A NOVEL ALZHEIMER DISEASE LOCUS LOCATED NEAR THE GENE ENCODING TAU PROTEIN

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Accessibility
A NOVEL ALZHEIMER DISEASE LOCUS LOCATED NEAR THE GENE ENCODING TAU PROTEIN

A full list of authors and affiliations appears at the end of the article.

Abstract

APOE ε4, the most significant genetic risk factor for Alzheimer disease (AD), may mask effects of other loci. We reanalyzed genome-wide association study (GWAS) data from the International Genomics of Alzheimer’s Project (IGAP) Consortium in APOE ε4+ (10,352 cases and 9,207 controls) and APOE ε4− (7,184 cases and 26,968 controls) subgroups as well as in the total sample testing for interaction between a SNP and APOE ε4 status. Suggestive associations (P<1x10−4) in stage 1 were evaluated in an independent sample (stage 2) containing 4,203 subjects (APOE ε4+: 1,250 cases and 536 controls; APOE ε4−: 718 cases and 1,699 controls). Among APOE ε4− subjects, novel genome-wide significant (GWS) association was observed with 17 SNPs (all between KANSL1 and LRRC37A on chromosome 17 near MAPT) in a meta-analysis of the stage 1 and stage 2 datasets (best SNP, rs2732703, P=5·8x10−9). Conditional analysis revealed that rs2732703 accounted for association signals in the entire 100 kilobase region that includes MAPT. Except for previously identified AD loci showing stronger association in APOE ε4+ subjects (CR1 and CLU) or APOE ε4− subjects (MS4A6A/MS4A4A/MS4A6E), no other SNPs were significantly associated with AD in a specific APOE genotype subgroup. In addition, the finding in the stage 1 sample that AD risk is significantly influenced by the interaction of APOE with rs1595014 in TMEM106B (P=1·6x10−7) is noteworthy because TMEM106B variants have previously been associated with risk of frontotemporal dementia. Expression quantitative trait locus analysis revealed that rs113986870, one of the GWS SNPs near rs2732703, is significantly associated with four KANSL1 probes that target transcription of the first translated exon and an untranslated exon in hippocampus (P≤1.3x10−8), frontal cortex (P≤3x10−9), and temporal cortex (P≤2x10−11). Rs113986870 is also strongly associated with a MAPT probe that targets transcription of alternatively spliced exon 3 in frontal cortex (P=9.2x10−6) and temporal cortex (P=2.6x10−6). Our APOE-stratified GWAS is the first to show GWS association for AD with SNPs in the chromosome 17q21.31 region. Replication of this finding in independent samples is needed to verify that SNPs in this region have significantly stronger effects on AD risk in persons lacking APOE ε4 compared to persons carrying this allele, and if this is found to hold, further examination of this region and studies aimed at deciphering the mechanism(s) are warranted.
INTRODUCTION

The common late-onset form of Alzheimer disease (AD) has a strong genetic component, a portion of which is explained by APOE and several other genes identified by positional mapping, targeted gene analysis and genome-wide association studies (GWAS). Together, these loci account for less than one-half of the heritable component in AD susceptibility, of which 20%-25% is due to APOE. Because many of the known AD loci cluster in biological pathways, including those involved in inflammation, lipid metabolism and processing, and intracellular trafficking of Aβ, there are likely more AD risk loci that are difficult to detect because of very weak effect size, allelic heterogeneity, or rare variants. To examine yet another hypothesis, namely, that associations for some loci may be obscured by confounding or interaction with other loci, we conducted a two-stage GWAS in APOE genotype subgroups using the large resources of the International Genomics of Alzheimer’s Project (IGAP).

METHODS

Study Population

Details of the stage 1 sample from the International Genomics of Alzheimer’s Project (IGAP) Consortium including subject recruitment, genotyping, imputation, quality control, population substructure, and statistical methods for association analyses were previously described. In brief, phenotype and genotype data, including APOE genotypes, for a total of 53,711 subjects were assembled by IGAP from the Alzheimer’s Disease Genetic Consortium (ADGC), the Cohorts for Heart and Ageing Research in Genomic Epidemiology (CHARGE) consortium, the European Alzheimer’s Disease Initiative (EADI), and the Genetic and Environmental Risk in Alzheimer’s Disease (GERAD) consortium. Characteristics of this sample are in Supplementary Table S1.

The stage 2 dataset included GWAS and APOE genotype data for 4,203 subjects of European ancestry from the ADC4, ADC5, ADC6, MTV, Pfizer, and TARCC datasets in the ADGC. These individuals were recruited under protocols approved by the appropriate Institutional Review Boards. Details of the individual datasets are provided in the Supplementary Materials and summarized in Supplementary Table S1.

Procedures

QC, Imputation, and Population Substructure in Stage 2 Datasets—Quality control of the clinical and genotype data in these cohorts was performed using procedures described elsewhere. SNP genotypes in each stage 2 dataset were imputed with IMPUTE2 using reference haplotypes from the March 2012 release of 1000 Genomes. We compared imputation results for selected variants in the stage 1 datasets using the March 2012 release of 1000 Genomes and prior imputation on the December 2010 release, and found no significant difference in the distribution of genotype probabilities between old and new imputations for the same samples among the original ADGC datasets. We used actual APOE genotypes when available because previously we observed that imputation in this region using the 1000 Genomes reference panel is unreliable. Population substructure was
evaluated within each dataset by principal components (PC) analysis using EIGENSTRAT (http://www.hsph.harvard.edu/alkes-price/software/) and a subset of 21,109 SNPs common to all genotyping platforms.

**Statistical Analysis**

**Genome-wide Association Study**—Within each stage 1 dataset, genome-wide association analyses were conducted separately in subgroups of subjects with and without the APOEε4 allele using a logistic generalized linear model (GLM) in case-control datasets and a logistic generalized estimating equation (GEE) in family-based datasets. The potential independent effect of the APOEε2 allele was not examined because of the paucity of carriers of this allele, thus rendering very small cell sizes particularly among AD cases and in smaller datasets. Cox-proportional hazards models were used to evaluate association with incident AD in three CHARGE cohorts. A quantitative estimate between 0 and 2 for the dose of the reference allele for a SNP was used to incorporate the uncertainty of the imputation estimates. Interaction between a SNP and APOE genotype was evaluated in the APOE genotype subgroups combined within each dataset using regression models including age, sex, the first three PCs, and terms for the SNP, APOEε4 status, and interaction between the SNP and APOEε4 status. Results for each model across 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/). Effect sizes were weighted by their inverse variance and a combined estimate was calculated by summing the weighted estimates and dividing by the summed weights. SNPs with a minor allele frequency >5% that were available in at least 50% of the datasets were included in the meta-analysis. The meta-analysis P-value for association was estimated by the summarized test statistic, after applying genomic control within each individual study.

**Follow-up Analysis in Stage 2 Datasets**—SNPs attaining a P-value <10^{-4} in the stage 1 GWAS were evaluated in each of the stage 2 GWAS datasets, containing a total of 1,786 APOEε4+ and 2,417 APOEε4− subjects (Supplementary Table S1), using the same approach described above.

**Gene Expression Analysis**

The effect of top-ranked SNPs on gene expression was evaluated using an open access database of control brain microarray data (BRAINEAC) made publically available by the UK Human Brain Expression Consortium (http://caprica.genetics.kcl.ac.uk/BRAINEAC). This dataset contains information generated by analysis of tissue samples obtained from 12 different central nervous system regions in 134 individuals. Details of the expression quantitative trait locus (eQTL) analysis are reported elsewhere.\(^6\) In this study, the experiment-wise significance threshold for association of a genetic marker with expression was determined to be 1.6x10^{-7} at the gene level and 1.8x10^{-6} for individual exons. Potential for functionality of the top-ranked SNPs was assessed using the Regulome database (http://www.regulomedb.org).
RESULTS

We conducted a genome-wide association study for AD using datasets stratified by APOE genotype assembled by IGAP which were from the ADGC, CHARGE consortium, EADI, and GERAD consortium. Meta-analyses were performed separately in APOE ε4+ (10,246 cases and 11,924 controls) and APOE ε4− (7,231 cases and 19,603 controls) subgroups, as well as the total sample using a model including a term for the interaction of the SNP with the APOE ε4 status. There was limited genomic inflation in the GWAS results in the APOE ε4+ (λ=1.05) and APOE ε4− (λ=1.06) groups, but not in the total sample (λ=0.98) testing the ε4 * SNP interaction (Supplementary Figure S1). Genome-wide significant (GWS) association (P<5x10^{-8}) for AD was found in five distinct regions (CR1, BIN1, CLU, PICALM and APOE) in the APOE ε4+ subgroup (Supplementary Figure S2A, Supplementary Table S2) and four distinct regions (BIN1, HBEGF, MS4A6A/MS4A4A, SLC24A4, and APOE) in the APOE ε4− subgroup (Supplementary Figure S2B, Supplementary Table S2). No significant SNP*APOE interactions were found in the total group (Supplementary Figure S2C). Suggestive association (P<10^{-6}) was observed with SNPs in five novel loci in the APOE ε4− subgroup (SOX14/CLDN18, ACSL6, FAM20C, MAPT region, and CDR2L; Supplementary Figure S2B, Supplementary Table S3) and with 21 TMEM106B SNPs (top result: rs1595014, P=1.6x10^{-7}) (Supplementary Figure S2C, Supplementary Table S3).

Approximately 1,130 SNPs from 38 regions (including seven previously established AD loci) were tested in Stage 2 (Supplementary Table S3). Follow-up analyses of the novel loci confirmed association with SNPs in CDC42SE2-ACSL6, KANSL1/LRRC37A, and CDR2L in the stage 2 sample (Table 1, Supplementary Table S2), but only SNPs near MAPT and between KANSL1 and LRRC37A (Figure 1A) were genome-wide significant after combining results from the stage 1 and stage 2 samples (best SNP: rs2732703, meta-analysis: P=5.8x10^{-9}). The association was consistent in nearly all datasets which contained rs2732703 information (Figure 1B). To verify the reliability of the association with rs2732703, an imputed SNP, we compared rs2732703 allele dosages obtained directly by genotyping using a Taqman assay with those derived from imputation among 1,010 subjects from the ACT, ADC4, ADC5 and ADC6 datasets. The correlation of these values, 0.813 in the entire sample and 0.834 among APOE ε4− subjects, as well as a genotype misclassification rate of only 3.5% among subjects with imputed probability scores > 0.8 for a particular genotype, suggest that our association findings were not influenced substantially by imputation quality.

Further examination of this region in the total sample revealed an association peak spanning more than 1.25 Mb that contains 15 genes (Figure 1A). Within this region, 17 SNPs were GWS, have MAFs ranging from 0.13 to 0.17, and are located in a 10.2 kb segment upstream of both KANSL1 and LRRC37A (Supplementary Table S4). Nominally significant association was observed with only one of these SNPs among ε4+ subjects (rs2732703, P=0.02) (Supplementary Table S3). Although the odds ratios (OR) for effect of the effect of minor allele on AD risk were substantially lower for all of the GWS SNPs in the ε4− group (0.54< OR <0.86) than in the ε4+ group (0.76< β <1.04), there was no evidence of interaction with APOE genotype (Supplementary Table S3). The minor alleles of these SNPs
reduced AD risk by 20%–37% in the ε4− group. The 350 kb gap in the broad association signal is punctuated at one end by a “cliff” adjacent to the MAPT-KANSL1-LRRC37A association peak (Figure 1). This gap is populated by relatively few SNPs and contains several copy number variation (CNV) polymorphisms. To explore the possibility that the association observed in the present analysis is explained by previously identified haplotypes H1/H2 in the MAPT region, we evaluated six models in the entire dataset conditioning on rs8070723 (an H1/H2 tagging SNP), rs2732703, or rs199533. Rs2732703 remained significant in models conditioning on rs8070723 (P=0.013) or rs199533 (P=0.0020), and rs8070723 was marginally significant in the model conditioning on rs199533 (P=0.043) (Supplementary Table S5, Supplementary Figure S3). These results suggest that KANSL1/LRRC37A is the only AD risk locus in this region.

We also examined the effect of APOE ε4 status on previously established AD loci (Supplementary Table S2). Four of these loci attained genome-wide significance in at least one of the APOE subgroups (Table 2), and the association signal in the MS4A cluster region was evident primarily in the APOE ε4− subgroup (Supplementary Figure S4). The association of AD with CR1, BIN1, and CLU was supported in both APOE subgroups.

Next, we interrogated the BRAINEAC database to determine whether any of the 17 GWS SNPs located between KANSL1 and LRRC37A are cis-eQTLs. Data were available for only one of these SNPs (rs113986870) which is in high LD with and 2,461 base pairs away from rs2732703 (r² and D′>0.9). Ten exon probes from four genes (KANSL1, LRRC37A4P, MAPT, and C17orf69) were significantly associated with rs113986870 when averaged across all brain regions (Table 3). Rs113986870 was significantly associated with gene-level expression (Figure 2A) as well as with exon-level expression (Figure 2B) in hippocampus, temporal cortex, and cerebellum. In these brain regions, rs113986870 was significantly associated with KANSL1 probes 3762011, 3762012 and 3762013 that measure expression of the first translated exon. Additionally, we observed that expression of probe 3760518 (Supplementary Figure S5A) present in all three transcripts (NM_001193466, NM_015443, and NM_001193465) and 3760219 in transcript variant 2 (NM_015443) was significantly associated with rs113986870 (Supplementary Figure S5B), while expression of probe 3760217 in transcript variant 1 ((NM_001193466) was not significant (Supplementary Figure SSC), indicating that alternative splicing may be a crucial mechanism for regulating KANSL1 expression. Rs113986870 was also strongly associated with MAPT transcription (Supplementary Figure S6A) and in particular with probe 3723712 that targets transcription of alternatively spliced exon 3 in frontal cortex (P =6.2x10⁻⁶) and temporal cortex (P =2.6x10⁻⁶) (Supplementary Figure S6B). The rs113986870 minor allele (A), which is associated with reduced risk of AD (Supplementary Table S4), increased expression of the target exons in KANSL1 and MAPT(Figure 2, Supplementary Figure S6, Supplementary Figure S7). The association with LRRC37A4P exon probe 3759898 was significant in all three AD-related brain regions (P =3.6x10⁻⁹). The association of rs113986870 with exon probe 3723594 for C17orf69 was significant in hippocampus only (P =1.6x10⁻⁷). Five of the GWS SNPs including rs2732703 and rs113986870 are located within a transcription factor binding site or a DNase sensitivity peak and two of these five SNPs, including rs2668626 which is only 47 bp from rs2732703, have also been identified within an eQTL (Supplementary Table S4).

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DISCUSSION

This study was undertaken to identify loci whose effect on AD risk may be obscured by confounding or interaction with APOE genotype. Our APOE-stratified GWAS is the first to show GWS association for AD with SNPs in the chromosome 17q21.31 region including MAPT, KANSL1 and LRRC37A. Among the genes expected to emerge from GWAS but never seen before is MAPT which encodes the microtubule-associated protein tau (MAPT) found in AD neurofibrillary tangles. The association peak is located between KANSL1 and LRRC37A, approximately 200 kb downstream of MAPT, in a subset of subjects that do not possess the APOE ε4 allele. Although the association signal includes MAPT, conditional analysis suggests that the causal variant(s) are more likely located in a DNA segment between the 5′ end of KANSL1 and 5′ end of LRRC37A and not within MAPT or another gene distal to LRRC37A.

The nature of the AD-related functional variant could not be discerned from our genetic association findings. None of the GWS SNPs are within 42.1 kb of the KANSL1 start site or 16.8 kb of the LRRC37A start site, suggesting that the functional variant is not within the promoter region of either gene. KANSL1 is a widely expressed gene encoding a member of the nonspecific lethal (NSL) complex. The KANSL1 protein is an evolutionarily conserved regulator of the chromatin modifier KAT8, which influences gene expression through histone H4 lysine 16 (H4K16) acetylation. Notably, mutations in KANSL1 cause the 17q21.31 microdeletion syndrome which is associated with a wide range of abnormalities including intellectual disability and developmental delay, and is therefore thought to be involved in neuronal development. LRRC37A encodes a member of the leucine-rich repeat containing 37 family. Leucine-rich repeats (LRRs) are protein-ligand interaction motifs found in a large number of proteins with different structure, localization, and function. LRR motifs are important for intermolecular or intercellular interactions with exogenous factors in the immune system and/or with different cell types in the developing nervous system.

However, expression analysis of exon array data in control brain tissue revealed that rs113986870, which is in high LD with the top-ranked SNP (rs2732703) in the GWAS, is an eQTL for expression of the first translated exon in KANSL1 and the alternatively spliced exon 3 in MAPT. Previous studies suggest that splicing of MAPT may be a crucial regulatory mechanism in the brain and tauopathies in particular, and that increased expression of exon 3 protects against neurodegeneration. Although rs113986870 is apparently not an eQTL for its adjacent gene LRRC37A, it was significantly associated with a closely related gene, LRRC37A4P, in all three AD-related brain regions. These results suggest that rs113986870 may have a potential function as a cis-acting regulatory element for multiple genes in this region. Another confounding feature of this region are copy number variations that in part overlap with the 5′ end of KANSL1 and possibly influence expression. Thus, it is possible that the exon probes targeting the first translated in KANSL1 may be tagging this duplication. In addition, interrogation of a database curating information about DNA features and regulatory regions revealed that five of the GWS SNPs, including rs2732703 and rs113986870, may have strong regulatory potential.
The association peak for AD on chromosome 17q21.31 is located in a well-recognized and perplexing genomic region containing a 900 kb inversion.\(^8\) Previous GWAS identified associations of variants within and at the edges of this inversion with Parkinson disease (PD)\(^{15}\) and progressive supranuclear palsy (PSP)\(^{16}\), but the most significant associations were not with SNPs between KANSL1 and LRRC37A (Supplementary Table S6). Multiple studies have identified more than 40 MAPT deletions, missense mutations, and splice site mutations that cause frontotemporal dementia (FTD).\(^{17}\) Although AD is only nominally associated with common variants in MAPT, previously we observed association of a rare MAPT variant (A152T) with increased risk for FTD and AD in a large sample,\(^{18}\) a finding which was supported by a subsequent smaller study.\(^{19}\) Ikram et al identified a GWS association peak with a KANSL1 SNP approximately 166 kb away from our most significant AD SNP (rs2732703) for a continuous measure of intracranial volume in a sample of nearly 10,000 community-dwelling elders (Supplementary Table S6).\(^{20}\) These two SNPs are moderately correlated (\(r^2=0.71\)) which indicates that they may tag the same functional variant.

Other studies have focused on two divergent extended MAPT haplotypes, H1 and H2, which are in near complete LD with status of the inversion and contain independently derived partial duplications of KANSL1.\(^8,16\) The common H1 haplotype is associated with increased risk of FTD,\(^21\) PD,\(^22\) PSP,\(^23\) and corticobasal degeneration (CBD),\(^23\) while H2 is linked to recurrent deletion events associated with the 17q21.31 microdeletion syndrome.\(^{10}\) Among these non-AD forms of dementia, it is possible for FTD to masquerade clinically as AD and thereby cases of FTD could be present in our study group; however, any inadvertent inclusion of FTD cases is expected to be very small since the minimum age of dementia onset in our study group was 60 years and onset of dementia from FTD after age 69 years is relatively rare compared to AD that in most cases occurs after age 69.\(^{24}\) Furthermore, a recent review of almost 5000 autopsy brains from a subset of cases in the ADGC cohort failed to identify any case of FTD.\(^{25}\) Myers et al. reported association of AD with H1 and with common MAPT SNPs,\(^{26}\) but this association is controversial\(^{27}\) and did not reach genomewide significance in our study or previous GWAS. Another recent study showed that carriers of at least one H2 allele had a 5.4-fold increased risk of worsening hallucinations, but this result was marginally significant.\(^{28}\) Previously, we observed in a subset of the sample studied here that the H2-haplotype tagging rs8070723-G allele was associated with reduced risk of AD.\(^{29}\) However, this variant is no longer associated after conditioning on rs2732703 (Supplementary Table S5). In carriers of H2, the ancestral haplotype in both humans and chimpanzees,\(^{30}\) increased expression of exon 3 in MAPT has been associated with an eQTL located approximately 1,500 bp from rs113986870 which decreases aggregation of microtubules.\(^{31,32}\) These observations are consistent with our results showing that the rs113986870 minor allele is protective for AD and associated with elevated exon3 expression.

There is a large body of experimental evidence linking tau protein to AD pathogenesis,\(^{33}\) and some studies show evidence of association of AD with common MAPT SNPs.\(^{29,34}\) However, analysis of the MAPT coding sequence did not reveal disease-causing variants for early-onset AD\(^{35}\) and other studies examining association of MAPT SNPs with late-onset AD were negative.\(^{27,36}\) Recently, Allen et al. reported that the rs8070723-G allele was
associated with reduced MAPT expression in the cerebellum and temporal cortex of AD subjects. Robust genetic associations have also been identified for AD with several genes in cytoskeletal and axonal transport pathways including tau or leading to neurofibrillary tangles, most notably BIN1, EPHA1, RIN3, CASS4, and FERMT2.

Based on the observation that overexpression of human ApoE4 in transgenic mouse neurons results in hyperphosphorylation of tau, it is possible that associations with AD-related loci in the chromosome 17q21.31 region are obscured by the much stronger effect of APOE ε4 on MAPT expression or function. This idea is consistent with lack of GWS association with 17q21.31 SNPs in the same dataset without stratification by APOE genotype, and no evidence for interaction between APOE and any SNPs in the MAPT-KANSL1-LRRC37A region in the current study. Another possible explanation for the significant association of 17q21.31 SNPs with AD only among subjects lacking APOE ε4 is genetic heterogeneity suggesting that variation at the chromosome 17q21.31 locus is associated with a distinct etiological subtype of AD where tau is the primary disease activator. Finally, the diagnosis of AD for most subjects in this dataset was established clinically suggesting the possibility of misdiagnosis or AD accompanied by other processes associated with other dementing illnesses. Further studies are needed to determine whether this subtype can be distinguished clinically or neuropathologically.

Our study also showed that the previously established association with the MS4A gene cluster is derived almost completely from subjects lacking APOE ε4, suggesting the contribution of the MS4A locus to AD may be mechanistically different than AD-related processes that are associated with APOE ε4. Members of the MS4A gene family encode membrane proteins, some of which have known roles in immune cell function, however, little is known about the function of MS4A6A, MS4A4A or MS4A6E in humans. Karch et al. showed that expression of MS4A6A was upregulated in AD brains of AD patients compared to brains of controls, and significantly correlated with AD status, AIF1 expression (a marker for microglia which is the immune cell of the brain), cognitive dementia rating score, and extent of AD neuropathologic change.

The observed statistical interaction of genotypes for TMEM106B with APOE on AD risk in the stage 1 GWAS is noteworthy (rs1595014, P=1.6x10−7) even though it is not supported by results in the comparatively small stage 2 sample. TMEM106B is a glycoprotein predominantly localized at the lysosomal membrane where it might interact with intracellular progranulin (GRN). TMEM106B variants, particularly the p. T185S (rs3173615) mutation, are risk factors for FTD, especially among persons carrying a GRN mutation. TMEM106B variants are also associated with development of cognitive impairment in amyotrophic lateral sclerosis and implicated in the pathologic presentation of AD. Cruchaga et al observed association of the TMEM106B SNP rs1990622 risk allele with younger onset of the FTLD subtype with TAR DNA-binding protein inclusions (FTLD-TDP), a pattern reminiscent of the association of APOE ε4 with increased risk and younger onset of AD. The biological underpinning of the interaction of TMEM106B with APOE affecting AD risk is unclear.
Our top findings, including those that are genome-wide significant, should be confirmed in independent samples. Functional studies will be needed to understand the relationship between APOE and the causative variant(s) in 17q21.31 once they are identified, as well as with other loci showing much stronger association with AD in particular APOE genotype strata (e.g., MS4A6A/MS4A4E/MS4A6E) or through interaction with APOE (e.g., TMEM106B). Our study provides a firm genetic connection of AD to several other pathologically distinct disorders in which dementia is a cardinal or common characteristic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Gyungah Jun1,2,3, Carla A. Ibrahim-Verbaas4,5, Maria Vronskaya6, Jean-Charles Lambert7,8,9, Jaeyoon Chung1, Adam C. Naj10, Brian W. Kunkle11, Li-San Wang10, Joshua C. Bis12, Céline Bellenguez7,8,9, Denise Harold13, Kathryn L. Lunetta3, Anita L. Destefano3, Benjamin Grenier-Boley7,8,9, Rebecca Sims6, Gary W. Beecham11,14, Albert V. Smith15,16, Vincent Chouraki17, Kara L. Hamilton-Nelson11, M. Arfan Ikram4,18,19, Nathalie Fievet7,8,9, Nicola Denning6, Eden R. Martin11,14, Helena Schmidt20, Yochiro Kamatani14, Melanie L. Dunstan9, Otto Valladares10, Agustin Ruiz Laaza23, Diana Zelenika, Alfredo Ramirez25,26, Tatiana M. Foroud27, Seung-Hoon Choi3, Anne Boland24, Tim Becker28,29, Walter A. Kukull30, Sven J. van der Lee4, Florence Pasquier8,31, Carlos Cruchaga32,33, Duane Beekly34, Annette L. Fitzpatrick30,35, Oliver Hanon36,37, Michael Gill38, Robert Barber39, Vilmundur Gudnason15,16, Dominique Campion40,41, Seth Love42, David A. Bennett43,44, Najaf Amin4, Claudine Ben245, Magda Tsolaki46, Joseph D. Buxbaum47,48,49, Oscar L. Lopez50,51, Vincent Deramecourt8,31, Nick C Fox52, Laura B. Cantwell10, Luís Tárraga53, Carole Dufouil54, John Hardy55,56, Paul K. Crane57, Gudny Eiriksdottir16, Didier Hannequin40,54, Robert Clarke58, Denis Evans59, Thomas H. Mosley Jr.60, Luc Letenneur54, Carol Brayne61, Wolfgang Maier25,28, Philip De Jager62,5,63, Valur Emilsson16,64, Jean-François Dartigues54,65, Harald Hampel66,67, M. Ilyas Kamboh50,68, Renee F. A.G. de Bruijn4, Christophe Tzouri54, Pau Pastor69,70, Eric B. Larson57,71, Jerome I. Rotter72,73, Michael C O’Donovan6, Thomas J. Montine74, Michael A. Nalls75, Simon Mead55, Eric M. Reiman76,77,78,79, Palmi V. Jonsson15,80, Clive Holmes81, Peter H. St George-Hyslop82,83, Mercè Boada53, Peter Passmore84, Jens R. Wendland85, Reinhold Schmidt86, Kevin Morgan87, Ashley R. Winslow85, John F. Powell88, Minerva Carasquillo89, Steven G. Youskin89, Jóhanna Jakobsdóttir16, John SK Kauwe90, Kirst C. Wilhelmsen91, Dan Rujescu92, Markus M Nöthen28,93, Albert Hofman4,19, Lesley Jones6, IGAP Consortium, Jonathan L. Haines94, Bruce M. Psaty12,30,35,71, Christine Van Broeckhoven95,96, Peter Holmans6, Lenore J. Launer97, Richard Mayeux98,99,100, Mark Lathrop24,101,102, Alison M. Goate32,33, Valentina Escott-Price8, Sudha Seshadri17, Margaret A. Pericak-Vance11,14, Philippe Amouyel7,8,9,103, Julie Williams6, Cornelia M. van Duijn4, Gerard D. Schellenberg10, and Lindsay A. Farrer1,2,3,17,104,†

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Affiliations

1Department of Medicine (Biomedical Genetics), Boston University School of Medicine, Boston, MA, USA  
2Department of Ophthalmology, Boston University School of Medicine, Boston, MA, USA  
3Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA  
4Department of Epidemiology, Erasmus University Medical Center, Erasmus, Rotterdam, The Netherlands  
5Department of Neurology, Erasmus University Medical Center, Erasmus, Rotterdam, The Netherlands  
6Institute of Psychological Medicine and Clinical Neurosciences, Medical Research Council (MRC) Centre for Neuropsychiatric Genetics & Genomics, Cardiff University, Cardiff, UK  
7Inserm U744, Lille, France  
8Université Lille 2, Lille, France  
9Institut Pasteur de Lille, Lille, France  
10Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA  
11The John P. Hussman Institute for Human Genomics, University of Miami, Miami, FL, USA  
12Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA  
13Trinity College, University of Dublin, Dublin, Ireland  
14Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami, Miami, FL, USA  
15University of Iceland, Faculty of Medicine, Reykjavik, Iceland  
16Icelandic Heart Association, Kopavogur, Iceland  
17Department of Neurology, Boston University School of Medicine, Boston, MA, USA  
18Netherlands Consortium for Healthy Aging, Leiden, The Netherlands  
19Department of Radiology, Erasmus University Medical Center, Erasmus, Rotterdam, The Netherlands  
20Institute for Molecular Biology and Biochemistry, Medical University of Graz, Graz, Austria  
21Laboratory for Statistical Analysis, Center for Integrative Medical Sciences, Riken, Kanagawa, Japan  
22Foundation Jean Dausset – CEPH, Paris, France  
23Memory Clinic of Fundació ACE. Institut Català de Neurociències Aplicades, Barcelona, Spain  
24Centre National de Genotypage, Institut Genomique, Commissariat a l’energie Atomique, Evry, France  
25Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany  
26Institute of Human Genetics, University of Bonn, Bonn, Germany  
27Department of Medical and Molecular Genetics, Indiana University, Indianapolis, IN, USA  
28German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany  
29Institute for Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn, Germany  
30Department of Epidemiology, University of Washington, Seattle, WA, USA  
31Centre National de Reference pour les Maladies Alzheimer Jeunes (CNR-MAJ), Centre Hospitalier Régional Universitaire de Lille, Lille, France  
32Hope Center Program on Protein Aggregation and Neurodegeneration, Washington University School of Medicine, St. Louis, MO, USA  
33Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA  
34National Alzheimer’s Coordinating Center, University of Washington, Seattle, WA, USA  
35Departments of Health Services, University of Washington, Seattle, WA, USA  
36University Paris Descartes, Sorbonne Paris V, France  
37Broca Hospital, Geriatrics Department, Paris, France  
38Mercer’s Institute for Research on Aging, St. James Hospital and Trinity College, Dublin, Ireland  
39Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth,
TX, USA 40CNR-MAJ, Inserm U1079, Rouen, France 41University Hospital, 76031 Rouen, France 42University of Bristol Institute of Clinical Neurosciences, School of Clinical Sciences, Frenchay Hospital, Bristol, UK 43Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA 44Rush Alzheimer’s Disease Center, Rush University Medical Center, Chicago, IL, USA 45Inserm U888, Hôpital La Colombière, Montpellier, France 46Department of Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece 47Department of Neuroscience, Mount Sinai School of Medicine, New York, NY, USA 48Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA 49Departments of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, NY, USA 50University of Pittsburgh Alzheimer’s Disease Research Center, Pittsburgh, PA, USA 51Departments of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA 52Dementia Research Centre, Department of Neurodegenerative Disease, University College London Institute of Neurology, London, UK 53Memory Clinic of Fundació ACE. Institut Català de Neurociències Aplicades, Barcelona, Spain 54Inserm U897, Victor Segalen University, F-33076, Bordeaux, France 55Department of Molecular Neuroscience, Institute of Neurology, London, UK 56Reta Lilla Weston Laboratories, Institute of Neurology, London, UK 57Department of Medicine, University of Washington, Seattle, WA, USA 58Oxford Healthy Aging Project (OHAP), Clinical Trial Service Unit, University of Oxford, Oxford, UK 59Rush Institute for Healthy Aging, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA 60Department of Medicine (Geriatrics), University of Mississippi Medical Center, Jackson, MS, USA 61Institute of Public Health, University of Cambridge, Cambridge, UK 62Program in Translational NeuroPsychiatric Genomics, Institute for the Neurosciences, Department of Neurology & Psychiatry, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA 63Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA 64Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland 65Centre de Mémoire et de Recherche de Bordeaux, CHU de Bordeaux, Bordeaux, France 66Department of Psychiatry, University of Frankfurt, Frankfurt am Main, Germany 67Department of Psychiatry, Ludwig Maximilians University, Munich, Germany 68Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA, USA 69Neurogenetics Laboratory, Division of Neurosciences, Center for Applied Medical Research, University of Navarra School of Medicine, Pamplona, Spain 70CIBERNED, Instituto de Salud Carlos III, Madrid, Spain 71Group Health, Group Health Research Institute, Seattle, WA, USA 72Institute for Translational Genomics and Population Sciences. Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA 73Division of Genetic Outcomes, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA 74Department of Pathology, University of Washington, Seattle, WA, USA 75Laboratory of Neurogenetics, Intramural Research Program, National Institute on Aging, Bethesda, MD, USA 76Arizona Alzheimer’s Consortium, Phoenix, AZ, USA 77Department of Psychiatry, University of Arizona, Phoenix, AZ, USA 78Banner
Alzheimer’s Institute, Phoenix, AZ, USA \textsuperscript{79} Neurogenomics Division, Translational Genomics Research Institute, Phoenix, Arizona \textsuperscript{80} Department of Geriatrics, Landspitali National University Hospital, Reykjavik, Iceland \textsuperscript{81} Division of Clinical Neurosciences, School of Medicine, University of Southampton, Southampton, UK \textsuperscript{82} Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Canada \textsuperscript{83} Cambridge Institute for Medical Research and Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK \textsuperscript{84} Ageing Group, Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen’s University, Belfast, UK \textsuperscript{85} PharmaTherapeutics Clinical Research, Pfizer Worldwide Research and Development, Cambridge, MA, USA \textsuperscript{86} Department of Neurology, Medical University of Graz, Graz, Austria \textsuperscript{87} Institute of Genetics, Queen’s Medical Centre, University of Nottingham, Nottingham, UK \textsuperscript{88} King’s College London, Institute of Psychiatry, Department of Neuroscience, De Crespigny Park, Denmark Hill, London, UK \textsuperscript{89} Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA \textsuperscript{90} Department of Biology, Brigham Young University, Provo, Utah, USA \textsuperscript{91} Department of Genetics, University of North Carolina Chapel Hill, Chapel Hill, NC, USA \textsuperscript{92} Department of Psychiatry, Psychotherapy and Psychosomatics Martin-Luther-University Halle-Wittenberg, Julius-Kühn-Str. 706112 Halle Germany \textsuperscript{93} Institute of Human Genetics, Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany \textsuperscript{94} Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, OH, USA \textsuperscript{95} Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, Antwerp, Belgium \textsuperscript{96} Institute Born-Bunge, University of Antwerp, Antwerp, Belgium \textsuperscript{97} Laboratory of Epidemiology, Demography, and Biometry, National Institute of Health, Bethesda, MD, USA \textsuperscript{98} Taub Institute on Alzheimer’s Disease and the Aging Brain, Columbia University, New York, NY, USA \textsuperscript{99} Gertrude H. Sergievsky Center, Columbia University, New York, NY, USA \textsuperscript{100} Department of Neurology, Columbia University, New York, NY, USA \textsuperscript{101} McGill University and Génome Québec Innovation Centre, Montreal, Canada \textsuperscript{102} Fondation Jean Dausset-CEPH, Paris, France \textsuperscript{103} University Hospital, CHRU Lille, Lille, France \textsuperscript{104} Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

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Figure 1.
Association of AD with SNPs in chromosome 17q21.31 in the combined stage 1 and stage 2 samples. (A) Regional Manhattan plot in the $APOE\varepsilon4+$ (upper panel) and the $APOE\varepsilon4-$ (lower panel) subgroups. SNPs with the lowest $P$-value are indicated with a purple diamond. Computed estimates of linkage disequilibrium ($r^2$) of SNPs in this region with the most significant SNP are shown as red circles for $r^2 \geq 0.8$, orange circles for $0.6 \leq r^2 < 0.8$, green circles for $0.4 \leq r^2 < 0.6$, light blue circles for $0.2 \leq r^2 < 0.4$, and blue circles for $r^2 < 0.2$. Unannotated SNPs are shown as grey circles. (B) Forest plot of association results for rs2732703 in the Stage 1, Stage 2 and total samples among $APOE\varepsilon4-$ subjects.
Figure 2.
Genotype specific effect of the eQTL rs113986870 on expression of KANSL1. (A) Gene-level expression of KANSL1 transcript t3760137. Transcript-level expression represents the average across all KANSL1 exon probe sets. (B) Expression of exon probe 3760212. Probes 3760211, 3760212, and 3760213 measure expression of the first translated exon, are present in all three transcript variants, and were significantly associated with the eQTL. Expression profiles for probes 3760211 and 3760213 showed similar to those for probe 3760212 (Table 3). The distance from 3760212 to rs113986870 is 85,431 base pairs. Log2 scale of expression (Y-axis) is shown for 10 regions of cognitively normal human brains (X-axis) ordered by mean expression level. Rs113986870 genotype counts: AA=0, AG=56, and GG=76. Rs113986870 allele frequencies are 0.21 (A) and 0.79 (G). CRBL = cerebellum, FCTX = frontal cortex, HIPP = hippocampus, MEDU = medulla (specifically inferior olivary nucleus), OCTX = occipital cortex (specifically primary visual cortex), PUTM = putamen, SNIG = substantia nigra (SNIG), THAL = thalamus, TCTX = temporal cortex, WHMT = intralobular white matter.
Table 1

Association results (P<10^{-6}) in novel AD loci among APOE ε4− subjects in the combined stage 1 and stage 2 samples.

| SNP         | CH | Region or Closest Gene | MA  | MAF  | Stage 1 | Stage 2 | Stages 1 + 2 |
|-------------|----|------------------------|-----|------|---------|---------|-------------|
|             |    |                        |     |      | OR (95% CI) | P       | OR (95% CI) | P             | OR (95% CI) | P       |
| rs16847609  | 3  | SOX14/CLDN18            | A   | 0.09 | 1.21 (1.12–1.29) | 2.3x10^{-7} | 1.09 (0.87–1.37) | 0.47 | 1.19 (1.11–1.28) | 5.3x10^{-7} |
| rs382216    | 5  | CDC42SE2-ACSL6          | T   | 0.36 | 0.88 (0.83–0.93)  | 6.5x10^{-6} | 0.78 (0.67–0.91) | 0.002 | 0.87 (0.82–0.92) | 2.0x10^{-7} |
| rs11168036  | 5  | PFDN1/HBEGF             | T   | 0.50 | 1.14 (1.09–1.19)  | 9.3x10^{-9} | 0.97 (0.85–1.11) | 0.64 | 1.12 (1.07–1.17) | 3.2x10^{-7} |
| rs2732703   | 17 | KANSL1/LRRC37A          | G   | 0.13 | 0.73 (0.65–0.83)  | 6.4x10^{-7} | 0.71 (0.58–0.88) | 0.001 | 0.73 (0.65–0.81) | 5.8x10^{-9} |
| rs71380849  | 17 | CDR2L                   | A   | 0.06 | 1.45 (1.24–1.70)  | 3.8x10^{-6} | 1.59 (1.01–2.50) | 0.04 | 1.47 (1.26–1.71) | 9.1x10^{-7} |
Results (P<10$^{-6}$) in previously known AD loci showing different pattern of association among APOE ε4+ and ε4− subjects in the combined datasets.

| SNP    | CH | Region or Closest Gene | MA     | MAF  | APOE ε4+ (OR 95% CI) | P       | APOE ε4− (OR 95% CI) | P       |
|--------|----|------------------------|--------|------|----------------------|---------|----------------------|---------|
| rs679515 | 1  | CR1                    | T      | 0.21 | 1.22 (1.14 –1.30)    | 3.6x10$^{-9}$ | 1.13 (1.07 – 1.19)   | 1.6x10$^{-5}$ |
| rs4663105 | 2  | BIN1                   | C      | 0.43 | 1.19 (1.12 – 1.25)   | 2.5x10$^{-9}$ | 1.19 (1.13 – 1.24)   | 1.8x10$^{-12}$ |
| rs9331896 | 8  | CLU                    | C      | 0.38 | 0.84 (0.80 – 0.89)   | 2.8x10$^{-9}$ | 0.90 (0.86 – 0.94)   | 9.6x10$^{-6}$ |
| rs1582763 | 11 | MS4 region             | A      | 0.37 | 0.92 (0.87 – 0.97)   | 0.003   | 0.87 (0.83 – 0.91)   | 2.2x10$^{-9}$ |

CH = chromosome; MA = minor allele; MAF = minor allele frequency.
Exon probes covering the region between 43.5 and 45.0 Mb on chromosome 17 that reveal significant rs113986870 allelic expression differences averaged over 10 brain areas

| Gene     | ExprID   | Start  | End    | AVGALL  | FCTX    | HIPP    | TCTX    |
|----------|----------|--------|--------|---------|---------|---------|---------|
| LRRC37A4P| 3759896  | 4358323| 4358380| 1.4x10^-15 | 6.4x10^-4 | 4.0x10^-6 | 2.4x10^-5 |
| LRRC37A4P| 3759898  | 4358426| 4358484| 1.7x10^-20 | 8.0x10^-11| 5.3x10^-10| 3.6x10^-9 |
| C17orf69 | 3723594  | 4371676| 4371685| 3.3x10^-13 | 2.8x10^-5 | 1.6x10^-7 | 8.3x10^-5 |
| C17orf69 | 3723604  | 4372339| 4372356| 4.9x10^-10 | 0.004   | 9.8x10^-4 | 1.3x10^-5 |
| MAPT     | 3723712  | 4405175| 4405183| 3.6x10^-14 | 9.2x10^-6 | 7.6x10^-4 | 2.6x10^-6 |
| KANSL1   | 3760158  | 4411706| 4411761| 9.8x10^-14 | 2.8x10^-5 | 0.008   | 6.2x10^-5 |
| KANSL1   | 3760211  | 4424765| 4424785| 4.0x10^-21 | 8.0x10^-13| 3.0x10^-17| 1.6x10^-15|
| KANSL1   | 3760212  | 4424822| 4424877| 1.4x10^-24 | 2.6x10^-18| 7.8x10^-20| 2.5x10^-21|
| KANSL1   | 3760213  | 4424952| 4424959| 7.7x10^-16 | 3.0x10^-11| 1.1x10^-13| 1.2x10^-11|
| KANSL1   | 3760219  | 4427018| 4427025| 4.3x10^-13 | 1.3x10^-9 | 1.3x10^-9 | 1.3x10^-11|

Map position is based on 1000 Genomes database release GRCh37/hg19 assembly, February 2009. Significance threshold after multiple testing determined as 0.05/292,000 exon probes = 1.7x10^-7; ExprID: exon-specific probeset ID. AVGALL: average expression levels across 10 regions including cerebellum (CRBL), frontal cortex (FCTX), hippocampus (HIPP), medulla (specifically inferior olivary nucleus, MEDU), occipital cortex (specifically primary visual cortex, OCTX), putamen (PUTM), substantia nigra (SNIG), thalamus (THAL), temporal cortex (TCTX), and intralobular white matter (WHMT).