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Novel Alzheimer Disease Risk Loci and Pathways in African American Individuals Using the African Genome Resources Panel

A Meta-analysis

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This genome-wide association study identifies additional Alzheimer disease risk loci in African American individuals using the African Genome Resource panel.

Key Points

Question

What genetic variants, genes, and pathways increase or decrease risk of Alzheimer disease in African American individuals?

Findings

In this genome-wide association meta-analysis of 2748 individuals with Alzheimer disease and 5222 controls, several novel genetic loci and pathways associated with Alzheimer disease in African American individuals were identified.

Meaning

While the major pathways involved in Alzheimer disease etiology in African American individuals are largely similar to those in non-Hispanic White individuals, many of the disease-associated loci within these pathways differ.

Abstract

Importance

Compared with non-Hispanic White individuals, African American individuals from the same community are approximately twice as likely to develop Alzheimer disease. Despite this disparity, the largest Alzheimer disease genome-wide association studies to date have been conducted in non-Hispanic White individuals. In the largest association analyses of Alzheimer disease in African American individuals, *ABCA7*, *TREM2*, and an intergenic locus at 5q35 were previously implicated.

Objective

To identify additional risk loci in African American individuals by increasing the sample size and using the African Genome Resource panel.

Design, Setting, and Participants

This genome-wide association meta-analysis used case-control and family-based data sets from the Alzheimer Disease Genetics Consortium. There were multiple recruitment sites throughout the United States that included individuals with Alzheimer disease and controls of African American ancestry. Analysis began October 2018 and ended September 2019.

Main Outcomes and Measures

Diagnosis of Alzheimer disease.

Results

A total of 2784 individuals with Alzheimer disease (1944 female [69.8%]) and 5222 controls (3743 female [71.7%]) were analyzed (mean [SD] age at last evaluation, 74.2 [13.6] years). Associations with 4 novel common loci centered near the intracellular glycoprotein trafficking gene *EDEM1* (3p26; $P = 8.9 \times 10^{-7}$), near the immune response gene *ALCAM* (3q13; $P = 9.3 \times 10^{-7}$), within *GPC6* (13q31; $P = 4.1 \times 10^{-7}$), a gene critical for recruitment of glutamatergic receptors to the neuronal membrane, and within *VRK3* (19q13.33; $P = 3.5 \times 10^{-7}$), a gene involved in glutamate neurotoxicity, were identified. In addition, several loci associated with rare variants, including a genome-wide significant intergenic locus near *IGF1R* at 15q26 ($P = 1.7 \times 10^{-9}$) and 6 additional loci with suggestive significance ($P \leq 5 \times 10^{-7}$) such as *API*5 at 11p12 ($P = 8.8 \times 10^{-8}$) and *RBFOX1* at 16p13 ($P = 5.4 \times 10^{-7}$) were identified. Gene expression data from brain tissue demonstrate association of *ALCAM, ARAP1, GPC6*, and *RBFOX1* with brain β-amyloid load. Of 25 known loci associated with Alzheimer disease in non-Hispanic White individuals, only *APOE*, *ABCA7*, *TREM2*, *BIN1*, *CD2AP*, *FERMT2*, and *WWOX* were implicated at a nominal significance level or stronger in African American individuals. Pathway analyses strongly support the notion that immunity, lipid processing, and intracellular trafficking pathways underlying Alzheimer disease in African American individuals overlap with those observed in non-Hispanic White individuals. A new pathway emerging from these analyses is the kidney system, suggesting a novel mechanism for Alzheimer disease that needs further exploration.

Conclusions and Relevance

While the major pathways involved in Alzheimer disease etiology in African American individuals are similar to those in non-Hispanic White individuals, the disease-associated loci within these pathways differ.

Introduction

Large-scale genomic studies identified more than 20 modest-effect Alzheimer disease (AD) risk loci besides the *APOE* gene.[1,2,3,4,5,6,7,8] However, these studies were predominantly conducted in individuals of non-Hispanic White ancestry and, taken together, the identified loci explain only 30% to 40% of the genetic contribution to AD,[9,10] substantially less than the heritability estimates from twin studies ranging from 60% to 80%.[11] Compared with non-Hispanic White individuals, African American individuals from the same community are twice as likely to develop AD.[12] Supporting the notion that there are many genetic loci with small effect sizes contributing to these observed ancestral differences in disease risk, we recently demonstrated that AD cases in African American individuals show higher levels of African ancestry than unaffected individuals, both globally and locally at AD-relevant loci.[13]

Various additional observations provide support for the genetic architecture of AD being partially ancestry-specific. In the largest genome-wide association study conducted to date and to our knowledge in African American individuals comprising 5896 participants from the Alzheimer Disease Genetics Consortium, we previously confirmed *ABCA7* and *APOE*, notably with substantial differences in odds ratios compared with non-Hispanic White individuals, and identified a novel intergenic locus at 5q35.[14] Of the additional common loci originally discovered in data sets of non-Hispanic White individuals, only a subset (*CR1, BIN1, EPHA1, CD33, TREM2)* replicated with nomi-

nal significance.[14,15] Importantly, the population differences in the effect of *APOE ε4* appear to be explained by the ancestral background on which the allele lies, as we have recently shown that *APOE ε4* alleles on an African background confer lower risk than those on a non-Hispanic White background.[16] Population-specific associations with AD in rare or low-frequency variants also have been identified. Several rare risk variants found in non-Hispanic White individuals do not show association with risk in African American individuals, possibly because they are extremely rare in African American individuals.[15,17] In a recent targeted sequencing study of *ABCA7,* we identified a novel 44 base pair frameshift deletion (rs142076058) in *ABCA7* in the same linkage disequilibrium block as the African American individuals' variant (rs115550680) identified by our previous genome-wide association study (GWAS)[18] that is common and associated with disease in African American individuals but present in very few non-Hispanic White individuals (minor allele frequency [MAF] = 0.12%). Two additional missense variants in *ABCA7* have been associated with AD in a separate African American population.[19] Finally, separate association studies of AD in African American individuals identified novel rare and low-frequency associations in *AKAP9*,[20] *COBL*, and *SLC10A2*[21] that appear specific to African American individuals. Neuropathologic differences in AD between populations[22,23,24,25,26] may also point toward population-specific risk loci for AD. The aim of the present analyses is to identify additional loci modulating risk in African American individuals.

Methods

To identify additional AD risk loci in African American individuals, we conducted a GWAS meta-analysis with a 37% increased sample size including individuals with AD and controls recruited from several case-control and family-based studies of African American individuals. A detailed description of the original cohorts and summary demographics of all samples included in this analysis are provided in the eAppendix and eTables 1-3 in Supplement 1. Written informed consent was obtained from all participants, and all study protocols were approved by the respective institutional review boards. Imputation was performed with the African Genome Resources panel,[27] which contains all African and non-African populations from 1000 Genomes phase 3 and more than 2000 individuals from various African regions, providing better coverage of ancestral haplotypes than the 1000 Genomes–based reference panels used in previous studies. In line with this notion, comparison of imputation quality of 1000 Genomes and African Genome Resources vs available whole-exome sequencing data in 800 participants demonstrated higher accuracy in the African Genome Resources (eTable 2 in Supplement 1). The final single-nucleotide variant set for analysis included 29 610 185 genotyped and imputed variants, more than doubling the number of variants from our previous analysis.[14] Genotype dosages were analyzed within each data set and subsequently meta-analyzed, adjusting for age, sex, and PCs for population substructure (model 1), and subsequently in addition for *APOE* genotype (model 2). Additional details on these analyses and the methods for gene, pathway, and expression association analyses can be found in the eMethods in Supplement 1. *P* values were 2-sided, and the standard GWAS threshold of 5×10^{-8} was used to define genome-wide significance. Analysis started October 2018 and ended September 2019.

Results

A total of 2784 individuals (1944 female [69.8%]) with AD and 5222 (3743 female [71.7%]) were analyzed (mean [SD] age at last evaluation, 74.2 [13.6] years). Single-variant meta-analyses replicated the *APOE* locus and both African American individuals' risk loci (rs115550680 [*ABCA7*] and rs145848414 [5q35]) from our previous analyses at $P < 5 \times 10^{-6}$ (Table 1 and Figure).[14] In addition, single-marker meta-analyses yielded 1 novel genome-wide significant ($P \leq 5 \times 10^{-8}$) disease locus associated with rare variants and 10 novel disease-associated loci (4 common variant loci, 6 rare variant loci) associated at $P \leq 5 \times 10^{-7}$ (Table 1; eFigures 1-2 in Supplement 1). There was no evidence for genomic inflation (model 1: $\lambda = 0.94$; model 2: $\lambda = 0.96$); see eFigure 3 in Supplement 1 for QQ plots). The 4 common loci were centered at (1) *EDEM1* on chromosome 3p26 (rs168193; MAF = 0.25; $P = 8.9 \times 10^{-7}$), a known linkage region for AD,[28] (2) *ALCAM* on chromosome 3q13 (rs2633682; MAF = 0.33; $P = 9.3 \times 10^{-7}$), (3) within *GPC6* on chromosome 13q31 (rs9516245; MAF = 0.04; $P = 4.1 \times 10^{-7}$), and (4) within *VRK3* on chromosome 19q13.33 (rs3745495; MAF = 0.10; $P = 3.5 \times 10^{-7}$). Three of 4 loci have strong regional support by variants in linkage disequilibrium (eFigure 1A in Supplement 1), and all 4 have consistent directions of effect across most individual data sets (eFigure 2A in Supplement 1). While *VRK3* is located approximately 5 megabases downstream of *APOE*, the *APOE*-adjusted model and analyses showing that rs3745495 is not in linkage disequilibrium with variants within *APOE* (eFigure 4 in Supplement 1) suggest that it represents an independent AD-associated signal in African American individuals. The identified rare variants include a genome-wide significant intergenic locus at 15q26 close to *ARRDC4* and *IGF1R* (rs570487962; MAF = 0.01; $P = 1.69 \times 10^{-9}$) and 6 loci with associations of $P < 5 \times 10^{-7}$ close to *SIPA1L2*, *WDR70*, *API5*, *ACER3*, *PIK3C2G*, and *RBFOX1* (Table 1 and eFigures 1 and 2 in Supplement 1). Repeating the analyses stratified by *APOEe4* carrier status revealed the association with *RBFOX1* was only present in cases without an *APOEe4* allele, while the intergenic association at *ARRDC4*/*IGF1R* was only found in carriers of the *APOEe4* allele (eTables 4-5 in Supplement 1). These results should be interpreted with caution because of the small sample sizes obtained after stratification on *APOEe4* status (eTable 5 in Supplement 1).

Of the variants previously implicated in AD in African American individuals by other studies,[15,17,20,21] rs112404845 in *COBL* showed association ($P = 5.4 \times 10^{-6}$), and 2 variants each in *TREM2* (rs7748513; $P = 3.6 \times 10^{-5}$ and rs2234256; $P = .001$) and *AKAP9* (rs149979685; $P = .005$ and rs914662445; $P = .01$) were replicated with at $P < .05$ (eTable 6 in Supplement 1). A low-frequency *TREM2* stop-gain variant previously reported at $P = .08$ in a sample of 906 load cases and 2487 controls, was associated at $P = 1.4 \times 10^{-3}$ (rs2234258).[17] Of the GWAS loci implicated in non-Hispanic White individuals besides *APOE* and *ABCA7*,[7] only the variants in *BIN1* ($P = 9 \times 10^{-4}$), *CD2AP* ($P = .02$), *FERMT2* ($P = .01$), and *WWOX* ($P = .04$) showed nominal association in this African American sample (eTable 6 in Supplement 1).

Gene-Based Analyses

Gene-based analyses confirmed at gene-wide significance the *TREM2* gene, originally identified in non-Hispanic White populations,[5,29] as an AD risk locus in African American individuals ($P = 9.89 \times 10^{-6}$) and identified 8 loci (*TRANK1*, *FABP2*, *LARP1B*, *TSRM*, *ARAP1*, *STARD10*, *SPHK1*, and SE*RPINB13*) with associations of $P \leq 1 \times 10^{-4}$ (Table 2 and eFigure 2 in Supplement 1). Of the

other risk loci previously reported in African American or non-Hispanic White individuals besides *TREM2*, only *C2DAP* ($P = .03$) was significant at $P \leq .05$ (eTable 7 in Supplement 1). Full summary statistics for the complete set of single-marker and gene-based analyses are available through the National Institute on Aging Genetics of Alzheimer Disease Data Storage Site.[30]

Validation and Prioritization of Identified Loci

To validate the identified loci and evaluate their biological significance, we examined differential expression of amyloid and tau pathology in AD vs control brains and conducted pathway analyses.

To explore differential expression, we capitalized on postmortem brain pathology quantified by immunohistochemistry and expression data from 478 individuals of European ancestry from the ROS/MAP study.[31] Covarying for sex, age at death (age at last visit for clinical AD diagnosis), postmortem interval, RNA integrity, *APOE ε4* status, and first 3 genomic principal components, higher expression of *ALCAM* ($\beta = 0.038$; $P = .003$) and *ARAP1* ($\beta = 0.058$; $P = 2.0 \times 10^{-4}$) and lower expression of *GPC6* ($\beta = -0.035$; $P = .001$) and *RBFOX1* ($\beta = -0.055$; $P = .001$) were associated with brain amyloid load after correction for multiple testing (Table 3; Bonferroni *P* value threshold for significance: $P = .05/19$ tested genes $= .003$). Higher expression of *STARD10* was associated with higher tau pathology burden ($\beta = 0.050$; $P = 8.46 \times 10^{-5}$). When covarying in addition for differences in cell type composition across samples, associations for *ALCAM* ($\beta = 0.033$; $P = .004$), *ARAP1* ($\beta = 0.06$; $P = 9.3 \times 10^{-6}$), *GPC6* ($\beta = -0.034$; $P = .002$), and *RBFOX1* ($\beta = -0.050$; $P = .001$) with brain amyloid load remained unchanged; association of *STARD10* with tau pathology burden was slightly attenuated ($\beta = 0.03$; $P = .01$).

Pathway analyses conducted using Multi-marker Analysis of GenoMic Annotation[32] identified 8 main functional groups at $P < 1 \times 10^{-3}$ (Table 4): (1) intracellular trafficking, (2) lipid and phospholipid metabolism, (3) transcription/DNA repair, (4) nervous system development/synaptic plasticity, (5) cell division, (6) immune response, (7) cellular signaling, and (8) kidney system development. With the exception of kidney system development, these pathways overlap with the key molecular mechanisms identified in the large-scale genomic studies in non-Hispanic White individuals.[7,33] However, enrichment of amyloid precursor protein/amyloid (A)-β and tau pathways, which recently emerged as top molecular pathways in the large-scale rare variant meta-analysis in non-Hispanic White individuals conducted by the International Genomics of Alzheimer Project (IGAP),[7] are notably absent among the top disease-associated pathways observed in this data set of African American individuals.

Examination of Identified Single-Variant, Gene-Based, and Pathway Associations in the IGAP Data Set of Non-Hispanic White Individuals

Comparison of the top single-variant associations in African American individuals with the results of the latest GWAS of non-Hispanic White individuals from the IGAP consortium (n = 94 437)[7] revealed nominal replication of the single-variant association in the *WDR70* gene ($P = .05$) and nearly nominal replication of the *RBFOX1* locus ($P = .07$) (eTable 8 in Supplement 1). Gene-based testing of loci resulting from the single-variant analysis of African American individuals revealed *PIK3C2G*

and *GPC6* to have significance at $P < .05$. For the gene-based loci, the only result with nominal replication in IGAP was *STARD10* ($P = .02$), although *ARAP1* also approached significance at $P < .05$. Of the 21 pathways associated at $P < 10^{-4}$ in African American individuals, only 2 replicated at a nominal level: inositol tetrakisphosphate phosphatase activity ($P = .02$) and positive regulation of nuclear division ($P = .05$), suggesting that while the major pathways are similar between African American and non-Hispanic White individuals, the subpathways defining these functions may differ slightly because of the specific genes involved.

Discussion

In the largest AD GWAS study on African American individuals conducted to date and to our knowledge, we confirmed *ABCA7*, the intergenic locus on chromosome 5q35, and several variants in or near *COBL*, *TREM2*, and *AKAP9* as associated with AD and identified 1 novel genome-wide significant disease locus and 10 novel disease-associated loci associated at $P \leq 5 \times 10^{-7}$. Gene-based analyses also confirmed *TREM2* as a risk locus in this population and nominated 8 additional loci with associations of $P \leq 1 \times 10^{-4}$. For 4 of these 8 novel loci, gene expression analysis from brain tissue demonstrated significant association with burden of brain amyloid (*ALCAM*, *ARAP1*, *GPC6*, *RBFOX1*), a key pathological hallmark of AD. Of 25 known loci in non-Hispanic White individuals,[7,34] only *APOE*, *ABCA7*, *TREM2*, *BIN1*, *CD2AP*, *FERMT2*, and *WWOX* were implicated at a nominal significance level or stronger in this African American sample.

Notably, the majority of novel loci identified in this study cluster in pathways was also implicated in non-Hispanic White individuals. The 4 common loci that were, because of their high allele frequencies, robustly present in all contributing data sets, cluster near or in genes involved in intracellular trafficking, immune response, and glutamatergic synaptic transmission. *EDEM1,* located in a known AD linkage region (3q26),[35] encodes a protein that sequesters misfolded proteins, including the amyloid precursor protein, away from productive folding cycles and redirects them to endoplasmic reticulum–associated degradation.[36,37,38] There is evidence that upregulation of endoplasmic reticulum–associated degradation leads to amyloid precursor protein degradation and reduced Aβ production.[39] *ALCAM* encodes CD166 antigen promoting T-cell activation, maturation of the immunological synapse, and axon growth. A recent GWAS on cognitive decline in older adults free of dementia identified a suggestive signal in the *ALCAM* gene region (rs34476301; $P = 6.5 \times 10^{-6}$) associated with longitudinal changes in the memory domain.[40] *GPC6* encodes glypican 6 belonging to a conserved family of heparan sulfate proteoglycans. Secreted by astrocytes, *GPC6* regulates recruitment of glutamate (GluA1 AMPA) receptors to the neuronal surface and promotes formation of excitatory synapses in neurons.[41] The locus at 19q13 shows different local ancestry with regard to AD status in African American individuals,[13] providing significant support for the importance of this region in AD etiology in this ethnic group. The signal falls within *VRK3* encoding a serine/threonine kinase modulating the activity of extracellular signal-regulated kinases[42] involved in the regulation of synaptic protein synthesis, dendritic morphology, and synaptic plasticity.[43,44] Dysregulation of glutamate-induced extracellular signal-regulated kinase signaling via *VRK3* is associated with Aβ accumulation,[45] and *VRK3* itself has been suggested as a potential therapeutic target for AD.[45] In expression data from the ROS/MAP study,[31] *ALCAM* and *GPC6* expression was associated with amount of brain amyloid pathology. Codeposition and association of

various heparan sulfate proteoglycans with Aβ has long been described,[46,47,48] and in vitro studies have shown that heparan sulfate proteoglycans can regulate Aβ production[49,50] and aggregation.[49,51]

The 7 identified rare variant loci include the 2 top loci identified in this study, centered in a non-coding RNA (LINC02254) near the *IGF1R* gene on chromosome 15q26 ($P = 1.69 \times 10^{-9}$) and *API5* on chromosome 11p12 ($P = 8.81 \times 10^{-8}$). The associated variants near *IGF1R* are all African-specific according to the Genome Aggregation Database.[52] Interestingly, a GWAS of cognitive flexibility, an AD-linked phenotype,[53] identified a genome-wide significant association approximately 80 kilobases upstream of this rare variant signal in African American individuals but not in non-Hispanic White individuals,[54] lending support to this locus as an AD locus specific to African American individuals. *IGF1R* is a receptor for insulinlike growth factor I (IGF-I) controlling stress resistance, aging, and lifespan.[55] Brains of individuals with AD show abnormalities in *IGF1R* expression and downstream signaling molecules, insulin and IGF1 resistance,[56,57] and long-term inhibition of IGF signaling supports neuronal function and neuroprotection.[57,58] Lifespan-extending heterozygous *IGF1R* knockout alleviates AD pathology through Aβ clearance,[56] confers neuroprotection against Aβ proteotoxicity, and improves behavior in mice with AD.[59,60] In this study, association of *IGF1R* expression with amyloid load was close to Bonferroni-corrected significance ($P = .005$). Apoptosis inhibitor-5 (*API5*) is a nuclear protein highly expressed in the brain whose expression prevents apoptotic cell death.[61]

While the top disease-associated variant at the chromosome 16p13 locus is located approximately 500 kilobases downstream of *RBFOX1*, analysis of expression data and findings from epidemiologic, animal, and experimental studies nominate *RBFOX1* as a potential candidate gene at this locus that warrants further scrutiny. *RBFOX1* is a critical regulator of splicing and cytoplasmic mRNA stability in neurons[62,63] that has been implicated across a series of neurodevelopmental and psychiatric disorders.[64] There is evidence from experimental studies that downregulation of *RBFOX1* leads to destabilization of messenger RNAs encoding for proteins involved in synaptic transmission and diminished synaptic function in AD[65,66] and that *RBFOX1* might regulate splicing of amyloid precursor protein.[67] Notably, a GWAS of positron emission tomography amyloid levels in individuals without dementia reported by Raghavan et al[68] nominates *RBFOX1* as a locus for brain amyloidosis, in line with this notion and our GWAS and brain amyloid pathology analyses.

Gene-based analyses confirmed *TREM2* as an AD risk gene in African American individuals and identified an additional 8 novel loci with associations of $P \leq 1 \times 10^{-4}$ (eFigure 5 in Supplement 1). Notably, also these genes largely cluster in AD pathways implicated by genomic studies in non-Hispanic White populations. While *TRANK1* at 3p22.2 is a known GWAS risk locus for bipolar disorder and schizophrenia[69,70,71,72] and potentially modulates expression of genes involved in neural development and differentiation,[73] *FABP2* and *STARD10* are involved in lipid metabolism, *SPHK1* and SE*RPINB13* in immune response, *LARP1B* in RNA transcription, and *ARAP1* in endocytosis and intracellular trafficking. Finally, the results of our pathway analyses also support the notion that the principal molecular pathways (eg, immunity, lipid processing, intracellular trafficking) underlying AD in African American individuals overlap with those observed in non-Hispanic White individuals, albeit largely with different disease-associated genes within these pathways. A novel AD pathway emerging from this pathway analyses is kidney system development. This finding is

particularly interesting given the observation that African American individuals are 3 times more likely to experience kidney failure compared with the non-Hispanic White population,[74] and along with Hispanic populations, have a higher rate of comorbidity for dementia and kidney disease.[75] Impaired kidney clearance of peripherally circulating Aβ results in elevated cerebral Aβ retention.[76] Determining the contribution of this comorbid condition to AD risk, and whether misdiagnosis of AD plays a role in this association,[77] could have important implications for the prevention and treatment of AD in African American individuals.

Compared with our previous analyses based on the 1000 Genomes panel (June 2011), the African Genome Resources reference panel used in the current analysis allowed us to include both a higher number of common variants and a significant set of low-frequency variants previously not included. While some of the newly identified common variants were assessed in the previous analyses but now reached genome-wide significance because of increased statistical power, most of the newly identified variants with rarer minor allele frequencies were previously not assessed. For all novel identified disease-associated variants, imputation quality was excellent. There was also no evidence of inflation in our study when including low-frequency variants, minimizing the likelihood that the observed associations are spurious.

Limitations

This study has limitations. First, given the paucity of available African American samples for genomic research on AD and the need to maximize sample size to reach sufficient statistical power to identify variants with low frequency or effect sizes, we combined all samples into 1 discovery set and relied on the IGAP data on non-Hispanic White individuals and ROS/MAP brain expression data sets for replication.[7,78] Additional validation will likely need to be derived from experimental studies. Second, while this is the largest GWAS data set on African American individuals to date and to our knowledge, our sample size was underpowered to detect associations with very rare single variants or rare variants exerting very small effects. Consequently, it is possible that there remain unidentified disease-associated variants.

Conclusions

Our study strongly suggests that the principal molecular pathways implicated in AD etiology in African American individuals largely overlap with those in non-Hispanic White individuals but that the disease-associated loci within these pathways differ. These observations are critical for several reasons. First, they provide significant support for the importance of native immune response, intracellular trafficking, lipid metabolism, nervous system development, and synaptic plasticity in AD etiology and suggest that these pathways are not ethnicity-specific but critical in disease etiology across ethnic groups. Second, this study suggests that there might also be pathways whose contributions to disease differ between ethnic groups. While amyloid and tau pathology did not emerge as top pathways in this data set on African American individuals, kidney system development was identified as a novel, plausible disease mechanism. Interestingly, cerebrospinal fluid concentrations of tau have been observed to be lower in African American individuals affected with AD compared with non-Hispanic White individuals with AD.[24] Finally, these observations strongly suggest that polygenic risk scores developed for non-Hispanic White populations will likely not be applica-

ble to this ethnic group and vice versa but that polygenic risk scores need to be developed and applied as ethnic group–specific. While additional validation is needed, the identified genomic loci and pathways significantly help to disentangle AD etiology in African American individuals, aid to clarify the molecular mechanisms underlying observed health disparities, and help to pinpoint molecular targets for therapeutic intervention in this ethnic group.

Notes

Supplement 1.

eAppendix. Description of cohorts

eMethods.

eTable 1. Genotyping Platforms used in the individual data sets

eTable 2. Comparison of imputation quality of 1000G Phase 2 and AGR reference vs whole-exome sequencing data in 800 subjects

eTable 3. Demographic characteristics of data sets

eTable 4. APOEe4-stratified results for top loci

eTable 5. Sample sizes for APOEe4-stratified analyses

eTable 6. Single-marker meta-analysis results for previously reported variants

eTable 7. Gene-based results for AD genes previously identified in non-Hispanic Whites or African Americans

eTable 8. Results of top African-American (A) single variant associations, (B) gene-based associations and (C) pathways in the IGAP non-Hispanic white data set

eFigure 1. Regional association plots for the (A) three novel common and (B) seven rare loci identified in single-variant meta-analysis

eFigure 2. Forest Plots of Odds Ratios (ORs) for the (A) three novel common and (B) seven rare loci identified in single-variant meta-analysis

eFigure 3. Quantile-quantile plots for single marker association analyses based (A) on the model adjusted for age, sex and population stratification and (B) age, sex, population stratification and APOE showing the deviation of observed from expected *P* values

eFigure 4. Linkage disequilibrium analyses between the top associated variant in 19q13.33 (rs3745495) and three variants in APOE: A) The top associated AA variant within APOE (rs147491), and B) The two variants that define the APOE genotype (rs429358 and rs7412). Analyses were done using LDLink

eFigure 5. Manhattan plot of gene-based analysis results. Model 1 (a) is adjusted for age, sex and population stratification; Model 2 (b) is adjusted for age, sex, population stratification and APOE

eReferences.

Supplement 2.

Nonauthor Collaborators. Alzheimer Disease Genetics Consortium (ADGC) collaborators.

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Figures and Tables

Table 1.

Results of SV Meta-analysis

Closest gene(s)	Marker	dbSNP	Major/minimum allele	MAF	Model 1[a]				I
					OR (95% CI)	*P* value	Direction[d]	*P* value for I^2, %	(((
Novel common loci									
EDEM1	3:5302077	rs168193	A/G	0.25	0.79 (0.72-0.87)	8.9×10^{-7}	−−−−−−+−−−−−+−	0.50	(((
ALCAM	3:104409208	rs2633682	C/A	0.33	0.78 (0.71-0.86)	9.3×10^{-7}	−−−−?−−−−−−−−−	0.86	(((
GPC6	13:94159800	rs9516245	T/C	0.04	1.61 (1.32-1.96)	2.5×10^{-6}	++++++++++++++	0.22	1 (2
VRK3	19:50524332	rs3745495	A/G	0.10	1.32 (1.17-1.48)	7.4×10^{-6}	−+−−−−+−−−+−+−	0.21	1 (1
Novel rare loci									
SIPA1L2	1:232376163[e]	rs115684722	A/T	0.01	12.6 (4.66-34.45)	6.3×10^{-7}	?+++?+?+++???+	0.70	3 (8
WDR70	5:37483940	rs184179037	C/T	0.006	5.00 (2.27-9.18)	1.8×10^{-7}	+++?++?+++????	0.64	5 (1
API5	11:43166842[e]	rs569584007	T/G	0.01	3.06 (1.26-7.40)	.013	????+??+++?+?+	0.92	1 (2
ACER3	11:76541840[e]	rs115816806	A/G	0.01	4.71 (2.15-10.31)	1.0×10^{-4}	?−+−?++?+?????+	0.42	((1
PIK3C2G	12:18471546	rs75739461	G/A	0.01	2.45 (1.59-	3.0×10^{-5}	+++?++−+++???+	0.94	3 (

Abbreviations: dbSNP, Single Nucleotide Polymorphism Database; MAF, minor allele frequency; NA, not applicable; NHW, non-Hispanic White; NP, not present; OR, odds ratio; SV, single variant.

[a]Model 1 is adjusted for PCs, age, and sex.

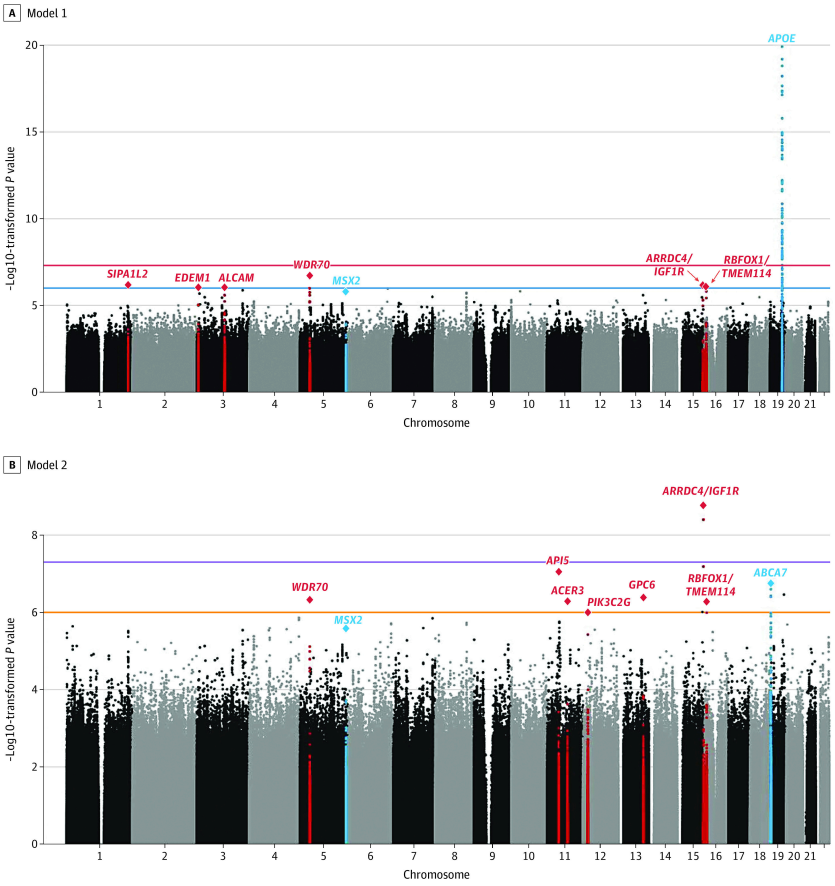
[b]Model 2 is adjusted for PCs, age, sex, and *APOE* genotype.

[c]*P* value for NHW individuals' SV and gene-based tests adjusted for PCs, age, and sex.

[d]Study-specific direction of the single-nucleotide variant β coefficient.

[e]Variant was not assessed in Reitz et al.[14]

Figure.



Association Plots From Single-Variant Meta-analysis

Manhattan plots showing negative $\log_{10}$-transformed *P* values from the single-variant meta-analysis adjusted for age, sex, and population stratification (A, model 1) and age, sex, population stratification, and *APOE* (B, model 2). The horizontal lines represent the genome-wide significance threshold ($P = 5 \times 10^{-8}$; red) and suggestive threshold ($P = 1 \times 10^{-6}$; orange). Loci are labeled with the closest gene(s) to the sentinel variant. Known loci are in blue and novel loci are in red. The *y*-axis is truncated, and the lowest *P* value on chromosome 19 was 1.8×10^{-25}.

Table 2.

Novel Top Loci Identified in Gene-Based Analyses

Gene	Chromosome	Start BP (hg37)	Stop BP (hg37)	No.	Model 1[a]			Model 2[b]			Pathw
					No. of SNVs	*z* Statistic	*P* value	No. of SNVs	*z* Statistic	*P* value	
TRANK1	3	36 858 311	37 021 548	7984	1221	2.83	2.2×10^{-3}	1201	3.83	6.4×10^{-5}	Neuro
FABP2	4	120 228 405	120 278 545	7984	411	2.66	3.8×10^{-3}	452	4.00	3.1×10^{-5}	Lipid r
LARP1B	4	128 947 423	129 154 086	7984	1071	4.11	1.9×10^{-5}	1334	1.93	2.6×10^{-2}	RNA tr
TSRM	7	113 056 127	113 101 457	7984	334	3.62	1.4×10^{-4}	334	4.02	2.7×10^{-5}	Zinc fi related
ARAP1	11	72 386 114	72 539 644	7984	1294	3.74	9.1×10^{-5}	1281	3.62	1.4×10^{-4}	Endocy traffick
STARD10	11	72 455 774	72 539 726	7984	664	3.94	3.9×10^{-5}	660	3.50	2.3×10^{-4}	Lipid r
SPHK1	17	74 337 665	74 393 941	7984	485	3.73	9.3×10^{-5}	482	3.48	2.5×10^{-4}	Immur
SE*RPINB13*	18	61 219 223	61 281 873	7984	633	3.10	9.4×10^{-4}	626	3.79	7.4×10^{-5}	Protea immur

Abbreviations: BP, base pair; SNV, single-nucleotide variant.

[a]Model 1 is adjusted for PCs, age, and sex.

[b]Model 2 is adjusted for PCs, age, sex, and *APOE* genotype.

Table 3.

Association of Gene Expression at Suggestive Loci With Neuropathological Measures of Alzheimer Disease in the ROS/MAP Data Set[31]

Chromosome	Band	Symbol	Amyloid pathology		Tau pathology	
			β[a]	*P* value	β[a]	*P* value
1	q42.2	*SIPA1L2*	−0.004	.72	−0.018	.08
3	p22.2	*TRANK1*	−0.057	.005	−0.046	.007
3	p26.1	*EDEM1*	0.002	.84	−0.022	.01
3	q13.11	*ALCAM*	0.038	.003	−0.023	.03
4	q26.2	*FABP2*	Not detected in DLPFC		Not detected in DLPFC	
4	q28.2	*LARP1B*	−0.017	.21	0.019	.10
5	p13.2	*WDR70*	−0.028	.05	0.036	.004
11	p12	*API5*	0.009	.24	−0.013	.04
11	q13.4	*ARAP1*	0.058	2.0×10^{-4}	0.019	.11
11	q13.4	*STARD10*	0.005	.71	0.050	8.46×10^{-5}
11	q13.5	*ACER3*	0.027	.08	−0.002	.91
12	p12.3	*PIK3C2G*	−0.011	.09	−0.001	.88
13	q31.3	*GPC6*	−0.035	.001	0.001	.91
15	q26.2	*ARRDC4*	0.017	.32	−0.023	.11
15	q26.2	*IGF1R*	0.031	.005	−0.005	.61
16	p13.3	*RBFOX1*	−0.055	.001	0.008	.57
17	q25.2	*SPHK1*	0.067	.01	0.015	.50
18	q21.33	SE*RPINB13*	Not detected in DLPFC		Not detected in DLPFC	
19	q13.33	*VRK3*	−0.001	.91	−0.022	.03

Abbreviation: DLPFC, dorsolateral prefrontal cortex.

[a]β Coefficient for the association between the expression of the gene and amyloid or tau pathology is reported. A positive β coefficient reflects an increased pathology burden in the presence of higher gene expression, and a negative β coefficient reflects an inverse association.

Table 4.

Top Associated Pathways Derived From MAGMA Pathway Analysis

Pathway (GO)	Model	No. of genes	*P* value	Pathway description
GO:0045898	2	13	2.0×10^{-5}	Transcription
GO:0051004	1	15	4.9×10^{-5}	Lipoprotein metabolism
GO:0072017	1, 2	12	1.0×10^{-4}	Kidney system development
GO:0072207	1	20	2.2×10^{-4}	Kidney system development
GO:0033363	1	27	3.4×10^{-4}	Intracellular trafficking
GO:0015693	2	11	3.4×10^{-4}	Magnesium ion transport
GO:0048169	1	23	3.5×10^{-4}	Synaptic plasticity
GO:0051785	2	62	4.3×10^{-4}	Cell division
GO:0009395	1	29	4.6×10^{-4}	Phospholipid metabolism
GO:0006266	2	16	4.7×10^{-4}	DNA repair
GO:0042493	2	422	5.2×10^{-4}	Drug response
GO:0044304	2	58	5.6×10^{-4}	Nervous system development
GO:1903533	1	296	5.7×10^{-4}	Intracellular trafficking
GO:0052743	1	10	6.5×10^{-4}	*ITPKB*/Ins(1,3,4,5)P4/ERK signaling
GO:0051717	1	10	6.5×10^{-4}	Cellular signaling
GO:1990782	1	55	6.5×10^{-4}	Cellular signaling
GO:0002281	2	11	6.6×10^{-4}	Immune response
GO:0046475	1	13	7.3×10^{-4}	Phospholipid metabolism
GO:0051103	2	12	8.4×10^{-4}	DNA repair
GO:0032386	1	597	8.8×10^{-4}	Intracellular trafficking
GO:0008143	2	12	9.3×10^{-4}	Transcription
GO:0045840	1	51	9.7×10^{-4}	Cell division

Abbreviations: ERK, extracellular signal-related kinase; MAGMA, Multi-marker Analysis of GenoMic Annotation.