Published in final edited form as:
Arch Neurol. 2010 December ; 67(12): 1473–1484. doi:10.1001/archneurol.2010.201.

Meta-Analysis confirms *CR1*, *CLU*, and *PICALM* as Alzheimer's disease risk loci and reveals interactions with *APOE* genotypes

Dr. Gyungah Jun, PhD, **Dr. Adam C. Naj, PhD**, **Dr. Gary W. Beecham, PhD**, **Dr. Li-San Wang, PhD**, **Ms. Jacqueline Buros, BS**, **Mr. Paul J. Gallins, MS**, **Dr. Joseph D. Buxbaum, PhD**, **Dr. Nilufer Ertekin-Taner, MD, PhD**, **Dr. M. Daniele Fallin, PhD**, **Dr. Robert Friedland, MD**, **Dr. Rivka Inzelberg, MD**, **Dr. Patricia Kramer, PhD**, **Dr. Ekaterina Rogaeva, PhD**, **Dr. Peter St George-Hyslop, MD, FRCP**, **ADGC**, **Ms. Laura B. Cantwell, MPH**, **Dr. Beth A. Dombroski, PhD**, **Dr. Andrew J. Saykin, PsyD***, **Dr. Eric M. Reiman, MD**, **Dr. David A. Bennett, MD**, **Dr. John C. Morris, MD**, **Dr. Kathryn L. Lunetta, PhD**, **Dr. Eden R. Martin, PhD**, **Dr. Thomas J. Montine, MD, PhD**, **Dr. Alison M. Goate, DPhil**, **Dr. Deborah Blacker, MD**, **Dr. Debby W. Tsuang, MD**, **Mr. Duane Beekly, BS**, **Dr. L. Adrienne Cupples, PhD**, **Dr. Hakon Hakonarson, MD, PhD**, **Dr. Walter Kukull, PhD**, **Dr. Tatiana M. Foroud, PhD**, **Dr. Jonathan Haines, PhD**, **Dr. Richard Mayeux, MD**, **Dr. Lindsay A. Farrer, PhD**, **Dr. Margaret A. Pericak-Vance, PhD**, and **Dr. Gerard D. Schellenberg, PhD**

Abstract

Objectives—To determine whether genotypes at *CLU*, *PICALM*, and *CR1* confer risk for Alzheimer's disease (AD) and whether risk for AD associated with these genes is influenced by *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—7,070 AD cases, 3,055 with autopsies, and 8,169 elderly cognitively normal controls, 1,092 with autopsies from 12 different studies, including Caucasians, African Americans, Israeli-Arabs, and Caribbean Hispanics.

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, CI = 1.07 – 1.22, SNP rs3818361), and *PICALM* (OR = 0.89, CI = 0.84 – 0.94, SNP rs3851179) were associated with AD in Caucasians. None were significantly associated with AD in the other ethnic groups. *APOE* ε4 was significantly associated with AD (ORs from 1.80 to 9.05) in all but one small Caucasian cohort and in the Arab cohort. Adjusting for age, sex, and the presence of at least one *APOE* ε4 allele greatly reduced evidence for association with *PICALM* but not *CR1* or *CLU*. Models with the main SNP effect, *APOE* ε4 (+/−), and an interaction term showed significant interaction between *APOE* ε4 (+/−) and *PICALM*.

Conclusions—We confirm in a completely independent dataset that *CR1*, *CLU*, and *PICALM* are AD susceptibility loci in European ancestry populations. Genotypes at PICALM confer risk predominantly in APOE ε4-positive subject. Thus, APOE and PICALM synergistically interact.

Corresponding author: Gerard D. Schellenberg, Ph.D., Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Room 609B Stellar-Chance Laboratories, 422 Curie Boulevard, Philadelphia, PA 19104-6100, Phone; (215) 746-4580, FAX; (215) 898-9969, gerardsc@mail.med.upenn.edu.

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. ADNI investigators include (complete listing available at http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Manuscript_Citations.pdf.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting 5% of the population over 65 years and 30–50% over 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 on 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, two 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 three loci reached genome wide significance in samples consisting of 5,964 cases and 10,188 controls (*PICALM* and *CLU*) and 5,887 cases and 8,508 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 GWAS data for 15,239 subjects from 9 Northern European Whites cohorts and 5 cohorts that included African Americans, Israeli Arabs, and Caribbean Hispanics (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 (age > 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 supplementary material provide online. 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 data collection is coordinated by the National Alzheimer's Coordinating Center (NACC). DNA from these samples for genotyping was prepared by the National Cell Repository for Alzheimer's Disease (NCRAD). The **Alzheimer's Disease Neuroimaging Initiative (ADNI)** subjects are AD cases and controls ascertained for neuroimaging, biomarker, and genetic studies. Data used here were generates as previously described[8] and obtained from the ADNI database (www.loni.ucla.edu/ADNI). The **Collaborative Aging and Memory Project (CAMP)** subjects are from the Amish communities of central Ohio and northern Indiana[9–10]. The **Columbia University (CU)** subjects are a Hispanic cohort described in detail elsewhere[11]. The **Framingham Heart Study (FHS)** is a single-site, community-based, ongoing cohort study described elsewhere[12–14]. Phenotype and genome-wide association study (GWAS) data were from dbGaP website (http://www.ncbi.nlm.nih.gov/gap). The **Johns Hopkins University (JHU) 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 **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-LOAD Family Study**[16] cohort are families with two or more affected siblings with LOAD and unrelated, non-demented control subjects similar in age and ethnic background. One case per family was selected and controls were deteremined to be cognitively normal after an in-person neurological examination and were not related to a study participant. The

Oregon Health and Science University (OHSU) were recruited from aging research cohorts at 10 NIA-funded ADCs and do not overlap with other ADGC samples. The **TGEN** dataset is a publicly available sample of AD cases and controls (http://www.tgen.org/research/index.cfm?pageid=1065[17]. The **University of Miami/ Vanderbilt University/Mt. Sinai School of Medicine (UM/VU/MSSM)** were new and previously published[18–22] subjects ascertained at the University of Miami, Vanderbilt University and Mt. Sinai School of Medicine. The **Wadi Ara** dataset are from an inbred Arab community in northern Israel[23–26].

GENOTYPING

The cohorts used were genotyped either on Illumina or Affymetrix SNP arrays (Table 2). We selected 17 SNPs from *CR1*, *CLU*, and *PICALM* that were recently reported to be significantly associated with AD in two large GWA studies[6–7] (Table 3). Additional genotypes were obtained using an Applied Biosystems' (ABI) TaqMan Assays including genotypes for rs7982. Genotyping for the *APOE* ε2/ε3/ε4 alleles was performed as described in the supplementary material provided online.

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 of 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 of last exam or death. (see also supplementary material provided online).

Imputation procedure—We imputed genotypes for all SNPs within 10Kb of the three genes using the Markov Chain haplotyping (MaCH) software[27] to obtain a common set of SNPs across all datasets. We imputed SNPs from both HapMap releases II and III and retained those with pairwise linkage disequilibrium (LD; $r^2 > 0.50$) for further analysis (see also the supplementary material online for more detail and for data cleaning protocols).

Population Substructure—To determine if population substructure existed in the different datasets, we used 30,000 – 100,000 SNPs with minor allele frequency (MAF) > 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[28–29]. To account for population substructure in association analyses, EIGENSTRAT[30] was used on each cohort to generate loadings from principal components analysis on the sampled SNPs sampled (see also supplementary material online).

Statistical Analysis—Genotyped and imputed SNPs were tested for association with AD using a logistic generalized linear model (GLM) in case-control datasets and a logistic generalized estimating equation (GEE) in family-based datasets. 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 were 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, gender 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[31]. Heterogeneity among odds ratios was assessed using Cochran's *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 is distributed as a χ^2 with k (number of studies) minus 1 degrees of freedom. The I^2 statistic[32–33] describes the percentage of variation across studies that is due to heterogeneity rather than chance and is calculated as follows: $I^2 = 100\% \times (Q - \mathrm{df})/Q$. I^2 is an intuitive and simple expression of the inconsistency of studies' results. Unlike Q it does not inherently depend upon the number of studies considered. SNP association results obtained from individual datasets 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 datasets 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.

RESULTS

To analyze the role 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 7,070 AD cases examined, 3,055 of had autopsy documentation of AD. Of the 8,169 cognitively normal elderly subjects (age >60) examined, 1,155 had autopsies documenting absence of significant AD neuropathology. The cohorts used included unrelated Caucasian cases and controls from the following sources: the NIA-funded ADCs, ADNI[8, 34], UM/VU/MSSM[18–21], TGEN[17], and OHSU[35]. Caucasian cases and controls from the following family-based studies were also included: the MIRAGE Study[15], FHS[13–14, 36], NIA-LOAD, and CAMP[9–10]. Populations not of Caucasian descent included African American subjects from several ADCs, a community-based (Detroit) study of AD, and the MIRAGE study[15]; Caribbean Hispanics from Manhattan, the Dominican Republic, and Puerto Rico; and members of a genetically isolated Arab community in Wadi Ara, Israel[23–26].

In each dataset, we evaluated 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 datasets using a meta-analysis approach (Table 3). We analyzed each racial/ethnic group separately. In Caucasians, the largest group (n = 5,935 cases, 7,034 controls), we found significant evidence of association with multiple SNPs at each locus. In the unadjusted analyses, we obtained an odds ratio (OR) of 0.91 with a 95% confidence interval (CI) of (0.85 – 0.96) for *CLU* SNP rs11136000, which is comparable to 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 (CI = 1.07 – 1.22) compared to the previous report of 1.19[7]. *PICALM* SNP rs3851179 had an OR of 0.89 (CI = 0.84 – 0.94) compared to 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 due to small sizes of these groups (1,135 cases and 1,135 controls, Supplementary eTable 1).

We also examined the influence of *APOE* on the associations of the three genes with AD, since *APOE* is a known AD susceptibility locus in most ethnic groups[5, 37] and several *APOE* genotypes have been reported to modify disease expression in persons with rare mutations in presenilin 1 (*PSEN1)*[38], presenilin 2 (*PSEN2)*[39], and the amyloid precursor protein (*APP)*[39–40] genes. For the 13 cohorts where *APOE* genotype data were available, presence of one or more *APOE* ε4 alleles was significantly associated with AD (ORs ranging from 1.80 to 9.05) in all groups except the Amish and Israeli-Arabs (Table 4). We next re-evaluated the association of AD with the *CR1*, *CLU* and *PICALM* SNPs in the Caucasian cohorts adjusting for age, sex, and the presence of at least one *APOE* ε4 allele and

found greatly reduced evidence for association with *PICALM* after adjustment (Table 3, Supplementary 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* is evident only among ε4 (−) subjects, whereas the association with *PICALM* is evident only among ε4 (+) subjects (Table 5). Analysis of models containing terms for the main effects of each SNP and *APOE* ε4 (+/−), and an interaction term showed significant evidence of interaction for *APOE* ε4 (+/−) and seven of the nine *PICALM* SNPs with indications of a synergistic effect of these two genes on AD risk (Table 5 and Supplementary eTable 3). Interactions of *CR1* and *CLU* SNPs with *APOE* ε4 (+/−) were not statistically significant.

COMMENTS

Using a large multi-center dataset 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 is similar to those obtained in the original discovery cohort, suggesting that these estimates of risk are quite accurate for the Caucasian AD population, reflecting in part the large size of the cohorts used[6–7]. Clearly a large dataset 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 manuscript was being prepared for publication, a GWAS on AD was reported by Seshadri *et al*.[41]. There was some overlap in that study and ours in that the TGEN and Framingham cohorts are used in both studies. However, whereas Seshadri *et al.* used only prospectively diagnosed AD cases (n=52) and unrelated controls (n=2,091) from the Framingham 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 2,392 controls. Both studies independently confirm that *CLU* and *PICALM* are AD susceptibility genes. A primary difference between the 2 studies is that here we confirm *CR1* as an AD locus while Seshadri *et al.*[41] obtained only nominal support for *CR1*.

The cohorts used here have several features worth mentioning in the context of GWAS for AD. First, the cohorts have a large number of autopsies in the cases (3,055). Because the gold standard for diagnosis is neuropathologic confirmation of AD pathology, using autopsied cases reduces etiologic heterogeneity. Second, the controls used here were elderly, of comparable age to case onset ages, and were 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 are used. In addition, cases and controls will be comparably censored at other non-AD loci responsible for common diseases of the elderly that are unrelated to AD. Third, the cohorts used here were not involved in the initial discovery of *CLU*, *CR1* and *PICALM* and thus represent a completely independent replication dataset. 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 who were elderly. In autopsy series of older cognitively normal subjects, most have some NFTs and some non-neuritic, 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[42–45]. In autopsy series of MCI subjects, up to two thirds of subjects have AD-level neuropathology[46]. 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[47]. Thus in persons without dementia, a fraction, mostly those with MCI, 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 MCI, we excluded them from these analyses and emphasized 1,155 controls with autopsy information (Table 1).

When we examined the interaction *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*[38], *PSEN2*[39], and *APP*[39–40], 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 Aβ 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 detemined. We did not detect an interaction of *APOE* with CR1 or CLU, though this could be due to 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[37], the age structure of our study and of others may not be optimal for detecting these interactions.

Our study and those from other consortia[6,7,56] show that AD susceptibility loci can be identified by GWAS. Initial AD GWAS had samples sizes that, in comparison to those from the large consortia, were modest and inadequately powered to detect the small effect loci replicated here[19, 48–53]. As sample sizes increase, as in other complex disorders, we expect additional loci to be identified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Alzheimer's Disease Genetics Consortium is funded by the U.S. National Institutes of Health, National Institute on Aging (NIH-NIA) grants U01-AG032984 and RC2-AG036528 and a grant from a private foundation wishing to remain anonymous. The NIH-NIA also provides financial support to NACC (U01-AG016976), NCRAD (U24-AG021886), and the Alzheimer's Disease Centers: Banner Alzheimer's Institute (P30 AG019610), Boston University (P30 AG013846, R01 HG02213, K24 AG027841, U01 AG10483, R01 CA129769, R01 MH080295), Columbia University (P50 AG008702), Duke University (P30 AG028377), Emory University (AG025688), Indiana University (P30 AG10133), Johns Hopkins University (P50 AG005146), Massachusetts General Hospital (P50 AG005134), Mayo Clinic (P50 AG016574), Mount Sinai School of Medicine (P50 AG005138), New York University (P30 AG08051, UO1 AG16976, MO1 RR00096, and UL1 RR029893), Northwestern University (P30 AG013854), Oregon Health & Science University (P30 AG008017), Rush University (P30 AG010161), University of Alabama at Birmingham (P50 AG016582, UL1 RR02777 through the UAB Center for Clinical and Translational Science), University of California, Davis (P30 AG010129), University of California, Irvine (P50 AG016573, P50 AG016574, P50 AG016575, P50 AG016576, P50 AG016577), University of California, Los Angeles (P50 AG016570), University of California, San Diego (P50 AG005131), University of California, San Francisco (P50 AG023501, P01 AG019724), University of Kentucky (P30 AG028383), University of Michigan (P50 AG008671), University of Pennsylvania (P30 AG010124), University of Pittsburgh (P50 AG005133), University of Southern California (P50 AG005142), University of Texas Southwestern (P30 AG012300), University of Washington (P50 AG005136), and the Washington University (P50 AG005681 and P01 AG03991). The work completed by Boston University is also supported by the Alzheimer's Association (IIRG-08-89720) and VA New England Geriatric Research Education and Clinical Center.

We thank Drs. Creighton Phelps, Ph.D., Marcelle Morrison-Bogorad, Ph.D., and Marilyn Miller Ph.D. from the National Institute on Aging for helping in acquiring samples and data and who are *ex-officio* members of the ADGC. Duke University would also like to acknowledge John Ervin from the Brain Bank and Kathleen Hayden in the Clinical Core for their respective efforts in the DNA/data pulls required. Dr. Rosenberg is Editor of Archives of Neurology and obtained an independent review and assessment of this paper from outside the editorial office prior to its acceptance.

This project was also made possible by the many contributions of individual study datasets, supported in part by NIH. These include NIA LOAD (NIH U24 AG026395), Columbia University study (NIH R37 AG015473), ADNI (U01 AG024904, RC2 AG036535), FHS (N01-HC-25195, R01-NS017950, R01-AG08122, R01-AG16495, R01-AG033193 and R01-AG031287), CAMP (R01 AG019085), JHU (R01 AG020688), MIRAGE (R01 AG009029), Wadi Ara (R01 AG017173), and the Multi-ethnic GWAS (Farrer - R01 AG025259). The UM/VU/MSS work was supported by grants from the NIA-NIH (AG010491, AG002219, AG005138, AG027944, AG021547, AG019757 and R01-AG-027944) and from the Alzheimer's Association (IIRG-05-14147). A subset of these participants was ascertained while Dr. Margaret A. Pericak-Vance was a faculty member at Duke University. The study by Oregon Health & Science University was supported by the National Institute on Aging (grants R01 AG026916, P30 AG028377, P50 AG005146, P30 AG028383, P50 AG16574, U01 AG06786, P30 AG008017, P30 AG10161, R01 AG17917, P30 AG10129, P50 AG05131, P50 AG08671, P50 AG05681, P01 AG03991, U01 AG016976) of the National Institutes of Health, and by the Natural Science Foundation of China NSFC, project number 30730057 and 30700442. TGEN is supported by NIH grant R01 AG031581, Kronos Life Sciences and the state of Arizona.

ADNI data collection and sharing for this project was funded by the National Institutes of Health Grant U01 AG024904 (PI Michael W. Weiner). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace, Inc., Merck and Co., Inc., Novartis AG, Pfizer Inc, F. Hoffman-La Roche, Schering-Plough, Synarc, Inc., and Wyeth, as well as non-profit partners the Alzheimer's Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (www.fnih.org <http://www.fnih.org/> <http://www.fnih.org > >). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles. This research was also supported by NIH grants P30 AG010129, K01 AG030514, and the Dana Foundation.

References

1. Goate A, Chartier-Harlin M-C, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 1991;349:704–706. [PubMed: 1671712]
2. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995;375:754–760. [PubMed: 7596406]
3. Rogaev EI, Sherrington R, Rogaeva EA, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature 1995;376:775–778. [PubMed: 7651536]
4. Levy-Lahad E, Wasco W, Poorkaj P, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 1995;269:973–977. [PubMed: 7638622]
5. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene Dose of Apolipoprotein-E Type-4 Allele and the Risk of Alzheimer's Disease in Late Onset Families. Science 1993;261:921–923. [PubMed: 8346443]
6. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 2009;41(10):1088–U1061. [PubMed: 19734902]
7. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet 2009;41(10):1094–U1068. [PubMed: 19734903]
8. Saykin A, Shen L, Foroud TM, Potkin SG, Swaminathan S, Kim S, Risacher SL, Nho K, Huentelman MJ, Craig DW, Thompson PM, Stein JL, Moore JH, Farrer LA, Green RC, Bertram L, Jack CR, Weiner MW. Alzheimer's Disease Neuroimaging Initiative ADNI biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans. Alzheimer's and Dementia 2010;6:265–273.
9. McCauley JL, Hahs DW, Jiang L, et al. Combinatorial Mismatch Scan (CMS) for loci associated with dementia in the Amish. BMC Med Genet 2006;7:19. [PubMed: 16515697]

10. Hahs DW, McCauley JL, Crunk AE, et al. A genome-wide linkage analysis of dementia in the Amish. American Journal of Medical Genetics Part B Neuropsychiatric Genetics 2006;141B(2): 160–166.
11. Lee JH, Barral S, Cheng R, et al. Age-at-onset linkage analysis in Caribbean Hispanics with familial late-onset Alzheimer's disease. Neurogenetics Feb 2008;9(1):51–60.
12. Dawber TR, Kannel WB. The Framingham study. An epidemiological approach to coronary heart disease. Circulation Oct;1966 34(4):553–555. [PubMed: 5921755]
13. Splansky GL, Corey D, Yang Q, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. Am J Epidemiol Jun 1;2007 165(11):1328–1335. [PubMed: 17372189]
14. Cobb JL, Wolf PA, Au R, White R, D'Agostino RB. The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study. Neurology Sep 1995;45(9):1707–1712.
15. Green RC, Cupples LA, Go R, et al. Risk of dementia among white and African American relatives of patients with Alzheimer disease. Jama - Journal of the American Medical Association January 16;2002 287(3):329–336.
16. Wijsman EMPN, Choi Y, Rothstein JH, Faber K, Cheng R, Lee JH, Bird T, Bennnett DA, Diaz-Arrastia R, Goate A, Farlow M, Sweet RA, Ghetti B, Foroud T, Mayeux R. for The NIA-LOAD/NCRAD Family Study Group. Genome wide association of familial late onset Alzheimer's disease replicates BIN1, and nominates CUGBP2 in interaction with APOE. 2010 submitted.
17. Coon KD, Myers AJ, Craig DW, et al. A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. J Clin Psychiatry 2007;68:613–618. [PubMed: 17474819]
18. Scott WK, Nance MA, Watts RL, et al. Complete genomic screen in Parkinson disease: evidence for multiple genes. JAMA 2001;286:2239–2244. [PubMed: 11710888]
19. Beecham GW, Martin ER, Li YJ, et al. Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. Am J Hum Genet Jan 2009;84(1):35–43.
20. Edwards C. Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease.pa. Annals of Human Genetics 2010:2010.
21. Naj. submitted. 2010
22. Haroutunian V, Perl DP, Purohit DP, et al. Regional distribution of neuritic plaques in the nondemented elderly and subjects with very mild Alzheimer disease. Archives of Neurology September;1998 55(9):1185–1191. [PubMed: 9740112]
23. Bowirrat A, Friedland RP, Chapman J, Korczyn AD. The very high prevalence of AD in an Arab population is not explained by APOE epsilon 4 allele frequency. Neurology 2000;55(5):731. [PubMed: 10980749]
24. Farrer LA, Bowirrat A, Friedland RP, Waraska K, Korczyn AD, Baldwin CT. Identification of multiple loci for Alzheimer disease in a consanguineous Israeli-Arab community. Hum Molec Genet 2003;12(4):415–422. [PubMed: 12566388]
25. Inzelberg R, Schechtman E, Abuful A, et al. Education effects on cognitive function in a healthy aged Arab population. Int Psychogeriatr Jun 2007;19(3):593–603.
26. IsraeliKorn SD, Masarwa M, Schechtman E, et al. Hypertension Increases the Probability of Alzheimer's Disease and of Mild Cognitive Impairment in an Arab Community in Northern Israel. Neuroepidemiology 34(2):99–105. [PubMed: 20016220]
27. Li M, Boehnke M, Abecasis GR. Efficient study designs for test of genetic association using sibship data and unrelated cases and controls. Am J Hum Genet 2006;78:778–792. [PubMed: 16642434]
28. Pritchard JK, Stephens M, Donnelly PJ. Inference of population structure using multilocus genotype data. Genetics 2000;155:945–959. [PubMed: 10835412]
29. Pritchard JK, Stephens M, Rosenberg NA, Donnelly P. Association mapping in structured populations. Am J Hum Genet 2000;67:170–181. [PubMed: 10827107]
30. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet 2006;38:904–909. [PubMed: 16862161]

31. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing V; Austria: 2009. URL http://www.R-project.org
32. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med Jun 15;2002 21(11):1539–1558. [PubMed: 12111919]
33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ Sep 6;2003 327(7414):557–560. [PubMed: 12958120]
34. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology Jan 19;2010 74(3):201–209. [PubMed: 20042704]
35. Kramer PL, Xu H, Woltjer RL, Westaway SK, Clark D, Erten-Lyons D, Kaye JA, Welsh-Bohmer KA, Troncoso JC, Markesbery WR, Petersen RC, Turner RS, Kukull WA, Bennett DA, Galasko D, Morris JC, Ott J. Alzheimer's disease pathology in cognitively healthy elderly: A genome-wide study. Neurobiology of Aging 2010:2010. (in press).
36. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. Prev Med Dec;1975 4(4):518–525. [PubMed: 1208363]
37. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: A meta-analysis. JAMA 1997;278:1349–1356. [PubMed: 9343467]
38. Pastor P, Roe CM, Villegas A, et al. Apolipoprotein E epsilon 4 modifies Alzheimer's disease onset in an E280A PS1 kindred. Ann Neurol 2003;54:163–169. [PubMed: 12891668]
39. Wijsman EM, Daw E, Yu X, et al. APOE and other loci affect age-at-onset in Alzheimer's disease families with PS2 mutation. Am J Med Genet Neuropsych Genet. (in press).
40. St George-Hyslop P, Crapper McLachlan D, Tuda T, et al. Alzheimer's disease and possible gene interaction. Science 1994;263:537. [PubMed: 8290965]
41. Seshadri S, Fitzpatrick AL, Ikram MA, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA May 12;2010 303(18):1832–1840. [PubMed: 20460622]
42. Price JL, McKeel DW, Buckles VD, et al. Neuropathology of nondemented aging: Presumptive evidence for preclinical Alzheimer disease. Neurobiol Aging 2009;30(7):1026–1036. [PubMed: 19376612]
43. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18(4):351–357. [PubMed: 9330961]
44. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology Jun 27;2006 66(12):1837–1844. [PubMed: 16801647]
45. Hulette CM, Welshbohmer KA, Murray MG, Saunders AM, Mash DC, Mcintyre LM. Neuropathological and neuropsychological changes in "normal" aging: Evidence for preclinical Alzheimer disease in cognitively normal individuals. J Neuropathol Exp Neurol 1998;57(12): 1168–1174. [PubMed: 9862640]
46. Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. Neurology 2005;64(5):834–841. [PubMed: 15753419]
47. Perrin RJ, Fagan AM, Holtzman DM. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. Nature 2009;461(7266):916–922. [PubMed: 19829371]
48. Reiman EM, Webster JA, Myers AJ, et al. GAB2 alleles modify Alzheimer's risk in APOE epsilon 4 carriers. Neuron 2007;54(5):713–720. [PubMed: 17553421]
49. Carrasquillo MM, Zou F, Pankratz VS, et al. Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. Nat Genet Feb 2009;41(2):192–198.
50. Poduslo SE, Huang R, Huang J, Smith S. Genome screen of late-onset Alzheimer's extended pedigrees identifies TRPC4AP by haplotype analysis. Am J Med Genet B Neuropsychiatr Genet Jan 5;2009 150B(1):50–55. [PubMed: 18449908]
51. Bertram L, Lange C, Mullin K, et al. Genome-wide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to APOE. Am J Hum Genet Nov 2008;83(5): 623–632.

52. Li H, Wetten S, Li L, et al. Candidate single-nucleotide polymorphisms from a genomewide association study of Alzheimer disease. Archives of Neurology 2008;65(1):45–53. [PubMed: 17998437]

53. Feulner TM, Laws SM, Friedrich P, et al. Examination of the current top candidate genes for AD in a genome-wide association study. Mol Psychiatry. Jan 6;2009

#: ADGC members

Steven E. Arnold, MD; Clinton T. Baldwin, PhD; Robert Barber, PhD; Thomas Beach, MD, PhD; Eileen H. Bigio, MD; Thomas D. Bird, MD; Adam Boxer, MD, PhD; James R. Burke, MD, PhD; Nigel Cairns, PhD FRCPath; Steven L. Carroll, MD, PhD; Helena C. Chui, MD; David G. Clark, MD; Carl W. Cotman, PhD; Jeffrey L. Cummings, MD; Charles DeCarli, MD; Ramon Diaz-Arrastia, MD, PhD; Malcolm Dick, PhD; Dennis W. Dickson, MD; William G. Ellis, MD; Kenneth B. Fallon, MD; Martin R. Farlow, MD; Steven Ferris, PhD; Matthew P. Frosch, MD, PhD; Douglas R. Galasko, MD; Marla Gearing, PhD; Daniel H. Geschwind, MD, PhD; Bernardino Ghetti, MD; Sid Gilman, MD FRCP; Bruno Giordani, PhD; Jonathan Glass, MD; Neill R. Graff-Radford, MD; Robert C. Green, MD; John H. Growdon, MD; Ronald L. Hamilton, MD; Lindy E. Harrell, MD, PhD; Elizabeth Head, PhD; Lawrence S. Honig, MD, PhD; Christine M. Hulette, MD; Bradley T. Hyman, MD, PhD; Gregory A. Jicha, MD, PhD; Lee-Way Jin, MD, PhD; Nancy Johnson, PhD; Jason Karlawish, MD; Anna Karydas, BA; Jeffrey A. Kaye, MD; Ronald Kim, MD; Edward H. Koo, MD; Neil W. Kowall, MD; James J. Lah, MD, PhD; Allan I. Levey, MD, PhD; Andrew Lieberman, MD, PhD; Oscar L. Lopez, MD; Wendy J. Mack, PhD; William Markesbery, MD; Daniel C. Marson, JD, PhD; Frank Martiniuk, PhD; Eliezer Masliah, MD; Ann C. McKee, MD; Marsel Mesulam, MD; Joshua W. Miller, PhD; Bruce L. Miller, MD; Carol A. Miller, MD; Joseph E. Parisi, MD; Daniel P. Perl, MD; Elaine Peskind, MD; Ronald C. Petersen, MD, PhD; Wayne Poon, PhD; Joseph F. Quinn, MD; Murray Raskind, MD; Barry Reisberg, MD; John M. Ringman, MD; Erik D. Roberson, MD, PhD; Roger N. Rosenberg, MD; Mary Sano, PhD; Julie A. Schneider, MD; Lon S. Schneider, MD; William Seeley, MD; Michael L. Shelanski, MD, PhD; Charles D. Smith, MD; Salvatore Spina, MD; Robert A. Stern, PhD; Rudolph E. Tanzi, PhD; John Q. Trojanowski, MD, PhD; Juan C. Troncoso, MD; Vivianna M. Van Deerlin, MD, PhD; Harry V. Vinters, MD; Jean Paul Vonsattel, MD; Sandra Weintraub, PhD; Kathleen A. Welsh-Bohmer, PhD; Randall L. Woltjer, MD, PhD; Steven G. Younkin, MD, PhD.

Author Affiliations

Departments of Medicine (Genetics Program) (Dr. Jun, Ms. Buros, and Drs. Farrer and Baldwin), Opthamology (Dr. Jun), Biostatistics (Drs. Jun, Lunetta and Cupples), Neurology (Drs. Farrer, Green, Kowall, McKee and Stern), Genetics & Genomics and Epidemiology (Drs. Farrer and Green), and Pathology (Drs. Kowall and McKee), Boston University, Massachusetts; The John P. Hussman Institute for Human Genomics (Drs. Naj and Beecham, Mr. Gallins, and Dr. Pericak-Vance), and Dr. John T. Macdonald Foundation Department of Human Genetics (Drs. Beecham, Martin and Pericak-Vance), University of Miami, Florida; Departments of Pathology and Laboratory Medicine (Dr. Wang, Ms. Cantwell, Drs. Dombroski, Schellenberg, Trojanowski, and Van Deerlin), Psychiatry (Dr. Arnold) and Medicine (Dr. Karlawish), University of Pennsylvania School of Medicine, Philadelphia; Departments of Psychiatry (Drs. Buxbaum, Perl and Sano), Neuroscience (Drs. Buxbaum and Perl), Genetics and Genomic Sciences (Dr. Buxbaum), and Pathology (Dr. Perl), Mount Sinai School of Medicine, New York, New York; Departments of Neuroscience (Drs. Ertekin-Taner and Dickson), Neurology (Drs. Ertekin-Taner and Graff-Radford), and Pharmacology (Dr. Younkin), Mayo Clinic Jacksonville, Florida; Departments of Epidemiology (Dr. Fallin) and Pathology (Dr. Troncoso), Johns Hopkins

University, Baltimore, Maryland; Department of Neurology, University of Louisville, Kentucky (Dr. Friedland); Sheba Medical Center, Departments of Neurology and Medicine, Tel Aviv University, Israel (Dr. Inzelberg); Departments of Neurology (Drs. Kramer, Kaye and Quinn), Molecular & Medical Genetics (Dr. Kramer), Biomedical Engineering (Dr. Kaye), and Pathology (Dr. Woltjer), Oregon Health & Science University, Portland, Oregon; Centre for Research in Neurodegenerative Diseases, Department of Medicine, University of Toronto, Ontario, Canada (Drs. Rogaeva and St George-Hyslop); Cambridge Institute for Medical Research, Department of Clinical Neurosciences, University of Cambridge, United Kingdom (Dr. St George-Hyslop); Departments of Radiology and Imaging Sciences (Dr. Saykin), Medical and Molecular Genetics (Drs. Saykin, Foroud), Neurology (Dr. Farlow), and Pathology and Laboratory Medicine (Drs. Ghetti and Spina), Indiana University, Indianapolis; Arizona Alzheimer's Consortium and Banner Alzheimer's Institute and Neurogenomics Division, Translational Genomics Research Institute and Department of Psychiatry, University of Arizona, University of Arizona, Phoenix (Dr. Reiman); Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, Arizona (Dr. Beach); Rush Alzheimer's Disease Center (Dr. Bennett) and Departments of Neurological Sciences (Drs. Bennett and Schneider) and Pathology (Dr. Schneider), Rush University Medical Center, Chicago, Illinois; Departments of Neurology (Dr. Morris), Pathology and Immunology (Drs. Morris and Cairns) and Psychiatry (Dr. Goate), Washington University, St. Louis, Missouri; Department of Pathology (Dr. Montine), Psychiatry and Behavioral Sciences (Drs. Tsuang, Peskind and Raskind), National Alzheimer's Coordinating Center (Mr. Beekly and Dr. Kukull), Departments of Epidemiology (Dr. Kukull), Neurology (Dr. Bird), University of Washington, Seattle; Departments of Psychiatry and Epidemiology (Dr. Blacker), C.S. Kubik Laboratory for Neuropathology (Dr. Frosch), Departments of Neurology (Drs. Growdon, Hyman, and Tanzi), Massachusetts General Hospital, Charlestown, Massachusetts; Center for Applied Genomics, Children's Hospital of Philadelphia, Pennsylvania (Dr. Hakonarson); Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee (Dr. Haines); Sergievsky Center (Dr. Mayeux), Taub Institute (Drs. Mayeux, Honig and Vonsattel), and Departments of Neurology (Dr. Honig), and Pathology (Dr. Shelanski), Columbia University, New York, New York; Departments of Pharmacology and Neuroscience (Dr. Barber) and Neurology (Drs. Diaz-Arrastia and Rosenberg), University of Texas Southwestern, Fort Worth, Texas; Departments of Pathology (Dr. Bigio), Psyhiatry and Behavioral Sciences (Dr. Johnson), and Cognitive Neurology and Alzheimer's Disease Center (Drs. Mesulam and Weintraub), Northwestern University, Chicago, Illinois; Departments of Neurology University of California San Francisco (Dr. Boxer, Ms. Karydas, and Drs. Miller and Seeley); Departments of Neurology (Drs. Clark, Harrell, Marson and Roberson), and Pathology (Drs. Carroll, Fallon), University of Alabama at Birmingham; Departments of Medicine (Drs. Burke and Welsh-Bohmer), Pathology (Dr. Hulette), and Psychiatry & Behavioral Sciences (Dr. Welsh-Bohmer), Duke University, Durham, North Carolina; Departments of Neurology (Drs. Chui and Schneider), Preventive Medicine (Dr. Mack), Pathology (Dr. Miller), and Psychiatry (Dr. Schneider), University of Southern California, Los Angeles; Institute for Memory Impairments and Neurological Disorders (Drs. Cotman, Dick, and Poon), and Departments of Molecular and Biomedical Pharmacology (Dr. Head), and Pathology and Laboratory Medicine (Dr. Kim), University of California Irvine; Department of Neurology (Drs. Cummings, Ringman and Vinters), Neurogenetics Program (Dr. Geschwind), and Department of Pathology & Laboratory Medicine (Dr. Vinters), University of California Los Angeles; Departments of Neurology (Dr. DeCarli) and Pathology and Laboratory Medicine (Drs. Ellis, Jin and Miller), University of California Davis; Departments of Psychiatry (Drs. Ferris and Reisberg) and Medicine (Dr. Martiniuk), and Alzheimer's Disease Center (Dr. Reisberg), New York University, New York; Departments of Neurosciences (Drs. Galasko, Koo and Masliah) and Pathology (Dr. Masliah), University of California San Diego; Department of Pathology and

Laboratory Medicine and Emory Alzheimer's Disease Center (Dr. Gearing), and Departments of Neurology (Drs. Glass, Lah and Levey), and Pathology (Dr. Glass), Emory University, Atlanta, Georgia; Departments of Neurology (Dr. Gilman), Psychiatry (Dr. Giordani), and Pathology (Dr. Lieberman), University of Michigan, Ann Arbor; Departments of Pathology (Neuropathology) (Dr. Hamilton) and Neurology (Dr. Lopez), University of Pittsburgh, Pennsylvania; Departments of Neurology (Drs. Jicha, Markesbery and Smith) and Pathology (Dr. Markesbery), University of Kentucky, Lexington; Departments of Anatomic Pathology, and Laboratory Medicine and Pathology (Dr. Parisi) and Neurology (Dr. Petersen) Mayo Clinic Rochester, New York.

Author Contributions

Study concept and design: Bennett, Blacker, Buxbaum, Ertekin-Taner, Farrer, Foroud, Goate, Haines, Hakonarson, Kramer, Kukull, Martin, Mayeux, Montine, Morris, Pericak-Vance, Reiman, Saykin, Schellenberg, and Tsuang. *Acquisition of data:* Arnold, Baldwin, Barber, Beach, Beekly, Bennett, Bigio, Bird, Boxer, Burke, Cairns, Cantwell, Carroll, Chui, Clark, Cotman, Cummings, DeCarli, Diaz-Arrastia, Dick, Dickson, Dombroski, Ellis, Fallin, Fallon, Farlow, Ferris, Foroud, Friedland, Frosch, Galasko, Gearing, Geschwind, Ghetti, Gilman, Giordani, Glass, Graff-Radford, Green, Growdon, Haines, Hakonarson, Hamilton, Harrell, Head, Honig, Hulette, Hyman, Inzelberg, Jicha, Jin, Johnson, Karlawish, Karydas, Kaye, Kim, Koo, Kowall, Lah, Levey, Lieberman, Lopez, Mack, Markesbery, Marson, Martiniuk, Masliah, Mayeux, McKee, Mesulam, Miller, Miller, Miller, Parisi, Perl, Peskind, Petersen, Poon, Quinn, Raskind, Reiman, Reisberg, Ringman, Roberson, Rogaeva, Rosenberg, Sano, Saykin, Schellenberg, Schneider, Schneider, Seeley, Shelanski, Smith, Spina, St George-Hyslop, Stern, Tanzi, Trojanowski, Troncoso, Van Deerlin, Vinters, Vonsattel, Weintraub, Welsh-Bohmer, Woltjer, and Younkin. *Analysis and interpretation of data:* Beecham, Buros, Cupples, Farrer, Gallins, Haines, Jun, Kramer, Kukull, Lunetta, Martin, Montine, Morris, Naj, Pericak-Vance, Schellenberg, Tsuang, and Wang. *Drafting of the manuscript:* Beecham, Bennett, Buros, Buxbaum, Ertekin-Taner, Farrer, Foroud, Gallins, Haines, Jun, Kramer, Mayeux, Morris, Naj, Pericak-Vance, Reiman, Saykin, Schellenberg, Wang. *Critical revision of the manuscript for important intellectual content:* Arnold, Baldwin, Barber, Beach, Beecham, Beekly, Bennett, Bigio, Bird, Blacker, Boxer, Burke, Buros, Buxbaum, Cairns, Cantwell, Carroll, Chui, Clark, Cotman, Cummings, Cupples, DeCarli, Diaz-Arrastia, Dick, Dickson, Dombroski, Ellis, Ertekin-Taner, Fallin, Fallon, Farlow, Farrer, Ferris, Foroud, Friedland, Frosch, Galasko, Gallins, Gearing, Geschwind, Ghetti, Gilman, Giordani, Glass, Goate, Graff-Radford, Green, Growdon, Haines, Hakonarson, Hamilton, Harrell, Head, Honig, Hulette, Hyman, Inzelberg, Jicha, Jin, Johnson, Jun, Karlawish, Karydas, Kaye, Kim, Koo, Kowall, Kramer, Kukull, Lah, Levey, Lieberman, Lopez, Lunetta, Mack, Markesbery, Marson, Martin, Martiniuk, Masliah, Mayeux, McKee, Mesulam, Miller, Miller, Miller, Montine, Morris, Naj, Parisi, Pericak-Vance, Perl, Peskind, Petersen, Poon, Quinn, Raskind, Reiman, Reisberg, Ringman, Roberson, Rogaeva, Rosenberg, Sano, Saykin*, Schellenberg, Schneider, , Schneider, Seeley, Shelanski, Smith, Spina, St George-Hyslop, Stern, Tanzi, Trojanowski, Troncoso, Tsuang, Van Deerlin, Vinters, Vonsattel, Wang, Weintraub, Welsh-Bohmer, Woltjer, and Younkin. *Statistical analysis:* Beecham, Buros, Cupples, Farrer, Gallins, Haines, Jun, Lunetta, Naj, Pericak-Vance, and Wang. *Obtained funding:* Bennett, Blacker, Farrer, Foroud, Goate, Haines, Hakonarson, Kukull, Mayeux, Montine, Morris, Pericak-Vance, Reiman, Saykin, Schellenberg, Tsuang, and Wang. *Administrative, technical, and material support:* Arnold, Baldwin, Barber, Beach, Beekly, Bigio, Bird, Boxer, Burke, Buros, Cairns, Cantwell, Carroll, Chui, Clark, Cotman, Cummings, DeCarli, Diaz-Arrastia, Dick, Dickson, Dombroski, Ellis, Fallin, Fallon, Farlow, Ferris, Friedland, Frosch, Galasko, Gallins, Gearing, Geschwind, Ghetti, Gilman, Giordani, Glass, Graff-Radford, Green, Growdon, Hakonarson, Hamilton, Harrell, Head, Honig, Hulette, Hyman, Inzelberg, Jicha, Jin,

Johnson, Karlawish, Karydas, Kaye, Kim, Koo, Kowall, Kukull, Lah, Levey, Lieberman, Lopez, Mack, Markesbery, Marson, Martiniuk, Masliah, McKee, Mesulam, Miller, Miller, Miller, Parisi, Perl, Peskind, Petersen, Poon, Quinn, Raskind, Reisberg, Ringman, Roberson, Rogaeva, Rosenberg, Sano, Schellenberg, Schneider, Schneider, Seeley, Shelanski, Smith, Spina, Stern, St George-Hyslop, Tanzi, Trojanowski, Troncoso, Van Deerlin, Vinters, Vonsattel, Weintraub, Welsh-Bohmer, Woltjer, and Younkin. *Study supervision:* Beekly, Cantwell, Farrer, Kukull, Pericak-Vance, Schellenberg.

Table 1

Sample Description

Cohort	Number of Cases	Number of autopsies	Mean onset age (SD)	Number of Controls	Number of autopsies	Mean age at last exam (SD)	Total	Percent of Ethnic group
Caucasian Subjects								
ADC	1,595	1,421	73 (7.7)	553	134	77 (8.7)	2,148	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)	2,392	0	73 (7.5)	2,589	20%
UM/VU/MSSM	1,170	370	74 (7.7)	1,169	75	74 (7.6)	2,339	18%
MIRAGE	560	0	71 (6.5)	790	0	72 (7.1)	1,350	10%
NIA LOAD	993	367	72 (6.9)	884	45	76 (8.4)	1,877	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)	1,337	10%
Totals	5,935	2,986		7,034	1,092		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%
Totals	462	61		449	63		911	100%
Arab Subjects								
Wadi Ara	124	0	78 (7.9)	142	0	72 (6.0)	266	100%
Caribbean Hispanic Subjects								
Columbia	549	8	80 (8.0)	544	0	79 (6.4)	1,093	100%
All Ethnic Groups								
Totals	7,070	3,055		8,169	1,155		15,239	

SD: standard deviation; ADC: Alzheimer Disease Centers cohort; ADNI: Alzheimer Disease Neuroimaging Initiative cohort; FHS.: Framingham Heart Study cohort; UM/VU/MSSM: University of Miami/ Vanderbilt University/Mt. Sinai School of Medicine cohort; MIRAGE: Multi Institutional Research on Alzheimer's Genetic Epidemiology cohort; NIA LOAD: National Institute on Aging Late-onset Alzheimer Disease cohort; OHSU: Oregon Health Sciences University cohort; TGEN: Translational Genomics Research Institute cohort; JHU: Johns Hopkins University cohort. Additional information on all cohorts is provided in the supplementary materials supplied online.

Table 2

GWAS genotyping platform, numbers of SNPs genotyped and imputed, and *APOE* genotype distribution for the study samples

Cohort	Genotyping platform	CRI, CLU & PICALM SNPs	
		Number genotyped†	Number Imputed‡
Caucasian 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	Illumina 660Quad	9	5
Carribean Hispanic Subjects			
Columbia	Illumina 650Y	10	0

Abbreviations are as in Table 1.

† The number of genotyped SNPs includes SNPs on the genotyping platform and SNPs genotyped individually by TaqMan or other techniques (see supplementary material online).

‡ The number of imputed SNPs reflects the number satisfying predetermined quality thresholds (R-squared > 0.5).

Table 3

Meta-analysis results for association of AD with SNPs in *CR1*, *CLU*, and *PICALM* in Caucasians

			Unadjusted			adjusted age sex & *APOE*			Effect direction: unadjusted/adjusted								
SNP	**MA**	**MAF**	**OR**	**95% CI**	**P‡**	**OR**	**95% CI**	**P‡**	**ADC**	**ADNI**	**CAMP**	**FHS**	**UM/VU/MSSM**	**MIRAGE**	**NIA LOAD**	**OHSU**	**TGEN**
CR1																	
rs3818361	A	0.26	1.14	1.07 – 1.22	6.1×10^{-5}	1.15	1.07 – 1.24	0.0002	+/−	+/+	−/−	+/+	+/+	+/+	+/+	+/+	+/+
rs6701713	A	0.26	1.14	1.07 – 1.22	8.8×10^{-5}	1.15	1.07 – 1.24	0.0002	+/−	+/+	−/−	+/+	+/+	+/+	+/+	+/+	+/+
rs1408077	A	0.26	1.14	1.07 – 1.22	0.0001	1.16	1.07 – 1.25	0.0002	+/+	+/+	−/−	+/+	+/+	+/+	+/+	+/+	+/+
CLU																	
rs7012010	C	0.39	1.10	1.03 – 1.17	0.0025	1.10	1.02 – 1.17	0.0081	+/+	+/+	?/?	+/−	+/−	+/+	+/+	−/−	+/+
rs3087554	C	0.16	1.00	0.92 – 1.09	0.92	0.98	0.89 – 1.08	0.71	−/−	−/+	+/+	−/+	+/+	−/−	+/+	+/+	?/?
rs11136000	T	0.43	0.91	0.85 – 0.96	0.0007	0.92	0.86 – 0.98	0.0096	−/−	−/−	−/−	−/−	−/+	−/+	−/−	−/−	−/+
rs9331888	G	0.25	0.99	0.92 – 1.06	0.76	0.99	0.91 – 1.07	0.74	−/−	−/−	+/+	−/−	+/+	−/−	+/+	+/+	−/−
rs7982	T	0.38	0.87	0.81 – 0.94	0.0002	0.89	0.83 – 0.97	0.0046	−/−	?/?	−/−	?/?	−/−	−/−	−/−	?/?	?/?
PICALM																	
rs532470	G	0.49	1.06	1.00 – 1.11	0.048	1.02	0.96 – 1.09	0.47	−/−	−/−	+/+	+/+	+/+	+/+	+/−	−/−	+/+
rs592297	C	0.20	0.92	0.86 – 0.99	0.02	0.96	0.89 – 1.04	0.33	−/−	+/+	−/−	−/−	−/+	−/−	−/+	+/+	−/−
rs677909	C	0.40	0.88	0.83 – 0.94	3.3×10^{-5}	0.94	0.88 – 1.00	0.056	−/−	+/+	−/+	−/−	−/−	−/−	−/−	+/+	−/−
rs636848	G	0.24	1.02	0.96 – 1.08	0.6	1.00	0.93 – 1.07	0.98	−/−	−/−	+/+	+/+	−/−	−/−	+/+	−/−	+/+
rs541458	C	0.39	0.88	0.83 – 0.93	2.6×10^{-5}	0.94	0.88 – 1.00	0.048	−/−	+/+	−/+	−/−	−/−	−/−	−/−	−/−	−/−
rs561655	G	0.29	0.89	0.84 – 0.94	3.4×10^{-5}	0.92	0.87 – 0.99	0.017	−/−	+/+	−/−	−/+	−/−	−/−	−/−	+/−	−/−
rs543293	A	0.36	0.88	0.83 – 0.93	2.3×10^{-5}	0.92	0.86 – 0.98	0.015	−/−	−/+	−/+	−/−	−/−	−/−	−/−	+/−	−/−
rs7941541	G	0.28	0.89	0.83 – 0.95	0.0007	0.95	0.88 – 1.03	0.21	−/−	−/+	−/+	−/−	−/−	?/?	−/−	?/?	−/−
rs3851179	T	0.35	0.89	0.84 – 0.94	3.9×10^{-5}	0.93	0.87 – 0.99	0.026	−/−	−/+	−/−	+/+	−/−	−/−	−/−	+/−	−/−

MA: minor allele; MAF: weighted-average minor allele frequency; OR: odd ratio; 95% CI: 95% confidence interval; P: meta-analysis P value; ?: no data. Other abbreviations are the same as in Table 1.

‡P-values and odd ratios estimated under an additive model using logistic regression without covariates (unadjusted) and with covariates (adjusted for age, gender, and *APOE*) in a meta-analysis of nine Caucasian cohorts comprising 5,935 cases and 7,034 cognitively normal controls. Generalized Linear Models were used to estimate case-control data, and Generalized Estimating Equations were used to estimate family-based data.

Table 4

APOE genotype and allele frequencies, and odds ratios for association of ε4 with Alzheimer's Disease

Cohort	Subject status	n	% ε4 positive	*APOE* Genotype frequencies (n/total)						*APOE* allele frequencies			Association of *APOE* ε4 with AD[†]		
				2/2	2/3	2/4	3/3	3/4	4/4	2	3	4	OR	95% CI	P Value
Caucasian Subjects															
ADC	Cases	1,582	68.0	0.00	0.03	0.02	0.29	0.49	0.16	0.03	0.55	0.42	5.22	(4.21 – 6.46)	9.3×10^{-52}
	Controls	540	28.2	0.01	0.14	0.01	0.57	0.27	0.01	0.08	0.77	0.15			
ADNI	Cases	286	67.7	0.00	0.02	0.03	0.3	0.47	0.18	0.02	0.55	0.43	4.50	(3.17 – 6.40)	5.1×10^{-17}
	Controls	195	26.7	0.01	0.11	0.02	0.62	0.23	0.02	0.07	0.79	0.14			
CAMP	Cases	123	36.6	0.00	0.1	0.02	0.54	0.27	0.08	0.06	0.72	0.22	1.20	0.70 – 2.07	5.1×10^{-01}
	Controls	102	31.7	0.00	0.11	0.02	0.58	0.28	0.02	0.06	0.77	0.17			
FHS	Cases	183	35.5	0.02	0.07	0.03	0.56	0.3	0.03	0.07	0.74	0.19	2.10	1.52 – 2.89	5.4×10^{-06}
	Controls	2,284	20.8	0.00	0.13	0.02	0.66	0.17	0.02	0.08	0.81	0.12			
UM/VU/MSSM	Cases	1,162	59.4	0.00	0.04	0.02	0.37	0.43	0.15	0.03	0.60	0.37	4.45	3.78 – 5.24	4.7×10^{-71}
	Controls	1,137	23.2	0.01	0.12	0.02	0.64	0.2	0.02	0.08	0.80	0.12			
MIRAGE	Cases	559	58.1	0.00	0.04	0.03	0.37	0.41	0.14	0.04	0.60	0.36	1.80	1.56 – 2.07	1.2×10^{-15}
	Controls	788	39.5	0.00	0.08	0.02	0.52	0.31	0.07	0.05	0.72	0.23			
NIA LOAD	Cases	985	75.6	0.00	0.02	0.02	0.22	0.55	0.19	0.02	0.51	0.47	9.05	7.34 – 11.17	6.1×10^{-94}
	Controls	881	25.5	0.01	0.14	0.03	0.59	0.21	0.01	0.09	0.77	0.14			
OHSU	Cases	186	40.3	0.00	0.09	0.05	0.51	0.32	0.03	0.07	0.72	0.22	2.30	1.62 – 3.24	2.4×10^{-06}
	Controls	421	21.2	0.00	0.17	0.02	0.62	0.18	0.01	0.09	0.80	0.11			
TGEN	Cases	819	61.5	0.00	0.03	0.04	0.35	0.43	0.15	0.04	0.58	0.38	4.75	3.78 – 5.96	6.9×10^{-41}
	Controls	517	21.5	0.03	0.12	0.02	0.63	0.19	0.01	0.10	0.79	0.11			
African American Subjects															
ADC	Cases	61	70.5	0.00	0.07	0.02	0.23	0.54	0.15	0.04	0.53	0.43	3.92	2.00 – 7.67	6.7×10^{-05}
	Controls	60	34.4	0.02	0.13	0.1	0.5	0.23	0.02	0.13	0.68	0.18			
JHU	Cases		nd	nd	nd	nd	Nd	nd	nd	nd	nd	nd	nd	nd	nd
	Controls		nd	nd	nd	nd	Nd	nd	nd	nd	nd	nd			
MIRAGE	Cases	180	69.4	0.00	0.03	0.03	0.28	0.49	0.17	0.03	0.54	0.43	2.17	1.65 – 2.85	2.4×10^{-08}
	Controls	199	48.2	0.00	0.08	0.04	0.44	0.39	0.06	0.06	0.67	0.27			

Cohort	Subject status	n	% ε4 positive	*APOE* Genotype frequencies (n/total)						*APOE* allele frequencies			Association of *APOE* ε4 with AD[†]		
				2/2	2/3	2/4	3/3	3/4	4/4	2	3	4	OR	95% CI	P Value
Arab Subjects															
Wadi Ara	Cases	73	6.8	0.00	0.00	0.00	0.93	0.07	0	0.00	0.97	0.03	2.87	0.54 – 15.26	0.217
	Controls	80	2.5	0.00	0.00	0.00	0.98	0.03	0	0.00	0.99	0.01			
Caribbean Hispanic Subjects															
Columbia	Cases	549	40.4	0.01	0.07	0.03	0.52	0.31	0	0.06	0.71	0.23	2.16	1.67 – 2.81	4.9×10^{-09}
	Controls	544	23.9	0.01	0.12	0.02	0.64	0.20	0	0.08	0.80	0.13			

Abbreviations are listed in Tables 1 and 3.

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 Caucasian cohorts

	APOE e4 (−)†			*APOE* e4 (+)†			SNP**APOE* interaction¶		
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	0.0170	1.14	1.03 – 1.26	0.0120	1.01	0.99 – 1.03	0.2800
rs6701713	1.10	1.01 – 1.19	0.0210	1.14	1.03 – 1.26	0.0110	1.01	0.99 – 1.04	0.2800
rs1408077	1.06	1.00 – 1.12	0.0360	1.15	1.03 – 1.27	0.0099	1.06	0.97 – 1.16	0.1900
CLU									
rs7012010	1.10	1.00 – 1.20	0.0430	1.05	1.00 – 1.10	0.0640	1.03	0.94 – 1.12	0.5100
rs3087554	1.01	0.90 – 1.14	0.8800	1.00	0.84 – 1.18	0.9700	1.00	0.82 – 1.22	1.0000
rs11136000	0.91	0.84 – 0.98	0.0150	0.93	0.84 – 1.03	0.1700	0.98	0.92 – 1.06	0.6500
rs9331888	1.03	0.93 – 1.14	0.5300	0.92	0.80 – 1.05	0.1900	0.89	0.77 – 1.04	0.1400
rs7982	0.87	0.79 – 0.97	0.0092	0.92	0.81 – 1.05	0.2200	1.06	0.91 – 1.24	0.4800
PICALM									
rs532470	0.99	0.92 – 1.08	0.8900	1.12	1.01 – 1.24	0.0300	1.11	0.98 – 1.25	0.1000
rs592297	1.04	0.97 – 1.11	0.3200	0.90	0.79 – 1.03	0.1200	0.85	0.73 – 1.00	0.0480
rs677909	0.99	0.91 – 1.08	0.8000	0.86	0.77 – 0.96	0.0062	0.86	0.75 – 0.98	0.0260
rs636848	0.96	0.88 – 1.06	0.4400	1.07	0.95 – 1.21	0.2700	1.07	0.92 – 1.23	0.3900
rs541458	0.99	0.91 – 1.08	0.8100	0.86	0.77 – 0.96	0.0066	0.86	0.75 – 0.98	0.0270
rs561655	0.97	0.89 – 1.06	0.5000	0.83	0.75 – 0.93	0.0009	0.82	0.73 – 0.93	0.0024
rs543293	1.00	0.92 – 1.09	0.9800	0.83	0.74 – 0.93	0.0011	0.81	0.71 – 0.93	0.0026
rs7941541	0.98	0.90 – 1.08	0.7300	0.90	0.79 – 1.02	0.0990	0.89	0.79 – 0.99	0.0360
rs3851179	0.99	0.91 – 1.07	0.7300	0.86	0.77 – 0.95	0.0034	0.84	0.74 – 0.95	0.0068

Abbreviations are as in Table 3.

† Meta-analysis P-values and odds ratios estimated under an additive model using logistic regression without covariates among subjects with no *APOE* ε4 alleles [*APOE* ε4 (−)] and among individuals with at least one *APOE* ε4 alleles (*APOE* ε4 (+)).

¶ 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 two main effects (SNP minor allele dosage and the presence of at least one *APOE* ε4 allele) and their interaction.