Background: Apolipoprotein E (APOE) is the most statistically significant genetic risk factor for late-onset Alzheimer disease (LOAD). The linkage disequilibrium pattern around the APOE gene has made it difficult to determine whether all the association signal is derived from APOE or whether there is an independent signal from a nearby gene.

Objective: To attempt to replicate a recently reported association of APOE 3–TOMM40 haplotypes with risk and age at onset.

Design: We used standard techniques to genotype several polymorphisms in the APOE–TOMM40 region in a large case-control series, in a series with cerebrospinal fluid biomarker data, and in brain tissue.

Setting: Alzheimer’s Disease Research Center.

Participants: Research volunteers who were cognitively normal or had Alzheimer disease.

Main Outcome Measures: Disease status and age at onset.

Results: We did not replicate the previously reported association of the polyT polymorphism (rs10524523) with risk and age at onset. We found a significant association between rs10524523 and risk of LOAD in APOE 33 homozygotes but in the opposite direction as the previously reported association (the very long allele was underrepresented in cases vs controls in this study (P = .004)). We found no association between rs10524523 and cerebrospinal fluid tau or β-amyloid 42 levels or TOMM40 or APOE gene expression.

Conclusions: Although we did not replicate the earlier association between the APOE 3–TOMM40 haplotypes and age at onset, we observed that the polyT polymorphism is associated with risk of LOAD in APOE 33 homozygotes in a large case-control series but in the opposite direction as in the previous study.

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of LOAD, cerebrospinal fluid (CSF) biomarker levels, and expression of TOMM40/APOE in the brain.

METHODS

PARTICIPANTS

Risk of disease and AAO analyses were performed in 1594 LOAD cases (474 APOE 33 homozygotes) and 1190 cognitively normal controls (701 APOE 33 homozygotes) matched for age, sex, and ethnicity. These samples were obtained from the Knight Alzheimer Disease Research Center at Washington University (WU-ADRC) (759 cases and 345 controls) and from the National Institute on Aging (NIA) LOAD Family Study (835 cases and 845 controls). Each case received a diagnosis of dementia of the Alzheimer type using criteria equivalent to those of the National Institute of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association for probable AD. Individuals with a Clinical Dementia Rating Scale (CDR) score of 0.5 who did not meet the clinical criteria for probable AD were not included in the analyses. Controls received the same assessment as cases but were cognitively normal. All the individuals were of European descent, and written consent was obtained from all the participants.

Expression studies were conducted using complementary DNA (cDNA) obtained from the parietal lobes of 82 AD cases and 39 cognitively normal individuals (CDR score=0) obtained through the WU-ADRC Neuropathology Core. Association with CSF tau, tau phosphorylated at threonine 181, β-amyloid (Aβ) 42, and Aβ40 levels was tested in an independent series of 474 samples from the WU-ADRC and 259 samples from the Alzheimers Disease Neuroimaging Initiative (ADNI) (Table 1). Cerebrospinal fluid was collected and biomarker measurements were obtained as described previously. A summary of the demographics of all the participants is given in Table 1.

GENOTYPING

rs7412 and rs429358 (which define the APOE ε2, ε3, and ε4 isoforms), rs1160985, and rs4420638 (TOMM40) were genotyped using KASPar (KBioscience, Herts, United Kingdom) and TaqMan (Applied Biosystems, Foster City, California) genotyping technologies. The APOE genotype for the NIA-LOAD and ADNI series was provided by the NIA-LOAD or ADNI. The polyT repeat in intron 6 of TOMM40 (rs10524523) was genotyped using fluorescence-based fragment size analysis (Supplemental Figure 1; http://neuroscienceresearch.wustl.edu/pages/cruchaga2011.aspx). A detailed explanation of the fluorescence-based fragment size genotyping, quality control steps, allele frequency, and linkage disequilibrium between the studied polymorphisms can be found at http://neuroscienceresearch.wustl.edu/Pages/cruchaga2011.aspx. The linkage disequilibrium between the genotyped variants can be found in Supplemental Table 1.

GENOTYPE CALLS

The polyT repeat (rs10524523) genotypes were placed into categories modeled after those reported by Roses et al: short (246-267 base pair [bp]), long (268-279 bp), and very long (280-289 bp) (Supplemental Figure 2; http://neuroscienceresearch.wustl.edu/Pages/cruchaga2011.aspx). The base pair numbers do not correspond to those provided by Roses et al because the present numbers refer to the total length of the polymerase chain reaction product, not the number of polyT repeats (see http://neuroscienceresearch.wustl.edu/Pages/cruchaga2011.aspx for quality control and call comparison between the present study and previous studies).

GENE EXPRESSION

Quantification of gene expression was performed by real-time polymerase chain reaction as explained previously. We also used the GEO data set GSE15222 for replication (see http://neuroscienceresearch.wustl.edu/Pages/cruchaga2011.aspx for a detailed explanation).

PHYLOGENETIC ANALYSES

Because the polyT repeat is reported as the key variant to define TOMM40 clades A and B, we used this marker and APOE isoform information to perform analyses based on phylogenetic groups as described by Roses et al. Haplotype phase was estimated using PHASE software. The phylogeny, which represents the evolutionary relatedness of the haplotypes, was estimated using neighbor-joining with 10,000 bootstrapping replicates in the CLC DNA workbench (CLC bio, Aarhus, Denmark) (Supplemental Figure 3; http://neuroscienceresearch.wustl.edu/Pages/cruchaga2011.aspx). We tested for differences in mean AAO
between APOE 3–TOMM40 clade A and B haplotypes using a t test. Association of APOE 3–TOMM40 clade A and B haplotypes with case-control status was performed using a Fisher exact test.

STATISTICAL ANALYSES

Additional association tests between the polyT repeat and disease status, AAO, TOMM40 and APOE brain expression, and CSF t-tau and Aβ42 levels were performed using UNPHASED v3.1.4 and SAS, version 9.2 (SAS Institute Inc, Cary, North Carolina). Several analyses were restricted to APOE 3 homozygotes, thus removing uncertainty in haplotype phasing as a possible confounding factor. (See http://neurosciences.wustl.edu/Pages/cruchaga2011.aspx for a detailed description of the statistical analyses.)

Multiple Test Correction

We tested 4 SNPs for association with 2 phenotypes. A conservative threshold for multiple test correction would be to set the significance at $P < .006$, which would be the Bonferroni correction for $4 \times 2$ tests. The SNPs that were associated with risk of disease or AAO were tested for association with CSF biomarker levels and gene expression to investigate potential pathogenic mechanisms. In this case, no multiple test correction was applied because only 1 or 2 SNPs with specific hypotheses were tested for association.

ADNI Material and Methods

Data used in the preparation of this article were obtained from the ADNI database (http://www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the NIA, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. The primary goal of the ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment and early AD. The principal investigator of this initiative is Michael W. Weiner, MD. The ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and participants have been recruited from more than 50 sites across the United States and Canada. The initial goal of the ADNI was to recruit 800 adults to participate in the research. For up-to-date information, see http://www.adni-info.org.

RESULTS

The main aim of this study was to attempt to replicate the association of the APOE 3–TOMM40 polyT repeat (rs10524523) haplotype groups with AAO and risk reported by Roses et al. Frequencies of APOE 3 alleles and APOE genotypes in TOMM40 clades A and B in the phased haplotype data were consistent with those reported (Supplemental Figure 2). We also included rs4420638 and rs1160985 (TOMM40), which have been reported to be associated with risk of disease or AAO independent of APOE genotype.

ASSOCIATION WITH AAO

When using sex, but not APOE genotype, as a covariate, we found a significant association between the polyT repeat (rs10524523) and AAO in the WU-ADRC + NIA-LOAD case-control series ($P = 1.03 \times 10^{-19}$). To discern whether this association was driven by the polyT repeat or by APOE genotype, we performed 2 additional analyses: 1 including APOE genotype as a covariate in the model and 2 analyzing the polyT association in the APOE 33 stratum. When APOE genotype was included as a covariate, the $P$ value dropped to .11, indicating that the association with AAO was driven by the APOE polymorphisms (Table 2). In the present analyses, the very long allele carriers had a higher, but not statistically significantly different, AAO than did the short allele carriers.

When the analyses were restricted to individuals with an APOE 33 genotype, the polyT repeat showed no association with AAO in the WU-ADRC + NIA-LOAD case-control series ($P = .19$) (Table 2). The same result was found when controls were included as censored data in the Kaplan-Meier analyses: in the APOE 33 stratum, the very long allele carriers had a higher, but not statistically significantly different, AAO than did the short allele carriers (Figure). We also found the same pattern in APOE 34 carriers: carriers of the long and very long alleles had a slightly higher, but not statistically significantly different, AAO than did carriers of the short alleles (Supplemental Figure 4; http://neurosciences.wustl.edu/Pages/cruchaga2011.aspx). Haplotype analyses showed similar results. We found a trend toward association between APOE 3–TOMM40 haplotypes and AAO ($P = .057$). Individuals with APOE 3–TOMM40 clade A haplotypes had a mean AAO of 73.31 years vs 72.93 years for APOE 3–TOMM40 clade B. Thus, in this much larger study (total cases = 1594, total controls = 1190; total APOE 33 cases = 474, total APOE 33 controls = 701) than the original study (N = 34), we found a trend toward association but in the opposite direction than previously reported. In the APOE 33 stratum, rs4420638 showed the most significant association with AAO ($P = .01$), but this association did not pass multiple test correction (Table 2).

ASSOCIATION WITH RISK OF DISEASE

We also analyzed whether the TOMM40 polyT repeat (rs10524523) was associated with risk of LOAD. We found an allelic association when sex and age, but not APOE genotype, were included as covariates ($P = 4.14 \times 10^{-88}$). The polyT repeat showed a trend toward association with risk of LOAD in the WU-ADRC + NIA-LOAD case-control series when APOE genotype was included in the model ($P = .08$) (Table 2). When we restricted this analysis to individuals with an APOE 33 genotype and used age and sex as covariates, there was a significant association with risk ($P = .004$) (Table 2). The frequency of the very long allele of the polyT repeat (rs10524523) was significantly lower in cases compared with controls in the WU-ADRC + NIA-LOAD series (0.41 vs 0.48, $P = .004$; odds ratio (OR) = 0.78, 95% confidence interval (CI) = 0.65–0.95) (Table 2). In this case, the association passed the multiple test correction threshold ($\alpha = .006$). No other studied SNP showed a significant association with risk.
**Table 2. MAF and P Values for Association With Risk and AAO in the Entire Series and in the APOE 33 Substratum**

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<th>APOE 33 Substratum</th>
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<td>Controls</td>
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Abbreviations: AAO, age at onset; APOE, apolipoprotein E; C, cytosine; CC, case-control; G, guanine; L, long; MAF, minor allele frequency; NA, not applicable; NIA-LOAD, National Institute on Aging Late-Onset Alzheimer Disease Family Study; T, thymine; VL, very long; WU-ADRC, Alzheimer Disease Research Center at Washington University.

a For association with disease status, age, sex, and APOE genotype were included as covariates in the entire series and sex and age in the APOE 33 substratum. The APOE genotype was not included as a covariate when rs429358 was tested for association. For association with AAO, sex and APOE genotype were included as covariates in the entire series and sex in the APOE 33 substratum.

b For association with disease status, age, sex, APOE genotype, and the first to the third principal component factors were included as covariates in the entire series and sex, age, and PC1/3 (principal components first to third) in the APOE 33 substratum. The APOE genotype was not included as a covariate when rs429358 was tested for association. For association with AAO, sex, APOE genotype, and PC1/3 were included as covariates in the entire series and sex and PC1/3 in the APOE 33 substratum.

c For association with disease status, sex, age, and site were included as covariates in the APOE 33 substratum. For association with AAO, sex and site included as covariates in the APOE 33 substratum.

**Figure.** rs10524523 is not associated with age at onset of late-onset Alzheimer disease (LOAD) in apolipoprotein E (APOE) 33 carriers. A, Age at onset was analyzed for association with rs10524523 in 282 APOE 33 LOAD cases from the Alzheimer Disease Research Center at Washington University (WU-ADRC) series and 213 controls from the WU-ADRC series with an APOE 33 substratum. The APOE genotype was not included as a covariate when rs429358 was tested for association. B, Age at onset was analyzed for association with rs10524523 in 282 LOAD cases and 213 controls from the WU-ADRC series with an APOE 33 genotype by the Kaplan-Meier method and was tested for significant differences using the log-rank test. All analyses, the short-short (S-S), short–very long (S-VL), and very long–very long (VL-VL) genotypes are highlighted because they were the most frequent in these strata. No significant differences in the survival curves were found ($P>0.05$). L-L indicates long-long; L-VL, long–very long; and S-L, short-long.

**EVALUATION OF POSSIBLE MECHANISMS OF DISEASE RISK: ASSOCIATION WITH CSF BIOMARKER LEVELS AND GENE EXPRESSION**

To determine a possible mechanism underlying the observed disease risk associated with the polyT repeat (rs10524523), we examined several endophenotypes, including CSF Aβ and tau levels and APOE and TOMM40 gene expression in the brain. A very strong association was observed between rs10524523 and CSF Aβ42 levels when CDR score, age, and sex, but not APOE genotype, were included as covariates ($P=4.50 \times 10^{-8}$ for the WU-ADRC CSF series and $P=2.42 \times 10^{-13}$ for the WU-ADRC + ADNI CSF series). However, this association was driven by APOE genotype because inclusion of APOE genotype as a covariate in the model eliminated the association between
Identification of new polymorphisms/genes that modify risk of LOAD and identify new drug targets for AD treatment. In this study, we attempted to replicate the previously reported association between the polyT repeat in TOMM40 and risk of AD in a large series of 2784 individuals (1175 APOE 33) provides high statistical power. Indeed, we found that in APOE 33 and 34 individuals, the longer alleles of the polyT polymorphism are associated with later onset and a protective effect in the opposite direction as that reported in the original study. We also studied 2 SNPs in TOMM40 that have been suggested to modify risk of AD or AAO but found no significant association when APOE genotype was included as a covariate or when the APOE 33 stratum was analyzed alone.

Last, we tested whether these polymorphisms are associated with variability in APOE or TOMM40 messenger RNA (mRNA) expression in the human parietal cortex. There was a marginal correlation between the cDNA levels of APOE and TOMM40, with P < .001 and a Pearson correlation coefficient of −0.33. Because the brain samples are derived from cognitively normal (CDR score = 0) and demented (CDR score ≥ 0.5) individuals, we first tested whether there was an association between mRNA levels and CDR score. We found no association between APOE cDNA levels and CDR score (P = .63; age, sex, and postmortem interval as covariates). We found a significant association between TOMM40 cDNA levels and CDR score (P = 3.55 × 10−3; age, sex, APOE genotype, and postmortem interval as covariates) in the WU-ADRC neuropathology series (82 AD cases and 39 cognitively normal individuals). However, we did not replicate this finding in the GEO data set GSE15222. In this data set, the TOMM40 cDNA levels in cases (n = 176) and controls (n = 188) are not significantly different (P = .17).

We found no association between any studied SNP and either TOMM40 or APOE cDNA levels (Supplemental Table 3; http://neurosciresearch.wustl.edu/Pages/crucchag2011.aspx). We also did not detect an association between TOMM40 cDNA expression and APOE genotype (P = .45 and P = .63, respectively). The association between TOMM40 cDNA levels and CDR score led us to stratify the samples by CDR scores for further analyses, but we did not detect association between any SNP in either cases or controls (Supplemental Table 3). We also analyzed the APOE 33 stratum alone but found no associations (data not shown).

It is unclear whether all the association with risk of LOAD found in the APOE–TOMM40 gene region in the genome-wide association studies is driven by APOE genotype. Identification of new polymorphisms/genes that modify risk of LOAD could provide a better understanding of the pathways involved in LOAD and identify new drug targets for AD treatment. In this study, we attempted to replicate the recent study by Roses et al that reported an association of APOE 3–TOMM40 polyT polymorphism (rs10524523) haplotypes with AAO and risk of AD. We also performed extensive analyses in individuals with APOE 33 and analyzed several endophenotypes for LOAD to investigate different potential effects of the TOMM40 polymorphisms. We did not find a significant association between the polyT polymorphism (rs10524523) and AAO despite the fact that this
TOMM40 codes for a mitochondrial protein, suggesting that mitochondrial integrity and energy metabolism could play an important role in LOAD. Mitochondrial morphologic features are altered in AD brains, and several studies have reported deficiencies in energy-related enzymes. The hypothesis that mitochondria may play an important role in LOAD is also supported by the fact that we did not find an association between the TOMM40 polymorphism and CSF Aβ42 and tau levels. However, more genetic and molecular studies are necessary to determine whether the reported genetic association with rs10524523 in TOMM40 is real.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cruchaga, Kauwe, Holtzman, and Goate. Acquisition of data: Nowotny, Mayo, Fagan, and Morris. Analysis and interpretation of data: Cruchaga, Kauwe, Ridge, Bertelsen, Hinrichs, Fagan, Holtzman, and Goate. Drafting of the manuscript: Cruchaga, Nowotny, Kauwe, Holtzman, and Goate. Critical revision of the manuscript for important intellectual content: Cruchaga, Nowotny, Kauwe, Ridge, Mayo, Bertelsen, Hinrichs, Fagan, Holtzman, Morris, and Goate. Obtained funding: Holtzman, Morris, and Goate. Administrative, technical, and material support: Nowotny, Ridge, Mayo, Bertelsen, Fagan, Holtzman, Morris, and Goate. Study supervision: Holtzman, Morris, and Goate.

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Role of the Sponsor: The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

A complete list of ADNI investigators can be found at http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Authorship_List.pdf.

Disclaimer: Data used in the preparation of this article were obtained from the ADNI database (http://www.loni.ucla.edu/ADNI). As such, the investigators in the ADNI contributed to the design and implementation of the ADNI and provided data but did not participate in analysis or writing of this report.

Previous Presentation: This study is presented in part at the International Conference on Alzheimer Disease; July 16–21, 2011; Paris, France.

Online-Only Materials: The supplemental figures and table can be found at http://neuroscienceresearch.wustl.edu/Pages/cruchaga2011.aspx.

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REFERENCES


