide polymorphism associations in *APOE* and 9 LOAD candidate genes. Scores are the product of the log-transformed odds ratio for LOAD risk for each single-nucleotide polymorphism multiplied by the minor allele dosage from the imputed genotype probabilities.

line model, 22.1% of the variation in AAO (R^2 = 0.221) was accounted for by population substructure and study-specific effects. The independent contributions of dosage of the *APOE* ε4 allele to the genetic burden was roughly 3.7% of AAO variation (R^2 = 0.256), while the cumulative effect of the 9 LOAD risk variants was 2.2% (R^2 = 0.242), together accounting for approximately 5.6% of genetic variation in AAO (R^2 = 0.277). Excluding study-specific effects, *APOE* accounts for 4.8% of the remaining variation, and the 9 LOAD risk variants account for another 2.8%, for a combined contribution of 7.2% 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 3 data sets with much later average AAO (Adult Changes in Thought, Oregon Health & Science University, and Religious Orders Study/Memory and Aging Project) and the 2 family-based data sets (National Institute on Aging-LOAD and Multi-Institutional Research on Alzheimer Genetic Epidemiology) on genetic burden analyses. In analyses that excluded the data sets with later average AAO (eTable 3 in the Supplement), we found that these data sets account for much of the data set-specific AAO variation, reducing the effect of data set on AAO variation from just over 22% to 2.5% (R^2 = 0.0251). In these analyses, after excluding data set-specific effects, the percentage variation attributable to *APOE* was slightly higher at 4.3% (R^2 = 0.0434), the effect attributable to the 9 LOAD risk variants was similar to before at 1.1% (R^2 = 0.0367), and the combined contribution of both was observed to be 5.5% (R^2 = 0.0799). Removal of the family data sets (eTable 4 in the Supplement) did not appreciably change the variation attributable to study-specific effects (R^2 = 0.225), nor did it substantially change the relative effects of *APOE* and the 9 LOAD risk variants on AAO variation.

To determine the aggregate effect of risk alleles from the 10 LOAD loci, we also tested the association of a risk genotype score derived from summed unweighted dosages of the risk alleles at the 10 LOAD risk loci examined (**Table 3**). We observed that, for each risk allele copy at these 9 LOAD risk loci, there was a lower AAO of 1.8 months (β = −0.15; 95% CI, −0.24 to −0.07; $P = 2.7 \times 10^{-4}$). Including *APOE* ε4 dosage, the combined effect of the 9 LOAD risk loci and *APOE* ε4 corresponded to a lower AAO of 4.2 months (β = −0.35; 95% CI, −0.43 to −0.27; $P = 1.0 \times 10^{-17}$) for each LOAD risk allele copy. Examining only the variants at *CR1*, *BIN1*, and *PICALM* that showed significant lowering of AAO, AAO is still lower for each risk copy (4.9 months) (β = −0.41; 95% CI, −0.54 to −0.27; $P = 1.9 \times 10^{-9}$) and more so when *APOE* ε4 is included in the score (10.1 months) (β = −0.84; 95% CI, −0.96 to −0.73; $P = 8.4 \times 10^{-44}$).

Discussion

Our analysis of more than 9000 affected participants having LOAD with AAO 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 3 of the other 9 established risk loci (*CR1*, *BIN1*, and *PICALM*). Burden analysis demonstrated that the cumulative variation explained by SNPs at 9 LOAD risk loci was about one-third as much as the percentage variation in AAO from *APOE*. A risk genotype score analysis found that, in aggregate, each additional risk allele at the major LOAD loci lowers AAO by as much as 10 months per copy, emphasizing that the aggregate effect of these risk loci may lead to much earlier onset for some affected participants with LOAD.

The *APOE* ε4 allele was observed to have a smaller effect on phenotype variation in AAO herein (3%-4%) than in some previous investigations (7%-9%).[29] This may be owing to differences in study design; for instance, all previous estimates were made in pedigrees enriched in cases and often the *APOE* ε4 allele, whereas most affected participants examined herein were unrelated (only 2302 of 9162 affected participants [25.1%] were from family data sets). However, this deflation is consistent with several recent findings: 2 recent analyses using GWAS data found that the *APOE* ε4 allele contributed to 4%[30] and 6%[31] of the phenotype variation in LOAD risk, with which *APOE* ε4 is more strongly associated than AAO.

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 the genetic burden of SNPs associated with AAO but with little or no effect on LOAD risk accounted for more variation in AAO compared with the non-*APOE* risk variants (2.2% vs 1.1%) but were still dwarfed by the effects of *APOE* on variation in AAO (approximately 4%).

The results of several previous studies have suggested potential associations of risk variants at these loci with AAO. A recent study[10] using a small subset of the cases used in this study (Alzheimer Disease Center 1, 2, and 3 [n = 2569]) identified an association with a *PICALM* risk variant (rs3851179, P = .009). A study[32] 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 = .041), as well as an association with a longer duration of disease. A study by Jones et al[33] among persons with Down syndrome, which is typically associated with elevated AD risk at an earlier AAO, showed that risk variants in *APOE* (P = .014) and *PICALM* (P = .011) were correlated with lower AAO in patients with AD having Down syndrome.

Daw et al[29] analyzed families with a high burden of AD and later AAO in a multiplex family data set and found evidence of at least 4 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 study by Daw et al and may reflect genetic heterogeneity of AAO genetics within LOAD or, more likely, may 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-

Table 3. Risk Genotype Score Burden Analysis of Age at Onset[a]

	9-Loci Risk Genotype Score Models				3-Loci Risk Genotype Score Models			
	1, Excluding *APOE* ε4		2, Including *APOE* ε4		3, Excluding *APOE* ε4		4, Including *APOE* ε4	
Variable	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Intercept	75.7 (74.6 to 76.7)	$<10^{-32}$	77.6 (76.6 to 78.7)	$<10^{-32}$	75.3 (74.5 to 76.1)	$<10^{-32}$	76.8 (76.0 to 77.7)	$<10^{-32}$
Risk genotype score	−0.15 (−0.24 to −0.07)	2.7×10^{-4}	−0.35 (−0.43 to −0.27)	1.0×10^{-17}	−0.41 (−0.54 to −0.27)	1.9×10^{-9}	−0.84 (−0.96 to −0.73)	8.4×10^{-44}
ACT	9.68 (8.66 to 10.7)	1.5×10^{-74}	9.63 (8.61 to 10.7)	2.1×10^{-74}	9.63 (8.59 to 10. 7)	3.7×10^{-72}	9.46 (8.43 to 10.5)	5.0×10^{-71}
ADC1	−1.78 (−2.60 to −0.96)	2.3×10^{-5}	−1.75 (−2.57 to −0.93)	2.9×10^{-5}	−1.76 (−2.59 to −0.92)	3.7×10^{-5}	−1.75 (−2.57 to −0.92)	3.5×10^{-5}
ADC2	−1.10 (−2.01 to −0.18)	.019	−1.04 (−1.95 to −0.13)	.026	−1.06 (−1.99 to −0.14)	.024	−0.94 (−1.86 to −0.02)	.044
ADC3	0.19 (−0.73 to 1.11)	.687	0.26 (−0.66 to 1.17)	.584	0.19 (−0.74 to 1.12)	.694	0.32 (−0.60 to 1.25)	.490
ADNI	−1.28 (−2.63 to 0.08)	.065	−1.18 (−2.53 to 0.17)	.086	−1.30 (−2.67 to 0.08)	.064	−1.19 (−2.54 to 0.17)	.087
GenADA	0.41 (−0.50 to 1.32)	.374	0.36 (−0.55 to 1.26)	.438	0.36 (−0.56 to 1.28)	.438	0.15 (−0.76 to 1.06)	.747
NIA-LOAD	−2.85 (−3.71 to −2.00)	7.5×10^{-11}	−2.71 (−3.57 to −1.86)	5.5×10^{-10}	−2.88 (−3.75 to −2.01)	8.7×10^{-11}	−2.62 (−3.48 to −1.76)	2.7×10^{-9}
MIRAGE	−3.31 (−4.28 to −2.35)	1.9×10^{-11}	−3.23 (−4.20 to −2.27)	4.5×10^{-11}	−3.20 (−4.18 to −2.23)	1.3×10^{-10}	−3.07 (−4.03 to −2.10)	5.0×10^{-10}
OHSU	11.9 (10.5 to 13.4)	2.7×10^{-61}	11.9 (10.5 to 13.3)	2.5×10^{-61}	11.8 (10.3 to 13.2)	2.9×10^{-58}	11.7 (10.3 to 13.1)	1.5×10^{-58}
ROSMAP	11.4 (10.3 to 12.4)	4.2×10^{-92}	11.3 (10.2 to 12.34)	2.3×10^{-91}	11.3 (10.2 to 12.4)	4.7×10^{-89}	11.1 (10.0 to 12.2)	7.1×10^{-88}
TGEN2	0.48 (−1.08 to 2.03)	.548	0.57 (−0.98 to 2.12)	.474	0.36 (−1.22 to 1.93)	.658	0.57 (−0.99 to 2.13)	.472
UM/VU/MSSM	−1.99 (−3.07 to −0.91)	3.0×10^{-4}	−1.97 (−3.05 to −0.90)	3.3×10^{-4}	−0.43 (−1.29 to 0.43)	.325	−0.52 (−1.37 to 0.34)	.234
UPITT	−1.42 (−2.26 to −0.58)	9.8×10^{-4}	−1.35 (−2.19 to −0.51)	.002	−1.34 (−2.19 to −0.49)	.002	−1.24 (−2.08 to −0.39)	.004
PC1	−27.5 (−39.9 to −15.1)	1.5×10^{-5}	−26.6 (−39.0 to −14.2)	2.5×10^{-5}	17.2 (7.20 to 27.3)	7.7×10^{-4}	17.2 (7.31 to 27.2)	6.7×10^{-4}
PC2	7.58 (−3.05 to 18.2)	.162	7.55 (−3.03 to 18.1)	.162	34.4 (24.6 to 44.2)	6.2×10^{-12}	32.5 (22.8 to 42.2)	5.8×10^{-11}
PC3	−4.41 (−17.1 to 8.26)	.495	−5.46 (−18.1 to 7.16)	.396	0.80 (−9.10 to 10.71)	.874	−0.34 (−10.2 to 9.47)	.946
F score	$142.1_{17,7487}$		$146.8_{17,7487}$		$140.8_{17,8227}$		$152.8_{17,8227}$	
P value	2.2×10^{-16}		2.2×10^{-16}		2.2×10^{-16}		2.2×10^{-16}	
Multiple R^2	0.2440		0.2500		0.2254		0.2400	
Adjusted R^2	0.2422		0.2483		0.2238		0.2384	

Abbreviations: ACT, Adult Changes in Thought; ADC, Alzheimer Disease Center; ADNI, Alzheimer's Disease Neuroimaging Initiative; β, β coefficient; GenADA, Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's Disease; MIRAGE, Multi-Institutional Research on Alzheimer Genetic Epidemiology; NIA-LOAD, National Institute on Aging–Late-Onset Alzheimer Disease; OHSU, Oregon Health & Science University; PC, principal components; ROSMAP, Religious Orders Study/Memory and Aging Project; TGEN2, Translational Genomics Research Institute 2; UM/VU/MSSM, University of Miami/Vanderbilt University/Mount Sinai School of Medicine; UPITT, University of Pittsburgh.

[a] *P* values are from 2 linear regression models examining a risk genotype score derived from the sum of genotype dosages for the risk-increasing allele from the 9 late-onset Alzheimer disease candidate loci, as well as the dosage of *APOE* ε4. Model 1 includes the sum of the genotype dosages for the 9 late-onset Alzheimer disease risk loci only. Model 2 also adds the number of *APOE* ε4 copies to the risk genotype score. Model 3 examines only the sum of the 3 variants associated with age at onset (variants at *CR1*, *BIN1*, and *PICALM*). Model 4 examines the *CR1*, *BIN1*, and *PICALM* variants and includes *APOE* ε4. Covariate adjustment in all 4 models includes the data set of origin and population substructure captured by the first 3 principal components from EIGENSTRAT (http://genepath.med.harvard.edu/~reich/EIGENSTRAT.htm).

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,[34-39] may also contribute to variation in AAO of AD. The identification of other genetic modifiers of AAO through studies of larger samples of affected participants with LOAD and studies using next-generation sequencing approaches, which can more thoroughly interrogate the genome, may yield additional genetic risk factors that influence AAO and provide new insights into the pathogenesis of LOAD.

Conclusions

We confirmed an association of *APOE* variants with AAO among affected participants with LOAD and observed novel associations of *CR1*, *BIN1*, and *PICALM* with AAO. In contrast to earlier hypothetical modeling, we show that the combined effects of AD risk variants on AAO are on the scale of, but do not exceed, the *APOE* effect. While the aggregate effects of risk loci on AAO may be significant, additional genetic contributions to AAO are individually likely to be small.

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