adsp
Alzheimer's Disease Sequencing Project

ADSP Case-Control Study Description

Sample selection for the ADSP was designed to address the issue of phenotypic heterogeneity and maximize statistical power. The WES case-control study, in particular, was designed to target low-frequency coding variation in genes that contribute to AD risk or protection. Over 30,000 samples from the Alzheimer Disease Genetics Consortium (ADGC) and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium were considered for inclusion in the case-control design.

Study participants were either European-American (EA) or Caribbean Hispanic (CH) ancestry and were sampled in two ways. To maximize contrast between cases and controls, and power to discover novel associations, the majority of participants were chosen using a risk score that included dosages of the *APOE* ε2/ε3/ε4 alleles, sex and either onset age (for cases) or age at last exam for controls (or pathology-based adjusted age at death for neuropathology control). All cases were at least 60 years old and met NINCDS-ADRDA criteria for possible, probable or definite AD based on clinical assessment, or had presence of AD (moderate or high likelihood) upon neuropathology examination. To maximize our ability to discover novel genetic associations, we chose cases whose AD risk score indicated that their disease was not well explained by age, sex, or dosages of the *APOE* ε2/ε3/ε4 alleles. Conversely, cognitively healthy controls were selected with the goal of identifying alleles associated with the increased risk of or protection from late-onset AD. At the time of last exam, all potential controls were at least 60 years old and were either judged to be cognitively normal or did not meet pathological criteria for AD following brain autopsy. Controls were selected for this study on the basis of the risk score indicating that they were the least likely to develop AD by age 85 years. Applying the risk score resulted in a sample that contained 2,220 AD cases (40%) and 752 controls (14%) who were ε4 heterozygotes and 161 AD cases (3%) and 17 controls (< 1%) who were ε4 homozygotes.

In addition, we sampled a set of "enriched" cases from families having at least three affected members for whom the diagnosis of AD was verified by direct examination or review of cognitive testing data and medical records. Cases from early-onset AD families or families with a known *PSEN1*, *PSEN2*, or *APP* mutation were excluded. Within each family, we selected only one AD case, typically the member with the lowest *a priori* AD risk (based on the risk score defined above), provided this person had sufficient genomic DNA. In addition, because 172 of the "enriched" cases described above were of CH ancestry, we also selected a set of 171 age- and sex-matched cognitively normal CH participants to serve as controls.