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).

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