Alzheimer's & Dementia 12 (2016) 233-243

Featured Article

Global and local ancestry in African-Americans: Implications for Alzheimer's disease risk

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http://dx.doi.org/10.1016/j.jalz.2015.02.012

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Abstract

Introduction: African-American (AA) individuals have a higher risk for late-onset Alzheimer's disease (LOAD) than Americans of primarily European ancestry (EA). Recently, the largest genome-wide association study in AAs to date confirmed that six of the Alzheimer's disease (AD)-related genetic variants originally discovered in EA cohorts are also risk variants in AA; however, the risk attributable to many of the loci (e.g., APOE, ABCA7) differed substantially from previous studies in EA. There likely are risk variants of higher frequency in AAs that have not been discovered.
Methods: We performed a comprehensive analysis of genetically determined local and global ancestry in AAs with regard to LOAD status.
Results: Compared to controls, LOAD cases showed higher levels of African ancestry, both globally and at several LOAD relevant loci, which explained risk for AD beyond global differences.
Discussion: Exploratory post hoc analyses highlight regions with greatest differences in ancestry as potential candidate regions for future genetic analyses.

Keywords: Local admixture; Local ancestry; Alzheimer's disease; Genome-wide association analysis (GWAS); African-American; Admixture mapping

1. Background

Late-onset Alzheimer's disease (LOAD) is a debilitating neurodegenerative disease with 4.7 million cases reported in the United States in 2010, a number that is projected to increase threefold by the year 2050 [1]. The strongest genetic risk factor for LOAD—the ε4 variant of the apolipoprotein E (*APOE*) gene on chromosome 19—was identified in 1993 and increases risk for LOAD in a dose-dependent manner [2]. Over the past 10 years, a number of genome-wide association studies (GWASs) have identified and replicated effects in 20 other loci that explain variance in LOAD risk [3–7]. Taken together, these loci are estimated to explain approximately 30%–40% of the total heritability for LOAD [8,9], and yet this still falls substantially below the 60%–80% heritability expected based on prior estimates from twin studies [10]. Multiple strategies, including the identification of rare variants and gene-gene interactions, will be needed to successfully explain all genetic variation associated with LOAD [8].

Although the number of GWAS has increased substantially in recent years, most of these studies have focused on individuals of mostly western European ancestry. This is particularly relevant because previous work has suggested the prevalence of LOAD may be higher in African-American (AA) individuals than in European Americans (EAs) within the same community [11], although findings have been somewhat variable depending on the geographic location from which the sample was ascertained [12]. Recently, a GWAS of LOAD in a large sample of AA individuals replicated many of the previous risk loci identified in EA individuals (*APOE, ABCA7, CR1, BIN1, EPHA1*, and *CD33*) [13]. Perhaps more importantly, however, was the discovery that in this AA data set, the amount of risk attributable to *APOE* and *ABCA7* differed substantially from previous studies in EA. This is interesting because the association between *APOE* genotype and AD differs by ancestral background. For example, previous work suggested that there is no effect of *APOE* genotype in Nigerian populations