REVIEW

Genetics of Alzheimer's Disease in Caribbean Hispanic and African American Populations

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Late-onset Alzheimer's disease (LOAD), which is characterized by progressive deterioration in cognition, function, and behavior, is the most common cause of dementia and the sixth leading cause of all deaths, placing a considerable burden on Western societies. Most studies aiming to identify genetic susceptibility factors for LOAD have focused on non-Hispanic white populations. This is, in part related to differences in linkage disequilibrium and allele frequencies between ethnic groups that could lead to confounding. However, in addition, non-Hispanic white populations are simply more widely studied. As a consequence, minorities are genetically underrepresented despite the fact that in several minority populations living in the same community as whites (including African American and Caribbean Hispanics), LOAD incidence is higher. This review summarizes the current knowledge on genetic risk factors associated with LOAD risk in Caribbean Hispanics and African Americans and provides suggestions for future research. We focus on Caribbean Hispanics and African Americans because they have a high LOAD incidence and a body of genetic studies on LOAD that is based on samples with genome-wide association studies data and reasonably large effect sizes to yield generalizable results.

Key Words: African American, Alzheimer's disease, Caribbean Hispanic, gene, genetics, minorities

Late-onset Alzheimer's disease (LOAD) places a considerable burden on Western societies. LOAD is the most common cause of dementia, increasing in frequency from 1% at age 65 years to more than 30% for people older than 80 years (1), and the fifth leading cause of death in persons aged 65 years and older. To date, an estimated 5.4 million Americans have LOAD, but the prevalence in 2050 is expected to reach 11 to 16 million patients (2).

Senile plaques (SPs) and neurofibrillary tangles (NFTs) are considered the key pathologic hallmarks of Alzheimer's disease. The identification of β-amyloid (Aβ) in SPs and genetic studies that identified mutations in the amyloid precursor protein (*APP*) (3,4), presenilin 1 (*PSEN1*) (5), and presenilin 2 (*PSEN2*) genes (5,6) leading to the accumulation of Aβ and early-onset familial dementia, resulted in the formulation of the "amyloid cascade hypothesis." According to this hypothesis, the deposition of Aβ is the initial pathologic trigger in the disease, which subsequently leads to the formation of NFTs, neuronal cell death, and dementia. Although there is considerable evidence supporting this hypothesis, there are observations that seem to be inconsistent. First, SPs and NFTs may be reactive products resulting from neurodegeneration in Alzheimer's disease rather than being its cause; second, it remains unclear whether and how the deposition of Aβ leads to the formation of NFTs.

It is clear that in non-Hispanic whites of European ancestry, as much as 20% of the population-attributable risk of LOAD is related to the ε4 variant in apolipoprotein E (*APOE*) (7–9). A series of large genome-wide association studies (GWASs) identified several additional variants that affect disease susceptibility in non-Hispanic whites, including *CR1*, *CLU*, *PICALM*, *BIN1*, *CD2AP*, *CD33*, *EPHA1*, *MS4A6A/MS4E4*, *SORL1*, and *ABCA7* (10–13). In addition, *SORCS1* was identified as a susceptibility gene in candidate gene and functional studies (14), and a rare variant in *TREM2* was identified in two recent sequencing studies (15,16). In summary, these variants point to three distinct pathways: lipid metabolism, inflammation, and endocytosis/intracellular trafficking. However, LOAD heritability estimates are high ($h^2 \approx$ 60%–80%), and a large part of the genetic contribution to LOAD in this ethnic group remains unexplained (17–20).

Most genetic association studies have focused on non-Hispanic white populations because there are differences in linkage disequilibrium (LD) and allele frequencies between ethnic groups that lead to genetic background noise and the likelihood of false-positive findings due to confounding. In addition, there is a paucity of data sets with appropriate genotyping and phenotyping in minority groups. As a consequence, ethnic groups other than non-Hispanic whites are genetically understudied despite the fact that in several minority populations living in the same communities as whites, LOAD incidence is higher (21). In addition, the reported LOAD risk associated with *APOE*-ε4 heterozygosity is inconsistent in most of these ethnic groups (22). This review summarizes the current knowledge on genetic risk factors associated with LOAD risk in Caribbean Hispanics and African Americans and provides suggestions for future research. We are focusing on these two ethnic groups because they are the best-studied minority groups with high LOAD incidence that have GWAS data and large enough sample sizes to reliably detect risk loci. We first discuss the epidemiology of LOAD and role of *APOE* genotype in both ethnic groups followed by a separate discussion on genetic studies performed in either ethnic group outside the *APOE* locus.

Epidemiology of LOAD in African Americans and Caribbean Hispanics

African Americans are 2 to 4 times and Caribbean Hispanics twice as likely as non-Hispanic whites to have LOAD (21,23). Although differences in LOAD etiology across populations have been widely studied, they are still poorly understood. The occurrence of multiple demented individuals in African American and Caribbean Hispanic families is significantly higher than in

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white families, although the genetic risk of LOAD is similar (24). Although comparisons of risk across ethnic groups are complicated by differences in assessment of cognitive decline across studies and by population differences in willingness to participate in medical research, the increased risk in these specific ethnic groups may be a result of higher rates of risk factors such as poor education, cardio- and cerebrovascular disease, and the metabolic syndrome (23).

APOE Region and Risk of LOAD in African Americans and Caribbean Hispanics

In non-Hispanic whites, the strongest susceptibility gene for LOAD is *APOE*, a lipid-binding protein expressed in humans as three common isoforms coded for by three alleles, APOEε2, ε3, and ε4. The first reports linking *APOE* with LOAD found a significant increase in the *APOEε4* allele frequency in white patients with the disease. The large body of epidemiologic data that subsequently accumulated in cohorts of whites supported this notion by demonstrating that *APOEε4* decreases the age at onset of LOAD in this ethnic group in a gene dosage-dependent manner (25–34) and that *APOEε4* is associated with lower cognitive performance—in particular, the memory domain. It is thought that in non-Hispanic whites, *APOE* may account for as much as 20% to 50% of LOAD risk (7,35). It is important to note that calculation of population attributable risk is specific for a genetic factor and does not allow conclusions for other genetic variants, meaning that the sum of all other population attributable risks can exceed 100%.

In vitro studies have indicated that the *APOE-ε4* isoform binds Aβ peptides with a higher avidity compared with APOE-ε3 (36). Furthermore, there is a strong correlation between the presence of an *APOE-ε4* allele and a higher Aβ burden in the brains of LOAD patients (37,38), suggesting that *APOE* interacts with Aβ in enhancing its deposition in plaques. This is supported by the observation that homozygous *APOE* knockout (*APOE*−/−) mice develop fewer and more diffuse, nonfibrillar Aβ deposits (39–41). Some but not all studies assessing the effect of different *APOE* isoforms on Aβ fibrillization showed that the ε4 isoform leads to increased Aβ aggregation in vitro (42,43). Similarly, in vivo studies in *APOE*−/− mice indicated that Aβ fibrillization and plaques formation was increased in mice expressing human *APOE-ε4* (APPV717F+/−, apo E−/−) compared with mice not expressing human *APOE* (44,45). Still, it is possible that *APOE* exerts its effects through different mechanisms—for example, *APOE* is a major cholesterol transporter, and high cholesterol levels have been associated with an increased Aβ load in animal models (46,47) and changes in *APP* processing (48,49). Thus, *APOE* isoform-specific changes in cholesterol binding and transport in brain might also affect plaque formation in LOAD brains.

As described earlier, in African Americans and Caribbean Hispanics, the reported LOAD risk associated with the *APOE-ε4* allele is inconsistent (18–20,22). Although in several studies number of copies of the e4 allele were not associated with risk or age-of onset of LOAD (18,20,22,50), other studies observed such effect (19). The disparity could be due to recruitment bias, differences in age distribution, sample size, population stratification, or differences in residual confounding through environmental or cultural factors. The largest GWAS performed to date in African Americans strongly suggests an increased risk of LOAD for *APOE4* carriers (51).

Roses *et al.* (52) previously reported an association between a variable length poly-T polymorphism ("poly-T") at rs10524523 in the gene encoding the channel-forming subunit of the translocase of the mitochondrial outer membrane (*TOMM40*) and risk for LOAD and age of onset of LOAD in a small sample of non-Hispanic whites ($n = 34$). Subsequently, the same group assessed both the "523" allele frequencies of this polymorphism and their linkage pattern with *APOE* (which resides in the same region on chromosome 19) and reported associations in non-Hispanic whites and other ethnic groups. However, a more recent study of this polymorphism in a much larger sample of non-Hispanic whites failed to confirm the original findings after adjusting for the effect of *APOE*-ϵ4 (53). In addition, in a large sample of more than 22,000 white subjects, the Alzheimer's Disease Genetics Consortium showed that *APOE* alleles ϵ2, ϵ3, and ϵ4 account for essentially all the inherited risk of LOAD associated with the *APOE* region and that other variants including the poly-T track in *TOMM40* are not independent risk or age-of-onset loci (54). Although no additional large-scale studies have reassessed this issue in other ethnic groups, it is likely that, due to the lesser extent of LD in African Americans and Caribbean Hispanics compared with whites, this is also true for these ethnic groups.

Genetic Studies in Caribbean Hispanics Outside the *APOE* Region

Family-Based Linkage Studies

Multiple genome-wide linkage studies for LOAD were published between 1997 and 2006, and most were performed on white populations. Although some chromosomal regions have been studied and replicated extensively using linkage (most notably chromosomes 9, 10, and 12) (55–58), no consistently replicated LOAD gene has yet been identified using this method. There are several reasons for these limited results, including the generally small data sets, the inability of the then-available molecular genotyping technologies to capture all the segregation information in the families, and the sensitivity of linkage studies to underlying locus heterogeneity when using data sets consisting of a large number of small families. However, the inability to conclusively identify causal genes within these regions supports the possibility that multiple rare variants could be involved in Alzheimer's disease risk in these families.

In linkage analyses of in 79 Caribbean Hispanic multiplex LOAD families from the participating in the Estudio Familiar de Influencia Genetica de Alzheimer (EFIGA) study using 35 microsatellite markers near the centromere of chromosome 12, Mayeux *et al.* (59) observed modest evidence of linkage with support for D12S1623 and D12S1042. Linkage varied by age at onset of LOAD and by the presence or absence of the APOE-epsilon 4 allele. In larger follow-up studies, first in 490 individuals from 96 Caribbean Hispanic families using 340 microsatellite markers (60) and then in 1075 individuals from 209 families (61,62), Lee *et al.* obtained support for linkage on 3q28, 10q26, 12p12–13, and 18q21, some of which had also been repeatedly reported by linkage or case–control studies in whites (in particular, 10q and 12p) or Amish (18q) on LOAD (55,60,63–70). All these regions include candidate genes that may be biologically plausible but still remain to be confirmed by sequencing and functional studies. Finally, the same group observed a small effect of the alpha-2 macroglobulin deletion/insertion polymorphism on familial LOAD risk. Alpha-2 macroglobulin is a proteinase inhibitor that binds β-amyloid peptide and prevents fibril formation (71).

Heritability of LOAD Endophenotypes

Johnson *et al.* and Lee *et al.* explored the heritability of several cognitive endophenotypes of LOAD in Caribbean Hispanics and observed high heritability for memory performance (delayed recall [h(2) = .60]; delayed recognition [h(2) = .41]; and abstract reasoning [h(2) = 32.6%]) (72,73).

GWAS and Candidate Gene Studies

Table 1 summarizes the GWAS and candidate gene studies performed. In a community-based case–control candidate-gene study on several ethnic groups that included 372 Caribbean Hispanic individuals, Lee *et al.* (74) identified multiple LOAD-associated single nucleotide polymorphisms (SNPs) and haplotypes in the 5′ and 3′ ends of the L(DLR class) A repeats-containing sortilin-related receptor (*SORL1*) that were associated in African Americans. *SORL1* is a cargo molecule of the retromer complex and involved in trafficking of *APP*, and underexpression of *SORL1* leads to overproduction of Aβ (75). The variants identified include SNPs 12 and 26 (rs12285364 and rs1784933, respectively) and the TTC haplotype at SNPs 23 through 25 (rs3824968, rs2282649, rs1010159), which was significantly associated with LOAD in the North European white individuals in previous reports (75,76).

Lee *et al.* (77) also performed the largest GWAS to date in Caribbean Hispanics. The study included 549 cases and 544 controls originating from the Dominican Republic and Puerto Rico who are part of the Washington Heights-Inwood Columbia Aging Project (WHICAP) and the Estudio Familiar de Influencia Genetica de Alzheimer (EFIGA) family study. Although the strongest support was observed for rs9945493 on 18q23, the study identified five SNPs that could subsequently be replicated in an independent Caucasian validation data set and are located near genes or regions that could be biologically relevant to LOAD and/or have also been reported other studies performed in Caucasians including SNPs on 2p25.1, 3q25.2, 7p21.1, and 10q23.1 containing *HPCAL1*, *DGKB*, *GHITM*, *C10orf99*, *PCDH21*, *LRIT2*, *LRIT1*, and *RGR*. In addition, the study replicated *CLU*, *PICALM*, and *BIN1*. The effect sizes for all observed variants were modest (.33 < odds ratio < 1.87).

In the same Caribbean Hispanic data set, Reitz *et al.* explored the association between variants in the Fat and Obesity Associated (*FTO*) gene and risk of LOAD (78). The authors identified three SNPs (rs17219084, rs11075996, and rs11075997) that were associated with LOAD, consistent with independent studies in non-Hispanic whites showing that polymorphisms in the *FTO* gene have robust effects on obesity, obesity-related traits, and endophenotypes associated with LOAD (79–82). In the same cohort, the authors explored the association between SNPs in leucine-rich repeat transmembrane 3 (*LRRTM3*) gene and LOAD (83). *LRRTM3* is a neuronal gene promoting APP processing by β-secretase 1, thereby modulating the levels of Aβ40 and Aβ42. In addition, *LRRTM3* is nested in the alpha-3 catenin gene (*CTNNA3*) on chromosome 10q22.2 that in turn binds presenilin 1. Four SNPs belonging to two distinct LD blocks and including one promoter SNP were associated (rs16923760, rs1925608, rs7082306, rs1925609) as were their corresponding haplotypes. In functional analyses LRRTM3 knockdown with small-hairpin RNAs caused a significant decrease in APP processing compared with the scrambled small-hairpin RNA condition consistent with the notion that that LRRTM3 may modulate gamma-secretase processing of APP (83).

A study by Ghani *et al.* (84) that conducted a genome-wide scan for large copy number variation (CNV) in this data set observed a nominal association between LOAD and an approximately 470-kb duplication on chromosome 15q11.2 that encompasses up to five genes (*TUBGCP5*, *CYFIP1*, *NIPA2*, *NIPA1*, and *WHAMML1*) and was present in 10 cases and 3 control subjects. The dosage increase of the *CYFIP1* and *NIPA1* genes was further confirmed by quantitative polymerase chain reaction. Both genes are interesting LOAD candidate genes. *NIPA1* encodes a magnesium transporter associated with early endosomes in neuronal and epithelial cells; CYFIP1 forms a complex at synapses with the fragile X mental retardation protein (FMRP) and eIF4E (FMRP-CYFIP1-eIF4E complex). FMRP acts as an APP translation repressor releasing CYFIP1 from the FMRP-CYFIP1-eIF4E complex in response to synaptic stimulation and unbalanced dosage of CYFIP1 might result in altered APP turnover in Alzheimer's disease patients. The study did not detect CNVs (including common variants) affecting the well-confirmed LOAD loci reported by large GWAS in non-Hispanic whites (*CLU*, *PICALM*, *BIN1*, *CR1*, *MS4A4/MS4A6E*, *CD2AP*, *CD33*, *EPHA1*, and *ABCA7*). However, this could be explained by analytical challenges in the detection of common CNVs from SNP-intensity data. In general, a case-control setting can only test common CNVs that cluster and are well tagged by common SNPs. These CNVs could be of a multiallelic or complex nature (e.g., a small deletion within a large CNV duplication) and can only be accurately genotyped using a combination of custom arrays and deep sequencing. Finally, in a subset of this data set that had information on plasma Aβ40 and 42 levels (160 cases, 294 controls), Reitz *et al.* (85) explored the association of genetic variation in the *IDE-KIF11-HHEX* complex with LOAD. Of 32 SNPs in this region, 3 (rs2421943, rs12264682, and rs11187060) were associated with plasma Aβ40 or Aβ42 levels in single marker and haplotype analyses after correction for multiple testing. These SNPs lie within the same LD block and are in LD with haplotypes previously reported in whites (86,87). IDE binds and degrades Aβ40 and Aβ42, and this Aβ degrading activity has been shown to be lower in LOAD brains than in controls (88). Consistent with this notion, in *IDE* knockout mice, brain Aβ levels are elevated (89). Polymorphisms in *IDE* may also contribute to the risk of type 2 diabetes (90), which itself is associated with LOAD. Taken together the findings reported here support the possibility that the *IDE-KIF11-HHEX* region on chromosome 10q may contain genetic variants modifying Aβ40 and 42 levels.

Sequencing Studies

Although a few sequencing studies of individual polymorphisms associated with the early-onset form of the disease have been performed in individual Caribbean Hispanic families (91,92), no targeted candidate gene sequencing or whole exome or genome sequencing studies have been conducted. Reasons for this include both the previous lack of high-throughput sequencing technology that was only developed over the past five years and the paucity of appropriate data sets.

Genetic Studies in African Americans Outside the *APOE* Region

GWAS and Candidate Gene Studies

Although no family-based linkage or sequencing studies on LOAD have been performed in African Americans outside the *APOE* region, several GWAS and candidate gene studies have been conducted (Table 1). Logue *et al.* (93) analyzed a genome-wide set of 2.5 million imputed markers in 513 well-characterized African American LOAD cases and 496 cognitively normal controls

Table 1. Genome-Wide Association and Candidate Gene Studies on Late-Onset Alzheimer's Disease Performed in Caribbean Hispanics and African Americans

Study	Source Population(s)	Cases (*n*)	Controls (*n*)	Age Range	Phenotype	Genotyping	Finding (Disease-Associated SNP, Allele)
Caribbean Hispanics							
Lee *et al.* (2007) (74)	WHICAP	178	194	>65 years	LOAD (NINCDS-ARDRA criteria)	29 *SORL1* SNPs	rs12285364 (T allele ,↑) associated with LOAD
Lee *et al.* (2011) (77)	WHICAP, EFIGA	549	544	>65 years	LOAD (NINCDS-ARDRA criteria)	Illumina 650Y	rs9945493 on 18q23; rs4669573 and rs10197851 on 2p25.1; rs11711889 on 3q25.2; rs1117750 on 7p21.1; and rs7908652 on 10q23.1); *CLU* (rs881146), *PICALM* (rs17159904), *BIN1* (rs7561528)
Reitz *et al.* (2012) (78)	WHICAP, EFIGA	549	544	>65 years	LOAD (NINCDS-ARDRA criteria)	Illumina 650Y	3 SNPs (rs17219084 [G allele, ↑], rs11075996 [T allele, ↑], rs11075997 [T allele, ↑]) and corresponding haplotypes in *FTO* associated with LOAD
Reitz *et al.* (2012) (85)	WHICAP, EFIGA	549	544	>65 years	LOAD (NINCDS-ARDRA criteria)	Illumina 650Y	4 SNPs (rs16923760 [C allele, ↓], rs1925608 [C allele, ↓], rs7082306 [A allele, ↓], rs1925609 [T allele, ↑]) and corresponding haplotypes in *LRRTM3* associated with LOAD
Ghani *et al.* (2012) (84)	WHICAP, EFIGA	549	544	>65 years	LOAD (NINCDS-ARDRA criteria)	Illumina 650Y	470-kb duplication on chromosome 15q11.2 with dosage increase of *CYFIP1* and *NIPA1* associated with LOAD
Reitz *et al.* (2012) (78)	WHICAP, EFIGA	160	294	>65 years	Plasma Aβ40 and Aβ42 levels	Illumina 650Y	3 SNPs in IDE (rs2421943 [A allele, ↑], rs12264682 [A allele, ↓], rs11187060 [T allele, ↓]) associated with plasma Aβ40 or Aβ42 levels
African Americans							
Lee *et al.* (2007) (74)	WHICAP	88	158	>65 years	LOAD (NINCDS-ARDRA criteria)	29 *SORL1* SNPs	rs12285364 (T allele,↓), rs1784933(G allele, ↑) associated with LOAD
Logue *et al.* (2011) (93)	MIRAGE, GenerAAtions	513	496	>65 years	LOAD (NINCDS-ARDRA criteria)	Illumina 610 Quad, Illumina 370 Duo	Various SNPs in *APOE*, *PVRL2*, *CLU*, *PICALM*, *BIN1*, *EPHA1*, *MS4A*, *ABCA7*, *CD33*, associated with LOAD[a]
Reitz *et al.* (2013) (51)	Multiple sites	1968	3928	>65 years	LOAD (NINCDS-ARDRA criteria)	multiple Illumina chips	*APOE*, *ABCA7*, *CR1*, *BIN1*, *EPHA1*, *CD33* associated with LOAD[a]
Burgess *et al.* (2011) (94)	Mayo Clinic, Jacksonville	119	252	>60 years	LOAD (NINCDS-ARDRA criteria)	15 *KIBRA* SNPs	Significantly reduced LOAD risk for rs17070145 T allele in the older subjects
Akomolafe *et al.* (2006) (96)	MIRAGE	241	226	>65 years	LOAD (NINCDS-ARDRA criteria)[b]	11 *NOS3* SNPs	Glu298 allele associated with higher LOAD risk
Erlich *et al.* (2006) (97)	MIRAGE	241	226	>65 years	LOAD (NINCDS-ARDRA criteria)[b]	29 SNPs in *PON* gene cluster	Eight SNPs and several haplotypes associated with increased LOAD including *PON1* promoter SNP-161[C/T]

EFIGA, Estudio Familiar de Influencia Genetica de Alzheimer; LOAD, late-onset Alzheimer's disease; MIRAGE, Multi-Institutional Research on Alzheimer Genetic Epidemiology; NINCDS-ADRDA criteria, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria; SNP, single nucleotide polymorphisms; WHICAP, Washington Heights-Inwood Columbia Aging Project.

[a]Disease-associated alleles differ compared with whites.

[b]Control status based on modified Telephone Interview of Cognitive Status.

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. The analyses identified rs6859 in *PVRL2* as a novel susceptibility locus and replicated *CLU*, *PICALM*, *BIN1*, *EPHA1*, *MS4A*, *ABCA7*, and *CD33* as susceptibility genes, although the effect direction for some SNPs and the most significant SNPs in these genes differed from findings of the white data sets (11–13).

The largest GWAS to date on LOAD in African Americans (51) was performed by the Alzheimer's Disease Genetics Consortium and included 5896 subjects (1968 cases and 3928 controls) that were collected from multiple sites within the United States. The top-ranked SNP observed in this study is located in *ABCA7* (rs115550680) and notably has an effect size that is nearly as strong as the effect size of *APOEε4* (70%–80% increase in risk). This observation clearly differs from the GWAS performed in whites in which the reported *ABCA7* SNPs (rs3752246, rs3764650) but also the SNPs in all other reported genes (*CR1*, *BIN1*, *PICALM*, *CLU*, *EPHA1*, *MS4A* cluster, *CD2AP*, *CD33*) have significantly lower effect sizes (~10%–20% increase in risk) (11–13). It remains possible that this could be due to population differences in the frequencies of the causative variant(s) tagged by the associated SNPs or the result of a bias in the estimated effect of a newly identified allele on disease (also termed "winner's curse"). However, it is also possible that the large difference in the effect size of the *ABCA7* locus on the risk of LOAD is explained by population-specific causative variants with variable impact on protein structure or function. The LD block in which rs115550680 is located spans across several introns and exons, which implies that rs115550680 is in LD with exonic variants that could be potentially causative. The study by Reitz *et al.* also replicated *CR1*, *BIN1*, *EPHA1*, and *CD33* with significance in gene-based analyses and effect sizes similar to those in whites, although with different disease-associated top SNPs (51). These differences in associated SNPs not allowing direct comparison between specific SNPs were expected due to the differences in minor allele frequencies or linkage disequilibrium patterns between the ethnic groups.

In addition to these GWAS studies, several studies on specific LOAD candidate genes were performed in African Americans (Table 1). In their candidate-gene study on *SOLRL1*, Lee *et al.* (74) also explored the associations of *SORL1* SNPs and haplotypes with LOAD in 246 African American individuals and observed several disease-associated SNPs and haplotypes in the 5′ and 3′ ends. Burgess *et al.* (94) genotyped 119 cases and 252 controls for 15 SNPs in the kidney and brain expressed protein (*KIBRA*), which included rs17070145 previously reported to be associated with better episodic memory performance in whites (95). Consistent with these earlier reports, the authors found a significantly reduced risk associated with the T allele of rs17070145 in the older African American subjects ($p = .007$), but there was no association with episodic memory in control subjects. *KIBRA* interacts with a multitude of proteins involved in synaptic function, cell polarity, vesicular transport, and neuronal plasticity. It is expressed in memory-related structures of the brain and has increased expression in laser-capture microdissected neurons from the hippocampus, middle temporal gyrus, and posterior cingulate of LOAD cases in comparison with controls. Akomolafe *et al* (96). assessed the effect of the Glu298Asp variant of the endothelial nitric oxide synthase (*NOS3*) gene, which is involved in oxidative stress, on LOAD in 467 sibships and unrelated controls in the MIRAGE African American data set, and observed an increased risk for carriers of the GG genotype. Oxidative stress accelerates degenerative changes including those leading to LOAD via β-amyloid/lipid interactions and can also lead to hypertension, ischemic heart disease, and other cardiovascular diseases that indirectly contribute to progression of LOAD. In the same data set, several SNPs and haplotypes in the paraoxonase (*PON*) gene cluster (*PON1*, *PON2*, *PON3*) were associated with LOAD (97). Paraoxonase is an arylesterase enzyme that is expressed in the liver and found in the circulation in association with apoA1 and the high-density lipoprotein and prevents the accumulation of oxidized lipids in low-density lipoproteins in vitro. Common polymorphisms in genes encoding paraoxonase are established risk factors in a variety of vascular disorders including coronary artery disease and carotid artery stenosis. As described earlier, genetic, epidemiologic, autopsy, and neuroimaging studies suggest that vascular disease increases risk of LOAD.

Genetics of LOAD Endophenotypes

Benke *et al.* (98) explored the association of genetic variants in interleukin-1 genes with cognition in the Cardiovascular Health Study and observed significant association of SNPs in the IL1B gene with baseline performance on the 3MS. Cuenco *et al.* (99) explored the effect of 16 SNPs in transthyretin, which inhibits the production of the amyloid β protein, with LOAD risk and measures of neurodegeneration and cerebrovascular disease defined by magnetic resonance imaging in African American sibships. They observed a marginal effect of two SNPs significant in Caucasian sibships with hippocampal atrophy. Melville *et al.* (100) conducted a 2-stage GWAS in non-Hispanic white and African Americans for measures of hippocampal volume, total cerebral volume, and white matter hyperintensities. They attained genome-wide significant associations for hippocampal volume with SNPs in the *APOE*, *F5/SELP*, *LHFP*, and *GCFC2* gene regions in both ethnic groups. Except for *APOE*, all these genes remain to be confirmed by independent African American data sets or functional studies.

Conclusions

Genetic differences in LOAD risk alleles across populations have not been studied sufficiently. In general, there is a paucity of data sets with appropriate phenotyping and genotyping, and most of the few studies that have these measures available are, because of small sample sizes, limited in their ability to detect the small effect sizes expected for this complex disease. Studies aiming to replicate the specific loci identified in non-Hispanic whites are furthermore often hampered by cross-population differences in allele frequencies of the identified SNPs and differences in linkage disequilibrium patterns.

As a consequence, loci recently identified in non-Hispanic whites may not modify LOAD risk in other ethnic groups; similarly, it remains unclear whether there are population-specific causative variants. The few studies performed in African Americans and Caribbean Hispanics suggest that these ethnic groups share some but not all LOAD susceptibility loci with whites. The linkage studies performed in Caribbean Hispanics further support the possibility that multiple rare variants could be involved in LOAD risk in multiplex LOAD families in this ethnic group. Whether the effect of these variants is modified by epistatic effects or environmental factors remains unclear. Although essential for further elucidating the pathogenic mechanism underlying LOAD,

these questions, because of limited statistical power, likely cannot be answered sufficiently by the currently available data sets.

Currently, large-scale whole exome and whole genome sequencing efforts are under way aiming to identify additional common and rare variants associated with LOAD. These efforts include whites and Caribbean Hispanics, and although variants identified by this effort will need to be functionally confirmed, these studies hold the promise to lead to a more accurate understanding of the genetic risk factors in these ethnic groups, which in turn can be incorporated in diagnostic and predictive testing protocols and help to identify novel targets for prevention and treatment. Similar efforts are needed for African Americans and additional ethnic groups that have a high prevalence of LOAD but have been widely neglected by genomic LOAD research.

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