EXTENDED DATASETS DESCRIPTION

The Alzheimer's disease genetics consortium (ADGC)

The National Institute on Aging (NIA) Alzheimer's Disease Centres (ADCs) cohort includes subjects ascertained and evaluated by the clinical and neuropathology cores of the 29 NIA-funded ADCs [1]. Data collection was coordinated by the National Alzheimer's Coordinating Center (NACC). The ADC cohort consists of autopsy-confirmed and clinically-confirmed AD cases, and cognitively normal elders (CNEs) with complete neuropathology data who were older than 60 years at age of death, and living CNEs evaluated using the Uniform dataset (UDS) protocol who were documented to not have mild cognitive impairment (MCI) and were between 60 and 100 years of age at assessment.

The AddNeuroMed study

AddNeuroMed was a public-private partnership for biomarker discovery and replication in Alzheimer’s disease [2, 3]. It was designed as a multi-center study in Europe with the first patient enrolled in January 2006 and the last in February 2008. The study protocol was planned for a baseline assessment visit with follow ups every 3 months for the first year, proceeded by annual visits that continued through 2013. The study enrolled a total of 258 AD, 257 MCI and 266 controls, not all with complete data at each assessment.

The Alzheimer’s disease neuroimaging initiative (ADNI)

Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer’s disease (AD). The ADNI study has three phases: ADNI1, ADNI GO and ADNI2. For up-to-date information, see [www.adni-info.org](http://www.adni-info.org).

The atherosclerosis risk in communities (ARIC)

The ARIC study is a population-based cohort study of atherosclerosis and clinical atherosclerotic diseases (ARIC Investigators 1989) [4]. At its inception (1987-1989), 15,792 men and women, including 11,478 white and 4,266 black participants were recruited from four U.S. communities: Suburban Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi. In the first 3 communities, the sample reflects the demographic composition of the community. In Jackson, only black residents were enrolled. Participants were between age 45 and 64 years at their baseline examination in 1987-1989 when blood was drawn for DNA extraction and participants consented to genetic testing. Vascular risk factors and outcomes, including transient ischemic attack, stroke and dementia, were determined in a standard fashion. During the first 2 years (1993-1994) of the third ARIC examination (V3), participants aged 55 and older from the Forsyth County and Jackson sites were invited to undergo cranial MRI. This subgroup of individuals with MRI scanning represents a random sample of the full cohort because examination dates were allocated at baseline through randomly selected induction cycles.

The Banner Sun Health Research Institute (Banner) study

This study is based on 201 post-mortem brain tissue samples obtained from the Banner Sun Health Research Institute's Brain and Body Donation Program. The tissue set came from 101 cognitively normal (controls) and 100 Alzheimer’s disease (AD) cases. Label free proteome analysis was done on the dorsolateral prefrontal cortex from all individuals. Post-mortem neuropathological evaluation was performed at Banner Sun Health Research Institute. This included amyloid plaque distribution according to CERAD criteria and neurofibrillary tangle pathology assessed with Braak staging. Control cases were defined as cognitively normal within on average 9 months of death with low CERAD (0.13 ±0.35) and Braak (2.26 ±0.94) measures for amyloid and tau neuropathology, respectively. In contrast, AD cases were demented at the last clinical research assessment, and the brains showed high CERAD (2.9 ±0.31) and Braak (5.4 ±0.82) scores consistent with moderate to severe neuropathological burden. There was no significant difference in age or post mortem interval (PMI) between control and AD.

The Baltimore longitudinal study on aging (BLSA) study

We BLSA study included 97 post-mortem brain tissue samples from the National Institute on Aging’s Baltimore Longitudinal Study of Aging (BLSA, <https://www.blsa.nih.gov/>). The tissue set came from 50 individuals representing 15 controls, 15 AsymAD and 20 AD cases. For 47 cases, we analyzed tissue from both the dorsolateral prefrontal cortex (FC, Brodmann Area 9) and precuneus (PC, Brodmann Area 7). Both regions are affected in AD, and PC is a site of early amyloid deposition and glucose hypometabolism. Post-mortem neuropathological evaluation was performed at the Johns Hopkins Alzheimer’s Disease Research Center with the Uniform Data Set including amyloid plaque distribution according to CERAD criteria and neurofibrillary tangle pathology assessed with Braak staging. Control cases were defined as cognitively normal within on average 9 months of death with low CERAD (0.13 ±0.35) and Braak (2.26 ±0.94) measures for amyloid and tau neuropathology, respectively [5]. In contrast, AD cases were demented at the last clinical research assessment, and the brains showed high CERAD (2.9 ±0.31) and Braak (5.4 ±0.82) scores consistent with moderate to severe neuropathological burden. AsymAD cases were cognitively normal proximate to death and had high CERAD (2.1 ±0.52) and moderate Braak (3.6 ±0.99).

The cohort for heart and ageing research in genomic epidemiology (CHARGE) consortium

The CHARGE consortium currently includes six large, prospective, community-based cohort studies that have genome-wide variation data coupled with extensive data on multiple phenotypes [5]. A neurology working-group arrived at a consensus on phenotype harmonization, covariate selection and analytic plans for within-study analyses and meta-analysis of results [6]. Consent procedures, examination and surveillance components, data security, genotyping protocols and study design at each study were approved by a local Institutional Review Board, details are provided below. Of the six studies, we included in this study the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS) and the Rotterdam Study (RS).

The cardiovascular health study (CHS)

The CHS is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥ 65 years conducted across four field centers [7]. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5,888. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. Genotyping was performed at the General Clinical Research Center’s Phenotyping/Genotyping Laboratory at Cedars-Sinai among CHS participants who consented to genetic testing and had DNA. European ancestry participants were excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack or lack of available DNA. Among those with successful GWAS, 567 European ancestry participants had available FreeSurfer measures for this analysis. CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

The European Alzheimer’s disease initiative (EADI) consortium

All the 2,240 Alzheimer’s disease cases were ascertained by neurologists from Bordeaux, Dijon, Lille, Montpellier, Paris, Rouen, and were identified as French NHW ancestry. Clinical diagnosis of probable Alzheimer’s disease was established according to the DSM-III-R and NINCDS-ADRDA criteria. Controls were selected from the 3C Study [8]. This cohort is a population-based, prospective (10-years follow-up) study of the relationship between vascular factors and dementia. It has been carried out in three French cities: Bordeaux (southwest France), Montpellier (southeast France) and Dijon (central eastern France). A sample of non-institutionalized, over-65 subjects was randomly selected from the electoral rolls of each city. Between January 1999 and March 2001, 9,686 subjects meeting the inclusion criteria agreed to participate. Following recruitment, 392 subjects withdrew from the study. Thus, 9,294 subjects were finally included in the study (2,104 in Bordeaux, 4,931 in Dijon and 2,259 in Montpellier). Genomic DNA samples of 7,200 individuals were transferred to the French Centre National de Génotypage (CNG). First stage samples that passed DNA quality control were genotyped with Illumina Human 610-Quad BeadChips. At the end we removed 308 samples because they were found to be first- or second-degree relatives of other study participants or were assessed non-European descent based on genetic analysis using methods described in 89. In this final sample,
at 10 years of follow-up, 564 individuals suffered
from Alzheimer’s disease with 95 prevalent and 469 incident cases.

The Framingham heart study (FHS)

The FHS is a three-generation, single-site, community-based, ongoing cohort study that was initiated in 1948 to investigate the risk factors for cardiovascular disease. It now comprises 3 generations of participants: the Original cohort followed since 19489; their Offspring and spouses of the Offspring (Gen 2), followed since 1971 [9]; and children from the largest Offspring families enrolled in 2000 (Gen 3) [10]. The Original cohort enrolled 5,209 men and women who comprised two-thirds of the adult population then residing in Framingham, MA. Survivors continue to receive biennial examinations. The Offspring cohort comprises 5,124 persons (including 3,514 biological offspring) who have been examined approximately once every 4 years. The Third-generation includes 4,095 participants with at least one parent in the Offspring Cohort. The first two generations were invited to undergo an initial brain MRI in 1999-2005, and for Gen 3, brain MRI began in 2009. The population of Framingham was virtually entirely white (Europeans of English, Scots, Irish and Italian descent) in 1948 when the Original cohort was recruited. Self-reports of ethnicity across all three generations were 99.7% whites, reflecting the ethnicity of the population of Framingham in 1948. FHS participants had DNA extracted and provided consent for genotyping, and eligible participants underwent genome-wide genotyping.

Multi-site collaborative study for genotype-phenotype associations in Alzheimer's disease and longitudinal follow-up of genotype-phenotype associations in Alzheimer's disease and neuroimaging component of genotype-phenotype associations in Alzheimer's disease (GenADA)

GenADA was a multi-site collaborative study, involving GlaxoSmithKline Inc and nine medical centers in Canada, including 1000 AD patients and 1000 ethnically-matched controls in order to associate DNA sequence (allelic) variations in candidate genes with AD phenotypes [11, 12]. The study consists of both retrospective and prospective data. Where possible, biological relatives with Alzheimer's (up to third degree relationship) and unaffected siblings of AD cases were also recruited.

The genetic and environmental risk for Alzheimer’s disease (GERAD1) consortium

The GERAD1 sample comprised up to 3941 AD cases and 7848 controls. A subset of this sample has been used in this study and were genotyped at the Sanger Institute on the Illumina 610-quad chip. These samples were recruited by the Medical Research Council (MRC) Genetic Resource for AD (Cardiff University; Kings College London; Cambridge University; Trinity College Dublin), the Alzheimer’s Research UK (ARUK) Collaboration (University of Nottingham; University of Manchester; University of Southampton; University of Bristol; Queen’s University Belfast; the Oxford Project to Investigate Memory and Ageing (OPTIMA), Oxford University); Washington University, St Louis, United States; MRC PRION Unit, University College London; London and the South East Region AD project (LASER-AD), University College London; Competence Network of Dementia (CND) and Department of Psychiatry, University of Bonn, Germany and the National Institute of Mental Health (NIMH) AD Genetics Initiative. All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower.”

The genome research @ fundació ACE project (GR@ACE) study

The GR@ACE study comprises 4,120 AD cases and 3,289 control individuals. Cases were recruited from Fundació ACE, Institut Català de Neurociències Aplicades (Catalonia, Spain). Diagnoses were established by a multidisciplinary working-group, including neurologists, neuropsychologists, and social workers, according to the DSM-IV criteria for dementia and to the National Institute on Aging and Alzheimer’s Association’s (NIA-AA) 2011 guidelines for defining AD [13]. Dementia individuals diagnosed with probable or possible AD at any moment of their clinical course were considered AD cases.

Briefly, participants were genotyped using the Axiom 815K Spanish Biobank Array (Thermo Fisher), performed in the Spanish National Center for Genotyping (CeGEN, Santiago de Compostela, Spain). Individuals were excluded for low-quality samples, (call rate <97%), excess heterozygosity, sample duplicates, or relation to another sample (PIHAT > 0.1875). Individuals were excluded if sex discrepancy was detected. Population outliers of European ancestry were also removed. Variants were excluded if they departed from the Hardy-Weinberg equilibrium (P-value ≤ 1 × 10-6), presented a different missing rate between cases and controls (P-value < 5 × 10-4 for the difference), or had a low frequency (MAF < 0.01) or low call rate < 95%. High-quality variants
were imputed in Michigan Server using the
Haplotype reference consortium (HRC) panel ([https://
imputationserver.sph.umich.edu](https://imputationserver.sph.umich.edu)). Only high imputation quality markers (MAF > 0.05 and R2>0·03) were used for downstream analysis. Further information about phenotyping and GWAS quality controls have been previously provided [14].

The Mayo clinic LOAD genome-wide association study (MAYO)

Subjects from the Mayo LOAD GWAS were selected from two clinical AD Case-Control series: Mayo Clinic Jacksonville (MCJ), Mayo Clinic Rochester (MCR)and a neuropathological series of autopsy-confirmed subjects from the Mayo Clinic Brain Bank [15]. All subjects from the clinical series (MCJ and MCR) were diagnosed by a Mayo Clinic neurologist; all control subjects had a Clinical Dementia Rating score of zero at the most recent time of testing; all LOAD patients had a diagnosis of probable or possible AD according to the NINCDS-ADRDA criteria [16]. All ADs had definite diagnosis according to the NINCDS-ADRDA criteria and had Braak scores of ≥4.0. All non–AD Controls had Braak scores of ≤2.5; many had brain pathology unrelated to AD.

The Mount Sinai brain bank (MSBB) study

Brain specimens were obtained from the Mount Sinai/JJ Peters VA Medical Center Brain Bank (MSBB) which holds over 1,700 samples. This cohort was assembled after applying stringent inclusion/exclusion criteria and represents the full spectrum of disease severity. Neuropathological assessments are performed according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol and include assessment by hematoxylin and eosin, modified Bielschowski, modified thioflavin S, and anti-β amyloid (4G8), anti-tau (AD2) and anti-ubiquitin (Daka Corp.). Each case is assigned a Braak AD-staging score for progression of neurofibrillary neuropathology. Quantitative data regarding the density of neuritic plaques in the middle frontal gyrus, orbital frontal cortex, superior temporal gyrus, inferior parietal cortex and calcarine cortex are also collected as described. Clinical dementia rating scale (CDR) and mini–mental state examination (MMSE) severity tests are conducted for assessment of dementia and cognitive status. Final diagnoses and CDR scores are conferred by consensus. Based on CDR classification, subjects are grouped as no cognitive deficits (CDR = 0), questionable dementia (CDR = 0.5), mild dementia (CDR = 1.0), moderate dementia (CDR = 2.0), and severe to terminal dementia (CDR = 3.0–5.0). Covariates including demographic and neuropathological data were collected on the samples used for this project including postmortem interval, race, age of death, clinical dementia rating, clinical neuropathology diagnosis, CERAD, Braak, sex, and a series of neuropathological variables.

The Neocodex-Murcia study (NXC)

The study includes 327 sporadic AD patients and 801 controls with unknown cognitive status from the Spanish general population collected by
Neocodex [17, 18]. AD patients were diagnosed as possible or probable AD in accordance with the
criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [16].

The National Institute on Aging - late onset Alzheimer's disease family study (NIA)

The goal of this study is to identify and recruit families with two or more siblings with the late-onset form of Alzheimer's disease and a cohort of unrelated, non-demented controls similar in age and ethnic background, and to make the samples, the clinical and genotyping data and preliminary analyses available to qualified investigators world-wide [19]. Genotyping by the Center for Inherited Disease Research (CIDR) was performed using the Illumina Infinium II assay protocol with hybridization to Illumina Human 610Quadv1\_B Beadchips.

The religious orders study and memory and aging project (ROS/MAP) study

The Religious Orders Study (ROS) is a longitudinal clinical-pathologic cohort study of aging and Alzheimer's disease (AD) from the Rush University that enrolled individuals from religious communities for longitudinal clinical analysis and brain donation [20]. Participants were enrolled from more than 40 groups of religious orders (nuns, priests, brothers) across the United States. Medical conditions are documented starting in 1994 by clinical evaluation or self-report. Alzheimer's Disease status was determined by a computer algorithm based on cognitive test performance with a series of discrete clinical judgments made in series by a neuropsychologist and a clinician.

The Memory and Aging Project (MAP) is a longitudinal, epidemiologic clinical-pathologic cohort study of common chronic conditions of aging with an emphasis on decline in cognitive and motor function and risk of Alzheimer’s disease that began in 1997 and is run from Rush University [20]. This study was designed to complement the ROS study by enrolling individuals with a wider range of life experiences and socioeconomic status into a study of similar structure and design as ROS. The study enrolled older individuals without any signs of dementia, primarily recruiting from continuous care retirement communities throughout north-eastern Illinois, USA. Diagnoses of dementia
and AD are performed in an identical manner to the ROS study.

The Rotterdam study

The Rotterdam Study is a prospective, population-based cohort study among individuals living in the well-defined Ommoord district in the city of Rotterdam in The Netherlands [21, 22]. The aim of the study is to determine the occurrence of cardiovascular, neurological, ophthalmic, endocrine, hepatic, respiratory, and psychiatric diseases in elderly people. The cohort was initially defined in 1990 among approximately 7,900 persons, aged 55 years and older, who underwent a home interview and extensive physical examination at the baseline and during follow-up rounds every 3-4 years (RS-I). The cohort was extended in 2000/2001 (RS-II, 3,011 individuals aged 55 years and older) and 2006/2008 (RS-III, 3,932 subjects, aged 45 and older). Written informed consent was obtained from all participants and the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the study.

The Translational Genomics Research Institute (TGEN) study

The TGEN GWAS study included 643 late onset AD cases and 404 controls from a neuropathological cohort, and 197 late onset AD cases and 114 controls from a clinical cohort [23].

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