A Comprehensive Genetic Association Study of Alzheimer Disease in African Americans

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Objectives: To evaluate the association of genetic variation with late-onset Alzheimer disease (AD) in African Americans, including genes implicated in recent genome-wide association studies of whites.

Design: We analyzed a genome-wide set of 2.5 million imputed markers to evaluate the genetic basis of AD in an African American population.

Subjects: Five hundred thirteen well-characterized African American AD cases and 496 cognitively normal African American control subjects.

Setting: Data were collected from multiple sites as part of the Multi-Institutional Research on Alzheimer Genetic Epidemiology (MIRAGE) Study and the Henry Ford Health System as part of the Genetic and Environmental Risk Factors for Alzheimer Disease Among African Americans (GenerAAtions) Study.

Results: Several significant single-nucleotide polymorphisms (SNPs) were observed in the region of the apolipoprotein E gene (APOE). After adjusting for the confounding effects of APOE genotype, one of these SNPs, rs6859 in PVRL2, remained significantly associated with AD (P = .0087). Association was also observed with SNPs in CLU, PICALM, BIN1, EPHA1, M54A, ABCA7, and CD33, although the effect direction for some SNPs and the most significant SNPs differed from findings in data sets consisting of whites. Finally, using the African American genome-wide association study data set as a discovery sample, we obtained suggestive evidence of association with SNPs for several novel candidate genes.

Conclusions: Some genes contribute to AD pathogenesis in both white and African American cohorts, although it is unclear whether the causal variants are the same. A larger African American sample will be needed to confirm novel gene associations, which may be population specific.

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ALZHEIMER DISEASE (AD) is the most common form of dementia. Environmental and host risk factors for common late-onset AD (LOAD) include low educational level, diabetes mellitus, hypertension, and head trauma. Genetic factors also influence LOAD risk, evidenced by heritability estimates as high as 75% and analyses showing transmission of a major gene for the disease in families. Until recently, the apolipoprotein E gene (APOE [OMIM *107741]) was the only one generally recognized to influence LOAD risk. In whites, homozygosity for the ε4 variant is associated with an increased risk by as much as 15 times that of the most common APOE genotype (ε3/ε3). Genome-wide association studies (GWASs) have reported genome-wide significant single-nucleotide polymorphisms (SNPs) across a 70-kilobase (kb) region that includes APOE and several neighboring genes, namely, poliovirus receptor–related 2 (PVRL2 [OMIM *600798]), translocase of outer mitochondrial membrane 40 yeast homologue (TOMM40 [OMIM *608061]), and apolipoprotein C-I (APOC1 [OMIM *107710]). Both the TOMM40 and APOC1 genes have been considered possible risk factors for AD independent of APOE. Several lines of inquiry have implicated TOMM40 as having an effect on AD risk, including evidence of a role of mitochondria in AD pathogenesis, association of an intronic TOMM40 repeat polymorphism with age at the onset of AD symptoms among subjects lacking the ε4 allele, and association of a haplotype spanning TOMM40 with expression of
APOE.\textsuperscript{8} However, other studies did not find an effect of \textit{TOMM40} after adjusting for APOE.\textsuperscript{9,10} A polymorphism immediately upstream of the APOC1 gene has also been proposed as a possible risk locus for AD.\textsuperscript{11,12} This polymorphism is in strong linkage disequilibrium (LD) with the APOE risk locus, but this pattern varies substantially by population.\textsuperscript{13} Studies in mice and humans indicate that APOC1 expression has an effect on memory.\textsuperscript{14-16} Other studies reported that APOC1 modifies the risk of AD independent of or through interaction with APOE.\textsuperscript{17,18}

The GWASs conducted by several large consortia have identified robust evidence of an association with genes outside the APOE region, including clusterin (\textit{CLU} [OMIM *185430]),\textsuperscript{19-21} phosphatidylinositol-binding clathrin assembly protein (\textit{PICALM} [OMIM *603025]),\textsuperscript{22} complement component (3b/4b) receptor 1 (\textit{CRI} [OMIM *120620]),\textsuperscript{23} bridging integrator 1 (\textit{BIN1} [OMIM *601248]),\textsuperscript{24} CD2-associated protein (\textit{CD2AP} [OMIM *604241]),\textsuperscript{25} ephrin type-A receptor 1 (\textit{EPHA1} [OMIM *179610]),\textsuperscript{26} the membrane-spanning 4A (MS4A) gene cluster,\textsuperscript{27,28} myeloid-associated antigen CD33 (\textit{CD33} [OMIM *185950]),\textsuperscript{29} and ATP-binding cassette, subfamily A (\textit{ABCA7}), member 7 (\textit{ABCA7} [OMIM *605414]).\textsuperscript{30} Findings with \textit{CLU}, \textit{PICALM}, \textit{CRI}, and \textit{ABCA7} have been replicated.\textsuperscript{22-24}

Because there are population differences in LD and allele frequencies, most association studies have focused on a single population to decrease genetic background noise and reduce the likelihood of false-positive findings due to confounding. Thus, confirmation in other populations is required to determine the generalizability of the contribution of each gene to AD risk and the possibility of population-specific causative variants. Although the effect of APOE has been investigated extensively in multiple populations,\textsuperscript{4,25,26} few African American cohorts have been included in GWASs for AD.

In the present study, we genotyped more than 1000 African American cases and controls for more than 600,000 SNPs covering the entire genome. Genotypes for 2.5 million SNPs imputed from HapMap reference panels were used to investigate the contribution of genes previously implicated in whites to AD risk and to identify novel AD risk variants in this population. We also analyzed a comparable set of SNPs in 5 white AD GWAS data sets containing more than 9700 subjects to replicate novel findings and for comparison with previously obtained results.

Subjects were ascertained from 2 genetic studies of AD focused on African Americans. One subject group includes participants of the Multi-Institutional Research on Alzheimer Genetic Epidemiology (MIRAGE) Study, which contains primarily discordant sibling pairs. Enrollment, data collection, and diagnostic procedures in the MIRAGE Study are explained in detail elsewhere.\textsuperscript{31} A second group of primarily unrelated individuals includes participants of the Genetic and Environmental Risk Factors for Alzheimer Disease Among African Americans (GenAdaAAttions) Study, who were identified through the electronic claims database of the Henry Ford Health System. Community-dwelling African Americans 65 years or older who had at least 1 encounter with the Henry Ford Health System in the 3 years before their recruitment and who had an available proxy informant were eligible for this study. Cases met criteria of the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer’s Disease and Related Disorders Association for possible or probable AD, determined in a consensus conference that included a behavioral neurologist (R.S.), psychiatrist, neuropsychologist, and a behavioral neurology nurse practitioner.

For comparison, we also examined 5 white AD GWAS data sets, containing 3568 cases and 6203 controls, namely, the MIRAGE Study white families, and 4 data sets obtained from a public database (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap), including the Alzheimer Disease Neuroimaging Initiative (ADNI),\textsuperscript{32,33} a Canadian study on genetics of Alzheimer disease associations (GenAdaAAttions), the National Institute on Aging–Late-Onset Alzheimer’s Disease Family Study (NIA-LOAD),\textsuperscript{34,35} and the Framingham Heart Study.\textsuperscript{36-38} The numbers of cases and controls in each data set are shown in Table 1.

Genotyping methods, procedures for data cleaning and imputation, and statistical methods are described in detail in the supplementary material (http://www.bumc.bu.edu/genetics/results/aa_alzheimer). Briefly, the APOE genotyping method varied by study. Imputation of autosomal SNP genotypes was performed using the Markov Chain Haplotyping (MaCH) software\textsuperscript{39} based on the HapMap 2 and 3 reference SNP panels (http://hapmap.ncbi.nlm.nih.gov/). Imputed SNPs were tested for association with AD in the family-based data sets using generalized estimating equations (GEE)\textsuperscript{36,37} to account for nonindependence of family members. Analysis of the case-control data sets was performed using logistic regression models. All tests of association were adjusted for sex and age at examination. Two models were evaluated for each SNP, one with and the other without a term for APOE genotype coded as the number of APOE ε4 alleles. Unless otherwise noted, all results are from the ε4-unadjusted model. An additional analysis of SNPs in the APOE region included an adjustment for APOE genotype classified into

| Table 1. Sample Sizes of African American (Discovery) and White (Replication) Data Sets |
|--------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                     | African American | White         |                |                |                |                |
|                                     | MIRAGE GenerAAttions | MIRAGE ADNI GenAAttions NIA-LOAD FHS |                |
| No. of cases                        | 267             | 246           | 513            | 609            | 254           | 669            | 1839           | 197            | 3568 |
| No. of controls                     | 292             | 204           | 496            | 875            | 169           | 713            | 1983           | 2465           | 6205 |
| Total                               | 559             | 450           | 1009           | 1484           | 423           | 1382           | 3822           | 2662           | 9773 |

Abbreviations: ADNI, Alzheimer Disease Neuroimaging Initiative; FHS, Framingham Heart Study; GenAAttions, Canadian study on genetics of Alzheimer disease associations; GenerAAttions, Genetic and Environmental Risk Factors for Alzheimer Disease Among African Americans; MIRAGE, Multi-Institutional Research on Alzheimer Genetic Epidemiology; NIA-LOAD, National Institute on Aging–Late-onset Alzheimer’s Disease Family Study.
one of the following 4 categories: ε2/ε2 and ε2/ε3; ε3/ε3; ε2/ε4 and ε3/ε4; and ε4/ε4. The SNP association results obtained from individual data sets were combined by meta-analysis using the inverse variance method implemented in the software package METAL. Nominal (uncorrected for multiple testing) P values are reported throughout. In the genome-wide analysis, a P value of \( 5 \times 10^{-8} \) was used as the threshold for significance, and a threshold of \( P < 10^{-3} \) was considered suggestive evidence of association.

### RESULTS

**APOE REGION**

The frequency distributions of APOE genotypes for African American and white cohorts are shown in Table 2. In the African American cohort, the ε4 allele is very significantly associated with AD (\( P = 9.69 \times 10^{-2} \)). Analysis of individual genotypes showed evidence of a significant protective effect of ε2 (ε2/ε2 and ε2/ε3 genotypes) compared with the ε3/ε3 genotype and an exponential increase in risk associated with the dose of ε4 (Table 3).

### PREVIOUSLY IMPLICATED REGIONS

Results for African Americans in the regions of AD association from the white GWASs are summarized in Table 5. There was no evidence of association in African Americans with 2 of these 3 CLU SNPs, including rs1136000, which was consistently significant across multiple studies in white samples. A nominally significant association (\( P = .034 \)) was observed with rs2279590 that had been previously reported in whites. However, the minor allele (T) was associated with increased AD risk in this African American sample (OR, 1.41), whereas the T allele is protective in the white sample (OR, 0.87). Two additional nominally significant SNPs were observed in CLU, the most significant of which was rs9331926 (\( P = .023 \)); complete results including all nominally significant SNPs in previously implicated regions are summarized in eTable 2 in the supplementary material.

Harold et al. found genome-wide significant evidence of association with rs3851179, located 88 kb upstream from PICALM. This SNP was not associated with AD in our African American sample (\( P = .16 \)), although the estimated OR (0.85) is nearly identical to the OR reported in the white sample (0.87). However, we observed nominally significant association with 8 of 287 other SNPs tested in the region, including rs12795381 (\( P = .0086 \)) and rs17148827 (\( P = .0089 \)), which is monomorphic in whites. The rs12795381 finding is consistent with modest evidence of association with multiple SNPs in the PICALM coding region. We also evaluated the interaction of PICALM SNPs with APOE, as reported...
in a large white sample. Stratified analysis revealed evidence of association with rs12795381 in subjects with the APOE e4 allele (P = .04) but not in those without it (P = .61). However, we were unable to perform a formal test of interaction owing to the relatively small sample size and low minor allele frequency.

None of the 88 tested CR1 SNPs (including the 2 reported as significant by Lambert et al9) and none of the 112 tested CD2AP SNPs (including rs9349407, which was reported as significant by Naj et al23) were associated with AD in African Americans. The most promising result among these SNPs was obtained with rs12734030 in CR1 (P = .09).

Seshadri et al20 proposed BIN1 as a candidate gene for AD on the basis of a genome-wide significant P value observed for rs744373 located 30 kb proximally from the BIN1 coding region. Although this result was not replicated in our African American sample (P > .99), several adjacent SNPs were nominally significant, including rs11685593 (P = .0098). Association was also observed with multiple SNPs within the BIN1 coding region, the most significant of which was rs11691237 (P = .0098). The most significant association in the region was observed with rs7585314 (P = .0030), which is 68 kb from rs744373 in CYP27C1.

Located approximately 6 kb from EPHA1, rs11767557 is the only genome-wide significant result in this region reported by Naj et al22 and was not associated with AD in African Americans (P = .59). However, rs11762262, which is approximately 1260 bp closer to EPHA1 than rs11767557, was nominally significant (P = .034). We observed multiple nominally significant SNPs spread throughout the EPHA1 region in the African American sample. The strongest evidence for association in this region was obtained with rs4595035 (P = .0094), which is 32 kb upstream from rs11767557.

Naj et al22 also observed genome-wide significant association with many SNPs in the MS4A cluster. We evaluated association with all SNPs across this cluster, which spans about 500 kb. The most significant finding in the MS4A region was observed with rs10792258 (P = .010). This SNP is 394 bp distal from rs1582763 and 253 bp proximal to rs1562990, both of which were strongly associated with AD (P = 5.92 × 10−11 and P = 2.47 × 10−9, respectively) in the meta-analysis of large white data sets by Naj et al. A similar level of significance was observed with rs3802957 (P = .011) in the 3’ untranslated region of MS4A1, 203 kb from rs10792258.

We did not see association (P = .38) with an SNP in ABCA7 (rs3752246), which approached genome-wide significant in the study by Naj et al.22 We did, however, observe nominally significant association with rs3764650 (P = .019), which was reported as genome-wide significant in the study by Hollingworth et al. The effect of this SNP on risk of AD in our study (OR, 1.27) was very similar to that observed previously (OR, 1.23). Several other nominally significant SNPs were observed in the region, of which the most significant, synonymous coding SNP rs376647 (P = .0087), is located 11 kb from rs3752246.

We also did not observe an association with CD33 SNP rs3865444 (P = .73), which was found to have genome-wide significance in the GWAS by Naj et al. The most significant result in the CD33 region in the African American sample was obtained with rs10419982 (P = .0005), 69 kb away from rs3865444. This SNP almost survives correction for the 200 SNPs examined in the region. However, given the great distance of this SNP from the CD33 region, this result is less likely to be true positive. We therefore consider the CD33 region as not modified in any of our African American samples.
from CD33, there is not adequate evidence to consider this result a replication.

NOVEL GENE DISCOVERY

Genotypes were evaluated for 2,505,093 imputed SNPs that passed minor allele frequency criteria and imputation quality thresholds. A Manhattan plot of the results of the genome screen is presented in Figure 3. No SNP achieved a genome-wide level of significance. Eleven SNPs achieved suggestive levels of association ($P < 10^{-5}$) (Table 6). The direction of effect for these SNPs was consistent across the African American cohorts. Four of these SNPs (rs11889338, rs2221154, rs956225, and rs10850408) are more than 50 kb from the nearest characterized gene. Strong evidence of association was obtained with rs340849 ($P = 7.52 \times 10^{-6}$), located 34 kb from PROX1, and with rs3889808 ($P = 9.52 \times 10^{-6}$), located 19 kb upstream from P4HA3. The most significant finding was obtained for rs10850408 ($P = 9.25 \times 10^{-7}$), a chromosome 12 SNP more than 250 kb from the nearest gene. The SNPs in $ZC3H3$, $TMTC1$, and $ENOX1$ showed suggestive evidence of an association in analyses adjusting for $APOE\varepsilon 4$ (see eTable 3 in the supplementary material for all SNPs with $P < 10^{-5}$). None of these findings were replicated in the white meta-

analysis (details are provided in the eAppendix in the supplementary material).

This is, to our knowledge, the first comprehensive genetic association study of AD in African Americans. This study is timely and important for several reasons. African Americans are about twice as likely as non-Hispanic whites to have AD. Although differences in AD etiology across populations have been widely studied, they are still poorly understood. The occurrence of multiple demented individuals in African American families is significantly higher than in white families, although the genetic risk of AD is similar in these 2 populations. The increased familial risk in African Americans is likely a result of higher rates of risk factors, such as poor education, diabetes mellitus, and smoking. However, comparisons of risk in African American and white cohorts are complicated by differences in assessment of cognitive decline across studies and by population differences in willingness to participate in medical research.

We obtained incontrovertible evidence of an association with the $APOE\varepsilon 4$ allele, thus confirming find-
ings from several smaller genetic studies of African Americans.4,26 In non-Hispanic whites, homozygosity for ε4 is associated with a 13- to 15-fold increased odds of developing AD compared with those with the most common genotype, ε3/ε3.4 We showed previously in a set of 308 African American AD cases and

Figure 2. Linkage disequilibrium in the apolipoprotein E (APOE) region. A, African American cohort data sets. B, White cohort data sets. Other gene names are described in the legend to Figure 1.
409 ethnically matched controls that persons with the ε3/ε4 and ε4/ε4 genotypes had 2.6- and 10.5-fold increased odds of AD, respectively, compared with persons with the ε3/ε3 genotype. These risks decreased substantially after 68 years of age. The risk of AD was lower among individuals with the ε2/ε3 genotype. We observed similar risks in the present study. Approximately one-third of the African American sample in this study overlaps with the sample in our earlier report.

Our present study and previous studies in white populations identified highly significant evidence of an association with genes adjacent to APOE, most notably TOMM40 and APOC1 (reviewed by Ertekin-Taner). Arguably, the distinction of such findings from confounding with APOE is intractable because of the tight LD spanning the genes in this region. However, we identified highly significant evidence of an association with several SNPs in the APOE region in African Americans and whites after adjustment for APOE genotype. This finding is consistent with an AD risk locus distinct from APOE. The observation that different SNPs in this region are significant in African Americans and whites after adjustment for APOE may reflect differences in LD structure in this region (Figure 2). The residual association in these other genes may also represent unmeasured effects of variants in regulatory regions of APOE. Additional studies in larger African American samples are needed to determine which of these explanations is more likely.

Among the African Americans in the present study, a subset of 180 cases and 200 controls from the MIRAGE

<table>
<thead>
<tr>
<th>Gene, SNP</th>
<th>Effect Allele</th>
<th>AF_CEU</th>
<th>Previously Reported Results in White Cohort</th>
<th>Results in African American Cohort</th>
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<td></td>
<td>Source AF</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>AF</td>
</tr>
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<tr>
<td></td>
<td>Seshadri et al, 2010 1.62 × 10⁻⁶</td>
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<td>1.62 × 10⁻⁶</td>
<td>0.85 (0.82-0.88)</td>
</tr>
<tr>
<td></td>
<td>Harold et al, 2009 8.5 × 10⁻¹⁰</td>
<td>0.40</td>
<td>8.5 × 10⁻¹⁰</td>
<td>0.86 (0.82-0.90)</td>
</tr>
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<td>Lambert et al, 2009 1.4 × 10⁻⁷</td>
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<td>Seshadri et al, 2010 3.16 × 10⁻¹²</td>
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</tr>
<tr>
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<td>Harold et al, 2009 1.3 × 10⁻⁸</td>
<td>0.37</td>
<td>1.3 × 10⁻⁸</td>
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<td>Harold et al, 2009 1.3 × 10⁻⁸</td>
<td>0.37</td>
<td>1.3 × 10⁻⁸</td>
<td>0.86 (0.82-0.90)</td>
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<td>0.27</td>
<td>Lambert et al, 2009 1.59 × 10⁻¹¹</td>
<td>0.10</td>
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<tr>
<td></td>
<td>rs7585314 T</td>
<td>0.85</td>
<td>Lambert et al, 2009 8.5 × 10⁻¹⁰</td>
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<tr>
<td>CD2AP</td>
<td>rs9349407 C</td>
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<td>Naj et al, 2011 2.27</td>
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<td>0.20</td>
<td>Naj et al, 2011 2.30</td>
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<tr>
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<tr>
<td></td>
<td>rs4595035 T</td>
<td>0.37</td>
<td>Naj et al, 2011 2.30</td>
<td>0.43</td>
</tr>
</tbody>
</table>

(continued)
Study and 221 cases and 186 controls from the Geno-
Aconditions Study was included in another recent study24
that evaluated the association of AD with PICALM,
CLU, and CRI SNPs highlighted in the original studies
reports.19,21 The authors did not find evidence of an
association with any of the SNPs examined in the Af-
rican American data sets. We did not replicate the
genome-wide significant associations with these loci in
a larger set of African American cases and controls,
even at a nominal significance level. However, we
observed an association in African Americans with
other previously unreported variants in each of these
regions and in the most recently reported regions of
genome-wide significant association.22,23 except CRI
and CD2AP. Only one previously reported genome-
wide significant association (rs3764650 in ABCA7) was
confirmed in our African American sample.23 Discord-
ance in the association patterns between whites and
African Americans could be related to population differ-
ences in allele frequencies or LD patterns. This explana-
tion is consistent with our findings of association in
the African Americans between SNPs, which have very low
frequency in whites (eg, rs17148827 in PICALM), and one
of the previously reported AD-associating CLU SNPs
(rs2279590), but with an opposite pattern of effect. Al-
ternatively, the AD risk variants in these genes may differ
across populations (ie, allelic heterogeneity), as we ob-
served previously in SORL1.49 However, lack of replica-
tion might also be a result of small sample size when com-
pared with recent consortium-based GWASs.19-23 In most
instances, the confidence intervals for the effect esti-
mates in African Americans included the point estimates
in whites.

Analysis of the entire autosome genome revealed evi-
dence suggestive of an association with several novel can-
didate genes that may play a role in AD pathogenesis.
PROX1 (OMIM *601546) is a prospero-related transcrip-
tion factor that plays a critical role in the development
of various organs, including the mammalian lymphatic
and central nervous systems.37,48 This transcription fac-
tor has recently been shown to play a key role in adult
neurogenesis, suggesting it may be involved in memory
development.49 The contactin-associated protein-like 2
gene (CNTNAP2 [OMIM *604569]) is involved in brain
development.47 The contactin-associated protein-like 2
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development.47 The contactin-associated protein-like 2
gen (CNTNAP2 [OMIM *604569]) is involved in brain
development.
pressed in the brain.\textsuperscript{23,36} An isoform of STK24 has been shown to be a regulator of axon growth and axon regeneration after injury.\textsuperscript{57,58} However, we did not observe association in these regions in a meta-analysis of a replication sample of 5 white AD data sets containing 3568 cases and 6205 controls. A study of a larger independent sample of African American and possibly white samples will be needed to determine whether these associations are spurious or reflect population-specific variants or variable LD patterns among populations.

This study represents an important step in elucidating the genetic basis of AD in African Americans. Our results suggest that African Americans share some but not all AD genetic risk factors with whites. Further research would not only lead to a more accurate understanding of the genetic risk factors that could be incorporated in diagnostic and predictive testing protocols specific for African Americans but may also yield new gene discovery and clues for subsequent interventions useful to all populations at risk for AD.

Table 6. Top-Ranked Genetic Association Findings From Genome-wide Survey in African Americans

<table>
<thead>
<tr>
<th>CHR Position, dbSNP Build 129, bp</th>
<th>Gene</th>
<th>SNP</th>
<th>P Value</th>
<th>Effect Allele</th>
<th>AF</th>
<th>OR (95% CI)</th>
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<tr>
<td>1 212184713</td>
<td>–</td>
<td>rs340849</td>
<td>7.52 × 10⁻⁴</td>
<td>A</td>
<td>0.20</td>
<td>0.59 (0.47-0.75)</td>
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<tr>
<td>2 17291066</td>
<td>–</td>
<td>rs1189338</td>
<td>8.94 × 10⁻⁴</td>
<td>A</td>
<td>0.26</td>
<td>1.55 (1.28-1.88)</td>
</tr>
<tr>
<td>2 27760977</td>
<td>SLC4A1AP</td>
<td>rs17006206</td>
<td>2.30 × 10⁻⁴</td>
<td>G</td>
<td>0.10</td>
<td>2.05 (1.52-2.76)</td>
</tr>
<tr>
<td>3 28903864</td>
<td>–</td>
<td>rs2221154</td>
<td>2.58 × 10⁻⁴</td>
<td>T</td>
<td>0.19</td>
<td>0.57 (0.45-0.72)</td>
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<td>–</td>
<td>rs1923775</td>
<td>5.61 × 10⁻⁴</td>
<td>T</td>
<td>0.25</td>
<td>1.60 (1.30-1.96)</td>
</tr>
<tr>
<td>7 14652836</td>
<td>CNTNAP2</td>
<td>rs10273775</td>
<td>8.94 × 10⁻⁴</td>
<td>G</td>
<td>0.42</td>
<td>1.52 (1.27-1.84)</td>
</tr>
<tr>
<td>8 12978868</td>
<td>–</td>
<td>rs956225</td>
<td>8.71 × 10⁻⁴</td>
<td>G</td>
<td>0.03</td>
<td>0.30 (0.18-0.51)</td>
</tr>
<tr>
<td>11 73710714</td>
<td>–</td>
<td>rs3888908</td>
<td>9.52 × 10⁻⁴</td>
<td>A</td>
<td>0.15</td>
<td>1.72 (1.36-2.20)</td>
</tr>
<tr>
<td>11 11386774</td>
<td>–</td>
<td>rs10850408</td>
<td>9.25 × 10⁻⁷</td>
<td>T</td>
<td>0.34</td>
<td>0.63 (0.52-0.76)</td>
</tr>
<tr>
<td>12 2562232</td>
<td>–</td>
<td>rs17511627</td>
<td>5.01 × 10⁻⁴</td>
<td>C</td>
<td>0.17</td>
<td>1.75 (1.37-2.22)</td>
</tr>
<tr>
<td>13 97929295</td>
<td>STK24</td>
<td>rs912330</td>
<td>3.79 × 10⁻⁴</td>
<td>T</td>
<td>0.14</td>
<td>0.54 (0.41-0.70)</td>
</tr>
</tbody>
</table>

Other SNPs of Interest From APOE ε4 Adjusted Analysis

<table>
<thead>
<tr>
<th>CHR Position, dbSNP Build 129, bp</th>
<th>Gene</th>
<th>SNP</th>
<th>P Value</th>
<th>Effect Allele</th>
<th>AF</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 144692178</td>
<td>ZC3H3</td>
<td>rs3750208</td>
<td>7.28 × 10⁻⁴</td>
<td>A</td>
<td>0.04</td>
<td>0.37 (0.24-0.57)</td>
</tr>
<tr>
<td>12 29812934</td>
<td>TMT21</td>
<td>rs302318</td>
<td>1.97 × 10⁻⁴</td>
<td>C</td>
<td>0.26</td>
<td>0.59 (0.48-0.74)</td>
</tr>
<tr>
<td>13 43064019</td>
<td>ENOX1</td>
<td>rs17460623</td>
<td>9.37 × 10⁻⁴</td>
<td>C</td>
<td>0.10</td>
<td>0.49 (0.36-0.67)</td>
</tr>
</tbody>
</table>

Abbreviations: AF, effect allele frequency; bp, base pairs; CHR, chromosome; CNTNAP2, contactin-associated protein-like 2; dbSNP, database single-nucleotide polymorphism; ENOX1, ecto-NOX disulfide-thiol exchanger 1; OR, odds ratio; POLN, polymerase (DNA directed) nu; SLC4A1AP, solute carrier family 4 (anion exchanger), member 1, adaptor protein; SNP, single-nucleotide polymorphism; STK24, serine/threonine kinase 24; TMT21, transmembrane and tetrapiricideptide repeat containing 1; ZC3H3, zinc finger CCHC-type containing 3; –, indicates that the SNP is more than 50 kilobases from the nearest characterized gene.

\textsuperscript{a}Does not include multiple SNPs on CHR 1 that were redundant owing to strong linkage disequilibrium (pairwise R² > 0.8) and CHR 3 (R² > 0.7) and 1 SNP that did not meet minor allele frequency criteria in subjects from the Genetic and Environmental Risk Factors for Alzheimer Disease Among African Americans Study.
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Online-Only Material: The eTables, eMethods, and eAppendix are available at http://www.bumc.bu.edu/genetics/results/aa_alzheimer.

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REFERENCES


