ONLINE FIRST

Meta-analysis Confirms *CR1*, *CLU*, and *PICALM* as Alzheimer Disease Risk Loci and Reveals Interactions With *APOE* Genotypes

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Objectives: To determine whether genotypes at *CLU*, *PICALM*, and *CR1* confer risk for Alzheimer disease (AD) and whether risk for AD associated with these genes is influenced by apolipoprotein E (*APOE*) genotypes.

Design: Association study of AD and *CLU*, *PICALM*, *CR1*, and *APOE* genotypes.

Setting: Academic research institutions in the United States, Canada, and Israel.

Participants: Seven thousand seventy cases with AD, 3055 with autopsies, and 8169 elderly cognitively normal controls, 1092 with autopsies, from 12 different studies, including white, African American, Israeli-Arab, and Caribbean Hispanic individuals.

Results: Unadjusted, *CLU* (odds ratio [OR], 0.91; 95% confidence interval [CI], 0.85-0.96 for single-nucleotide polymorphism [SNP] rs11136000), *CR1* (OR, 1.14; 95% CI, 1.07-1.22; SNP rs3818361), and *PICALM* (OR, 0.89; 95% CI, 0.84-0.94, SNP rs3851179) were associated with AD in white individuals. None were significantly associated with AD in the other ethnic groups. *APOE* ε4 was significantly associated with AD (ORs, 1.80-9.05) in all but 1 small white cohort and in the Arab cohort. Adjusting for age, sex, and the presence of at least 1 *APOE* ε4 allele greatly reduced evidence for association with *PICALM* but not *CR1* or *CLU*. Models with the main SNP effect, presence or absence of *APOE* ε4, and an interaction term showed significant interaction between presence or absence of *APOE* ε4 and *PICALM*.

Conclusions: We confirm in a completely independent data set that *CR1*, *CLU*, and *PICALM* are AD susceptibility loci in European ancestry populations. Genotypes at *PICALM* confer risk predominantly in *APOE* ε4–positive subjects. Thus, *APOE* and *PICALM* synergistically interact.

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ALZHEIMER DISEASE (AD) IS the most common form of dementia, affecting 5% of the population older than 65 years and 30% to 50% older than 80 years. Substantial progress was made identifying genes for rare forms of early-onset AD[1-4] and this early success significantly contributed to biologic study of AD mechanisms and, more recently, multiple drug discovery approaches. Late-onset AD, the common form of the disease, has been more difficult to solve, with apolipoprotein E (*APOE*) being the only confirmed susceptibility locus.[5] The combination of high-density genotyping methods, large well-characterized AD and control populations, and statistical methods to evaluate population stratification now provide the tools to identify additional genes contributing to AD risk.

Recently, 2 genome-wide association studies (GWAS) reported evidence that variations in *CLU* (encoding clusterin), *PICALM* (encoding the phosphatidylinositol binding clathrin assembly protein), and *CR1* (encoding complement component [3b/4b] receptor 1) confer genetic risk for AD.[6,7] Evidence for these 3 loci reached genome-wide significance in samples consisting of 5964 cases and 10 188 controls (*PICALM* and *CLU*) and 5887 cases and 8508 controls (*CRI* and *CLU*). To analyze the role of these genes in AD risk, the Alzheimer's Disease Genetics Consortium (ADGC) performed a meta-analysis using

Table 1. Sample Description[a]

Cohort	No. of Cases	No. of Autopsies	Onset Age, y, Mean (SD)	No. of Controls	No. of Autopsies	Age at Last Examination, y, Mean (SD)	Total	Ethnic Group, %
White subjects								
ADC	1595	1421	73 (7.7)	553	134	77 (8.7)	2148	17
ADNI	286	0	74 (8.1)	195	0	78 (5.4)	481	4
CAMP	127	0	79 (7.9)	105	0	76 (7.8)	232	2
FHS	197	0	83 (6.4)	2392	0	73 (7.5)	2589	20
UM/VU/MSSM	1170	370	74 (7.7)	1169	75	74 (7.6)	2339	18
MIRAGE	560	0	71 (6.5)	790	0	72 (7.1)	1350	10
NIA-LOAD	993	367	72 (6.9)	884	45	76 (8.4)	1877	14
OHSU	187	215	87 (7.3)	429	461	86 (7.2)	616	5
TGEN	820	613	80 (8.3)	517	377	83 (8.9)	1337	10
Total	**5935**	**2986**		**7034**	**1092**		**12 969**	100
African American subjects								
ADC	61	61	75 (7.0)	63	63	76 (6.2)	124	14
JHU	221	0	77 (6.6)	186	0	78 (6.6)	407	45
MIRAGE	180	0	70 (8.9)	200	0	71 (10.0)	380	42
Total	**462**	**61**		**449**	**63**		**911**	100
Arab subjects								
Wadi Ara cohort	124	0	78 (7.9)	142	0	72 (6.0)	266	100
Caribbean Hispanic subjects								
Columbia University cohort	549	8	80 (8.0)	544	0	79 (6.4)	1093	100
All ethnic groups								
Total	**7070**	**3055**		**8169**	**1155**		**15 239**	

Abbreviations: ADC, Alzheimer's Disease Centers cohort; ADNI, Alzheimer's Disease Neuroimaging Initiative cohort; CAMP, Collaborative Aging and Memory Project cohort; FHS, Framingham Heart Study cohort; JHU, Johns Hopkins University cohort; MIRAGE, Multi-Institutional Research on Alzheimer's Genetic Epidemiology cohort; NIA-LOAD, National Institute on Aging Late-Onset Alzheimer's Disease cohort; OHSU, Oregon Health and Science University cohort; TGEN, Translational Genomics Research Institute cohort; UM/VU/MSSM, University of Miami/Vanderbilt University/Mount Sinai School of Medicine cohort.

[a] Additional information on all cohorts is provided in the eAppendix and eTables 1, 2, and 3 (http://www.archneurol.com).

GWAS data for 15 239 subjects from 9 Northern European white cohorts and 5 cohorts that included African American, Israeli-Arab, and Caribbean Hispanic individuals (**Table 1**). Genotypes for *CR1*, *CLU*, and *PICALM* were analyzed for association with AD using cohorts that are completely independent of those originally used to identify these 3 loci as AD susceptibility factors. The controls used are all elderly (>60 years). We also examined the interaction of *APOE* with *CR1*, *CLU*, and *PICALM* on AD risk.

METHODS

SUBJECTS

All cohorts are described in more detail in the eAppendix and eTables 1, 2, and 3 (http://www.archneurol.com). The National Institute on Aging (NIA) Alzheimer's Disease Center (ADC) subjects were ascertained, evaluated, and sampled by the clinical and neuropathology cores of the 29 NIA-funded ADCs (Table 1). Subject data collection is coordinated by the National Alzheimer's Coordinating Center. DNA from these samples for genotyping was prepared by the National Cell Repository for Alzheimer's Disease. The Alzheimer's Disease Neuroimaging Initiative (ADNI) subjects are AD cases and controls ascertained for neuroimaging, biomarker, and genetic studies. Data used herein were generated as previously described[8] and obtained from the ADNI database (http://www.loni.ucla.edu/ADNI/). The Collaborative Aging and Memory Project subjects are from the Amish communities of central Ohio and northern Indiana.[9,10] The Columbia University subjects are a Hispanic cohort described in detail elsewhere.[11] The Framingham Heart Study is a single-site, community-based, ongoing cohort study described elsewhere.[12-14] Phenotype and GWAS data were from the dbGaP Web site (http://www.ncbi.nlm.nih.gov/gap). The Johns Hopkins University subjects are from the Genetic and Environmental Risk Factors for Alzheimer's Disease Among African Americans (GenerAAtions) Study identified through the electronic claims database of the Henry Ford Health System. The Multi-Institutional Research on Alzheimer's Genetic Epidemiology (MIRAGE) Study is a family-based genetic epidemiological study of AD in which AD cases and unaffected sibling controls were enrolled at 17 clinical centers in the United States, Canada, Germany, and Greece.[15] The NIA Late-Onset Alzheimer's Disease (NIA-LOAD) Family Study (E. M. Wijsman, PhD, Y Choi, MS, J. H. Rothstein, MS, et al, unpublished data, June 2010) cohort are families with 2 or more affected siblings with late-onset AD and unrelated control subjects without dementia similar in age and ethnic background. One case per family was selected and controls were determined to be cognitively normal after an in-person neurological examination and were not related to a study participant. The Oregon Health and Science University cohort were recruited from aging research cohorts at 10 NIA-funded ADCs and do not overlap with other ADGC samples. The Translational Genomics Research Institute data set is a publicly available sample of AD cases and controls (http://www.tgen.org/research/index.cfm?pageid=1065).[16] The University of Miami/Vanderbilt University/Mount Sinai School of Medicine cohort were new and previously published[17-20] subjects ascertained at the University of Miami, Vanderbilt University, and Mount Sinai School of Medicine. The Wadi Ara data set are from a inbred Arab community in northern Israel.[21-24]

GENOTYPING

The cohorts used were genotyped either on Illumina (San Diego, California) or Affymetrix (Santa Clara, California) single-nucleo-

Table 2. GWAS Genotyping Platform, Numbers of SNPs Genotyped and Imputed, and *APOE* Genotype Distribution for the Study Samples

Cohort	Genotyping Platform[a]	*CRI*, *CLU*, and *PICALM* SNPs: No. Genotyped[b]	*CRI*, *CLU*, and *PICALM* SNPs: No. Imputed[c]
White subjects			
ADC	Illumina 660Quad	11	6
ADNI	Illumina 610Quad	10	6
CAMP	Affymetrix 6.0	16	0
FHS	Affymetrix 5.0	3	13
UM/VU/MSSM	Illumina 550, 610Quad, 1M, 1M-duo; Affymetrix 6.0	17	0
MIRAGE	Illumina 660Quad	8	8
NIA-LOAD	Illumina 610Quad	11	6
OHSU	Illumina 370K	9	6
TGEN	Affymetrix 500K	3	12
African American subjects			
ADC	Illumina 660Quad	10	5
JHU	Illumina 660Quad	10	4
MIRAGE	Illumina 660Quad	8	7
Arab subjects			
Wadi Ara cohort	Illumina 660Quad	9	5
Caribbean Hispanic subjects			
Columbia University cohort	Illumina 650Y	10	0

Abbreviations: ADC, Alzheimer's Disease Centers cohort; ADNI, Alzheimer's Disease Neuroimaging Initiative cohort; APOE, apolipoprotein E; CAMP, Collaborative Aging and Memory Project cohort; FHS, Framingham Heart Study cohort; GWAS, genome-wide association studies; JHU, Johns Hopkins University cohort; MIRAGE, Multi-Institutional Research on Alzheimer's Genetic Epidemiology cohort; NIA-LOAD, National Institute on Aging Late-Onset Alzheimer's Disease cohort; OHSU, Oregon Health and Science University cohort; SNP, single-nucleotide polymorphism; TGEN, Translational Genomics Research Institute cohort; UM/VU/MSSM, University of Miami/Vanderbilt University/Mount Sinai School of Medicine cohort.

[a] Illumina (San Diego, California) or Affymetrix (Santa Clara, California).

[b] The number of genotyped SNPs includes SNPs on the genotyping platform and SNPs genotyped individually by TaqMan (Applied Biosystems, Foster City, California) or other techniques (eAppendix and eTables 1, 2, and 3 [http://www.archneurol.com]).

[c] The number of imputed SNPs reflects the number satisfying predetermined quality thresholds ($R^2 > 0.5$).

tide polymorphism (SNP) arrays (**Table 2**). We selected 17 SNPs from *CR1*, *CLU*, and *PICALM* that were recently reported to be significantly associated with AD in 2 large GWAS[6,7] (**Table 3**). Additional genotypes were obtained using TaqMan assays (Applied Biosystems, Foster City, California) including genotypes for rs7982. Genotyping for the *APOE* ε2/ε3/ε4 alleles was performed as described in the eAppendix and eTables 1, 2, and 3.

ANALYSIS

The analysis included only individuals with a censoring age of 60 years or older. The age used for cases was that most closely approximating the age at disease onset. For some cohorts, age at onset was ascertained while for others, only age at ascertainment was available. For some autopsied subjects, only age at death was available and was used as the censoring age. For all studies, the age used for controls was the age at last examination or death (eAppendix and eTables 1, 2, and 3).

IMPUTATION PROCEDURE

We imputed genotypes for all SNPs within 10 kilobases of the 3 genes using the Markov chain haplotyping software[25] to obtain a common set of SNPs across all data sets. We imputed SNPs from both HapMap releases 2 and 3 (International HapMap Project, http://snp.cshl.org/) and retained those with pairwise linkage disequilibrium ($r^2 > 0.50$) for further analysis (see eAppendix and eTables 1, 2, and 3 for more detail and for data cleaning protocols).

POPULATION SUBSTRUCTURE

To determine if population substructure existed in the different data sets, we used 30 000 to 100 000 SNPs with minor allele frequency more than 0.25 and minimal between-SNP linkage disequilibrium ($r^2 < 0.20$) sampled at random from the autosomes and analyzed with the STRUCTURE software package.[26,27] To account for population substructure in association analyses, EIGENSTRAT[28] was used on each cohort to generate loadings from principal components analysis on the sampled SNPs (eAppendix and eTables 1, 2, and 3).

STATISTICAL ANALYSIS

Genotyped and imputed SNPs were tested for association with AD using a logistic generalized linear model in case-control data sets and a logistic generalized estimating equation in family-based data sets. Genotyped SNPs were coded as 0, 1, or 2 according to the number of minor alleles under the additive genetic model, whereas *APOE* was coded as 0 or 1 according to the presence or absence of the ε4 allele. For imputed SNPs, a quantitative estimate between 0 and 2 for the dose of the minor allele was used to incorporate the uncertainty of the imputation estimates. Regression models for each SNP without covariates were evaluated for comparison with results from the original reports[6,7] Additional models containing all permutations of covariates for age, sex, and *APOE* ε4 status were also tested. Formal tests of interaction between the SNPs and *APOE* were assessed by including the main effects and an interaction term. Regression models were evaluated using the R package.[29] Heterogeneity among odds ratios (ORs) was assessed using the Cochran Q, which was calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. Q was distributed as a χ^2 with k (number of studies) minus 1 *df*. The I^2 statistic[30,31] describes the percentage of variation across studies that is due to heterogeneity rather than chance and was calculated as follows: $I^2 = 100\% \times (Q - df)/Q$. I^2 is an intuitive and simple expression of the inconsistency of studies' results. Unlike Q, it does not inherently depend on the number of studies considered. The SNP association results obtained from individual data sets were combined by meta-analysis using the inverse variance method implemented in the software package METAL (http://www.sph.umich.edu/csg/abecasis/Metal/index.html). An additive model was assumed and the association results across data sets were combined by summing the regression coefficients weighted by the inverse variance of the coefficients. The meta-analysis *P* value of the association was estimated by the summarized test statistic.

Table 3. Meta-analysis Results for Association of AD With SNPs in *CR1*, *CLU*, and *PICALM* in White Individuals

SNP	MA	MAF	Unadjusted		Adjusted for Age, Sex, and *APOE*	
			OR (95% CI)	*P* Value[a]	OR (95% CI)	*P* Value[a]
CR1						
rs3818361	A	0.26	1.14 (1.07-1.22)	6.1×10^{-5}	1.15 (1.07-1.24)	.0002
rs6701713	A	0.26	1.14 (1.07-1.22)	8.8×10^{-5}	1.15 (1.07-1.24)	.0002
rs1408077	A	0.26	1.14 (1.07-1.22)	.0001	1.16 (1.07-1.25)	.0002
CLU						
rs7012010	C	0.39	1.10 (1.03-1.17)	.0025	1.10 (1.02-1.17)	.0081
rs3087554	C	0.16	1.00 (0.92-1.09)	.92	0.98 (0.89-1.08)	.71
rs11136000	T	0.43	0.91 (0.85-0.96)	.0007	0.92 (0.86-0.98)	.0096
rs9331888	G	0.25	0.99 (0.92-1.06)	.76	0.99 (0.91-1.07)	.74
rs7982	T	0.38	0.87 (0.81-0.94)	.0002	0.89 (0.83-0.97)	.0046
PICALM						
rs532470	G	0.49	1.06 (1.00-1.11)	.048	1.02 (0.96-1.09)	.47
rs592297	C	0.20	0.92 (0.86-0.99)	.02	0.96 (0.89-1.04)	.33
rs677909	C	0.40	0.88 (0.83-0.94)	3.3×10^{-5}	0.94 (0.88-1.00)	.056
rs636848	G	0.24	1.02 (0.96-1.08)	.6000	1.00 (0.93-1.07)	.98
rs541458	C	0.39	0.88 (0.83-0.93)	2.6×10^{-5}	0.94 (0.88-1.00)	.048
rs561655	G	0.29	0.89 (0.84-0.94)	3.4×10^{-5}	0.92 (0.87-0.99)	.017
rs543293	A	0.36	0.88 (0.83-0.93)	2.3×10^{-5}	0.92 (0.86-0.98)	.015
rs7941541	G	0.28	0.89 (0.83-0.95)	.0007	0.95 (0.88-1.03)	.21
rs3851179	T	0.35	0.89 (0.84-0.94)	3.9×10^{-5}	0.93 (0.87-0.99)	.026

SNP	MA	MAF	Effect Direction: Unadjusted/Adjusted								
			ADC	ADNI	CAMP	FHS	UM/VU/MSSM	MIRAGE	NIA-LOAD	OHSU	TGEN
CR1											
rs3818361	A	0.26	+/–	+/+	–/–	+/+	+/+	+/+	+/+	+/+	+/+
rs6701713	A	0.26	+/–	+/+	–/–	+/+	+/+	+/+	+/+	+/+	+/+
rs1408077	A	0.26	+/+	+/+	–/–	+/+	+/+	+/+	+/+	+/+	+/+
CLU											
rs7012010	C	0.39	+/+	+/+	?/?	+/–	+/–	+/+	+/+	–/–	+/+
rs3087554	C	0.16	–/–	–/+	+/+	–/+	+/+	–/–	+/+	+/+	?/?
rs11136000	T	0.43	–/–	–/–	–/–	–/–	–/+	–/+	–/–	–/–	–/+
rs9331888	G	0.25	–/–	–/–	+/+	–/–	+/+	–/–	+/+	+/+	–/–
rs7982	T	0.38	–/–	?/?	–/–	?/?	–/–	–/–	–/–	?/?	?/?
PICALM											
rs532470	G	0.49	–/–	–/–	+/+	+/+	+/+	+/+	+/–	–/–	+/+
rs592297	C	0.20	–/–	+/+	–/–	–/–	–/+	–/–	–/+	+/+	–/–
rs677909	C	0.40	–/–	+/+	–/+	–/–	–/–	–/–	–/–	+/+	–/–
rs636848	G	0.24	–/–	–/–	+/+	+/+	–/–	–/–	+/+	–/–	+/+
rs541458	C	0.39	–/–	+/+	–/+	–/–	–/–	–/–	–/–	–/–	–/–
rs561655	G	0.29	–/–	+/+	–/–	–/+	–/–	–/–	–/–	+/–	–/–
rs543293	A	0.36	–/–	–/+	–/+	–/–	–/–	–/–	–/–	+/–	–/–
rs7941541	G	0.28	–/–	–/+	–/+	–/–	–/–	?/?	–/–	?/?	–/–
rs3851179	T	0.35	–/–	–/+	–/–	+/+	–/–	–/–	–/–	+/–	–/–

Abbreviations: AD, Alzheimer disease; ADC, Alzheimer's Disease Centers cohort; ADNI, Alzheimer's Disease Neuroimaging Initiative cohort; APOE, apolipoprotein E; CAMP, Collaborative Aging and Memory Project cohort; CI, confidence interval; FHS, Framingham Heart Study cohort; JHU, Johns Hopkins University cohort; MA, minor allele; MAF, weighted-average minor allele frequency; MIRAGE, Multi-Institutional Research on Alzheimer's Genetic Epidemiology cohort; NIA-LOAD, National Institute on Aging Late-Onset Alzheimer's Disease cohort; OHSU, Oregon Health and Science University cohort; OR, odds ratio; SNP, single-nucleotide polymorphism; TGEN, Translational Genomics Research Institute cohort; UM/VU/MSSM, University of Miami/Vanderbilt University/Mount Sinai School of Medicine cohort; ?, no data; +, positive; –, negative.

[a] *P* values and ORs estimated under an additive model using logistic regression without covariates (unadjusted) and with covariates (adjusted for age, sex, and *APOE*) in a meta-analysis of 9 white cohorts composed of 5935 cases and 7034 cognitively normal controls. Generalized linear models were used to estimate case-control data, and generalized estimating equations were used to estimate family-based data.

RESULTS

To analyze the role of *CR1*, *CLU*, and *PICALM* in AD risk, the ADGC performed a meta-analysis using phenotypes and GWAS data from 12 different cohorts (Table 1). The ADGC is a collaborative network in the United States that includes the 29 NIA-funded ADCs and numerous AD genetics investigators who are working to identify genes responsible for AD. Of 7070 cases with AD examined, 3055 had autopsy documentation of AD. Of the 8169 cognitively normal elderly subjects (>60 years) examined, 1155 had autopsies documenting absence of significant AD neuropathology. The cohorts used included unrelated white cases and controls from the following sources: the NIA-funded ADCs, ADNI,[8,32] University of Miami/Vanderbilt University/Mount Sinai School of Medicine[17-19] (A.C.N, G.W.B, and E.R.M, unpublished data, November 2009), Translational Genomics Research Institute,[16] and Oregon Health and Science University.[33] White cases and controls from the following family-based studies were also included: the MIRAGE

Table 4. *APOE* Genotype and Allele Frequencies and ORs for Association of *APOE* ε4 Allele With AD

Cohort and Subject Status	Sample Size	*APOE* ε4 Positive, %	*APOE* Genotype Frequency (No./Total No.)					
			2/2	2/3	2/4	3/3	3/4	4/4
White subjects								
ADC								
Cases	1582	68.0	0.00	0.03	0.02	0.29	0.49	0.16
Controls	540	28.2	0.01	0.14	0.01	0.57	0.27	0.01
ADNI								
Cases	286	67.7	0.00	0.02	0.03	0.3	0.47	0.18
Controls	195	26.7	0.01	0.11	0.02	0.62	0.23	0.02
CAMP								
Cases	123	36.6	0.00	0.1	0.02	0.54	0.27	0.08
Controls	102	31.7	0.00	0.11	0.02	0.58	0.28	0.02
FHS								
Cases	183	35.5	0.02	0.07	0.03	0.56	0.3	0.03
Controls	2284	20.8	0.00	0.13	0.02	0.66	0.17	0.02
UM/VU/MSSM								
Cases	1162	59.4	0.00	0.04	0.02	0.37	0.43	0.15
Controls	1137	23.2	0.01	0.12	0.02	0.64	0.2	0.02
MIRAGE								
Cases	559	58.1	0.00	0.04	0.03	0.37	0.41	0.14
Controls	788	39.5	0.00	0.08	0.02	0.52	0.31	0.07
NIA-LOAD								
Cases	985	75.6	0.00	0.02	0.02	0.22	0.55	0.19
Controls	881	25.5	0.01	0.14	0.03	0.59	0.21	0.01
OHSU								
Cases	186	40.3	0.00	0.09	0.05	0.51	0.32	0.03
Controls	421	21.2	0.00	0.17	0.02	0.62	0.18	0.01
TGEN								
Cases	819	61.5	0.00	0.03	0.04	0.35	0.43	0.15
Controls	517	21.5	0.03	0.12	0.02	0.63	0.19	0.01
African American subjects								
ADC								
Cases	61	70.5	0.00	0.07	0.02	0.23	0.54	0.15
Controls	60	34.4	0.02	0.13	0.1	0.5	0.23	0.02
JHU								
Cases		ND	ND	ND	ND	ND	ND	ND
Controls		ND	ND	ND	ND	ND	ND	ND
MIRAGE								
Cases	180	69.4	0.00	0.03	0.03	0.28	0.49	0.17
Controls	199	48.2	0.00	0.08	0.04	0.44	0.39	0.06
Arab subjects								
Wadi Ara cohort								
Cases	73	6.8	0.00	0.00	0.00	0.93	0.07	0
Controls	80	2.5	0.00	0.00	0.00	0.98	0.03	0
Caribbean Hispanic subjects								
Columbia University cohort								
Cases	549	40.4	0.01	0.07	0.03	0.52	0.31	0
Controls	544	23.9	0.01	0.12	0.02	0.64	0.20	0

(continued)

Study,[15] Framingham Heart Study,[13,14,34] NIA-LOAD Family Study, and Collaborative Aging and Memory Project.[9,10] Populations not of white descent included African American subjects from several ADCs, a community-based (Detroit, Michigan) study of AD, and the MIRAGE Study[15]; Caribbean Hispanic individuals from Manhattan, New York, the Dominican Republic, and Puerto Rico; and members of a genetically isolated Arab community in Wadi Ara, Israel.[21-24]

In each data set, we evaluated the association of AD with SNPs in or near *CR1*, *CLU*, and *PICALM* that were genotyped on various platforms or imputed (Table 2). Results were combined across data sets using a meta-analysis approach (Table 3). We analyzed each racial/ethnic group separately. In white individuals, the largest group (5935 cases, 7034 controls), we found significant evidence of association with multiple SNPs at each locus. In the unadjusted analyses, we obtained an OR of 0.91 with a 95% confidence interval (CI) of 0.85 to 0.96 for *CLU* SNP rs11136000, which is comparable with the effect size reported previously for the same SNP (ORs, 0.86[7] and 0.91[6]). For the *CR1* SNP rs3818361, we obtained an OR of 1.14 (95% CI, 1.07-1.22) compared with the previous report of 1.19.[7] *PICALM* SNP rs3851179 had an OR of 0.89 (95% CI, 0.84-0.94) compared with 0.86 observed previously.[6] None of the SNPs were significantly associated with AD in any of the other ethnic groups analyzed together or separately, possibly because of small sizes of these groups (1135 cases and 1135 controls, eTable 1).

We also examined the influence of *APOE* on the associations of the 3 genes with AD, since *APOE* is a known

Table 4. *APOE* Genotype and Allele Frequencies and ORs for Association of *APOE* ε4 Allele With AD (continued)

Cohort and Subject Status	*APOE* Allele Frequency			Association of *APOE* ε4 With AD[a]	
	2	3	4	OR (95% CI)	*P* Value
White subjects					
ADC					
Cases	0.03	0.55	0.42	5.22 (4.21-6.46)	9.3×10^{-52}
Controls	0.08	0.77	0.15		
ADNI					
Cases	0.02	0.55	0.43	4.50 (3.17-6.40)	5.1×10^{-17}
Controls	0.07	0.79	0.14		
CAMP					
Cases	0.06	0.72	0.22	1.20 (0.70-2.07)	5.1×10^{-1}
Controls	0.06	0.77	0.17		
FHS					
Cases	0.07	0.74	0.19	2.10 (1.52-2.89)	5.4×10^{-6}
Controls	0.08	0.81	0.12		
UM/VU/MSSM					
Cases	0.03	0.60	0.37	4.45 (3.78-5.24)	4.7×10^{-71}
Controls	0.08	0.80	0.12		
MIRAGE					
Cases	0.04	0.60	0.36	1.80 (1.56-2.07)	1.2×10^{-15}
Controls	0.05	0.72	0.23		
NIA-LOAD					
Cases	0.02	0.51	0.47	9.05 (7.34-11.17)	6.1×10^{-94}
Controls	0.09	0.77	0.14		
OHSU					
Cases	0.07	0.72	0.22	2.30 (1.62-3.24)	2.4×10^{-6}
Controls	0.09	0.80	0.11		
TGEN					
Cases	0.04	0.58	0.38	4.75 (3.78-5.96)	6.9×10^{-41}
Controls	0.10	0.79	0.11		
African American subjects					
ADC					
Cases	0.04	0.53	0.43	3.92 (2.00-7.67)	6.7×10^{-5}
Controls	0.13	0.68	0.18		
JHU					
Cases	ND	ND	ND	ND	ND
Controls	ND	ND	ND		
MIRAGE					
Cases	0.03	0.54	0.43	2.17 (1.65-2.85)	2.4×10^{-8}
Controls	0.06	0.67	0.27		
Arab subjects					
Wadi Ara cohort					
Cases	0.00	0.97	0.03	2.87 (0.54-15.26)	.217
Controls	0.00	0.99	0.01		
Caribbean Hispanic subjects					
Columbia University cohort					
Cases	0.06	0.71	0.23	2.16 (1.67-2.81)	4.9×10^{-9}
Controls	0.08	0.80	0.13		

Abbreviations: AD, Alzheimer disease; ADC, Alzheimer's Disease Centers cohort; ADNI, Alzheimer's Disease Neuroimaging Initiative cohort; APOE, apolipoprotein E; CAMP, Collaborative Aging and Memory Project cohort; CI, confidence interval; FHS, Framingham Heart Study cohort; JHU, Johns Hopkins University cohort; MIRAGE, Multi-Institutional Research on Alzheimer's Genetic Epidemiology cohort; ND, not determined; NIA-LOAD, National Institute on Aging Late-Onset Alzheimer's Disease cohort; OHSU, Oregon Health and Science University cohort; OR, odds ratio; TGEN, Translational Genomics Research Institute cohort; UM/VU/MSSM, University of Miami/Vanderbilt University/Mount Sinai School of Medicine cohort.

[a] Odds ratio for association of *APOE* ε4 with AD under an additive model, evaluated using logistic regression in the case-control cohorts and generalized estimating equations in the family cohorts.

AD susceptibility locus in most ethnic groups[5,35] and several *APOE* genotypes have been reported to modify disease expression in persons with rare mutations in presenilin 1 (*PSEN1*),[36] presenilin 2 (*PSEN2*),[37] and the amyloid precursor protein (*APP*)[37,38] genes. For the 13 cohorts where *APOE* genotype data were available, presence of 1 or more *APOE* ε4 alleles was significantly associated with AD (ORs, 1.80-9.05) in all groups except the Amish and Israeli-Arab individuals (**Table 4**). We next reevaluated the association of AD with the *CR1, CLU*, and *PICALM* SNPs in the white cohorts adjusting for age, sex, and the presence of at least 1 *APOE* ε4 allele and found greatly reduced evidence for association with *PICALM* after adjustment (Table 3 and eTable 2), an effect that is attributable primarily to *APOE* (eTable 2). To explore this effect further, we analyzed the association of *CR1*, *CLU*, and *PICALM* SNPs with AD in subgroups stratified by the presence or absence of the *APOE* ε4 allele. This analysis revealed that the association with *CLU* was evident only among subjects without the *APOE* ε4 allele, whereas the association with *PICALM* was evi-

Table 5. Association of AD With *CR1*, *CLU*, and *PICALM* SNPs Stratified by *APOE* ε4 Carrier Status and Testing Statistical Interaction With *APOE* ε4 Carrier Status in White Cohorts

	Absence of *APOE* ε4[a]		Presences of *APOE* ε4[a]		SNP × *APOE* Interaction[b]	
Gene/SNP	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CR1						
rs3818361	1.10 (1.02-1.19)	.0170	1.14 (1.03-1.26)	.0120	1.01 (0.99-1.03)	.2800
rs6701713	1.10 (1.01-1.19)	.0210	1.14 (1.03-1.26)	.0110	1.01 (0.99-1.04)	.2800
rs1408077	1.06 (1.00-1.12)	.0360	1.15 (1.03-1.27)	.0099	1.06 (0.97-1.16)	.1900
CLU						
rs7012010	1.10 (1.00-1.20)	.0430	1.05 (1.00-1.10)	.0640	1.03 (0.94-1.12)	.5100
rs3087554	1.01 (0.90-1.14)	.8800	1.00 (0.84-1.18)	.9700	1.00 (0.82-1.22)	>.9999
rs11136000	0.91 (0.84-0.98)	.0150	0.93 (0.84-1.03)	.1700	0.98 (0.92-1.06)	.6500
rs9331888	1.03 (0.93-1.14)	.5300	0.92 (0.80-1.05)	.1900	0.89 (0.77-1.04)	.1400
rs7982	0.87 (0.79-0.97)	.0092	0.92 (0.81-1.05)	.2200	1.06 (0.91-1.24)	.4800
PICALM						
rs532470	0.99 (0.92-1.08)	.8900	1.12 (1.01-1.24)	.0300	1.11 (0.98-1.25)	.1000
rs592297	1.04 (0.97-1.11)	.3200	0.90 (0.79-1.03)	.1200	0.85 (0.73-1.00)	.0480
rs677909	0.99 (0.91-1.08)	.8000	0.86 (0.77-0.96)	.0062	0.86 (0.75-0.98)	.0260
rs636848	0.96 (0.88-1.06)	.4400	1.07 (0.95-1.21)	.2700	1.07 (0.92-1.23)	.3900
rs541458	0.99 (0.91-1.08)	.8100	0.86 (0.77-0.96)	.0066	0.86 (0.75-0.98)	.0270
rs561655	0.97 (0.89-1.06)	.5000	0.83 (0.75-0.93)	.0009	0.82 (0.73-0.93)	.0024
rs543293	1.00 (0.92-1.09)	.9800	0.83 (0.74-0.93)	.0011	0.81 (0.71-0.93)	.0026
rs7941541	0.98 (0.90-1.08)	.7300	0.90 (0.79-1.02)	.0990	0.89 (0.79-0.99)	.0360
rs3851179	0.99 (0.91-1.07)	.7300	0.86 (0.77-0.95)	.0034	0.84 (0.74-0.95)	.0068

Abbreviations: AD, Alzheimer disease; APOE, apolipoprotein E; CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

[a] Meta-analysis *P* values and ORs estimated under an additive model using logistic regression without covariates among subjects with no *APOE* ε4 alleles and among individuals with at least 1 *APOE* ε4 allele.

[b] Meta-analysis *P* values and ORs for the interaction term (SNP × *APOE* interaction) were evaluated using logistic regression under an additive model including terms for the 2 main effects (SNP minor allele dosage and the presence of at least 1 *APOE* ε4 allele) and their interaction.

dent only among subjects with the *APOE* ε4 allele (**Table 5**). Analysis of models containing terms for the main effects of each SNP and the presence or absence of the *APOE* ε4 allele and an interaction term showed significant evidence of interaction for the presence or absence of the *APOE* ε4 allele and 7 of the 9 *PICALM* SNPs, with indications of a synergistic effect of these 2 genes on AD risk (Table 5 and eTable 3). Interactions of *CR1* and *CLU* SNPs with the presence or absence of the *APOE* ε4 allele were not statistically significant.

COMMENT

Using a large multicenter data set of AD cases and controls, we confirm that *CR1*, *CLU*, and *PICALM* are AD susceptibility loci in European ancestry populations. The ORs we get for each are similar to those obtained in the original discovery cohort, suggesting that these estimates of risk are quite accurate for the white AD population, reflecting in part the large size of the cohorts used.[6,7] Clearly, a large data set is required to replicate these small-effect loci. We were unable to replicate the association of these 3 genes in the African-American, Arab, and Hispanic populations. However, further analysis is merited in these racial/ethnic groups using larger cohorts.

While this article was being prepared for publication, a GWAS on AD was reported by Seshadri et al.[39] There was some overlap in that study and ours in that the Translational Genomics Research Institute and Framingham Heart Study cohorts are used in both studies. However, whereas Seshadri et al used only prospectively diagnosed AD cases (n=52) and unrelated controls (n=2091) from the Framingham Heart Study, we included these subjects as well as prevalent and newly diagnosed cases and related controls, yielding a total sample of 197 AD cases and 2392 controls. Both studies independently confirm that *CLU* and *PICALM* are AD susceptibility genes. A primary difference between the 2 studies is that herein we confirm *CR1* as an AD locus while Seshadri et al[39] obtained only nominal support for *CR1*.

The cohorts used herein have several features worth mentioning in the context of GWAS for AD. First, the cohorts have a large number of autopsies in the cases (n=3055). Because the gold standard for diagnosis is neuropathologic confirmation of AD pathology, using autopsied cases reduces etiologic heterogeneity. Second, the controls used herein were elderly, of comparable age to case onset ages, and cognitively normal. Since these subjects lived to a comparable age to cases without developing AD, the case-control contrast should be more robust than if young controls were used. In addition, cases and controls will be comparably censored at other non-AD loci responsible for common diseases of elderly individuals that are unrelated to AD. Third, the cohorts used herein were not involved in the initial discovery of *CLU*, *CR1*, and *PICALM* and thus represent a completely independent replication data set. This is critical in terms of evaluating evidence that these genes are truly AD risk loci. The ideal controls for an AD GWAS would be subjects who were cognitively normal at death, had autopsy documentation that plaque load and tangle distribution did not reach criteria for AD pathology, and were elderly. In autopsy se-

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(continued)

ries of older cognitively normal subjects, most have some neurofibrillary tangles and some nonneuritic, and possibly spare neuritic, amyloid deposits but do not reach the accepted threshold for AD, although about a third of these normal subjects do meet neuropathologic criteria for AD.[40-43] In autopsy series of subjects with mild cognitive impairment, up to two-thirds of subjects have AD-level neuropathology.[44] These findings give rise to the hypothesis that amyloid deposition and tangle formation begin before cognitive decline becomes detectable, an idea strengthened by recent biomarker and amyloid imaging work.[45] Thus, in persons without dementia, a fraction, mostly those with mild cognitive impairment, will develop AD within a few years and this conversion rate increases with the age of the population, decreasing the contrast between cases and controls and reducing power. To minimize the potential confounding effect of mild cognitive impairment, we excluded them from these analyses and emphasized 1155 controls with autopsy information (Table 1).

When we examined the interaction of the *CR1, CLU,* and *PICALM* and *APOE* genotypes, we detected synergy between *APOE* and *PICALM* but not with *CR1* or *CLU*. Our results show that the *PICALM* association is predominantly in subjects carrying the *APOE* ε4 allele. Consistent with conclusions from previous studies showing interaction of *APOE* with *PSEN1*,[36] *PSEN2*,[37] and *APP*,[37,38] our results suggest that the *APOE* and *PICALM* gene products participate in a common pathogenic pathway leading to AD. Since *PSEN1*, *PSEN2*, and *APP* are all involved in β-amyloid production, *PICALM* may also participate in this process, though a more indirect involvement cannot be ruled out and the biology of these interactions remains to be determined. We did not detect an interaction of *APOE* with *CR1* or *CLU*, though this could be because of sample size, which was not large enough to detect very weak interactions. Also, since the *APOE* effect on AD risk is much stronger in young case populations,[35] the age structure of our study

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and of others may not be optimal for detecting these interactions.

Our study and those from other consortia[6,7] (E. M. Wijsman, PhD, Y. Choi, MS, J. H. Rothstein, MS, et al, unpublished data, June 2010) show that AD susceptibility loci can be identified by GWAS. Initial AD GWAS had samples sizes that, in comparison with those from the large consortia, were modest and inadequately powered to detect the small effect loci replicated herein.[18,46-51] As sample sizes increase, as in other complex disorders, we expect additional loci to be identified.

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Online-Only Material: The eAppendix and eTables are available at http://www.archneurol.com.

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